2024 EACTS/EACTAIC Guidelines on patient blood management in adult cardiac surgery in collaboration with EBCP

Authors/Task Force Members: Filip P. A. Casselman[a,*,†] (Co-Chairperson) (Belgium), Marcus D. Lance[b,*,†] (Co-Chairperson) (Kenya), Aamer Ahmed[c,d] (United Kingdom), Alice Ascari[e,] (Italy); Juan Blanco-Morillo[f] (Spain); Daniel Bolliger[g] (Switzerland); Maroua Eid[h,**] (France); Gabor Erdoes[i] (Switzerland); Renard Gerhardus Haumann[j,k] (The Netherlands); Anders Jeppsson[l,m] (Sweden); Hendrik J. van der Merwe[n]; Erik Ortmann[o] (Germany); Mate Petricevic[p,q] (Croatia); Luca Paolo Weltert[r,s] (Italy); Milan Milojevic[t] (Serbia), EACTS/EACTAIC/EBCP Scientific Document Group.**

From: [a]Department of Cardiovascular Surgery, Heart Center OLV Clinic, Aalst, Belgium; Aga [b]Khan University Hospital Nairobi, Department of Anesthesiology, Nairobi, Kenya; [c]Department of Anaesthesia and Critical Care, Glenfield Hospital, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [d]Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom; [e]Department of Cardiovascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy; [f]ECLS Care and Perfusion Unit, Cardiac Surgery Department, University Hospital Virgen de la Arrixaca, Murcia, Spain; [g]Clinic for Anaesthesia, Intermediate Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Basel, Switzerland; [h]University Hospital of Angers, Department of Cardiac Surgery, Angers, France; [i]Department of Anesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [j]Department of Cardio-thoracic surgery, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, The Netherlands; [k]Department Of Biomechanical Engineering, TechMed Centre, University of Twente, Enschede, The Netherlands; [l]Department of Cardiothoracic Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden; [m]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [n]Netcare Blaauwberg and Christiaan Barnard Memorial Hospital, The Keyhole Thorax Centre, Cape Town, South Africa; [o]Department of Anaesthesiology Schüchtermann-Klinik Heart Centre, Bad Rothenfelde, Germany; [p]Department of Cardiac Surgery, University Hospital Center Split, Split, Croatia; [q]University Department of Health Studies, University of Split, Split, Croatia; [r]European Hospital, Cardiac Surgery Department, Rome, Italy; [s]Saint Camillus International University for Health Sciences, Heart Surgery Department, Rome, Italy; [t]Department of Cardiac Surgery and Cardiovascular Research, Dedinje Cardiovascular Institute, Belgrade, Serbia.

***Corresponding authors:** Heart Center OLV Clinic, Moorselbaan 164, 9300 Aalst, Belgium. E-mail: filip.casselman@olvz-aalst.be. (F. Casselman). Aga Khan University Hospital, 3rd Parklands Avenue, Limuru Road, Nairobi, Kenya. E-mail: marcus.lance@aku.edu. (M. Lance).

† These authors contributed equally to this work.

**Junior members.

Text word count: 49027 (including references, tables, and legends)

Subject category: Adult cardiac Surgery

EACTS/EACTAIC/EBCP Scientific Document Group (Collaborators): J. Rafael Sadaba (EACTS Review Coordinator) (Spain), Marco Ranucci (EACTAIC Review Coordinator) (Italy), Seema Agrawal (UK), Adrian Bauer (Germany), Denis Berdajs (Switzerland), Stewart McCluskey (Canada), Daniel Engelman (USA), Tomas Gudbjartsson (Iceland), Emma Hansson (Sweden), Andreas Koster (Germany), Filip De Somer (Belgium), Eric De Waal (The Netherlands), Alexander Wahba (Norway), Fernando Yévenes (Chile).

Disclaimer: A clinical guideline aims to apply to all patients with a specific condition. However, there will inevitably be situations where its recommendations aren't suitable for a particular patient. While healthcare professionals and others are encouraged to consider these guidelines in their professional judgment, they don't override the responsibility of healthcare professionals to make decisions tailored to each patient's unique circumstances. Such decisions should be aligned with the latest official recommendations, guidelines from relevant public health authorities, and applicable rules and regulations. It's important that these decisions are made in collaboration with, and agreed upon by, the patient and/or their guardian or carer.

Graphical Abstract

Central Illustration. Multidisciplinary patient blood management approach.

CPB: cardiopulmonary bypass; DAPT: dual antiplatelet therapy; DDAVP: desmopressin; FFP: fresh-frozen plasma; PCC: prothrombin complex concentrate; POC: point-of-care; PRBCs: packed red blood cells.

Keywords: Guidelines, cardiac surgery, patient blood management, haemostasis, blood transfusion, bleeding, anticoagulation, coagulation factors, evidence based practice

Table of Contents

Abbreviations and acronyms

ACS: Acute coronary syndrome

ACT: Activated clotting time

AFib: Atrial fibrillation

AKI: Acute kidney injury

ANH: Acute normovolaemic haemodilution

aPTT: Activated partial thromboplastin time

ASA: Acetylsalicylic acid

AT: Antithrombin

ATACAS: Aspirin and Tranexamic Acid for Coronary Artery Surgery

AVR: Aortic valve replacement

BSA: Body surface area

CABG: Coronary artery bypass grafting

CI: Confidence interval

CPB: Cardiopulmonary bypass

CS: Cell salvage

DAPT: Dual antiplatelet therapy

DDAVP: Desmopressin

dMCS: Durable mechanical circulatory support

DOAC: Direct oral anticoagulant

DTI: Direct thrombin inhibitor

EACA: Epsilon-aminocaproic acid

EACTAIC: European Association of Cardiothoracic Anaesthesiology and Intensive Care

EACTS: European Association for Cardio-Thoracic Surgery

EBCP: European Board of Cardiovascular Perfusion

eGFR: Estimated glomerular filtration rate

EPO: Erythropoietin

Factor XIII: FXIII

FFP: Fresh frozen plasma

FXa: activated factor X

FXIII: Factor XIII

GDT: Goal-directed therapy

GPIIb/IIIa: Glycoprotein IIb/IIIa

Hb: Haemoglobin

HCT: Haematocrit

HES: Hydroxyethyl starch

HIT: Heparin-induced thrombocytopenia

IABP: Intra-aortic balloon pump

ICU: Intensive care unit

INR: International normalized ratio

JW: Jehovah's Witness

LMWH: Low-molecular-weight heparin

LVAD: Left ventricular assist device

MCS: Mechanical circulatory support

MHVs: Mechanical heart valves

MI: Myocardial infarction

MiECC: Minimally invasive extracorporeal circulation

OAC: Oral anticoagulant

OR: Odds ratio

PABD: Preoperative autologous blood donation

PBM: Patient blood management

PCC: Prothrombin complex concentrate

PC-ECLS: Post-cardiotomy extracorporeal life support

PE: Pulmonary embolism

PF4: Platelet factor 4

PLTC: Platelet concentrate

POC: Point-of-care (coagulation testing)

PRBC: Packed red blood cells

PSM: Propensity score matching

PT: Prothrombin time

RAP: Retrograde autologous priming

RBC: red blood cell

RCT: Randomized controlled trial

rFVIIa: Recombinant factor VIIa

ROTEM: Rotational thromboelastometry

RR: Risk ratio

TEG: Thromboelastography

TEM: Thromboelastometry

tMCS: Temporary mechanical circulatory support

TRALI: Transfusion-related acute lung injury

TRICS III: Transfusion Requirements in Cardiac Surgery III

TRIM: Transfusion-related immune modulation

TXA: Tranexamic acid

UFH: Unfractionated heparin

VKA: Vitamin K antagonist

VTE: venous thromboembolism

WHO: World Health Organization

Preamble

These guidelines are dedicated to the memory of Dr. Blanca Martinez Lopez de Arroyabe, who served as the co-chair of the task force until January 2024 and passed away during the course of this work.

Clinical practice guidelines consolidate and evaluate all pertinent evidence available at their time of formulation on a specific topic, the goal being to assist physicians in determining the most effective management strategies for patients with a particular condition. These guidelines assess the impact on patient outcomes and weigh the risk–benefit ratio of various diagnostic or therapeutic approaches. Although not a replacement for textbooks, they provide supplementary information on topics relevant to current clinical practice, becoming an essential tool to support physicians' decision making in daily practice. Nonetheless, it is crucial to understand that these recommendations are intended to guide but not dictate clinical practice; they should be adapted to each patient's unique needs. Clinical situations vary, presenting a diverse array of variables and circumstances. Thus, the guidelines are meant to inform, not replace, the clinical judgement of physicians, which is grounded in their professional knowledge, experience and comprehension of the patient's specific context. Moreover, these guidelines are not to be considered legally binding; the legal duties of health-care professionals are defined by prevailing laws and regulations, and adherence to these guidelines does not modify such responsibilities.

The European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology and Intensive Care (EACTAIC), in partnership with the European Board of Cardiovascular Perfusion (EBCP), created a task force of professionals specializing in patient blood management. To ensure transparency and maintain integrity, all task force members involved in the development and review of the guidelines submitted conflict of interest declarations that were compiled into a single document, which is available as supplementary material. Any alterations to these declarations during the development process were promptly reported to the EACTS, EACTAIC and EBCP. Funding for this task force was provided exclusively by the EACTS and EACTAIC, with no health-care industry or other entities involved.

Following this collaborative endeavour, the governing bodies of the EACTS, EACTAIC and EBCP oversaw the formulation, refinement and endorsement of these extensively revised guidelines. An external panel of subject-matter experts thoroughly reviewed the initial draft, and their input guided subsequent amendments. After this detailed revision process, the final document was ratified by all task force experts and the leadership of the EACTS, EACTAIC and EBCP, enabling its publication in the EACTS and the *Journal of Cardiothoracic and Vascular Anesthesia*.

These guidelines have been endorsed by the EACTS, EACTAIC and EBCP and represent their official position on this subject. They demonstrate a dedication to continual enhancement, with routine updates planned to ensure that the guidelines remain current and valuable in the ever-progressing arena of clinical practice.

1. Introduction

Cardiac surgery is a distinctive surgical discipline that often necessitates the use of cardiopulmonary bypass (CPB) and full anticoagulation intraoperatively, along with varying levels of antithrombotic treatments both before and after the cardiac procedures. As a result, implementing precise anticoagulation strategies and meticulously monitoring reversal throughout the perioperative period to re-establish adequate coagulation effects at clinically relevant levels is a crucial endeavour in improving outcomes. These procedures are associated with an increased incidence of bleeding complications, frequently requiring allogeneic blood transfusions, which also are known to have associated short- and long-term risks.

The goal of the 2017 EACTS/EACTAIC guidelines on patient blood management (PBM) for adult cardiac surgery was to provide guidance for optimal patient preparation and for intra- and postoperative management (1), leading to recommended management of clinical conditions that affect bleeding, thrombosis and transfusion risks. Continuous research has since produced a plethora of advancements in the PBM field.

This document serves as an update to those guidelines, incorporating recent findings and technologies. Its goal is to summarize the clinical and scientific bases for the various aspects of PBM. Building on previous guidelines and statements that have offered valuable insights into modern PBM, these updated guidelines contain specific recommendations that reflect European practice.

A number of chapters were added in order to expand the scope of the application of the guidelines, such as haemostatic management in patients requiring temporary (tMCS) and durable mechanical circulatory support (dMCS). It is important to note that, due to the content specificity, PBM for paediatric cardiac surgery has been covered in a separate document that has been developed in parallel with this one. When covering broad topics, such as surgical and CPB techniques, the recommendations in these guidelines are focused on PBM aspects, trying not to compromise the general procedural approach.

1.1 What is new

Compared to the 2017 document, this comprehensive revision involves collaboration with colleagues from the EBCP and features revisions of all sections based on new available evidence as well as the addition of several new chapters. The preoperative management

section has been updated to include more precise estimations of bleeding risk and adjustments to platelet inhibitor and anticoagulant therapy. Additionally, preoperative anaemia now involves a more thorough investigation and timely preoperative intervention.

The intraoperative management section has been updated to address various CPB techniques, anticoagulation management and intravascular volume management. Specifically, the approach to perioperative coagulation and transfusion in section 5 has been revised to include updates on procoagulant interventions, blood and blood product utilization.

A new section 6 on postoperative management has been added, covering chest tube drainage management, recommendations for postoperative re-exploration, postoperative transfusion triggers, resumption of pre-existing antithrombotic therapy and venous thromboembolism (VTE) prophylaxis. Additionally, a subsection has been included to address specific patient populations requiring special attention, such as patients with haemophilia and those who are Jehovah's Witnesses.

Section 7 introduces comprehensive guidelines on transfusion and haemostatic therapy during short- and long-term MCS. This section provides detailed recommendations for managing bleeding and thrombotic complications in patients undergoing MCS. It also covers the selection of appropriate blood products, the use of anticoagulants and antiplatelet agents and the management of coagulation parameters to address the unique challenges posed by these circulatory support devices and to ensure optimal outcomes in these high-risk patients.

Finally, section 8 provides recommendations for organizing an institutional comprehensive PBM programme, an essential step in the day-to-day implementation of these guidelines.

This document concludes by highlighting areas where knowledge is lacking and proposes directions for future research and enhancement strategies in adult cardiac surgery. These areas require the attention and collaboration of the entire academic community to advance the field and further improve patient outcomes.

2. Methodology

To keep the evidence-based, best-practice guidelines up to date, the EACTS Council, the Board of Directors of the EACTAIC and the Scientific Committee of the EBCP regularly review new pieces of evidence and revise them based on established standards for the development and implementation of clinical practice documents (2). In light of significant advances in the field of PBM since the first publication (1) and the fact that most guidelines become obsolete 5 years after their last revision (3), a comprehensive joint update of the PBM guidelines for adult cardiac surgery was deemed necessary.

A multidisciplinary task force was established to represent a wide range of expertise involved in cardiac surgery, selecting specialists from various fields, regions and clinical and research settings. The scope of the guidelines was agreed upon by the governing bodies of the societies, and the task force members determined the final table of contents. To systematically evaluate the latest evidence, the task force conducted a systematic literature review using the standardized Population, Intervention, Comparison, Outcome and Time (PICOT) questions format, with the help of a medical informatics specialist. The literature search included all study types, such as randomized controlled trials (RCTs), registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews and meta-analyses and expert opinions. An initial systematic literature review focused on human research published in English from January 2016 and indexed in MEDLINE, EMBASE and the Cochrane Library was conducted from September to December 2023 (see search strings for each chapter in the supplementary material). Additional studies published after December 2023, during the guideline-writing and external validation processes, were also considered and included when relevant. The references in this document are representative but not exhaustive. The guideline recommendations are, whenever possible, evidence-based and primarily derived from RCTs.

To ensure that the document's development remains unbiased and impartial, task force members were required to declare any conflicts of interest before starting the project and to inform the co-chairs of EACTS and EACTAIC of any changes until the publication of the guideline. Members could only work on recommendations and supporting text if they had no relevant conflicts. All chapters were collaboratively written by the members. Each recommendation was developed based on the entirety of current scientific and medical knowledge, assessing the risks and benefits of the intervention using established methods (see

Tables 1 and 2) (2). In areas lacking strong evidence, expert consensus was used to address important daily practice issues. Preliminary consensus was reached through conference calls and in-person meetings; a minimum of 75% agreement among present members allowed the draft recommendations to move forward. The votes on each recommendation were gathered via an anonymous electronic survey, along with the corresponding Class of Recommendation and Level of Evidence. A consensus was achieved with an 80% response rate and at least 75% affirmative votes on each recommendation. Each participating society appointed a peer review committee to examine the document, which was then extensively reviewed and endorsed for publication by the governing bodies of the EACTS, EACTAIC and EBCP.

Table 1: Levels of evidence	
Level of evidence A	**Data derived from multiple randomized clinical trials or meta-analyses**
Level of evidence B	**Data derived from a single randomized clinical trial or from large non-randomized studies**
Level of evidence C	**The consensus of expert opinion and/or small studies, retrospective studies and registries**

Table 2: Classes of recommendations		
Class of recommendations	**Definition**	**Suggested wording**
Class I	**Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective**	**Is recommended/is indicated**
Class II	**Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure**	

Class IIa	**Weight of evidence/opinion is in favour of usefulness/efficacy**	**Should be considered**
Class IIb	**Usefulness/efficacy is less well established by evidence/opinion**	**May be considered**
Class III	**Evidence/general agreement that the given treatment/procedure is not useful/effective and may sometimes be harmful**	**Is not recommended**

3. Preoperative management

Proper patient optimization prior to surgery is essential for minimizing the risk of bleeding and transfusions. Preoperative strategies should focus on the effective management of antithrombotic medications, optimization of haemoglobin (Hb) and platelet levels according to patient comorbidities and body surface dimensions, blood conservation and a thorough assessment and evaluation of patient haemostatic risk factors, including the presence of congenital disorders.

3.1 Strategies for assessing perioperative bleeding and transfusion risks: Laboratory and point-of-care tests, risk scores

A physical examination, preoperative bleeding history and review of medications are the foundational elements of preoperative risk assessment (4-6). In addition to these, laboratory testing can further clarify the potential side effects of pharmacotherapy (4-6). Building on this foundation, the preoperative evaluation of haemostatic blood properties, which includes assessing both primary and secondary haemostasis, can be conducted through the history, review of medications and physical examination and standard laboratory testing or point-of-care (POC) viscoelastic and platelet function testing. This approach has been proposed as a means to predict bleeding outcomes, such as postoperative bleeding volume and transfusion requirements in cardiac surgery.

3.1.1 Standard laboratory testing

The utilization of standard laboratory testing as a preoperative screening tool to stratify bleeding risk and identify patients with a high risk of bleeding who are at risk for transfusion(s) has been researched and debated. Prothrombin time (PT) or the activated partial thromboplastin time (aPTT), as assessed preoperatively, was not found to be associated with the amount of perioperative bleeding or transfusion requirements (7-9). Considering standard laboratory parameters, a low fibrinogen level was found to be the most commonly identified risk factor for the amount of postoperative bleeding and bleeding-related re-exploration (10-17). However, despite its association with bleeding, the positive predictive value of a low level of fibrinogen remains poor (positive predictive value for bleeding > 1000 ml/12 h is as low as 19% for a fibrinogen level less than 2.5 g/L) (10). A similar association was found for a low platelet count and the risk of massive packed red blood cell (PRBC) transfusions (18, 19), and patients with the highest postoperative blood loss volumes show the lowest platelet counts (8, 19). Furthermore, the association between preoperative fibrinogen levels and severe perioperative bleeding has been reported to have a U-shaped relationship (20). Whereas a low level of fibrinogen is associated with a high risk of bleeding, a high level of fibrinogen does not protect against bleeding risk and could even be a risk factor for perioperative bleeding (20). The preoperative haemostatic disorder is usually multifactorial with impaired thrombin generation considered as one important contributing factor (21). Platelet dysfunction may also impair thrombin generation (21, 22), which leads to excessive bleeding (8, 22, 23). Currently, no assays designed specifically to measure thrombin generation are available for clinical use (21). A calibrated automated thrombogram is a research-based assay that can reliably measure thrombin generation; however, it is used mainly for research purposes, is not routinely used in everyday clinical practice and lacks standardization (21). A calibrated automated thrombogram cannot measure thrombin generation in whole blood, which prevents its use in a POC setting. Next-generation assays are being developed to address this drawback and provide reliable POC measures of thrombin generation capacity in whole blood (21, 24, 25).

In summary, a comprehensive preoperative evaluation, including bleeding history, medication review and physical examination, is recommended to identify patients at increased risk of bleeding. Preoperative fibrinogen levels may also be considered for further

risk stratification in selected scenarios. The routine clinical application of thrombin generation assays requires further validation through additional studies.

3.1.2 Viscoelastic testing and platelet function tests

Preoperative assessment of haemostatic parameters using viscoelastic tests, such as rotational thromboelastometry (ROTEM) and thromboelastography (TEG), has been found to have a limited association with the risk of postoperative bleeding (26, 27). Abnormal preoperative platelet function testing has been shown to be associated with an increased risk of bleeding complications in patients with and without ongoing or recently stopped dual antiplatelet therapy (DAPT) (27-35). Therefore, testing of platelet function may be used to guide the timing of cardiac surgery in this group of patients and to determine those who are non-responders to the indicated DAPT (31, 36-39). Between 2011 and 2020, a total of 10 meta-analyses on the effect of the implementation of TEG-/ROTEM-guided bleeding management algorithms in cardiovascular surgery have been published (40-49), including 2 Cochrane reviews (43, 44). All meta-analyses consistently demonstrated a significant reduction in perioperative transfusion requirements for PRBCs, fresh frozen plasma (FFP) and platelet concentrates (PLTCs) after the implementation of TEG-/ROTEM-guided bleeding management algorithms in cardiovascular surgery (40-50). The latest meta-analysis published by Santos *et al.* (49) (based on 21 RCTs including 8,900 participants) showed a statistically significant reduction in mortality [7.3% vs 12.1%; risk ratio (RR) 0.64, 95% confidence interval (CI) 0.43–0.96) and in the risk of acute kidney injury (AKI) (10.5% vs 17.6%; RR 0.53, 95% CI 0.34–0.83) in the TEG-/ROTEM-guided group (49). However, a significant reduction in the risk of AKI could only be demonstrated in a subgroup analysis that included ROTEM studies specifically (49).

This result confirms the findings from the Cochrane meta-analysis published by Wikkelsø *et al.* (44) in 2016 based on 17 studies and 1493 participants. In this meta-analysis, 8 studies including 717 participants were analysed concerning a primary outcome of mortality (44). Mortality in the TEG/ROTEM group was 3.9% vs 7.4% in the control group (RR 0.52, 95% CI 0.28–0.95) (44). This meta-analysis also showed fewer participants with dialysis-dependent AKI in the ROTEM group (no TEG studies available) (15.5% vs 30.9%; RR 0.46, 95% CI 0.28–0.76) (44). The meta-analysis published by Serraino *et al.* (45) in 2017, based on 7 studies, reported a reduction in mortality in the TEG/ROTEM group with a similar effect size. The use of viscoelastic testing reduced the frequency of severe AKI versus controls with an RR of 0.42

(95% CI 0.20–0.86) (45). Again, Li *et al.* (47) reported that TEG-/ROTEM-guided bleeding management reduced mortality in 5 RCTs from 8.9% to 4.4% (RR 0.50, 95% CI 0.26–0.96). The avoidance of AKI after cardiac surgery seems to be of significant importance for long-term mortality in cardiovascular surgery (51).

In summary, platelet function testing may be considered to guide the timing of cardiac surgery in patients who have recently received P2Y12 inhibitors. Despite the low positive predictive values obtained in systematic literature reviews, the low false negative rates for predicting bleeding in the early postoperative period may still play an important role in cardiac surgical patients. However, the routine clinical application of platelet function testing of all patients on antiplatelet therapy requires further validation through additional studies before broader clinical use.

3.1.3. Bleeding risk scores

Numerous scoring methods are available to predict bleeding risk in adult cardiac surgery (14, 52-57). Although the majority of available scores are designed for the general cardiac surgery population (53-56), the "WILL BLEED" and "SHOULD NOT BLEED" scores are focused primarily on patients undergoing coronary artery bypass grafting (CABG) (14, 52). The SHOULD-NOT-BLEED risk score calculator showed an adequate discriminatory ability (area under the curve 0.72, 95% CI 0.69–0.75), similar to the WILL-BLEED score (area under the curve 0.72, 95% CI 0.69–0.76), as assessed by receiver operating characteristic curve analysis (14, 52). The majority of currently available scores, such as WILL BLEED (52), the ACTION score (58), the CRUSADE score (59), the Papworth score (53), the TRUST (Transfusion Risk Understanding Scoring Tool) score (54) and the TRACK (Transfusion Risk And Clinical Knowledge) bleeding score (55), are designed to identify patients at high risk of bleeding, whereas the SHOULD-NOT-BLEED score is designed to recognize patients at low risk for bleeding (14). The use of risk scores to identify patients at low risk of bleeding may be considered routinely, given the relatively low costs, high negative predictive values and low positive predictive values reported for predictors of bleeding.

Recommendation Table 1. Recommendations for preoperative assessment, laboratory and point-of-care testing to predict perioperative bleeding complications

Recommendations	Class[a]	Level[b]	Ref[c]

Preoperative bleeding history, review of medications and physical examination are recommended to identify patients at increased risk of bleeding.	I	C	(4, 5)
Risk scores may be considered for initial screening to identify patients at increased risk of bleeding complications.	IIb	B	(14, 52, 57)
Preoperative fibrinogen levels may be considered to stratify risk of bleeding.	IIb	B	(9, 10, 14-17)
Platelet function testing may be considered to guide the decision on the timing of cardiac surgery in patients who have recently received P2Y12 inhibitors.	IIb	B	(31, 34-37, 39)
Routine use of viscoelastic testing or platelet function testing is not recommended to predict bleeding.	III	C	-

[a] Class of recommendation.
[b] Level of evidence.
[c] References.

3.2 Management of preoperative antiplatelet and anticoagulant drugs

Antithrombotic therapy is vital for managing various cardiovascular diseases and is also a fundamental aspect of secondary prevention following cardiac surgery. Therefore, developing strategies that balance the risks of thrombosis and clinically significant bleeding continues to be a dynamic area of research, particularly with the introduction of new agents, which are designed for wider use without intensive monitoring, and their reversal strategies. Careful planning and strategic decision making in anticoagulation management are essential before, during and after cardiac surgery (60). This approach is crucial for reducing the risks of bleeding and its associated complications, a challenge that is intensified by the widespread use of different treatment options.

3.2.1 Acetylsalicylic acid

Acetylsalicylic acid (ASA) is a fundamental treatment for patients with cardiovascular disease. It reduces the risk of thromboembolic complications but increases the risk of bleeding

complications. Almost all patients undergoing CABG have already been treated with ASA preoperatively. Figure 1 provides an overview of the management of antiplatelet therapy in patients undergoing CABG surgery.

Discontinuation before surgery

A meta-analysis comparing the continuation of ASA administration with placebo or no treatment until the operation in patients undergoing CABG included 13 RCTs (n = 2399 patients) (61). The meta-analysis showed that continuing ASA was associated with a reduced risk of perioperative myocardial infarction (MI) [odds ratio (OR) 0.56, 95% CI 0.33–0.96] but not a reduced risk of death (OR 1.16, 95% CI 0.42–3.22). ASA was associated with increased postoperative blood loss (mean difference 168 ml, 95% CI 39–297 ml; *P*=0.01), PRBCs (mean difference 141 ml, 95% CI, 55–226; *P* = 0.001) and need for surgical re-exploration (OR 1.85, 95% CI 1.15–2.96; *P* = 0.01). A more recent meta-analysis yielded similar results (62). The meta-analyses are limited by substantial heterogeneity regarding the duration and timing of ASA administration, concomitant use of antifibrinolytics and outcome definitions.

In patients undergoing CABG who are not already taking ASA or in whom ASA has been discontinued, preoperative initiation of ASA is not recommended. In the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial, patients who received 100 mg ASA 1 to 2 h before CABG had a similar risk of the composite outcome of death or thrombotic complications at 30 days and a similar risk of bleeding compared to those who received placebo (63). Because patients were only eligible for inclusion in the trial if they were not using ASA or had stopped ASA >4 days before the operation, the findings are difficult to generalize. Another RCT demonstrated that preoperative administration of ASA (300 mg) resulted in significantly more perioperative blood loss and transfusions compared to placebo but no difference in major cardiovascular events during the first 30 days postoperatively (64).

Discontinuation of ASA is associated with an increased risk of perioperative ischaemic events, especially (61, 62) in patients with high-risk coronary artery disease or recent acute coronary syndrome (ACS), and must be balanced against an increased risk of surgical bleeding and transfusion. Preoperative ASA discontinuation at least 4 days preoperatively should therefore only be considered in patients at high bleeding risk (e.g. redo surgery, severe kidney disease, haematological disease), those undergoing non-coronary cardiac surgery and in patients who refuse a blood transfusion. This finding is substantiated by pharmacodynamic

studies indicating sufficient recovery of cyclooxygenase-dependent platelet function within the proposed time frame (65-67).

Early (re)initiation of ASA after CABG, as soon as it is deemed safe but within 24 h, is associated with a reduced risk of death and ischaemic complications (68) and should be continued lifelong in patients who do not have contraindications to ASA (69). Treatment with ASA may also be considered to prevent saphenous vein graft occlusion, based on small RCTs and a meta-analysis of 17 RCTs (1,443 patients) based on a mean follow-up time of 7.8 months (70). In the meta-analysis, ASA significantly reduced saphenous vein graft occlusion compared with no-ASA treatment (OR 0.60, 95% CI 0.51–0.71). A low (75 mg) to medium (325 mg) daily dose of ASA initiated within 6 h of CABG appears to be most effective and did not increase bleeding (70, 71).

In summary, there is sufficient evidence to recommend the continuation of ASA before cardiac operations, and if discontinued, it should be restarted in all patients undergoing CABG to prevent thromboembolic complications as soon as there is no concern about bleeding.

3.2.2. Dual antiplatelet therapy

Dual antiplatelet therapy with ASA and the $P2Y_{12}$-receptor antagonist clopidogrel reduces the risk of thrombotic complications in patients with ACS, compared with ASA treatment alone, as shown in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial (72). Later, it was shown that 2 other $P2Y_{12}$ inhibitors, ticagrelor and prasugrel, more effectively reduced thromboembolic events than clopidogrel (73, 74). The duration of DAPT treatment in patients with ACS varies depending on the indication and the bleeding risk. Cangrelor, a reversible intravenous $P2Y_{12}$ inhibitor with an ultrashort half-life, has also become available (75).

Description of the evidence

Discontinuation of the $P2Y_{12}$ inhibitor preoperatively reduces the risk of postoperative bleeding, transfusion and re-exploration for bleeding (76). It is therefore recommended to discontinue the $P2Y_{12}$-receptor inhibitors before elective surgery while continuing ASA therapy. Alternatively, elective procedures may be postponed until the DAPT treatment period is completed. In extremely high-risk patients [e.g. patients with recent percutaneous coronary intervention (PCI) with a stent implant], bridging therapy with cangrelor, a reversible

intravenous P2Y12 inhibitor with an ultrashort half-life, may be considered (77, 78) (Fig. 1). In an RCT, the use of cangrelor compared with placebo resulted in a higher rate of maintenance of platelet inhibition without increasing bleeding risk (RR 1.1, 95% CI 0.5–2.5) among 210 patients who discontinued thienopyridine therapy prior to cardiac surgery (77).

The discontinuation interval before elective CABG differs among the $P2Y_{12}$ inhibitors due to variations in platelet inhibitory potency and pharmacodynamic and pharmacokinetic properties. In the CABG substudy of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, discontinuation of clopidogrel for more than 5 days preoperatively did not increase the risk of major bleeding (RR 0.83, 95% CI 0.46–1.48] (79). For prasugrel, a time interval of 7 days is recommended due to longer offset time compared with clopidogrel (80) and the high incidence of bleeding complications reported in the CABG substudy of the TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction) (81). For ticagrelor, discontinuation at least 3 days before the operation is recommended, based mainly on the results from a large observational study in patients who had CABG in whom discontinuation of ticagrelor for 3 or 4 days before surgery did not relate to an incidence of bleeding complications greater than 5 days (82). In patients with recent ACS or PCI undergoing CABG, (re)starting the $P2Y_{12}$ inhibitor for the intended duration is recommended postoperatively to reduce the risk of stent thrombosis and major cardiovascular events (79, 81, 83, 84). The $P2Y_{12}$ inhibitor should be (re)started as soon as it is considered safe from a bleeding perspective.

There is individual variation in the magnitude and duration of the antiplatelet effect among the $P2Y_{12}$ inhibitors (85). The remaining platelet responsiveness may be considered when determining the timing of the operation in patients taking DAPT. It has been demonstrated that the platelet inhibitory response assessed by platelet function testing is associated with CABG-related bleeding (34-36). A strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients led to a 50% shorter waiting time for surgical treatment compared to a discontinuation time-based strategy, without any increase in bleeding complications (39). It should be noted that no RCT with sufficient statistical power has compared time since discontinuation-based and platelet function test-based timing of CABG, focusing on perioperative bleeding complications. Furthermore, an association between residual platelet function and CABG-related bleeding

has only been established for patients with ongoing or recently stopped DAPT and not for patients on single antiplatelet therapy.

Recently, the use of haemadsorption devices for removing ticagrelor in emergency settings has been introduced. However, the available research is limited (86-88), and the technology is still under investigation, which prevents any definitive conclusions from being made.

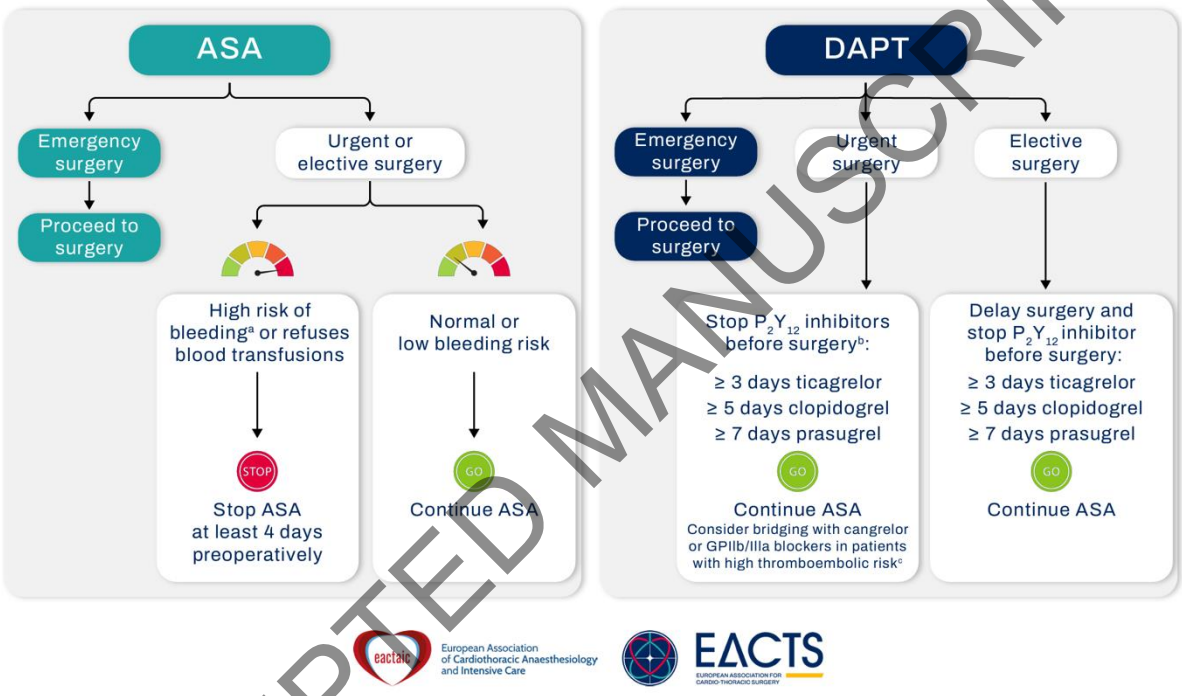


Figure 1. Management of antiplatelet therapy in patients having coronary artery bypass grafting surgery. [a]Complex and redo surgery, severe renal insufficiency, congenital and acquired bleeding and anaemia. [b]Platelet function testing in urgent cases may be considered to optimize the timing and safety of surgery. [c]Recent stent implant, recent thromboembolic event and alarming angiographic results. ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; GPIIb/IIIa: glycoprotein IIb/IIIa.

3.2.2 Glycoprotein IIb/IIIa inhibitors

Inhibitors of glycoprotein IIb/IIIa (GPIIb/IIIa), such as eptifibatide, tirofiban and abciximab, are primarily utilized in conjunction with PCI, though they may also serve as bridging agents for high-risk patients on oral $P2Y_{12}$ inhibitors awaiting surgery (89).

Description of the evidence

The ideal timing for halting GPIIb/IIIa inhibitors before surgery depends largely on pharmacokinetic considerations. Recovery of platelet function occurs within 48 h after stopping abciximab and 4–8 h after halting eptifibatide and tirofiban (90). For abciximab, a pooled analysis of 82 patients from the EPILOG (Evaluation of PTCA to Improve Long-term Outcome by c7E3 GP IIb/IIIa Receptor Blockade) trial and the EPISTENT (Evaluation of platelet IIb/IIIa inhibitor for stenting trial) undergoing urgent CABG found no significant difference in bleeding when abciximab was discontinued less than 6 h before CABG in 61% of the cases (91). A recent meta-analysis encompassing 10 studies with 382 patients undergoing surgery following PCI assessed the efficacy of preoperative bridging using tirofiban and eptifibatide (92). The analysis suggests a reduction in preventing ischaemic events and reducing the need for reoperations due to bleeding, indicating that intravenous platelet GPIIb/IIIa inhibitors could be a safe and effective bridging strategy in this patient population (92). Additionally, a small observational study investigating patients undergoing hybrid carotid artery stenting and off-pump CABG found that tirofiban bridging therapy was safe, with a trend towards reducing ischaemic events (93).

In summary, for patients scheduled for CABG, it is advisable to cease GPIIb/IIIa inhibitors at least 4 h before the operation to minimize the risk of postoperative bleeding. Specifically, discontinuing eptifibatide and tirofiban ≥4 h before open heart surgery, and abciximab ≥12 h before, is recommended to reduce bleeding risk.

3.2.4 Low-molecular-weight heparin, unfractionated heparin and fondaparinux

Low-molecular-weight heparin (LMWH), such as enoxaparin and dalteparin, and unfractionated heparin (UFH) provide their anticoagulant activity by activating antithrombin (AT). Both LMWH and UFH achieve peak plasma levels approximately 2 to 4 h following subcutaneous administration, although individual variations are considerable (94). In individuals with normal renal function, LMWH has a half-life of about 5 h, whereas UFH has a shorter half-life, necessitating more frequent dosing or continuous infusion (94). The anticoagulant effects of LMWH can be monitored through plasma anti-activated factor X (FXa) activity whereas the UFH effect is typically monitored using the aPTT, despite its poor correlation with UFH concentration. These anticoagulants are commonly used for prophylactic

and therapeutic purposes following cardiac surgery. Both LMWH and UFH are utilized for the bridging of oral anticoagulants (OACs) that need to be interrupted before and restarted after a procedure to prevent massive bleeding complications. Whereas protamine can partially reverse LMWH-induced bleeding, it does not completely reverse the anticoagulant effects of LMWH (95). In contrast, protamine is also used to reverse the effects of UFH, typically with a more complete reversal.

Fondaparinux is not a heparin; it is a synthetic selective inhibitor of FXa, commonly used in the treatment of ACS (96, 97). The half-life of fondaparinux is approximately 20 h. Fondaparinux is administered once daily and should be discontinued at least 24 h before major surgery. After surgery, fondaparinux can be (re)started after 48 h (96).

Description of the evidence

Preoperative bridging of OACs with either LMWH or UFH is associated with increased intra- and postoperative bleeding; therefore, not all patients on OACs undergoing cardiac surgery should be bridged. In the BRIDGE (Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation) trial with 1884 patients with atrial fibrillation (AFib), the patients were randomized to LMWH (dalteparin) or placebo after interruption of warfarin. Thromboembolic event rates were similar between groups (0.3% vs 0.4%), but major bleeding was significantly higher in the dalteparin group (3.2% vs 1.3%) (98). However, the trial excluded high-risk patients with mechanical heart valves (MHVs) or recent (within 12 weeks) stroke, embolism or transient ischaemic attack and valvular AFib (98). Similarly, a recent meta-analysis of 6 RCTs and 12 observational studies showed a similar risk of thromboembolism between bridging and non-bridging, but bridging was associated with an increased risk of major bleeding (99). Consequently, a bridging oral anticoagulant (OAC) is recommended only for patients at high risk of thrombotic events, such as those with MHVs, AFib with rheumatic valvular disease or a recent acute thrombotic event within the past 12 weeks and those with severe acquired or congenital pro-thrombotic defects.

Once an OAC is discontinued, bridging therapy should be initiated when the international normalized ratio (INR) value or the specific level of the direct oral anticoagulant (DOAC) is below specific therapeutic ranges, as outlined in Fig. 2. Although UFH has traditionally been the preferred choice for bridging in patients with ACS and MHVs due to its

superior safety profile in reducing postoperative major bleeding and the need for re-exploration (100, 101), recent studies suggest that LMWHs may offer similar or even lower rates of adverse events, including thromboembolism and bleeding (102-104). Moreover, UFH typically requires in-hospital administration and monitoring, unlike LMWH, which offers a more convenient option for outpatient bridging. Nonetheless, the effectiveness of LMWH can vary depending on renal function and obesity, and its bleeding complications are not fully reversible with protamine sulphate. Fondaparinux, with its long half-life (17–21 h) and lack of an antidote, is generally not recommended for bridging, except in patients with a history of heparin-induced thrombocytopenia (HIT) (105), although spontaneous HIT has been reported in conjunction with fondaparinux as well (106).

