Journal of Clinical Anesthesia 72 (2021) 110311

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

A survey of patient blood management for patients undergoing cardiac surgery in nine European countries

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ARTICLE INFO

Keywords:
Patient blood management
PBM
Cardiac surgery
Europe

ABSTRACT

Study objective: To describe and compare patient blood management (PBM) practices in cardiac surgery in nine European countries and identify the main risk factors for bleeding or transfusion according to the surveyed centres.
Design: We set up an online survey to evaluate PBM practices in two clinical scenarios, risk factors for bleeding or transfusion, and previous experience with antifibrinolytics.
Setting: This survey was completed by European anesthesiologists in 2019.
Patients: No patients were included in the survey.
Intervention: None.
Measurements: We evaluated the degree of implementation of PBM practices in patients undergoing cardiac surgery.
Main results: Ninety-eight of 177 responses (38%) were complete with variable response rates by country. In a non-emergent situation, no respondents would transfuse red cells preoperatively in an anaemic patient, while cell salvage (89%) and antifibrinolytics (82%) would almost always be used. Optimization of Hemoglobin level (36%) and use of off-pump techniques (34%), minimally invasive surgery (25%) and relatively recently-developed CPB technologies such as mini-bypass (32%) and autologous priming (38%), varied greatly across countries. In an emergent clinical situation, topical haemostatic agents would frequently be used (61%). Tranexamic acid (72%) and aprotinin (20%) were the main antifibrinolytics used, with method of administration and dose varying markedly across countries. Five factors were considered to increase risk of bleeding or transfusion by at least 90% of respondents: pre-operative anaemia, prior cardiac surgery, clopidogrel 5 days or less before surgery, use of other P2Y12 inhibitors at any point, and thrombocytopenia $<100.10^9$ platelets/mm^3.
Conclusion: PBM guidelines are not universally implemented in European cardiac surgery centres or countries, resulting in discrepancies in techniques and products used for a given clinical situation.

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https://doi.org/10.1016/j.jclinane.2021.110311
Received 14 January 2021; Received in revised form 30 March 2021; Accepted 1 April 2021
Available online 24 April 2021

1. Introduction

Patient blood management (PBM) is defined as "*the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize haemostasis and minimize blood loss in an effort to improve patient's outcome*". [1,2] Its adoption has been recommended by the WHO since 2010, as well as by national health regulation agencies, international professional societies, and the European Commission. [3–10]

In surgical patients, both perioperative anaemia and blood transfusion are associated with serious adverse outcomes, including prolonged hospital stay, infection, transfusion-related acute lung injury (TRALI) and transfusion-associated cardiac overload (TACO). [11–13] One major challenge of PBM is to minimize blood transfusion by addressing anaemia and risk of bleeding. [14–17] Several studies show that implementation of PBM is beneficial in reducing unnecessary blood transfusions and achieving cost savings. Moreover, active PBM implementation reduces perioperative complications. [17–21]

Guidelines have been published to address PBM in the specific context of cardiac surgery, both at the European and national level. [7,22] The three pillars of PBM in cardiac surgery consist of preoperative identification of patients at high risk of bleeding and optimisation of anaemia including administration of iron; intraoperative maintenance of hemostasis and minimizing blood loss; and treatment of postoperative microvascular bleeding after cardiopulmonary bypass (CPB). [22]

A number of observational studies and online surveys on PBM and transfusion practices have been published to date in non-cardiac surgery [23,24]. The objective of the present work was to conduct an online survey to describe PBM practices across cardiac surgical centres in various European countries. The research hypothesis was that, despite the numerous available guidelines on PBM, the responding centres would follow mainly the same recommendations and PBM would be implemented similarly in all the surveyed centres.

2. Materials and methods

This survey was initiated and funded by Nordic Pharma to better understand the current environment of patient blood management and condition of use of aprotinin in European countries where it is marketed.

2.1. Questionnaire

A preliminary version of the questionnaire was written by the primary author based on clinical experience and having examined current available national and international guidelines and regulations in the relevant nations. This questionnaire was then validated by the remaining authors, one from each of the countries to be surveyed, so that it was representative of the population to be sampled. They made sure that the questions were easy to understand regardless of nationality of respondent thus minimizing bias [25,26].

