



## Patient blood management in cardiac surgery: The “Granducato algorithm”☆☆☆



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### ABSTRACT

**Background:** Patients undergoing cardiac surgery are subject to severe alterations of the coagulation system. The four cardiac surgery centers in Tuscany (Italy) structured and shared an algorithm (Granducato Patient Blood Management algorithm, G-PBMa) with predefined interventions for patient blood management. The aim of the study is to analyze the impact of that algorithm on the transfusion needs and bleeding-related outcomes in a large patient population.

**Methods:** Multicenter retrospective observational study on 3839 patients undergoing cardiac surgery at the four cardiac centers in Tuscany. The G-PBMa was released at the end of 2015 and it was structured in three parts: pre-, intra-, and post-operative. The year 2014, before the G-PBMa (1955 patients) and the year 2016 (1884 patients) after the G-PBMa in place were compared. Logistic regression analyses were used.

**Results:** The main changes introduced were the routine application of viscoelastic tests in bleeding patients (+72%) and the use of fibrinogen and prothrombin complex concentrate (+67%). The G-PBMa resulted in a significant reduction in the overall transfusion rate and in the transfusion rate of the separate blood products (relative risk for transfusions: 0.75, 95% confidence interval 0.65–0.85,  $P = 0.001$ ). For preoperative hemoglobin values of between 8 and 10 g/dL, the absolute difference in RBC transfusion rate before and after the G-PBMa introduction ranged around 15%–17%. The G-PBMa introduction determined lower ( $P = 0.02$ ) chest drain blood loss, lower ( $P = 0.001$ ) postoperative acute kidney injury and shorter ( $P = 0.001$ ) hospital stay.

☆ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

☆☆ This paper is dedicated to the memory of our wonderful colleague, Dr. Alessandra Rossi, who participated to the early phases of the Granducato Study, and recently passed away.

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**Conclusions:** The G-PBMA was effective in reducing blood loss, transfusion requirements, and resulted in a better outcome.

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## 1. Introduction

Patients undergoing cardiac surgery are subject to severe alterations of the coagulation system, including hemodilution and consumption of coagulation factors, thrombocytopenia or platelet dysfunction, and hyperfibrinolysis [1–3]. The clinical pattern that triggering such a complex pathological pathway is multifactorial and involves patient-related factors, anticoagulant therapies and surgery itself, particularly when the surgical procedure is conducted with the aid of cardiopulmonary bypass (CPB) [2]. The haemostatic unbalance determined by the loss of procoagulant and anticoagulant factors exposes the patient to haemorrhagic and thrombotic complications, which increase mortality, morbidity, and hospital length of stay [4].

The 2016 ESA guidelines [5] on the management of severe perioperative bleeding emphasize the importance of using an integrated and multidisciplinary management for a targeted and individualized patient's blood products supply. Indeed, the ESA guidelines and scientific literature, including the more recent EACTS/EACTA guidelines [6] on patient blood management for adult cardiac surgery, recommend to adhere to standardized algorithms with predefined intervention triggers, and to apply evidence-based decision-making instead of empiric approaches based on clinical judgement alone.

However, the application of different algorithms in clinical practice appears challenging, as these do not always take into account a number of pre- and intra-operative factors and actions that may prevent bleeding and anemia. In addition, such algorithms are often quite complex or not applicable in most hospitals [7,8].

To this purpose, four cardiac surgery centers in Italy (Tuscany region) structured and shared a simple and standardized algorithm with predefined intervention triggers for “patient blood management” (PBM). This shared protocol is now used simultaneously in the four centers. It focuses on three different moments of the cardiac surgical procedure (preoperative, intraoperative and postoperative period) as each of them would impact significantly on patient's bleeding.

The aim of the study was to assess the impact of that algorithm on the transfusion needs, bleeding-related outcomes, and general outcome in a large patient population.