At present, there is no definitive evidence specifying the time intervals for discontinuing preoperative UFH and LMWH. Based on drug half-life, it is recommended that intravenous UFH be discontinued 2–4 h before the operation (107). It is advised to stop administration of LMWH at least 12 h before surgery, considering the particular LMWH type and dosage regimen (107, 108). When the last dose of a twice-daily LMWH regimen is administered about 14 h prior to surgery (such as the evening before), relatively high anti-FXa activity may still be present at the time of surgery (109).

The administration of heparin postoperatively should be approached with caution, especially in patients with multiple comorbidities and those undergoing major aortic surgery. Lifelong vitamin K antagonist (VKA) therapy is required for patients with MHVs and should be initiated alongside therapeutic bridging therapy. Therapeutic bridging with either UFH or LMWH is begun when post-surgical bleeding is deemed minimal, typically within the first 24 h of admission to the postoperative care unit. This strategy is associated with a lower rate of thromboembolic events compared to no bridging (110). Whereas intravenous UFH has traditionally been the preferred choice for bridging, subcutaneous LMWH is increasingly used due to its ease of administration and the facilitation of early patient mobilization. Evidence from older studies (111-114) and from a recent single-centre observational study that categorized patients into UFH, LMWH and UFH-LMWH sequential therapy groups (115) demonstrated comparable safety and efficacy outcomes. However, randomized studies are necessary to establish the optimal timing and dosage for UFH and LMWH bridging strategies. Bridging should be discontinued once the INR reaches the target range in 2 consecutive tests.

3.2.5 Vitamin K antagonists

The VKAs represent a class of anticoagulant medications that have been a cornerstone in the management of thromboembolic disorders before and after cardiac surgery for several decades. The most widely used VKAs are warfarin and acenocoumarol, which have been extensively employed for the treatment and secondary prevention of venous thromboembolism, the management of persistent and new onset AFib and the maintenance of MHVs and durable artificial pump function. The efficacy of VKAs is monitored through the measurement of the prothrombin time, expressed as the INR, which provides a standardized assessment of the anticoagulant effect. Despite their proven effectiveness, VKAs require careful monitoring and dose adjustments due to their narrow therapeutic window and susceptibility to interactions with food, genetics and other medications (116) (Fig. 2).

Description of the evidence

VKAs are regularly stopped 4–5 days before surgery to achieve an INR < 1.5 when there is no indication for a bridging OAC (6). The high variability in INR reduction necessitates preoperative INR testing. For elevated INR levels (usually > 1.8), administering low-dose oral vitamin K (1–2.5 mg) can effectively reverse this trend without risking VKA re-anticoagulation resistance postoperatively (117, 118).

In patients undergoing urgent or emergency surgery, the benefits of performing the procedure as soon as possible must be weighed against the risk of major bleeding. When it is not feasible to stop VKAs at the recommended time to achieve an INR level deemed safe for these procedures, the effect of VKA can be completely reversed by administering prothrombin complex concentrate (PCC) as the first-line therapy for reversal or FFP as the second-line therapy for reversal, along with vitamin K (intravenous or oral) to prevent rebound anticoagulation (119, 120). RCTs have consistently shown that PCC reduces the INR more rapidly than does FFP (121-123). The time from the start of infusion to the start of the operation was significantly shorter with PCC than with patients who received FFP (3.6 h vs 8.5 h). However, PCC administration must be balanced against an increased risk of perioperative thrombosis and AKI following cardiac surgery with CPB (124, 125).

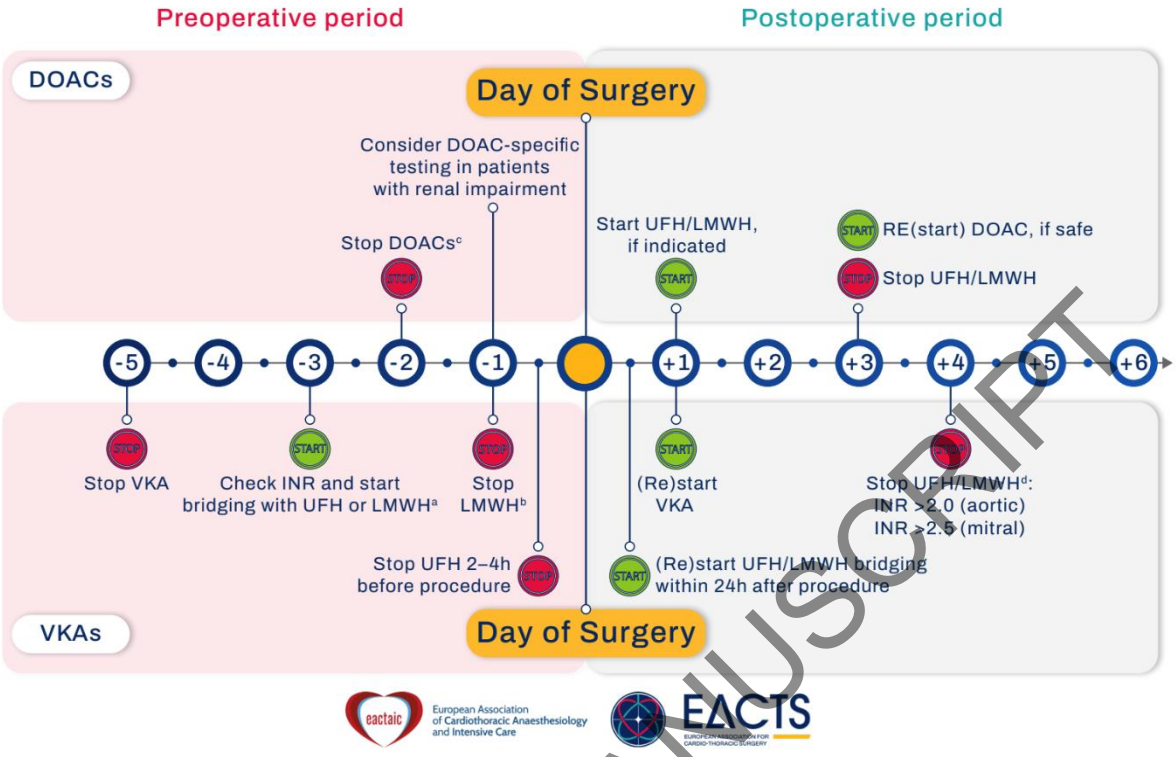


Figure 2. Management of oral anticoagulation in patients with an indication for preoperative bridging and/or postoperative anticoagulation therapy. [a]Patients with mechanical prosthetic heart valve, atrial fibrillation with rheumatic valvular disease, acute thrombotic event within the prior 12 weeks, acquired or congenital pro-thrombotic defects and left ventricular apex thrombus. [b]Discontinuation of LMWH depends on the type and dosing of the medication. [c]For dabigatran, discontinuation should be prolonged to > 48 h if the estimated glomerular filtration rate (eGFR) is 50–80 ml/min/1.73 m^2 and ≥96 h if eGFR is <50 ml/min/1.73 m^2; it is contraindicated if the eGFR is <30 ml (min/1.73 m^2 for other DOACs, discontinuation should be ≥ 72 h if the eGFR is 30–50 ml/min/1.73 m^2 and > 96 h if the eGFR is 15–30 ml/min/1.73 m2. [d]Bridging for VKA only with UFH/LMWH should be discontinued once the INR reaches the adequate target range, confirmed by 2 consecutive tests. DOAC: direct oral anticoagulant; INR: International normalized ratio; LMWH: low-molecular-weight heparin; UFH, unfractionated heparin; VKA: vitamin K antagonists.

3.2.6 Direct oral anticoagulants and direct reversal agents

Direct thrombin inhibitors such as dabigatran and Xa inhibitors like apixaban, edoxaban and rivaroxaban are types of DOACs, and new versions are being developed. Currently, DOACs are the preferred first-line treatment for VTE and non-valvular AFiB (126-128). The introduction of DOACs has presented new challenges in cardiac surgery, particularly regarding the timing of

safely stopping the medication before surgery due to potentially life-threatening bleeding complications (129, 130) (Fig. 2).

Description of the evidence

For patients undergoing elective surgery on DOACs, it is crucial to discontinue these medications in advance to minimize the risk of significant bleeding complications (129, 131, 132). The duration of discontinuation varies depending on the specific drug, its half-life and renal function. DOACs should generally be stopped at least 48 h before surgery in patients with normal renal function (eGFR >80 ml/min), considering their reversible pharmacodynamics and half-life (126, 133). Dabigatran, with its high renal clearance, requires discontinuation 72 h before surgery if the eGFR is between 50 and 80 ml/min. An additional 24 h (approximately 1 drug half-life) is needed for patients with eGFRs between 30 and 50 ml/min. Of note, dabigatran is contraindicated for an eGFR < 30 ml/min (126, 133).

In urgent scenarios, delaying surgery to allow for DOAC clearance is preferred when possible. If there is uncertainty about residual DOAC activity, performing a specific DOAC activity test is advised. For anti-FXa drugs, normal PT results suggest minimal residual anticoagulation (134, 135), whereas normal aPTT suggests minimal dabigatran concentrations. The diluted thrombin time is sensitive to dabigatran concentrations, with a normal value below 21 s (136). Calibrated anti-FXa tests are crucial for measuring drug levels of anti-FXa DOACs, with levels <30 ng/ml considered insignificant for bleeding risk irrespective of the type of agent (137, 138).

In emergency operations, the benefits of immediate procedures must be balanced against significant life-threatening bleeding risks. For non-bleeding patients on anti-FXa DOACs with high plasma concentrations preoperatively, off-label use of 4-factor PCC (50 U/kg) should be considered as the therapy for reversal (137, 139, 140). Activated PCC or recombinant factor VIIa (rFVIIa) may also be considered for non-bleeding patients on dabigatran but must be balanced against an increased risk of thrombosis (137, 141).

Direct reversal agents for DOACs, such as idarucizumab for dabigatran, have been recently approved and introduced in clinical practice. The efficacy and safety of 5 g intravenous idarucizumab in reversing the anticoagulant effects of dabigatran were confirmed in the RE-

VERSE AD (RE-VERSal Effects of Idarucizumab on Active Dabigatran) trial (142). Idarucizumab completely reverses dabigatran in over 98% of patients (142). Although re-elevation of dabigatran levels within 12 to 24 h is more common in patients with renal impairment, the time to bleeding cessation and the extent of haemostasis during procedures are similar (143). In urgent cardiac surgery, including heart transplants, limited data support the safety and effectiveness of idarucizumab (130, 144). Following the administration of idarucizumab, treatment with dabigatran can be resumed 24 h later if the patient is clinically stable and has achieved adequate haemostasis (145). Importantly, other antithrombotic therapies can also be initiated post-idarucizumab, provided the patient is stable and has sufficient haemostasis.

The efficacy and safety of andexanet alfa in reversing the anticoagulant actions of rivaroxaban and apixaban in patients undergoing emergency cardiac surgery have yet to be conclusively established in prospective research. Thus, the utilization of andexanet alfa in surgical settings is deemed off-label, because the ANNEXA-4 (Andexanet alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors) trial exclusively involved patients experiencing severe bleeding who were not undergoing any surgical interventions (146). Although andexanet alfa is known to decrease anti-FXa activity and enhance clinical haemostasis in individuals with significant bleeding from direct FXa inhibitors, such as enoxaparin (147), its off-label usage prior to cardiac surgery has been associated with heparin resistance during CPB (130), resulting in clotting of the CPB circuit and serious adverse events. As a result, the European Medicines Agency advises against the preoperative application of andexanet alfa in cardiac surgical procedures due to the risk of temporary, iatrogenic heparin resistance when heparin is essential to success of the procedure (148). Therefore, in contrast to idarucizumab, the unconfirmed safety profile and significant expense of andexanet alfa call for prudent judgement and general avoidance in cardiac surgery involving CPB. Nevertheless, in particular emergency situations where the likelihood of heparin resistance is low, such as following transcatheter interventions or massive bleeding after CPB weaning, andexanet alfa might be considered to reverse the anticoagulation impact of anti-FXa DOAC. If andexanet alfa is administered before procedures that necessitate heparinization, the use of AT concentrate and substantially increased doses of heparin may be required to attain the desired activated clotting time (ACT) levels. Alternatively, anticoagulants like bivalirudin or argatroban can replace heparin to prevent resistance (130). Recently, the use of haemadsorption devices for

managing DOACs in emergency settings have completed preclinical investigations (149). However, the available clinical results are limited (88, 150), and the method is still under clinical investigation.

Recommendation Table 2. Recommendations for management of preoperative anticoagulant and antiplatelet drugs

Recommendations	Class[a]	Level[b]	Ref[c]
Antiplatelet management			
In patients undergoing CABG who are taking ASA preoperatively, continuing ASA throughout the perioperative period is recommended to reduce myocardial ischaemic events.	I	B	(61, 62)
In patients at high risk of bleeding and transfusion[d] or refusing blood transfusions, stopping ASA should be considered at least 4 days preoperatively.	IIa	C	(65-67)
In patients undergoing CABG, (re)starting ASA within 24 h postoperatively to reduce myocardial ischaemic events is recommended.	I	B	(68, 71)
In elective cardiac surgery patients taking DAPT, discontinuation of ticagrelor for at least 3 days, of clopidogrel for at least 5 days and of prasugrel for at least 7 days is recommended prior to surgery to reduce bleeding complications.	I	B	(79, 81, 82)
Testing residual platelet function may be considered in patients who have received P2Y12 inhibitors <7 days for guidance on the timing of cardiac surgery to reduce bleeding complications.	IIb	B	(34-36)
Bridging P2Y12 inhibitors with low-dose cangrelor until surgery may be considered in patients with high myocardial ischaemic risk to reduce thrombotic complications.	IIb	C	(77, 78)

In patients undergoing CABG, it is recommended to discontinue eptifibatide and tirofiban ≥4 h before open-heart surgery, and abciximab ≥12 h before, to reduce the risk of bleeding.	**I**	**C**	**(92)**
In patients with recent ACS or PCI, and not at high bleeding risk, (re)starting DAPT should be considered as soon as it is considered safe after surgery to reduce the risk of major adverse cardiovascular events.	**IIa**	**B**	**(79, 81, 83)**
Anticoagulation management			
In patients who are preoperatively bridged with therapeutic LMWH, it is recommended to give the last dose 12 to 24 h before surgery, depending on the type and dosing of LMWH.	**I**	**B**	**(108, 109)**
It is recommended that OACs be bridged with either UFH or LMWH perioperatively, when indicated[e].	**I**	**B**	**(100-104, 111-115)**
Postponing elective cardiac surgery until the INR is <1.5 should be considered in patients taking VKAs.	**IIa**	**C**	-
In patients having elective cardiac surgery, it is recommended to discontinue DOACs at least 48 h before surgery. A longer interval may be necessary for patients with impaired drug clearance.	**I**	**B**	**(129, 131, 132)**
In emergency open-heart surgery involving CPB, preoperative administration of andexanet alpha is not recommended for patients on DOAC inhibiting FXa.	**III**	**C**	**(130)**
In patients exposed to DOAC inhibiting FXa with refractory bleeding following the weaning of CPB, andexanet alpha or PCC may be considered to improve haemostasis.	**IIb**	**C**	**-**
In emergency open-heart surgery, perioperative administration of idarucizumab should be considered to reverse the effects of dabigatran.	**IIa**	**B**	**(142, 144)**

After direct reversal of dabigatran with idaricizumab, monitoring of the dabigatran concentration is recommended.	I	B	(142, 143)

ACS: acute coronary syndrome; ASA: acetylsalicylic acid; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulant; FXa: activated factor X; INR: international normalized ratio; LMWH: low molecular weight heparin; OAC: oral anticoagulants; PCC; prothrombin complex concentrates; PCI: percutaneous coronary intervention; UFH: unfractionated heparin; VKA: vitamin K antagonist.

[a] Class of recommendation.

[b] Level of evidence.

[c] References.

[d] Complex and redo surgery, end-stage renal insufficiency, haematological diseases, anaemia and hereditary deficiencies in platelet function.

[e] Mechanical prosthetic heart valve, atrial fibrillation with rheumatic valvular disease, acute thrombotic event within the prior 12 weeks, acquired or congenital pro-thrombotic defects and left ventricular apex thrombus (6).

3.3 Management of preoperative anaemia

Preoperative anaemia, a condition characterized by insufficient Hb levels before surgery, is defined primarily as Hb levels <120 g/L in women and <130 g/L in men by the World Health Organization (WHO) (151). This criterion is widely used in research studies and has a significant impact on surgical outcomes. It is important to note that normal Hb levels vary not only by sex but also by age, ethnicity and physiological status (152, 153). Thus, classification and diagnosis of anaemia should consider haematologic parameters, underlying pathological mechanisms and patient history. The scope of this guideline does not extend to a comprehensive discussion of the definition of anaemia in clinical practice (151). However, it is critical to recognize that anaemia increases the risk of transfusions, postoperative complications, prolonged hospital stays and higher mortality rates. Anaemia affects the body's ability to carry oxygen to tissues, which is crucial for healing and recovery after any surgical procedure. Therefore, addressing anaemia before surgery, through proper diagnosis and management, can improve outcomes, reduce the need for blood transfusions and enhance overall recovery processes.

3.3.1 Implications of preoperative anaemia for clinical outcomes

Preoperative anaemia is a common concern in cardiac surgery, affecting up to 40% of elective patients according to the WHO’s definition. Recognized as a major predictor of adverse

outcomes following cardiac surgery, there is an urgent need for the medical community to engage in early identification and intervention to address anaemia before hospital admission in outpatient clinics.

Description of the evidence

Even mild preoperative anaemia has been linked to poorer clinical outcomes after cardiac surgery, including increased blood transfusion requirements, higher incidence of AKI and elevated mortality rates (154-156). Additionally, patients with anaemia have increased hospital resource utilization, such as more PRBC transfusions, longer stays in the intensive care unit (ICU) and longer total hospital lengths of stay (157). Several observational studies have found a significant effect on patient outcomes of the interaction between preoperative anaemia and blood transfusions, highlighting a pronounced detrimental effect of perioperative blood transfusions on anaemic patients (158-160). When comparing mildly anaemic patients with moderate to severely anaemic patients, the risks of intraoperative transfusions and mid-term 120-day mortality were significantly increased with the degree of anaemia (161). However, the optimal Hb value associated with reduction of blood transfusions or improved clinical outcome remains unclear and might be higher than the WHO criteria for anaemia suggest (162, 163). Potentially, the total red blood cell mass could be a more accurate predictor than Hb levels (164) and may account for the increased frequency of allogeneic transfusions in women (165). Although uncertainties still surround the optimal preoperative red blood cell (RBC) mass in cardiac surgery, a recently published meta-analysis sheds some light on the potential consequences. The meta-analysis, which summarizes findings from 35 studies with a total of 159,025 patients using the WHO's definitions, suggests that preoperative anaemia is associated with increased mortality (OR 2.5, 95% CI 2.2–2.9) (166). Additionally, preoperative anaemia was linked to an increase in total hospital length of stay and postoperative complications. Despite the need for further research to address remaining uncertainties, these findings underscore the importance of an evidence-based, multimodal and multidisciplinary approach to conserving blood resources and optimizing outcomes in patients at high risk of transfusion.

3.3.2 Iron supplementation

Iron is essential for oxygen binding and transport in the human body, making it crucial for maintaining normal erythroid content in the blood. Iron deficiency anaemia is the most common type, affecting up to 40% of elective heart surgery patients. Furthermore, an even higher percentage show iron deficiency without anaemia, with up to 70% of elective heart surgery patients, which is associated with increased mortality and morbidity (167). Iron replenishment can be achieved through oral ingestion or intravenous administration, each with distinct onset times, logistical efforts and risks. When feasible, the operation should be postponed to allow for oral supplementation over 1 to 3 months, because contemporary oral iron formulations are well tolerated and highly effective. When the operation is planned within 2 to 4 weeks or when gastroenteric absorption is impaired, intravenous iron should be preferred. Normalizing iron bioavailability is beneficial not only for achieving normal preoperative Hb levels but also for enabling the bone marrow to produce new erythrocytes in response to operative haemorrhage.

Description of the evidence

Recent research has highlighted the effectiveness of oral iron supplementation. A large RCT involving non-urgent patients compared the impact of 30-day treatment with oral Sucrosomial iron to no treatment at a single centre, revealing a significant improvement in Hb levels at the time of surgery and a reduction in PRBC transfusions for those treated with iron (168). Further analysis of this cohort emphasized greater benefits among female subjects and those with severe anaemia (169). Additionally, a retrospective study assessing the efficacy of oral Sucrosomial versus intravenous iron post-surgery found both approaches to be reasonably effective in the medium term (170).

On the other hand, intravenous iron supplementation has been studied extensively, with a focus on its use in conjunction with erythropoiesis-stimulating agents. A specific RCT dedicated to patients undergoing on-pump CABG found that iron sucrose combined with erythropoiesis-stimulating agents was highly effective (171). Similarly, ferric carboxymaltose showed positive results in an RCT involving patients who had off-pump CABG (172). Additional RCTs have corroborated the efficacy of intravenous iron in a broader population of elective heart surgery patients (173, 174).

In summary, whether administered orally with sufficient lead time or intravenously for more immediate needs, iron replenishment is a crucial element of modern, comprehensive multimodal preoperative strategies (174, 175).

3.3.3 Erythropoietin

The discovery of erythropoietin (EPO), the endogenous growth factor responsible for red blood cell production in the bone marrow, and the subsequent development of its recombinant form in 1983, marked a significant milestone in understanding and treating anaemia. Despite the technology's long history, ongoing concerns about side effects and relevant cost have limited its routine use. However, this limitation should not deter its use in preparing for heart surgery, because the benefits far outweigh the risks associated with preoperative anaemia (156, 176).

Description of the evidence

The efficacy and safety of EPO in cardiac surgery were well established even before the previous edition of these guidelines, as evidenced by several studies (177-179). More recent research has continued to bolster confidence in the treatment's effectiveness and safety profile. A notable finding from a study on off-pump CABG is that most patients undergoing heart surgery exhibited depressed levels of endogenous EPO (180). In light of this discovery, a recent small RCT investigated a lower dosage of 500 IU/kg administered 1 to 3 days preoperatively. Despite the reduced dosage, the study found a significant impact on lowering postoperative transfusion requirements (181).

Treatment with EPO is often combined with iron supplementation. This approach has been shown to significantly reduce the need for perioperative blood transfusions, offering a more effective solution than oral ferrous sulphate alone (173, 175). An RCT that included 253 patients with preoperative anaemia (Hb <120 g/L for women, Hb <130 g/L for men) and 252 patients with isolated iron deficiency (ferritin <100 mcg/L, no anaemia present) undergoing elective cardiac surgery demonstrated that a combination treatment of intravenous iron, subcutaneous EPO alpha, vitamin B12 and oral folic acid significantly decreased the need for allogeneic blood product transfusions (182).

A meta-analysis conducted more recently has also confirmed a positive outcome for the use of EPO in preparing patients with anaemia for heart surgery (183). Two decades after the pioneering studies of EPO in heart surgery, a substantial body of evidence now supports the use of erythropoiesis-stimulating agents in anaemic patients and confirms the safety profile of the drug. However, the lack of cost-effective analyses remains a significant barrier to broader adoption.

3.3.4 Blood transfusions for anaemia management

Blood transfusions are used preoperatively to treat anaemia and improve perioperative symptoms associated with low Hb levels. In cardiac surgery, transfusing blood prior to the operation or with the initiation of CPB in patients with pre-existing anaemia involves significant risks. These include an immunologic response to foreign, albeit "compatible" tissue injection, and triggering immune reactions and inflammatory responses, potentially leading to transfusion-related organ injury, which can significantly hinder recovery. Therefore, a blood transfusion should always be considered a last-resort strategy and prescribed after careful evaluation of the risk–benefit ratio.

Description of the evidence

An RCT investigated the impact of preoperative PRBC transfusions on intraoperative transfusion requirements and AKI in anaemic patients. Prophylactic transfusion of 2 PRBC units was associated with a lower rate of intraoperative transfusions [0 (0–2) vs 2 (1–4) units, $P<0.001$] compared with standard care, but it did not significantly reduce the rate of AKI (184). Perioperative transfusions showed a direct relationship with postoperative transferrin saturation (correlation coefficient 0.6; $P = 0.0002$), and elevated transferrin saturation levels (over 80%) correlated with the occurrence of AKI (5/5 vs 8/30; $P = 0.005$), suggesting that iron overload due to transfusions could be a contributing factor to AKI (184). Given the absence of new evidence, the previously established expert consensus recommendation against routine transfusions for patients with preoperative anaemia has been reaffirmed. However, in emergencies or when faced with life-threatening anaemia, preoperative blood transfusions to elevate Hb levels are deemed a clinically reasonable intervention.

Recommendation Table 3. Recommendations for preoperative management of patients with anaemia

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended to investigate newly diagnosed patients with anaemia to determine the aetiology and initiate causal treatment.	I	B	(156, 157, 166)
Oral iron supplementation with a Sucrosomial formulation prior to cardiac surgery should be considered in iron-depleted anaemic patients (females: Hb less than 120 g/L; males: Hb less than 130 g/L) to improve erythropoiesis and reduce postoperative transfusions if the time frame allows it.	IIa	B	**(168-170)**
Intravenous iron supplementation prior to cardiac surgery should be considered in iron-depleted patients with anaemia (females: Hb less than 120 g/L; males: Hb less than 130 g/L) to improve erythropoiesis and reduce postoperative transfusions when the time frame of the operation does not allow the use of oral iron supplementation.	IIa	A	**(171-175)**
Erythropoietin supplementation in addition to iron should be considered to improve erythropoiesis and reduce postoperative transfusions in anaemic patients when rapid Hb increase is required.	IIa	A	**(173, 175-183)**
Preoperative erythrocyte transfusion is not routinely recommended to treat anaemic patients.	III	B	**(184)**

EPO: erythropoietin; Hb: haemoglobin.
[a] Class of recommendation.
[b] Level of evidence.
[c] References.

3.4 Preoperative thrombocytopenia

Preoperative evaluation plays a critical role in assessing the risk of bleeding in patients due to various conditions, including thrombocytopenia. This blood disorder, characterized by a

platelet count below 150,000/μL, can be either inherited or acquired due to other health issues and medications used (see section 5.3.5). Thrombocytopenia may substantially increase the potential for bleeding complications following cardiac surgery with CPB (17, 185, 186).

Description of the evidence

For major non-cardiac operations, a platelet count above 100,000/μL is generally considered safe and is not associated with a high risk of surgical bleeding (187). However, even mild preoperative thrombocytopenia (100,000–150,000/μL) has been linked to an increased risk of severe bleeding, death and other major adverse events following CABG and other cardiac procedures (19, 186). The risks are further exacerbated in patients with moderate (50,000–100,000/μL) to severe (below 50,000/μL) preoperative thrombocytopenia, showing a stepwise increase in risk (186, 188). The decision-making process to proceed with the operation is complex due to the unpredictable nature of bleeding risks associated with different platelet counts and patients' varying health conditions. This complexity necessitates careful consideration regarding the timing of the operation and the potential need for interventions to increase platelet counts. Furthermore, there is a noticeable gap in knowledge on managing thrombocytopenia in cardiac surgery, emphasizing the need for urgent research. A Cochrane review highlighted the knowledge gap regarding prophylactic PLTC transfusions before surgery for patients with low platelet counts, noting that existing studies do not include those patients requiring major or emergency surgical procedures (189).

Given the current state of knowledge, the urgency of the surgical procedure heavily influences the management approach. In non-emergency situations, delaying surgery may be safer, and consulting a haematologist is recommended to determine the cause and explore treatment strategies to increase the platelet count. For pregnant women, consultation with an obstetric medicine specialist is crucial to manage thrombocytopenia effectively while ensuring the safety of both the mother and the foetus. In emergency cases, transfusions of PLTCs may be required following weaning from CPB. However, the routine recommendation of preoperative PLTC transfusions as a preventive measure is currently not supported, highlighting the need for a cautious approach until more definitive research can guide clinical practices.

Recommendation Table 4. Recommendations for management of patients with preoperative thrombocytopenia

Recommendations	Class[a]	Level[b]	Ref[c]
Preoperative platelet transfusion is not routinely recommended in patients with thrombocytopenia regardless of platelet count.	III	C	-

[a] Class of recommendation.
[b] Level of evidence.
[c] References.

3.5 Preoperative autologous blood donation

A preoperative autologous blood donation (PABD), performed in the hours, days or weeks before surgery, may reduce the need for allogeneic blood transfusions. This practice is typically limited to patients with a relatively high RBC mass [e.g. high haematocrit (HCT) levels and body surface area (BSA)] and no pre-existing coagulation abnormalities.

Description of the evidence

A PABD has been suggested to reduce the occurrence of allogeneic blood transfusions (190, 191) and to be cost-effective in a retrospective cohort analysis including >4300 patients undergoing elective CABG or valve surgery (191). However, this study was limited by the lack of statistical adjustment for possible confounding factors (191). In a matched-pair analysis with 432 patients, a PABD was associated with a reduction in the PRBC transfusion rate from 55% to 32% and a 50% reduction in the administration of FFP and PLTCs (192). A nested case-control study, corrected for confounding factors, revealed that PABDs reduced PRBC transfusions by 18.3% in valve surgery (193). However, this study was limited by the absence of preoperative Hb and HCT data (193). A prospective cohort study comparing 44 patients before and 69 patients after the introduction of PABDs in elective minimally invasive cardiac surgery found that PABDs were not effective in further reducing allogeneic blood transfusion in this setting with a low probability of transfusions (194).

Based on the current evidence, a PABD may be considered for patients without severe aortic stenosis and left main coronary artery disease, Canadian Cardiovascular Society class 3–4 angina or ACS within the last 4 weeks and with high Hb levels (>110 g/L) who are undergoing

elective surgery with a greater than 10% risk of allogeneic blood transfusion. This approach may help reduce the number of postoperative transfusions.

Recommendation Table 5. Recommendation for preoperative autologous blood donation

Recommendation	Class[a]	Level[b]	Ref[c]
A preoperative autologous blood donation in patients with haemoglobin levels over 110 g/L may be considered to reduce postoperative transfusions.	IIb	B	(190-194)

[a] Class of recommendation.
[b] Level of evidence.
[c] References.

4. Intraoperative management

Intraoperative preservation of patient haemostasis is a complex, multidisciplinary challenge. Although surgeons meticulously achieve haemostasis and wait for clot formation, these measures are effective only when accompanied by strategies that minimize haemodilution, maintain normothermia, ensure appropriate anticoagulation and include haemostatic monitoring throughout the procedure.

4.1 Surgical techniques

Various techniques and surgical approaches are increasingly being adopted to achieve a less invasive approach in cardiac surgery patients, including the use of minimally invasive surgical techniques and the avoidance of CPB whenever possible (195). In particular, off-pump CABG gained popularity in the mid-1980s. However, nowadays, it is primarily practiced by dedicated centres and surgeons, resulting in less than 10% of CABG procedures being performed without CPB, according to Veterans Affairs hospitals data (196).

Additionally, a minimally invasive extracorporeal circulation circuit (MiECC) represents a specialized perfusion technique designed to minimize the side effects associated with conventional CPB (197). It is important to distinguish between minimally invasive procedures regarding the use of CPB (off-pump or MiECC) and minimally invasive surgical approaches

(hemisternotomy, thoracotomy, endoscopic procedures, robotic procedures). These approaches can interfere with each other, leading to prolonged CPB times, which may not always yield beneficial effects, especially concerning bleeding complications and transfusion requirements.

Furthermore, the implementation of minimally invasive cardiac surgery is not universal and typically offers the most benefit in centres where such techniques are efficiently performed and integrated into the daily clinical routine (198). Recommendations for the use of these techniques are therefore directed at centres with adequate experience and a sufficient caseload.

For specific subgroups at risk for bleeding complications, such as patients with anaemia, the collaboration of a multidisciplinary team comprising cardiologists, surgeons, anaesthesiologists and perfusionists is highly recommended. This team should discuss optimal treatment strategies, including surgical techniques, the limitations of haemodilution associated with CPB, cardioplegia delivery and improved CPB systems to avoid excessive bleeding necessitating massive transfusions.

4.1.1 Off-pump coronary artery bypass grafting

Off-pump CABG surgery has been proposed to preserve blood haemostatic properties, potentially reducing bleeding and the need for blood product transfusions. This effect could be due to lower levels of systemic heparinization, standard use of cell-saving techniques and avoidance of haemodilution and haemostatic alterations caused by CPB (199).

Description of the evidence

Although no RCTs have directly compared off-pump and on-pump CABG with bleeding, transfusion or the need for reoperation as the primary end point, evidence is extrapolated from robust studies in which these end points were secondary outcomes (200-203). In the secondary analyses of the CORONARY [Coronary Artery Bypass Surgery (CABG) Off or On Pump Revascularization Study] and the GOPCABE (German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients) trials, off-pump CABG was associated with lower transfusion rates (50.7% vs 63.3% and 56.3% vs 62.7%, respectively; both $P<0.001$) (201, 203). However, in these RCTs, physicians were not blinded to treatment allocation, and the transfusion protocol was

not prespecified. Therefore, the treatment received might have influenced the decision to transfuse. Meta-analyses of RCTs indicated that transfusion rates were significantly lower in off-pump CABG compared to on-pump CABG with no differences in re-exploration for excessive bleeding (204). However, studies show large variability in patient selection and study results, suggesting that such benefits might not be consistently reproducible across all RCTs.

In summary, off-pump CABG may be considered a surgical technique associated with fewer transfusion requirements compared to on-pump CABG in selected patients operated on in experienced centres.

4.1.2 Minimally Invasive Cardiac Surgery

Minimally invasive cardiac surgery, which requires smaller incisions and less tissue dissection, may play a role in reducing the need for transfusions and reoperations for bleeding. However, less experienced centres may encounter prolonged CPB times with this approach, potentially offsetting benefits regarding postoperative bleeding and transfusion requirements.

Description of the evidence

A systematic review comparing mitral valve surgery via a right lateral mini-thoracotomy to a sternotomy analysed 45 studies conducted until 2014, including 3 RCTs, and found that the minimally invasive approach was linked to a decrease in chest tube drainage and significant reduction in transfusion risk (205). A recent robust RCT by Akowuah *et al.* provided further insights by comparing a mini-thoracotomy with a conventional sternotomy for mitral valve repair. This study revealed comparable safety outcomes and valve repair rates between the 2 approaches at 1 year, with similar rates of transfusions between groups. However, it noted a significantly higher rate of reoperation for bleeding in the sternotomy group (206). Building on this recent evidence, the latest systematic literature review and meta-analysis of conventional versus minimally invasive mitral valve surgery for degenerative mitral valve disease further supported the advantages of the minimally invasive approach. It found that minimally invasive mitral valve surgery was associated with better short-term outcomes, including a clinically significant reduction in transfusion rates, favouring this approach over conventional surgery (207).

In a systematic review comparing aortic valve replacement (AVR) through minimally invasive access versus a full sternotomy approach, pooled data from 3 RCTs showed no significant difference in the rate of allogeneic blood transfusions (RR 0.77, 95% CI 0.58–1.03). However, pooled data from observational studies suggested a potential benefit of the minimally invasive approach (208). Subsequently, Vukovic *et al.* conducted an RCT comparing an upper hemisternotomy versus a full sternotomy in patients undergoing AVR (209). Whereas there were no differences in morbidity and mortality between the 2 groups, the minimally invasive approach resulted in shorter hospital stays and significantly faster recovery times after discharge, with a trend towards lower transfusion rates. In contrast, Hancock *et al.* compared a mini-sternotomy versus a conventional sternotomy for AVR (210). They found that AVR via a mini-sternotomy did not significantly reduce PRBC transfusions within 7 days of surgery compared to a conventional sternotomy.

The trend towards minimally invasive cardiac surgery is expanding beyond valve surgery. Teman *et al.* (211) conducted a comprehensive multi-institutional analysis comparing minimally invasive cardiac surgery CABG with traditional open CABG. Their findings revealed that patients undergoing open CABG were more likely to require transfusions of PRBCs and PLTCs compared to those in the minimally invasive cardiac surgery group. In another study, Shah *et al.* (212) evaluated the mini-Bentall procedure versus the traditional Bentall procedure performed via a median sternotomy. The results demonstrated that the mini-Bentall group had a significantly lower rate of reoperations for bleeding and shorter ventilation times, underscoring the potential benefits of minimally invasive approaches. Additionally, a meta-analysis by Rayner *et al.* (213) compared operations on the ascending aorta and root through both median sternotomy and minimally invasive approaches. The analysis indicated that patients undergoing a median sternotomy were more likely to require reoperation for bleeding, suggesting that minimally invasive approaches might again offer advantages in blood conservation.

Despite the growing evidence supporting minimally invasive cardiac surgery, it remains a specialized practice limited to a few high-volume centres. To truly assess its potential for widespread adoption and its role in blood conservation, large, well-powered RCTs are needed.

4.1.3 Topical haemostatic agents

Topical haemostatic agents are utilized in cardiac surgery to supplement conventional measures for reducing blood loss. These agents can be classified into active haemostatic agents (containing blood-clotting components), non-active haemostatic agents (lacking intrinsic haemostatic activity) and flowable haemostatic agents (with characteristics of both categories). They are locally applied and include haemostatic sealants and topical antifibrinolytic agents such as aprotinin, tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) (214, 215).

Description of the evidence

A Cochrane review (214) on fibrin sealants highlighted their efficacy in reducing postoperative blood loss (mean difference 161 ml, 95% CI 98.25–224.53 ml) in patients undergoing major surgery. However, this Cochrane review was limited by the inclusion of only 1 cardiac surgery study with 23 participants, so applicability to cardiac surgery patients is questionable. Furthermore, Alizadeh *et al.*'s prospective cohort study reported a significant reduction in the need for blood transfusions with the use of sealants, although no significant difference in blood loss was observed (216). The rate of re-exploration for excessive bleeding was comparable between groups. On the other hand, Tavilla *et al.*'s multicentre RCT evaluated the cost-effectiveness of fibrin sealant after CABG and concluded that its use was not health-beneficial due to the high cost per avoided transfusion (217).

A meta-analysis on topical antifibrinolytic agents indicated a reduction in chest tube blood loss and savings in PRBC units per patient, despite high heterogeneity among the included RCTs (215). No adverse effects were reported following the topical use of these medications. Recently, in a multicentre RCT involving 3242 cardiac surgery patients, topical TXA did not reduce seizure incidence compared to intravenous TXA administration, but it increased the need for blood transfusions by 8.3% (218). The study was terminated early for safety reasons after preliminary results suggested an increased risk of transfusion with topical use. Finally, Daud *et al.*'s systematic review and meta-analysis (219) on fibrin and thrombin sealants in vascular and cardiac surgery suggested a selective rather than a routine use due to a small reduction in blood loss and time to haemostasis, without a significant impact on blood transfusions.

Based on the available evidence, the routine use of topical sealants in cardiac surgery is not recommended and may only be considered in cases of persistent bleeding where haemostasis cannot be achieved with mechanical haemostatic agents in the absence of coagulopathy.

Recommendation Table 6. Recommendations for surgical techniques in patient blood management

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that the members of the multidisciplinary team[d] discuss the optimal surgical strategy based on clinical status, comorbidities, bleeding risk and team expertise.	I	C	-
Off-pump CABG surgery may be considered in selected patients[e] to reduce perioperative transfusions.	IIb	B	(199-204)
Minimally invasive cardiac surgery may be considered to reduce bleeding complications and the need for transfusion.	IIb	B	(205-210)
Routine use of topical sealants in cardiac surgery is not recommended to reduce blood loss and the need for transfusions.	III	B	(217-219)
Topical sealants may be considered in clinical situations where conventional approaches to surgical and medical improvement of haemostasis are insufficient and where bleeding problems are more local than generalized.	IIb	C	(219)

CABG: coronary artery bypass grafting.

[a] Class of recommendation.

[b] Level of evidence.

[c] References.

[d] Surgeons, cardiologists, anaesthesiologists and perfusionists.

[e] Dialysis-dependent patients, patients operated on under DAPT and anaemic patients with low body surface area.

4.2 Cardiopulmonary bypass

The perfusion approach during on-pump cardiac surgery plays a relevant role in postoperative bleeding and increased blood products requirements. Although individual interventions during CPB mainly represent a contributory factor, current evidence indicates that the adequate training of the team to safely implement measures to reduce the blood trauma, like the reduction of the circuits, the ultrafiltration techniques and the antegrade autologous priming/retrograde autologous priming (RAP), may represent clinical differences favouring the reduction of postoperative complications, which favours an enhanced recovery after cardiac surgery.

4.2.1 Priming volume and haemodilution

Managing the dilution of blood during cardiac surgery is crucial, because it often results from multifactorial volume infusion from the surgical field, anaesthesia and CPB. Whether it results from inherent processes or from deliberate acute normovolemic haemodilution (ANH), this phenomenon warrants careful oversight. Determining the target Hb/HCT threshold to maintain during CPB remains a topic of debate. Significant dilution could precipitate ischaemic conditions in vital organs due to a diminished capacity for oxygen transport, which may not be sufficiently counterbalanced by self-regulatory mechanisms or improvements in blood flow to the vital organs (220, 221).

