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A review of European guidelines for patient blood management with a particular emphasis on antifibrinolytic drug administration for cardiac surgery

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ABSTRACT

The concept of patient blood management (PBM) was introduced by the World Health Organization in 2011 and is defined as a "patient-focused, evidence-based and systematic approach for optimizing the management of patients and transfusion of blood products to ensure high quality and effective patient care". Patient blood management is a multimodal approach based on three pillars: optimization of blood mass, minimization of blood loss and optimization of patient tolerance to anaemia.

Antifibrinolytics play a major role in cardiac surgery, where the risk of perioperative bleeding is high and affects a majority of patients, by effectively reducing bleeding, transfusions, re-operations, as well as their associated morbidity and mortality. They represent an essential part of the pharmacological arsenal of patient blood management.

However, despite the trend towards high-level PBM practices, currently very few European countries have national PBM guidelines and these guidelines, taken as a whole, are heterogeneous in form and content. In particular, the use of antifibrinolytics in cardiac surgery is often not discussed in detail beyond general prophylactic use and any recommendations lack detail including choice of drug, dosing, and mode of administration.

Thus, the implementation of PBM programs in Europe is still challenging.

In 2021, the WHO published a new document highlighting the urgent need to close the gap in PBM awareness and implementation and announced their upcoming initiative to develop specific PBM implementation guidelines.

This review aims first, to summarize the role played by fibrinolysis in haemostatic disorders; second, to give an overview of the current available guidelines in Europe detailing PBM implementation in cardiac surgery; and third, to analyse the place and use of antifibrinolytics in these guidelines.

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1. Introduction

Cardiac surgery carries a high risk of peri-operative bleeding [1], as evidenced by the high proportion (50–60%) of cardiac surgical patients who require allogeneic blood transfusion during and after surgery [2,3]. The risk of bleeding in cardiac surgery is affected by numerous factors: invasiveness of the procedure; use of anticoagulant and antiplatelet medication; use of hypothermia; and use of cardiopulmonary bypass (CPB) [1]. Several factors have been associated with an increased risk of bleeding such as advanced age, poor platelet function, preoperative anaemia, small body size, female sex, non-elective surgery, and repeat surgery [1].

Peri-operative bleeding has been shown to be an independent predictor of hospital mortality. In a study including more than 9000 patients undergoing cardiac surgery with CPB, massive blood loss (defined by the transfusion of at least five units of packed red blood cells on the day of surgery) was associated with an 8-fold increase in mortality [4]. Other studies have also reported excess morbidity, particularly in terms of thromboembolic complications, infections and higher rates of surgical re-exploration [5]. Notably, surgical re-exploration and transfusion following bleeding are also associated with increased infection, mortality, and a longer stay in ICU and hospital [2,6]. Finally, excessive postoperative haemorrhage in cardiac surgery has a significant economic impact: a retrospective German analysis of more than 1100 patients estimated its average additional cost to be €6251 per patient [7].

The concept of patient blood management (PBM), defined by the World Health Organization as a "patient-focused, evidence based and systematic approach for optimising the management of patients and transfusion of blood products to ensure high quality and effective patient care" [8] includes an anaesthetic, pharmacological and surgical approach. It is based on three pillars: optimization of blood mass, minimization of blood loss and optimization of patient tolerance to anaemia. In cardiac surgery, the use of antifibrinolytics is an essential component of the pharmacological approach in PBM and follows recommendations from the European Association for Cardiothoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA) [1].

This review provides an overview of the major role of fibrinolysis in haemostatic disorders after cardiac surgery and how it influences their management, compares the current available guidelines in PBM and analyses the place of different antifibrinolytics in cardiac surgery in Europe, according to these guidelines.

2. Fibrinolysis and heart surgery – antifibrinolytic treatments

2.1. Haemostatic disorders induced by cardiac surgery

CPB used during cardiac surgery leads to activation of the coagulation system due to blood coming into contact with foreign surfaces such as plastic [9,10]. Thus, by the end of CPB, a significant proportion of coagulation factors will have been consumed; fibrinogen levels are decreased by approximately 40% [9] and platelets are activated, consumed and show a selective loss of alpha granules. In contrast, thrombin levels are elevated, which is not the case in other types of surgery [10]. Along with activating the generation of fibrin, thrombin is also an activator of fibrinolysis.

