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Postoperative bleeding in myocardial revascularization under cardiopulmonary bypass for patients treated with aspirin or dual antiplatelet therapy using reduced goal-directed anticoagulation

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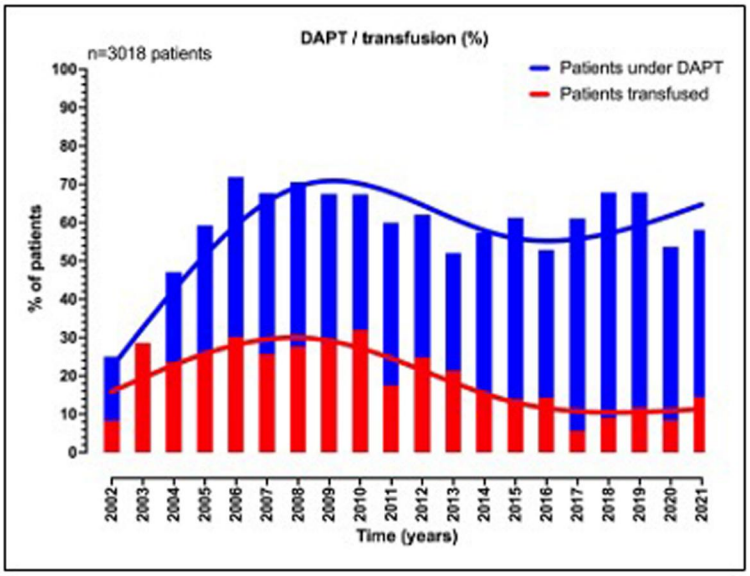
Reduced Goal Directed Anticoagulation for myocardial revascularization

Summary

Despite higher bleeding score in DAPT compared to ASA group, transfusion rate remained below 20% without increasing mortality or thromboembolic events.
In an era with increased use of DAPT for patients undergoing CABG, OpECC associated with RGDA is a helpful approach to achieve safe practice of myocardial revascularization.



CABG: coronary artery bypass grafting; OpECC: optimized extra corporeal circulation; RGDA: reduced goal directed anticoagulation; ASA: aspirin; DAPT: dual antiplatelet therapy.

Abstract

OBJECTIVES: Antiplatelet therapy increases the risk of bleeding and transfusion in patients undergoing extracorporeal circulation. Reduced goal-directed anticoagulation is a personalized approach to reduce the anticoagulation based on a lower targeted activated clotting time. We assessed whether reduced goal-directed anticoagulation using optimized extracorporeal circulation alleviates the risk

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of severe bleeding in patients treated by dual antiplatelet therapy (DAPT) compared to aspirin alone during coronary artery bypass grafting (CABG).

METHODS: A total of 2275 patients undergoing CABG from 2002 to 2022 were selected after propensity matching from a retrospective cohort of 3018 patients. Patients treated with a combination of aspirin and prasugrel or ticagrelor or clopidogrel were included in the DAPT group ($n = 1111$). Patients treated with aspirin alone (ASA) constituted the control group ($n = 1164$). Optimized extracorporeal circulation was conducted under reduced systemic anticoagulation with a target activated clotting time 250 s. Severe bleeding was assessed using 3 validated scores of bleeding: UDPB, E-CABG, and BARC-4.

RESULTS: While all scores showed low ranges of severe bleeding (<6%), they were significantly higher after DAPT compared to ASA (P values for UDPB, E-CABG, and BARC-4 at 0.016, 0.006, and 0.063, respectively). Higher maximal activated clotting time was associated with higher rate of transfusion ($P < 0.001$) and bleeding ($P < 0.001$) after multivariate adjustment. Mortality was 1.24% in DAPT vs 0.94% in ASA group (P = NS), whereas cardiac death, myocardial infarction, stroke, and transient ischaemic attack were low (<1%) and similar between groups.

CONCLUSIONS: Despite higher bleeding under DAPT compared to ASA alone, optimized extracorporeal circulation with reduced goal-directed anticoagulation alleviated severe bleeding which remained low in patients undergoing CABG.