Description of the evidence

CPB plays a significant role in inducing haemodilution, primarily due to the fluid infusion needed for priming the circuit and the administration of the cardioplegic solution (222). Consequently, the detrimental effects of haemodilution extend beyond the mere direct impact of induced anaemia. Various studies have corroborated that haemodilution can lead to altered coagulation, heightened bleeding, an increased necessity for transfusions and overall worse outcomes related to thromboembolic complications (222, 223).

Historically, the strategy of combining the use of colloids and crystalloids in CPB priming was adopted to mitigate the adverse effects of haemodilution. However, recent evidence suggests that this approach does not confer additional benefits in terms of blood management and clinical outcomes (224-227). Moreover, the utilization of dextran-based

solutions during CPB has been linked to increased postoperative bleeding and transfusion requirements (228), as well as to a potential rise in the incidence of AKI (227). In contrast, strategies aimed at reducing the total priming volume have shown promise in promoting blood conservation. Specifically, the net priming volume has been directly associated with the incidence of transfusion (222), and several meta-analyses have demonstrated that the implementation of measures to reduce CPB priming, such as MiECC or autologous priming, can lead to a reduction in exposure to transfusion and postoperative bleeding (229-231).

Therefore, it is recommended that PBM programmes consider the inclusion of measures aimed at limiting CPB-related haemodilution, with the goal of mitigating the drop in Hb levels, thereby enhancing haemostasis and promoting blood conservation.

4.2.2 Optimizing the cardiopulmonary bypass system

During CPB, the primary objectives include maintaining and stabilizing physiological parameters to ensure optimal function of vital organs. This approach necessitates the implementation of various targeted management strategies during CPB to modify factors that significantly affect both short-term and long-term outcomes following cardiac surgical procedures. One of the main challenges for perfusionists is optimizing the CPB system to minimize its impact.

Description of the evidence

The use of tip-to-tip biocompatible coating is becoming increasingly common in certain CPB settings, such as MiECC. However, the benefits of biocompatible coating as an isolated measure remain limited. Basic research studies have shown that biopassive coated circuits attenuated platelet degranulation and inhibition when compared to non-coated circuits (232). Additionally, several studies found that biocompatible coating in an MiECC circuit allowed for effective anticoagulation with a lower ACT range, leading to reductions in hospital stay, chest-tube drainage and PRBC transfusions (233, 234). Furthermore, Ranucci *et al.* highlighted that reducing the circuit surface area by applying minimized systems and shed-blood separation can reduce inflammatory responses and coagulopathy, which are closely related (235). Supporting this finding, an RCT from Bauer *et al.* confirmed that, when using MiECC systems, avoiding direct shed-blood reinfusion into the CPB system lessens the inflammatory response

(236). However, a recent Cochrane review indicated that the application of current cell-salvage (CS) techniques results in a 20% risk reduction in PRBC transfusions. This finding is based on 5 RCTs deemed to have a low risk of bias involving patients undergoing cardiovascular surgery with CPB. In contrast, results for procedures without CPB results are inconclusive due to an extremely low number of studied patients (237).

In summary, although biocompatible coating and minimized CPB systems show promise in reducing adverse effects related to CPB, the evidence suggests that their benefits are context-dependent and may vary based on the specific characteristics of the surgical procedure and the CPB system employed.

4.2.3 Minimally invasive extracorporeal circulation circuit

The use of the MiECC has been a subject of debate for decades, with varying opinions on its efficacy in reducing transfusions and coagulopathy. The challenges in reaching a consensus stem from the heterogeneity in defining MiECC and determining the maximum priming volume that distinguishes a conventional from a minimized circuit. An MiECC represents a fusion of advancements in perfusion science, featuring a closed circuit with biologically inert and reduced blood contact surfaces, a centrifugal pump, a membrane oxygenator, a heat exchanger, a venous bubble trap or air removal device, a cardioplegia system and a shed-blood management device (238). These systems are designed to minimize the adverse effects associated with conventional CPB by avoiding blood–air contact and separating shed blood (239-241). However, the use of an MiECC presents several concerns, including difficulty in removing air from the venous line, challenges in managing inadequate pump function due to insufficient preload and an increased risk of embolization (242). Adequate training is essential to mitigate these issues and derive the most benefits from the technique.

Description of the evidence

There is considerable heterogeneity among studies when reporting the clinical benefits of MiECC. A retrospective study involving 5,164 patients compared the effects of MiECC with a priming volume of 600 mL to conventional CPB with 1200 mL. The study found significant differences in the drop in Hb levels favouring the minimized circuit. However, it deemed both systems equivalent due to a lack of clinical differences, aligning with findings from other

authors (243). Conversely, several studies demonstrated a reduction in the use of allogeneic PRBCs with the application of an MiECC system following mitral and aortic valve surgery (244-247). A meta-analysis also indicated that MiECC correlates with reduced blood loss, arrhythmias and hospital stay (229). Additionally, a Bayesian meta-analysis suggested that MiECC is clinically comparable to off-pump CABG in terms of chest tube drainage (248).

Given the diversity of outcomes reported by various authors, Anastasiadis *et al.* proposed a classification of MiECC types to address this heterogeneity and facilitate the acquisition of more robust evidence (249). Despite this proposal, some RCTs have not found MiECC to be superior to conventional CPB systems (250-252). Moreover, considering that modified conventional CPB systems have proven effective in reducing blood transfusions (253, 254) and given that the most significant effort to demonstrate the benefits of MiECC over the conventional technique, the multicentric COMICS (Conventional versus Minimally Invasive Extracorporeal Circulation) trial, did not yield the expected results (255), there is a limitation in recommending MiECC over conventional CPB. Consequently, it should be noted that MiECC may be considered over conventional CPB systems to reduce the risk of transfusion and bleeding, but only when used for selected patients by experienced teams.

4.2.4 Cell salvage

Cell salvage (CS), a process that involves the recovery of blood lost during the operation and residual blood from the circuit after CPB, can significantly reduce the reliance on allogeneic blood products, particularly PRBCs. This practice not only mitigates blood loss by returning the surgical bleeding to the patient, thereby decreasing the need for allogenic transfusions, but also offers additional benefits when surgical bleeding and the remaining volume in the circuit after CPB are processed using a CS system instead of direct reinfusion. Specifically, the use of a CS system has been associated with a more favourable inflammatory response, enhancing the overall benefits of using CS during CPB (236).

Description of the evidence

Conventional CS systems operate on the principle of centrifugation and washing, as exemplified by the Latham bowl, allowing for the recovery of erythrocytes and the removal of the majority of other blood components. However, it has been observed that processing larger

volumes of blood with a conventional CS system can lead to coagulation disorders, resulting in increased bleeding and the need for transfusions of other blood components (256, 257).

The use of the CS technique in specific scenarios, such as infective endocarditis and oncological surgery, remains controversial (257). Although some studies have reported contamination of processed blood with gram-positive cocci and an association between CS use and higher rates of infection, others argue that the overall benefit in reducing transfusions outweighs the potential adverse effects of infection, which can be managed with antibiotic therapy. This perspective even extends to its application in operations for infective endocarditis (258-260).

In addition, emerging CS technologies based on filtration methods, such as adsorption or diffusion, have demonstrated the ability to produce a final blood product that retains platelets and fibrinogen. This approach could offer additional advantages when processing larger volumes of bleeding. However, the current body of evidence supporting these new technologies is limited, and well-designed RCTs are needed to assess their safety and efficacy. The decision to incorporate these filtration-based CS techniques into a PBM programme requires a careful evaluation of the risks and benefits (261-264).

A recently updated Cochrane review analysing 25 RCTs of elective cardiac operations with CPB indicates that the use of conventional CS significantly reduces the risk of PRBC transfusions (RR 0.81, 95% CI 0.73–0.89) without increasing blood loss (mean difference 4.7 ml, 95% CI -49.9–59.3 ml) (237). In a network meta-analysis of RCTs comparing the rates of transfusions, it was also found that conventional CS reduced the risk of PRBC transfusions (RR 0.59, 95% CI 0.50–0.69) with incremental benefit when this intervention is combined with restrictive transfusion strategies and POC testing (RR 0.22, 95% CI 0.14–0.34) (265).

In summary, the regular implementation of the CS technique should be considered to minimize transfusions, because there are no consistent signals of significant safety hazards including infection and bleeding associated with its use. However, particular caution is warranted when re-transfusing substantial volumes of salvaged blood (exceeding 1000 ml) (257), especially in patients with a lower BSA (<1.5 m^2), due to the potential for coagulation impairment.

4.2.5 Autologous priming

The initiation of CPB with a non-blood fluid results in haemodilution, subsequently elevating the likelihood of requiring blood transfusions, especially in patients with a smaller BSA (266). In response to this challenge, autologous priming techniques, either retrograde or antegrade, have been introduced as straightforward, economical and effective methods to counteract this problem.

Description of the evidence

Autologous priming techniques are founded on the principle of displacing the priming solution with the patient's own blood to counteract the abrupt haemodilution associated with the initiation of CPB. A robust body of evidence supports the use of autologous priming, either retrograde or antegrade (224, 231, 267-273), as well as modified ultrafiltration (274, 275). These techniques are recognized as safe and effective therapeutic options to reduce haemodilution-associated complications, including transfusion requirements. However, studies have found conflicting results regarding the potential association between ultrafiltration and AKI (276, 277), indicating the need for a patient-tailored approach and further prospective investigations.

However, it is important to note that there is considerable inconsistency among studies regarding the magnitude of the clinical effects of autologous priming on blood loss and transfusions when applying different techniques and volume removal (230). For instance, Foreman *et al.* observed no blood conservation benefits when RAP was applied in a retrospective study (278), and Hofmann *et al.* indicated that the number needed to treat to reduce the use of 1 unit of PRBCs was greater than 7 patients (270). Conversely, a propensity score matching (PSM) study demonstrated that the implementation of a standardized approach of antegrade autologous priming, known as haematic antegrade repriming, effectively reduced the priming-related haemodilution to 300 mL, resulting in substantial savings in terms of blood components and stay in the ICU (253).

Although the advantages of containing haemodilution with autologous priming are undisputed and highly recommended as part of a blood conservation strategy, the use of the generic term RAP to encompass a wide array of procedures leading to varying levels of haemodilution should be avoided. It is imperative to determine the optimal priming volume to achieve the greatest benefit without adverse effects (274). Furthermore, there is a need to

explore the advantages of standardized methods such as haematic antegrade repriming (279), which has been shown to be a safe strategy, primarily benefiting from a standardized reduction of CPB priming to 300 ml (253, 280).

4.2.6 Coagulation-friendly environment

The biochemical reactions involved in coagulation depend on an optimal temperature and pH level for efficient functioning. Hypothermia and acidosis can compromise the generation of thrombin, a key enzyme in the coagulation cascade, leading to impaired haemostasis in patients. This disruption in the coagulation process can have significant implications for patient outcomes, particularly in surgical settings where maintaining haemostasis is crucial (281).

Description of the evidence

Creating a coagulation-friendly environment involves managing several factors, as various authors have noted. Significantly, exposure to temperatures below 32°C, metabolic acidosis, prolonged aPTT of more than 40 s post-CPB, hypocalcaemia and the ratio of C-reactive protein to albumin have been identified as critical contributors to postoperative coagulopathy and the subsequent increased requirements for blood products (282, 283).

There is robust evidence that maintaining strict normothermia throughout the surgical process reduces blood loss by better preserving coagulation (284, 285). A recent meta-analysis by Shimamura *et al.* found that during aortic arch surgery, mild hypothermia (28°C) offers organ protection similar to that of lower temperatures, while also being independently associated with significantly better outcomes in terms of postoperative bleeding, stroke and mortality compared to deep hypothermia (286).

Although hypothermia can lead to altered coagulation (287), mild-to-moderate temperatures (34°C–36°C) appear to preserve coagulation more effectively than lower temperatures (285). Ku *et al.* indicated that exposure to severe hypothermia (<26 °C) is associated with decreased reversal activity of protamine after CPB weaning (288). Furthermore, a network meta-analysis focused on temperature management during aortic arch surgery found that mild hypothermia (> 28°C) combined with selective cerebral perfusion improved postoperative outcomes and reduced the incidence of postoperative bleeding. Progressive rewarming has been shown to be beneficial in reducing pH derangements,

coagulopathy and blood loss (281, 289). Additionally, it has been suggested that lower intraoperative core temperatures exacerbated coagulation and fibrinolysis disorders, altering the procoagulant function of platelets in the postoperative period (290). In line with recent recommendations from the EACTS/Society of Thoracic Surgeons (STS) Guidelines for the Management of Aortic Disease, Tveita *et al.* indicated that rapid rewarming after hypothermia is associated with coagulopathy, and therefore, maintaining gradients while increasing the patient's core temperature seems to be beneficial in reducing bleeding complications (291, 292).

The importance of maintaining a coagulation-friendly environment also extends to keeping a physiological pH balance. Retrospective studies have indicated that metabolic acidosis, hypoalbuminemia and hypocalcaemia are predictors of severe bleeding in cardiac surgery patients and should be treated in a timely manner (283, 293).

Although some authors have hypothesized that nitric oxide (NO) delivery during CPB may positively affect coagulation preservation, the evidence is still evolving. Toomasian *et al.* found that the addition of NO mitigated platelet loss and the expression of CD11b on granulocytes in an animal model, which exposed piglets to an air–blood interface (294). A recent meta-analysis concluded that delivery of NO through the extracorporeal membrane provides anti-inflammatory effects in children (295). However, the potential benefits in adults and the indirect contribution to coagulation still need to be clarified.

Finally, considering that the RBC concentration affects bleeding and thrombosis due to its interaction with cellular and molecular components of the haemostatic system and its impact on blood viscosity, a coagulation-friendly environment should include the avoidance of severe anaemia. Some authors have observed that low haematocrit levels are associated with bleeding, whereas high haematocrit levels are associated with thrombosis and the formation of RBC aggregates. Therefore, optimizing RBC levels during CPB is also a crucial factor to consider for preserving haemostasis, beyond its role in oxygen transport (296).

In summary, to effectively reduce bleeding and minimize the need for transfusions, it is essential to maintain physiological conditions, particularly normothermia and a pH level near 7.4, which are crucial for the optimal functioning of the coagulation system.

Recommendation Table 7. Recommendations for cardiopulmonary bypass techniques in patient blood management

Recommendations	Class[a]	Level[b]	Ref[c]
Implementation of multiple institutional measures to reduce haemodilution during CPB is recommended to reduce anaemia, transfusion and postoperative bleeding.	I	B	(222, 223, 229, 230)
Combining the priming volume with colloids to reduce transfusions is not recommended.	III	A	(224-228, 273)
Optimizing CPB systems using coated and reduced surface areas and avoiding direct blood reinfusion are recommended to increase haemocompatibility and reduce bleeding complications.	I	B	(229, 232, 233, 235-237)
MiECC should be considered over conventional CPB systems to reduce the risk of transfusions and bleeding.	IIa	B	(229, 239, 243, 245-247, 251, 252)
The use of cell salvage should be considered in order to prevent transfusions.	IIa	B	(237, 256-258, 262, 265)
Modified ultrafiltration should be considered as part of a blood conservation strategy.	IIa	A	(274, 275)
Autologous priming, either retrograde or antegrade, is recommended as part of a blood conservation strategy.	I	A	(224, 231, 253, 267-273)
Maintenance of normothermia during the entire surgical process should be considered to reduce coagulopathy and blood loss.	IIa	B	(284, 289, 290)
Maintenance of normal pH during the entire surgical process should be considered to reduce coagulopathy and blood loss.	IIa	B	(293)
In cases requiring hypothermia, mild hypothermia (above 28ºC) is recommended over lower targeted temperatures to minimize postoperative blood loss.	I	B	(285, 286)

CPB: cardiopulmonary bypass; MiECC: minimally invasive extracorporeal circulation circuit.

[a] Class of recommendation.

[b] Level of evidence.

[c] References.

4.3 Intraoperative anticoagulation

Anticoagulation during CPB is an important part of the surgical procedure. Heparin is the anticoagulant most commonly used due to its rapid onset of action and the ability to safely reverse its effects with protamine sulphate. The protamine dose is calculated based on the dose of heparin administered to ensure effective reversal while minimizing the risk of protamine-related complications. Proper anticoagulation and its reversal are essential for a successful outcome of cardiac surgery with CPB.

4.3.1 Heparin and anticoagulation monitoring

Heparin binds to AT and significantly increases the ability of AT to deactivate thrombin and FXa, which increases their inactivation by up to a thousand-fold. The efficacy of heparin anticoagulation is assessed using the ACT test, with target values between 300 and 600 s. These values vary depending on the measurement method and the heparin dosing strategy. In addition, the varying efficacy of heparin may require personalized anticoagulation approaches. Heparin dosing is generally based on the patient's body weight and starts with a dose of 300 to 600 units per kilogram body weight (IU/kg). If ACT levels drop significantly during the CPB procedure, additional doses should be administered. However, this approach has its pitfalls, e.g. heparin resistance, which can lead to inadequate anticoagulation, and post-operative heparin rebound, which can increase the risk of bleeding. To mitigate these challenges, continuous monitoring and adjustments of heparin dosing during surgery are essential to optimize anticoagulation therapy and enhance patient outcomes.

Description of the evidence

Although the management of heparin anticoagulation in cardiac surgery is of critical importance, the available evidence is weak and inconsistent. Whereas some studies suggest that a heparin level-guided management strategy may improve perioperative blood conservation (297, 298), others showed no significant differences in blood loss or transfusion requirements when comparing heparin management strategies guided by ACT or heparin level-guided measurements (299, 300). Despite potential benefits in reducing heparin dosage

using heparin level-guided management, several RCTs have found no significant differences in postoperative bleeding and transfusion rates when comparing different heparin dosages across diverse surgical contexts (301-304). Optimization of heparin anticoagulation is an attractive concept, but the lack of solid evidence from comparative studies limits definitive recommendations. In current practice, both ACT with kaolin- or celite-guided anticoagulation (305) and heparin level-guided measurement are used for anticoagulation management during cardiac surgery. Further research is needed to clarify the optimal approach and to ensure patient safety and effective blood conservation.

4.3.2 Protamine

Protamine plays a vital role in neutralizing the anticoagulant effect of heparin following weaning from CPB. Typically, its dosage is calculated in relation to the initial heparin dose, functioning by binding to and inactivating circulating heparin–AT complexes, thereby restoring procoagulant properties to the blood. However, inappropriate protamine dosing can lead to postoperative bleeding due to incomplete heparin neutralization or, conversely, to excessive bleeding due to overdosing. Overdosing can suppress platelet function, diminish clot firmness and excessively activate fibrinolysis (306). Furthermore, even with optimal dosing, administration of protamine can induce various adverse reactions, such as immunologic and inflammatory changes, which can present as hypotension, bradycardia, pulmonary vasoconstriction or allergic responses. To mitigate these risks, a slow infusion of protamine is recommended, and prophylactic measures, including the use of ASA or antihistamines, may be taken.

Description of the evidence

A statistical model for protamine titration compared to a fixed protamine-to-heparin dose ratio (1:1) showed a significant reduction in total protamine dose with beneficial effects on coagulation as measured by ROTEM (307). Individualized heparin monitoring resulted in a significant reduction in the protamine dose, which in turn was associated with less postoperative chest drainage (304, 308, 309). Several studies have found an association between a higher protamine-to-heparin ratio and a higher need for postoperative blood products (310, 311). Further studies have confirmed that a protamine-to-heparin ratio in the

range of 0.6:1 resulted in a significant reduction in postoperative blood loss and transfusion requirements compared to a ratio of 1:1 or higher (301-303). In addition, an RCT showed that patients who received a protamine-to-heparin dose ratio of 0.8:1 had less attenuation of thrombin generation, less postoperative bleeding and a lower requirement for blood products than patients who received a higher protamine dose (312).

In summary, reducing the protamine-to-heparin dose ratio < 1.0 based on the initial heparin dose is recommended as part of a patient blood conservation strategy in cardiac surgery, because this approach may contribute to better postoperative outcomes and a reduced need for blood products

4.3.3 Heparin resistance

Patients who are resistant to heparin may have low AT levels or a dysfunctional form of AT. Heparin resistance is usually defined as achieving an ACT of less than 400 s after administration of 300 IU/kg heparin. This resistance may necessitate higher heparin doses to reach the desired ACT, increasing the risk of residual heparin postoperatively. Alternatively, given the elevated clotting risk in patients with AT deficiency, AT levels can be replenished by administering recombinant AT prior to or during CPB. The goal of strategy is to improve the efficacy of heparin anticoagulation and reduce the risk of postoperative complications related to heparin resistance.

Description of the evidence

Heparin sensitivity can be influenced by several factors, including hypoalbuminemia, hereditary and acquired AT deficiency, active endocarditis, high fibrinogen levels, thrombocytosis, smoking behaviour, chronic aortic dissection, high paraprotein levels and even a history of COVID-19 (313-318). In a retrospective study of CABG patients who underwent cardiac surgery and were previously treated with LMWH, a 1- to 5-times higher risk of developing heparin resistance was observed (319). Several RCTs have shown that treatment with recombinant human AT restores heparin sensitivity and promotes therapeutic anticoagulation in CPB (320-322). Although the effects on postoperative bleeding are variable, the primary benefit is in improving heparin sensitivity and ensuring effective anticoagulation during CPB. Observational studies suggest that AT supplementation can effectively resolve heparin resistance even when preoperative AT levels are in the normal range (316). In addition,

administration of AT was associated with a significantly lower risk of death than transfusion of FFP in these cases (323). In an RCT involving 425 adult patients who received either a single dose of AT to achieve a 20% absolute increase in AT activity over pretreatment or a placebo prior to surgical incision, AT supplementation did not result in a reduction in postoperative morbidity and mortality (324). Consistent with this finding, a recent meta-analysis of RCTs of preoperative AT supplementation in patients with lower AT levels found no significant benefit from blood conservation and indicated a potential increase in hospital deaths and AKIs after cardiac surgery (325).

In summary, AT supplementation is indicated in patients with AT deficiency to improve heparin sensitivity, with the primary role of AT supplementation being to ensure effective anticoagulation during CPB rather than to reduce postoperative bleeding. FFP may be considered as an alternative to AT supplementation in patients with AT deficiency to improve heparin sensitivity.

4.3.4 Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia is a major challenge for patients undergoing CPB procedures due to the immune-mediated reaction between heparin and platelets. This reaction can lead to potentially life-threatening complications such as thrombosis and severe bleeding. Therefore, early detection of anti-heparin antibodies and the use of alternative anticoagulation strategies are crucial.

Description of the findings

Several treatment options have been proposed for the management of HIT, including direct thrombin inhibitors (DTIs) such as bivalirudin or argatroban, plasma exchange, intravenous immunoglobulin and the combination of potent antiplatelet agents such as tirofiban or cangrelor with heparin (326). However, intravenous immunoglobulin and plasma exchange have been associated with a significantly increased risk of major bleeding (327), and the evidence for the use of cangrelor is limited and consists mainly of case reports (328). Special attention should be given to identifying anti-platelet factor 4 (PF4) antibodies, because these are positive during active heparin-induced thrombocytopenia and thrombosis but may disappear over time. If this occurs, heparin can be administered as the sole anticoagulant

(329). A systematic review found that DTIs such as bivalirudin, lepirudin and argatroban may be the anticoagulant of choice for patients with HIT (330); however, no universal protocol is approved for the latter. Despite the lack of antidotes for DTIs, bivalirudin is often considered the preferred alternative anticoagulant in CPB due to its shorter metabolization time and lower incidence of adverse events when used at an appropriate dose (331-334). In patients without HIT undergoing cardiac surgery, the safety data for bivalirudin were comparable to those of the heparin-protamine administration strategy (335).

Nevertheless, further RCTs are needed to gain more solid insights into the optimal anticoagulation strategy for patients with suspected or confirmed HIT undergoing cardiac surgery.

Recommendation Table 8. Recommendations for intraoperative anticoagulation

Recommendations	Class[a]	Level[b]	Ref[c]
Management of heparin anticoagulation with either ACT-guided measurements or heparin-level guided measurements is recommended.	I	A	(297-300, 303-305)
Protamine administration is recommended in a protamine-to-heparin dosing ratio[d] <1.0 to avoid overdosing and reduce bleeding complications.	I	B	(307, 308, 310-312)
Individualized heparin and protamine management should be considered to reduce postoperative coagulation abnormalities and bleeding complications after cardiac surgery with CPB.	IIa	B	(304, 308, 309)
When starting surgery, AT supplementation is recommended in patients with AT deficiency to improve heparin sensitivity.	I	A	(320-322)
Perioperative AT supplementation is not routinely recommended to reduce bleeding following CPB.	III	B	(324, 325)
In patients with HIT antibodies for whom surgery cannot be postponed, anticoagulation with bivalirudin rather than with argatroban should be considered during CPB.	IIa	B	(331-333, 335)

ACT: activated clotting time; AT: antithrombin; CPB: cardiopulmonary bypass; HIT: heparin-induced thrombocytopenia.

[a] Class of recommendation.

[b] Level of evidence.

[c] References.

[d] Protamine-to-heparin dosing ratio based on the initial heparin dose.

4.4 Intravascular volume

Intravascular volume management is essential during cardiac surgery to minimize haemodilution from fluid infusion and CPB. Implementing effective institutional strategies and fostering multidisciplinary collaboration to control intravascular volume can help reduce the risk of bleeding and the need for transfusions.

4.4.1 Goal-directed haemodynamic therapy

Goal-directed haemodynamic therapy (GDT) refers to the use of various haemodynamic measurements, such as heart rate, blood pressure, cardiac output and regional cerebral oxygen saturation, to guide the administration of intravenous fluids, vasopressors and inotropes. The goal is to optimize oxygen perfusion and delivery while limiting the haemodilution.

Description of the evidence

Several studies have examined the impact of GDT on outcomes in high-risk cardiac surgery patients but a limited number focused on researching bleeding complications. An RCT included a parallel meta-analysis of RCTs focused on patients with a EuroSCORE >6 and/or a recent MI within 14 days. The findings showed that patients receiving GDT were administered more intravenous fluids compared to controls from the cessation of CPB until the eighth hour following admission to the ICU [1000 ml (625–1500) vs 500 ml (500–1000)], yet there was no significant difference in intraoperative PRBC transfusion volumes between the 2 groups [0 (0) units vs 1 (1.6) units, respectively; $P = 0.32$] (336). Another limited RCT involving 146 patients evaluated 30-day mortality rates among high-risk patients (EuroSCORE > 6; left ventricular ejection fraction < 50% and/or combined surgical procedure) where GDT was used. No

difference in 30-day mortality was observed between the GDT and usual care groups. Additionally, there were no significant differences in secondary outcomes, including crystalloid [550 ml (500–660) vs 540 ml (500–630); *P* = 0.16] and colloid [390 ml (340–500) vs 370 (330–460); *P* = 0.07] fluid usage, as well as red blood cell transfusions (20 ± 31 units vs 10 ± 16 units; *P* = 0.06) (337).

Although vasopressors are often used to treat low blood pressure perioperatively, their excess use may potentially lead to increased blood loss due to the rise in blood pressure. On the other hand, using a vasopressor to regulate mean arterial pressure could alleviate the haemodilution that occurs during anaesthesia and CPB (338). One RCT demonstrated that the implementation of GDT, which includes the administration of fluids, inotropes and vasopressors, did not significantly impact transfusion requirements (2.1 ± 2.8 units in the study group vs 1.8 ± 2.7 units in the control group; *P* = 0.47), despite a higher utilization of vasopressor therapy compared to the control group (339). Due to the limited data available, it is challenging to make evidence-based conclusions regarding the benefits of GDT specifically in the PBM setting.

4.4.2 Crystalloids and colloids

Perspectives on the optimal fluid management strategies for cardiac surgery are diverse. The majority of conducted RCTs are limited in sample size and focus on the effects of different priming solutions on patient-specific outcomes, such as renal protection or haemostasis, with the need for allogeneic transfusions serving mainly as a secondary end point.

Description of the evidence

Priming solutions

The impact of priming solutions on postoperative bleeding and blood product transfusions was evaluated by comparing 6% hydroxyethyl starch (HES) 130/0.4 (mean molecular weight, 130 kDa; degree of substitution) and 6% HES 400/0.7 prime with gelatine, albumin or Ringer's acetate. The use of 6% HES 130/0.4 did not significantly affect blood loss or transfusions. However, adding albumin to an HES 130/0.4 prime (339) or using 6% HES 200/0.5 with 3.5% gelatine (340) was associated with reduced postoperative blood loss. Conversely, a synthesis of prospective studies, which scrutinized priming solutions against blood loss and transfusion

requirements as their main outcomes, revealed no significant disparities in postoperative blood loss when comparing different HES solutions (341-344).

Volume therapy

A PSM analysis assessed the effect of colloid use versus non-colloid administration on postoperative renal function and transfusions (345). Although no significant differences were found in the number of PRBC transfusions between groups with no HES versus those receiving HES (47% received < 1,000 mL and 53% received ≥ 1,000 mL of HES), a significant increase in the odds of receiving FFP, PLTC and cryoprecipitate was observed particularly in patients who received ≥ 1,000 mL of HES.

Furthermore, postoperative bleeding and transfusions were the major end points of 2 non-blinded RCTS evaluating intraoperative volume therapies. The first compared 6% HES to 5% albumin during off-pump CABG procedures, resulting in considerably higher 12-h chest drainage volume in the HES group (732 vs 563 ml; $P<0.001$) (346). Additionally, the second study investigated blood loss when using 6% HES 130/0.4 (instead of HES 200/0.5) or 3.5% gelatine and found similar blood loss (19.4 vs 19.2 ml/kg) in cardiac surgery patients with cardiopulmonary bypass (347). Similarly, a 3-armed RCT found no difference in 24-h blood loss between 5% albumin or Ringer's lactate and 6% HES 130/0.4 (835 vs 670 vs 700 ml; $P=0.085$). However, the albumin and HES groups had greater PRBC transfusion rates than the Ringer's lactate group (58% vs 61% vs 24%, respectively; $P = 0.001$), whereas the HES group had the highest creatinine levels (348).

In summary, studies designed to demonstrate differences in blood loss or transfusion requirements have shown comparable results across various priming solutions and perioperative volume strategies. However, concerns regarding the potential association of HES with AKI and increased mortality rates have led to a decrease in the use of starches as volume therapy during cardiac surgery (349). Consequently, it is not recommended to use modern low-molecular-weight starches in either priming or non-priming solutions to reduce bleeding and allogenic transfusions.

4.4.3 Haemodilution and cardioplegia

Haemodilution has the potential to enhance microcirculatory perfusion and reduce blood viscosity, both of which can be beneficial to a certain extent. However, it also leads to a decrease in the concentration of blood cells and coagulation factors during and after CPB, which may impact organ function and postoperative haemostasis. Despite the increased adoption of strategies to reduce priming volume, certain types of cardioplegias, such as high-volume crystalloid cardioplegia, still induce significant intraoperative haemodilution.

Description of the evidence

Haemodilution effects

The effects of haemodilution have been a significant focus in recent research. Large database studies have linked lower HCT values to increased morbidity (350), more in-hospital deaths (351) and a greater need for PRBC transfusions (222). The authors of a meta-analysis concluded that using smaller circuits could mitigate haemodilution, lessen postoperative bleeding and reduce transfusion requirements (240). Further, 2 prospective studies explored strategies to manage haemodilution without MiECC systems, employing either a multimodality blood conservation approach or a reduction in intravenous fluids during surgery (352, 353). Both identified a notable decline in transfusion rates as HCT values increased. Additionally, an RCT examining the impact of mild versus moderate haemodilution found significantly fewer neurologic complications with restricted haemodilution (354), including a lower rate of neurocognitive dysfunction in patients with limited haemodilution (18.7% vs 32.2%; $P = 0.042$). Another RCT that compared a haemodilution strategy with standard care—including ANH, autologous priming and oxygenator size reduction—observed that the group with reduced haemodilution required significantly fewer PRBC transfusions. This group also experienced shorter extubation times, less chest tube drainage and reduced hospital stays (355).

In light of these findings, limiting haemodilution is advisable as a component of blood conservation strategies to decrease both bleeding and the necessity for transfusions.

Cardioplegia effects

Although the differences in outcomes between crystalloid and blood cardioplegia solutions have been extensively studied for decades (356), most studies did not reveal the risk of

bleeding complications and transfusion rates. In an RCT including 100 patients, crystalloid cardioplegia was compared to blood cardioplegia and was associated with significantly higher intraoperative haemodilution, greater blood loss and more PRBC transfusions (357). On the other hand, a large registry-based study found no statistically significant relationship between the type of cardioplegia and the likelihood of receiving a transfusion of PRBCs (358). Even higher transfusion rates were reported among those receiving blood cardioplegia compared to those receiving del Nido cardioplegic solution (359).

In summary, there appears to be a difference in the approach to haemodilution management when different crystalloid cardioplegias are used. Haemofiltration is utilized more often in combination with large-volume crystalloids such as Custodiol (histidine-tryptophan-ketoglutarate) and del Nido solutions, diminishing the effects of intraoperative haemodilution. When the utilization of haemofiltration to reduce haemodilution is not possible, cardioplegia with a limited crystalloid content should be considered as the preferred strategy in patients with anaemia, low BSA or chronic kidney disease or in patients undergoing complex procedures to reduce the risk of complications.

4.4.4 Acute normovolaemic haemodilution

During ANH, the patient donates blood just before the onset of surgery that is replaced by an equal amount of volume to maintain normovolaemia. The donated blood is retransfused after CPB, but this practice comes at the cost of lower HCT values during surgery.

Description of the evidence

A recent systematic review and meta-analysis including 29 RCTs investigated the effect of AHN using a variation of colloid, albumin and crystalloid volume replacement on allogeneic PRBC transfusion requirements in adult and paediatric cardiac surgical procedures (360). In the 21 studies with allogeneic blood transfusions as a predefined study end point, patients subjected to ANH received fewer PRBC transfusions (−0.79 units; 95% CI −1.25 to −0.34; $P = 0.001$), albeit with a considerable variation in the effect size between studies (360). Moreover, most of the studies with a large benefit of ANH on PRBC transfusions were published before 2001. In the studies reported after 2001, only half of the studies showed a benefit of ANH for PRBC transfusions. ANH was also associated with a statistically significant, but clinically irrelevant,

reduction in postoperative bleeding compared to the control (388 ml vs 450 ml, *P*<0.001). These findings have been similar to those from another meta-analysis that indicated that ANH could reduce the number of PRBCs transfused in the CABG operation (361). In a PSM analysis including 168 patients, it was suggested that the large-volume ANH (median 1100 ml) versus the low volume ANH (median 400 ml) resulted in a transfusion RR of 0.58 (95% CI 0.39–0.88) for RBCBs and 0.63 (95% CI 0.44–0.89) for other blood components (362).

In a more recent RCT, a haemodilution reduction technique was compared to the standard CPB technique (355). This technique incorporated a combination of ANH, RAP and reduction in oxygenator size. The haemodilution reduction group received significantly fewer PRBC transfusions than the standard care group (0.0±0.1 vs 1.4±0.6; *P* < 0.001). This finding is not surprising, given the massive contrast in net prime volumes: 400 ml in the intervention group versus 1500 ml in the standard care group. This significant difference complicates attributing the reduction in PRBC transfusions specifically to ANH.

In summary, ANH may have a beneficial effect on postoperative transfusion rates, especially with higher volumes of ANH and especially when combined with other haemodilution reduction techniques.

Recommendation Table 9. Recommendations for intravascular volume

Recommendations	Class[a]	Level[b]	Ref[c]
Limitation of haemodilution is recommended as part of a blood conservation strategy to reduce bleeding and transfusions.	I	A	(222, 350, 352-355)
Acute normovolaemic haemodilution may be considered to reduce postoperative transfusions.	IIb	A	(355, 360-362)
The use of modern low-molecular-weight starches in priming and non-priming solutions to reduce bleeding and transfusions is not recommended.	III	B	(345, 346, 348)

CPB: cardiopulmonary bypass.

[a] Class of recommendation.

[b] Level of evidence.

[c] References.

5. Perioperative coagulation and transfusion

Effective perioperative management of patient haemostasis is crucial in closing the circle of PBM in cardiac surgery. Diagnosing and guiding the treatment of haemostatic abnormalities through specific procoagulant interventions or the use of blood transfusion products is essential to ensure optimal patient outcomes. This approach not only addresses immediate postoperative bleeding concerns but also contributes to the overall success of PBM strategies in cardiac surgical procedures.

5.1 Procoagulant interventions

Procoagulant interventions play a pivotal role in managing haemostasis during and after cardiac surgery. These strategies include the use of antifibrinolytics, FFP, factor XIII (FXIII), fibrinogen supplementation, PCC, desmopressin (DDAVP) and rFVIIa. Each intervention plays a specific role in enhancing the coagulation process, addressing deficiencies in coagulation factors or stabilizing the formation of blood clots. The careful selection and application of these procoagulant measures are essential components of a comprehensive approach to PBM in cardiac surgery.

5.1.1 Antifibrinolytics

Antifibrinolytic therapy is commonly used in cardiac surgery to minimize bleeding, the need for blood product transfusions and the incidence of reoperations for bleeding. Three antifibrinolytics—TXA, EACA and aprotinin—are utilized for this purpose. Although aprotinin was withdrawn from the market in 2007, it is today approved in Europe for on-pump CABG.

Description of the evidence

Tranexamic acid

The ATACAS RCT compared TXA with placebo in patients undergoing CABG surgery and demonstrated a reduction with TXA in the risk for re-exploration (1.4% vs 2.8%, *P*<0.001) and in the need for any blood product transfusion (37.9% vs 54.7%; *P*<0.001) (363). These results have also been demonstrated in several meta-analyses summarizing available RCTs (364, 365).

The most significant reported side effect of TXA is convulsive seizures (366). The ATACAS trial showed that low-dose (50 mg/kg) versus high-dose (100 mg/kg) TXA was not safer in terms of seizures (0.7% vs 0.6%, respectively), but the higher dose significantly reduced blood loss and red blood cell transfusions (363). High-dose TXA was more effective than low-dose TXA in reducing red blood cell transfusions (21.6% vs 26.0%) in a large recently published randomized trial (367). Seizures occurred in 1.0% of the patients in the high-dose group versus 0.4% in the low-dose group (P = 0.05). The optimal dosing of TXA and possible dose adjustments in patients with reduced renal function are not yet clearly defined (367, 368).

Epsilon-aminocaproic acid

In comparison with TXA, limited data are available to support the use of EACA in cardiac surgery (369). Smaller randomized and observational studies directly comparing EACA and TXA have not revealed any consistent differences (370, 371).

Aprotinin

Several RCTs and meta-analyses have demonstrated aprotinin's efficacy in reducing the risk of reoperation for bleeding (RR 0.46, 95% CI 0.34–0.63; P<0.001) and the need for blood product transfusion (RR 0.68, 95% CI 0.63–0.73; P <0.001) (369). It was suggested that aprotinin was a more effective agent than TXA and EACA in reducing allogeneic blood exposure, but the difference was small (369). There have been safety concerns with aprotinin, which led to a temporary suspension by the European Medicines Agency, but after further investigations (372), the suspension was lifted for patients who had CABG. However, in a PSM subgroup analysis from the ART (Arterial Revascularization Trial), aprotinin was associated with a significantly increased risk of hospital death (1.7% vs 0.2%), acute renal failure (19.0% vs 14.2%) and 5-year death (10.6% vs 7.3%) (373). Aprotinin was not associated with a reduced risk for transfusion or re-exploration in this study.

In summary, safety studies should be designed to define the dose–response relationship of the adverse effects observed following the administration of TXA, considering the positive impact these agents have on reducing bleeding. In addition, the role of aprotinin in cardiac surgery needs to be explored in further studies.

5.1.2 Fresh frozen plasma

FFP is derived from donated blood by separating the plasma, which contains coagulation factors, other proteins and soluble constituents, from cellular elements. An increasing number of countries use pooled plasma, which combines plasma from multiple donors and undergoes virus inactivation, thus reducing the risk of transfusion-related complications.

Description of the evidence

A Cochrane review based on RCTs found that prophylactic administration of FFP to patients without coagulopathy did not reduce blood loss or transfusion requirements (374). These results were consistent with those of previous meta-analyses (375, 376). Additionally, therapeutic use of FFP in patients with established coagulopathy or for the reversal of OACs had no effect on 24-hour blood loss (375, 377). However, RCTs included in these meta-analyses were limited by small sample sizes, varied doses of FFP and low methodological quality.

In summary, FFP may be used to reverse the effects of OACs or in cases of persistent perioperative bleeding. However, there is no evidence to support the use of prophylactic or therapeutic FFP transfusions to reduce bleeding complications following cardiac surgery.

5.1.3 Fibrinogen supplementation

Endogenous plasma fibrinogen levels are the first coagulation factors to be depleted during significant bleeding and haemodilution. Observational studies have suggested an association between lower pre- and postoperative plasma fibrinogen levels and higher bleeding risk after cardiac surgery (11, 378, 379). Therefore, fibrinogen supplementation has been advocated as one of the primary haemostatic goals in patients who bleed after cardiac surgery (380).