The final survey comprised 24 questions in three parts. The first part included questions on respondents' specialty, country of practice, number of cardiac surgeries with CPB performed in the cardiac centre, the proportion of patients undergoing coronary artery bypass graft surgery (CABG) and receiving blood transfusion and the existence of PBM guidelines. The second part included two clinical scenarios with two sets of questions on preoperative blood management (biological testing, use of iron, erythropoietin, or RBC transfusion), techniques (cell salvage, topical haemostatic agents, off-pump, minimally invasive surgery), bypass strategies (normothermia, autologous priming, mini bypass), and intraoperative coagulants (heparin/protamine, anti-fibrinolytics). The first clinical situation was based on a female patient requiring a non-emergent isolated CABG, while the second clinical situation was based on a male patient with acute aortic dissection who was about to undergo an emergency Bentall procedure with valvular prosthesis. The third part included questions on the use of anti-fibrinolytics. The detailed questionnaire and clinical situations are provided in the supplementary section.

2.2. Survey development and distribution

The online survey was designed using the web-platform SurveyMonkey® (Palo Alto, CA, USA). Respondents completed the survey anonymously. The survey link was available between February 21st and October 21st 2019. It was distributed by e-mail, newsletters, websites and social media of the Network for the Advancement of Patient Blood Management, Hemostasis and Thrombosis (NATA) and the European Association of Cardiothoracic Anesthesiologists (EACTA), as well as by some national scientific societies.

2.3. Inclusion criteria

Cardiac centres performing cardiac surgery with CPB and located in the authors' countries of medical practice (namely Austria, Belgium, Finland, France, Germany, Ireland, Switzerland, the Netherlands, and the United Kingdom), were included. In case of multiple answers originating from the same centre, the response with the highest number of completed questions was selected.

2.4. Exclusion criteria

Respondents who did not specify their centre of practice, respondents who declared that no cardiac surgery with bypass were performed in their centre, and respondents from centres already covered, were excluded.

2.5. Response rate

Response rate was defined as the ratio between the number of national centres that answered the online survey, and the total number of surgical centres performing cardiac surgery with CPB within every specific country.

2.6. European overview and view by country

Two levels of analyses were performed. First, we analysed data from all 9 European countries, according to the inclusion and exclusion criteria. Second, we analysed data in countries in which the response rate (as defined in the previous section) was 60% or higher, as recommended for surveys amongst medical doctors [27,28].

2.7. Statistical analysis

Data management and descriptive statistics (mean, median, frequency and standard deviation) were performed using Microsoft Excel for Windows. The percentage of patients undergoing cardiac surgery with bypass and receiving transfusion was calculated by multiplying the declared frequency of transfusion with the declared number of cardiac surgery patients. No missing data was imputed – the respondents completed all questions in all sections.

3. Results

3.1. Response rate

As shown in the study flow chart in Fig. 1, of the 177-total number of respondents who filled in the questionnaire between February 21st and October 21st 2019, 98 were included in the analysis. The overall response rate was 38% (Table 1). Response rates were $> 60\%$ in Finland, Ireland, the Netherlands, the UK and Belgium; these countries were therefore included in the detailed analysis while Austria, Germany, France and Switzerland were excluded.

