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Review Article

Methodologic Quality and Pharmacotherapy Recommendations for Patient Blood Management Guidelines for Cardiac Surgery on Cardiopulmonary Bypass

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Patient blood management (PBM) guidelines for patients undergoing cardiac surgery under cardiopulmonary bypass (CPB) have increased during the past decade, and pharmacotherapy plays an important role in PBM. In the face of the undefined consistency in the methodologic quality and pharmacotherapy recommendations across multiple guidelines, this study exclusively evaluated methodologies of the related guideline development process, and compiled medication recommendations of PBM for cardiac surgery patients. PBM guidelines for cardiac surgery under CPB were searched through some mainstream literature and guideline databases from database establishment to May 15, 2023. Nine guidelines meeting inclusion criteria were included in this study. The quality of the guidelines was evaluated using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool. "Stakeholder involvement" received the lowest mean score of 49.38% in the AGREE II scoring among the guidelines. PBM for cardiac surgery patients spans the perioperative phase. Drug therapy strategies of PBM for cardiac surgery patients involve anemia therapy, perioperative administration of antithrombotic drugs, intraoperative anticoagulation, and the use of hemostatic drugs. Unlike for adults, there is less evidence about the management of antithrombotic drugs and hemostatic drugs for pediatric cardiac surgery patients. Recombinant activated factor VII (rFVIIa) and desmopressin (DDAVP) are not recommended after pediatric cardiac surgery, whereas prothrombin complex concentrate could be considered in clinical trials. As for the controversies regarding the administration of rFVIIa and DDAVP after adult cardiac surgery by different societies, clinicians should exercise their clinical judgment based on individual patient features.

Key Words: cardiopulmonary bypass; cardiac surgery; patient blood management; Appraisal of Guidelines for Research and Evaluation II; pharmacotherapy recommendation

HEMORRHAGE OCCURRING during cardiac surgery constitutes a severe clinical occurrence, often linked to perioperative anemia and the need for allogeneic blood transfusion.[1] Among various surgical procedures, cardiac surgery has the highest rate of allogeneic blood transfusion, primarily due to the unique intricacies of the surgical site and the impact of cardiopulmonary bypass (CPB).[2] The coagulation system in pediatric patients, as opposed to adults, is characterized by immaturity, rendering it more susceptible to blood dilution during CPB. Notably, intricate surgical interventions addressing cyanotic congenital heart diseases amplify the complexity further, accentuating the propensity for postoperative bleeding and the subsequent requirement for reoperation.[3] Recognizing

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this context, Resolution WA63.12 of the 63rd World Health Assembly in 2010 ardently advocated for the adoption of patient blood management (PBM). This approach hinges on collaborative efforts across multidisciplinary domains such as cardiac surgery, anesthesiology, and extracorporeal circulation. The central objective is to enhance patients' clinical outcomes by rectifying anemia, optimizing blood volume, augmenting coagulation function, and strategically minimizing the need for allogeneic blood transfusions.

Blood management of cardiac patients undergoing surgery with CPB covers a wide range of factors, such as blood transfusion management, surgical technology innovation, extracorporeal circulation support, and pharmacotherapy management, each of which is crucial. In the past decade, guidelines around PBM have been continuously emerging, but the development period of different guidelines is long, the expert panels are different, the research population is wide (including adults and children), and the methods for evaluating evidence quality are not completely consistent. The above factors probably lead to significant heterogeneity in the recommendations of PBM guidelines for patients undergoing cardiac surgery with CPB, which is a dilemma that clinicians have to face when making therapy decisions.

In this article, the authors used the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool to evaluate the methodologic strictness and clarity of the blood management guidelines for patients undergoing CPB cardiac surgery, and assembled drug therapy recommendations among different guidelines to provide detailed medication references for blood management of patients undergoing cardiac surgery with CPB.