Description of the evidence

A 2018 meta-analysis incorporating 8 RCTs with 597 patients undergoing various cardiac operations (381) found that, whereas fibrinogen significantly decreased the proportion of patients requiring PRBC transfusions (RR 0.64, 95% CI, 0.49–0.83), it did not substantially

reduce overall allogeneic blood product exposure (RR 0.79, 95% CI, 0.53–1.18), including PRBC, PLTCs or FFP.

This meta-analysis included 3 studies with 128 patients given preoperative fibrinogen (1–2 g); none reported a decrease in allogeneic blood transfusions. Of the 5 studies with intraoperative fibrinogen administration (2–8 g), 1 study juxtaposed fibrinogen infusion with PLTC transfusions (382). In 4 studies in which fibrinogen was administered based on ROTEM or plasma fibrinogen levels, 2 studies (383, 384) with 167 patients undergoing complex cardiac operations reported fewer allogeneic blood products required in the intervention group. The other 2 RCTs with 272 patients who experienced bleeding after complex cardiac operations did not observe a favourable impact of fibrinogen concentrate infusion on bleeding volume or transfusion of blood products (385, 386). A post hoc RCT analysis indicated that elevating fibrinogen concentrate beyond 2.87 g/L (or maximal clot firmness of 14 mm in FIBTEM) did not further diminish bleeding volume (387).

Additionally, the 2018 meta-analysis observed no decrease in deaths or other significant clinical events, including reoperation, stroke, MI or thromboembolic events (381). Nonetheless, due to the limited number of adverse events, more comprehensive safety data from larger RCTs are warranted. An international consensus statement has suggested considering administering fibrinogen concentrate in patients with microvascular bleeding following cardiac surgery and confirmed hypofibrinogenaemia to curtail the need for allogeneic blood transfusions (388). However, the evidence is still insufficient to advocate conclusively for or against the routine perioperative use of fibrinogen. In an RCT with 735 patients experiencing relevant post-cardiac surgery bleeding and hypofibrinogenaemia, treatment with 4 g of fibrinogen concentrate was found to be non-inferior to 10 units of cryoprecipitate in terms of the number of blood components transfused within 24 h postoperatively, indicating comparable clinical efficacy between fibrinogen concentrate and cryoprecipitate (389).

In summary, prophylactic fibrinogen administration is not recommended for reducing postoperative bleeding and transfusion risks. However, in patients with a low fibrinogen level (<1.5 g/L) and signs of persistent microvascular bleeding, fibrinogen substitution should be considered to reduce the requirement for transfusions.

5.1.4 Prothrombin complex concentrate

Prothrombin complex concentrate comprises lyophilized, human plasma-derived vitamin K-dependent coagulation factors. In Europe, only 4-factor concentrates are available, containing coagulation factors II, VII, IX and X. Although the concentration of factor IX is standardized, the other factors might vary among the different available products. Additionally, PCCs might contain various amounts of AT, proteins C, S and Z and heparin (380, 390). When fibrinogen levels are low, clot formation times are prolonged. Therefore, administering PCC should be considered only after fibrinogen levels have been corrected.

Description of the evidence

In patients with very high INR values (>4–5) taking VKAs long term who need urgent or emergency surgery, the use of PCCs might be advantageous compared to FFP due to the more rapid reversal of the anticoagulant effect. In 40 patients with an INR >2.1, the perioperative administration of PCC reversed anticoagulation safely; reversal was faster and postoperative bleeding volume was lower compared to the administration of FFP (122). However, a 2015 Cochrane review on the reversal of VKA in patients undergoing cardiac surgery showed no evidence of a difference between PCC and FFP in terms of postoperative bleeding and transfusion risks (391). Nonetheless, a recent European consensus statement recommended considering the use of PCC for patients treated with VKA requiring urgent cardiac surgery (392).

The 2019 Cochrane review (124) on the use of PCC for the treatment of coagulopathic bleeding in cardiac surgery, including 2 RCTs (151 patients) and 16 non-RCTs (4842 patients), concluded that PCC could potentially be used as an alternative to standard therapy for coagulopathy bleeding after cardiac surgery compared to FFP, as shown by moderate quality evidence from non-RCTs. This conclusion agrees with a more stringent meta-analysis including 4 studies with a total of 861 patients (393). The authors of this meta-analysis concluded that PCC seems to be more effective than FFP in reducing perioperative blood transfusions in patients with significant bleeding after cardiac surgery. Both meta-analyses found no additional risk of thromboembolic events and fewer deaths (124, 393). Accordingly, the European experts' consensus statement suggested that PCC at a dose of 25 U/kg might be considered in post-cardiac surgery patients with coagulopathy and severe bleeding (392).

Neither meta-analysis included the more recently published RCT comprising 100 patients with excessive microvascular bleeding after cardiac surgery randomized to a PCC dose of 15 U/kg or an FFP dose at a volume of 10 to 15 ml/kg. This study suggested no significant differences in postoperative chest tube output and in major adverse events. However, administration of PCC resulted in enhanced PT and INR correction and fewer PRBC transfusions (394). Based on a moderate to a very low quality of evidence, PCC and activated PCC might be used as an alternative in refractory non-surgical bleeding after cardiac surgery (124, 395).

In summary, in patients whose bleeding is related to a coagulation factor deficiency, PCC should be considered over FFP to reduce bleeding and transfusions. Additionally, PCC should be preferred over FFP when rapid normalization of coagulation factors is needed.

5.1.5 Desmopressin

DDAVP stimulates the release of von Willebrand factor from endothelial cells. It is used as a haemostatic agent to prevent and treat bleeding in patients with mild haemophilia (5–50% of the normal concentration of clotting factors VIII and IX) and patients with von Willebrand's deficiency. DDAVP is sometimes administered to treat postoperative bleeding in patients with impaired platelet function undergoing cardiac surgery.

Description of the evidence

The effects of DDAVP on bleeding in patients undergoing cardiac surgery are summarized in an updated Cochrane review of 39 RCTs focusing on cardiac surgery (396) and 2 other meta-analyses (397, 398). Overall, differences in blood loss when patients were treated with the prophylactic use of DDAVP or placebo were small, with low methodological quality and unlikely to be clinically important (weighted mean difference, 135 ml; 95% CI −210 to −60 ml, and −0.1 units, 95% CI −1.22–1.02 units, respectively). Other meta-analyses indicated as well that DDAVP has a small effect on the volume of blood loss and allogeneic blood product transfusions (397, 398). Furthermore, they observed that the effect of DDAVP may be more profound in subgroups, e.g. for patients on platelet inhibitors, patients with reduced platelet function and patients exposed to prolonged CPB times (397). There was no increased risk for MI, stroke or any other major thromboembolic complications after the administration of

DDAVP (396, 398, 399). However, the risk of clinically important hypotension that required fluids and/or vasoactive drugs was more frequent for participants treated with DDAVP than for those given placebo (RR 2.81; 95% CI 1.50–5.27) (399).

In summary, prophylactic use of DDAVP cannot be routinely recommended, but its administration might be beneficial in patients who are bleeding and have inherited or acquired bleeding disorders or platelet dysfunction (397, 400).

5.1.6 Factor XIII

FXIII is the terminal enzyme in the coagulation cascade, essential for cross-linking fibrin monomers to form a stable fibrin clot. Specific immunologic assays are required to determine functional FXIII activity. Low postoperative FXIII levels have been associated with an increased risk of bleeding and re-exploration for bleeding after cardiac surgery (401-403).

Description of the evidence

Two RCTs have evaluated the effect of FXIII supplementation on bleeding and transfusion requirements following protamine administration (402, 404). The results showed no differences in postoperative bleeding volumes or transfusion rates with any FXIII dosage regimen in either study. Additionally, there was no difference in adverse events, including thromboembolic events and death, between the intervention and control groups. However, subgroup analyses in 1 study suggested that FXIII supplementation in patients with a postoperative FXIII level <70% might be beneficial (402).

Currently, there is no evidence to support the administration of FXIII as beneficial in reducing postoperative bleeding volumes or transfusion rates in patients with normal FXIII concentrations (>70%).

5.1.7 Recombinant factor VIIa

rFVIIa is used in the treatment and prevention of bleeding in patients with inherited bleeding disorders. The observed haemostatic properties of this agent led to its off-label use in life-threatening bleeding, but nowadays, its use is considered to be a last resort in the event of uncontrollable blood loss.

Description of the evidence

The medical literature increasingly describes the "off-label" use of rFVIIa to treat severe bleeding after major surgery in patients without haemophilia and in those with different antithrombotic treatments requiring urgent or emergency surgery. Although some studies have used it for prophylaxis to prevent bleeding and transfusion, raising caution due to an increase in the number of critical serious adverse events, including stroke (405), the majority have used it as rescue therapy when conventional surgical exploration and the administration of blood products and antifibrinolytic agents have failed to stop the bleeding. Recent findings suggest that administering rFVIIa in very low doses (less than 20 mcg/kg) can achieve haemostasis without increasing thromboembolic events in patients with refractory bleeding (406). Still, extreme caution should be applied, and more research is needed to assess the safety and effectiveness of these low doses compared to high-dose rescue treatments before modifying the indications and timing for rFVIIa.

A 2012 Cochrane review analysed 29 RCTs with respect to the prophylactic (1361 patients) and therapeutic use (2,929 patients) of rFVIIa in patients with or without haemophilia (407). Prophylactic rFVIIa use just failed to reach significance in reducing transfusion rates (RR 0.85, 95% CI 0.72–1.01) compared to placebo, but this result was associated with an increased risk of thromboembolic adverse events (RR 1.35, 95% CI 0.82–2.25). There was no benefit of the therapeutic use of rFVIIa compared with placebo with respect to transfusion rates, but the administration of rFVIIa was associated with reduced mortality rates (RR 0.91, 95% CI 0.78–1.06) at the cost of more major thromboembolic events (RR 1.14, 95% CI 0.89–1.47). Therefore, the prophylactic use of rFVIIa cannot be recommended in cardiac surgery. Its therapeutic use should be considered only in patients with uncontrollable bleeding that cannot be managed by other procoagulant interventions. A 2022 Cochrane review concluded that 4-factor PCC may have equal efficacy compared to rFVIIa for patients experiencing significant bleeding during cardiac surgery (124).

Recommendation Table 10. Recommendations for procoagulant interventions

Recommendations	Class[a]	Level[b]	Ref[c]

Antifibrinolytic therapy is recommended to reduce bleeding and transfusions of blood products and reoperations for bleeding[d].	I	A	(363-365)
The prophylactic use of FFP to reduce bleeding is not recommended.	III	B	(374, 376, 377)
For rapid reversal of VKAs, PCC should be considered over FFP.	IIa	A	(122, 391)
Prophylactic fibrinogen administration is not recommended.	III	A	(381, 385)
In the bleeding patient with a low fibrinogen level (<1.5 g/L) or the equivalent value in viscoelastic testing, fibrinogen supplementation should be considered to reduce postoperative bleeding and transfusions.	IIa	B	(381)
In patients with significant bleeding after cardiac surgery due to coagulation factor deficiency, the administration of PCC should be considered instead of FFP to reduce postoperative blood transfusions.	IIa	B	(124, 393)
The prophylactic use of DDAVP is not recommended to reduce bleeding complications.	III	A	(396-398)
In bleeding patients with platelet dysfunction, the use of DDAVP should be considered to reduce bleeding complications.	IIa	C	(397)
In bleeding patients with FXIII activity <70% after CPB, the administration of factor FXIII may be considered to reduce coagulopathy and blood transfusions.	IIb	B	(402)
The prophylactic use of rFVIIa is not recommended to prevent bleeding complications.	III	B	(405, 407)
In patients with refractory, non-surgical bleeding, off-label use of rFVIIa may be considered to reduce bleeding complications.	IIb	B	(407)

CPB: cardiopulmonary bypass; DDAVP: desmopressin; FFP: fresh frozen plasma; FXIII: factor XIII; PCC: prothrombin complex concentrate; rFVIIa: recombinant activated factor VII; VKA: vitamin K antagonist.

[a] Class of recommendation.

[b] Level of evidence.

[c] References.

[d] Bleeding is defined as persistent, non-surgical microvascular blood loss.

5.2 Transfusion strategies

Effective transfusion strategies are crucial in cardiac surgery to minimize the risks associated with transfusions while providing essential support for haemostasis and tissue oxygenation. These strategies encompass ensuring the quality of blood products, implementing algorithm-guided therapy for perioperative bleeding and establishing transfusion triggers for PRBCs and PLTCs. By adhering to evidence-based, patient-centred care, health-care professionals can mitigate potential problems by optimizing blood use, minimizing unnecessary transfusions and improving patient outcomes through practices tailored to individual patient needs. Implementing a blood use initiative significantly improves postoperative morbidity and mortality, reduces health-care costs by limiting intraoperative and postoperative blood product transfusions and is bolstered by effective collaboration, making it a highly recommended significant step in improving patient care (408-411).

5.2.1 Quality of blood products

Stored PRBCs or FFP shows efficacy comparable to that of fresh products but differs in terms of the risk of transmission of bacterial or viral infections (412, 413), transfusion-related acute lung injury (TRALI) (414, 415), and transfusion-related immune modulation (TRIM) (416-418). To reduce TRALI, FFP and PLTCs must be collected from men, women who have not been pregnant and women who have tested negative for HLA antibodies (414). The effects of TRIM are assumed to be caused by allogeneic mononuclear cells, white-blood-cell-derived soluble mediators and HLA peptides, transfused mainly via PRBCs (416). TRIM has been associated with increased rates of mortality and morbidity in cardiac surgery and an increased risk of developing infections (417, 418).

Description of the evidence

In the RECESS (Red-Cell Storage Duration) study, 1,098 cardiac surgical patients were randomized to receive exclusively "new" (≤ 10 days) or "old" (≥ 21 days) leucocyte-depleted PRBCs (419). No differences were found in multiple organ dysfunction and mortality rates between the 2 groups. These results are in line with those of a large Swedish registry that compared the outcomes of 47,071 cardiac surgery patients from 1997 to 2012 who were transfused exclusively with PRBCs stored for <14 days (36.6%), 14–27 days (26.8%), 28–42 days (8.9%) or of mixed age (27.8%) (420). No differences were noted in terms of 30-day, 2-year and 10-year mortality rates or in relation to 30-day organ dysfunction or serious infection (420). A current meta-analysis that included the RECESS and the large ABLE (Age of Blood Evaluation) trial (420, 421) showed that red blood cell storage time does not impact mortality rates, adverse events or nosocomial infections (422).

Leucocyte reduction of PRBCs is standard practice across Europe and preserves the quality of PRBCs during storage and impacts favourably on morbidity (418). In a prospective RCT including 1,085 patients undergoing cardiac surgery, patients received either buffy coat-depleted or leucocyte-depleted erythrocytes. Although no differences in mortality rates were shown, patients receiving leucocyte-depleted PRBCs had a reduced infection rate compared to controls (21.6% vs 31.6%; OR 1.64, 95% CI 1.08–2.49) (418). Similarly, a large retrospective study of roughly 10,000 patients showed no association of mortality rate when 1 to 2 units of leucodepleted PRBCs were transfused (423). A smaller prospective study investigated the effects of leucodepletion on early postoperative outcome. The duration of mechanical ventilation was lower in the leucodepleted group (10.2 vs 14.7 h), and the risk of AKI was 1.3 to 2.6 times higher. However, there was no difference in the occurrence of infections (424).

PLTCs can be produced as single-donor apheresis PLTC or as pooled (4–5 donors) whole blood-derived PLTCs. Whereas the risk for TRALI appears to be comparable, an increased risk of transmitting infections is associated with whole blood-derived PLTC transfusions (425). A retrospective study of 3,272 patients who received single-donor PLTCs aged 2–5 days showed no association between PLTC storage age and short-term outcome, survival or postoperative infections (426).

In summary, the present guidelines recommend the use of PRBCs of all ages, because the storage time of PRBCs does not impact outcomes. The use of leucocyte-depleted PRBCs should be considered due to their association with decreased mortality, although more robust research to prove their effectiveness is warranted.

5.2.2 Algorithm-guided therapy of perioperative bleeding

Cardiac surgery accounts for 20% of all national blood product consumption in the United States (427). Various reports demonstrate significant institutional variation in the indications and utilization of blood components in cardiac surgery. They progressively emphasize the importance of a multidisciplinary approach to blood component administration and management during the preoperative, intraoperative and postoperative phases (44, 428). (Potential preoperative and intraoperative haemostasis checklists are outlined in Figs. 1 and 2, with provisional ideas for illustrations provided below.) Postoperative impairment of haemostasis following cardiac surgery is well described and may result in significant postoperative bleeding in 5–10% of patients, with independently associated increases in morbidity and mortality (44, 427-429).

Structured blood component therapy algorithms and protocols guided by POC TEG and thromboelastometry (TEM) are progressively implemented to identify specific coagulation disorders in a timely manner, allowing for specific and rapid treatment (430-435). Results from TEG/TEM are usually available within 10 to 30 min, and recent RCTs suggest that the application of TEG-/TEM-guided algorithms results in a significant reduction in the amounts of transfusion products, the rate of severe acute renal dysfunction, other transfusion-related complications and the total cost of postoperative cardiac surgery (432). Other potential benefits include improved re-exploration rates for bleeding, shorter ventilation times, decreased length of stay in the ICU and hospitalization periods compared to traditional haemostasis monitoring and empiric transfusion strategies (432-435).

Large meta-analyses comparing TEG-/TEM-guided transfusion protocols and traditional strategies (42) suggest that the use of allogeneic blood products is significantly less with TEG-/TEM-guided strategies, which is also confirmed by various RCTs (432, 435-437). These studies also demonstrate significant benefits with TEG-/TEM-guided transfusion strategies in "high-risk for bleeding" patients, which include emergency procedures in anticoagulated patients and complex procedures with prolonged CPB times. Current data on the rate of surgical re-exploration for bleeding favour TEG-/TEM-guided strategies, but recently published meta-analyses and large institutional reports do not demonstrate statistically significant differences compared to traditional strategies (45, 433, 435). Recent investigations

propose that TEG/TEM may provide reliable negative predictive values of up to 82% for potentially excluding diffuse coagulopathy and may assist in differentiating between surgical bleeding and coagulopathy (432). The previously appraised meta-analyses and RCTs also suggest that the incidence of coagulopathy overcorrection (iatrogenic hypercoagulability) and subsequent postoperative thromboembolic events are reduced with TEG-/TEM-guided strategies compared to traditional postoperative coagulation monitoring. Despite the additional costs of performing TEG/TEM investigations, recent RCTs suggest that TEG/TEM-guided transfusion strategies are associated with significant cost reductions (432, 438).

In summary, previous and recent evidence supports the use of perioperative POC testing in cardiac surgery to potentially reduce the requirements for blood transfusions, enhance resource management and improve clinical outcomes, including bleeding rates, ICU and hospital lengths of stay and overall all-cause mortality. The value of performing additional specific platelet function tests in combination with TEG/TEM is currently not well defined (436).

5.2.3 Transfusion Triggers

Transfusion thresholds for PRBC or PLTC transfusions are typically specified as critical HCT/Hb values, RBC volume or platelet count/function. However, dynamic techniques also consider tissue perfusion and oxygenation (439, 440). Due to different transfusion criteria for PRBC transfusions and variations in blood product quality, comparing findings from RCTs in cardiac surgery is challenging.

Description of the evidence

A 2016 Cochrane review that included a total of 31 RCTs involving 12,587 patients across various clinical specialties examined different triggers guiding PRBC transfusions (441). In the subgroup analysis of 16 RCTs focusing on cardiac surgery patients only, no significant difference was found in terms of 30-day mortality and MI between liberal and restrictive transfusion strategies. The findings from the Cochrane review served as a basis for a meta-analysis on patients with cardiovascular disease (442), which concluded that a restrictive transfusion strategy safely reduced red blood cell usage by 24% without increasing the risk of 30-day mortality. Another meta-analysis compared restrictive (Hb 70–80 g/L) to liberal transfusion strategies (Hb 90–100 g/L) in cardiac surgery patients. This analysis included 6

RCTs with 3,352 patients and showed a reduction in the number of deaths in the restrictive regimen group by approximately 30% (440). A more recent meta-analysis of studies published from 2012 to 2017 on restricted versus liberal transfusion strategies in cardiac surgery patients (443) also concluded that a restricted strategy was non-inferior to a liberal strategy. No statistically significant differences were found in the analysis for MI, stroke, AKI or infection.

Landmark clinical trials that compared liberal with restrictive transfusion triggers

TRACS trial: The TRACS (Transfusion Requirements After Cardiac Surgery) trial examined the difference between liberal (HCT ≥ 30%) and restrictive (HCT ≥ 24%) transfusion thresholds on 30-day all-cause mortality and severe morbidity. No significant difference in the composite end point of 30-day mortality or severe morbidity was found (10% liberal vs 11% restrictive, 95% CI, -0.6%–4%; *P* = 0.85) (444). However, a subgroup analysis of 260 older patients (> 60 years old) revealed a higher incidence of cardiogenic shock in the restricted transfusion threshold group (12.8% vs 5.2%; *P* = 0.031) (445).

TITRe2 trial: In the TITRe2 (UK Transfusion Indication Threshold Reduction) study, 2,000 patients undergoing cardiac surgery were compared between a liberal (Hb < 90 g/L) and a restrictive threshold (Hb < 75 g/L) for leucocyte-depleted red blood cells (446). Red blood cell distribution was lower in the restrictive group (63.7% vs 94.9%, OR 0.58; 95% CI, 0.54–0.62; *P* < 0.001), while the 90-day mortality rate was twice as high (4.2% vs 2.6%, OR 1.64; 95% CI, 1.00–2.67; *P* = 0.045). The trial faced considerable criticism due to issues with transfusion thresholds and confounders.

TRICS III trial: The multicentre, open-label, non-inferiority TRICS III (Transfusion Requirements in Cardiac Surgery III) trial investigated the difference in composite outcomes (death from any cause, non-fatal MI, stroke or new-onset AKI with dialysis) between a liberal (<95 g/L) and restrictive (<75 g/L) transfusion strategy in patients undergoing cardiac surgery (447). Patients in the restrictive group received 20% fewer PRBC transfusions (52.3% vs 72.6%, OR 0.41, 95% CI 0.37–0.47). No significant difference was found in the primary end point between groups with an absolute risk difference of -1.11% in favour of the restrictive strategy (OR 0.90, 95% CI 0.76–1.07). Subgroup analysis revealed an interaction of age and the primary outcome. Interestingly, the older subgroups (75 years +) favoured a restricted transfusion strategy, with younger age groups favouring a liberal approach. A prespecified subgroup analysis of the

TRICS III trial investigating the effect of transfusion strategies in 679 diabetic patients on a composite postoperative outcome did not find a meaningful association (OR 1.10, 95% CI 0.93–1.31) at 6 months of follow-up (448). In summary, a restricted transfusion strategy proved non-inferior to a liberal transfusion approach.

MINT trial*:* The recently published MINT (Myocardial Ischemia and Transfusion) trial focused on the potential benefit of adhering to a liberal transfusion strategy in patients with acute MI (449). In this study, 3,504 patients were randomized to a liberal (<100 g/L) or restricted (< 70 or 80 g/L) group. Transfusions were permitted when the Hb was 80 g/L and strongly recommended at an Hb of 70 g/L. No significant difference in the composite end point (MI or death at 30 days) was found (RR 1.15, 95% CI 0.99–1.34). Subgroup analysis also revealed an interaction with age. All age subgroups favoured liberal transfusions, with a trend towards restrictive for older patients (>80 years). In summary, the trial did not show a clear benefit in terms of mortality and recurrent myocardial ischaemia reduction when a liberal transfusion strategy was followed.

Balancing risk trial: Another RCT conducted at 2 centres in the United States and India was designed to test the hypothesis that transfusion triggers of 24% versus 28% HCT result in similar postoperative morbidities and mortality and resource use after cardiac surgery (450). At the second planned interim analysis, the study was stopped due to crossing the a priori futility boundary, i.e. not detecting any treatment effect on the primary composite outcome of major postoperative morbidities and mortality. However, the low-transfusion group received significantly fewer PRBC transfusions than the high-transfusion group (54% vs 75%, $P < 0.001$), mainly administered in the operating room (low group, 31%; high group, 59%).

The REALITY trial: The goal of the REALITY (Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction) trial, conducted in 35 centres in Spain and France, was to evaluate the safety and efficacy of a restrictive versus liberal PRBC transfusion strategy in patients with acute MI and anaemia (451). Patients with AMI and Hb levels between 80 to 100 g/L upon admission were randomly assigned to either a liberal strategy (transfusion for Hb ≤100 g/L, with a target Hb >110 g/L) or a restrictive strategy (transfusion for Hb ≤80 g/L, with a target Hb of 80–100 g/L). The results of the trial showed that the restrictive PRBC transfusion strategy is non-inferior to the liberal strategy at 30 days. However, infections and acute lung injury were more common with the liberal strategy. Additionally, total blood utilization and costs were lower with the restrictive approach, making it the cost-dominant

strategy. However, at the 1-year follow-up, the outcomes between the 2 strategies diverged at around 5 months (452). The restrictive strategy was no longer non-inferior to the liberal strategy and may even be associated with higher rates of adverse events.

Although there are notable differences in the practices surrounding platelet concentrate transfusion (453), no research has definitively determined a specific platelet count or platelet function assay value as a definitive threshold for PLTC transfusions to stop or reduce microvascular bleeding due to inadequate platelet count or function (454). Observational studies provide limited evidence that platelet transfusion does not correlate with an increase in mortality or perioperative complications among cardiac surgery patients (454, 455). However, due to the limited number of such studies, their results should primarily be viewed as preliminary and hypothesis-generating. In the absence of new findings, the writing committee has reaffirmed the expert consensus previously established, which aligns with other guidelines dealing with cardiac and other major operations, recommending that PLTCs be transfused in patients who are bleeding with a platelet count under 50 (10^9/L) or those experiencing bleeding complications while on antiplatelet therapy.

In summary, current studies support the use of restrictive PRBC transfusion strategies, which include rigorous transfusion triggers during the CPB procedure (456). However, it is important to emphasize, based on signals of later hazards, that the patient's clinical condition and optimizing the balance between oxygen delivery and extraction in the tissue are more critical than adhering to a specific Hb level threshold. The acceptable HCT levels during CPB and immediate postoperative care should be tailored based on the patient's risk profile and their ability to maintain adequate tissue perfusion and oxygenation.

Recommendation Table 11. Recommendations for transfusion strategies

Recommendations	Class[a]	Level[b]	Ref[c]
Implementation of a patient blood management protocol for the bleeding patient is recommended.	I	B	(408-411)
The use of PRBCs of all ages is recommended because the storage time of the PRBCs does not affect outcomes.	I	A	(419-421)
The use of leucocyte-depleted PRBCs is recommended.	I	B	(418, 423, 424)

Perioperative treatment algorithms for the bleeding patient based on viscoelastic POC testing is recommended to reduce the number of transfusions.	**I**	**A**	**(42, 45, 47, 436)**
Restrictive transfusion triggers (≤75 g/L) are recommended over liberal triggers (≤90 g/L) if the clinical condition of the patient allows it.	**I**	**A**	**(443, 444, 446, 447)**
For HCT values between 18% and 24%, PRBCs may be considered if other measures are not sufficient to maintain the adequacy of tissue oxygenation during CPB, including DO_2 and cerebral oximetry.	**IIb**	**B**	**(456)**
Platelet concentrate should be considered in bleeding patients with a platelet count below 50 (10^9/L) or those patients on antiplatelet therapy with bleeding complications after cardiac surgery.	**IIa**	**C**	-

CPB: cardiopulmonary bypass; HCT: haematocrit; POC: point of care; PRBCs: packed red blood cells.

[a] Class of recommendation.

[b] Level of evidence.

[c] References.

6. Postoperative management

Postoperative bleeding is a common complication following open-heart surgery, primarily resulting from coagulopathies or mechanical factors. Although the risk of reoperation due to bleeding after cardiac surgery remains below 4%, more than 50% of postoperative bleeding is still due to surgically correctable causes (457). Coagulopathy is present to some extent in all patients following CPB, with drug-induced coagulopathy frequently observed due to the administration of antithrombotic therapies for various health conditions in the perioperative period. Blood component therapy, which includes PRBCs, FFP, cryoprecipitate and PLTCs, plays a vital role in managing postoperative anaemia and bleeding. The administration of these blood components should adhere to established protocols and be customized to the patient's clinical status, with special attention to maintaining appropriate HCT/Hb levels and

addressing the clinically relevant coagulopathy. If severe bleeding persists, packing and/or delayed sternal closure can be considered.

6.1 Chest tube drainage management

Effective chest tube drainage is essential in the postoperative management of patients undergoing cardiac surgery. This process involves the removal of blood, fluid and air from the chest cavity to prevent complications such as haemothorax, pneumothorax, infection and cardiac tamponade. The timing of chest tube removal is important, because premature removal can lead to retained fluids, and delayed removal can increase the risk of infection and prolong the hospital stay.

Description of the evidence

No robust data exist regarding the optimal timing or fluid output threshold for chest tube removal. Previous studies have found an association between chest tube regimens longer than 24 h and an increased need for analgesics postoperatively, which may prolong postoperative recovery. However, no significant difference in the rate of pleural effusions between the groups in these studies was observed (458-460). In a recent RCT comparing 2 fast-track chest tube removal protocols following cardiac surgery (≤ 24 h vs >24 h), provided there was no air leakage and output <200 mL within the last 4 h, there were no significant differences in the need for drainage of the pleural cavity or the requirement for analgesics (461). A high rate of effusions requiring drainage was found in both groups, and no clinical benefit of a shorter protocol could be shown; thus, further RCTs comparing fast-track with prolonged chest tube removal protocols are warranted to guide treatment interventions.

Until recently, drainage collection systems were analogue, relying on manual monitoring to evaluate air leaks and fluid characteristics. The lack of automation in these systems led to user-dependent variations in data collection and their interpretation. Digital drainage systems have revolutionized the way data are collected, providing quantitative, longitudinal measurements of both air leaks and fluid discharge (462, 463). Compared to the analogue system, the application of the digital drainage system demonstrated a significantly decreased incidence of drainage-associated complications and shortened chest tube duration in a recent single-centre RCT (464). Still, before more extensive application, these findings require confirmation by additional studies.

Blood conservation strategies in cardiac surgery have expanded to include postoperative autotransfusion of unwashed shed mediastinal blood, which has shown positive effects in reducing allogeneic PRBC transfusions (465, 466). However, concerns about inducing coagulopathy with the re-transfusion of activated and inflammatory blood have limited its use (467). In a study of 1,047 cardiac surgery patients, those assigned to an intra- and postoperative blood salvage strategy using the Haemonetics cardioPAT system experienced a significant reduction in exposure to PRBCs and slightly fewer complications compared to the traditional intraoperative CS group (468). However, a more recent study found that postoperative CS did not reduce transfusion requirements compared to intraoperative salvage alone and was associated with elevated creatine kinase levels, suggesting haemolysis and increased risk of micro fat emboli (469). These findings underscore the importance of evaluating the potential risks and benefits of postoperative cell salvage on a case-by-case basis. Although minimizing PRBC transfusions in patients experiencing significant bleeding complications in the early postoperative period can be an effective strategy, its routine use requires careful consideration.

6.2 Triggers for reintervention for bleeding

Haemodynamic instability often serves as an early warning sign for bleeding and the need for reintervention after cardiac surgery. Clinical deterioration is usually indicated by a combination of factors such as transoesophageal echocardiography findings, increased inotropic and fluid requirements, elevated central venous pressure and falling systemic blood pressure, which may suggest the development of cardiac tamponade requiring resternotomy. This situation often coincides with the need for blood product transfusions, such as FFP, cryoprecipitate, PLTCs and PRBCs. Early re-exploration is recommended to improve survival, along with the correction of acid–base disturbances, hypothermia, haemodilution, ionized calcium levels and any associated coagulopathy.

Description of the evidence

Several studies have examined the outcomes of re-exploration after cardiac surgery. A retrospective study of 209 patients who underwent re-exploration between January 2005 and December 2011 found that patients in the re-exploration group had significantly higher transfusion requirements, incidences of postoperative AKI, sternal wound and pulmonary

infections, longer ventilation times and ICU stays and higher mortality rates compared to those who were not re-explored (470). Another study analysing 3,256 patients undergoing isolated off-pump CABG from 2013 through 2020 found that the mortality rate of patients undergoing re-exploration for bleeding or tamponade was 28% (471).

The Association of Cardiothoracic Anaesthesia and Critical Care's national audit in 2018 revealed that resternotomy after cardiac surgery is associated with a prolonged stay in the ICU (median, 5 days), very high rates of PRBC transfusions (89%), renal replacement therapy (23%) and a very high mortality rate of 15% (95% CI 12.7–17.5) (472). Moreover, a retrospective analysis of 75 patients who had open-heart surgery and subsequently underwent chest re-exploration for excessive bleeding between March 2018 and March 2020 found that timely intervention and early re-exploration were associated with low mortality (473). Another study reviewing 10,070 patients found that delayed re-exploration for bleeding after cardiac surgery is associated with increased risk for morbidity and mortality, suggesting that early surgical intervention, particularly within 4 h, may improve outcomes (474). These findings highlight the importance of timely and efficient management of medical coagulopathy and the necessity of ruling out surgical bleeding in patients with intractable postoperative bleeding and normal coagulation status. The decision for re-exploration should be based on a comprehensive assessment of the patient's haemodynamic status and bleeding risk.

6.3 Transfusion triggers

Postoperative transfusion triggers are essential for optimizing patient outcomes and ensuring efficient use of blood products. These triggers should be based on a combination of clinical judgement, laboratory values and the patient's overall haemodynamic status. Individualized assessment is key, because the decision to transfuse blood should consider factors such as the patient's risk for bleeding, oxygenation status and the presence of comorbidities. For treatment recommendations, please refer to section 5.2.

6.4 Management of antiplatelet and anticoagulation treatment

The management of antiplatelet and anticoagulation treatment in the postoperative period is critical for balancing the risk of thrombosis and bleeding. Decisions regarding the continuation, modification or initiation of these therapies should be guided by a thorough evaluation of the patient's clinical history, surgical procedure and current haemodynamic and bleeding status.

Close monitoring and interdisciplinary collaboration are essential to ensure optimal patient safety and outcomes. For comprehensive guidance, please refer to section 3.2.

6.5 Venous thromboembolism prophylaxis

VTE, which encompasses deep venous thrombosis and pulmonary embolism, is a significant contributor to morbidity and mortality following cardiac surgery (475). An extensive study of nearly 400,000 patients from the US National Inpatient Sample who underwent CABG revealed an incidence of VTE of 1.3% during the hospital stay, with patients diagnosed with VTE facing a doubled adjusted risk of mortality compared to those without VTE (476). Risk factors for VTE include a history of VTE, obesity, heart failure, chronic obstructive pulmonary disease and prolonged immobilization (476). A meta-analysis comprising 16 RCTs and 49 observational studies indicated that early pharmacologic VTE prophylaxis significantly lowers the risks of pulmonary embolisms and symptomatic VTE without substantially increasing bleeding risk and its associated complications (475). For thrombosis prophylaxis, both UFH and LMWH are effective options (477). LMWH is often preferred due to its simpler administration and reduced monitoring requirements, although dose adjustments may be necessary in patients with renal impairment (478). UFH is typically chosen in scenarios with a higher bleeding risk, albeit it carries the risk of HIT (479). Given the considerable incidence and high mortality risk associated with VTE, prophylaxis with either LMWH or UFH should be initiated postoperatively as soon as it is deemed safe and continued until full mobilization is achieved.

6.6 Detection and treatment of heparin-induced thrombocytopenia

HIT is an immunologic syndrome triggered by antibodies targeting heparin and PF4. It presents clinically as severe thromboembolism due to platelet activation, resulting in consumption-driven thrombocytopenia. The diagnosis relies on the identification of heparin and/or PF4 antibodies via enzyme-linked immunosorbent assay tests and platelet serotonin-release assays, which are now available in most haematological laboratories. Second-generation tests, which focus on immunoglobin G and exclude immunoglobin M and immunoglobin A, have reduced the overdiagnosis of HIT that was initially common (480, 481). Recent studies have further stratified patients into those who are antibody-positive (HIT+) but without ongoing thrombosis (HITT-), aiding in risk profiling (482). The onset of antibody formation typically

occurs 7 to 14 days after exposure to the antigen, with antibodies persisting for up to 3 months. Consequently, the risk of HIT is up to tenfold higher in patients undergoing heparin infusion prior to surgery (483). With the greater experience of implementing alternative anticoagulants in treatment pathways, it is advisable to carefully evaluate the immediate suspension of heparin and switch to an alternative treatment, weighing the risks on a case-by-case basis (484).

Description of the evidence

Early detection and treatment of this potentially life-threatening condition should be systematically organized in steps to minimize risks: A daily platelet count should be performed as a baseline filter for early suspicion. At any confirmed sign of platelet drop, immediate cessation of heparin and its analogues should take place, and a prompt blood sample should be sent for antibody testing. In parallel, a thorough ultrasound evaluation looking for signs of thrombosis should be performed. Risk stratification should also take into consideration the DTI of the positive HIT Expert Probability or the Lillo-Le Louët score to help evaluate and time the therapy. The current body of evidence suggests replacing the 4Ts score with either the HIT Expert Probability or the Lillo-Le Louët score, both of which have proven to be more reliable and consistent (485-488). Regarding substitutes for heparin to consider when a significant risk state is detected, prospective studies have addressed bivalirudin use in CABG and valvular operations, with risks almost aligned with traditional approaches. Furthermore, recent algorithms have been proposed for managing specific risks in patients scheduled for aortic and valvular surgery (489). Bivalirudin has shown particular advantages in off-pump CABG, where it might be considered as a first-choice agent in the future to improve early patency (490). Argatroban is well-studied with a good risk profile, and ongoing trials may further increase confidence in its use and dosage. Due to the favourable safety profiles of these alternatives, strategies combining heparin with antiplatelet agents (such as tirofiban and iloprost) have become less appealing, especially because of the potential for a rebound in the immunologic profile immediately upon suspension of the antiplatelet agent. Finally, plasmapheresis has been reported in various studies as a therapeutic option for HIT, presenting mixed outcomes and numerous challenges in clinical implementation (484).

6.7 Management of bleeding and anaemia in specific patient populations

Several patient groups present unique challenges in the management of bleeding and anaemia during cardiac surgery, necessitating careful consideration of their specific needs in the perioperative period.

Jehovah's Witnesses

Jehovah's Witnesses (JWs) typically refuse allogeneic blood transfusions because of their religious beliefs, making them fully dependent on PBM interventions throughout the entire perioperative period. Most JWs accept coagulation factor concentrates and intraoperative CS, but each patient's preferences should be discussed individually. Dedicated centres have successfully performed various cardiac operations without transfusions by adhering strictly to PBM protocols at every stage. Recent studies, including a meta-analysis of 780 JW and 1182 non-JW patients undergoing elective cardiac surgery, found no significant difference in perioperative mortality or postoperative complications between the 2 groups (491-493). However, severe acute blood loss anaemia in JW patients was associated with increased 30-day and 1-year deaths (494). The evidence suggests that refusal of transfusions should not be considered an absolute contraindication for cardiac surgery in selected cases, although the inability to use allogeneic transfusions can increase the risk of death in the event of serious haemorrhagic complications (495).

Haemophilia

Patients with haemophilia, who are intrinsically prone to bleeding, pose a significant challenge for cardiac surgery. The availability of recombinant factors VII, VIII and IX has improved the surgical risk profile for these patients. A multidisciplinary team approach involving surgeons, anaesthesiologists and haematologists is essential for managing these rare cases, which should ideally be centralized in centres with specific expertise. The literature on this topic is limited, consisting mostly of retrospective reports and expert consensus papers (496-499), making it difficult to formulate generalized recommendations. Centralizing care for these patients is advised to manage the logistical challenges of administering and monitoring recombinant drugs effectively.

Recommendation Table 12. Recommendations for postoperative tube drainage management

Recommendations	Class[a]	Level[b]	Ref[c]
Tube drainage management			
Active chest tube drainage systems may be considered to reduce re-exploration and chest tube clotting.	IIb	B	(462, 463)
Shed-blood management using cell salvage should be considered in patients with excessive bleeding.	IIa	B	(468, 469)
Triggers for reintervention for bleeding			
Haemodynamic instability and/or evidence of cardiac tamponade is recommended as a trigger for re-exploration for bleeding.	I	B	(470-472)
Prompt correction of hypothermia, acid–base disturbance, coagulopathy and ionized calcium is recommended.	I	C	-
In the absence of coagulopathy, re-exploration should be considered in the context of changing the rate or the total volume of chest tube blood loss.	IIa	C	(473)
Early re-exploration for bleeding should be considered over delayed re-exploration to improve survival.	IIa	B	(474)
VTE prophylaxis			
VTE prophylaxis with LMWH should be considered after surgery as soon as there is no safety concern.	IIa	B	(475, 476)
Detection and treatment of HIT			
The HIT Expert Probability Score or the Lillo-Le Louët Score is recommended over the 4Ts[d] score to evaluate the suspicion of HIT.	I	B	(485-488)

In patients with suspected or confirmed HIT, it is recommended to stop heparin and consider non-heparin anticoagulation.	I	B	**(482-484)**
Immunoglobin G-based second-generation immunoassays are recommended to confirm diagnosis of HIT.	I	B	**(480, 481)**

HIT: heparin-induced thrombocytopenia; VTE: venous thromboembolism.