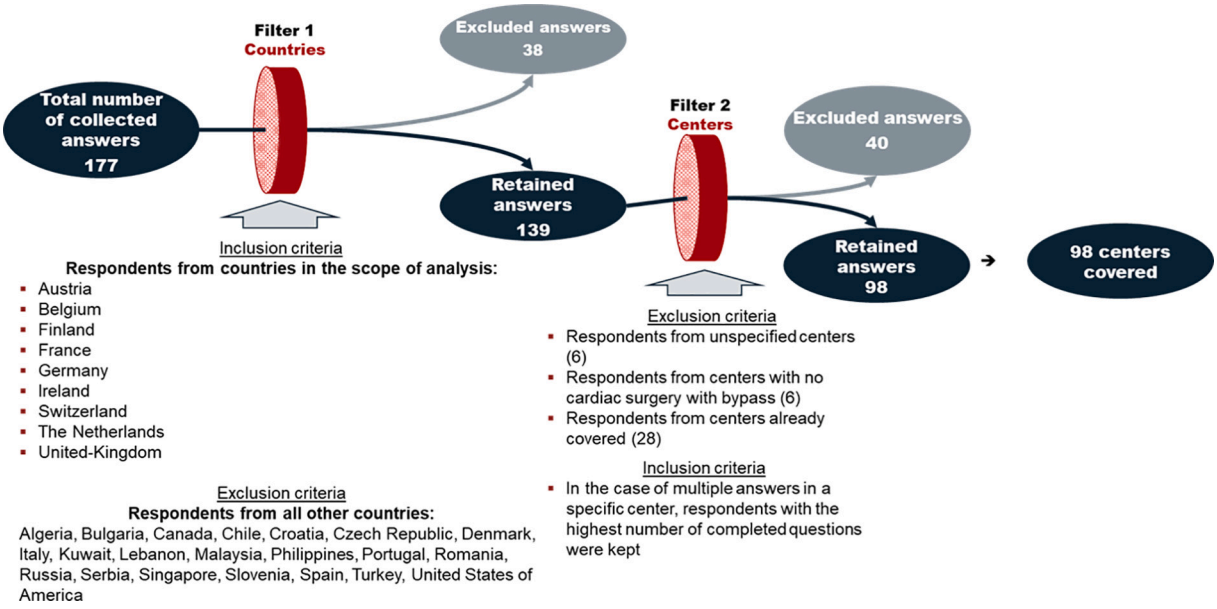

Fig. 1. Study flow chart.

Table 1
Response rates.

	Total of 9 countries	Austria	Belgium	Finland	France	Germany	Ireland	Switzerland	The Netherlands	United-Kingdom
Number of centres per country	254	5	29	5	55	78	8	27	15	32
Number of responding centres	98	1	19	5	15	5	6	4	13	30
Ratio of responding centres to total cardiac centres in the country	38%	20%	66%	100%	27%	6%	75%	15%	87%	94%

3.2. Characteristics of respondents and responding centres

Almost all respondents were anesthesiologists except in the Netherlands (9/13; 69% anesthesiologists and 3/13, 23% cardiac surgeons) (Table 2). The proportion of centres with hospital PBM guidelines in place was less than 70% in each country, except in the Netherlands where it was 100%. The proportion of patients receiving allogeneic transfusion during cardiac surgery with CPB was distributed around a median of 40–45%, except in Belgium where it was only 25%. Coronary artery bypass grafting was the most frequently performed surgical procedure in all centres but there was considerable inter-centre variability across Europe (Fig. 2 and Fig. S1).

3.3. Suggested predictors of high risk of bleeding or transfusion during cardiac surgery with CPB

At the European level, five main risk factors were considered predictors by more than 90% of the respondents, namely pre-operative anaemia, prior cardiac surgery, clopidogrel 5 days or less before surgery, use of other P2Y12 inhibitors at any point, and thrombocytopenia $<100.10^9$ platelets/mm^3 (Fig. 3). Amongst them, preoperative anaemia was identified as a predictor of high risk by all centres in all countries, whilst treatment with clopidogrel and thrombocytopenia were less commonly qualified as a risk factor, especially in Finland, Ireland and The Netherlands (Fig. S2).

Table 2
Profile of respondents and cardiac surgery centres.