Methods

Guideline Search Strategy, Guideline Selection, and Data Extraction

A comprehensive search was conducted across multiple literature databases, including Foreign Medical Literature Retrieval Service, PubMed, China National Knowledge Infrastructure, and WanFang Data, to October 15, 2023. The objective was to identify relevant guidelines for PBM in the context of CPB cardiac surgery, incorporating a range of keywords such as "cardiac surgery," "cardiovascular surgery," "patient blood management," "PBM," "cardiopulmonary bypass," and "CPB." Furthermore, guideline databases, including National Guideline Clearinghouse, National Institute for Health and Clinical Excellence, Scottish Intercollegiate Guidelines Network, and Guidelines International Network, were also searched.

The authors incorporated guidelines on PBM for cardiac surgery under CPB. In instances in which a guideline was available in both English and Chinese, only the English version was included. Furthermore, in cases in which updates had been published, only the most recent version of the guideline was included. Literature falling into the following categories was excluded: (1) expert consensus; (2) interpretations of existing guidelines; (3) guidelines inaccessible in their full text; and (4) guidelines published in languages other than English or Chinese.

Two researchers independently assessed the identified literature for the title and abstract, and conducted independent screening of literature directly from official websites. Divergences were resolved by a third researcher in instances when disparities in judgment arose. Subsequently, a comprehensive review of the full texts was undertaken, which was overseen exclusively by a fourth researcher.

For every included guideline on PBM for cardiac surgery, the following data were collected systematically: (1) fundamental characteristics about the guideline, such as the title, the platform or journal of publication, publication date, country of origin, the institution responsible for the development process, and target patient population; and (2) characteristics about the development of the guideline, including the type of evidence and the tools employed for evidence evaluation. The above data were extracted independently by 2 researchers. Examination of the extracted data was conducted subsequently by a third researcher. Any discrepancies that surfaced were resolved by a fourth researcher.

Quality Evaluation of Guidelines

The AGREE II tool was used to assess the methodologic quality of the included guidelines. This instrument comprises a set of 23 items categorized into 6 domains. The score of each item spans a range from 1 (indicating strong disagreement) to 7 (reflecting strong agreement). The cumulative score for each domain was computed by summing the individual scores of all items within the domain, a process independently undertaken by 4 researchers. These domain scores were then normalized using the following formula: (acquired score − minimum possible score) / (maximum possible score − minimum possible score). Finally, mean scores for each domain among all the included guidelines were calculated.

Data Analysis

A descriptive analysis was carried out to elucidate the characteristics of the guidelines encompassed in the study. To ensure the consistency of evaluation among the 4 researchers regarding AGREE II scores, intraclass correlation coefficients were calculated. Furthermore, guidance on drug therapy was gathered systematically concerning PBM in the context of cardiac surgery from the included guidelines.

Results

Search Results

A total of 483 publications were identified initially, and 9 guidelines[2-10] were deemed eligible for inclusion in the study through rigorous screening. All of these guidelines were published exclusively in English. The guideline selection procedure is presented in Fig 1.