[a] Class of recommendation.

[b] Level of evidence.

[c] References.

[d] 4 Ts: (i) magnitude of thrombocytopenia; (ii) timing of thrombocytopenia with respect to heparin exposure; (iii) thrombosis or other sequelae of HIT; and (iv) likelihood of other causes of thrombocytopenia.

7. Management of haemostasis and transfusion during mechanical circulatory support

The MCS devices are crucial in maintaining cardiovascular function, playing a well-established role in treating post-cardiotomy cardiogenic shock and refractory heart failure (500-502). However, bleeding and thrombotic events are significant complications that can negatively impact patient outcomes and quality of life. Except for intra-aortic balloon pumps (IABPs) and transcatheter MCS platforms (503-505), the exposure of circulating blood to artificial surfaces typically triggers inflammatory and coagulopathic reactions. Managing anticoagulation during MCS use is complicated due to the primary patient morbidity, interactions between the patient and the MCS device, associated inflammatory cascades and other factors that contribute to haemostasis imbalances (506, 507).

Although the principles of haemostasis, anticoagulation and transfusion are similar across all MCS devices, practical management varies significantly between the different types of tMCS and dMCS (501, 502). Recently, there has been a significant paradigm shift towards a patient-specific and individualized anticoagulation monitoring strategy. This approach prioritizes the patient's coagulation profile over standard laboratory values, taking into account the overall inflammatory state, end-organ dysfunction (particularly hepatic and renal status) and the potential risks of bleeding and thrombosis. Several studies and recent guidelines recommend using both plasma-based tests to measure specific anticoagulant

effects and whole-blood tests to assess POC haemostasis (501, 502, 508, 509). Each type of monitoring test has its advantages and disadvantages, highlighting the need for a dedicated MCS team to provide individualized treatment plans.

7.1 Temporary mechanical circulatory support

The tMCS devices are essential tools in the management of patients with post-cardiotomy cardiogenic shock, which is reported to occur in less than 4% of routine adult cardiac surgical procedures. Transcatheter tMCS includes pneumatic IABP and microaxial flow pump devices (e.g. Impella), which reduce left ventricular end-diastolic pressure and improve ventricular unloading (501, 503). Several studies suggest that anticoagulation should not be mandatory for IABP and should be administered in an individualized patient context, whereas microaxial flow pump usage requires therapeutic UFH or a bicarbonate-based purge solution administered according to the manufacturer's guidelines (510, 511). Anticoagulation for post-cardiotomy extracorporeal life support (PC-ECLS) devices, which include the Tandemheart, Centrimag and Rotaflow centrifugal systems (500), is mandatory. The bridging role of PC-ECLS before and after a heart transplant or a left ventricular assist device (LVAD) implant is also well established (508, 509, 512, 513). Bleeding remains the most common complication and is related mainly to the operation and the coagulopathy associated with CPB utilization. Many patients are transitioned from CPB to PC-ECLS while receiving an anticoagulant, resulting in limited opportunity to achieve optimal haemostasis. Additionally, the coagulopathy associated with ECLS is well-recognized and frequently leads to severe bleeding or significant thrombosis, making diagnosing and treating these disorders, which can be complex and at times, non-intuitive (514, 515), more difficult. A PC-ECLS reoperation for bleeding occurs in 11% to 62% of patients, requiring the transfusion of blood products, which increases the economic burden, morbidity and mortality. The optimal blood product replacement strategy for PC-ECLS is not well defined and is based on clinical experience and local centre guidelines. Surveys of ECLS centres identified significant variation in blood product transfusion triggers, with HCT and platelet values ranging between 25% and 40% and 50 000 to 200 000 x 10^9/L, respectively (516, 517). Various centres are re-evaluating transfusion triggers to determine whether conservative strategies in conjunction with adequate systemic and regional oxygen delivery values are potentially safer.

Perioperative anticoagulation, bleeding and thrombosis management

When transitioning from CPB to PC-ECLS, it is important to note that alterations in haemostasis differ between patients undergoing cardiac surgery with CPB and those with tMCS. Among the most significant factors are the duration of support and the physiological state of the patient before transition to tMCS. Therefore, the monitoring, workup and treatment of coagulopathy should consider these factors and be based on specific guidelines according to the type of patient and support.

Several reports suggest that partial reversal of UFH with protamine improves postoperative bleeding and outcomes (507). It is recommended that anticoagulation be discontinued until haemostasis is achieved (518, 519). The administration of UFH may be delayed up to 24 to 48 h if coagulopathic bleeding persists and if it appears that bolus dosing is not mandatory (507-509, 512, 518, 519). If postoperative PC-ECLS is required, UFH should be administered prior to cannulation at the discretion of the treatment team. Several institutions report switching from UFH to bivalirudin when PC-ECLS support is required for more than 48 h (507, 509). Both bleeding and thrombotic complications are associated with adverse outcomes, and no coagulation test is currently predictive of these events. In cases of massive bleeding, it is considered reasonable to withhold UFH for 4 to 6 h if bleeding is controllable and for up to 12 h if bleeding persists. In extreme cases, additional pharmacologic agents including PCC and rFVIIa may be used. Surgical site bleeding can be controlled locally by compressive manoeuvres or procoagulant topical products. The use of prophylactic TXA or EACA, each of which inhibits plasminogen conversion and fibrinolysis, is not currently proven to be efficient. Frequent coagulation and circuit monitoring for thrombosis are recommended to guide the urgency of restarting UFH. Heparin-free PC-ECLS circuits are increasingly being used in patients at risk for bleeding, with various centres reporting outcomes comparable to those of standard circuits and anticoagulation regimens in terms of survival after decannulation, after discharge, bleeding, thromboembolic complications and transfusion requirements (509). Monitoring UFH anticoagulation can be achieved through serial measurements using a time-based strategy (aPTT and ACT) and anti-FXa (513, 520-523). Comparatively, the anti-FXa-based anticoagulation strategy has suggested less bleeding without an increase in thrombotic events (521, 522), offering crucial insights into the real-world effects of UFH (524, 525).

Recommendation Table 13. Recommendations for blood product replacement strategies in centrifugal temporary mechanical circulatory support

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that each centre develop an inter-disciplinary algorithm/protocol for transfusion, anticoagulation and thrombosis treatment.	I	C	-
Transfusing PRBCs to maintain haemoglobin levels between 70 and 90 g/L should be considered.	IIa	C	(517)
It is recommended that a blood count, plasma fibrinogen level, INR, AT, D-dimer, free haemoglobin in plasma and a viscoelastic POC test be performed at least daily or more frequently in patients with coagulopathy.	I	C	(506)
Maintaining platelet counts above 100 x 10^9/l in bleeding patients and above 50 x 10^9 /l in non-bleeding patients should be considered.	IIa	C	(517)
Maintaining a plasma fibrinogen level above 1.5 g/L in bleeding patients or before a surgical intervention is recommended.	I	C	(517)

AT: antithrombin; INR: international normalized ratio; POC: point-of-care; PRBC: packed red blood cells; tMCS: temporary mechanical circulatory support.

[a] Class of recommendation.

[b] Level of evidence.

[c] References.

Recommendation Table 14. Recommendation for transcatheter pneumatic and axial flow temporary mechanical temporary support anticoagulation post-cardiac surgery

Recommendations	Class[a]	Level[b]	Ref[c]
Therapeutic anticoagulation is not routinely recommended in patients with an IABP.	III	C	(500, 503)
Therapeutic anticoagulation is recommended in patients with an mAFP.	I	B	(500, 504, 505)

IABP: intra-aortic balloon pump; mAFP: microaxial flow pump.

[a] Class of recommendation.

[b] Level of evidence.
[c] References.

Recommendation Table 15. Recommendations for perioperative centrifugal temporary mechanical circulatory support/post-cardiotomy extracorporeal life support anticoagulation, bleeding and thrombosis management

Recommendations	Class[a]	Level[b]	Ref[c]
Intraoperative anticoagulation			
The use of UFH as the primary anticoagulant for PC-ECLS is recommended.	I	B	(506, 513, 516, 517)
Delaying UFH therapy during the initiation of PC-ECLS until satisfactory haemostasis is achieved should be considered.	IIa	B	(518, 519)
Procoagulant interventions, guided by viscoelastic POC tests, may be considered in cases of significant non-surgical bleeding.	IIb	C	(518, 519)
Postoperative anticoagulation			
Monitoring UFH anticoagulation using serial measurements of aPTT and/or the anti-Xa assay is recommended.	I	B	(506, 513, 520-522)
Reducing the level of anticoagulation in the event of a new episode of bleeding, as long the pressure and flow values of the tMCS are adequate, is recommended.	I	C	(509)

aPTT: activated partial thromboplastin time; PC-ECLS: post-cardiotomy extracorporeal life support; POC: point-of-care; tMCS: temporary mechanical circulatory support; UFH: unfractionated heparin.
[a] Class of recommendation.
[b] Level of evidence.
[c] References.

7.2 Durable mechanical circulatory support

The increasing incidence of patients suffering from end-stage heart failure refractory to optimal medical and interventional therapies has been paralleled by increasing experience with dMCS devices and new/total artificial heart technology capable of supporting the left, right or both ventricles (500, 501, 526, 527). Although still approved for clinical use, first-

generation pulsatile dMCS devices are now rarely used due to advances in second-generation continuous axial flow and third-generation centrifugal dMCS devices. In addition to circuit-related coagulopathy, other mechanisms associated with increased bleeding in dMCS include acquired von Willebrand syndrome, development of arteriovenous fistulae secondary to loss of pulsatile flow and gastrointestinal angiodysplasia due to increased angiogenesis. Perioperative anticoagulation management of dMCS requires specific considerations, whereas long-term antithrombotic therapy can be standardized according to patient profiles, device type, pump flow, coagulation testing and institutional experience.

Perioperative anticoagulation, bleeding and thrombosis management

It is recommended that an elective dMCS implant be preceded by normalization of coagulation status to minimize the risk of perioperative bleeding requiring blood product transfusion. The risk of subsequent systemic volume overload, right ventricular failure, possible surgical re-exploration and other significant morbidities should be minimized preoperatively. If a dMCS implant is preceded by extracorporeal tMCS, the administration of intravenous UFH is recommended. Intraoperatively, therapeutic anticoagulation with UFH is recommended, which can be completely reversed after the procedure. However, off-pump dMCS implant techniques and the continuous postoperative need of PC-ECLS may warrant a reduction of the UFH dose. For all devices, initiation of therapeutic anticoagulation may be delayed up to 8 h postoperatively if bleeding is greater than 50 ml/h (502). Several reports recommend that intravenous UFH doses should be adjusted to achieve an initial aPTT target of 40 s and a subsequent target of 55–60 s within the next 48–72 h (502). If HIT is confirmed or suspected, the intravenous use of a DTI may be considered. An OAC with VKAs and antiplatelet therapy should be initiated once the clinical condition is considered stable and oral intake is established. The target INR is dMCS device-specific and ranges from 2.0 to 3.0. The need for additional ASA should be determined by the patient profile and device manufacturer specifications. The use of DOACs is not currently recommended.

Pump thrombosis is a devastating complication. Acute catastrophic pump thrombosis usually results from red thrombi, which consist primarily of red blood cells trapped in a fibrinous mesh, whereas subacute white thrombi result from platelet aggregates secondary to dMCS shear stress. UFH and LMWH can be used as primary anticoagulants, whereas the roles of GPIIb/IIIa inhibitors and DTIs are not established. Patients with refractory haemolysis

and who are not considered candidates for urgent device exchange may be considered for high-risk thrombolysis if no other anticoagulation options are available. Out-of-hospital anticoagulation includes discontinuation of VKA while bridging with UFH or LMWH if the INR is less than 2 for non-cardiac surgery cases. Frequent anticoagulation and haemolysis monitoring using home INR devices and local facilities under the supervision of dedicated dMCS teams who can guide strict anticoagulation management isrecommended. The Aries-HM3 (Antiplatelet Removal and Hemocompatibility Events With the HeartMate 3 Pump) trial, an international, randomized, double-blind, placebo-controlled study of ASA (100 mg/day) versus placebo with VKA therapy in patients with advanced heart failure and an LVAD, was conducted across 51 centres and included 589 patients. The researchers found that in patients treated with a fully magnetically levitated LVAD, avoiding ASA as part of an antithrombotic regimen, which includes VKA, is not inferior to a regimen containing ASA, does not increase the risk of thromboembolism and is associated with a reduction in bleeding events (528). However, confirmatory studies are needed before this option can be introduced as the standard of care.

Recommendation Table 16. Recommendations for perioperative anticoagulation, bleeding and thrombosis management during durable mechanical circulatory support

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that an elective dMCS implant be performed in the context of a normal preoperative coagulation profile, if possible.	I	C	-
Initiation of UFH is recommended shortly after the dMCS is implanted.	I	C	-
The initiation of oral antithrombotic therapies (VKAs and antiplatelet agents) after the dMCS is implanted is recommended as soon as there is no longer a risk of bleeding and oral intake is established.	I	C	**(528)**
DOACs are not recommended in patients with dMCS.	III	C	-

DOAC: direct oral anticoagulant; dMCS: durable mechanical circulatory support; VKA: vitamin-K antagonist; UFH: unfractionated heparin.

[a] Class of recommendation.

[b] Level of evidence.
[c] References.

Recommendation Table 17. Recommendations for haemostasis and transfusion in haemorrhagic and thrombotic complications during durable mechanical circulatory support

Recommendations	Class[a]	Level[b]	Ref[c]
Discontinuation of any anticoagulation in case of severe bleeding and correction of the detected coagulopathy is recommended.	I	C	-
When thrombi are detected in the circuit, it is recommended to undertake corrective actions that should include adjusting anticoagulation and/or exchanging the component of the circuit.	I	C	**(506, 526)**
It is recommended that a blood count, plasma fibrinogen level, INR, AT, D-dimer, free Hb in plasma and a viscoelastic POC test be performed at least daily in the early postoperative period and less frequently in stable patients.	I	C	-

AT: antithrombin; Hb: haemoglobin; INR: international normalized ratio; POC: point-of-care.
[a] Class of recommendation.
[b] Level of evidence.
[c] References.

8. Comprehensive institutional patient blood management programme

The benefits of structured institutional and national PBM programmes are well-documented: They include significant reductions in empirical blood product transfusions, transfusion-related costs and transfusion-related adverse events (408, 529, 530). However, evidence on initiating safe and sustainable PBM programmes is limited, consisting primarily of descriptive expert reports (531-535).

These reports highlight the importance of a collaborative team approach and the progressive implementation of evidence-based protocols tailored to institutional capabilities and infrastructure. Key steps for implementing a structured PBM programme include securing support from health system leadership and stakeholders (local and regional), establishing a

PBM coordinator, fostering collaboration among multidisciplinary team members, investing in education and data management, incorporating best practice clinical guidelines into institutional protocols, creating institution-specific standard operating procedures and vigorously pursuing compliance, quality assurance and improvement and clinical governance feedback for all involved (529, 532).

The organization of PBM programmes should also encompass cost-effective and evidence-based anaemia management, effective multidisciplinary blood conservation strategies, optimization of haemostasis and patient-centred care (536). Challenges in initiating new PBM programmes include time and human-resource constraints, apprehension or reluctance to adopt new guidelines and the lack of appropriate post-implementation monitoring systems (537, 538). Key clinical end points for evaluating PBM programmes can include length of hospital stay, mortality and transfusion reaction events. The use of electronic medical records can facilitate the evaluation of adherence to and the effects of PBM implementation (534).

To successfully introduce PBM strategies, the implementation team should start with manageable interventions, continuously assess performance and conduct regular evaluations to ensure quality and cost-effectiveness. Implementing a blood use initiative, focusing on transfusion outcomes and adopting blood conservation techniques can significantly enhance postoperative outcomes, reduce health-care costs and minimize adverse events (539, 540). Collaborative efforts in guideline development and monitoring perioperative transfusion rates as a quality metric have been linked to a notable decrease in blood product utilization and improvements in perioperative outcomes, without increasing mortality risks (539, 540).

Recommendation Table 18. Recommendations for organization of an institutional patient blood management programme

Recommendations	Class[a]	Level[b]	Ref[c]
A collaborative approach that includes a PBM coordinator leading a multidisciplinary team is recommended.	**I**	**B**	**(532, 534, 537)**

The progressive implementation of evidence-based protocols that are tailored to institutional capabilities and infrastructure is recommended.	I	B	(532, 534, 537)
Quality assurance initiatives that systematically measure PBM components, along with quality improvement programmes, are recommended.	I	B	(539, 540)

PBM: patient blood management.

[a] Class of recommendation.

[b] Level of evidence.

[c] References.

9. Knowledge gaps

The management of a patient's own blood in cardiac surgery is characterized by complex challenges encompassing each stage of the surgical timeline. Notably, the treatment of preoperative anaemia is paramount in ongoing efforts to significantly improve clinical outcomes. However, the definition of anaemia itself, which traditionally proposes different levels for males and females, poses some challenges. In fact, the concept of tolerating a lower level of "normality" in female subjects does not rely on physiologic evidence of different cellular pathways regarding oxygen utilization between genders. A new level of consciousness at present suggests that the 2 levels should be unified in the near future. Additionally, greater emphasis should be placed on education and efforts to uncover and treat anaemia in a more comprehensive manner, beyond Hb levels only. Moreover, the current evidence underscores the necessity for individualized transfusion strategies. The findings from the TITRe2 (UK Transfusion Indication Threshold Reduction) and TRICS III trials suggest that these strategies should be customized according to patient age, advocating for a personalized approach for those with mild preoperative anaemia. Treatments with iron and EPO have proven advantageous in reducing reliance on blood transfusions. It is crucial, however, to perform an economic assessment in this context, ensuring that the value of these treatments justifies the investment. In addition, urgent research is warranted to compare prophylactic platelet transfusions with no transfusion or alternative treatments across all ages, considering different platelet thresholds before planned and emergency operations.

When considering intraoperative management, the selection of an appropriate cardioplegia solution has yet to be determined based on conclusive evidence. To date, RCTs have not clearly favoured blood cardioplegia over crystalloid cardioplegia, possibly due to the influence of ultrafiltration techniques. Furthermore, it is an ongoing endeavour to identify which patient subgroups are most vulnerable to adverse outcomes from decreases in HCT and its repercussions on coagulation and haemostasis. Establishing a definitive CPB haemodilution threshold that requires a transfusion also remains an area of active research. In addition, the role of an albumin solution in contemporary adult cardiac surgery with CPB remains unclear due to advanced technologies. This factor highlights the need for further research to definitively establish its efficacy and safety.

When transitioning to topics of procoagulant medication, whereas antifibrinolytic therapy has gained wide acceptance as a gold standard of care, the quest to find dosages and applications for TXA that are effective yet safe is crucial. Furthermore, the current role of aprotinin continues to be debated within the medical community, as does the influence of decreased FXIII activity on perioperative bleeding in cardiac surgery. Equally important is the need for further research into the efficacy of innovative cell-saving technologies that safeguard platelet function and fibrinogen. This issue is particularly pertinent when considering the standardization of perioperative anticoagulation, especially for patients at risk of HIT.

Postoperative care also poses numerous questions, particularly concerning the ideal approach to haemostatic therapy and the appropriate targets for interventions in clinically relevant bleeding patients. Moreover, exploring alternatives to blood products that could reduce patient immunologic effects is critical for future research.

When studying postoperative procedures, the strategies concerning chest tube drainage and the criteria for surgical re-exploration continue to be grounded in the clinician's expertise, with a pressing need for evidence-based algorithms. Such algorithms would benefit greatly from validation against established clinical markers.

In the broader scope of MCS, whether temporary and/or durable, a significant gap exists in the evidence base for anticoagulation protocols. Hence, well-designed and conducted RCTs are urgently needed to scrutinize the variety of protocols currently in international use.

Finally, at the institutional level, the establishment of comprehensive patient blood management programmes has not been guided by rigorous clinical trials but rather by

consensus among experts. Nevertheless, the potential role of artificial intelligence-derived algorithms and clinical decision support systems in the decision-making process for managing bleeding from the preoperative through the postoperative periods is a prospect filled with promise and deserving of a thorough investigation.

10. Key messages

Patient blood management in cardiac surgery is a comprehensive, multidisciplinary approach that necessitates collaboration among surgeons, anaesthetists, clinical perfusionists, intensivists and patients. The goal of this updated guideline, developed collaboratively by EACTS and EACTAIC in collaboration with EBCP, is to integrate new evidence that has emerged since the previous publication to provide updated, evidence-based recommendations where possible. It underscores the importance of teamwork in PBM and advocates for broader collaborations with other societies and patient representatives to enhance patient care and outcomes. Moreover, it highlights the need for a better understanding of the mechanisms of coagulopathy, the identification of clinical parameters associated with poor prognosis and the development of a set of recommendations to prevent and treat bleeding complications and improve clinical outcomes (Fig. 3).

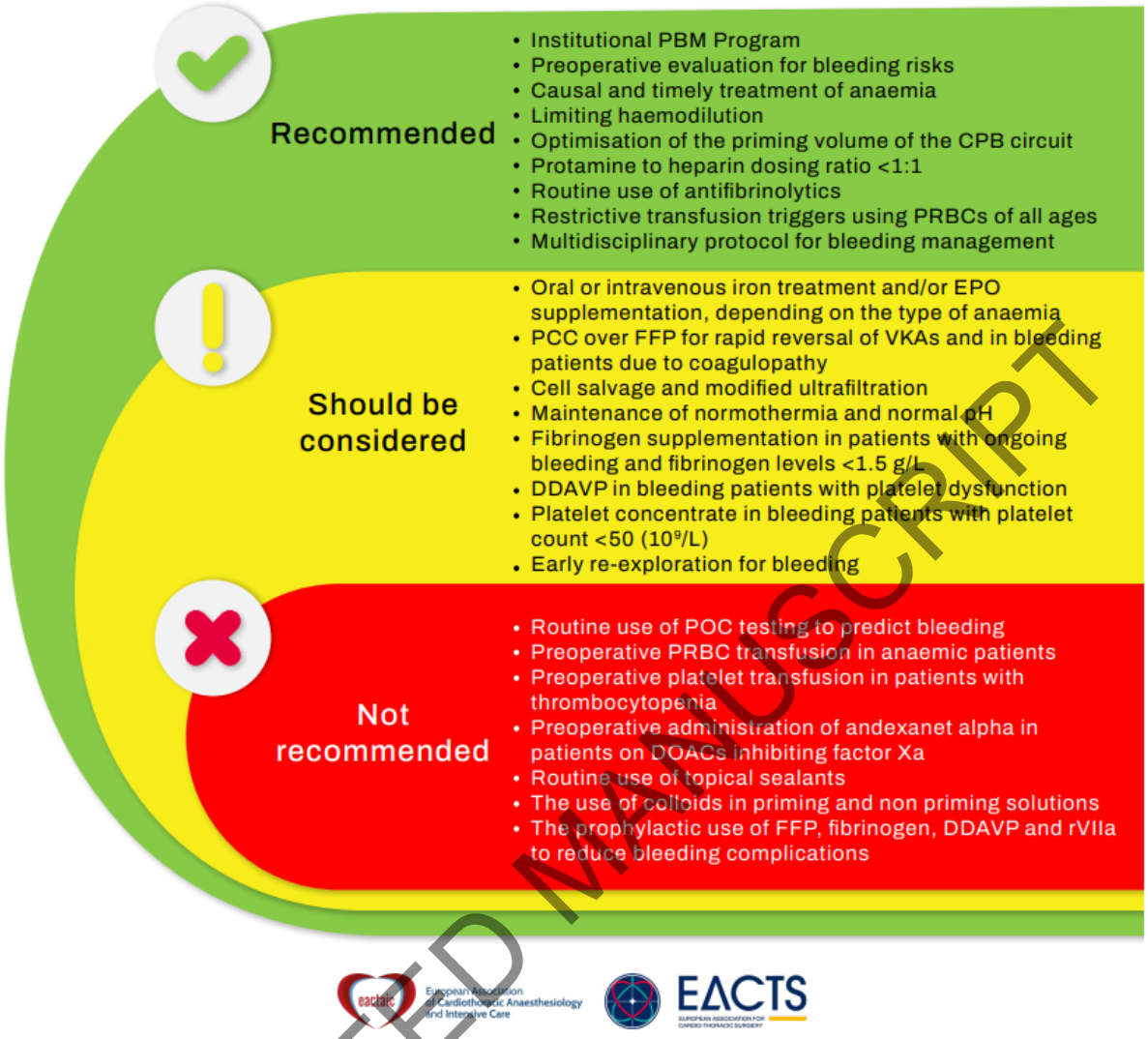


Figure 3. Key messages from the Multidisciplinary Patient Blood Management Guidelines for Adult Cardiac Surgery. CPB: cardiopulmonary bypass; DDAVP: desmopressin; DOAC: direct oral anticoagulant; EPO: erythropoietin; FFP: fresh-frozen plasma; PBM: patient blood management; PCC: prothrombin complex concentrate; POC: point-of-care; PRBCs: packed red blood cells; rFVIIa: recombinant factor VIIa; VKAs: vitamin-K antagonists.

Timely diagnosis and treatment of anaemia, thrombocytopenia and various coagulopathies are crucial for preventing bleeding complications. These conditions require comprehensive assessment and interventions before hospital admission because delays or misdiagnoses can significantly limit the ability of the healthcare team to intervene effectively. Therefore, patient-centred care in the outpatient clinic in preparation for cardiac surgery is recommended as a critical component of routine clinical management. This approach should address the patient's physical and psychological needs alongside the treatment interventions.

Patients should be informed about and included in the PBM programme as much as possible because preparation for discharge should begin upon indication for cardiac surgery.

Our objective was to combine new findings with existing knowledge to offer evidence-based recommendations for PBM, encompassing blood-conservation strategies, preoperative optimization, intraoperative interventions and postoperative management of bleeding disorders. Although the focus on bleeding-related end points has limited our reference list, the absence of a standardized definition for bleeding outcomes underscores the need for consensus in future studies. Although several aspects of PBM are supported by moderate-quality evidence, further large-scale RCTs are necessary to enhance the evidence base of this guideline.

It is important to note that a significant portion of the studies referenced in this guideline, particularly those reporting haemovigilance data, are from non-European countries. Given the differences in national regulations for PRBC processing and leucodepletion, the applicability of non-European data to European patients remains uncertain. Through this updated guideline, our goal is to contribute to the establishment of European standards for blood product quality, a European haemovigilance database and comprehensive standards for PBM irrespective of country of clinical practice.

11. Supplementary data

Supplementary data are available online.

12. Data availability statement

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST

Filip Casselman reports payment (to the institution) from Abbott and Edwards Lifesciences for lecturing; Filip Casselman reports being Edwards Lifesciences Residents Course Director (payment to the institution); Filip Casselman also reports a leadership role in EACTS as Councillor and Chair of the Acquired Cardiac Disease Domain. Aamer Ahmed reports research funding from LFB Pharma (payment made to the institution), payment from AstraZeneca for taking part in an advisory board, and participation in meetings sponsored by Medtronic; Aamer Ahmed also reports a leadership role in ESAIC as Council UK Representative (unpaid). Gabor Erdoes reports receiving an honorarium for a lecture for CSL Behring; Gabor Erdoes also reports a leadership role in EACTAIC as Guideline Committee Chair and Co-Chair of the Transfusion and Hemostasis Subcommittee. Juan Blanco Morillo reports participation in ECMO trainings, talks and workshops sponsored by EUROSETS and Abbott, and scientific outreach activities sponsored by TERUMO (Wetlab); Juan Blanco Morillo reports consulting fees from Livanova for MDR strategy and for one event on AI implementation in HLM; Juan Blanco Morillo also reports a role in AEP (Spanish perfusion association) as Continuous Training delegate (unpaid) and in ICEBP International Council for Evidence-Based Perfusion (AmSECT) as ICEBP Steering Committee Normothermic Regional Perfusion Submcommitee Coordinator (unpaid). Anders Jeppsson reports direct personal consulting fees from AstraZeneca, Pharmacosmos, Novo Nordisk, Werfen, and LFB Biotechnologies, and honoraria from Bayer and Boehringer-Ingelheim; Anders Jeppsson also reports grants from the Swedish Heart-Lung Foundation and from the Swedish State (both to the institution). Milan Milojevic reports participation in meeting sponsored by Corcym in relation to ERAS and participation in meeting sponsored by Medtronic in relation to CPB. Milan Milojevic also reports a role of Guidelines Program Director at EACTS. Erik Ortmann reports direct personal consulting fees from Haemonetics GmbH in relation to Cell Saver, Clotpro.

ACKNOWLEDGEMENTS

We would like to extend our sincere gratitude to Giulia Zuodar, the Guidelines Programme Manager, Deirbhile McQuillan, Managing Editor at EACTS, and Ash Merrifield, Publication Director at EACTS, for their invaluable support during the development process.

FUNDING

This article was produced by and is the sole responsibility of the European Association for Cardio-Thoracic Surgery and the European Association of Cardiothoracic Anaesthesiology and Intensive Care.

13. References

1. Pagano D, Milojevic M, Meesters MI, Benedetto U, Bolliger D, von Heymann C, et al. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. Eur J Cardiothorac Surg. 2018;53(1):79-111.
2. Sousa-Uva M, Head SJ, Thielmann M, Cardillo G, Benedetto U, Czerny M, et al. Methodology manual for European Association for Cardio-Thoracic Surgery (EACTS) clinical guidelines. Eur J Cardiothorac Surg. 2015;48(6):809-16.
3. Shaneyfelt TM, Centor RM. Reassessment of clinical practice guidelines: go gently into that good night. Jama. 2009;301(8):868-9.
4. Böhmer AB, Wappler F, Zwissler B. Preoperative risk assessment--from routine tests to individualized investigation. Dtsch Arztebl Int. 2014;111(25):437-45; quiz 46.
5. Matejic-Spasic M, Hassan K, Thielmann M, Geidel S, Storey RF, Schmoeckel M, et al. Management of perioperative bleeding risk in patients on antithrombotic medications undergoing cardiac surgery-a systematic review. J Thorac Dis. 2022;14(8):3030-44.
6. Sousa-Uva M, Head SJ, Milojevic M, Collet JP, Landoni G, Castella M, et al. 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg. 2018;53(1):5-33.
7. Blome M, Isgro F, Kiessling AH, Skuras J, Haubelt H, Hellstern P, et al. Relationship between factor XIII activity, fibrinogen, haemostasis screening tests and postoperative bleeding in cardiopulmonary bypass surgery. Thromb Haemost. 2005;93(6):1101-7.
8. Bosch Y, Al Dieri R, ten Cate H, Nelemans P, Bloemen S, Hemker C, et al. Preoperative thrombin generation is predictive for the risk of blood loss after cardiac surgery: a research article. J Cardiothorac Surg. 2013;8:154.
9. Karlsson M, Ternström L, Hyllner M, Baghaei F, Nilsson S, Jeppsson A. Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: a prospective observational study. Transfusion. 2008;48(10):2152-8.
10. Ranucci M, Jeppsson A, Baryshnikova E. Pre-operative fibrinogen supplementation in cardiac surgery patients: an evaluation of different trigger values. Acta Anaesthesiol Scand. 2015;59(4):427-33.
11. 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(4):1199-206.
12. Gielen C, Dekkers O, Stijnen T, Schoones J, Brand A, Klautz R, et al. The effects of pre- and postoperative fibrinogen levels on blood loss after cardiac surgery: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2014;18(3):292-8.
13. Essa Y, Zeynalov N, Sandhaus T, Hofmann M, Lehmann T, Doenst T. Low Fibrinogen Is Associated with Increased Bleeding-Related Re-exploration after Cardiac Surgery. Thorac Cardiovasc Surg. 2018;66(8):622-8.
14. Petricevic M, Petricevic M, Pasalic M, Golubic Cepulic B, Raos M, Vasicek V, et al. Bleeding risk stratification in coronary artery surgery: the should-not-bleed score. J Cardiothorac Surg. 2021;16(1):103.
15. Liu X, Zhang W, Chen N, Wang L, Wang S, Yu Y, et al. Can Preoperative C-Reactive Protein Predict Bleeding After On-Pump Coronary Artery Bypass Grafting? Ann Thorac Surg. 2020;109(2):541-6.
16. Alagha S, Songur M, Avci T, Vural K, Kaplan S. Association of preoperative plasma fibrinogen level with postoperative bleeding after on-pump coronary bypass surgery: does

plasma fibrinogen level affect the amount of postoperative bleeding? Interact Cardiovasc Thorac Surg. 2018;27(5):671-6.
17. Lopes CT, Dos Santos TR, Brunori EH, Moorhead SA, Lopes Jde L, Barros AL. Excessive bleeding predictors after cardiac surgery in adults: integrative review. J Clin Nurs. 2015;24(21-22):3046-62.
18. Karkouti K, O'Farrell R, Yau TM, Beattie WS. Prediction of massive blood transfusion in cardiac surgery. Can J Anaesth. 2006;53(8):781-94.
19. Ranucci M, Baryshnikova EFTS, Clinical Outcome Research Score G. The interaction between preoperative platelet count and function and its relationship with postoperative bleeding in cardiac surgery. Platelets. 2017;28(8):794-8.
20. Mion S, Duval B, Besnard T, Darné B, Mouton C, Jecker O, et al. U-shaped relationship between pre-operative plasma fibrinogen levels and severe peri-operative bleeding in cardiac surgery. Eur J Anaesthesiol. 2020;37(10):889-97.
21. Fitzgerald J, McMonnies R, Sharkey A, Gross PL, Karkouti K. Thrombin generation and bleeding in cardiac surgery: a clinical narrative review. Can J Anaesth. 2020;67(6):746-53.
22. Monroe DM, Hoffman M, Roberts HR. Platelets and thrombin generation. Arterioscler Thromb Vasc Biol. 2002;22(9):1381-9.
23. Coakley M, Hall JE, Evans C, Duff E, Billing V, Yang L, et al. Assessment of thrombin generation measured before and after cardiopulmonary bypass surgery and its association with postoperative bleeding. J Thromb Haemost. 2011;9(2):282-92.
24. Lin Y, Sun Y, Dai Y, Sun W, Zhu X, Liu H, et al. A "signal-on" chemiluminescence biosensor for thrombin detection based on DNA functionalized magnetic sodium alginate hydrogel and metalloporphyrinic metal-organic framework nanosheets. Talanta. 2020;207:120300.
25. Moorlag M, Schurgers E, Krishnamoorthy G, Bouwhuis A, Lindhout T, Kelchtermans H, et al. Near-Patient Thrombin Generation in Patients Undergoing Elective Cardiac Surgery. J Appl Lab Med. 2017;1(6):613-25.
26. Reinhöfer M, Brauer M, Franke U, Barz D, Marx G, Lösche W. The value of rotation thromboelastometry to monitor disturbed perioperative haemostasis and bleeding risk in patients with cardiopulmonary bypass. Blood Coagul Fibrinolysis. 2008;19(3):212-9.
27. Petricevic M, Biocina B, Milicic D, Konosic S, Svetina L, Lekić A, et al. Bleeding risk assessment using whole blood impedance aggregometry and rotational thromboelastometry in patients following cardiac surgery. J Thromb Thrombolysis. 2013;36(4):514-26.
28. Petricevic M, Kopjar T, Biocina B, Milicic D, Kolic K, Boban M, et al. The predictive value of platelet function point-of-care tests for postoperative blood loss and transfusion in routine cardiac surgery: a systematic review. Thorac Cardiovasc Surg. 2015;63(1):2-20.
29. Corredor C, Wasowicz M, Karkouti K, Sharma V. The role of point-of-care platelet function testing in predicting postoperative bleeding following cardiac surgery: a systematic review and meta-analysis. Anaesthesia. 2015;70(6):715-31.
30. Petricevic M, Konosic S, Biocina B, Dirkmann D, White A, Mihaljevic MZ, et al. Bleeding risk assessment in patients undergoing elective cardiac surgery using ROTEM(®) platelet and Multiplate(®) impedance aggregometry. Anaesthesia. 2016;71(6):636-47.
31. Petricevic M, Knezevic J, Biocina B, Mikus M, Konosic L, Rasic M, et al. Association among Clopidogrel Cessation, Platelet Function, and Bleeding in Coronary Bypass Surgery: An Observational Trial. Thorac Cardiovasc Surg. 2021;69(7):630-8.

32. Petricevic M, Biocina B, Zrno Mihaljevic M, Kolic K. Association between adenosine diphosphate-induced platelet aggregation and bleeding outcome in coronary artery surgery. J Cardiothorac Vasc Anesth. 2014;28(6):e58-9.
33. Petricevic M, Biocina B, Milicic D, Konosic S, Ivancan V, Milosevic M, et al. Bleeding risk assessment using multiple electrode aggregometry in patients following coronary artery bypass surgery. J Thromb Thrombolysis. 2013;35(1):31-40.
34. Kwak YL, Kim JC, Choi YS, Yoo KJ, Song Y, Shim JK. Clopidogrel responsiveness regardless of the discontinuation date predicts increased blood loss and transfusion requirement after off-pump coronary artery bypass graft surgery. J Am Coll Cardiol. 2010;56(24):1994-2002.
35. Ranucci M, Colella D, Baryshnikova E, Di Dedda U. Effect of preoperative P2Y12 and thrombin platelet receptor inhibition on bleeding after cardiac surgery. Br J Anaesth. 2014;113(6):970-6.
36. Malm CJ, Hansson EC, Åkesson J, Andersson M, Hesse C, Shams Hakimi C, et al. Preoperative platelet function predicts perioperative bleeding complications in ticagrelor-treated cardiac surgery patients: a prospective observational study. Br J Anaesth. 2016;117(3):309-15.
37. Mahla E, Prueller F, Farzi S, Pregartner G, Raggam RB, Beran E, et al. Does Platelet Reactivity Predict Bleeding in Patients Needing Urgent Coronary Artery Bypass Grafting During Dual Antiplatelet Therapy? Ann Thorac Surg. 2016;102(6):2010-7.
38. Di Dedda U, Ranucci M, Baryshnikova E, Castelvecchio S. Thienopyridines resistance and recovery of platelet function after discontinuation of thienopyridines in cardiac surgery patients. Eur J Cardiothorac Surg. 2014;45(1):165-70.
39. Mahla E, Suarez TA, Bliden KP, Rehak P, Metzler H, Sequeira AJ, et al. Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. Circ Cardiovasc Interv. 2012;5(2):261-9.
40. Afshari A, Wikkelsø A, Brok J, Møller AM, Wetterslev J. Thrombelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. Cochrane Database Syst Rev. 2011(3):Cd007871.
41. Wikkelsoe AJ, Afshari A, Wetterslev J, Brok J, Moeller AM. Monitoring patients at risk of massive transfusion with Thrombelastography or Thromboelastometry: a systematic review. Acta Anaesthesiol Scand. 2011;55(10):1174-89.
42. Deppe AC, Weber C, Zimmermann J, Kuhn EW, Slottosch I, Liakopoulos OJ, et al. Point-of-care thromboelastography/thromboelastometry-based coagulation management in cardiac surgery: a meta-analysis of 8332 patients. J Surg Res. 2016;203(2):424-33.
43. Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. Anaesthesia. 2017;72(4):519-31.
44. Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. Cochrane Database Syst Rev. 2016;2016(8):Cd007871.
45. Serraino GF, Murphy GJ. Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis. Br J Anaesth. 2017;118(6):823-33.