	Total of 9 countries	Belgium	Finland	Ireland	The Netherlands	United-Kingdom
Specialties						
Anesthesiologists (% of respondents in the country)	90 (92%)	18 (95%)	5 (100%)	5 (83%)	9 (69%)	30 (100%)
Cardiac surgeons (% of respondents in the country)	3 (3%)	–	–	–	3 (23%)	
Perfusionists (% of respondents in the country)	3 (3%)	1 (5%)	–	1 (17%)	1 (8%)	–
Intensivists (% of respondents in the country)	2 (3%)	–	–	–	–	–
Total number of respondents on this item	98	19	5	6	13	30
Existence of guidelines regarding patient blood management in the responding center						
Yes	32 (58%)	7 (47%)	2 (67%)	3 (60%)	7 (100%)	5 (42%)
No	23 (42%)	8 (53%)	1 (33%)	2 (40%)	–	7 (58%)
Total number of respondents of this item	55	15	3	5	7	12
Percentage of patients undergoing cardiac surgery with cardiopulmonary bypass receiving a blood transfusion (allogeneic donor blood) during or after surgery						
Median [Minimum; Maximum]	40% [3%; 80%]	25% [9%; 60%]	40% [40%; 50%]	40% [10%; 50%]	45% [20%; 80%]	40% [5%; 60%]
Standard deviation	16%	17%	6%	16%	17%	13%
Total number of respondents of this item	72	13	3	5	9	21

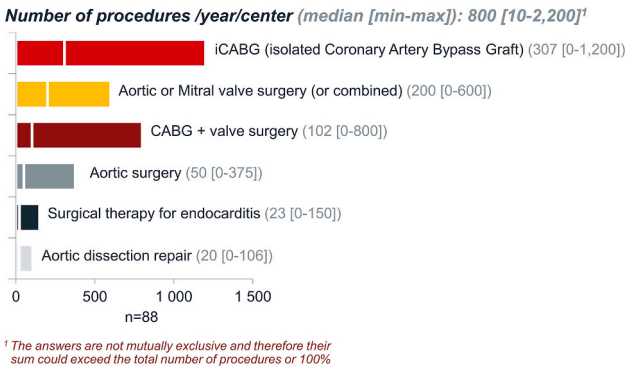

Fig. 2. Number of procedures per year per center.

3.4. Patient blood management in a non-emergency context: clinical case 1

More than one third of the respondents would not try to preoperatively optimize the patient's hemoglobin level (Fig. 4A), while nearly two third of the centres would prescribe iron. The proportion of centres who would administer intravenous iron varied across the countries surveyed (Table S1). None of the responding centres would make use of preoperative red blood cell transfusion, while nearly all of them would use cell salvage intraoperatively (65/73; 89%) (Fig. 4B), regardless of the country of practice (Table S1). One third of the respondents would use off-pump techniques and 25% would use minimally invasive surgery (Fig. 4), with high inter-country variability (Table S1). Likewise, the use of relatively recently developed CPB technologies such as normothermia, autologous priming and miniaturized bypass systems, differed greatly from country to country (Table S1).

Most centres would use antifibrinolytics intraoperatively (59/72; 82%) (Fig. 4D) except in the Netherlands, where only 50% would use an

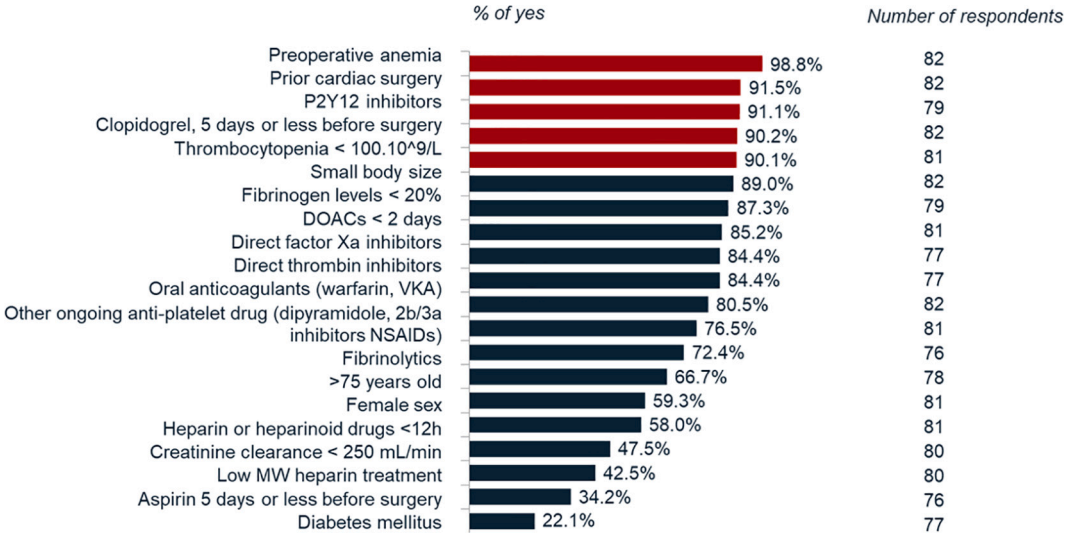

Fig. 3. Predictors of high risk of bleeding or transfusion during cardiac surgery with CPB, as suggested by all respondents.