## 2. Methods

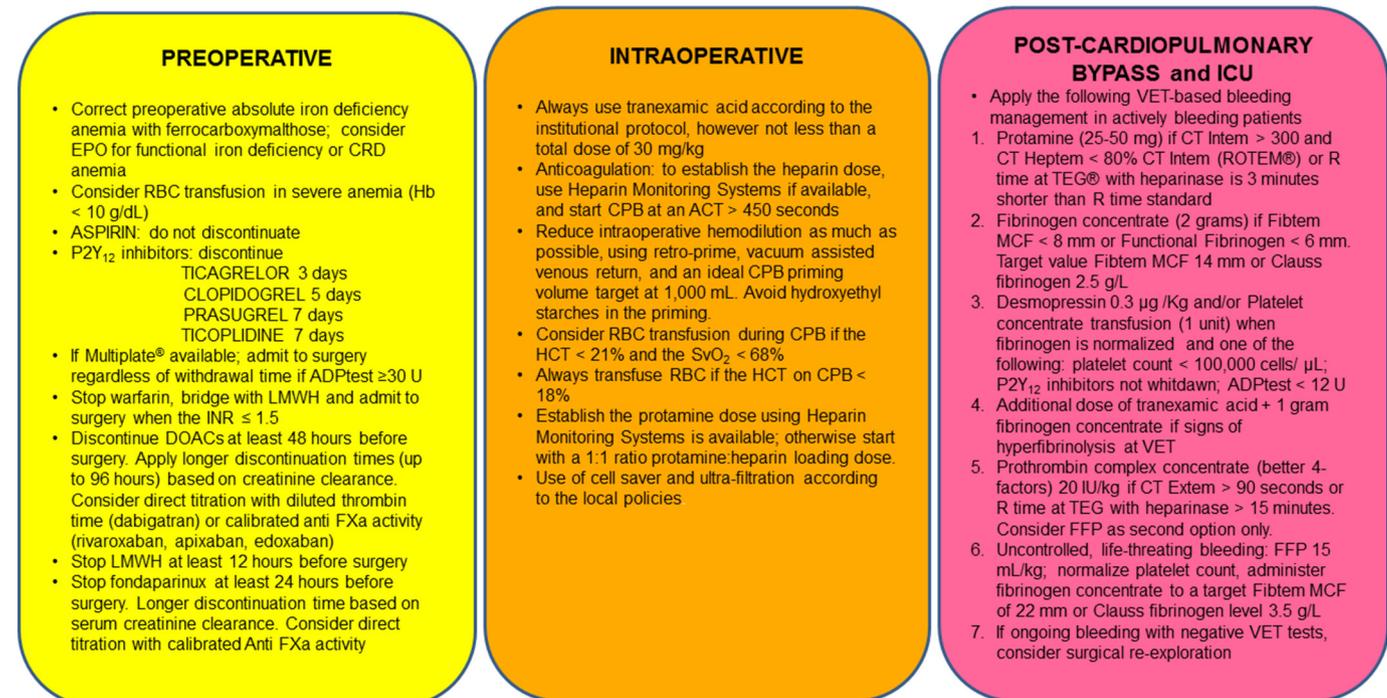
The Granducato Research Group (GRG) for PBM was established late in 2014. The purpose of this group was to develop a common PBM algorithm to be applied to the four cardiac surgery institutions in Tuscany (Firenze, Massa, Pisa, Siena), with the final aim to contain the allogeneic blood products use in adult cardiac surgery. The GRG was composed by cardiac anesthesiologists/intensivists, hematologists, cardiac surgeons, perfusionists, and was chaired by two external experts from Milan (M.R., cardiac anesthesiologist) and Padua (P.S., hematologist).

During the period between late 2014 and late 2015 the GRG met three times, developing an algorithm (Granducato Patient Blood Management algorithm, G-PBMA) to reduce the use of allogeneic blood products in adult cardiac surgery, structured in three parts: preoperative, intraoperative, and postoperative (after cardiopulmonary bypass).