Keywords: Coronary artery bypass grafting • Cardiopulmonary bypass • Antiplatelet therapy • Bleeding • Transfusion • Optimized extracorporeal circulation

ABBREVIATIONS

ACT	Activated clotting time
ASA	Aspirin group
BARC-4	Bleeding Academic Research Consortium
CABG	Coronary artery bypass grafting
CPB	Cardiopulmonary bypass
DAPT	Dual antiplatelet therapy
E-CABG	European Coronary Artery Bypass Grafting bleeding classification
HMS	Hepcon Heparin Management system®
OpECC	Optimized extracorporeal circulation
RGDA	Reduced goal-directed anticoagulation
STS	Society of Thoracic Surgery
UDPB	Universal Definition of Perioperative Bleeding in Cardiac Surgery

INTRODUCTION

Since 1975, anticoagulation protocols for cardiopulmonary bypass (CPB) have been based on patient's weight, with a loading heparin dose of 300 UI/kg targeting an activated clotting time (ACT) over 480 s [1, 2]. This strategy is still recommended by the guidelines [3, 4]. However, the profile of patients referred for coronary artery bypass grafting (CABG) has changed over the last 20 years, with an increased preference for the use of arterial grafts and the introduction of antiplatelet agents [5]. The use of P2Y12 receptor inhibitors in patients who have already experienced acute coronary syndrome or percutaneous intervention before CABG expose patients to major bleeding and the need for transfusion [6, 7]. Surgical revascularization guidelines therefore recommend that the operation should be postponed in patients under dual antiplatelet therapy (DAPT) [8]. Epidemiological studies in the USA have reported that during the first decade of the 21st century roughly 60% of patients undergoing CABG were transfused with homologous products [9], a rate reduced to 40% in the second decade [10]—although most CABG patients received aspirin only. This silent transfusion epidemic [11] may represent something of an Achilles heel for surgical myocardial revascularization compared to percutaneous intervention or off-pump coronary artery bypass grafting. Several attempts have been made to better understand this issue [12]. Initially, improved results have been obtained through the simple reduction of the weight-related heparin dose (150 UI/kg) during CPB [13]. Reduced goal-directed anticoagulation (RGDA) is a dedicated and personalized approach to further reduce the anticoagulation process [14] based on a lower target ACT of 250 s. We started to apply this CPB approach in 2002 [15] and it soon became our routine strategy with a targeted ACT of 250 s rather than 480 s to run CPB. According to our encouraging results, confirmed by a two-centre observational study [16], we abandoned the conventional practice of weight-based anticoagulation.

This study aimed to assess whether RGDA associated with optimized extracorporeal circulation (OpECC) alleviates the risk of severe bleeding in patients treated with DAPT compared to aspirin alone during CABG.

PATIENTS AND METHODS

This monocentric study, conducted between January 1 2002 and December 31, 2022, included all patients undergoing isolated first-time CABG under OpECC with a targeted ACT lowered empirically of 250 s, for whom aspirin (ASA group) or DAPT (DAPT group) had not been discontinued before surgery. Included patients were considered to have had effective DAPT if clopidogrel, ticagrelor, or prasugrel were discontinued after fewer than 5, 3, or 7 days, respectively. Patients under 18 years of age, pregnant female patients, patients under circulatory support, and patients treated either with no or more than 2 antiplatelet therapies in the preoperative period were excluded. Preoperative patients' characteristics as well as intra- and postoperative variables were gathered from our prospectively collected database, which was approved by the French data protection authority (CNIL—approval number 2029504-V-1). All the included data answered to the definitions described in the data collection form field from the Society of Thoracic Surgery (STS), last updated in July 2021 (v4.20.2). This study was approved by the Ethical Committee of the University Hospital of Angers, France (Approval number: 2021-038).

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CPB was performed for all included patients using closed biocompatible circuits under normothermia. Myocardial protection was achieved using anterograde cardioplegia. No cardiotomy suction was used during the procedure [15, 16]. All patients received tranexamic acid between the injection of non-fractionated heparin and the initiation of CPB. The heparin dose was measured by a dose–response assay using the Hepcon Heparin Management system® (HMS) (Medtronic© Hemotec, Englewood, CO, USA) and titrated to achieve and maintain an ACT >250 s. Measurement of the ACT was done by the perfusionist every 20 min. The protamine reversal dose was determined using the Hepcon HMS.