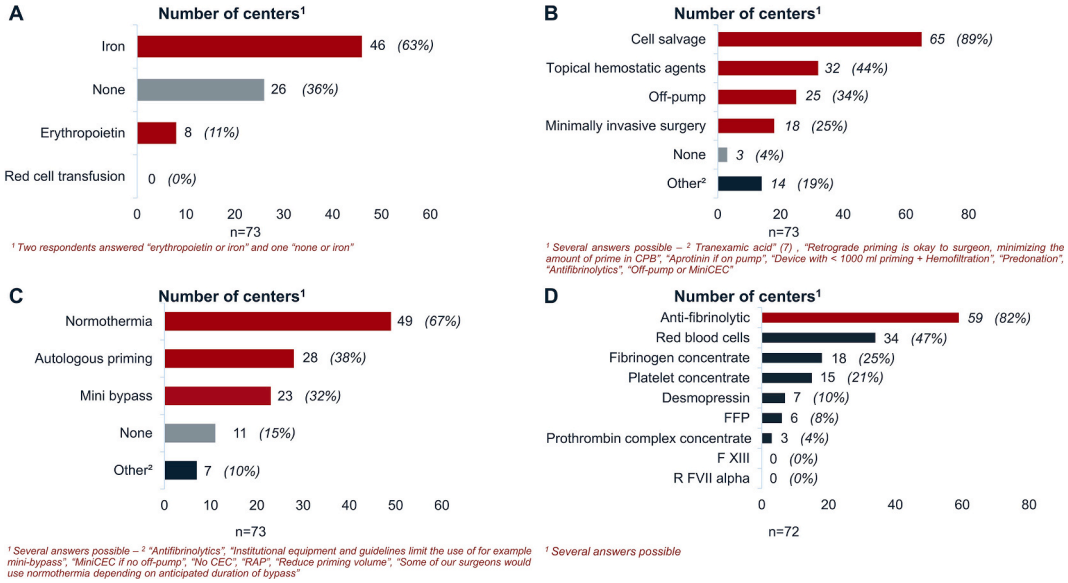

Fig. 4. PBM practices for a non-emergency case of a patient requiring iCABG (First clinical situation).
A: Preoperative patient blood management.
B-D: Perioperative patient blood management including techniques used (B), bypass strategies (C) and pharmacological treatments (D).

antifibrinolytic. (Table S1).

3.5. Patient blood management in a non-emergency context: clinical case 2

Topical hemostatic agents would be frequently used on this patient (38/62; 61%) while a third of centres would not use any specific technique (18/62; 29%). A significant number of centres declared that they would use autologous priming and normothermia, with autologous priming being used more frequently in Belgium (7/13; 54%) and the UK (8/17, 47%) and normothermia being used more frequently in Belgium (5/13; 38%) and Ireland (3/6; 50%) (Table S2). Tranexamic acid (43/60; 72%) and aprotinin (18/60; 30%) were the two main antifibrinolytics. Tranexamic acid would be used more frequently in Belgium (11/13; 85%) and the Netherlands (5/5; 100%), while aprotinin would be used more frequently in the UK (7/17; 41%) and Finland (3/5; 40%).

3.6. Previous experience with fibrinolytics

Respondents used tranexamic acid in all proposed procedures (Fig. 5A) except in Finland where this agent was mostly used in patients with endocarditis (Fig. S3). By contrast, the use of aprotinin was restricted to specific procedures, the main one being redo sternotomy (24/37; 65%), followed by complex valve surgery and endocarditis (17/37; 46%), aortic surgery (16/37; 43%) and emergency procedures (15/37; 41%) (Fig. 5B). The procedures in which aprotinin was chosen varied across countries (Fig. S3). The dose of tranexamic acid that would be used was highly heterogenous, whereas the dose of aprotinin showed almost no variation at all (Fig. S3).