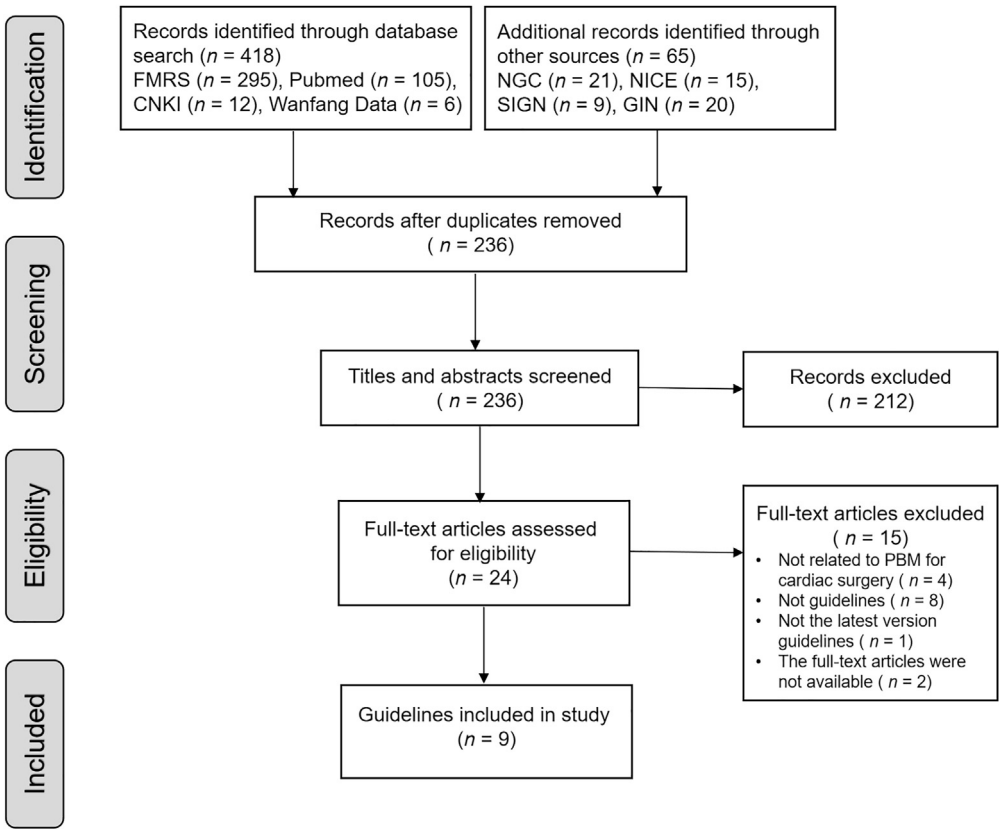

Fig 1. Flowchart of guideline selection procedure. CNKI, China National Knowledge Infrastructure; FMRS, Foreign Medical Literature Retrieval Service; GIN, Guidelines International Network; NGC, National Guideline Clearinghouse; NICE, National Institute for Health and Clinical Excellence; SIGN, Scottish Intercollegiate Guidelines Network.

Characteristics of the Included Guidelines

Among the 9 included guidelines, 2[2,3] were formulated by international panels, whereas an additional 2[6,10] originated from European panels. In the remaining 5 guidelines, 2[4,7] hailed from America, 1[5] from Australia, 1[8] from France, and 1[9] from Britain. These guidelines were published within the time span from December 24, 2014 to April 1, 2023. The detailed guideline characteristics are shown in Table 1.

Quality of the Included Guidelines

The interrater reliability among the 4 researchers for AGREE II evaluations yielded a high intraclass correlation coefficient value of 0.927 (95% CI, 0.908-0.935). All the guidelines included in this study were considered of medium-to-high quality according to the AGREE II assessment. When examining individual domains, "stakeholder involvement" received the lowest mean score of 49.38% across all of the guidelines. The guideline developed by the 2018 PBM International Consensus Conference[2] achieved the highest score (91.32%), whereas the guideline formulated by the European Society of Anaesthesiology and Intensive Care[10] obtained the lowest score (74.54%) (Fig 2).

Compilation of Pharmacotherapy Recommendations

All the included guidelines[2-10] provided evidence-based medication recommendations for the blood management of patients undergoing cardiac surgery with CPB. This guidance encompassed anemia therapy, administration of various antithrombotic drugs, and the use of hemostatic agents.