46. Lodewyks C, Heinrichs J, Grocott HP, Karkouti K, Romund G, Arora RC, et al. Point-of-care viscoelastic hemostatic testing in cardiac surgery patients: a systematic review and meta-analysis. Can J Anaesth. 2018;65(12):1333-47.
47. Li C, Zhao Q, Yang K, Jiang L, Yu J. Thromboelastography or rotational thromboelastometry for bleeding management in adults undergoing cardiac surgery: a systematic review with meta-analysis and trial sequential analysis. J Thorac Dis. 2019;11(4):1170-81.
48. Meco M, Montisci A, Giustiniano E, Greco M, Pappalardo F, Mammana L, et al. Viscoelastic Blood Tests Use in Adult Cardiac Surgery: Meta-Analysis, Meta-Regression, and Trial Sequential Analysis. J Cardiothorac Vasc Anesth. 2020;34(1):119-27.
49. Santos AS, Oliveira AJF, Barbosa MCL, Nogueira J. Viscoelastic haemostatic assays in the perioperative period of surgical procedures: Systematic review and meta-analysis. J Clin Anesth. 2020;64:109809.
50. Deppe AC, Arbash W, Kuhn EW, Slottosch I, Scherner M, Liakopoulos OJ, et al. Current evidence of coronary artery bypass grafting off-pump versus on-pump: a systematic review with meta-analysis of over 16,900 patients investigated in randomized controlled trials†. Eur J Cardiothorac Surg. 2016;49(4):1031-41; discussion 41.
51. Dardashti A, Ederoth P, Algotsson L, Brondén B, Bjursten H. Incidence, dynamics, and prognostic value of acute kidney injury for death after cardiac surgery. J Thorac Cardiovasc Surg. 2014;147(2):800-7.
52. Biancari F, Brascia D, Onorati F, Reichart D, Perrotti A, Ruggieri VG, et al. Prediction of severe bleeding after coronary surgery: the WILL-BLEED Risk Score. Thromb Haemost. 2017;117(3):445-56.
53. Vuylsteke A, Pagel C, Gerrard C, Reddy B, Nashef S, Aldam P, et al. The Papworth Bleeding Risk Score: a stratification scheme for identifying cardiac surgery patients at risk of excessive early postoperative bleeding. Eur J Cardiothorac Surg. 2011;39(6):924-30.
54. Alghamdi AA, Davis A, Brister S, Corey P, Logan A. Development and validation of Transfusion Risk Understanding Scoring Tool (TRUST) to stratify cardiac surgery patients according to their blood transfusion needs. Transfusion. 2006;46(7):1120-9.
55. Ranucci M, Castelvecchio S, Frigiola A, Scolletta S, Giomarelli P, Biagioli B. Predicting transfusions in cardiac surgery: the easier, the better: the Transfusion Risk and Clinical Knowledge score. Vox Sang. 2009;96(4):324-32.
56. Madhu Krishna NR, Nagaraja PS, Singh NG, Nanjappa SN, Kumar KN, Prabhakar V, et al. Evaluation of risk scores in predicting perioperative blood transfusions in adult cardiac surgery. Ann Card Anaesth. 2019;22(1):73-8.
57. Salsano A, Dominici C, Nenna A, Olivieri GM, Miette A, Barbato R, et al. Predictive scores for major bleeding after coronary artery bypass surgery in low operative risk patients. J Cardiovasc Surg (Torino). 2020;61(2):234-42.
58. Mathews R, Peterson ED, Chen AY, Wang TY, Chin CT, Fonarow GC, et al. In-hospital major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation and validation of a model from the ACTION Registry®-GWTG™. Am J Cardiol. 2011;107(8):1136-43.
59. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation. 2009;119(14):1873-82.

60. Jeppsson A, Rocca B, Hannsson E, Pan E, Milojevic M et al. 2024 EACTS Guideline on Perioperative Medication in Adult Cardiac Surgery. Eur J Cardiothorac Surg. 2024. In press.
61. Hastings S, Myles P, McIlroy D. Aspirin and coronary artery surgery: a systematic review and meta-analysis. Br J Anaesth. 2015;115(3):376-85.
62. Aboul-Hassan SS, Stankowski T, Marczak J, Peksa M, Nawotka M, Stanislawski R, et al. The use of preoperative aspirin in cardiac surgery: A systematic review and meta-analysis. J Card Surg. 2017;32(12):758-74.
63. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T, et al. Stopping vs. Continuing Aspirin before Coronary Artery Surgery. N Engl J Med. 2016;374(8):728-37.
64. Deja MA, Kargul T, Domaradzki W, Stącel T, Mazur W, Wojakowski W, et al. Effects of preoperative aspirin in coronary artery bypass grafting: a double-blind, placebo-controlled, randomized trial. J Thorac Cardiovasc Surg. 2012;144(1):204-9.
65. Li C, Hirsh J, Xie C, Johnston MA, Eikelboom JW. Reversal of the anti-platelet effects of aspirin and clopidogrel. J Thromb Haemost. 2012;10(4):521-8.
66. Santilli F, Rocca B, De Cristofaro R, Lattanzio S, Pietrangelo L, Habib A, et al. Platelet cyclooxygenase inhibition by low-dose aspirin is not reflected consistently by platelet function assays: implications for aspirin "resistance". J Am Coll Cardiol. 2009;53(8):667-77.
67. Lee J, Kim JK, Kim JH, Dunuu T, Park SH, Park SJ, et al. Recovery time of platelet function after aspirin withdrawal. Curr Ther Res Clin Exp. 2014;76:26-31.
68. Mangano DT. Aspirin and mortality from coronary bypass surgery. N Engl J Med. 2002;347(17):1309-17.
69. Björklund E, Nielsen SJ, Hansson EC, Karlsson M, Wallinder A, Martinsson A, et al. Secondary prevention medications after coronary artery bypass grafting and long-term survival: a population-based longitudinal study from the SWEDEHEART registry. Eur Heart J. 2020;41(17):1653-61.
70. Fremes SE, Levinton C, Naylor CD, Chen E, Christakis GT, Goldman BS. Optimal antithrombotic therapy following aortocoronary bypass: a meta-analysis. Eur J Cardiothorac Surg. 1993;7(4):169-80.
71. Musleh G, Dunning J. Does aspirin 6 h after coronary artery bypass grafting optimise graft patency? Interact Cardiovasc Thorac Surg. 2003;2(4):413-5.
72. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494-502.
73. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57.
74. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001-15.
75. De Luca L, Steg PG, Bhatt DL, Capodanno D, Angiolillo DJ. Cangrelor: Clinical Data, Contemporary Use, and Future Perspectives. J Am Heart Assoc. 2021;10(13):e022125.
76. Cao C, Indraratna P, Ang SC, Manganas C, Park J, Bannon PG, et al. Should clopidogrel be discontinued before coronary artery bypass grafting for patients with acute coronary syndrome? A systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2014;148(6):3092-8.

77. Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutyra M, Welsby IJ, et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. Jama. 2012;307(3):265-74.
78. Rossini R, Masiero G, Fruttero C, Passamonti E, Calvaruso E, Cecconi M, et al. Antiplatelet Therapy with Cangrelor in Patients Undergoing Surgery after Coronary Stent Implantation: A Real-World Bridging Protocol Experience. TH Open. 2020;4(4):e437-e45.
79. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation. 2004;110(10):1202-8.
80. Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. Eur Heart J. 2009;30(16):1964-77.
81. Smith PK, Goodnough LT, Levy JH, Poston RS, Short MA, Weerakkody GJ, et al. Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis. J Am Coll Cardiol. 2012;60(5):388-96.
82. Hansson EC, Jidéus L, Åberg B, Bjursten H, Dreifaldt M, Holmgren A, et al. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. Eur Heart J. 2016;37(2):189-97.
83. Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol. 2011;57(6):672-84.
84. Agrawal A, Kumar A, Majid M, Badwan O, Arockiam AD, El Dahdah J, et al. Optimal antiplatelet strategy following coronary artery bypass grafting: a meta-analysis. Heart. 2024;110(5):323-30.
85. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009;120(25):2577-85.
86. Hassan K, Kannmacher J, Wohlmuth P, Budde U, Schmoeckel M, Geidel S. Cytosorb Adsorption During Emergency Cardiac Operations in Patients at High Risk of Bleeding. Ann Thorac Surg. 2019;108(1):45-51.
87. Hassan K, Geidel S, Zamvar V, Tanaka K, Knezevic-Woods Z, Wendt D, et al. Intraoperative ticagrelor removal via hemoadsorption during on-pump coronary artery bypass grafting. JTCVS Open. 2023;15:190-6.
88. Schmoeckel M, Thielmann M, Hassan K, Geidel S, Schmitto J, Meyer AL, et al. Intraoperative haemoadsorption for antithrombotic drug removal during cardiac surgery: initial report of the international safe and timely antithrombotic removal (STAR) registry. J Thromb Thrombolysis. 2024.
89. Savonitto S, D'Urbano M, Caracciolo M, Barlocco F, Mariani G, Nichelatti M, et al. Urgent surgery in patients with a recently implanted coronary drug-eluting stent: a phase II study of 'bridging' antiplatelet therapy with tirofiban during temporary withdrawal of clopidogrel. Br J Anaesth. 2010;104(3):285-91.
90. Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):234s-64s.

91. Lincoff AM, LeNarz LA, Despotis GJ, Smith PK, Booth JE, Raymond RE, et al. Abciximab and bleeding during coronary surgery: results from the EPILOG and EPISTENT trials. Improve Long-term Outcome with abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibition in STENTing. Ann Thorac Surg. 2000;70(2):516-26.
92. Wu F, Ma K, Xiang R, Han B, Chang J, Zuo Z, et al. Efficacy and safety of a bridging strategy that uses intravenous platelet glycoprotein receptor inhibitors for patients undergoing surgery after coronary stent implantation: a meta-analysis. BMC Cardiovasc Disord. 2022;22(1):125.
93. Liu C, Wang S, Xue Y, Wang J, Li H. Safety and Efficacy of Tirofiban Bridging Therapy During a Hybrid Carotid Artery Stenting and Off-pump Coronary Artery Bypass Grafting Surgery: A Single-center Study. Clin Ther. 2023;45(3):292-8.
94. Fareed J, Hoppensteadt D, Walenga J, Iqbal O, Ma Q, Jeske W, et al. Pharmacodynamic and pharmacokinetic properties of enoxaparin : implications for clinical practice. Clin Pharmacokinet. 2003;42(12):1043-57.
95. van Veen JJ, Maclean RM, Hampton KK, Laidlaw S, Kitchen S, Toth P, et al. Protamine reversal of low molecular weight heparin: clinically effective? Blood Coagul Fibrinolysis. 2011;22(7):565-70.
96. Blick SK, Orman JS, Wagstaff AJ, Scott LJ. Fondaparinux sodium: a review of its use in the management of acute coronary syndromes. Am J Cardiovasc Drugs. 2008;8(2):113-25.
97. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006;354(14):1464-76.
98. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015;373(9):823-33.
99. Kuo HC, Liu FL, Chen JT, Cherng YG, Tam KW, Tai YH. Thromboembolic and bleeding risk of periprocedural bridging anticoagulation: A systematic review and meta-analysis. Clin Cardiol. 2020;43(5):441-9.
100. Jones HU, Muhlestein JB, Jones KW, Bair TL, Lavasani F, Sohrevardi M, et al. Preoperative use of enoxaparin compared with unfractionated heparin increases the incidence of re-exploration for postoperative bleeding after open-heart surgery in patients who present with an acute coronary syndrome: clinical investigation and reports. Circulation. 2002;106(12 Suppl 1):I19-22.
101. Spyropoulos AC, Turpie AG, Dunn AS, Kaatz S, Douketis J, Jacobson A, et al. Perioperative bridging therapy with unfractionated heparin or low-molecular-weight heparin in patients with mechanical prosthetic heart valves on long-term oral anticoagulants (from the REGIMEN Registry). Am J Cardiol. 2008;102(7):883-9.
102. Spyropoulos AC, Turpie AG, Dunn AS, Spandorfer J, Douketis J, Jacobson A, et al. Clinical outcomes with unfractionated heparin or low-molecular-weight heparin as bridging therapy in patients on long-term oral anticoagulants: the REGIMEN registry. J Thromb Haemost. 2006;4(6):1246-52.
103. Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized periprocedural anticoagulation regimen. Arch Intern Med. 2004;164(12):1319-26.
104. Iliuta L, Andronesi A, Camburu G, Rac-Albu M. Enoxaparin versus Unfractionated Heparin for the Perioperative Anticoagulant Therapy in Patients with Mechanical Prosthetic Heart Valve Undergoing Non-Cardiac Surgery. Medicina (Kaunas). 2022;58(8).

105. Gellatly RM, Leet A, Brown KE. Fondaparinux: an effective bridging strategy in heparin-induced thrombocytopenia and mechanical circulatory support. J Heart Lung Transplant. 2014;33(1):118.
106. Burch M, Cooper B. Fondaparinux-associated heparin-induced thrombocytopenia. Proc (Bayl Univ Med Cent). 2012;25(1):13-5.
107. Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):141s-59s.
108. Kovacs MJ, Kearon C, Rodger M, Anderson DR, Turpie AG, Bates SM, et al. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. Circulation. 2004;110(12):1658-63.
109. O'Donnell MJ, Kearon C, Johnson J, Robinson M, Zondag M, Turpie I, et al. Brief communication: Preoperative anticoagulant activity after bridging low-molecular-weight heparin for temporary interruption of warfarin. Ann Intern Med. 2007;146(3):184-7.
110. Passaglia LG, de Barros GM, de Sousa MR. Early postoperative bridging anticoagulation after mechanical heart valve replacement: a systematic review and meta-analysis. J Thromb Haemost. 2015;13(9):1557-67.
111. Meurin P, Tabet JY, Weber H, Renaud N, Ben Driss A. Low-molecular-weight heparin as a bridging anticoagulant early after mechanical heart valve replacement. Circulation. 2006;113(4):564-9.
112. Ferreira I, Dos L, Tornos P, Nicolau I, Permanyer-Miralda G, Soler-Soler J. Experience with enoxaparin in patients with mechanical heart valves who must withhold acenocumarol. Heart. 2003;89(5):527-30.
113. Caldeira D, David C, Santos AT, Costa J, Pinto FJ, Ferreira JJ. Efficacy and safety of low molecular weight heparin in patients with mechanical heart valves: systematic review and meta-analysis. J Thromb Haemost. 2014;12(5):650-9.
114. Tao E, Luo YL, Tao Z, Wan L. A meta-analysis of bridging anticoagulation between low molecular weight heparin and heparin. Medicine (Baltimore). 2020;99(3):e18729.
115. Li BX, Liu SD, Qi L, Sun S, Sun W, Li YM, et al. Comparison of different bridging anticoagulation therapies used after mechanical heart valve replacement in Chinese patients - a prospective cohort study. J Cardiothorac Surg. 2020;15(1):40.
116. Wang M, Zeraatkar D, Obeda M, Lee M, Garcia C, Nguyen L, et al. Drug-drug interactions with warfarin: A systematic review and meta-analysis. Br J Clin Pharmacol. 2021;87(11):4051-100.
117. Woods K, Douketis JD, Kathirgamanathan K, Yi Q, Crowther MA. Low-dose oral vitamin K to normalize the international normalized ratio prior to surgery in patients who require temporary interruption of warfarin. J Thromb Thrombolysis. 2007;24(2):93-7.
118. Boer C, Meesters MI, Milojevic M, Benedetto U, Bolliger D, von Heymann C, et al. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. J Cardiothorac Vasc Anesth. 2018;32(1):88-120.
119. Levy JH, Douketis J, Steiner T, Goldstein JN, Milling TJ. Prothrombin Complex Concentrates for Perioperative Vitamin K Antagonist and Non-vitamin K Anticoagulant Reversal. Anesthesiology. 2018;129(6):1171-84.
120. Desmettre T, Dehours E, Samama CM, Jhundoo S, Pujeau F, Guillaudin C, et al. Reversal of Vitamin K Antagonist (VKA) effect in patients with severe bleeding: a French multicenter

observational study (Optiplex) assessing the use of Prothrombin Complex Concentrate (PCC) in current clinical practice. Crit Care. 2012;16(5):R185.
121. Goldstein JN, Refaai MA, Milling TJ, Jr., Lewis B, Goldberg-Alberts R, Hug BA, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. Lancet. 2015;385(9982):2077-87.
122. Demeyere R, Gillardin S, Arnout J, Strengers PF. Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: a randomized study. Vox Sang. 2010;99(3):251-60.
123. Fariborz Farsad B, Golpira R, Najafi H, Totonchi Z, Salajegheh S, Bakhshandeh H, et al. Comparison between Prothrombin Complex Concentrate (PCC) and Fresh Frozen Plasma (FFP) for the Urgent Reversal of Warfarin in Patients with Mechanical Heart Valves in a Tertiary Care Cardiac Center. Iran J Pharm Res. 2015;14(3):877-85.
124. Hayes K, Fernando MC, Jordan V. Prothrombin complex concentrate in cardiac surgery for the treatment of coagulopathic bleeding. Cochrane Database Syst Rev. 2022;11(11):Cd013551.
125. Cappabianca G, Mariscalco G, Biancari F, Maselli D, Papesso F, Cottini M, et al. Safety and efficacy of prothrombin complex concentrate as first-line treatment in bleeding after cardiac surgery. Crit Care. 2016;20:5.
126. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021;23(10):1612-76.
127. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543-603.
128. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. Journal of the American College of Cardiology. 2024;83(1):109-279.
129. Hassan K, Bayer N, Schlingloff F, Oberhoffer M, Wohlmuth P, Schmoeckel M, et al. Bleeding Complications After Use of Novel Oral Anticoagulants in Patients Undergoing Cardiac Surgery. Ann Thorac Surg. 2018;105(3):702-8.
130. Heuts S, Ceulemans A, Kuiper G, Schreiber JU, van Varik BJ, Olie RH, et al. Optimal management of cardiac surgery patients using direct oral anticoagulants: recommendations for clinical practice. Eur J Cardiothorac Surg. 2023;64(4).
131. Fox V, Kleikamp A, Dittrich M, Zittermann A, Flieder T, Knabbe C, et al. Direct oral anticoagulants and cardiac surgery: A descriptive study of preoperative management and postoperative outcomes. J Thorac Cardiovasc Surg. 2021;161(5):1864-74.e2.
132. Godier A, Dincq AS, Martin AC, Radu A, Leblanc I, Antona M, et al. Predictors of pre-procedural concentrations of direct oral anticoagulants: a prospective multicentre study. Eur Heart J. 2017;38(31):2431-9.
133. Mar PL, Familtsev D, Ezekowitz MD, Lakkireddy D, Gopinathannair R. Periprocedural management of anticoagulation in patients taking novel oral anticoagulants: Review of the literature and recommendations for specific populations and procedures. Int J Cardiol. 2016;202:578-85.

134. Ono R, Nishimura K, Takahashi H, Hori Y, Fukushima K, Kobayashi Y. Anti-factor Xa activity, prothrombin time, and activated partial thromboplastin time in patients treated with factor Xa inhibitors. Naunyn Schmiedebergs Arch Pharmacol. 2023;396(2):323-36.
135. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory Assessment of the Anticoagulant Activity of Direct Oral Anticoagulants: A Systematic Review. Chest. 2017;151(1):127-38.
136. Douxfils J, Ageno W, Samama CM, Lessire S, Ten Cate H, Verhamme P, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. J Thromb Haemost. 2018;16(2):209-19.
137. Erdoes G, Faraoni D, Koster A, Steiner ME, Ghadimi K, Levy JH. Perioperative Considerations in Management of the Severely Bleeding Coagulopathic Patient. Anesthesiology. 2023;138(5):535-60.
138. Erdoes G, Martinez Lopez De Arroyabe B, Bolliger D, Ahmed AB, Koster A, Agarwal S, et al. International consensus statement on the peri-operative management of direct oral anticoagulants in cardiac surgery. Anaesthesia. 2018;73(12):1535-45.
139. Levy JH, Spyropoulos AC, Samama CM, Douketis J. Direct oral anticoagulants: new drugs and new concepts. JACC Cardiovasc Interv. 2014;7(12):1333-51.
140. Song Y, Wang Z, Perlstein I, Wang J, LaCreta F, Frost RJA, et al. Reversal of apixaban anticoagulation by four-factor prothrombin complex concentrates in healthy subjects: a randomized three-period crossover study. J Thromb Haemost. 2017;15(11):2125-37.
141. Dickneite G, Hoffman M. Reversing the new oral anticoagulants with prothrombin complex concentrates (PCCs): what is the evidence? Thromb Haemost. 2014;111(2):189-98.
142. Pollack CV, Jr., Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017;377(5):431-41.
143. Eikelboom JW, van Ryn J, Reilly P, Hylek EM, Elsaesser A, Glund S, et al. Dabigatran Reversal With Idarucizumab in Patients With Renal Impairment. J Am Coll Cardiol. 2019;74(14):1760-8.
144. Crespo-Leiro MG, López-Vilella R, López Granados A, Mirabet-Pérez S, Díez-López C, Barge-Caballero E, et al. Use of Idarucizumab to reverse the anticoagulant effect of dabigatran in cardiac transplant surgery. A multicentric experience in Spain. Clin Transplant. 2019;33(12):e13748.
145. European Medicines Agency. Idarucizumab. https://www.ema.europa.eu/en/medicines/human/EPAR/praxbind (Last accessed 10 August 2024).
146. Connolly SJ, Milling TJ, Jr., Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2016;375(12):1131-41.
147. Milling TJ, Jr., Middeldorp S, Xu L, Koch B, Demchuk A, Eikelboom JW, et al. Final Study Report of Andexanet Alfa for Major Bleeding With Factor Xa Inhibitors. Circulation. 2023;147(13):1026-38.
148. European Medicines Agency. Andexanet Alfa. https://www.ema.europa.eu/en/medicines/human/EPAR/ondexxya (Last Accessed 10 August 2024)
149. Tripathi R, Morales J, Lee V, Gibson CM, Mack MJ, Schneider DJ, et al. Antithrombotic drug removal from whole blood using Haemoadsorption with a porous polymer bead sorbent. Eur Heart J Cardiovasc Pharmacother. 2022;8(8):847-56.

150. Hassan K, Brüning T, Caspary M, Wohlmuth P, Pioch H, Schmoeckel M, et al. Hemoadsorption of Rivaroxaban and Ticagrelor during Acute Type A Aortic Dissection Operations. Ann Thorac Cardiovasc Surg. 2022;28(3):186-92.
151. Cappellini MD, Motta I. Anemia in Clinical Practice-Definition and Classification: Does Hemoglobin Change With Aging? Semin Hematol. 2015;52(4):261-9.
152. Braat S, Fielding KL, Han J, Jackson VE, Zaloumis S, Xu JXH, et al. Haemoglobin thresholds to define anaemia from age 6 months to 65 years: estimates from international data sources. Lancet Haematol. 2024;11(4):e253-e64.
153. Pasricha SR, Rogers L, Branca F, Garcia-Casal MN. Measuring haemoglobin concentration to define anaemia: WHO guidelines. Lancet. 2024;403(10440):1963-6.
154. Matsuda S, Fukui T, Shimizu J, Takao A, Takanashi S, Tomoike H. Associations between preoperative anemia and outcomes after off-pump coronary artery bypass grafting. Ann Thorac Surg. 2013;95(3):854-60.
155. Cutrell JB, Barros N, McBroom M, Luby J, Minhajuddin A, Ring WS, et al. Risk factors for deep sternal wound infection after cardiac surgery: Influence of red blood cell transfusions and chronic infection. Am J Infect Control. 2016;44(11):1302-9.
156. Karkouti K, Wijeysundera DN, Beattie WS. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. Circulation. 2008;117(4):478-84.
157. Dai L, Mick SL, McCrae KR, Houghtaling PL, Sabik JF, 3rd, Blackstone EH, et al. Preoperative Anemia in Cardiac Operation: Does Hemoglobin Tell the Whole Story? Ann Thorac Surg. 2018;105(1):100-7.
158. Abreu A, Máximo J, Almeida C, Lourenço A, Leite-Moreira A. The additive effects of anaemia and transfusion on long-term survival after coronary artery bypass surgery. Eur J Cardiothorac Surg. 2024;65(3).
159. Engoren M, Schwann TA, Habib RH, Neill SN, Vance JL, Likosky DS. The independent effects of anemia and transfusion on mortality after coronary artery bypass. Ann Thorac Surg. 2014;97(2):514-20.
160. von Heymann C, Kaufner L, Sander M, Spies C, Schmidt K, Gombotz H, et al. Does the severity of preoperative anemia or blood transfusion have a stronger impact on long-term survival after cardiac surgery? J Thorac Cardiovasc Surg. 2016;152(5):1412-20.
161. Hazen Y, Noordzij PG, Gerritse BM, Scohy TV, Houterman S, Bramer S, et al. Preoperative anaemia and outcome after elective cardiac surgery: a Dutch national registry analysis. Br J Anaesth. 2022;128(4):636-43.
162. Ripoll JG, Smith MM, Hanson AC, Schulte PJ, Portner ER, Kor DJ, et al. Sex-Specific Associations Between Preoperative Anemia and Postoperative Clinical Outcomes in Patients Undergoing Cardiac Surgery. Anesth Analg. 2021;132(4):1101-11.
163. Cavalli LB, Pearse BL, Craswell A, Anstey CM, Naidoo R, Rapchuk IL, et al. Determining sex-specific preoperative haemoglobin levels associated with intraoperative red blood cell transfusion in cardiac surgery: a retrospective cohort study. Br J Anaesth. 2023;131(4):653-63.
164. Tanaka KA, Alejo D, Ghoreishi M, Salenger R, Fonner C, Ad N, et al. Impact of Preoperative Hematocrit, Body Mass Index, and Red Cell Mass on Allogeneic Blood Product Usage in Adult Cardiac Surgical Patients: Report From a Statewide Quality Initiative. J Cardiothorac Vasc Anesth. 2023;37(2):214-20.
165. Wester ML, Sampon F, Olsthoorn JR, Soliman-Hamad MA, Houterman S, Maas A, et al. Gender is Independently Associated With Red Blood Cell and Platelet Transfusion in Patients Undergoing Coronary Artery Bypass Grafting: Data From the Netherlands Heart Registration. J Cardiothorac Vasc Anesth. 2024;38(4):924-30.

166. Lau M, Low CJW, Ling RR, Liu NSH, Tan CS, Ti LK, et al. Preoperative anemia and anemia treatment in cardiac surgery: a systematic review and meta-analysis. Can J Anaesth. 2024;71(1):127-42.
167. Rössler J, Schoenrath F, Seifert B, Kaserer A, Spahn GH, Falk V, et al. Iron deficiency is associated with higher mortality in patients undergoing cardiac surgery: a prospective study. Br J Anaesth. 2020;124(1):25-34.
168. Pierelli L, De Rosa A, Falco M, Papi E, Rondinelli MB, Turani F, et al. Preoperative Sucrosomial Iron Supplementation Increases Haemoglobin and Reduces Transfusion Requirements in Elective Heart Surgery Patients: A Prospective Randomized Study. Surg Technol Int. 2021;39:321-8.
169. Weltert LP, De Rosa A, Rondinelli MB, Falco M, Turani F, Pierelli L. Benefits of pre-operative oral Sucrosomial® iron supplementation in cardiac surgery: influence of patient's baseline hemoglobin and gender. Blood Transfus. 2023;21(4):305-13.
170. Venturini E, Iannuzzo G, A DIL, Cuomo G, D'Angelo A, Merone P, et al. Short-term treatment of iron deficiency anemia after cardiac surgery. Int J Cardiol Heart Vasc. 2022;40:101038.
171. Jafari S, Talasaz AH, Salehiomran A, Ariannejad H, Jalali A. Effects of Iron Sucrose and Erythropoietin on Transfusion Requirements in Patients with Preoperative Iron Deficiency Anemia Undergoing on-Pump Coronary Artery Bypass Graft. J Tehran Heart Cent. 2022;17(1):7-14.
172. Kim HH, Park EH, Lee SH, Yoo KJ, Youn YN. Effect of Preoperative Administration of Intravenous Ferric Carboxymaltose in Patients with Iron Deficiency Anemia after Off-Pump Coronary Artery Bypass Grafting: A Randomized Controlled Trial. J Clin Med. 2023;12(5).
173. Kong R, Hutchinson N, Hill A, Ingoldby F, Skipper N, Jones C, et al. Randomised open-label trial comparing intravenous iron and an erythropoiesis-stimulating agent versus oral iron to treat preoperative anaemia in cardiac surgery (INITIATE trial). Br J Anaesth. 2022;128(5):796-805.
174. Leviner DB, Abraham D, Shiner M, Schwartz N, Lavon O, Sharoni E. Implementation of a Short-term Treatment Protocol in Anemic Patients before Cardiac Surgery. Thorac Cardiovasc Surg. 2023.
175. Peel JK, Trudeau J, Tano R, Jadunandan S, Callum J, Moussa F, et al. Determining Optimal Treatment to Correct Preoperative Anemia and Reduce Perioperative Allogeneic Blood Transfusions in Cardiac Surgery: A Retrospective Cohort Study. J Cardiothorac Vasc Anesth. 2021;35(9):2631-9.
176. Kulier A, Levin J, Moser R, Rumpold-Seitlinger G, Tudor IC, Snyder-Ramos SA, et al. Impact of preoperative anemia on outcome in patients undergoing coronary artery bypass graft surgery. Circulation. 2007;116(5):471-9.
177. Weltert L, Rondinelli B, Bello R, Falco M, Bellisario A, Maselli D, et al. A single dose of erythropoietin reduces perioperative transfusions in cardiac surgery: results of a prospective single-blind randomized controlled trial. Transfusion. 2015;55(7):1644-54.
178. Weltert L, D'Alessandro S, Nardella S, Girola F, Bellisario A, Maselli D, et al. Preoperative very short-term, high-dose erythropoietin administration diminishes blood transfusion rate in off-pump coronary artery bypass: a randomized blind controlled study. J Thorac Cardiovasc Surg. 2010;139(3):621-6; discussion 6-7.
179. Yoo YC, Shim JK, Kim JC, Jo YY, Lee JH, Kwak YL. Effect of single recombinant human erythropoietin injection on transfusion requirements in preoperatively anemic patients undergoing valvular heart surgery. Anesthesiology. 2011;115(5):929-37.

180. Drohomirecka A, Kuśmierczyk M, Kocańda S, Kuśmierski K, Kołsut P, Kotliński K, et al. Endogenic erythropoietin secretion in patients undergoing off-pump coronary artery bypass grafting. Kardiol Pol. 2017;75(5):470-5.
181. Totonchi Z, Noohi F, Futuhi F, Azarfarin R, Radbin P. Effects of recombinant erythropoietin on hemoglobin levels and blood transfusion needs in patients with preoperative anemia undergoing cardiac surgery. Ann Card Anaesth. 2022;25(4):466-71.
182. Spahn DR, Schoenrath F, Spahn GH, Seifert B, Stein P, Theusinger OM, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. Lancet. 2019;393(10187):2201-12.
183. Ali SME, Hafeez MH, Nisar O, Fatima S, Ghous H, Rehman M. Role of preoperative erythropoietin in the optimization of preoperative anemia among surgical patients - A systematic review and meta-analysis. Hematol Transfus Cell Ther. 2022;44(1):76-84.
184. Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, Chan CT, Wong PY, et al. Advance targeted transfusion in anemic cardiac surgical patients for kidney protection: an unblinded randomized pilot clinical trial. Anesthesiology. 2012;116(3):613-21.
185. Wei XB, Jiang L, Liu YH, Feng D, He PC, Chen JY, et al. Thrombocytopenia as a Preoperative Risk Assessment Tool in Patients With Rheumatic Heart Disease Undergoing Valve Replacement Surgery. J Am Heart Assoc. 2017;6(12).
186. Nammas W, Dalén M, Rosato S, Gherli R, Reichart D, Gatti G, et al. Impact of preoperative thrombocytopenia on the outcome after coronary artery bypass grafting. Platelets. 2019;30(4):480-6.
187. Kuter DJ. 7 - General Aspects of Thrombocytopenia, Platelet Transfusions, and Thrombopoietic Growth Factors. In: Kitchens CS, Kessler CM, Konkle BA, Streiff MB, Garcia DA, editors. Consultative Hemostasis and Thrombosis (Fourth Edition). Philadelphia: Elsevier; 2019. p. 108-26.
188. Kertai MD, Zhou S, Karhausen JA, Cooter M, Jooste E, Li YJ, et al. Platelet Counts, Acute Kidney Injury, and Mortality after Coronary Artery Bypass Grafting Surgery. Anesthesiology. 2016;124(2):339-52.
189. Estcourt LJ, Malouf R, Doree C, Trivella M, Hopewell S, Birchall J. Prophylactic platelet transfusions prior to surgery for people with a low platelet count. Cochrane Database Syst Rev. 2018;9(9):Cd012779.
190. Carless P, Moxey A, O'Connell D, Henry D. Autologous transfusion techniques: a systematic review of their efficacy. Transfus Med. 2004;14(2):123-44.
191. Dietrich W, Thuermel K, Heyde S, Busley R, Berger K. Autologous blood donation in cardiac surgery: reduction of allogeneic blood transfusion and cost-effectiveness. J Cardiothorac Vasc Anesth. 2005;19(5):589-96.
192. Martin K, Keller E, Gertler R, Tassani P, Wiesner G. Efficiency and safety of preoperative autologous blood donation in cardiac surgery: a matched-pair analysis in 432 patients. Eur J Cardiothorac Surg. 2010;37(6):1396-401.
193. Lewis CE, Hiratzka LF, Woods SE, Hendy MP, Engel AM. Autologous blood transfusion in elective cardiac valve operations. J Card Surg. 2005;20(6):513-8.
194. Lim MH, Je HG, Ju MH, Lee JH, Oh HR, Kim YR. Effects of Preoperative Autologous Blood Donation in Patients Undergoing Minimally Invasive Cardiac Surgery. Korean J Thorac Cardiovasc Surg. 2019;52(6):385-91.
195. Beckmann A, Meyer R, Lewandowski J, Markewitz A, Blaßfeld D, Böning A. German Heart Surgery Report 2021: The Annual Updated Registry of the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiovasc Surg. 2022;70(5):362-76.

196. Deo SV, Elgudin Y, Shroyer ALW, Altarabsheh S, Sharma V, Rubelowsky J, et al. Off-Pump Coronary Artery Bypass Grafting: Department of Veteran Affairs' Use and Outcomes. J Am Heart Assoc. 2022;11(6):e023514.
197. Wahba A, Kunst G, De Somer F, Kildahl H, Milojevic M, et al. 2024 EACTS/EACTAIC/EBCP Guidelines on cardiopulmonary bypass in adult cardiac surgery. Eur J Cardiothorac Surg. 2024. In press.
198. Joffe M, Hunter S, Casula R, Birdi I, Deshpande R, Bharami T, et al. Adoption of minimally invasive mitral valve surgery in the National Health Service: a blend of science, psychology and human factors. Interdiscip Cardiovasc Thorac Surg. 2023;36(3).
199. Shaefi S, Mittel A, Loberman D, Ramakrishna H. Off-Pump Versus On-Pump Coronary Artery Bypass Grafting-A Systematic Review and Analysis of Clinical Outcomes. J Cardiothorac Vasc Anesth. 2019;33(1):232-44.
200. Puskas JD, Williams WH, Duke PG, Staples JR, Glas KE, Marshall JJ, et al. Off-pump coronary artery bypass grafting provides complete revascularization with reduced myocardial injury, transfusion requirements, and length of stay: a prospective randomized comparison of two hundred unselected patients undergoing off-pump versus conventional coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2003;125(4):797-808.
201. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med. 2012;366(16):1489-97.
202. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, et al. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med. 2009;361(19):1827-37.
203. Diegeler A, Börgermann J, Kappert U, Breuer M, Böning A, Ursulescu A, et al. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. N Engl J Med. 2013;368(13):1189-98.
204. Puskas JD, Martin J, Cheng DC, Benussi S, Bonatti JO, Diegeler A, et al. ISMICS Consensus Conference and Statements of Randomized Controlled Trials of Off-Pump Versus Conventional Coronary Artery Bypass Surgery. Innovations (Phila). 2015;10(4):219-29.
205. Sündermann SH, Sromicki J, Rodriguez Cetina Biefer H, Seifert B, Holubec T, Falk V, et al. Mitral valve surgery: right lateral minithoracotomy or sternotomy? A systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2014;148(5):1989-95.e4.
206. Akowuah EF, Maier RH, Hancock HC, Kharatikoopaei E, Vale L, Fernandez-Garcia C, et al. Minithoracotomy vs Conventional Sternotomy for Mitral Valve Repair: A Randomized Clinical Trial. Jama. 2023;329(22):1957-66.
207. Hussain S, Swystun AG, Caputo M, Angelini GD, Vohra HA. A review and meta-analysis of conventional sternotomy versus minimally invasive mitral valve surgery for degenerative mitral valve disease focused on the last decade of evidence. Perfusion. 2023:2676591231174579.
208. Phan K, Xie A, Di Eusanio M, Yan TD. A meta-analysis of minimally invasive versus conventional sternotomy for aortic valve replacement. Ann Thorac Surg. 2014;98(4):1499-511.
209. Vukovic PM, Milojevic P, Stojanovic I, Micovic S, Zivkovic I, Peric M, et al. The role of ministernotomy in aortic valve surgery-A prospective randomized study. J Card Surg. 2019;34(6):435-9.
210. Hancock HC, Maier RH, Kasim A, Mason J, Murphy G, Goodwin A, et al. Mini-sternotomy versus conventional sternotomy for aortic valve replacement: a randomised controlled trial. BMJ Open. 2021;11(1):e041398.

211. Teman NR, Hawkins RB, Charles EJ, Mehaffey JH, Speir AM, Quader MA, et al. Minimally Invasive vs Open Coronary Surgery: A Multi-Institutional Analysis of Cost and Outcomes. Ann Thorac Surg. 2021;111(5):1478-84.
212. Shah VN, Kilcoyne MF, Buckley M, Sicouri S, Plestis KA. The mini-Bentall approach: Comparison with full sternotomy. JTCVS Tech. 2021;7:59-66.
213. Rayner TA, Harrison S, Rival P, Mahoney DE, Caputo M, Angelini GD, et al. Minimally invasive versus conventional surgery of the ascending aorta and root: a systematic review and meta-analysis. Eur J Cardiothorac Surg. 2020;57(1):8-17.
214. Carless PA, Henry DA, Anthony DM. Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Cochrane Database Syst Rev. 2003;2003(2):Cd004171.
215. Abrishami A, Chung F, Wong J. Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-analysis. Can J Anaesth. 2009;56(3):202-12.
216. Alizadeh Ghavidel A, Mirmesdagh Y, Samiei N, Gholampour Dehaki M. Haemostatic Role of TachoSil Surgical Patch in Cardiac Surgery. J Cardiovasc Thorac Res. 2014;6(2):91-5.
217. Tavilla G, Bruggemans EF, Gielen CL, Brand A, van den Hout WB, Klautz RJ, et al. Multicentre randomized clinical trial to investigate the cost-effectiveness of an allogeneic single-donor fibrin sealant after coronary artery bypass grafting (FIBER Study). Br J Surg. 2015;102(11):1338-47.
218. Lamy A, Sirota DA, Jacques F, Poostizadeh A, Noiseux N, Efremov S, et al. Topical Versus Intravenous Tranexamic Acid in Patients Undergoing Cardiac Surgery: The DEPOSITION Randomized Controlled Trial. Circulation. 2024.
219. Daud A, Kaur B, McClure GR, Belley-Cote EP, Harlock J, Crowther M, et al. Fibrin and Thrombin Sealants in Vascular and Cardiac Surgery: A Systematic Review and Meta-analysis. Eur J Vasc Endovasc Surg. 2020;60(3):469-78.
220. Ranucci M, Carboni G, Cotza M, Bianchi P, Di Dedda U, Aloisio T. Hemodilution on cardiopulmonary bypass as a determinant of early postoperative hyperlactatemia. PLoS One. 2015;10(5):e0126939.
221. LaPar DJ, Hawkins RB, McMurry TL, Isbell JM, Rich JB, Speir AM, et al. Preoperative anemia versus blood transfusion: Which is the culprit for worse outcomes in cardiac surgery? J Thorac Cardiovasc Surg. 2018;156(1):66-74.e2.
222. Dickinson TA, Wu X, Sturmer DL, Goldberg J, Fitzgerald DC, Paone G, et al. Net Prime Volume Is Associated with Increased Odds of Blood Transfusion. J Extra Corpor Technol. 2019;51(4):195-200.
223. A HS, Francis S, Tesdahl EA, Miller R, Nostro A, Mongero LB. The Effect of Standardizing Autologous Prime Techniques in Patients Undergoing Cardiac Surgery with Cardiopulmonary Bypass. J Extra Corpor Technol. 2019;51(4):227-37.
224. Beukers AM, de Ruijter JAC, Loer SA, Vonk A, Bulte CSE. Effects of crystalloid and colloid priming strategies for cardiopulmonary bypass on colloid oncotic pressure and haemostasis: a meta-analysis. Interact Cardiovasc Thorac Surg. 2022;35(3).
225. Ghijselings I, Himpe D, Rex S. Safety of gelatin solutions for the priming of cardiopulmonary bypass in cardiac surgery: a systematic review and meta-analysis. Perfusion. 2017;32(5):350-62.
226. Pesonen E, Vlasov H, Suojaranta R, Hiippala S, Schramko A, Wilkman E, et al. Effect of 4% Albumin Solution vs Ringer Acetate on Major Adverse Events in Patients Undergoing Cardiac Surgery With Cardiopulmonary Bypass: A Randomized Clinical Trial. Jama. 2022;328(3):251-8.