4. Discussion

We surveyed PBM practices in the specific context of cardiac surgery across Europe and showed that there was considerable heterogeneity or failure of implementation, contrary to our research hypothesis. This is despite the numerous available guidelines on a national and international level. The survey represents current European practices in nine countries (namely Austria, Belgium, Finland, France, Germany, Ireland, Switzerland, the Netherlands, and United Kingdom). Sub-analyses by countries have been made for Belgium, Ireland, Finland, the United Kingdom, and the Netherlands, which achieved a 60% response rate (or higher). It covered multiple aspects of preoperative and perioperative pillars of PBM.

We acknowledge that this survey suffers from several limitations. First, it is based on declarative answers and is thus subject to reporting bias. Regarding the self-reported transfusion rates for example, we know that some of the responding centres do not have electronic records keeping track of transfusion during the post-operative period. The answers are thus only based on the respondent's experience and might have been under- or over-estimated. Because we did not want the questionnaire to be too long and therefore risk it not being completed by the respondents, we decided not to include questions to control the consistency of the responses. Our aim was to obtain an understanding of current practices, according to the opinions of responding physicians. Respondents were free to choose to answer the questionnaire if they chose to without any financial or other incentive. Therefore, we conclude the answers provided were representative. Second, we decided to consider only one answer from each cardiac surgical centre, which was then considered to be representative of their existing PBM practice. Thus, it enabled us to observe discrepancies between countries, but we did not evaluate heterogeneities at the level of each individual country or cardiac centre. Third, we may expect that only the most interested anesthesiologists responded to the online survey, leading to a selection bias. Last, we did not survey every country in Europe as we only had access to contact centres via the authors. Additionally, low response rates were obtained for four countries (Austria, Germany, France, and Switzerland). While we included them in the global analysis (main figures), the representation was relatively poor, so we decided not to present individualized data for those countries (supplemental materials). The differences in response rates amongst countries may be explained by the ability to reach cardiac centres successfully. In particular, the two professional societies that shared the survey link may not have equal access to all target countries: for instance, France and Germany account for fewer EACTA members than other countries. Moreover, we acknowledge that our taskforce was not part of a professional society, which may have affected response rates. Regarding the overall response rate (38%), this is not dissimilar to those generally obtained in the same kind of online studies [29–32]. Centres were only contacted by email to complete the online questionnaire, which allowed us to contact more people and obtain wider geographical coverage but limited the number of respondents as physicians very frequently asked to complete surveys and may thus refuse [33].

The very low rate of pre-operative red blood cell transfusion for the management of both clinical situations is very encouraging and suggests that at least some PBM practices have been widely adopted over the years [22]. However, several results showed that, despite national and international PBM guidelines being in place [22], there is great variability as to what clinicians are doing in their cardiac anaesthesia and surgery practice across Europe. In the Netherlands, all respondents declared that they had PBM guidelines in their centres (Table 1), yet clinical practices were still highly heterogeneous, for instance regarding the use of antifibrinolytics in the non-emergent clinical situation (Table S3). Thus, even though guidelines may be in place, it does not