Generally, fibrinolysis is a protective physiological response, proportionately inhibiting excess clot formation. However, after massive trauma, surgery, or with the use of CPB, local regulation of this response may be overwhelmed, so that the systemic and simultaneous production of thrombin and plasmin induces consumption coagulopathy, which prevents the formation of a stable clot, resulting in bleeding [11,12]. Fibrinolysis is also associated with impaired platelet function during and after CPB due to the action of plasmin and tissue plasminogen activator (tPA) [11]. tPA is responsible for inhibition of platelet aggregation, and high plasmin levels can cause damage to platelets through cleavage of the GPIb receptor and triggering their partial activation, thus inducing a loss of responsiveness to further activation [13,14] (Fig. 1). Thus, fibrinolysis plays a major role in the pathophysiology of haemorrhage during cardiac surgery, as evidenced by the strong correlation of fibrinolytic markers and the magnitude of blood loss after CPB [9,15].

2.2. Antifibrinolytic treatment

Antifibrinolytic drugs inhibit fibrinolysis and, when administered prophylactically, help prevent peri-operative bleeding [16,17]. Commonly used antifibrinolytics include protease inhibitors (aprotinin) and lysine analogues (tranexamic acid (TXA) and ε-aminocaproic acid (EACA)).

Aprotinin is a potent inhibitor of free plasmin which has a limited effect on physiological fibrinolysis [9,18]. Aprotinin is a broad-spectrum protease inhibitor, which also interacts with various other plasma proteases such as trypsin, kallikrein and elastase. Among the antifibrinolytics, it has the most potent activity [1,12]. It also has an anti-inflammatory effect decreasing systemic inflammation after CPB [19].

Lysine analogues are currently the most widely used antifibrinolytics. These synthetic derivatives of lysine inhibit fibrinolysis by preventing the formation of plasmin through their capacity to bind to plasminogen at the lysine binding site, thus preventing its binding to fibrin [11,18] (Fig. 2).

The prophylactic administration of antifibrinolytics in surgery has been widely researched and discussed. Antifibrinolytics reduce peri and post-operative bleeding, transfusions, re-operations as well as morbidity, mortality, and associated costs, without increasing the incidence of acute graft thrombosis or thromboembolism [20]. Data suggest that aprotinin has an advantage over lysine analogues in reducing peri- and post-operative blood loss [21]. When trial results for the two lysine analogues were combined and compared with aprotinin alone, aprotinin was found to be slightly more effective in reducing the need for red blood cell transfusion. The data from 150 trials performed in cardiac surgery in more than 17,000 patients are consistent with these results [21] (Table 1).

In 2008, aprotinin was withdrawn from the market following the publication of observational studies that reported an increased risk of adverse cardiological, neurological and renal events [9,22], as well as the preliminary results from a comparative, randomized, double-blind study (the BART trial), which raised suspicion of excess mortality linked to aprotinin [23]. However, thereafter, numerous methodological flaws were found in these analyses that could have influenced their results. Furthermore, a meta-analysis of data from 88 trials including over 15,000 patients found no increased risk of mortality associated with aprotinin compared with other antifibrinolytics [24]. In 2012, after re-evaluation of the data, the European Medicines Agency (EMA) concluded that: "the data from the BART study concerning excess mortality associated with aprotinin were not reliable" and lifted the suspension of aprotinin's marketing authorization, but restricted its indication to the prophylactic use in adult patients at high risk of major bleeding undergoing isolated coronary artery bypass graft (CABG) surgery [25].

For the lysine analogues, attention has recently been drawn to the possible but rare occurrence of epileptic seizures [9]. A large retrospective study of over 11,000 patients undergoing CPB reported an incidence of seizures of 0.9% in those treated with TXA. Patients with epileptic seizures had a 2.5 to 3-fold higher death rate, and hospital stay was twice as long. The administration of TXA has been shown to be an independent predictor of seizures, correlated with higher doses [26,27].

3. PBM guidelines and antifibrinolytics use in cardiac surgery in Europe

Patient blood management (PBM) is a proactive approach towards improving the quality and appropriateness of care and has been