After surgery, transfusion of red blood cells was indicated if haemoglobin was <8 g/dl. Transfusion of fresh frozen plasma was indicated in cases of haemostasis and/or active postoperative bleeding requiring reoperation. Transfusion of platelets was indicated in cases of postoperative bleeding and/or a CPB duration exceeding 120 min, with a lower threshold of 80G/l. Fibrinogen was administered if the dosage was lower than 2 g/l.

The primary outcome was the evaluation of postoperative severe bleeding using the Universal Definition of Perioperative Bleeding in cardiac surgery (UDPB) [17], the European Coronary Artery Bypass Grafting bleeding classification (E-CABG) [18], and the Bleeding Academic Research Consortium (BARC-4) score [19]. Secondary outcomes were postoperative (30-day) mortality, chest tube blood loss at 12 h, 24 h, overall transfusion, occurrence of major adverse cardiovascular, and cerebrovascular event such as cardiac death, myocardial infarction, stroke, and transient ischaemic attack.

Statistics

Quantitative variables were expressed as mean ± standard deviation or median with interquartile range. Continuous variables were evaluated using Student's *t*-tests. Qualitative variables were expressed as percentages and analysed using the chi-squared test. Statistical significance was retained for a $P < 0.05$. Weighting-based propensity scores (inverse probability weighting) were performed using the average treatment effect in the control (ATC), to balance covariates between the ASA and DAPT arms (Supplementary Material, Fig. S1). The use of ATC estimand aims to study the effect of DAPT approach for a population of patients like those who received the ASA chirurgical approach in