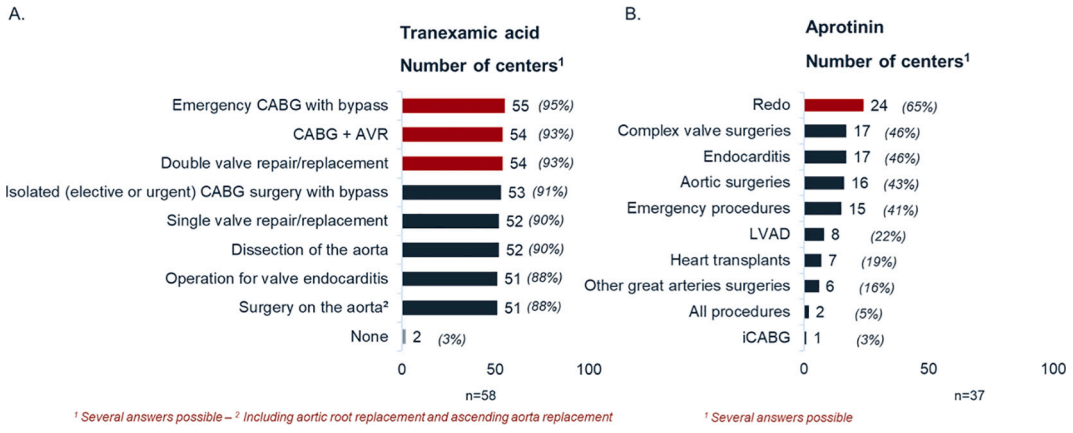

Fig. 5. Experience with antifibrinolytics.

mean that they are implemented or followed.

The variation in the use of preoperative iron infusion (Table S3) might partly be driven by its reimbursement status, since it is less frequently used in Belgium and the Netherlands, where it is not reimbursed (Table S3). Preoperative iron requires specific resources such as a dedicated preoperative facility and trained staff to administer the infusion, which all cardiac surgery centres might not have. Moreover, some cardiac surgery centres experience high levels of competition resulting in very short delay to surgery: this may also constrain the use of iron and/or EPO to correct preoperative anaemia. The use of oral or intravenous iron with or without erythropoietin for anaemia is recommended in the European guidelines (Class IIb/IIa grade of evidence).

There was striking variation amongst European countries in the use of normothermia during CPB for the first clinical scenario (Fig. 3A and Table S3). There is controversy in the literature as to whether maintaining normothermia during CPB in adult cardiac surgery is as safe as hypothermic surgery, and whether this reduces the risk of allogeneic blood transfusion [34,35]. Normothermia during bypass may be considered according to European guidelines (Class IIb/Grade B level of evidence) [22].

In addition, there is a lack of consensus regarding the effect of minimally invasive surgery on transfusion and this can be seen from the results of this survey regarding its use across Europe. Minimally invasive surgery may be considered according to European guidelines (Class IIb Grade B level of evidence) [22] The use of miniaturized CPB systems is also different between countries, although they are generally considered more efficient than conventional CPB in reducing hemodilution and blood transfusion requirements [36–38]. European guidelines recommend considering the use of mini-CPB over standard conventional CPB systems to reduce perioperative transfusion (Class IIa, Grade B level of evidence) [22] The positive impact of retrograde autologous priming (RAP) on hemodilution and thus on deleterious effects associated with low level of hematocrit (impairment of hemostasis, end-organ function and cognitive outcomes) has also been demonstrated [39,40]. Besides, RAP is responsible for a reduction in transfusion need and thus reducing costs for hospitals.

It appears that another driver for the heterogeneity of PBM practices across Europe may be differences in regulations. Indeed, countries where aprotinin has been introduced more recently report lower use of aprotinin. This point could be also explained by the wider indications for tranexamic acid, as aprotinin is only authorized in isolated CABG procedures. In the UK, where the use of aprotinin has continued in many centres despite its temporary marketing cessation, aprotinin is used much more commonly [41]. Conversely, the use of tranexamic acid is less frequent in Finland.

To sum up, for a given procedure or technique, differences in practice in European countries may be driven by heterogeneity in guidelines, lack of evidence-based medicine, registration or reimbursement status or a possible unmet need of resources. Regarding respondents' previous experience with antifibrinolytics, it is interesting that the dose and method of administration of tranexamic acid greatly varies across countries (Fig. S3). The lack of consensus regarding dose and use of bolus vs. infusion implies that current evidence regarding effectiveness is not conclusive and further trials comparing regimens are required [42,43]. There is also a great variation in the choice of procedures and patients eligible for aprotinin (Fig. 5 and Fig. S3). European guidelines recommend the routine use of antifibrinolytics during cardiac surgery (Class I Grade A level of evidence) [22]. However, they do not recommend any particular dose or regimen, nor do they state when one drug should be used above another, which clearly needs addressing.