Preoperative anemia was recommended to be corrected according to the etiology, either by iron supplements[2,3,5-8,10] or erythropoietin,[2,3,5-7,10] to reduce the need for transfusion for both adult and pediatric patients. Aspirin as secondary prevention for cardiovascular events was not recommended to be interrupted before cardiac surgery,[6,10] except for primary prevention.[6,7,10] In patients at high risk of thrombosis, warfarin was recommended to be bridged with unfractionated heparin or low-molecular- weight heparin before surgery.[6,10] Regarding intraoperative anticoagulation, protamine was recommended to neutralize heparin upon withdrawal of CPB, with a protamine-to-heparin dosing ratio of less than 1:1 to reduce the risk of bleeding for both adult and pediatric patients.[3,6,10] Unlike other hemostatic agents, systematic antifibrinolytics could be administered prophylactically in cardiac surgery under CPB, whereas others were mainly for the treatment of hemorrhage.[3-7,9,10] Prothrombin complex concentrate was recommended in deficiency of coagulation factors,[3-7,10] whereas fibrinogen was recommended for bleeding patients with hypofibrinogenemia.[3-7,9,10] More details are shown in Table 2.

Table 1
Characteristics of the PBM Guidelines Included for Cardiac Surgery

Title	Platform or Journal of Publication	Publication Date	Country of Origin	Institution Responsible for the Development	Target Patient Population	Type of Evidence	Tools for Evidence Evaluation	Reference Number
Patient blood management recommendations from the 2018 Frankfurt consensus conference	The Journal of the American Medical Association	March 12, 2019	International	2018 PBM International Consensus Conference	Adults	Systematic retrieval of currently available evidence	GRADE	2
Patient blood management for neonates and children undergoing cardiac surgery: 2019 NATA guidelines	Journal of Cardiothoracic and Vascular Anesthesia	March 20, 2019	International	NATA	Neonates and Children	Systematic retrieval of currently available evidence	GRADE	3
Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management	Anesthesiology	December 24, 2014	America	ASA	Adults	Systematic retrieval of currently available evidence	ASA criteria	4
Patient blood management guidelines: module 6 − neonatal and paediatrics	NBA website	April 29, 2016	Australia	NBA	Neonates and Children	Systematic retrieval of currently available evidence	NHMRC criteria	5
2017 EACTS/ EACTA Guidelines on patient blood management for adult cardiac surgery	European Journal of Cardio-Thoracic Surgery	September 30, 2017	Europe	EACTS/EACTA	Adults	Systematic retrieval of currently available evidence	EACTS criteria	6
STS/SCA/AmSECT/SABM Update to the clinical practice guidelines on patient blood management	Journal of Cardiothoracic and Vascular Anesthesia	June 30, 2021	America	STS/SCA/AmSECT/ SABM	Adults	Systematic retrieval of currently available evidence	ACC/AHA criteria	7
Guidelines on enhanced recovery after cardiac surgery under cardiopulmonary bypass or off-pump	Anaesthesia Critical Care & Pain Medicine	April 30, 2022	France	SFAR/SFCTCV	Adults	Systematic retrieval of currently available evidence	GRADE	8
Haematological management of major haemorrhage: a British Society for Haematology Guideline	British Journal of Haematology	August 20, 2022	Britain	BSH	Adults	Systematic retrieval of currently available evidence	GRADE	9
Management of severe peri-operative bleeding: guidelines from the European Society of Anaesthesiology and Intensive Care: Second update 2022	European Journal of Anaesthesiology	April 1, 2023	Europe	ESAIC	Adults, neonates, and children	Systematic retrieval of currently available evidence	GRADE	10

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; AmSECT, American Society of Extra Corporeal Technology; ASA, American Society of Anesthesiologists; BSH, British Society for Haematology; EACTA, European Association of Cardiothoracic Anesthesiology; EACTS, European Association for Cardio-Thoracic Surgery; ESAIC, European Society of Anaesthesiology and Intensive Care; GRADE, Grading of Recommendation, Assessment, Development, and Evaluation; NATA, Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis; NBA, National Blood Authority (Australian); NHMRC, National Health and Medical Research Council; PBM, Patient Blood Management; SABM, Society for Advancement of Blood Management; SCA, Society of Cardiovascular Anesthesiologists; SFAR, French Society of Anaesthesia and Intensive Care Medicine; SFCTCV, French Society of Thoracic and Cardiovascular Surgery; STS, Society of Thoracic Surgeons.