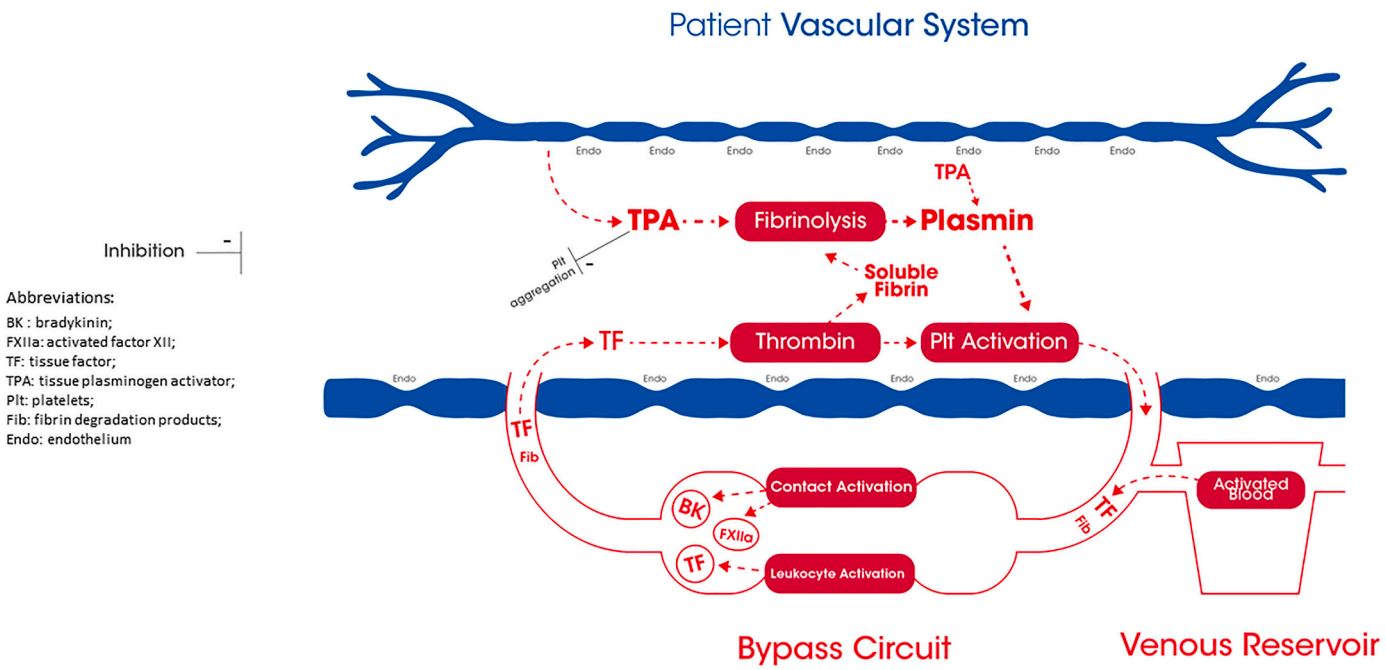

Fig. 1. Fibrinolysis during cardiopulmonary bypass. Adapted from *Snieczki* et al [13].