At the end of 2015, the final G-PBMA was released. It is composed by a preoperative and a perioperative part, with a bleeding treatment algorithm (Fig. 1). Triggers for red blood cell (RBC) transfusions were addressed separately, suggesting the following:

- (i) Never transfuse if the hemoglobin (Hb) is  $\geq 10$  g/dL and/or hematocrit (HCT)  $\geq 30\%$ .
- (ii) Always transfuse if  $HB < 7$  g/dL and/or  $HCT < 21\%$ .

## THE GRANDUCATO PATIENT BLOOD MANAGEMENT ALGORITHM



**Fig. 1.** The three pillars of the Granducato Patient Blood Management algorithm. ACT: activated clotting time; CPB: cardiopulmonary bypass; CRD: chronic renal disease; CT: clotting time; DOACs: direct oral anticoagulants; EPO: erythropoietin; FFP: fresh frozen plasma; HCT: hematocrit; ICU: intensive care unit; INR: international normalized ratio; LMWH: low molecular weight heparin; R: reaction time; RBC: red blood cell; VET: viscoelastic tests.

- (iii) Transfusion is possible without clinical justification for Hb between 7 and 7.9 g/dL, HCT between 21% and 23.9%.
- (iv) Transfusions should be avoided for Hb values  $\geq 8$  g/dL, HCT  $\geq 24\%$ , unless in case of a strong clinical indication. This includes a central venous oxygen saturation  $<65\%$ ; arterial blood lactates  $>4.0$  mmol/L; poor cardiac output despite major inotropic support and/or mechanical circulatory support; severe active bleeding; signs of end-organ ischemia (myocardial ischemia at the EKG, stroke, anuria...). Elderly patients should be considered at higher risk and may benefit from RBC transfusions even if Hb  $> 8$  g/dL.

The four Tuscany institutions agreed to apply this algorithm starting on January 1st, 2016. It was agreed that each institution would try to comply as much as possible with the G-PBMA, taking into consideration the differences in availability of devices, products, and other items.

In 2017 the Group met again to collate the clinical judgement of the various professionals involved in the project. The general feeling was positive, and it was decided to retrospectively test the efficacy of the G-PBMA. To do this, it was decided to compare the year 2014 (before the G-PBMA) to the year 2016 (after G-PBMA in place), in terms of allogeneic blood product transfusions and other items related to postoperative hemostasis and coagulation. It was decided not to consider the year 2015 being a transition period from the previous protocols to the G-PBMA.

The Ethics Committee of the Tuscany region and of each institution were addressed to approve this retrospective study. This process ended May 23rd, 2018 with the final approval of the protocol (Protocol codes: Siena ALGO-EMO-2017, 12079/2017 - principal investigator center; Florence 12079, 10/04/2018; Massa 27925, 23/05/2018; Pisa 27918 23/05/2018).

### 2.1. Entry criteria and patient population

During the two years considered, a total of 4125 adult patients was operated in the four institutions (2096 in 2014 and 2029 in 2016). The only selection criterion applied at this stage was the exclusion of patients receiving heart or heart/lung transplantation. Subsequently, it was considered mandatory the availability of preoperative hemoglobin values to be included in the study, being this factor the major determinant of transfusions [9,10]. Applying this criterion, the population was reduced to 3839 patients. The two groups to be compared included 1955 patients (2014, before the G-PBMA) and 1884 patients (2016, after the G-PBMA). The contribution of the four institutions to the total patient population was as follows: Firenze: 1005 (26.2%); Massa: 1818 (47.4%); Pisa: 580 (15.1%); Siena: 436 (11.4%).