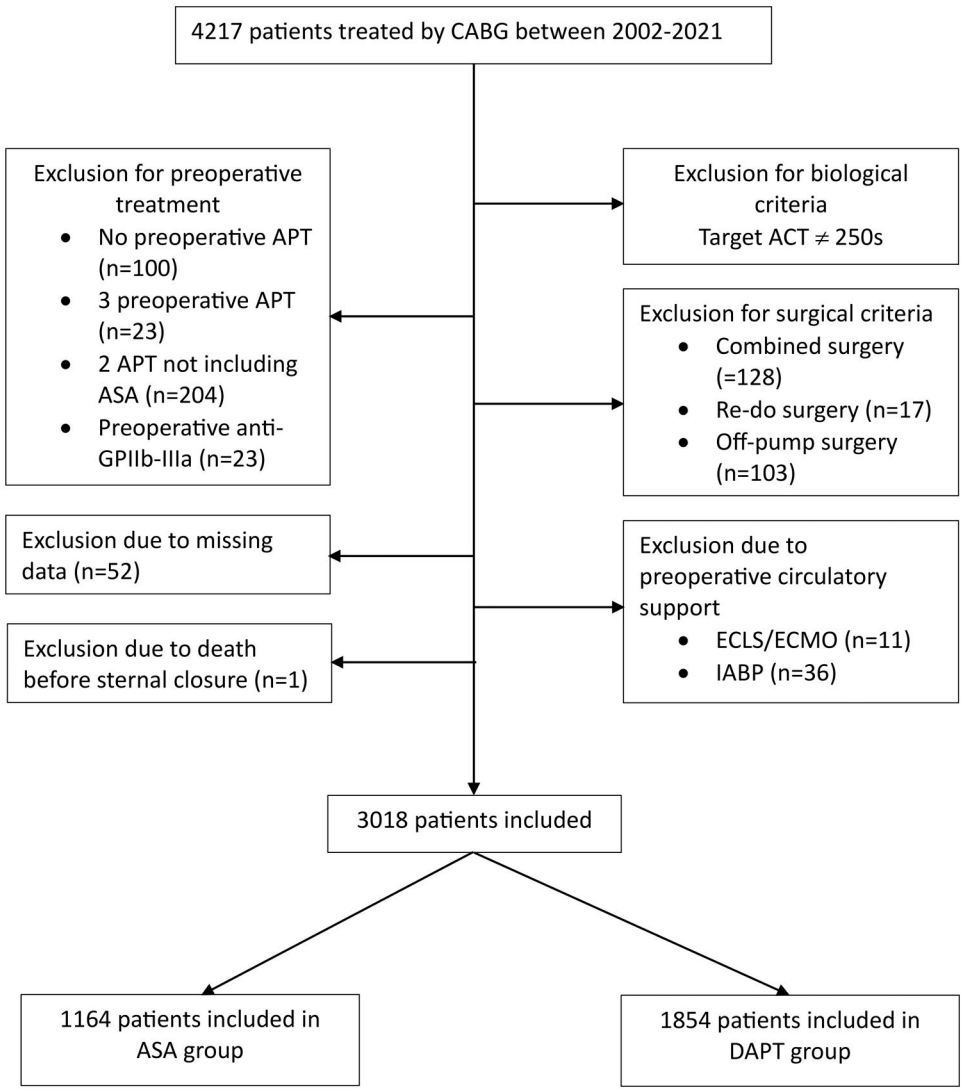

Figure 1: Flowchart of patients. ACT: activated clotting time; APT: antiplatelet therapy; ASA: aspirin group; CABG: coronary artery bypass grafting.

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the study. Balance between groups was performed using ATC estimand and weighted logistic and linear regression were performed enabling, respectively, the computation of event rates and mean outcome measures in each cohort. For each outcome of interest, a statistical comparison of both cohorts, based on previous regression, was performed.

On the whole population, a logistic regression and a linear regression were further performed to analyse the risk factors involved in postoperative transfusion and blood loss 12 h postoperatively.

Data were analysed using the statistical software SPSS (SPSS© for Mac v21, Chicago, IL, USA) and R version 4.1.

RESULTS

The flowchart of patients is depicted in Fig. 1. Patients' characteristics are reported in Table 1. Overall, 61.4% of patients underwent CABG under DAPT. The combination of antiplatelet therapies used preoperatively differed among patients according to the years of follow-up and the overall transfusion rate was 16.2% (Fig. 2). In DAPT patients, clopidogrel was used more frequently than ticagrelor, which was introduced in patients since 2012 only. Overall, 57.3% of patients were treated with both internal mammary arteries (Supplementary Material, Fig. S2).

After PS matching, the population included 2275 well-balanced patients. Operative characteristics are presented in Table 2. Although baseline ACT was similar between groups, the total dose of heparin to reach and maintain a target ACT over 250 s was significantly lower with DAPT. In the meantime, maximum and minimum ACTs were higher with DAPT, as well as ACT after neutralization by protamine.

According to UDPB, E-CABG, and BARC-4 scores, DAPT was associated with more frequent severe bleeding than in ASA group (Table 3). However, all of them were maintained below a 6% rate. Likewise, overall transfusion was higher in DAPT group as well as chest tube blood loss volumes at any time after surgery and reoperation for bleeding.

Secondary clinical end-points have been detailed in Table 4. Overall mortality at 30 days and cardiac death were similar between groups, as well as thrombo-embolic complications. However, acute kidney injury, wound infections, and prolonged ventilation (>24 h) were more frequent in DAPT group.

In the overall population, using a multivariate approach, independently of DAPT, maximal value of ACT during CPB was strongly associated ($P < 0.001$) to the risk of transfusion (Supplementary Material, Table S1) and volume of bleeding at 12 h after surgery (Supplementary Material, Table S2).

COMMENT

Combining RGDA with OpECC, our study showed significant differences in severe bleeding, as reflected by higher UDPB, E-CABG, and BARC-4 scores between ASA and DAPT groups, as in many other large studies [18, 20, 21]. However, the impact of RGDA during OpECC likely alleviated the clinical impact of CPB in patients under DAPT. A recent meta-analysis pooled the data of 4837 patients from 7 studies and showed that a shorter preoperative withdrawal than 5 days for clopidogrel and 3 days for