227. Svendsen Ø S, Farstad M, Mongstad A, Haaverstad R, Husby P, Kvalheim VL. Is the use of hydroxyethyl starch as priming solution during cardiac surgery advisable? A randomized, single-center trial. Perfusion. 2018;33(6):483-9.
228. Barbu M, Kolsrud O, Radulovic V, Dellgren G, Björk K, Thorén A, et al. Hemostatic effects of a dextran-based priming solution for cardiopulmonary bypass: A secondary analysis of a randomized clinical trial. Thromb Res. 2023;223:139-45.
229. Cheng T, Barve R, Cheng YWM, Ravendren A, Ahmed A, Toh S, et al. Conventional versus miniaturized cardiopulmonary bypass: A systematic review and meta-analysis. JTCVS Open. 2021;8:418-41.
230. Hensley NB, Gyi R, Zorrilla-Vaca A, Choi CW, Lawton JS, Brown CHt, et al. Retrograde Autologous Priming in Cardiac Surgery: Results From a Systematic Review and Meta-analysis. Anesth Analg. 2021;132(1):100-7.
231. Gupta S, McEwen C, Basha A, Panchal P, Eqbal A, Wu N, et al. Retrograde autologous priming in cardiac surgery: a systematic review and meta-analysis. Eur J Cardiothorac Surg. 2021;60(6):1245-56.
232. Suehiro S, Shimizu K, Imai K, Niii A, Akeho K, Nakata H, et al. Polymer-coated cardiopulmonary bypass circuit attenuates upregulation of both proteases/protease inhibitors and platelet degranulation in pigs. Perfusion. 2017;32(8):645-55.
233. Hanedan MO, Yürük MA, Arslan AK, Kılıç A, Sayar U, Mataracı İ. Heparin-coated vs. Non-coated Cardiopulmonary Bypass Circuits: Comparing Immediate Results with Different Target Activated Clotting Time. Braz J Cardiovasc Surg. 2020;35(6):913-7.
234. Bauer A, Hausmann H, Schaarschmidt J, Szlapka M, Scharpenberg M, Eberle T, et al. Is 300 Seconds ACT Safe and Efficient during MiECC Procedures? Thorac Cardiovasc Surg. 2019;67(3):191-202.
235. Ranucci M, Baryshnikova E. Inflammation and coagulation following minimally invasive extracorporeal circulation technologies. J Thorac Dis. 2019;11(Suppl 10):S1480-s8.
236. Bauer A, Hausmann H, Schaarschmidt J, Scharpenberg M, Troitzsch D, Johansen P, et al. Shed-blood-separation and cell-saver: an integral Part of MiECC? Shed-blood-separation and its influence on the perioperative inflammatory response during coronary revascularization with minimal invasive extracorporeal circulation systems - a randomized controlled trial. Perfusion. 2018;33(2):136-47.
237. Lloyd TD, Geneen LJ, Bernhardt K, McClune W, Fernquest SJ, Brown T, et al. Cell salvage for minimising perioperative allogeneic blood transfusion in adults undergoing elective surgery. Cochrane Database Syst Rev. 2023;9(9):Cd001888.
238. Anastasiadis K, Antonitsis P, Murkin J, Serrick C, Gunaydin S, El-Essawi A, et al. 2021 MiECTiS focused update on the 2016 position paper for the use of minimal invasive extracorporeal circulation in cardiac surgery. Perfusion. 2023;38(7):1360-83.
239. El-Essawi A, Hajek T, Skorpil J, Böning A, Sabol F, Ostrovsky Y, et al. Are minimized perfusion circuits the better heart lung machines? Final results of a prospective randomized multicentre study. Perfusion. 2011;26(6):470-8.
240. Harling L, Warren OJ, Martin A, Kemp PR, Evans PC, Darzi A, et al. Do miniaturized extracorporeal circuits confer significant clinical benefit without compromising safety? A meta-analysis of randomized controlled trials. Asaio j. 2011;57(3):141-51.
241. El-Essawi A, Abdelhalim A, Groeger S, Breitenbach I, Brouwer R, Kück F, et al. Predictors of postoperative atrial fibrillation persisting beyond hospital discharge after coronary artery bypass grafting. Perfusion. 2022;37(1):62-8.

242. Amac B, Engin M, As AK, Savran M, Guvenc O, Eskici H, et al. Minimal Invasive Extracorporeal Circulation (MiECC) in Car-diac Surgery: A Narrative Review. Journal of Biomedical and Life Sciences. 2021;1(1):15-21.
243. Provaznik Z, Unterbuchner C, Philipp A, Foltan M, Creutzenberg M, Schopka S, et al. Conventional or minimized cardiopulmonary bypass support during coronary artery bypass grafting? - An analysis by means of perfusion and body mass index. Artif Organs. 2019;43(6):542-50.
244. Räsänen J, Ellam S, Hartikainen J, Juutilainen A, Halonen J. Impact of perfusion method on perioperative red blood cell transfusions and new-onset postoperative atrial fibrillation in mitral valve surgery patients. Perfusion. 2023;38(8):1600-8.
245. Halfwerk FR, Knol K, Mariani S, Grandjean JG, Mecozzi G. Randomized Trial of Miniaturized Versus Standard Extracorporeal Circulation in Aortic Valve Surgery. Ann Thorac Surg. 2019;108(1):37-44.
246. Gygax E, Kaeser HU, Stalder M, Gahl B, Rieben R, Carrel T, et al. Type II Minimal-Invasive Extracorporeal Circuit for Aortic Valve Replacement: A Randomized Controlled Trial. Artif Organs. 2018;42(6):620-9.
247. Baumbach H, Rustenbach CJ, Ahad S, Nagib R, Albert M, Ratge D, et al. Minimally Invasive Extracorporeal Bypass in Minimally Invasive Heart Valve Operations: A Prospective Randomized Trial. Ann Thorac Surg. 2016;102(1):93-100.
248. Winkler B, Heinisch PP, Gahl B, Aghlmandi S, Jenni HJ, Carrel TP. Minimally Invasive Extracorporeal Circulation Circuit Is Not Inferior to Off-Pump Coronary Artery Bypass Grafting: Meta-Analysis Using the Bayesian Method. Ann Thorac Surg. 2017;103(1):342-50.
249. Anastasiadis K, Murkin J, Antonitsis P, Bauer A, Ranucci M, Gygax E, et al. Use of minimal invasive extracorporeal circulation in cardiac surgery: principles, definitions and potential benefits. A position paper from the Minimal invasive Extra-Corporeal Technologies international Society (MiECTiS). Interact Cardiovasc Thorac Surg. 2016;22(5):647-62.
250. Kiessling AH, Keller H, Moritz A. Prospective, Randomized Un-Blinded Three Arm Controlled Study in Coronary Artery Revascularization with Minimal Invasive Extracorporeal Circulation Systems (MiECC): Surrogate Parameter Analysis of Biocompatibility. Heart Surg Forum. 2018;21(3):E179-e86.
251. Modrau IS, Halle DR, Nielsen PH, Kimose HH, Greisen JR, Kremke M, et al. Impact of minimally invasive extracorporeal circulation on coagulation-a randomized trial. Eur J Cardiothorac Surg. 2020;57(6):1145-53.
252. Ellam S, Räsänen J, Hartikainen J, Selander T, Juutilainen A, Halonen J. Impact of minimal invasive extracorporeal circulation on perioperative intravenous fluid management in coronary artery bypass surgery. Perfusion. 2023;38(1):135-41.
253. Blanco-Morillo J, Salmerón Martínez D, Arribas-Leal JM, Farina P, Puis L, Sornichero-Caballero AJ, et al. Haematic antegrade repriming to enhance recovery after cardiac surgery from the perfusionist side. J Extra Corpor Technol. 2023;55(1):30-8.
254. Yang K, Huang H, Dai R, Zhang J, Wei X, Gao F, et al. Modified cardiopulmonary bypass with low priming volume for blood conservation in cardiac valve replacement surgery. J Cardiothorac Surg. 2023;18(1):56.
255. Conventional versus minimally invasive extracorporeal circulation in patients undergoing cardiac surgery: protocol for a randomised controlled trial (COMICS). Perfusion. 2021;36(4):388-94.

256. Tachias F, Samara E, Petrou A, Karakosta A, Siminelakis S, Apostolakis E, et al. The Effect of Cell Salvage on Bleeding and Transfusion Needs in Cardiac Surgery. Anesthesiol Res Pract. 2022;2022:3993452.
257. Merkel KR, Lin SD, Frank SM, Kajstura TJ, Cruz NC, Lo BD, et al. Balancing the Blood Component Transfusion Ratio for High- and Ultra High-Dose Cell Salvage Cases. J Cardiothorac Vasc Anesth. 2021;35(4):1060-6.
258. Sponholz C, Sommerfeld O, Moehl C, Lehmann T, Franz M, Bauer M, et al. Intraoperative Cell Savage, Infection and Organ Failure in Infective Endocarditis Patients-A Retrospective Single Center Evaluation. J Clin Med. 2023;12(1).
259. van Klarenbosch J, van den Heuvel ER, van Oeveren W, de Vries AJ. Does Intraoperative Cell Salvage Reduce Postoperative Infection Rates in Cardiac Surgery? J Cardiothorac Vasc Anesth. 2020;34(6):1457-63.
260. Luque-Oliveros M. Bacteremia in the red blood cells obtained from the cell saver in patients submitted to heart surgery. Rev Lat Am Enfermagem. 2020;28:e3337.
261. Boyle AJ, Holmes DN, Hackett J, Gilliland S, McCloskey M, O'Kane CM, et al. Hyperoxaemia and hypoxaemia are associated with harm in patients with ARDS. BMC Pulm Med. 2021;21(1):285.
262. Gunaydin S, Robertson C, Budak AB, Gourlay T. Comparative evaluation of blood salvage techniques in patients undergoing cardiac surgery with cardiopulmonary bypass. Perfusion. 2018;33(2):105-9.
263. Mansour A, Beurton A, Godier A, Rozec B, Zlotnik D, Nedelec F, et al. Combined Platelet and Red Blood Cell Recovery during On-pump Cardiac Surgery Using same™ by i-SEP Autotransfusion Device: A First-in-human Noncomparative Study (i-TRANSEP Study). Anesthesiology. 2023;139(3):287-97.
264. Schreiber K, Decouture B, Lafragette A, Chollet S, Bruneau M, Nicollet M, et al. A novel autotransfusion device saving erythrocytes and platelets used in a 72 h survival swine model of surgically induced controlled blood loss. PLoS One. 2022;17(3):e0260855.
265. Roman MA, Abbasciano RG, Pathak S, Oo S, Yusoff S, Wozniak M, et al. Patient blood management interventions do not lead to important clinical benefits or cost-effectiveness for major surgery: a network meta-analysis. Br J Anaesth. 2021;126(1):149-56.
266. Hou X, Yang F, Liu R, Yang J, Zhao Y, Wan C, et al. Retrograde autologous priming of the cardiopulmonary bypass circuit reduces blood transfusion in small adults: a prospective, randomized trial. Eur J Anaesthesiol. 2009;26(12):1061-6.
267. Moscarelli M, Condello I, Mancini A, Rao V, Fiore F, Bonifazi R, et al. Retrograde Autologous Priming for Minimally Invasive Mitral Valve Surgery. J Cardiothorac Vasc Anesth. 2022;36(8 Pt B):3028-35.
268. Chen RQ, Li JB, Lin J, Lin ZJ. Retrograde autologous priming during cardiopulmonary bypass reduces blood transfusion rate in adult cardiac surgery: A prospective randomized clinical trial. Asian J Surg. 2021;44(8):1083-4.
269. Stammers AH, Mongero LB, Tesdahl E, Stasko A, Weinstein S. The effectiveness of acute normolvolemic hemodilution and autologous prime on intraoperative blood management during cardiac surgery. Perfusion. 2017;32(6):454-65.
270. Hofmann B, Kaufmann C, Stiller M, Neitzel T, Wienke A, Silber RE, et al. Positive impact of retrograde autologous priming in adult patients undergoing cardiac surgery: a randomized clinical trial. J Cardiothorac Surg. 2018;13(1):50.

271. Sun P, Ji B, Sun Y, Zhu X, Liu J, Long C, et al. Effects of retrograde autologous priming on blood transfusion and clinical outcomes in adults: a meta-analysis. Perfusion. 2013;28(3):238-43.
272. Saczkowski R, Bernier PL, Tchervenkov CI, Arellano R. Retrograde autologous priming and allogeneic blood transfusions: a meta-analysis. Interact Cardiovasc Thorac Surg. 2009;8(3):373-6.
273. Wang T, Wang J, Zhang M, Zhang H, Zhang Q, Liu G, et al. Effects of albumin and crystalloid priming strategies on red blood cell transfusions in on-pump cardiac surgery: a network meta-analysis. BMC Anesthesiol. 2024;24(1):26.
274. Hensley NB, Colao JA, Zorrilla-Vaca A, Nanavati J, Lawton JS, Raphael J, et al. Ultrafiltration in cardiac surgery: Results of a systematic review and meta-analysis. Perfusion. 2023:2676591231157970.
275. Low ZK, Gao F, Sin KYK, Yap KH. Modified ultrafiltration reduces postoperative blood loss and transfusions in adult cardiac surgery: a meta-analysis of randomized controlled trials. Interact Cardiovasc Thorac Surg. 2021;32(5):671-82.
276. Kandil OA, Motawea KR, Darling E, Riley JB, Shah J, Elashhat MAM, et al. Ultrafiltration and cardiopulmonary bypass associated acute kidney injury: A systematic review and meta-analysis. Clin Cardiol. 2021;44(12):1700-8.
277. Manning MW, Li YJ, Linder D, Haney JC, Wu YH, Podgoreanu MV, et al. Conventional Ultrafiltration During Elective Cardiac Surgery and Postoperative Acute Kidney Injury. J Cardiothorac Vasc Anesth. 2021;35(5):1310-8.
278. Foreman E, Eddy M, Holdcombe J, Warren P, Gebicke L, Raney P, et al. To RAP or Not to RAP: A Retrospective Comparison of the Effects of Retrograde Autologous Priming. J Extra Corpor Technol. 2021;53(4):279-85.
279. Blanco-Morillo J, Arribas-Leal JM, Farina P, Fernández-González AL, Sornichero-Caballero Á, Ramírez-Romero P, et al. Hematic Antegrade Repriming: A Reproducible Method to Decrease the Cardiopulmonary Bypass Insult. J Extra Corpor Technol. 2021;53(1):75-9.
280. Blanco-Morillo J, Salmerón Martínez D, Morillo-Cuadrado DV, Arribas-Leal JM, Puis L, Verdú-Verdú A, et al. Hematic Antegrade Repriming Reduces Emboli on Cardiopulmonary Bypass: A Randomized Controlled Trial. Asaio j. 2023;69(3):324-31.
281. Van Poucke S, Stevens K, Kicken C, Simons A, Marcus A, Lancé M. Platelet Function During Hypothermia in Experimental Mock Circulation. Artif Organs. 2016;40(3):288-93.
282. Braga DV, Brandão MAG. Diagnostic evaluation of risk for bleeding in cardiac surgery with extracorporeal circulation. Rev Lat Am Enfermagem. 2018;26:e3092.
283. Bademsi S, Yuksel A, Kilic AO, Pekcolaklar A, Binicier NA, Cetintas D, et al. Plasma Calcium Level and C-Reactive Protein Albumin Ratio Affect Severe Bleeding After Coronary Artery Bypass Grafting. Braz J Cardiovasc Surg. 2023;38(4):e20220378.
284. Lee BR, Song JW, Kwak YL, Yoo KJ, Shim JK. The influence of hypothermia on transfusion requirement in patients who received clopidogrel in proximity to off-pump coronary bypass surgery. Yonsei Med J. 2014;55(1):224-31.
285. Haider A, Khwaja IA, Qureshi AB, Khan I, Majeed KA, Yousaf MS, et al. Effectiveness of Mild to Moderate Hypothermic Cardiopulmonary Bypass on Early Clinical Outcomes. J Cardiovasc Dev Dis. 2022;9(5).
286. Shimamura J, Yokoyama Y, Kuno T, Fujisaki T, Fukuhara S, Takayama H, et al. Systematic review and network meta-analysis of various nadir temperature strategies for hypothermic circulatory arrest for aortic arch surgery. Asian Cardiovasc Thorac Ann. 2023;31(2):102-14.

287. Ise H, Kitahara H, Oyama K, Takahashi K, Kanda H, Fujii S, et al. Hypothermic circulatory arrest induced coagulopathy: rotational thromboelastometry analysis. Gen Thorac Cardiovasc Surg. 2020;68(8):754-61.
288. Ku MJ, Kim SW, Lee S, Chang JW, Lee J. Risk Factors Associated with Difficult Reversal of Heparin by Protamine Sulfate in Cardiopulmonary Bypass: An Ignored Issue. Korean J Thorac Cardiovasc Surg. 2020;53(5):258-62.
289. Williams B, Chriss E, Kaplan J, Cartron A, Taylor B, Gammie J, et al. Hypothermia, pH, and Postoperative Red Blood Cell Transfusion in Massively Transfused Adult Cardiac Surgery Patients: A Retrospective Cohort Study. J Cardiothorac Vasc Anesth. 2018;32(4):1642-7.
290. Zhou C, Li Y, Yan Y, Feng D, Wei M, Wen J. Changes in Coagulation and Fibrinolysis Systems During the Perioperative Period of Acute Type A Aortic Dissection. Heart Surg Forum. 2021;24(2):E223-e30.
291. Tveita T, Sieck GC. Physiological Impact of Hypothermia: The Good, the Bad, and the Ugly. Physiology (Bethesda). 2022;37(2):69-87.
292. Czerny M, Grabenwöger M, Berger T, Aboyans V, Della Corte A, Chen EP, et al. EACTS/STS Guidelines for diagnosing and treating acute and chronic syndromes of the aortic organ. Eur J Cardiothorac Surg. 2024;65(2).
293. Ranucci M, Baryshnikova E, Simeone F, Ranucci M, Scolletta S. Moderate-degree acidosis is an independent determinant of postoperative bleeding in cardiac surgery. Minerva Anestesiol. 2015;81(8):885-93.
294. Toomasian JM, Jeakle MMP, Langley MW, Poling CJ, Lautner G, Lautner-Csorba O, et al. Nitric Oxide Attenuates the Inflammatory Effects of Air During Extracorporeal Circulation. Asaio j. 2020;66(7):818-24.
295. Elnaiem W, Mohamed Elnour A, Koko AEA, Madany M, Hemmeda L. Efficacy and safety of inhaled nitric oxide administered during cardiopulmonary bypass for pediatric cardiac surgery: a systematic review and meta-analysis. Ann Med Surg (Lond). 2023;85(6):2865-74.
296. Weisel JW, Litvinov RI. Red blood cells: the forgotten player in hemostasis and thrombosis. J Thromb Haemost. 2019;17(2):271-82.
297. Vonk AB, Veerhoek D, van den Brom CE, van Barneveld LJ, Boer C. Individualized heparin and protamine management improves rotational thromboelastometric parameters and postoperative hemostasis in valve surgery. J Cardiothorac Vasc Anesth. 2014;28(2):235-41.
298. Noui N, Zogheib E, Walczak K, Werbrouck A, Amar AB, Dupont H, et al. Anticoagulation monitoring during extracorporeal circulation with the Hepcon/HMS device. Perfusion. 2012;27(3):214-20.
299. Nuttall GA, Smith MM, Smith BB, Christensen JM, Santrach PJ, Schaff HV. A Blinded Randomized Trial Comparing Standard Activated Clotting Time Heparin Management to High Target Active Clotting Time and Individualized Hepcon HMS Heparin Management in Cardiopulmonary Bypass Cardiac Surgical Patients. Ann Thorac Cardiovasc Surg. 2022;28(3):204-13.
300. Hoenicka M, Rupp P, Müller-Eising K, Deininger S, Kunert A, Liebold A, et al. Anticoagulation management during multivessel coronary artery bypass grafting: a randomized trial comparing individualized heparin management and conventional hemostasis management. J Thromb Haemost. 2015;13(7):1196-206.
301. Chakravarthy M, Prabhakumar D, Thimmannagowda P, Krishnamoorthy J, George A, Jawali V. Comparison of two doses of heparin on outcome in off-pump coronary artery bypass

surgery patients: A prospective randomized control study. Ann Card Anaesth. 2017;20(1):8-13.
302. Lwin TN, Mudannayake R, MacDonald S, Arrowsmith JE, Burt C, Besser M, et al. Assessing the impact of different heparin dosing regimens for cardiopulmonary bypass on anticoagulation: the HepDOSE pilot study. Can J Anaesth. 2024;71(2):234-43.
303. Vienne M, Haas E, Wipf T, Grunebaum L, Levy F, Sattler L, et al. Adjusted calculation model of heparin management during cardiopulmonary bypass in obese patients: A randomised controlled trial. Eur J Anaesthesiol. 2018;35(8):613-20.
304. Gkiouliava A, Argiriadou H, Antonitsis P, Goulas A, Papapostolou E, Sarridou D, et al. Individualized heparin monitoring and management reduces protamine requirements in cardiac surgery on minimal invasive extracorporeal circulation; A prospective randomized study. Perfusion. 2023:2676591231204284.
305. De Vries AJ, Lansink-Hartgring AO, Fernhout FJ, Huet RCG, van den Heuvel ER. The activated clotting time in cardiac surgery: should Celite or kaolin be used? Interact Cardiovasc Thorac Surg. 2017;24(4):549-54.
306. Boer C, Meesters MI, Veerhoek D, Vonk ABA. Anticoagulant and side-effects of protamine in cardiac surgery: a narrative review. Br J Anaesth. 2018;120(5):914-27.
307. Hällgren O, Svenmarker S, Appelblad M. Implementing a Statistical Model for Protamine Titration: Effects on Coagulation in Cardiac Surgical Patients. J Cardiothorac Vasc Anesth. 2017;31(2):516-21.
308. Vespe MW, Stone ME, Lin HM, Ouyang Y. Accurate protamine:heparin matching (not just smaller protamine doses) decreases postoperative bleeding in cardiac surgery; results from a high-volume academic medical center. Perfusion. 2023:2676591231190739.
309. Khan NU, Wayne CK, Barker J, Strang T. The effects of protamine overdose on coagulation parameters as measured by the thrombelastograph. Eur J Anaesthesiol. 2010;27(7):624-7.
310. Kunz SA, Miles LF, Ianno DJ, Mirowska-Allen KL, Matalanis G, Bellomo R, et al. The effect of protamine dosing variation on bleeding and transfusion after heparinisation for cardiopulmonary bypass. Perfusion. 2018;33(6):445-52.
311. Abuelkasem E, Mazzeffi MA, Henderson RA, Wipfli C, Monroe A, Strauss ER, et al. Clinical Impact of Protamine Titration-Based Heparin Neutralization in Patients Undergoing Coronary Bypass Grafting Surgery. J Cardiothorac Vasc Anesth. 2019;33(8):2153-60.
312. Meesters MI, Veerhoek D, de Lange F, de Vries JW, de Jong JR, Romijn JW, et al. Effect of high or low protamine dosing on postoperative bleeding following heparin anticoagulation in cardiac surgery: A randomised clinical trial. Thromb Haemost. 2016;116(2):251-61.
313. Kimura Y, Okahara S, Abo K, Koyama Y, Kuriyama M, Ono K, et al. Infective Endocarditis Is a Risk Factor for Heparin Resistance in Adult Cardiovascular Surgical Procedures: A Retrospective Study. J Cardiothorac Vasc Anesth. 2021;35(12):3568-73.
314. Khuong JN, Forsyth CJ, Manuel L, Kingsford-Smith K, Srivastava A, Bassin L. Paraprotein associated heparin resistance during cardiopulmonary bypass. Perfusion. 2023;38(6):1319-21.
315. Edwards JK, Sniecinski RM, Scott KJ. Non-Antithrombin-Mediated Heparin Resistance During Cardiac Surgery: Two Case Reports. A A Pract. 2019;13(6):211-4.
316. Kawatsu S, Sasaki K, Sakatsume K, Takahara S, Hosoyama K, Masaki N, et al. Predictors of Heparin Resistance Before Cardiovascular Operations in Adults. Ann Thorac Surg. 2018;105(5):1316-21.

317. Lippi G, Henry BM, Sanchis-Gomar F. Plasma Antithrombin Values Are Significantly Decreased in Coronavirus Disease 2019 (COVID-19) Patients with Severe Illness. Semin Thromb Hemost. 2021;47(4):460-2.
318. Ma HP, Xu WF, Yu J, Wang J, Zheng H. Heparin sensitivity and postoperative blood loss in patients undergoing cardiac surgery with cardiopulmonary bypass. Eur J Anaesthesiol. 2020;37(3):162-9.
319. Saydam O, Atay M, Serefli D, Doganci S, Kumabasar U, Yılmaz M, et al. Preoperative Low-Molecular-Weight Heparin Prophylaxis Associated with Increased Heparin Resistance Frequency in On-Pump Coronary Artery Bypass Graft Surgery. Cardiol Res Pract. 2019;2019:4310407.
320. Avidan MS, Levy JH, van Aken H, Feneck RO, Latimer RD, Ott E, et al. Recombinant human antithrombin III restores heparin responsiveness and decreases activation of coagulation in heparin-resistant patients during cardiopulmonary bypass. J Thorac Cardiovasc Surg. 2005;130(1):107-13.
321. Avidan MS, Levy JH, Scholz J, Delphin E, Rosseel PM, Howie MB, et al. A phase III, double-blind, placebo-controlled, multicenter study on the efficacy of recombinant human antithrombin in heparin-resistant patients scheduled to undergo cardiac surgery necessitating cardiopulmonary bypass. Anesthesiology. 2005;102(2):276-84.
322. Stammers AH, Francis SG, Miller R, Nostro A, Tesdahl EA, Mongero LB. Application of goal-directed therapy for the use of concentrated antithrombin for heparin resistance during cardiac surgery. Perfusion. 2021;36(2):171-82.
323. Bader SO, Marinaro XF, Stone G, Lodaya K, Spears JB, Shander A. Antithrombin concentrates may benefit cardiopulmonary bypass patients with suspected heparin resistance: A retrospective analysis of real-world data. Heliyon. 2023;9(9):e19497.
324. Moront MG, Woodward MK, Essandoh MK, Avery EG, Reece TB, Brzezinski M, et al. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Preoperative Antithrombin Supplementation in Patients at Risk for Antithrombin Deficiency After Cardiac Surgery. Anesth Analg. 2022;135(4):757-68.
325. Li T, Bo F, Meng X, Wang D, Ma J, Dai Z. The effect of perioperative antithrombin supplementation on blood conservation and postoperative complications after cardiopulmonary bypass surgery: A systematic review, meta-analysis and trial sequential analysis. Heliyon. 2023;9(11):e22266.
326. Revelly E, Scala E, Rosner L, Rancati V, Gunga Z, Kirsch M, et al. How to Solve the Conundrum of Heparin-Induced Thrombocytopenia during Cardiopulmonary Bypass. J Clin Med. 2023;12(3).
327. Soares Ferreira Júnior A, Boyle SH, Kuchibhatla M, Onwuemene OA. Bleeding is associated with intravenous immunoglobulin and therapeutic plasma exchange use in heparin-induced thrombocytopenia: A propensity matched analysis. EJHaem. 2021;2(3):466-70.
328. Gernhofer YK, Banks DA, Golts E, Pretorius V. Novel Use of Cangrelor With Heparin During Cardiopulmonary Bypass in Patients With Heparin-Induced Thrombocytopenia Who Require Cardiovascular Surgery: A Case Series. Semin Thorac Cardiovasc Surg. 2020;32(4):763-9.
329. Murphy GS, Marymont JH. Alternative anticoagulation management strategies for the patient with heparin-induced thrombocytopenia undergoing cardiac surgery. J Cardiothorac Vasc Anesth. 2007;21(1):113-26.

330. Sun Z, Lan X, Li S, Zhao H, Tang Z, Xi Y. Comparisons of argatroban to lepirudin and bivalirudin in the treatment of heparin-induced thrombocytopenia: a systematic review and meta-analysis. Int J Hematol. 2017;106(4):476-83.
331. Meshulami N, Murthy R, Meyer M, Meyer AD, Kaushik S. Bivalirudin anticoagulation for cardiopulmonary bypass during cardiac surgery. Perfusion. 2023:2676591231221708.
332. McNair E, Marcoux JA, Bally C, Gamble J, Thomson D. Bivalirudin as an adjunctive anticoagulant to heparin in the treatment of heparin resistance during cardiopulmonary bypass-assisted cardiac surgery. Perfusion. 2016;31(3):189-99.
333. Koster A, Faraoni D, Levy JH. Argatroban and Bivalirudin for Perioperative Anticoagulation in Cardiac Surgery. Anesthesiology. 2018;128(2):390-400.
334. Willers A, Arens J, Mariani S, Pels H, Maessen JG, Hackeng TM, et al. New Trends, Advantages and Disadvantages in Anticoagulation and Coating Methods Used in Extracorporeal Life Support Devices. Membranes (Basel). 2021;11(8).
335. Dyke CM, Smedira NG, Koster A, Aronson S, McCarthy HL, 2nd, Kirshner R, et al. A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: the EVOLUTION-ON study. J Thorac Cardiovasc Surg. 2006;131(3):533-9.
336. Osawa EA, Rhodes A, Landoni G, Galas FR, Fukushima JT, Park CH, et al. Effect of Perioperative Goal-Directed Hemodynamic Resuscitation Therapy on Outcomes Following Cardiac Surgery: A Randomized Clinical Trial and Systematic Review. Crit Care Med. 2016;44(4):724-33.
337. Cheng XQ, Zhang JY, Wu H, Zuo YM, Tang LL, Zhao Q, et al. Outcomes of individualized goal-directed therapy based on cerebral oxygen balance in high-risk patients undergoing cardiac surgery: A randomized controlled trial. J Clin Anesth. 2020;67:110032.
338. Damén T, Reinsfelt B, Redfors B, Nygren A. Pressure-dependent changes in haematocrit and plasma volume during anaesthesia, a randomised clinical trial. Acta Anaesthesiol Scand. 2016;60(5):560-8.
339. Goepfert MS, Richter HP, Zu Eulenburg C, Gruetzmacher J, Rafflenbeul E, Roeher K, et al. Individually optimized hemodynamic therapy reduces complications and length of stay in the intensive care unit: a prospective, randomized controlled trial. Anesthesiology. 2013;119(4):824-36.
340. Van der Linden PJ, De Hert SG, Daper A, Trenchant A, Schmartz D, Defrance P, et al. 3.5% urea-linked gelatin is as effective as 6% HES 200/0.5 for volume management in cardiac surgery patients. Can J Anaesth. 2004;51(3):236-41.
341. Kasper SM, Meinert P, Kampe S, Görg C, Geisen C, Mehlhorn U, et al. Large-dose hydroxyethyl starch 130/0.4 does not increase blood loss and transfusion requirements in coronary artery bypass surgery compared with hydroxyethyl starch 200/0.5 at recommended doses. Anesthesiology. 2003;99(1):42-7.
342. Gurbuz HA, Durukan AB, Salman N, Tavlasoglu M, Durukan E, Ucar H, et al. Hydroxyethyl starch 6%, 130/0.4 vs. a balanced crystalloid solution in cardiopulmonary bypass priming: a randomized, prospective study. J Cardiothorac Surg. 2013;8:71.
343. Ooi JS, Ramzisham AR, Zamrin MD. Is 6% hydroxyethyl starch 130/0.4 safe in coronary artery bypass graft surgery? Asian Cardiovasc Thorac Ann. 2009;17(4):368-72.
344. Vanhoonacker J, Ongenae M, Vanoverschelde H, Donadoni R. Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for cardiopulmonary bypass priming: the effects on postoperative bleeding and volume expansion needs after elective CABG. Acta Anaesthesiol Belg. 2009;60(2):91-7.

345. Tobey R, Cheng H, Gao M, Li Z, Young JN, Boyd WD, et al. Postoperative Acute Kidney Injury and Blood Product Transfusion After Synthetic Colloid Use During Cardiac Surgery. J Cardiothorac Vasc Anesth. 2017;31(3):853-62.
346. Hecht-Dolnik M, Barkan H, Taharka A, Loftus J. Hetastarch increases the risk of bleeding complications in patients after off-pump coronary bypass surgery: a randomized clinical trial. J Thorac Cardiovasc Surg. 2009;138(3):703-11.
347. Van der Linden PJ, De Hert SG, Deraedt D, Cromheecke S, De Decker K, Paep R, et al. Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for volume expansion in cardiac surgery patients: the effects on perioperative bleeding and transfusion needs. Anesth Analg. 2005;101(3):629-34.
348. Skhirtladze K, Base EM, Lassnigg A, Kaider A, Linke S, Dworschak M, et al. Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery. Br J Anaesth. 2014;112(2):255-64.
349. Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. Jama. 2013;309(7):678-88.
350. Ranucci M, Conti D, Castelvecchio S, Menicanti L, Frigiola A, Ballotta A, et al. Hematocrit on cardiopulmonary bypass and outcome after coronary surgery in nontransfused patients. Ann Thorac Surg. 2010;89(1):11-7.
351. DeFoe GR, Ross CS, Olmstead EM, Surgenor SD, Fillinger MP, Groom RC, et al. Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. Northern New England Cardiovascular Disease Study Group. Ann Thorac Surg. 2001;71(3):769-76.
352. Tran MH, Lin DM, Wilcox T, Schiro D, Cannesson M, Milliken J. Effects of a multimodality blood conservation schema toward improvement of intraoperative hemoglobin levels and off-pump transfusions in coronary artery bypass graft surgery. Transfusion. 2014;54(10 Pt 2):2769-74.
353. Vretzakis G, Kleitsaki A, Stamoulis K, Bareka M, Georgopoulou S, Karanikolas M, et al. Intra-operative intravenous fluid restriction reduces perioperative red blood cell transfusion in elective cardiac surgery, especially in transfusion-prone patients: a prospective, randomized controlled trial. J Cardiothorac Surg. 2010;5:7.
354. Soliman R, Saad D, Abukhudair W, Abdeldayem S. The neurocognitive outcomes of hemodilution in adult patients undergoing coronary artery bypass grafting using cardiopulmonary bypass. Ann Card Anaesth. 2022;25(2):133-40.
355. Aykut K, Albayrak G, Cetin Y, Ciftci N, Ciftci S. Coronary artery bypass surgery without blood transfusion; is it possible? Niger J Clin Pract. 2021;24(1):59-63.
356. Guru V, Omura J, Alghamdi AA, Weisel R, Fremes SE. Is blood superior to crystalloid cardioplegia? A meta-analysis of randomized clinical trials. Circulation. 2006;114(1 Suppl):I331-8.
357. Günday M, Bingöl H. Is crystalloid cardioplegia a strong predictor of intra-operative hemodilution? J Cardiothorac Surg. 2014;9:23.
358. Likosky DS, Wu X, Fitzgerald DC, Haft JW, Paone G, Romano MA, et al. Evaluating Changes in del Nido Cardioplegia Practices in Adult Cardiac Surgery. J Extra Corpor Technol. 2020;52(3):173-81.

359. Hawkins RB, Stewart JW, 2nd, Wu X, Goldberg J, Fitzgerald D, DeLucia A, 3rd, et al. del Nido versus blood cardioplegia in cardiac surgery: A multicenter analysis of over 40,000 patients. J Thorac Cardiovasc Surg. 2023.
360. Barile L, Fominskiy E, Di Tomasso N, Alpìzar Castro LE, Landoni G, De Luca M, 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(3):743-52.
361. 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;83:131-9.
362. Henderson RA, Mazzeffi MA, Strauss ER, Williams B, Wipfli C, Dawood M, 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(6):2023-9.
363. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T, et al. Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. N Engl J Med. 2017;376(2):136-48.
364. Zhang Y, Bai Y, Chen M, Zhou Y, Yu X, Zhou H, et al. The safety and efficiency of intravenous administration of tranexamic acid in coronary artery bypass grafting (CABG): a meta-analysis of 28 randomized controlled trials. BMC Anesthesiol. 2019;19(1):104.
365. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2011(1):Cd001886.
366. Takagi H, Ando T, Umemoto T. Seizures associated with tranexamic acid for cardiac surgery: a meta-analysis of randomized and non-randomized studies. J Cardiovasc Surg (Torino). 2017;58(4):633-41.
367. Shi J, Zhou C, Pan W, Sun H, Liu S, Feng 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(4):336-47.
368. Jerath A, Yang QJ, Pang KS, Looby N, Reyes-Garces N, Vasiljevic T, et al. Tranexamic Acid Dosing for Cardiac Surgical Patients With Chronic Renal Dysfunction: A New Dosing Regimen. Anesth Analg. 2018;127(6):1323-32.
369. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, McClelland B, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2007(4):Cd001886.
370. Broadwin M, Grant PE, Robich MP, Palmeri ML, Lucas FL, Rappold J, et al. Comparison of intraoperative tranexamic acid and epsilon-aminocaproic acid in cardiopulmonary bypass patients. JTCVS Open. 2020;3:114-25.
371. 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(3):265-72.
372. Howell N, Senanayake E, Freemantle N, Pagano D. Putting the record straight on aprotinin as safe and effective: results from a mixed treatment meta-analysis of trials of aprotinin. J Thorac Cardiovasc Surg. 2013;145(1):234-40.

373. Benedetto U, Altman DG, Gerry S, Gray A, Lees B, Angelini GD, et al. Safety of Perioperative Aprotinin Administration During Isolated Coronary Artery Bypass Graft Surgery: Insights From the ART (Arterial Revascularization Trial). J Am Heart Assoc. 2018;7(5).
374. Desborough M, Sandu R, Brunskill SJ, Doree C, Trivella M, Montedori A, et al. Fresh frozen plasma for cardiovascular surgery. Cochrane Database Syst Rev. 2015;2015(7):Cd007614.
375. Yang L, Stanworth S, Hopewell S, Doree C, Murphy M. Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials. Transfusion. 2012;52(8):1673-86; quiz
376. Casbard AC, Williamson LM, Murphy MF, Rege K, Johnson T. The role of prophylactic fresh frozen plasma in decreasing blood loss and correcting coagulopathy in cardiac surgery. A systematic review. Anaesthesia. 2004;59(6):550-8.
377. Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, Murphy MF. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. Br J Haematol. 2004;126(1):139-52.
378. Bolliger D, Görlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. Anesthesiology. 2010;113(5):1205-19.
379. Karkouti K, Callum J, Crowther MA, McCluskey SA, Pendergrast J, Tait G, 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(1):14-22.
380. Tanaka KA, Esper S, Bolliger D. Perioperative factor concentrate therapy. Br J Anaesth. 2013;111 Suppl 1:i35-49.
381. Li JY, Gong J, Zhu F, Moodie J, Newitt A, Uruthiramoorthy L, et al. Fibrinogen Concentrate in Cardiovascular Surgery: A Meta-analysis of Randomized Controlled Trials. Anesth Analg. 2018;127(3):612-21.
382. Tanaka KA, Egan K, Szlam F, Ogawa S, Roback JD, Sreeram G, et al. Transfusion and hematologic variables after fibrinogen or platelet transfusion in valve replacement surgery: preliminary data of purified lyophilized human fibrinogen concentrate versus conventional transfusion. Transfusion. 2014;54(1):109-18.
383. Rahe-Meyer N, Solomon C, Hanke A, Schmidt DS, Knoerzer D, Hochleitner G, et al. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. Anesthesiology. 2013;118(1):40-50.
384. Ranucci M, Baryshnikova E, Crapelli GB, Rahe-Meyer N, Menicanti L, Frigiola A. Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery. J Am Heart Assoc. 2015;4(6):e002066.
385. Bilecen S, de Groot JA, Kalkman CJ, Spanjersberg AJ, Brandon Bravo Bruinsma GJ, Moons KG, et al. Effect of Fibrinogen Concentrate on Intraoperative Blood Loss Among Patients With Intraoperative Bleeding During High-Risk Cardiac Surgery: A Randomized Clinical Trial. Jama. 2017;317(7):738-47.
386. Rahe-Meyer N, Levy JH, Mazer CD, Schramko A, Klein AA, Brat R, et al. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. Br J Anaesth. 2016;117(1):41-51.
387. Ranucci M, Baryshnikova E. Fibrinogen supplementation after cardiac surgery: insights from the Zero-Plasma trial (ZEPLAST). Br J Anaesth. 2016;116(5):618-23.
388. Erdoes G, Koster A, Meesters MI, Ortmann E, Bolliger D, Baryshnikova E, et al. The role of fibrinogen and fibrinogen concentrate in cardiac surgery: an international consensus

statement from the Haemostasis and Transfusion Scientific Subcommittee of the European Association of Cardiothoracic Anaesthesiology. Anaesthesia. 2019;74(12):1589-600.
389. Callum J, Farkouh ME, Scales DC, Heddle NM, Crowther M, Rao V, et al. Effect of Fibrinogen Concentrate vs Cryoprecipitate on Blood Component Transfusion After Cardiac Surgery: The FIBRES Randomized Clinical Trial. Jama. 2019;322(20):1966-76.
390. Ghadimi K, Levy JH, Welsby IJ. Prothrombin Complex Concentrates for Bleeding in the Perioperative Setting. Anesth Analg. 2016;122(5):1287-300.
391. Johansen M, Wikkelsø A, Lunde J, Wetterslev J, Afshari A. Prothrombin complex concentrate for reversal of vitamin K antagonist treatment in bleeding and non-bleeding patients. Cochrane Database Syst Rev. 2015;2015(7):Cd010555.
392. Erdoes G, Koster A, Ortmann E, Meesters MI, Bolliger D, Baryshnikova 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(3):381-92.
393. Roman M, Biancari F, Ahmed AB, Agarwal S, Hadjinikolaou L, Al-Sarraf A, et al. Prothrombin Complex Concentrate in Cardiac Surgery: A Systematic Review and Meta-Analysis. Ann Thorac Surg. 2019;107(4):1275-83.
394. Smith MM, Schroeder DR, Nelson JA, Mauermann WJ, Welsby IJ, Pochettino A, et al. Prothrombin Complex Concentrate vs Plasma for Post-Cardiopulmonary Bypass Coagulopathy and Bleeding: A Randomized Clinical Trial. JAMA Surg. 2022;157(9):757-64.
395. Pupovac SS, Catalano MA, Hartman AR, Yu PJ. Factor eight inhibitor bypassing activity for refractory bleeding in coronary artery bypass grafting: A propensity-matched analysis. Res Pract Thromb Haemost. 2022;6(8):e12838.
396. Desborough MJ, Oakland K, Brierley C, Bennett S, Doree C, Trivella M, et al. Desmopressin use for minimising perioperative blood transfusion. Cochrane Database Syst Rev. 2017;7(7):Cd001884.
397. Wademan BH, Galvin SD. Desmopressin for reducing postoperative blood loss and transfusion requirements following cardiac surgery in adults. Interact Cardiovasc Thorac Surg. 2014;18(3):360-70.
398. Crescenzi G, Landoni G, Biondi-Zoccai G, Pappalardo F, Nuzzi M, Bignami E, et al. Desmopressin reduces transfusion needs after surgery: a meta-analysis of randomized clinical trials. Anesthesiology. 2008;109(6):1063-76.
399. Carless PA, Henry DA, Moxey AJ, O'Connell D, McClelland B, Henderson KM, et al. Desmopressin for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2004(1):Cd001884.
400. Desborough MJ, Oakland KA, Landoni G, Crivellari M, Doree C, Estcourt LJ, et al. Desmopressin for treatment of platelet dysfunction and reversal of antiplatelet agents: a systematic review and meta-analysis of randomized controlled trials. J Thromb Haemost. 2017;15(2):263-72.
401. Karkouti K, McCluskey SA, Syed S, Pazaratz C, Poonawala H, Crowther MA. The influence of perioperative coagulation status on postoperative blood loss in complex cardiac surgery: a prospective observational study. Anesth Analg. 2010;110(6):1533-40.
402. Gödje O, Gallmeier U, Schelian M, Grünewald M, Mair H. Coagulation factor XIII reduces postoperative bleeding after coronary surgery with extracorporeal circulation. Thorac Cardiovasc Surg. 2006;54(1):26-33.
403. Ternström L, Radulovic V, Karlsson M, Baghaei F, Hyllner M, Bylock A, et al. Plasma activity of individual coagulation factors, hemodilution and blood loss after cardiac surgery: a prospective observational study. Thromb Res. 2010;126(2):e128-33.