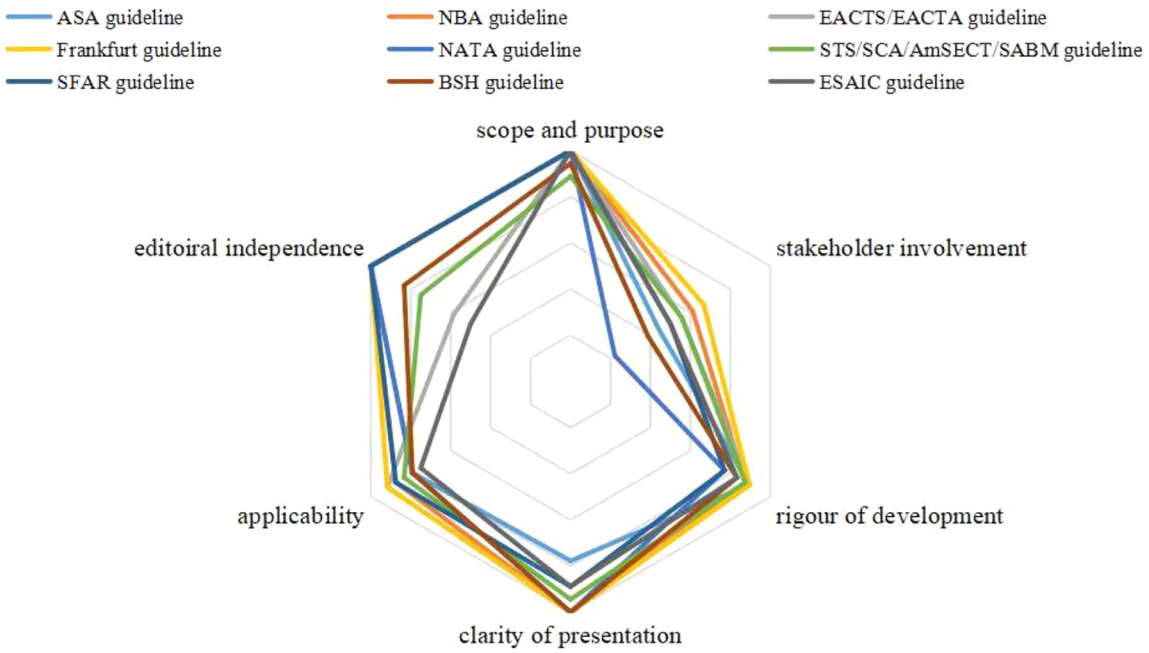

Fig 2. AGREE II scores by domain of the included guidelines. The different lines represent guidelines developed in different institutes or organizations. The radial coordinates represent the scores of the AGREE II tool. AmSECT, American Society of Extra Corporeal Technology; ASA, American Society of Anesthesiologists; BSH, British Society for Haematology; EACTA, European Association of Cardiothoracic Anesthesiology; EACTS, European Association for Cardio-Thoracic Surgery; ESAIC, European Society of Anaesthesiology and Intensive Care; NATA, Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis; NBA, National Blood Authority(Australian); SABM, Society for Advancement of Blood Management; SCA, Society of Cardiovascular Anesthesiologists; SFAR, French Society of Anaesthesia and Intensive Care Medicine; STS, Society of Thoracic Surgeons.

Discussion

This study estimated the methodologic rigor and transparency in the guideline development process and compiled pharmacotherapy recommendations from PBM guidelines for cardiac surgery. Overall, the 9 guidelines included were of medium-to-high quality, and the guidance they provided varied depending on the target patients and the development societies.