Table 1: Preoperative patient characteristics

Variable	Unadjusted population 3018 patients			Propensity score-matched population 2275 patients		
	ASA, $n = 1164$	DAPT, $n = 1854$	SMD	ASA, $n = 1164$	DAPT, $n = 1111$	SMD
Female, *n* (%)	156 (13)	279 (15)	0.05	156 (13)	161 (15)	0.03
Age (years), median (IQR)	68 (61–74)	66 (59–74)	0.17	68 (61–74)	68 (61–75)	−0.03
BMI (kg/m^2), median (IQR)	26.4 (24.6–29.7)	27 (24.6–29.6)	0.03	26.9 (24.6–29.7)	27.3 (24.7–29.8)	−0.01
Diabetes, *n* (%)	359 (31)	473 (26)	0.12	359 (31)	347 (31)	0.01
CKI, *n* (%)	154 (13)	249 (13)	0.01	154 (13)	163 (15)	0.04
Hypertension, *n* (%)	848 (73)	1282 (69)	0.08	848 (73)	818 (74)	0.02
Dyslipidaemia, *n* (%)	1047 (90)	1614 (87)	0.09	1047 (90)	1011 (91)	0.03
Respiratory disease, *n* (%)	119 (10)	174 (9.4)	0.03	119 (10)	107 (9.6)	0.02
Cerebrovascular disease, *n* (%)	82 (7)	157 (8.5)	0.05	82 (7)	116 (10)	0.13
Vascular disease, *n* (%)	173 (15)	285 (15)	0.01	173 (15)	180 (16)	0.04
Current smoker, *n* (%)	120 (10)	274 (15)	0.14	120 (10)	116 (10)	0.00
Preoperative altered LVEF (<50%), *n* (%)	177 (15)	375 (20)	0.13	177 (15)	190 (17)	0.05
Previous ACS, *n* (%)	312 (27)	1141 (62)	0.75	312 (27)	339 (31)	0.08
Previous PCI, *n* (%)	203 (17)	880 (47)	0.68	203 (17)	218 (20)	0.05
Anemia, *n* (%)	189 (16)	371 (20)	−0.10	189 (16)	186 (17)	−0.01
Euroscore II, median (IQR)	0.98 (0.7–1.52)	1.17 (0.8–1.96)	−0.24	0.98 (0.70–1.52)	1.08 (0.77–1.69)	−0.09
Urgent status, *n* (%)	274 (24)	943 (51)	0.59	274 (24)	277 (25)	0.03
Number of diseased coronary arteries, mean (SD)	1.6 (0.5)	1.6 (0.5)	0.05	1.6 (0.5)	1.5 (0.5)	0.05
Clopidogrel, *n* (%)	0 (0)	1085 (59)	1.7	0 (0)	840 (76)	2.2
Ticagrelor, *n* (%)	0 (0)	719 (39)	1.1	0 (0)	260 (23)	0.68
Prasugrel, *n* (%)	0 (0)	50 (2.7)	0.24	0 (0)	12 (1.1)	0.09
Preoperative heparin, *n* (%)	85 (7.3)	469 (25)	0.50	85 (7.3)	86 (7.7)	0.01
Haemoglobin (g/dl), median (IQR)	14.1 (13.2–14.9)	14 (13–14.9)	0.08	14.1 (13.2–14.9)	14 (13.1–15)	0.00
Leucocytes (G/l) median (IQR)	7.14 (6.05–8.40)	7.42 (6.20–9.01)	−0.18	7.14 (6.05–8.4)	7.02 (6.01–8.40)	−0.01
Platelet count (G/l) median (IQR)	225 (190–263)	230 (193–271)	−0.11	225 (190–263)	225 (189–267)	0.00
Fibrinogen (g/l) median (IQR)	3.51 (3.05–4.07)	3.68 (3.11–4.36)	−0.19	3.51 (3.05–4.07)	3.55 (3.02–4.16)	−0.03

ACS: acute coronary syndrome; ASA: Aspirin group; BMI: body mass index; CKI: chronic kidney insufficiency; DAPT: dual antiplatelet therapy group; IQR: interquartile range; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; SMD: standardized mean difference.

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ticagrelor was associated with BARC-4 scores of 33% for both drugs and mortality rates of 8.7% and 9.1%, respectively [22]. In our PS-matched population, the BARC-4 score of 5.09% for DAPT patients was even lower than the 9.9% and 8.2% scores after the withdrawal of clopidogrel and ticagrelor, respectively, in patients conforming to preoperative guidelines [22]. Considering the advantage of DAPT on grafts patency [23] and the fact that neither mortality nor postoperative ischaemic adverse events were significantly affected, it may be argued that RGDA during OpECC offered safety without rejecting the incentives of BIMA. Bauer *et al.* already concluded in a small, randomized trial that lowering ACT during minimally invasive ECC was safe from a laboratory standpoint [24].