### 2.2. Data collection and definitions

The following data were collected using a common database, fed by the local databases of the participating institutions. Preoperative data: demographics, serum creatinine (mg/dL), diabetes, preoperative Hb (g/dL), and HCT (%), ejection fraction (EF), use of P2Y<sub>12</sub> inhibitors not discontinued within 5 days from surgery, redo surgery, non-elective surgery, mortality risk according to the ACEF II score [11]. Intraoperative data: type of surgery (isolated coronary artery bypass graft; isolated valve; combined surgery [coronary plus valve, double valve]; ascending aorta surgery; others); cardiopulmonary bypass (CPB) priming volume (mL); CPB duration (min); lowest Hb/HCT on CPB. Postoperative: chest drain blood loss in the first 12 postoperative hours (mL); surgical re-exploration due to bleeding; intensive care unit (ICU) stay (days); hospital stay (days); acute kidney injury (AKI) defined as an increase in postoperative serum creatinine  $>1.5 \times$  baseline value; hospital mortality.

The primary outcome measure was the need for any kind of allogeneic blood products throughout the whole hospital stay; secondary outcomes included the need for RBC, fresh frozen plasma (FFP), and platelet concentrate transfusions, and the amount of each blood product transfused. When retrievable, data on the use of synthetic pro-coagulants were recorded.

For all the variables listed before, the EuroSCORE II [12] definitions were applied.

### 2.3. Statistics

Continuous data are presented as median with interquartile range when non-normally distributed, and as mean (standard deviation) when normally distributed. The normality assumption was checked with the Kolmogorov-Smirnov test. Categorical binary data are presented as number (%). Differences between groups were tested using a Student's *t*-test for continuous, normally distributed data, and non-parametric tests for non-normally distributed data. Differences between frequencies were tested using a Pearson's chi-square test, producing a relative risk (95% confidence interval) when relevant.

The different covariates were investigated as above for association with the primary outcome (transfusion of any kind), and those being significantly ( $P < 0.05$ ) associated with the outcome were entered into a multivariable logistic regression analysis, together with the G-PBMA, to verify the independent role of the G-PBMA in changing the primary outcome, and producing odds ratios (95% confidence interval). To avoid overfitting of the multivariable model, a maximum of 1 independent variable per each ten events (any transfusion) was admitted to the model.

A multivariable linear regression model for decrease in RBC transfusions with respect to different interventions was applied.

Finally, the association between the preoperative Hb value and the risk of receiving RBC transfusions was investigated using a logistic regression analysis, separately for the patients before and after the implementation of the G-PBMA.

All the statistical analyses were performed with computerized packages (SPSS 20.0, IBM, Chicago, IL, and MedCalc, MedCalc Software, Ostend, Belgium). A *P* value  $<0.05$  was considered significant for all the statistical tests.

## 3. Results

Table 1 reports the general data of the two groups. The only significant differences before and after the G-PBMA introduction were a higher rate of diabetes and non-elective surgery in the 2014 series, and a larger percentage of patients with P2Y<sub>12</sub> not discontinued before surgery in 2016. Combined surgery was significantly more frequent in 2016. As a result of the G-PBMA application, in 2016 there was a significantly lower CPB priming volume that resulted in a higher nadir HCT on CPB.

The percentage of adherence to the different interventions before and after the G-PBMA as self-reported by the four institutions is shown in the e-component 1. Basically, the main changes were in the routine use of viscoelastic tests in bleeding patients (+72%), the substitution of FFP with fibrinogen concentrate (+71%) or prothrombin complex concentrate (+63%) triggered by the results of viscoelastic tests, the use of heparin/protamine titration tools (+44%), a strict application of transfusion triggers for RBC transfusions (+43%) and a containment of intraoperative hemodilution (+42%). Conversely, preoperative correction of anemia with iron supplementation of erythropoietin had a very limited impact (around +12%).