Quality of the Included Guidelines

Out of the 9 included guidelines, 8[3-10] demonstrated a medium level of quality, whereas 1[2] exhibited high-quality attributes. The domain of "stakeholder involvement" recorded lower scores across all guidelines, with a particularly low score observed in 1 guideline,[3] at <30%. This pattern can be attributed to 2 primary factors. Firstly, there appeared to be a widespread lack of emphasis on incorporating and prioritizing the perspectives of the target population within the guideline development process. Secondly, guideline development panels often consist of cardiac surgeons, anesthesiologists, and specialists in extracorporeal circulation. However, not all pertinent professionals are always included in the development process. To elevate stability in guideline quality, it is imperative that guideline developers earnestly consider the viewpoints of the population the guidelines are intended to serve. Furthermore, the inclusion of a broader array of relevant professionals, including pharmacists, can greatly enhance the comprehensive nature of guideline creation.

Pharmacotherapy Recommendations in PBM for Cardiac Surgery

Pharmacotherapy recommendations for blood management in cardiac surgery patients are not completely consistent among adult and pediatric patients across different guidelines. For example, there is high consistency in the management of preoperative anemia and intraoperative anticoagulation, but there are certain differences in perioperative antithrombotic drug utility and administration of individual hemostatic drugs.

Within the realm of cardiac patients, iron deficiency anemia stands out as the prevailing form of anemia, followed closely by noniron deficiency anemia.[11,12] Although the significance of iron supplementation for correcting anemia was ambiguous in early studies,[13-15] more and more recent evidence[16-21] suggests that both iron and erythropoietin play indispensable therapeutic roles, which is beneficial for reducing blood transfusion requirement. In future research, more attention should be paid to the initiation window and therapeutic regimen for treating preoperative anemia of cardiac patients.

For intraoperative anticoagulation, the administration of protamine is recommended while adhering to a ratio of less than 1:1 with the initial heparin dose. This cautionary approach aims to avert excessive protamine administration, which could potentially trigger perioperative bleeding.[6] In patients in whom heparin is contraindicated, as is the situation with heparin-induced thrombocytopenia (HIT), direct thrombin inhibitors (DTIs) offer an alternative for intraoperative anticoagulation. Among the various DTIs, bivalirudin emerges

Table 2
Pharmacotherapy Recommendations of Included Guidelines

Drugs/Situations	Pharmacotherapy Recommendations	Reference
Preoperative and Postoperative		
Anemia	Use of erythropoietin with or without iron is recommended to reduce the need of transfusion.	4
	Use of iron supplementation in preoperative patients undergoing elective surgery to correct iron deficiency anemia.	2, 3, 5-8, 10
	Use of erythropoietin in preoperative patients undergoing elective surgery to correct non-iron deficiency anemia.	2, 3, 5-7, 10
Antiplatelet drugs	No need to interrupt aspirin for secondary prevention throughout the preoperative period, especially in patients undergoing CABG.	6, 10
	Interruption of aspirin for primary prevention before elective non-CABG.	6, 7, 10
	Regarding discontinuation of aspirin, a time of 5 d from the last intake to intervention is recommended for surgeries at high risk of bleeding.	6, 10
	Ticagrelor should be ceased preoperatively for a minimum of 3 d, clopidogrel for 5 d, and prasugrel for 7 d.	6, 7, 10
	No need to bridge oral antiplatelet therapy with LMWH in general.	10
	In high−ischemic-risk patients, P2Y12 inhibitors bridged with glycoprotein IIbIIIa inhibitors or cangrelor may be considered.	10
	Aspirin or P2Y12 inhibitors may be resumed postoperatively in the early period without increasing the risk of bleeding.	6, 10
Anticoagulants	In high−thrombotic-risk patients, bridging warfarin with UFH or LMWH before cardiac surgery may be considered.	6, 10
	Elective cardiac surgery should be performed if INR is <1.5 in patients taking warfarin. If necessary, coagulation factors should be used to reverse the effect.	6, 10
	Patients taking warfarin preoperatively should resume warfarin within first day after surgery, using prophylactic doses of LMWH to bridge warfarin until the target INR.	10
	For patients with postoperative bleeding, start bridging warfarin with therapeutic doses of LMWH 2 to 3 d after surgery once the hemorrhage has been controlled.	10
	DOACs should be stopped at least 2 d before elective cardiac surgery. A longer interval may be necessary for patients with impaired renal function.	6, 10
Intraoperative and Postoperative		
Anticoagulation	Upon withdrawal from CPB, heparin monitoring is recommended to avoid protamine-to-heparin dosing ratios above 1:1.	3, 6, 10
	In case of heparin contraindication, DTIs should be considered as alternative for anticoagulation during CPB with extreme caution as the last resort.	3, 6
Antifibrinolytics	Systematic administration of antifibrinolytics (TXA and EACA) is recommended before cardiac surgery on CPB.	3-7, 9, 10
	Local application of antifibrinolytics to the surgical site after cardiac surgery is recommended to limit drainage from the chest tube.	7
PCC	The administration of PCC may be considered to reverse the action of VKAs.	6, 10
	PCC is recommended for refractory bleeding related to coagulation factor deficiency.	3-7, 10
Fibrinogen	Prophylactic fibrinogen administration is not recommended.	6
	Fibrinogen substitution may be considered in bleeding patients with a low fibrinogen level (<1.5 g/L).	3-7, 9, 10
rFVIIa	The prophylactic use of rFVIIa to prevent bleeding is not recommended.	6
	Off-label use of rFVIIa may be considered for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures.	7, 10
	Not recommended in the treatment of massive bleeding after surgery unless in the context of clinical trials.	9
	The administration of rFVIIa to treat acquired coagulopathy in neonates and children undergoing cardiac surgery is not recommended.	3, 5
DDAVP	The prophylactic use of DDAVP to reduce bleeding is not recommended.	6
	In bleeding patients with platelet dysfunction based on an inherited or acquired bleeding disorder, the use of DDAVP should be considered.	4, 6, 7
	Not recommended in the treatment of massive bleeding after surgery unless in the context of clinical trials.	9
	Not recommended for bleeding management in children undergoing cardiac surgery.	3, 5