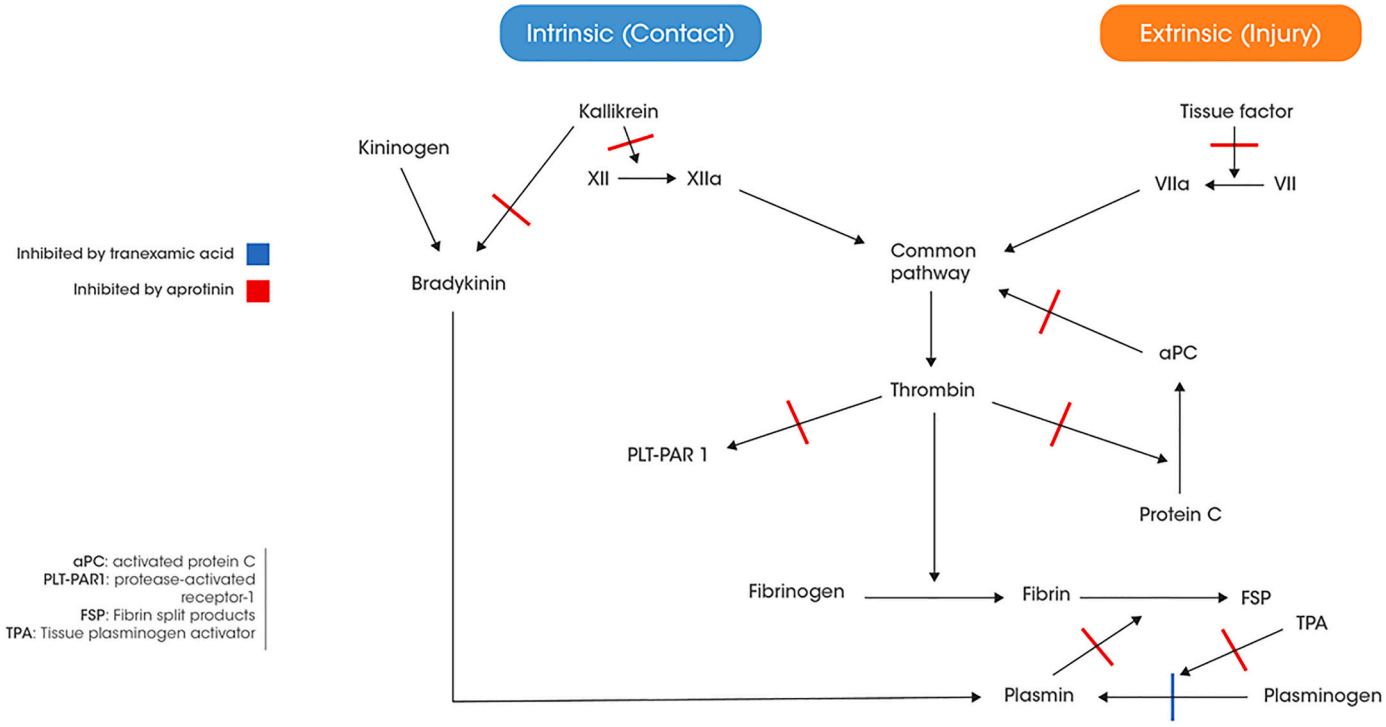

Fig. 2. Mechanism of action of antifibrinolytics. Adapted from *McEvoy* et al [47]*; Ng* et al. [48]*, 2015.*

Table 1
Overview of comparative studies of antifibrinolytic drugs in cardiac surgery, with blood transfusion as primary endpoint [21].

	Studies	Patients	Risk ratio	95% CI
Aprotinin vs. control	84	9497	0.68	0.63–0.73
Tranexamic acid vs. control	34	3006	0.68	0.57–0.81
EACA vs. control	11	649	0.70	0.52–0.93
Aprotinin vs. tranexamic acid	21	3983	0.87	0.76–0.99

EACA: ε-aminocaproic acid, CI: confidence interval.

recommended by the World Health Organization (WHO) since 2011 [8]. The aim is to manage anaemia and bleeding in surgical patients with the objective to minimize the need for transfusion as much as possible. It consists of implementing an integrated, multimodal and multidisciplinary strategy that is based on three "pillars": optimisation of the patient's blood mass, minimisation of blood loss and optimisation of the patient's tolerance to anaemia, applied during the 3 periods of the surgical intervention (preoperative, perioperative and postoperative).

3.1. Methodology for the overview of PBM guidelines in Europe

A literature search was performed in December 2020 and repeated in January 2021 using PubMed, Cochrane Database and Google Scholar databases. Twelve documents were identified containing or related to PBM guidelines. Of these 13 articles, 8 were actual PBM guidelines (Table 2).

3.2. European guidelines

The European Commission promotes the implementation of PBM programs, by supporting the "Optimal Blood Use Project" which led to the creation of a website and to publication in 2016 of the "Manual of Optimal Blood Use" [28]. The use of antifibrinolytics is mentioned to avoid the need for transfusion during elective surgery, notably TXA for patients with high risk of bleeding. The following year, the European Commission published a guide for building national PBM programs for health authorities and for hospitals inside the EU [29,30]. This guide defines the basics of PBM, presents some successful non-European PBM initiatives and identifies current gaps and limiting factors in the implementation of PBM at a large scale (lack of PBM awareness, lack of undergraduate education on PBM and transfusion in nursing and medical schools, lack of coordinated patient care, etc.). This guide is to be used as a tool setting the framework for national authorities to support the implementation and dissemination of PBM programs across Europe.

At the European level, an update of the "Management of severe perioperative bleeding" guidelines was published in 2017 by the ESAIC [31]. These general PBM recommendations are not focused on cardiac surgery; nevertheless, the management of cardiac surgical patients is discussed. The recommendations are classified according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. In cardiovascular surgery, the authors recommend the prophylactic administration of TXA before CPB in patients undergoing CABG (level of evidence (LoE) 1A). Besides, topical application of TXA to the chest cavity in order to reduce blood loss following cardiac surgery is also suggested (LoE 2C). Aprotinin is mentioned throughout the document, with comparison of the efficacy data from several clinical trials. No detailed protocol or dosing regimens for the use of antifibrinolytics (either TXA or aprotinin) is provided in these guidelines and the indications for the use of aprotinin are not defined.