Overall transfusion after matching was higher in DAPT group, but at a rate that was markedly lower than in previous studies in which more than 50% of patients under DAPT were transfused [20, 21]. Chest tube blood loss was also higher in the DAPT group, but the clinical relevance of this slight difference was questionable. Interestingly, next to DAPT and among other well-known variable of bleeding, the maximal value of ACT during CPB was strongly associated with an increased rate of transfusion and the amount of blood loss postoperatively. Patients treated with DAPT received significantly less heparin than those in the ASA group. Thus, one of the advantages of RGDA based on a target ACT is that it compensates for the preoperative treatments of each patient, such as antiplatelet agents, which can interfere with ACT determination [25, 26]. Using ACT as an *in vivo* whole blood coagulation test reflects a reliable level of clotting time that must be prolonged enough to avoid clotting within the ECC equipment, but not until an unwise level that could compromise the safety of the CPB procedure in high-risk bleeding patients.

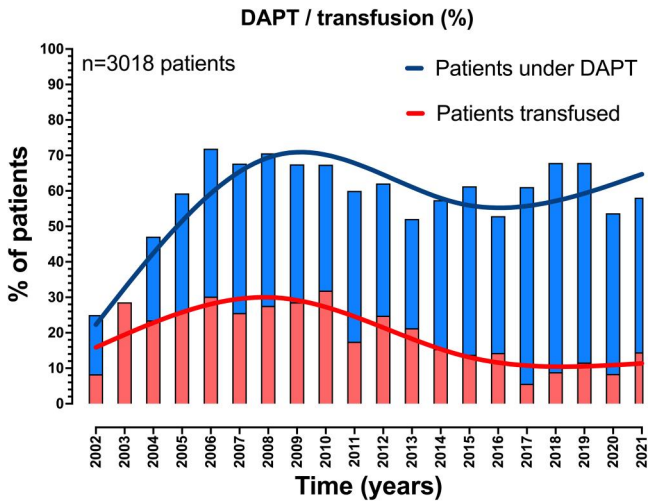

Figure 2: Yearly incidence of patients (%) undergoing coronary artery bypass grafting using optimized extracorporeal circulation (OpECC) combined with reduced goal directed anticoagulation (RGDA) under dual antiplatelet therapy (DAPT), and transfusion rates. Spline fitting curves were depicted for both events (continuous lines) to show inflections and trends over time.

The multivariate analysis found that higher ACT peak values implied a higher risk of transfusion and bleeding. Thus, instead of the weight-related dose of heparin, the achievement of RGDA with a target ACT at 250 s rather than 480 s was helpful. Guidelines are known to be based on a misinterpretation of the initial works of Bull *et al.* [1, 2] and on limited scientific evidence [4]. A spectrum of improvements has been introduced in our so-called OpECC management, such as coated closed circuits including a soft-shell reservoir drained by declivity therby eliminating vacuum-assisted venous drainage and the blood–air interface, tranexamic acid, limited haemodilution, normothermia, the use of point-of-care systems to manage anticoagulation, control of pericardial shed blood suction, and low-dose protamine based on heparin-protamine titration [27]. Once ticagrelor became embedded in our practice around 2012, we observed a trend towards a greater reduction of transfusion compared to the first decade of experience. This might be due to the earlier recovery of platelet function following the discontinuation of this medication [28].

To our knowledge, the present study is the largest observational study conducted on CABG patients treated using OpECC combined with RGDA without the discontinuation of antiplatelet therapy. These results agree with those of a smaller prospective randomized pilot study by Karlsonn *et al.* [29]. We are aware that the interpretation of our results is limited by the absence of a standard anticoagulation regimen control group (ACT above 480 s) without discontinuation of DAPT and by the lack of platelet function assessment.