In Table 2, the primary and secondary outcomes of our study are reported, together with the general outcome before and after the G-PBMA introduction. At this univariate analysis, the G-PBMA resulted in a significant ( $P = 0.001$ ) reduction in the overall transfusion rate and in the transfusion rate of the separate blood products, with risk ratios ranging from 0.5 to 0.75. The mean amount of blood products utilized was significantly ( $P = 0.001$ ) lower after the G-PBMA introduction. Regarding the general outcome, the G-PBMA introduction resulted in

**Table 1**  
General characteristics of the two groups.

Variable	Before G-PBMA N = 1955, year 2014	After G-PBMA N = 1884, year 2016	<i>P</i>
Age (years)	72 (63–78)	72 (64–78)	0.333
Gender male	1234 (63.1)	1194 (63.4)	0.870
Weight (kg)	74 (65–83)	75 (65–83)	0.882
Body mass index (kg/m <sup>2</sup> )	25.8 (23.4–28.7)	25.9 (23.7–28.5)	0.575
Serum creatinine (mg/dL)	0.9 (0.78–1.12)	0.93 (0.8–1.12)	0.130
Diabetes	383 (19.6)	282 (15)	0.001
Preoperative hemoglobin (g/dL)	13 (11.7–14.2)	13.1 (11.8–14.2)	0.823
Preoperative hematocrit (%)	39 (35–42.8)	39.3 (35.7–42.9)	0.296
Ejection fraction (%)	55 (49–60)	55 (50–60)	0.234
Predicted mortality (%) <sup>a</sup>	5.99 (5.54–6.44)	5.22 (4.83–5.61)	0.076
P2Y <sub>12</sub> inhibitors (not discontinued)	98 (5%)	143 (7.6)	0.003
Redo surgery	147 (7.5)	132 (7)	0.538
Non-elective surgery	251 (12.8)	196 (10.4)	0.025
Type of surgery			
Isolated coronary surgery	531 (27.2)	533 (28.3)	0.434
Isolated valve surgery	862 (44.1)	775 (41.1)	0.064
Combined operation	334 (17.1)	370 (19.6)	0.041
Ascending aorta surgery	158 (8.1)	155 (8.2)	0.869
Others	70 (3.6)	51 (2.7)	0.121
CPB duration (min)	114 (86–150)	113 (85–148)	0.561
Priming volume (mL)	1360 (1000–1560)	1300 (900–1410)	0.001
Priming volume $\leq 1000$ mL	474 (24.2)	588 (31.2)	0.001
Lowest hematocrit on CPB (%)	24 (21.4–27.4)	25.6 (22.5–29)	0.001

CPB: cardiopulmonary bypass; G-PBMA: Granducato Patient Blood Management algorithm.

Data are median (interquartile range) or number (%).

<sup>a</sup> Measured according to the ACEF II score (mean value with 95% confidence interval).

**Table 2**  
Transfusion needs and general outcome of the two groups.

Variable	Before G-PBMa N = 1955, year 2014	After G-PBMa N = 1884, year 2016	Relative risk or mean difference (95% confidence interval)	P
Transfusion				
Any kind	753 (38.5)	600 (31.8)	0.75 (0.65–0.85)	0.001
Red blood cells	725 (37.1)	583 (30.9)	0.76 (0.66–0.87)	0.001
Fresh frozen plasma	251 (12.8)	102 (5.4)	0.39 (0.31–0.49)	0.001
Platelet concentrate	168 (8.6)	85 (4.5)	0.50 (0.38–0.66)	0.001
Transfused volume (units)				
Red blood cells	1.17 (2.25)	0.77 (1.57)	0.41 (0.28–0.53)	0.001
Fresh frozen plasma	0.63 (2.1)	0.15 (0.84)	0.48 (0.38–0.58)	0.001
Platelet concentrate	0.13 (0.57)	0.05 (0.27)	0.15 (0.05–0.10)	0.001
Chest drain blood loss (mL/12 h)	320 (220–480)	300 (200–500)	N/A	0.020
Surgical re-exploration	93 (4.8)	80 (4.3)	0.90 (0.66–1.21)	0.489
Intensive care unit stay (days)	1 (1–3)	1 (1–2)	N/A	0.168
Hospital stay (days)	7 (6–11)	7 (6–10)	N/A	0.001
Hospital mortality	73 (3.7)	68 (3.6)	0.96 (0.69–1.21)	0.837

a significantly ( $P = 0.02$ ) lower chest drain blood loss and shorter ( $P = 0.001$ ) hospital stay.