European PBM guidelines specifically dedicated to cardiac surgery were published jointly in 2018 by the EACTS and the EACTA [1]. The recommendations are divided according to the three steps of the surgical procedure: preoperative management, intraoperative management, and postoperative management. During the preoperative phase, the authors suggest a potential interest for point-of-care (POC) testing, which is meant to predict perioperative bleeding. Thus, a preoperative assessment of some specific haemostasis parameters has been proposed (standard laboratory testing, viscoelastic testing and/or platelet function evaluation). The recommendations are as follow: 1/ preoperative levels of fibrinogen may be considered to identify patients at high-risk of bleeding (Class IIb – level C), and 2/ platelet function testing may be considered only in patients who recently received P2Y12 inhibitors or who have ongoing dual antiplatelet therapy, to guide the decision on the timing of cardiac surgery (Class IIb – Level B). In the perioperative setting, treatment algorithms based on viscoelastic POC tests should be considered in order to reduce the number of transfusions for the bleeding patient (Class IIa – Level B).

Antifibrinolytics (TXA, aprotinin or EACA) are recommended during the intraoperative period to reduce blood loss and the need for transfusion, and also to reduce the risk of reoperation for bleeding (TXA and aprotinin) (level of evidence 1A). No therapeutic protocols or dosing regimens for the use of antifibrinolytics are recommended. Finally, the implementation of a PBM protocol for bleeding patients is recommended (LoE1C).

3.3. National guidelines

3.3.1. France

Specific guidelines dedicated to PBM are currently not available in France, however, a White Paper was published in 2018 [32] by several learned societies (French Society of Anaesthesia and Resuscitation; Study Group on Haemostasis and Thrombosis; French Society of Thoracic and Cardiovascular Surgery; French Society of Vigilance and Therapeutics).

This publication summarizes the principles of PBM with the three-pillars-based approach and presents a series of recommendations for the implementation of PBM in France. It includes an international literature review, a multidisciplinary field survey and recommendations from the scientific committee to provide guidance on the implementation of PBM programs. The field survey demonstrated that PBM as a formalized concept was not very well known by French practitioners. Regarding the use of antifibrinolytics, the authors recommended TXA (1 g) at anaesthetic induction and at the end of the surgical procedure (1 g). The authors considered that the topical application of TXA needs further research. It should serve as a basis for French guidelines on PBM, which are expected soon by the *Haute Autorité de Santé* (HAS) [33].

3.3.2. Germany

In 2020, cross-sectional guidelines on therapy with blood components and plasma derivatives were published by the Executive board of the German Medical Association [34]. Cardiac surgery is mentioned throughout the document, but without any discussion on the potential use of antifibrinolytics. However, the use of TXA is recommended to limit blood loss in several types of surgical procedures and for the peri- and postpartum period.

3.3.3. Italy

The Italian Society of Anaesthesia, Analgesia, Resuscitation and Intensive Care has written a position paper on the clinical standards for PBM, and perioperative haemostasis and coagulation management in 2019 [35]. These recommendations are divided according to the three steps of any surgical procedure (pre-, peri- and postoperative period), each one being subdivided according to the three pillars of PBM approach. Cardiac surgery is discussed throughout the document. The use of antifibrinolytics is discussed in the "Pillar 2 – Blood containment" section of the chapter on perioperative management. No detailed guidelines are provided, but prophylactic administration of TXA is recommended before CPB in patients undergoing CABG, as advised in the ESAIC guidelines [31]. Finally, the authors mentioned that to decrease the risk of postoperative blood loss following cardiac surgery, TXA can be applied topically.

3.3.4. The Netherlands

Guidelines on blood transfusion have been published in 2011 by the Dutch Institute For Healthcare Improvement [36]. They are not dedicated to PBM, which is not surprising as this concept was just emerging at that time. However, these guidelines include "Blood saving techniques and medications," which covers the following points: techniques to limit blood loss during surgical procedures; preoperative and perioperative autologous blood transfusion techniques; and combination of blood saving techniques. Cardiac surgery and the use of antifibrinolytics are discussed through the document. Aprotinin and TXA are mentioned. However, at the time of publication, aprotinin had been withdrawn from the market, thus its use is not recommended. TXA is described as a safe and effective drug to reduce blood loss and transfusion in cardiac surgery (evidence Level 1A1).

3.3.5. Romania

The Romanian Patient Blood Management Initiative Group published national recommendations about perioperative PBM programme in 2017 [37]. The use of tranexamic acid is recommended to minimize

Table 2
Overview of European PBM guidelines.