Abbreviations: CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; DDAVP, desmopressin; DOACs, direct oral anticoagulants; DTIs, direct thrombin inhibitors; EACA, ε-aminocaproic acid; INR, international normalized ratio; LMWH, low molecular weight heparin; PCC, prothrombin complex concentrate; Ref, reference; rFVIIa, recombinant activated factor VII; TXA, tranexamic acid; UFH, unfractionated heparin; VKAs, vitamin K antagonist.

as the primary focus, notably studied in prospective multicenter clinical trials involving patients with HIT undergoing adult cardiac surgery,[22-24] as well as in a prospective randomized clinical trial concerning cardiac surgery in noncyanotic pediatric patients.[25] However, due to the unique pharmacokinetic characteristics of bivalirudin and the lack of specific antidotes, both medical and perfusion management must be modified to maximize the balance between hemorrhage and thrombosis for patients with HIT antibodies.[26] At present, further clarification is needed on the standardized medication regimen for patients undergoing cardiac surgery.

The perioperative management of antithrombotic drugs is aimed at mitigating the risks of bleeding while addressing cardiovascular events. To date, constantly refined evidence-based proof relates exclusively to adult cardiac patients, and the evidence provided by different societies is not completely

consistent. Compared with cardiac surgery, anesthesiology, and extracorporeal societies, an intensive care society provided more comprehensive recommendations, even including guidance for preoperative antiplatelet drug bridging and postoperative resumption of vitamin K antagonist.[6,7,10]