The univariate association between transfusions of any kind and the pre- and intraoperative variables was investigated to select the possible co-variables for the multivariable analysis. A number of variables were found significantly associated with transfusions of any kind. A positive association was found for age, serum creatinine, diabetes, redo surgery, non-elective surgery, ACEF II, ascending aorta surgery, and combined surgery ( $P$  value for association: 0.001 for all the variables). A negative association was found for gender male, preoperative hemoglobin, ejection fraction, isolated coronary or valve surgery, priming volume, and nadir HCT on CPB ( $P$  value for association: 0.001 for all the variables except body mass index: 0.05). Priming volume and the nadir HCT on CPB were not admitted to the model being part of the G-PBMa.

The final multivariable model is presented in Table 3. Within this model, age, serum creatinine, diabetes, redo surgery, non-elective surgery, ascending aorta and combined surgery remained independently and positively associated with the use of any kind of transfusions; gender male and preoperative hemoglobin remained independently and negatively associated with this outcome. After correction for these confounders, the application of the G-PBMa resulted independently associated with a 27% relative reduction in transfusions of any kind.

Preoperative Hb is the main determinant of RBC transfusions [9,10], and the association between this variable and the use of RBC transfusions was tested with logistic regression models separately for the periods before and after the G-PBMa application (e-component 2). The two functions appear overlapping in the area of Hb > 14 g/dL. They are significantly different (95% confidence intervals not

overlapping) below a Hb value of 12 g/dL. For values between 8 and 10 g/dL, the absolute difference in RBC transfusion rate ranges around 15%–17%.

### 3.1. Post-hoc analyses

For some items, data were not available in the totality of the population, and post-hoc analyses limited to the available data were applied. Data on the use of synthetic pro-coagulants were available in three centers out of four, for a total of 3259 cases. Fibrinogen concentrate was used in 152 (9.1%) patients before and 142 (8.9%) patients after the application of the G-PBMa ( $P = 0.830$ ); prothrombin complex concentrates were used in 216 (13%) patients before and 155 (9.7%) patients after the application of the G-PBMa ( $P = 0.004$ ); rFVIIa was never used before or after the application of the G-PBMa.

Data on peak postoperative values of serum creatinine were available in 2056 patients. The median increase in serum creatinine was 0.17 mg/dL (interquartile range 0.05–0.44 mg/dL) before the introduction of the G-PBMa and 0.14 mg/dL (0.1–0.40 mg/dL) after its introduction ( $P = 0.002$ ). Patients experiencing an AKI of any kind were 282 (22.6%) before the G-PBMa and 135 (16.7%) after the G-PBMa, with a relative risk reduction of 0.687 (95% confidence interval 0.547–0.863,  $P = 0.001$ ).

An analysis focused on the impact of the different interventions included in the G-PBMa was applied, having as dependent variable the RBC transfusion percentage decrease. The six mostly implemented interventions were tested as independent variables: containment of intraoperative hemodilution; heparin/protamine titration with specific

**Table 3**  
Multivariable logistic regression model for association with transfusions of any kind.

Variable	Regression coefficient	Odds ratio (95% C.I.)	P
Age (years)	0.028	1.028 (1.020–1.036)	0.001
Gender male	−0.539	0.553 (0.471–0.649)	0.001
Serum creatinine (mg/dL)	0.255	1.291 (1.156–1.442)	0.001
Body mass index (kg/m <sup>2</sup> )	−0.010	0.990 (0.977–1.003)	0.120
Diabetes	0.333	1.396 (1.144–1.702)	0.001
Preoperative hemoglobin (g/dL)	−0.256	0.774 (0.731–0.820)	0.001
Ejection fraction (%)	−0.009	0.991 (0.981–1.001)	0.072
ACEF II score	0.126	1.134 (0.947–1.359)	0.171
Redo surgery	0.611	1.842 (1.386–2.448)	0.001
Non-elective surgery	0.735	2.085 (1.148–3.786)	0.016
Isolated coronary surgery	0.254	1.289 (0.759–2.189)	0.347
Isolated valve surgery	0.169	1.184 (0.705–1.988)	0.524
Ascending aorta	0.924	2.519 (1.426–4.451)	0.001
Combined operation	0.874	2.397 (1.406–4.085)	0.001
Granducato PBM algorithm	−0.318	0.727 (0.625–0.846)	0.001