Country	Publication	Authors	Year	PBM guidelines	Cardiac surgery	Use of antifibrinolytics
Europe	2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery [1]	Pagano D et al.	2017	YES	YES (dedicated guidelines)	YES (detailed)
	Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. First update 2016 [31]	Kozek-Langenecker SA et al.	2016	YES	YES (throughout the text)	YES (detailed)
	Building national programmes of Patient Blood Management in the EU – a guide for Health Authorities [29]	European Commission	2017	NO	NO	YES (mentioned)
	Manual of optimal blood use [28]	European Commission	2016	NO	NO	YES
France	Livre blanc du Patient Blood Management. Gestion personnalisée du capital sanguin en chirurgie programmée [32]	Capdevilla et al.	2018	NO	YES (throughout the text)	YES (mentioned)
Germany	Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten [34]	German Medical Association	2020	NO	YES (mentioned)	YES (mentioned)
Italy	Clinical standards for patient blood management and perioperative haemostasis and coagulation management. Position Paper of the Italian Society of Anaesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI) [35]	Cinnella G et al.	2019	YES	YES (throughout the text)	YES (detailed)
Romania	Perioperative Patient Blood Management Programme. Multidisciplinary recommendations from the Patient Blood Management Initiative Group [37]	Filipescu D et al.	2017	YES	YES (mentioned)	YES (detailed)
United Kingdom	Patient Blood Management – An evidence-based approach to patient care (2014) [38]	National Blood Transfusion Committee, NHS England	2014	YES	NO	YES (mentioned)
	British Committee for Standards in Haematology Guidelines on the Identification and Management of Pre-Operative Anaemia [39]	Kotzé A et el.	2015	YES	YES (mentioned)	NO
	A practical guideline for the haematological management of major haemorrhage [40]	Hunt BJ et al.	2015	YES	YES (mentioned)	YES (detailed)
	AAGBI guidelines: the use of blood components and their alternatives 2016 [41]	Klein AA et al.	2016	YES	YES (throughout the text)	YES (mentioned)
The Netherlands	Blood transfusion guidelines [36]	Dutch Institute For Healthcare Improvement	2011	NO	YES (throughout the text)	YES (detailed)

Table 3
Recommendations for the use of antifibrinolytics in European PBM guidelines.

Region/ country	Author	Recommended antifibrinolytics	Context	Practicalities
Europe	ESAIC 2016(31)	• Tranexamic acid	• Major surgery • Before CPB in patients undergoing CABG	• Can be applied topically to the chest cavity • Dose of 20 to 25 mg/kg
Europe	EACTS/ EACTA 2017(1)	• Tranexamic acid • Aprotinin • ε-Aminocaproic acid	• Cardiac surgery	
Germany	German medical association (34) (2020)	• Tranexamic acid	• Platelet transfusion • Dental procedure (local administration of tranexamic acid) • Severe Factor XI deficiency (FXI residual activity <5%) and slight Factor XI deficiency with a severe tendency to bleed	
Italy	SIAARTI 2019(35)	• Tranexamic acid	• Cardiac surgery	
Romania	Patient Blood Management Initiative Group [37]	• Tranexamic acid	• Surgery with high risk of bleeding or suspected hyperfibrinolysis	• Dose of 20 to 25 mg/kg
The Netherlands	CBO 2011(36)	• Tranexamic acid	• Cardiac surgery • Orthopaedic surgery • Liver transplants (with the exception of the hypo-fibrinolytic phase)	
United Kingdom	NHS 2014(37)	• Tranexamic acid	• Non-traumatic major bleeding	
United Kingdom	AAGBI 2016(40)	• Tranexamic acid	• All non-obstetric patients where blood loss >500 ml is possible	• Consider giving tranexamic acid 1 g if blood loss >500 ml is anticipated • Dose is variable, 1 g bolus is recommended, and additional infusion of 500 $mg.h^{-1}$ may also be considered • Loading dose of 15 $mg.kg^{-1}$ followed by infusion 2 $mg.kg^{-1}.h^{-1}$ should be used in trauma
United Kingdom	BCSH (2015)(39)	• Tranexamic acid	• Traumatic and obstetric major haemorrhage. • Paediatric population • Adult trauma patients, with or at risk of, major haemorrhage (in whom antifibrinolytics are not contraindicated) • In high-risk surgery such as cardiac surgery	• Should be given as soon as possible after the injury, at a dose of 1 g intravenously over 10 min, followed by a maintenance infusion of 1 g over 8 h • Dose of 10 $mg.kg^{-1}$ followed by 1 $mg.kg^{-1}.h^{-1}$ is recommended to prevent bleeding

ESAIC: European Society of Anaesthesia and Intensive Care – EACTS: European Association for Cardio-Thoracic Surgery – EACTA: European Association of Cardiothoracic Anaesthesiology – SIAARTI: Italian Society of Anaesthesia, Analgesia, Resuscitation and Intensive Care – CBO: Centraal Begeleidingorgaan voor de Intercollegiale Toetsing – BCSH: British Committee for Standards in Haematology – AAGBI: Association of Anaesthetists of Great Britain and Ireland CBP: Cardiopulmonary bypass – CABG: Coronary Artery Bypass Grafting.