Respondents were asked to classify preoperative factors as being at high risk, or not being at high risk for transfusion. The top 5 risk factors included pre-operative anaemia, thrombocytopenia and clopidogrel 5 days or less before surgery and prior cardiac surgery (Fig. 3). These same risk factors have been used in risk of bleeding scores like ACTAPORT, Papworth and WILL-BLEED [44–46]. Further studies comparing the sensitivity and specificity and validating risk scores are required. Risk factors for transfusion can be classified according to the ability for clinicians to treat them. Such a classification could be of interest for PBM implementation in clinical practice. Indeed, while certain factors such as gender/sex or prior cardiac surgery cannot be modified, anesthesiologists' decision-making is directed towards treatable factors. For instance, preoperative anaemia might be treated by elective iron infusion, DOACs may need to be stopped temporarily, but there is no consensus on whether aspirin treatment should be discontinued. Future work is needed to provide evidence and guidance on the management of treatable risk factors. The existence of multiple PBM guidelines, which are formulated at the level of cardiac centres, countries, or continents, makes the appropriate management of patients challenging for clinicians. A detailed review and comparison of such guidelines, including the underlying rational that led to their elaboration, could be of interest for cardiac anesthesiologists. In addition to this variability in available guidelines, the disparity of practices observed between the centres across Europe might also be explained by an economic side of patient's management. It could be of interest to set up an economic analysis in the surveyed countries to investigate the possible impact of the cost of available products and techniques vs. benefits for patients and hospitals. Finally, an in-depth analysis of the potential effect of these differences in care on patient outcomes could be an important research angle to follow as a next step. It could also allow to highlight how the 'high-performing' centres succeed in implementing PBM and how their practice and protocols could be used as a model for other centres and countries.

5. Conclusion

Contrary to the hypothesis formulated at the beginning of the survey, PBM guidelines are not universally or consistently implemented in European cardiac surgery centres, resulting in discrepancies in techniques and products used for a given clinical situation. However, five main risk factors for high risk of bleeding or transfusion are very consistently identified independent of the country: pre-operative anaemia, prior cardiac surgery, clopidogrel 5 days or less before surgery, use of other P2Y12 inhibitors at any point, and thrombocytopenia $<100.10^9$ platelets/mm^3. In conclusion, more efforts are needed to clarify and complement the current available guidelines and to define a homogenous landscape for PBM practices implementation.

Author contributions

All the authors elaborated the practice survey, analysed the results, wrote and reviewed this manuscript.

Funding

This work was supported by Nordic Pharma, which hired Sirius-Customizer (France), a data management consulting company, to assist the authors in the development of the online survey, data management and statistical analyses. Nordic Pharma did not have access to the raw data and did not participate in either the analysis of the data or the writing of the manuscript.

Declaration of Competing Interest

AK has received funding for research to his institution or honoraria from Massimo, Fisher Paykel, Haemonetics, Hemosonics, Pharmacosmos and Nordic Pharma. AK is the Editor-in-Chief of Anaesthesia.

SA has received honoraria and/or research funding from Haemonetics, Nordic Pharma, Octopharma and Pharmacosmos.

BC has received honoraria from Nordic Pharma, Edwards Life Sciences, Orion Pharma, and Amomed for participating in advisory boards as well as for lectures.

JF declares no interest other than the support of Nordic Pharma for

the purpose of this study.

MG declares no interest other than the support from Nordic Pharma for the purpose of this study.

TK has received honoraria from Nordic Pharma.

ZB declares no interest other than the support from Nordic Pharma for the purpose of this study.

PP declares the support from Nordic Pharma for the purpose of this study as well as honoraria from Mitsubishi-Tanabe Pharma.

SR has received funding for research to his institution or honoraria from Nordic Pharma, Vifor Pharma, Air Liquide, Orion, and Edwards Lifesciences.

MS declares no interest other than the support from Nordic Pharma for the purpose of this study.

AvS declares no interest other than the support from Nordic Pharma for the purpose of this study.

Acknowledgment

The authors would like to thank Sirius-Customizer (Paris, France) and Public Health Expertise, Parisfor medical writing assistance provided during the project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2021.110311.

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