ACEF: age, creatinine, ejection fraction; C.I.: confidence interval; PBM: Patient Blood Management.

tools; routine use of viscoelastic tests in bleeding patients; use of FC; use of PCC; and strict observation of a transfusion algorithm. The two most effective interventions were a containment of intraoperative hemodilution and the routine use of viscoelastic tests.

#### 4. Discussion

The results of our retrospective, before vs. after analysis on the application of a PBM algorithm in four cardiac surgery institutions, demonstrate its effectiveness in containing allogeneic blood products use and postoperative chest drain blood loss. Additionally, the hospital stay was significantly reduced as well as the postoperative AKI rate.

Given the retrospective nature of our study, and the multifactorial interventions included in the G-PBMA, it is difficult to separate the effects of each single intervention, even if a containment in intraoperative hemodilution and the routine use of viscoelastic tests in bleeding patients were the most effective interventions leading to a decrease in RBC transfusions. Some interpretation of the effectiveness of the global protocol is however possible.

##### 4.1. Effects on bleeding

A number of perioperative interventions included in the G-PBMA is focused on bleeding containment. Among these, a careful management of pre-operative anticoagulants and antiplatelet agents, and a diagnostic approach to bleeding based on coagulation point-of-care (POC) tests. This led to a significant reduction in 12-hour chest drain blood loss. The preoperative management (especially of P<sub>2</sub>Y<sub>12</sub> inhibitors) and the timing of surgery based on platelet function tests are included in the existing guidelines [6] and in the G-PBMA, and may be responsible for the bleeding containment. However, platelet function tests were available in only 2 institutions, and this might have limited their impact on chest drain blood loss. Conversely, visco-elastic tests to correctly diagnose the nature of bleeding and guide the therapeutic approach were available in all institutions. A recent stepped-wedge clustered randomized controlled trial [13] demonstrated that the standard application of a point-of-care-based transfusion algorithm resulted in a significant reduction in major bleeding, and our results are confirmative of this finding. Of course, POC-based algorithms to diagnose and treat postoperative bleeding in cardiac surgery may differ for the type of devices used, the cut-off values triggering specific interventions, and the type of intervention. The study of Karkouti et al. [13] was based on Rotem, whereas in the G-PBMA either TEG or Rotem could be used. The trigger values prompting specific interventions in the G-PBMA and in Karkouti's study were similar; conversely, the interventions were partially different. Correction of low fibrinogen levels was achieved with either cryoprecipitate or fibrinogen concentrate in Karkouti's study, whereas only fibrinogen concentrate was considered in the G-PBMA; and desmopressin was included only in the G-PBMA. It is not the purpose of the present study to address the superiority of one algorithm vs. the others, and we share the concept that regardless of the specific nature of the algorithm, POC-based algorithms should be used [5,6].

##### 4.2. Red blood cell transfusions

RBC needs demonstrated a reduced rate of transfusions and a lower amount transfused after the G-PBMA introduction. The reduction in RBC transfusions can be attributed to (i) a better preservation of the own patient blood with higher Hb values; (ii) the observed reduction in bleeding rate; and (iii) the adherence to a RBC transfusion protocol. We cannot address this last point, because we are lacking data on the compliance to the protocol, and we have already addressed the second point. The first mechanism can be addressed based on our data collection. There were no differences in the preoperative Hb values, so the two patient population may be considered homogeneous at their entrance in the operating room. Conversely, the nadir HCT value on CPB

was significantly higher in the G-PBMA group. Within the G-PBMA, a great focus is applied on hemodilution containment during surgery, and in particular during CPB, with a suggested priming volume ≤1000 mL. This aim was achieved at a significantly higher rate in the G-PBMA group, and this probably justifies the reduced hemodilution on CPB. This is likely to translate into higher Hb values after CPB and in the ICU, therefore reducing the rate of patients meeting the trigger values for RBC transfusions.