Table 4
Commonly used dosages for antifibrinolytics.

Drug	Suggested dosing in adults
Aprotinin	"Full dose": 2×10^6 KIU bolus patient, 2×10^6 KIU bolus CPB, continuous infusion of 5×10^5 KIU per hour "Half dose": 1×10^6 KIU bolus patient, 1×10^6 KIU bolus CPB, continuous infusion of 2.5×10^5 KIU per hour
Tranexamic acid	"High dose": 30 mg/kg bolus patient, 2 mg/kg CPB, and continuous infusion of 16 mg/kg/h "Low dose": 10 mg/kg bolus patient, 1–2 mg/kg CPB, and continuous infusion of 1 mg/kg/h
ε-Aminocaproic acid	100 mg/kg bolus patient, 5 mg/kg CPB, and continuous infusion of 30 mg/kg/h

CPB: Cardiopulmonary bypass – KIU = Kallikrein International Unit.
Adapted from Levy et al. 2018 [12].

blood loss during surgical procedures with a high risk of bleeding or in cases with suspected hyperfibrinolysis, at doses of 20 to 25 mg per kg of body weight.

3.3.6. *The United Kingdom*

The UK has several guidelines, each dealing with a particular aspect of PBM. A short document entitled "Patient blood management – an evidence-based approach to patient care," published in 2014 by the National Blood Transfusion Committee (NBTC) and the NHS (National Health Service) [38] provides recommendations for the implementation of PBM, but not specific to cardiac surgery. TXA is cited as a pharmacological drug to be used to reduce blood loss in intraoperative management, and in case of major bleeding. Nevertheless, no specific protocol on the use of TXA is proposed or discussed. The British Committee for Standards in Haematology (BCSH) published two different guidelines in 2015, under the GRADE rating system. The first covers the identification and management of preoperative anaemia [39], and the second covers haematological management of major bleeding [40] and provides an overview of the organisational principles, transfusion of different blood products, pharmacological agents and addresses different specific situations. TXA and aprotinin are discussed, but only the use of TXA is recommended in case of major bleeding after injury, 1 g intravenously over 10 min, followed by a maintenance administration of 1 g over 8 h (LoE1A). In non-traumatic major haemorrhage, the use of TXA should be considered but not aprotinin (LoE1B). Regarding the prevention of bleeding in high-risk patients undergoing cardiac surgery, the authors recommended initial administration of TXA (10 $mg.kg^{-1}$) followed by 1 $mg.kg^{-1}.h^{-1}$ to prevent bleeding (LoE1B). Finally, guidelines from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) were published in 2016, which address the use of blood products and their alternatives [41]. They are not focused on cardiac surgery but devote a chapter specifically to it. PBM measures are recommended in patients who are at high risk of bleeding, and TXA and aprotinin are mentioned. TXA is recommended to be used as a 1 g bolus, with an additional infusion of 500 $mg.h^{-1}$ that could be considered. Aprotinin is recommended in case of myocardial revascularisation, as licensed.

4. Discussion

In March 2011, the WHO held a "Global Forum on Blood Safety: Patient Blood Management" aimed at establishing a framework for the WHO Member States to actively support PBM dissemination and implementation [8]. Since then, PBM programs have been implemented in many countries around the world. In 2021, the WHO published a new document to highlight the urgent need to close the gap in PBM awareness and implementation and announced their upcoming initiative to develop PBM implementation guidelines [42].

At the European level, guidelines on bleeding management were published in 2017 by the ESAIC [31] and PBM guidelines specifically focussed on cardiac surgery were published in 2018 jointly by the EACTS and the EACTA [1].

Furthermore, the implementation of PBM programs has been actively supported by the European Commission, in particular through guides intended for national health authorities and hospitals, meant to help EU member states make PBM a standard for improving the quality and safety of patient care. [29,30]

However, while PBM practices are increasingly being used, national guidelines are still rare and very few are specific to cardiac surgery. All the current available guidelines follow and agree on the definition of PBM as defined by the WHO [8], supported by three pillars: optimizing blood volume, minimising blood loss and optimizing the patient's tolerance to anaemia.