The strategic use of various hemostatic drugs is equally a pivotal facet of cardiac surgery, aimed at reducing bleeding and mitigating the associated risk. Before surgery, the prophylactic systematic administration of lysine analogs emerges as an effective approach to substantially curtail total blood loss, volume of blood transfusion, and transfusion rate.[27,28] Notably, further research is warranted to illuminate the intricate interplay between dosage and efficacy, as well as the optimal drug concentration for these lysine analogs, whether for adults or children undergoing cardiac surgery with CPB.[3,6] The recommendation for local application of antifibrinolytics after cardiac surgery with CPB is relatively limited and only reflected in one guideline[7] for adult cardiac patients, largely due to the difficulty of conducting clinical randomized controlled trials for local application of hemostatic drugs. In addition, for several other hemostatic drugs, especially PCC, rFVIIa, and DDAVP, relatively few studies have been conducted in pediatric patients in the context of cardiac surgery with CPB. Up to now, rFVIIa and DDAVP are not recommended for blood management in pediatric patients undergoing CPB surgery,[3,5] whereas PCC is recommended only for pediatric patients undergoing surgery with CPB in special situations, such as clinical trials.[3,5] Furthermore, as a result of different tools adopted for evidence quality evaluation by different development panels and the continuous advancement of clinical research, recommendations for the application of rFVIIa and DDAVP in bleeding in adult cardiac surgery patients are not quite consistent across different guidelines. Based on the 2012 Cochrane review[29] suggesting that rFVIIa has only a mild effect on reducing bleeding, induces a controversial reduction in mortality, and confers an increased risk of arterial embolism, the British Society for Haematology guideline[9] does not recommend rFVIIa for postoperative major bleeding unless in clinical trials, which is more stringent than the other 2 guidelines.[6,7] Though the benefit of DDAVP in reducing blood loss and blood transfusion has been indicated, especially in patients with platelet dysfunction,[30] DDAVP also has been shown to be associated with an increased risk of cardiovascular events, including hyponatremia and hypotension.[31,32] Considering the lack of robust evidence of the definite effectiveness and the need for further data on the safety profile of cardiovascular patients, DDAVP is not recommended for treating massive bleeding after surgery unless in the situation of clinical trials.[9] Overall, the administration of hemostatic agents in cardiac surgery is guided by a complex interplay of factors, necessitating a tailored approach that aligns with the specific needs and characteristics of both adult and pediatric patient populations.

Limitations

It is important to acknowledge the study's limitations. Firstly, some guidelines may have been omitted due to being published after the search end date used in this study. Secondly, guidelines were written in different years, and different evidence was available at different periods, which led to inconsistency in the evidence. Thirdly, the evidence quality evaluation tools adopted in different guidelines were inconsistent, which unavoidably impacted the overall reliability of the study's findings. Fourthly, although the management of antithrombotic drugs is critical for both adult and pediatric patients, this study focused primarily on medication strategies for adults. The absence of clear recommendations for children highlights an important gap that warrants further research and consideration.

Conclusions

The existing PBM guidelines for cardiac surgery are of medium-to-high quality. Pharmacotherapy strategies span the entire spectrum of blood management throughout the cardiac surgery process. Studies on PBM in children's cardiac surgery are limited, resulting in no recommendations about antithrombotic drugs and the lack of definite recommendations for rFVIIa and DDAVP. Consequently, it is incumbent upon clinicians to enhance their adherence to established guidelines, as well as to compare guidance from different societies on the same issue. They should adopt controversial views with caution based on individual patient characteristics, especially avoiding applying hemostatic agents with insufficient evidence for pediatric cardiac surgery patients. In addition, a detailed preoperative anemia intervention plan, the optimal drug concentration for lysine analogs, the exact dose ratio of protamine to heparin, and a standard anticoagulant strategy for bivalirudin in cardiac surgery with CPB deserve further attention in future studies.

Declaration of competing interest

None.

CRediT authorship contribution statement

Xiaojing Huang: Writing – original draft, Methodology, Conceptualization. **Pengqiang Du:** Investigation, Data curation. **Haipan Jia:** Investigation, Data curation. **Aifeng Wang:** Validation, Supervision. **Ying Hua:** Project administration, Formal analysis. **Xuelan Liu:** Project administration, Formal analysis. **Kaiyuan Wu:** Project administration, Formal analysis. **Bin Li:** Validation, Supervision. **Hongwei Zhao:** Writing – review & editing, Validation, Supervision.

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