Additionally, the reduced bleeding rate again better preserved the Hb values in the G-PBMA group. This effect was already observed in the previously cited study [13].

Of notice, the beneficial effects of the G-PBMA in terms of RBC transfusion containment were mostly relevant in patients with moderately to severely low preoperative Hb values (e-component 2). This highlights the importance of PBM-based strategies especially in high-risk and anemic patients.

Regarding the incorporation of non-Hb based trigger values for RBC transfusions, they were applied at a limited rate, with the most relevant change for the assessment of arterial blood lactates as a marker of poor oxygen delivery (+17%).

##### 4.3. Pro-coagulant interventions

Different considerations apply to pro-coagulant blood products (FFP and platelet concentrate), blood derivatives (PCC and FC) and synthetic products (desmopressin, rFVIIa). In our study, both FFP and platelet concentrate transfusions were reduced in rate and amount after the G-PBMA application. This should reasonably be attributed to a more effective approach to postoperative bleeding. Other studies have found similar results through the application of POC-based algorithms [7,8,13]; in our series, the most impressive effect is on FFP transfusions (odds ratio 0.39 in favor of the G-PBMA). This is reasonable, because FFP may theoretically be totally replaced by fibrinogen concentrate and PCC [14]. Conversely, the decrease in platelet transfusions (odds ratio 0.50 in favor of the G-PBMA) is less related to substitutive approaches. We can only speculate that this could be attributed to a better management of P<sub>2</sub>Y<sub>12</sub> inhibitors (included in the G-PBMA), to a wider use of desmopressin (data not available in data collection) and to a better diagnosis of the other possible causes of bleeding. However, the reduction in platelet concentrate use was already observed in studies on POC-based algorithms [7,13].

Of notice, the use of FC, and rFVIIa was not increased after the introduction of the G-PBMA, and the PCC use was significantly reduced. This underscores the fact that the application of POC-based algorithms does not necessarily lead to an increased use of these products, with consequent increase in some related costs. Conversely, it is reasonable that the use of these products is much more tailored when guided by specific algorithms rather than by clinical judgement.

##### 4.4. Correction of preoperative anemia

Interventions aimed to correct preoperative anemia had a very limited increase after the introduction of the G-PBMA. Correction of iron deficiency increased by 13% and the use of erythropoietin by 12%. As a result, no changes in preoperative hemoglobin were observed. This brings to the conclusion that larger savings in transfusion of RBC may be anticipated by a greater effort in the correction of preoperative anemia.

##### 4.5. Clinical outcomes

In a post-hoc analysis, we could demonstrate that the postoperative AKI rate was reduced by the application of the G-PBMA. There are many interpretations for this effect. The most reasonable is based on the evidence that patients treated with the G-PBMA had significantly higher nadir HCT values on CPB. Hemodilution on CPB has been identified as

a risk factor for AKI in cardiac surgery in many different studies [15–18]. A second interpretation is that the reduced use of blood products resulted in a lower renal risk, as already showed in other studies [19].

The combination of the significant reduction in postoperative AKI, chest drain blood loss, and transfusions, finally led to a significantly shorter hospital stay after the application of the G-PBMA, even if other hard outcomes (like mortality) did not change.

#### 4.6. Limitations and conclusions

There are of course major limitations in our study, deriving from the retrospective nature and the multifactorial pattern of the G-PBMA. Some data were not retrieved in the institutional databases and could not be addressed, or could be analyzed only in subgroups. Given these limitations, our study demonstrate that the introduction of a PBM strategy, based on preoperative, intraoperative, and postoperative interventions, is effective in reducing blood loss and transfusion requirements, and may translate in a better outcome of the cardiac surgery patients.

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#### Conflict of interest

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