404. Karkouti K, von Heymann C, Jespersen CM, Korte W, Levy JH, Ranucci M, et al. Efficacy and safety of recombinant factor XIII on reducing blood transfusions in cardiac surgery: a randomized, placebo-controlled, multicenter clinical trial. J Thorac Cardiovasc Surg. 2013;146(4):927-39.
405. Gill R, Herbertson M, Vuylsteke A, Olsen PS, von Heymann C, Mythen M, et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. Circulation. 2009;120(1):21-7.
406. Flynn BC, Steiner ME, Mazzeffi M. Off-label Use of Recombinant Activated Factor VII for Cardiac Surgical Bleeding. Anesthesiology. 2023;139(2):197-210.
407. Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database Syst Rev. 2012(3):Cd005011.
408. Scolletta S, Simioni P, Campagnolo V, Celiento M, Fontanari P, Guadagnucci A, et al. Patient blood management in cardiac surgery: The "Granducato algorithm". Int J Cardiol. 2019;289:37-42.
409. Pavenski K, Howell A, Mazer CD, Hare GMT, Freedman J. ONTraC: A 20-Year History of a Successfully Coordinated Provincewide Patient Blood Management Program: Lessons Learned and Goals Achieved. Anesth Analg. 2022;135(3):448-58.
410. Leahy MF, Hofmann A, Towler S, Trentino KM, Burrows SA, Swain SG, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. Transfusion. 2017;57(6):1347-58.
411. Rapier JJ, Daley M, Smith SE, Goh SL, Margale S, Smith I, et al. Implementation of Patient Blood Management in Orthotopic Heart Transplants: A Single Centre Retrospective Observational Review. Heart Lung Circ. 2024.
412. Klausen SS, Hervig T, Seghatchian J, Reikvam H. Bacterial contamination of blood components: Norwegian strategies in identifying donors with higher risk of inducing septic transfusion reactions in recipients. Transfus Apher Sci. 2014;51(2):97-102.
413. Dwyre DM, Fernando LP, Holland PV. Hepatitis B, hepatitis C and HIV transfusion-transmitted infections in the 21st century. Vox Sang. 2011;100(1):92-8.
414. Dunbar NM. Current options for transfusion-related acute lung injury risk mitigation in platelet transfusions. Curr Opin Hematol. 2015;22(6):554-8.
415. Shaz BH, Stowell SR, Hillyer CD. Transfusion-related acute lung injury: from bedside to bench and back. Blood. 2011;117(5):1463-71.
416. Vamvakas EC, Blajchman MA. Transfusion-related immunomodulation (TRIM): an update. Blood Rev. 2007;21(6):327-48.
417. Rohde JM, Dimcheff DE, Blumberg N, Saint S, Langa KM, Kuhn L, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. Jama. 2014;311(13):1317-26.
418. Bilgin YM, van de Watering LM, Eijsman L, Versteegh MI, Brand R, van Oers MH, et al. Double-blind, randomized controlled trial on the effect of leukocyte-depleted erythrocyte transfusions in cardiac valve surgery. Circulation. 2004;109(22):2755-60.
419. Steiner ME, Ness PM, Assmann SF, Triulzi DJ, Sloan SR, Delaney M, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. N Engl J Med. 2015;372(15):1419-29.
420. Sartipy U, Holzmann MJ, Hjalgrim H, Edgren G. Red Blood Cell Concentrate Storage and Survival After Cardiac Surgery. Jama. 2015;314(15):1641-3.

421. Lacroix J, Hébert PC, Fergusson DA, Tinmouth A, Cook DJ, Marshall JC, et al. Age of transfused blood in critically ill adults. N Engl J Med. 2015;372(15):1410-8.
422. Alexander PE, Barty R, Fei Y, Vandvik PO, Pai M, Siemieniuk RA, et al. Transfusion of fresher vs older red blood cells in hospitalized patients: a systematic review and meta-analysis. Blood. 2016;127(4):400-10.
423. Bjursten H, Dardashti A, Björk J, Wierup P, Algotsson L, Ederoth P. Transfusion of sex-mismatched and non-leukocyte-depleted red blood cells in cardiac surgery increases mortality. J Thorac Cardiovasc Surg. 2016;152(1):223-32.e1.
424. Khan AI, Patidar GK, Lakshmy R, Makhija N, Talwar S, Hazarika A. Effect of leukoreduction on transfusion-related immunomodulation in patients undergoing cardiac surgery. Transfus Med. 2020;30(6):497-504.
425. Vamvakas EC. Relative safety of pooled whole blood-derived versus single-donor (apheresis) platelets in the United States: a systematic review of disparate risks. Transfusion. 2009;49(12):2743-58.
426. Welsby IJ, Lockhart E, Phillips-Bute B, Campbell ML, Mathew JP, Newman MF, et al. Storage age of transfused platelets and outcomes after cardiac surgery. Transfusion. 2010;50(11):2311-7.
427. Whitlock R, Crowther MA, Ng HJ. Bleeding in cardiac surgery: its prevention and treatment--an evidence-based review. Crit Care Clin. 2005;21(3):589-610.
428. Emmert MY, Salzberg SP, Theusinger OM, Felix C, Plass A, Hoerstrup SP, et al. How good patient blood management leads to excellent outcomes in Jehovah's witness patients undergoing cardiac surgery. Interact Cardiovasc Thorac Surg. 2011;12(2):183-8.
429. Karkouti K, Wijeysundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA, et al. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion. 2004;44(10):1453-62.
430. Royston D, von Kier S. Reduced haemostatic factor transfusion using heparinase-modified thrombelastography during cardiopulmonary bypass. Br J Anaesth. 2001;86(4):575-8.
431. Theusinger OM, Spahn DR, Ganter MT. Transfusion in trauma: why and how should we change our current practice? Curr Opin Anaesthesiol. 2009;22(2):305-12.
432. Haensig M, Kempfert J, Kempfert PM, Girdauskas E, Borger MA, Lehmann S. Thrombelastometry guided blood-component therapy after cardiac surgery: a randomized study. BMC Anesthesiol. 2019;19(1):201.
433. Dias JD, Sauaia A, Achneck HE, Hartmann J, Moore EE. Thromboelastography-guided therapy improves patient blood management and certain clinical outcomes in elective cardiac and liver surgery and emergency resuscitation: A systematic review and analysis. J Thromb Haemost. 2019;17(6):984-94.
434. Kuiper G, van Egmond LT, Henskens YMC, Roekaerts PM, Maessen JG, Ten Cate H, 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(2):307-17.
435. Lehmann F, Rau J, Malcolm B, Sander M, von Heymann C, Moormann T, et al. Why does a point of care guided transfusion algorithm not improve blood loss and transfusion practice in patients undergoing high-risk cardiac surgery? A prospective randomized controlled pilot study. BMC Anesthesiol. 2019;19(1):24.

436. Karkouti K, Callum J, Wijeysundera DN, Rao V, Crowther M, Grocott HP, et al. Point-of-Care Hemostatic Testing in Cardiac Surgery: A Stepped-Wedge Clustered Randomized Controlled Trial. Circulation. 2016;134(16):1152-62.
437. Weber CF, Görlinger K, Meininger D, Herrmann E, Bingold T, Moritz A, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. Anesthesiology. 2012;117(3):531-47.
438. Whiting P, Al M, Westwood M, Ramos IC, Ryder S, Armstrong N, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2015;19(58):1-228, v-vi.
439. Ranucci M, Aloisio T, Carboni G, Ballotta A, Pistuddi V, Menicanti L, et al. Acute Kidney Injury and Hemodilution During Cardiopulmonary Bypass: A Changing Scenario. Ann Thorac Surg. 2015;100(1):95-100.
440. Patel NN, Avlonitis VS, Jones HE, Reeves BC, Sterne JA, Murphy GJ. Indications for red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis. Lancet Haematol. 2015;2(12):e543-53.
441. Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2016;10(10):Cd002042.
442. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ, et al. Clinical trials evaluating red blood cell transfusion thresholds: An updated systematic review and with additional focus on patients with cardiovascular disease. Am Heart J. 2018;200:96-101.
443. Shehata N, Mistry N, da Costa BR, Pereira TV, Whitlock R, Curley GF, et al. Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis. Eur Heart J. 2019;40(13):1081-8.
444. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. Jama. 2010;304(14):1559-67.
445. Nakamura RE, Vincent JL, Fukushima JT, de Almeida JP, Franco RA, Lee Park C, et al. A liberal strategy of red blood cell transfusion reduces cardiogenic shock in elderly patients undergoing cardiac surgery. J Thorac Cardiovasc Surg. 2015;150(5):1314-20.
446. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med. 2015;372(11):997-1008.
447. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. N Engl J Med. 2017;377(22):2133-44.
448. Mistry N, Shehata N, Carmona P, Bolliger D, Hu R, Carrier FM, et al. Restrictive versus liberal transfusion in patients with diabetes undergoing cardiac surgery: An open-label, randomized, blinded outcome evaluation trial. Diabetes Obes Metab. 2022;24(3):421-31.
449. Carson JL, Brooks MM, Hébert PC, Goodman SG, Bertolet M, Glynn SA, et al. Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia. N Engl J Med. 2023;389(26):2446-56.
450. Koch CG, Sessler DI, Mascha EJ, Sabik JF, 3rd, Li L, Duncan AI, et al. A Randomized Clinical Trial of Red Blood Cell Transfusion Triggers in Cardiac Surgery. Ann Thorac Surg. 2017;104(4):1243-50.
451. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, Lemesle G, Cachanado M, Durand-Zaleski I, 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(6):552-60.
452. Gonzalez-Juanatey JR, Lemesle G, Puymirat E, Ducrocq G, Cachanado M, Arnaiz JA, et al. One-Year Major Cardiovascular Events After Restrictive Versus Liberal Blood Transfusion Strategy in Patients With Acute Myocardial Infarction and Anemia: The REALITY Randomized Trial. Circulation. 2022;145(6):486-8.
453. Zhou X, Fraser CD, 3rd, Suarez-Pierre A, Crawford TC, Alejo D, Conte JV, Jr., et al. Variation in Platelet Transfusion Practices in Cardiac Surgery. Innovations (Phila). 2019;14(2):134-43.
454. Fletcher CM, Hinton JV, Xing Z, Perry LA, Karamesinis A, Shi J, et al. Platelet Transfusion After Cardiac Surgery. J Cardiothorac Vasc Anesth. 2023;37(4):528-38.
455. Yanagawa B, Ribeiro R, Lee J, Mazer CD, Cheng D, Martin J, et al. Platelet Transfusion in Cardiac Surgery: A Systematic Review and Meta-Analysis. Ann Thorac Surg. 2021;111(2):607-14.
456. von Heymann C, Sander M, Foer A, Heinemann A, Spiess B, Braun J, et al. The impact of an hematocrit of 20% during normothermic cardiopulmonary bypass for elective low risk coronary artery bypass graft surgery on oxygen delivery and clinical outcome--a randomized controlled study [ISRCTN35655335]. Crit Care. 2006;10(2):R58.
457. Kristensen KL, Rauer LJ, Mortensen PE, Kjeldsen BJ. Reoperation for bleeding in cardiac surgery. Interact Cardiovasc Thorac Surg. 2012;14(6):709-13.
458. Mueller XM, Tinguely F, Tevaearai HT, Ravussin P, Stumpe F, von Segesser LK. Impact of duration of chest tube drainage on pain after cardiac surgery. Eur J Cardiothorac Surg. 2000;18(5):570-4.
459. Abramov D, Yeshayahu M, Tsodikov V, Gatot I, Orman S, Gavriel A, et al. Timing of chest tube removal after coronary artery bypass surgery. J Card Surg. 2005;20(2):142-6.
460. Mirmohammad-Sadeghi M, Etesampour A, Gharipour M, Shariat Z, Nilforoush P, Saeidi M, et al. Early chest tube removal after coronary artery bypass graft surgery. N Am J Med Sci. 2009;1(7):333-7.
461. El-Akkawi AI, Media AS, Eykens Hjørnet N, Nielsen DV, Modrau IS. Timing of Chest Tube Removal Following Adult Cardiac Surgery: A Cluster Randomized Controlled Trial. Scand Cardiovasc J. 2024;58(1):2294681.
462. Anderson D, Chen SA, Godoy LA, Brown LM, Cooke DT. Comprehensive Review of Chest Tube Management: A Review. JAMA Surg. 2022;157(3):269-74.
463. Lobdell KW, Engelman DT. Chest Tube Management: Past, Present, and Future Directions for Developing Evidence-Based Best Practices. Innovations (Phila). 2023;18(1):41-8.
464. Van Linden A, Hecker F, Courvoisier DS, Arsalan M, Köhne J, Brei C, et al. Reduction of drainage-associated complications in cardiac surgery with a digital drainage system: a randomized controlled trial. J Thorac Dis. 2019;11(12):5177-86.
465. Marberg H, Jeppsson A, Brandrup-Wognsen G. Postoperative autotransfusion of mediastinal shed blood does not influence haemostasis after elective coronary artery bypass grafting. Eur J Cardiothorac Surg. 2010;38(6):767-72.
466. Folkersen L, Tang M, Grunnet N, Jakobsen CJ. Transfusion of shed mediastinal blood reduces the use of allogenic blood transfusion without increasing complications. Perfusion. 2011;26(2):145-50.
467. Lau K, Shah H, Kelleher A, Moat N. Coronary artery surgery: cardiotomy suction or cell salvage? J Cardiothorac Surg. 2007;2:46.

468. Weltert L, Nardella S, Rondinelli MB, Pierelli L, De Paulis R. Reduction of allogeneic red blood cell usage during cardiac surgery by an integrated intra- and postoperative blood salvage strategy: results of a randomized comparison. Transfusion. 2013;53(4):790-7.
469. Vermeijden WJ, Hagenaars JA, Scheeren TW, de Vries AJ. Additional postoperative cell salvage of shed mediastinal blood in cardiac surgery does not reduce allogeneic blood transfusions: a cohort study. Perfusion. 2016;31(5):384-90.
470. Haneya A, Diez C, Kolat P, Suesskind-Schwendi M, Ried M, Schmid C, et al. Re-exploration for bleeding or tamponade after cardiac surgery: impact of timing and indication on outcome. Thorac Cardiovasc Surg. 2015;63(1):51-7.
471. Luan T, Zhuang Y, Nie W, Yang S, Wu Y, Wang R, et al. The death risk factors of patients undergoing re-exploration for bleeding or tamponade after isolated off-pump coronary artery bypass grafting: a case-control study. BMC Cardiovasc Disord. 2021;21(1):204.
472. 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(1):19-26.
473. Ul Islam M, Ahmad I, Khan B, Jan A, Ali N, Hassan Khan W, et al. Early Chest Re-Exploration for Excessive Bleeding in Post Cardiac Surgery Patients: Does It Matter? Cureus. 2021;13(5):e15091.
474. Shou BL, Aravind P, Ong CS, Alejo D, Canner JK, Etchill EW, et al. Early Reexploration for Bleeding Is Associated With Improved Outcome in Cardiac Surgery. Ann Thorac Surg. 2023;115(1):232-9.
475. Ho KM, Bham E, Pavey W. Incidence of Venous Thromboembolism and Benefits and Risks of Thromboprophylaxis After Cardiac Surgery: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2015;4(10):e002652.
476. Panhwar MS, Ginwalla M, Kalra A, Gupta T, Kolte D, Khera S, et al. Association of Acute Venous Thromboembolism With In-Hospital Outcomes of Coronary Artery Bypass Graft Surgery. J Am Heart Assoc. 2019;8(19):e013246.
477. Ahmed AB, Koster A, Lance M, Faraoni D. European guidelines on perioperative venous thromboembolism prophylaxis: Cardiovascular and thoracic surgery. Eur J Anaesthesiol. 2018;35(2):84-9.
478. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e24S-e43S.
479. Cuker A, Arepally GM, Chong BH, Cines DB, Greinacher A, Gruel Y, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2(22):3360-92.
480. Warkentin TE, Sheppard JA. Serological investigation of patients with a previous history of heparin-induced thrombocytopenia who are reexposed to heparin. Blood. 2014;123(16):2485-93.
481. Bakchoul T, Zöllner H, Greinacher A. Current insights into the laboratory diagnosis of HIT. Int J Lab Hematol. 2014;36(3):296-305.
482. Eisenberger J, Somer S, Ram E, Nachum E, Frogal J, Levin S, et al. Treating Heparin-Induced Thrombocytopenia in Patients Undergoing HeartMate 3 Left Ventricular Assist Device Implantation. Isr Med Assoc J. 2023;25(11):757-9.

483. Crow JR, Nam L, Chasler JE, Ong CS, Dane KE, Kickler T, et al. Association of Heparin Dose, Route, Timing, and Duration With Heparin-Induced Thrombocytopenia. Ann Thorac Surg. 2021;112(1):32-7.
484. Hogan M, Berger JS. Heparin-induced thrombocytopenia (HIT): Review of incidence, diagnosis, and management. Vasc Med. 2020;25(2):160-73.
485. Stewart JJ, Turgeon R, Parker A, Koshman S, Omar MA. Comparison of risk-scoring systems for heparin-induced thrombocytopenia in cardiac surgery patients. Pharmacotherapy. 2021;41(12):1033-40.
486. Cutler NS, Marchant BE. Comparison of Screening Scores for Heparin- Induced Thrombocytopenia After Cardiopulmonary Bypass. J Cardiothorac Vasc Anesth. 2022;36(9):3570-5.
487. Joseph L, Gomes MP, Al Solaiman F, St John J, Ozaki A, Raju M, et al. External validation of the HIT Expert Probability (HEP) score. Thromb Haemost. 2015;113(3):633-40.
488. Younis M, Ya'qoub L, Ali Z, Grover P, Ya'acoub R, Hamarshi MS. Comparison of a clinical-laboratory algorithm, 4t and heparin-induced thrombocytopenia expert probability scores in the diagnosis of heparin-induced thrombocytopenia in the critical care setting. Am J Blood Res. 2019;9(3):25-33.
489. Zapata D, Binongo J, Lasanajak Y, Wei J, Leshnower BG, Chen EP, et al. Heparin-Induced Thrombocytopenia in Patients Undergoing Valvular and Aortic Surgery: A Modern Assessment of Risk. Innovations (Phila). 2020;15(3):229-34.
490. Erdoes G, Ortmann E, Martinez Lopez De Arroyabe B, Reid C, Koster A. Role of Bivalirudin for Anticoagulation in Adult Perioperative Cardiothoracic Practice. J Cardiothorac Vasc Anesth. 2020;34(8):2207-14.
491. Gemelli M, Italiano EG, Geatti V, Addonizio M, Cao I, Dimagli A, et al. Optimizing Safety and Success: The Advantages of Bloodless Cardiac Surgery. A Systematic Review and Meta-Analysis of Outcomes in Jehovah's Witnesses. Curr Probl Cardiol. 2024;49(1 Pt B):102078.
492. Chambault AL, Brown LJ, Mellor S, Harky A. Outcomes of cardiac surgery in Jehovah's Witness patients: A review. Perfusion. 2021;36(7):661-71.
493. Vitolo M, Mei DA, Cimato P, Bonini N, Imberti JF, Cataldo P, et al. Cardiac Surgery in Jehovah's Witnesses Patients and Association With Peri-Operative Outcomes: A Systematic Review and Meta-Analysis. Curr Probl Cardiol. 2023;48(9):101789.
494. Helwani MA, De Wet CJ, Pennington B, Abdulnabi S, Moon MR. Severe Acute Blood Loss Anemia in Jehovah's Witnesses Undergoing Cardiac Surgery: Single Academic Center Experience. J Cardiothorac Vasc Anesth. 2023;37(4):513-8.
495. Bolliger D, Erb JM, Tanaka KA. Caring for Jehovah's Witness Patients Undergoing Complex Cardiac Surgery. J Cardiothorac Vasc Anesth. 2023;37(4):519-21.
496. Drillaud N, Cussac V, Bertho PO, Horvais V, Beurrier P, Ternisien C, et al. Efficacy and safety of turoctocog alfa in patients with hemophilia A requiring surgical procedures: A multicentre retrospective study. Transfusion. 2023;63(12):2321-7.
497. Milano G, Banov L, Svahn J, Gucciardo M, Marotta F, Molinari AC. Successful Multidisciplinary Management of Aortic Valve Repair in Severe Hemophilia B with Extended Half-Life Recombinant Factor IX Concentrate. Acta Haematol. 2023;146(4):322-5.
498. Bolliger D, Vandyck K, Tanaka KA. Management of Patients With Hemophilia Undergoing Cardiac Surgery. J Cardiothorac Vasc Anesth. 2022;36(2):539-41.
499. Rajasekhar A, Arnaoutakis GJ, Janelle GM, Harris N, Wynn T, Anderson RD, et al. Multidisciplinary Management of a Hemophilia A Patient Requiring Coronary Artery Bypass Graft Surgery. J Cardiothorac Vasc Anesth. 2022;36(2):534-8.

500. Atti V, Narayanan MA, Patel B, Balla S, Siddique A, Lundgren S, et al. A Comprehensive Review of Mechanical Circulatory Support Devices. Heart Int. 2022;16(1):37-48.
501. Lorusso R, Whitman G, Milojevic M, Raffa G, McMullan DM, Boeken U, et al. 2020 EACTS/ELSO/STS/AATS expert consensus on post-cardiotomy extracorporeal life support in adult patients. Eur J Cardiothorac Surg. 2021;59(1):12-53.
502. Potapov EV, Antonides C, Crespo-Leiro MG, Combes A, Färber G, Hannan MM, et al. 2019 EACTS Expert Consensus on long-term mechanical circulatory support. Eur J Cardiothorac Surg. 2019;56(2):230-70.
503. Kelly J, Malloy R, Knowles D. Comparison of anticoagulated versus non-anticoagulated patients with intra-aortic balloon pumps. Thromb J. 2021;19(1):46.
504. Leick J, Grottke O, Oezkur M, Mangner N, Sanna T, Al Rashid F, et al. What is known in pre-, peri-, and post-procedural anticoagulation in micro-axial flow pump protected percutaneous coronary intervention? Eur Heart J Suppl. 2022;24(Suppl J):J17-j24.
505. Balthazar T, Vandenbriele C, Verbrugge FH, Den Uil C, Engström A, Janssens S, et al. Managing Patients With Short-Term Mechanical Circulatory Support: JACC Review Topic of the Week. J Am Coll Cardiol. 2021;77(9):1243-56.
506. Adatya S, Bennett MK. Anticoagulation management in mechanical circulatory support. J Thorac Dis. 2015;7(12):2129-38.
507. Raffini L. Anticoagulation with VADs and ECMO: walking the tightrope. Hematology Am Soc Hematol Educ Program. 2017;2017(1):674-80.
508. Helms J, Frere C, Thiele T, Tanaka KA, Neal MD, Steiner ME, et al. Anticoagulation in adult patients supported with extracorporeal membrane oxygenation: guidance from the Scientific and Standardization Committees on Perioperative and Critical Care Haemostasis and Thrombosis of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2023;21(2):373-96.
509. Rajsic S, Breitkopf R, Jadzic D, Popovic Krneta M, Tauber H, Treml B. Anticoagulation Strategies during Extracorporeal Membrane Oxygenation: A Narrative Review. J Clin Med. 2022;11(17).
510. Sigala MI, Harris JE, Morton C, Donahue KR, Kim JH. A case series analysis of bicarbonate-based purge solution administration via Impella ventricular assist device. Am J Health Syst Pharm. 2024;81(5):e115-e21.
511. Bashline M, DiBridge J, Klass WJ, Morelli B, Kaczorowski D, Schmidhofer M, et al. Outcomes of systemic bivalirudin and sodium bicarbonate purge solution for Impella 5.5. Artif Organs. 2023;47(2):361-9.
512. De Paulis S, Cavaliere F. Anticoagulation Management in High Bleeding-Risk ECMO in Adults. Front Cardiovasc Med. 2022;9:884063.
513. Levy JH, Staudinger T, Steiner ME. How to manage anticoagulation during extracorporeal membrane oxygenation. Intensive Care Med. 2022;48(8):1076-9.
514. Frantzeskaki F, Konstantonis D, Rizos M, Kitsinelis V, Skyllas G, Renieris I, et al. Extracorporeal Membrane Oxygenation (ECMO)-Associated Coagulopathy in Adults. Diagnostics (Basel). 2023;13(23).
515. Mirus M, Heubner L, Kalbhenn J, Spieth PM. Hemostatic disorders associated with extracorporeal membrane oxygenation. Minerva Anestesiol. 2023;89(6):586-96.
516. Bembea MM, Annich G, Rycus P, Oldenburg G, Berkowitz I, Pronovost P. Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey. Pediatr Crit Care Med. 2013;14(2):e77-84.

517. Esper SA, Welsby IJ, Subramaniam K, John Wallisch W, Levy JH, Waters JH, et al. Adult extracorporeal membrane oxygenation: an international survey of transfusion and anticoagulation techniques. Vox Sang. 2017;112(5):443-52.
518. Guglin M, Zucker MJ, Bazan VM, Bozkurt B, El Banayosy A, Estep JD, et al. Venoarterial ECMO for Adults: JACC Scientific Expert Panel. J Am Coll Cardiol. 2019;73(6):698-716.
519. Chung YS, Cho DY, Sohn DS, Lee WS, Won H, Lee DH, et al. Is Stopping Heparin Safe in Patients on Extracorporeal Membrane Oxygenation Treatment? Asaio j. 2017;63(1):32-6.
520. Fitousis K, Klasek R, Mason PE, Masud F. Evaluation of a pharmacy managed heparin protocol for extracorporeal membrane oxygenation patients. Perfusion. 2017;32(3):238-44.
521. Feih JT, Wallskog KE, Rinka JRG, Juul JJ, Rein L, Gaglianello N, et al. Heparin Monitoring with an Anti-Xa Protocol Compared to Activated Clotting Time in Patients on Temporary Mechanical Circulatory Support. Ann Pharmacother. 2022;56(5):513-23.
522. Willems A, Roeleveld PP, Labarinas S, Cyrus JW, Muszynski JA, Nellis ME, et al. Anti-Xa versus time-guided anticoagulation strategies in extracorporeal membrane oxygenation: a systematic review and meta-analysis. Perfusion. 2021;36(5):501-12.
523. Rajsic S, Treml B, Jadzic D, Breitkopf R, Oberleitner C, Bachler M, et al. aPTT-guided anticoagulation monitoring during ECMO support: A systematic review and meta-analysis. J Crit Care. 2023;77:154332.
524. Ranucci M, Cotza M, Isgrò G, Carboni G, Ballotta A, Baryshnikova E. Anti-Factor Xa-Based Anticoagulation during Extracorporeal Membrane Oxygenation: Potential Problems and Possible Solutions. Semin Thromb Hemost. 2020;46(4):419-27.
525. Nguyen TP, Phan XT, Huynh DQ, Viet Truong HT, Hai Le YN, Nguyen TM, et al. Monitoring Unfractionated Heparin in Adult Patients Undergoing Extracorporeal Membrane Oxygenation (ECMO): ACT, APTT, or ANTI-XA? Crit Care Res Pract. 2021;2021:5579936.
526. Morici N, Varrenti M, Brunelli D, Perna E, Cipriani M, Ammirati E, et al. Antithrombotic therapy in ventricular assist device (VAD) management: From ancient beliefs to updated evidence. A narrative review. Int J Cardiol Heart Vasc. 2018;20:20-6.
527. McDavid A, MacBrair K, Emani S, Yu L, Lee PHU, Whitson BA, et al. Anticoagulation management following left ventricular assist device implantation is similar across all provider strategies. Interact Cardiovasc Thorac Surg. 2018;26(1):60-5.
528. Mehra MR, Netuka I, Uriel N, Katz JN, Pagani FD, Jorde UP, et al. Aspirin and Hemocompatibility Events With a Left Ventricular Assist Device in Advanced Heart Failure: The ARIES-HM3 Randomized Clinical Trial. Jama. 2023;330(22):2171-81.
529. Sadana D, Pratzer A, Scher LJ, Saag HS, Adler N, Volpicelli FM, et al. Promoting High-Value Practice by Reducing Unnecessary Transfusions With a Patient Blood Management Program. JAMA Intern Med. 2018;178(1):116-22.
530. Althoff FC, Neb H, Herrmann E, Trentino KM, Vernich L, Füllenbach C, et al. Multimodal Patient Blood Management Program Based on a Three-pillar Strategy: A Systematic Review and Meta-analysis. Ann Surg. 2019;269(5):794-804.
531. Gammon RR, Blanton K, Gilstad C, Hong H, Nichols T, Putnam H, et al. How do we obtain and maintain patient blood management certification? Transfusion. 2022;62(8):1483-94.
532. Sullivan HC, Roback JD. The pillars of patient blood management: key to successful implementation (Article, p. 2840). Transfusion. 2019;59(9):2763-7.
533. Auron M. Blood Management: A Current Opportunity in Perioperative Medicine. JMIR Perioper Med. 2024;7:e57012.

534. Hofmann A, Spahn DR, Holtorf AP. Making patient blood management the new norm(al) as experienced by implementors in diverse countries. BMC Health Serv Res. 2021;21(1):634.
535. Mehaffey JH, Schubert SA, Gelvin MG, Charles EJ, Hawkins RB, Johnston LE, et al. A New Intraoperative Protocol for Reducing Perioperative Transfusions in Cardiac Surgery. Ann Thorac Surg. 2017;104(1):176-81.
536. 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(5):788-94.
537. Fischer DP, Zacharowski KD, Müller MM, Geisen C, Seifried E, Müller H, et al. Patient blood management implementation strategies and their effect on physicians' risk perception, clinical knowledge and perioperative practice - the frankfurt experience. Transfus Med Hemother. 2015;42(2):91-7.
538. Rancati V, Scala E, Ltaief Z, Gunga MZ, Kirsch M, Rosner L, et al. Challenges in Patient Blood Management for Cardiac Surgery: A Narrative Review. J Clin Med. 2021;10(11).
539. LaPar DJ, Crosby IK, Ailawadi G, Ad N, Choi E, Spiess BD, et al. Blood product conservation is associated with improved outcomes and reduced costs after cardiac surgery. J Thorac Cardiovasc Surg. 2013;145(3):796-803; discussion -4.
540. Paone G, Brewer R, Likosky DS, Theurer PF, Bell GF, Cogan CM, et al. Transfusion rate as a quality metric: is blood conservation a learnable skill? Ann Thorac Surg. 2013;96(4):1279-86.

Central image

Click here to access/download;Figure;Central illustration_EJCTS.pdf

Multidisciplinary patient blood management approach

1 Prior admission

- Physical examination, bleeding history and medication review
- Evaluation by risk scores, complete blood count, and coagulation tests
- Identification of anaemia, its causes, and its timely treatment

2 Preoperative

- Identification of patients with high risk of bleeding
- Guideline-directed management of antithrombotic medication
- Platelet function testing in patients on DAPT
- Fibrinogen level testing

3 Intraoperative

- Maintenance of haemostasis and minimising blood loss
- Minimising haemodilution through optimising CPB systems, autologous priming, and ultrafiltration
- Identification of anaemia, its causes, and its timely treatment
- Maintenance of normothermia and normal pH
- Management of heparin and protamine dosage
- Prevention of fibrinolysis
- Cell salvage usage

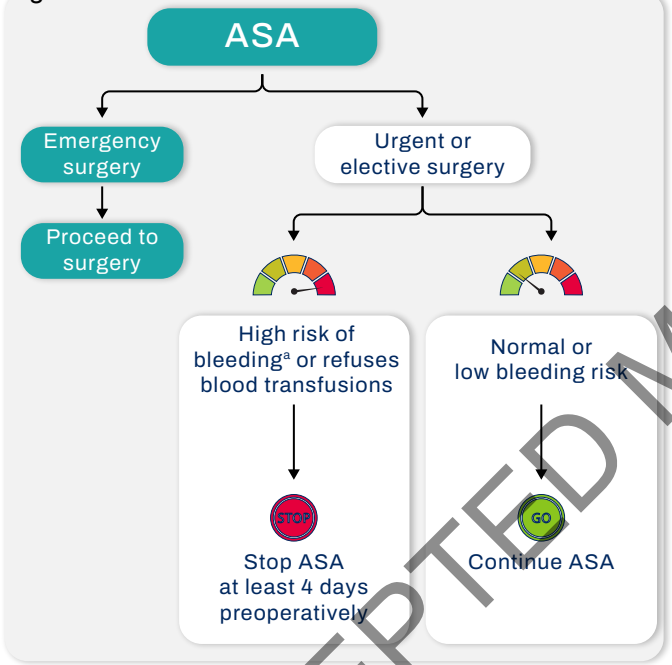
4 Postoperative

- Algorithms for bleeding patients using POC tests
- Fibrinogen supplementation in bleeding patients with low leveles (<1.5 g/L)
- Identification of anaemia, its causes, and its timely treatment
- PCC or FFP in bleeding patients with coagulation factor deficiency
- Platelet transfusion in bleeding patients if platelet count is $<50x10^9$/L and/or DDAVP on antiplatelets
- PRBC of all ages using restrictive transfusion triggers
- Early reexploration for bleeding

eactaic European Association of Cardiothoracic Anaesthesiology and Intensive Care

EACTS EUROPEAN ASSOCIATION FOR CARDIO-THORACIC SURGERY

Figure 1



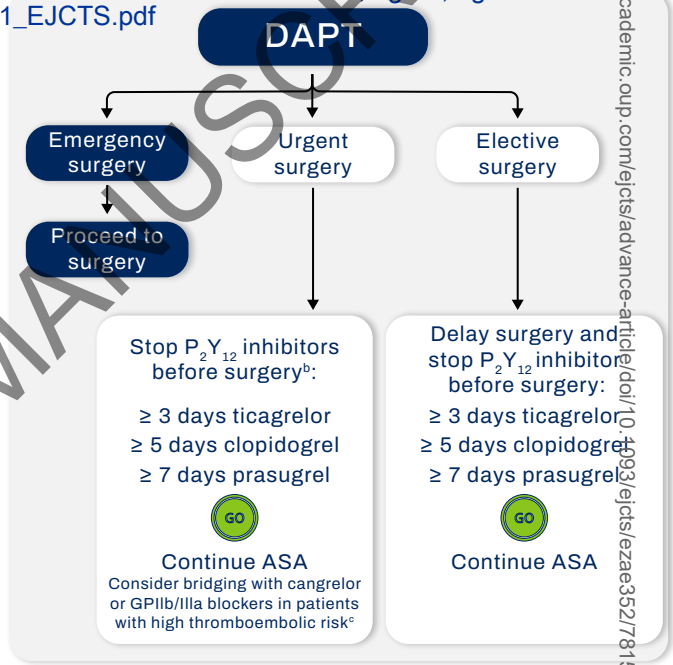


Figure 2

Click here to access/download:Figure:Figure 2_EJCTS.pdf

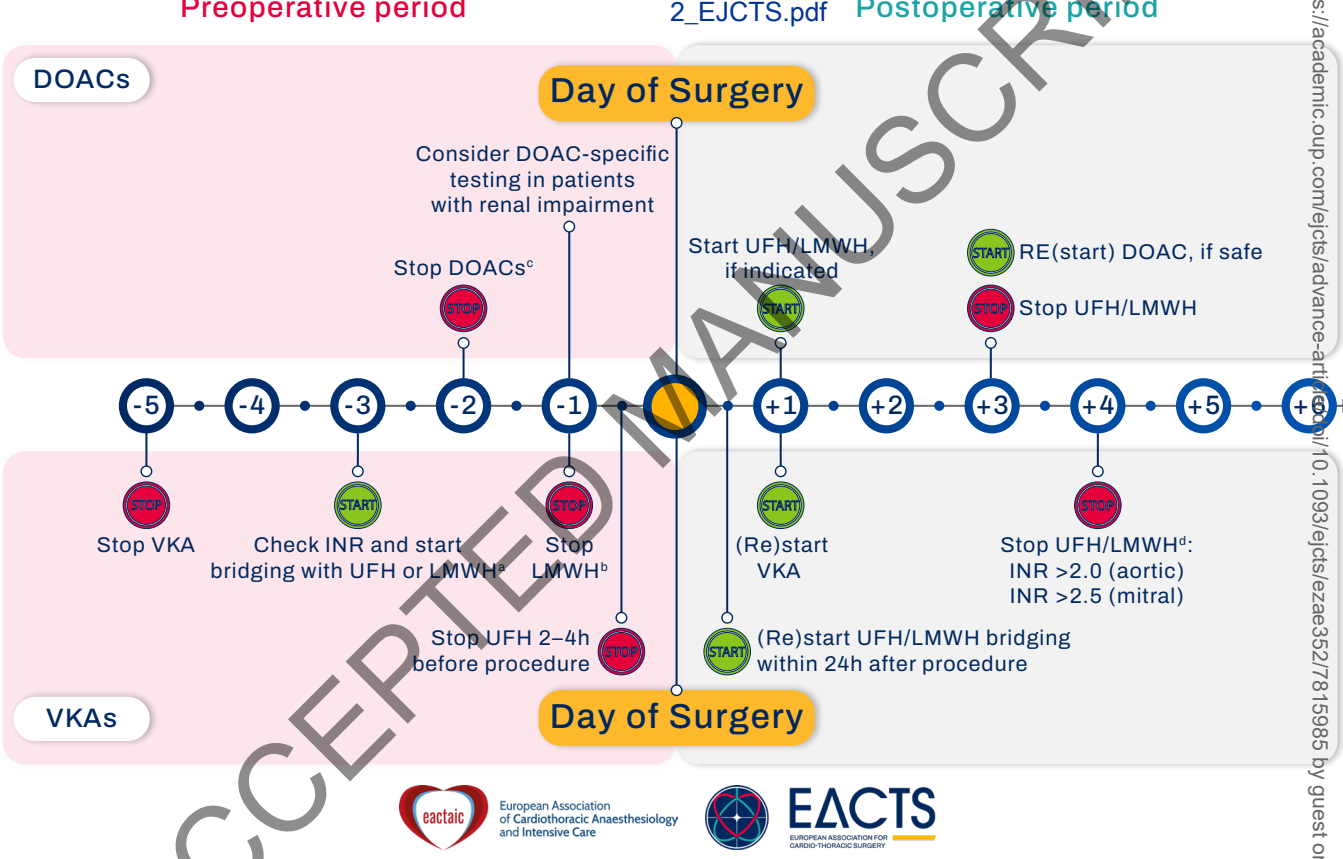


Figure 3

Click here to access/download;Figure;Figure 3_EJCTS FINAl.pdf

eacta ic European Association of Cardiothoracic Anaesthesiology and Intensive Care

EACTS EUROPEAN ASSOCIATION FOR CARDIO-THORACIC SURGERY