To decrease blood loss during cardiac surgery, European guidelines mention that the assessment of specific haemostasis parameters in the preoperative setting (such as fibrinogen level and platelet function for specific patients…) could be useful to predict perioperative bleeding and to decrease transfusion rates [1,43].

Anaemia is known to be a predictor of postoperative adverse outcomes for patients, so its management is the cornerstone of PBM. Limiting blood loss during surgical procedures is also of paramount importance to reduce the use of blood products transfusions and limit the risk for reoperation for bleeding. In this context, the European and national PBM guidelines all recommend the prophylactic use of antifibrinolytics to avoid or reduce perioperative bleeding. However, they differ in the type of antifibrinolytic recommended, when it should be given and how (bolus or infusion or both), including the dose (Table 3). Most guidelines recommend only the use of tranexamic acid. Aprotinin is rarely mentioned, partly because of its recent reintroduction in Europe, and its continued non-availability on the market in some countries such as Italy. How Aprotinin should be given and when, as well as the dose and timing of administration are mostly not discussed (Table 4). National PBM guidelines for European countries therefore appear to be both few in number and heterogeneous. This situation could partly explain the marked discrepancies found in a recent survey of PBM practices in cardiac surgery across different European countries [44]. In this survey, it appears that PBM programs are not universally or consistently implemented in European cardiac surgical centres, resulting in differences in patient's management for the same clinical situation. The survey highlights that, the differences observed in guidelines, including antifibrinolytic use, exist between countries at an international level and also at a national level with different protocols in individual cardiac surgical centres within a specific country, and sometimes, different protocols within the same cardiac surgical centre.

The situation is quite different in the United States and in Australia, where PBM practices are more widely implemented. The American Society of Anesthesiologists (ASA) published its "Practice guidelines for perioperative blood management" in 2015 giving general recommendations for PBM [45]. However, although the use of antifibrinolytic therapy is mentioned to reduce blood loss and risk of transfusion for patient at high-risk of bleeding, or undergoing CPB, no detailed protocol is provided. Furthermore, institutions such as the Society for the Advancement of Blood Management (SABM) and the American Association of Blood Banks (AABB)) actively promote the implementation of PBM in the US by providing educational resources, partnerships and certification to hospitals.

Australia appears to be one of the countries with the most comprehensive "supply" of PBM literature. The National Blood Authority (NBA) administers a website dedicated to PBM, including extensive PBM guidelines (Critical bleeding/massive transfusion; Perioperative; Medical; Critical care; Obstetrics and maternity; and Neonatal and paediatrics). These PBM guidelines were published in 2012, and in 2019 a survey assessed how blood transfusions and patient outcomes in cardiac surgery changed after the guidelines were published [46]. The authors demonstrated that, thanks to the implementation of PBM guidelines, there was a significant reduction in intraoperative blood transfusions in

patients undergoing cardiac surgery, and an associated reduction in hospital length of stay. The NBA also provides a national PBM implementation strategy guide covering 2017–2021 (updated every 4 years), as well as patient information documents. It defines the principle of PBM and the objectives of the national strategy, including implementation of nationally coordinated measures for PBM, decreasing discrepancies in clinical practices, consolidating existing PBM programs, identifying gaps in knowledge and patient care, and increasing awareness and understanding of PBM.

All in all, European countries could benefit from the experience gained through these programs developed by other countries to improve, accelerate and deploy the implementation of PBM at a large scale.

5. Conclusion

Despite the trend towards high-level PBM practices, currently very few European countries have national PBM guidelines and these guidelines, taken as a whole, are heterogeneous in form and content. Antifibrinolytics play a major role in cardiac surgery, where the risk of perioperative bleeding is high and affects a majority of patients, by effectively reducing bleeding, transfusions and re-operations, as well as their associated morbidity and mortality. They represent an essential part of the pharmacological arsenal of patient blood management. However, the use of these drugs in cardiac surgery in Europe is not covered in sufficient detail by national recommendations. This lack of common recommendations is partly due to the scarcity of available robust data. It would be of particular interest to set up comparative clinical studies with the major antifibrinolytics to determine the best protocols and dosages to use in practice and thus to homogenize practice. To complement these trials, a network meta-analysis or a systematic review of the evidence to date on antifibrinolytics in cardiac surgery and their effects on major patients' outcomes might be useful to generate important data to rely on for daily practices.

To conclude, implementation of PBM programs in Europe is challenging, as there is a real need for homogenous guidance in PBM and the use of antifibrinolytics, especially in cardiac surgery.

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