Our goal was to reduce the risk of severe bleeding in our patients by primarily fixing the target ACT for safety. Moreover, when comparing the 2 groups, this OpECC strategy associated

Table 2: Operative data

Variable	Propensity score-matched population			
	Overall, $n = 2275$	ASA, $n = 1164$	DAPT, $n = 1111$	*P*-value
Arterial grafts				
LIMA, *n* (%)	2259 (99.3)	1156 (99.3)	1103 (99.3)	0.984
BIMA, *n* (%)	1298 (57)	694 (59.6)	604 (54.3)	0.019
Aortic cross-clamp time (min), mean (SD)	63.1 (24)	62.7 (24.5)	63.6 (23.4)	0.408
CPB time (min), mean (SD)	89.8 (30.9)	88.9 (31.4)	90.7 (30.3)	0.213
Total heparin dose delivered (IU.10^2), mean (SD)	139.6 (50.7)	144.7 (51.9)	134.3 (48.8)	<0.0001
Total protamine dose delivered (mg), mean (SD)	67.5 (26.6)	69.6 (26.5)	65.3 (26.4)	0.0004
Baseline ACT before CPB (s), mean (SD)	137.6 (12.4)	137.2 (12.3)	137.9 (12.5)	0.222
Maximum ACT (s) on pump, mean (SD)	322.3 (45.7)	318.7 (43.7)	326.0 (47.4)	0.0006
Minimum ACT (s) on pump, mean (SD)	240.9 (30.1)	239.5 (29.1)	242.4 (31.1)	0.0404
Post-protamine ACT (s), mean (SD)	137.6 (14.1)	136.6 (13.9)	138.7 (14.1)	0.0011

ACT: activated clotting time; ASA: aspirin group; BIMA: bilateral internal mammary arteries; CPB: cardiopulmonary bypass; DAPT: dual antiplatelet therapy group; LIMA: left internal mammary artery.

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Table 3: Postoperative bleeding

Variable	Propensity score-matched population			
	Overall, $n = 2275$	ASA, $n = 1164$	DAPT, $n = 1111$	*P*-value
E-CABG score ≧2, *n* (%)	94 (4.11)	34 (2.92)	59 (5.31)	0.0065
UDPB score ≧3, *n* (%)	61 (2.68)	21 (1.8)	40 (3.57)	0.0162
BARC 4, *n* (%)	96 (4.2)	40 (3.44)	57 (5.09)	0.0626
Reoperation for bleeding, *n* (%)	75 (3.33)	29 (2.49)	46 (4.18)	0.03
Pleural effusion, *n* (%)	84 (3.70)	32 (2.75)	51 (4.62)	0.033
Units of RBC transfused, mean (SD)	0.402 (1.3)	0.248 (1.1)	0.56 (1.5)	<0.0001
Units of FFP transfused, mean (SD)	0.071 (0.5)	0.045 (0.5)	0.098 (0.5)	0.021
Units of PLT transfused, mean (SD)	0.016 (0.18)	0.009 (0.18)	0.023 (0.17)	0.08
Overall transfusion, *n* (%)	349 (15.3)	109 (9.5)	239 (21.5)	<0.0001
Chest tube blood loss volume at 12H (ml), mean (SD)	224 (161.9)	192 (136.4)	258 (178.8)	<0.0001
Chest tube blood loss volume at 24H (ml), mean (SD)	322 (211.3)	284 (187.8)	361 (226.9)	<0.0001
Overall chest tube blood loss volume (ml), mean (SD)	386 (296)	338 (274.8)	435 (309)	<0.0001

ASA: aspirin group; BARC 4: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy group; E-CABG: European Coronary Artery Bypass Grafting bleeding classification; FFP: fresh frozen plasma; PLT: platelets; RBC: red blood cells; UDPB: Universal Definition of Perioperative Bleeding in cardiac surgery.

Table 4: Postoperative outcomes

Variable	Propensity score-matched population			
	Overall, $n = 2275$	ASA, $n = 1164$	DAPT, $n = 1111$	*P*-value
30-days mortality, *n* (%)	25 (1.09)	11 (0.94)	14 (1.24)	0.497
Death of cardiac cause, *n* (%)	10 (0.44)	3 (0.26)	7 (0.64)	0.278
Postoperative myocardial infarction, *n* (%)	6 (0.26)	2 (0.17)	4 (0.34)	0.415
Stroke, *n* (%)	15 (0.67)	5 (0.43)	10 (0.91)	0.217
TIA, *n* (%)	9 (0.38)	2 (0.17)	7 (0.6)	0.185
AKI, *n* (%)	189 (8.3)	75 (6.44)	113 (10.17)	0.0025
Wound infection, *n* (%)	44 (1.94)	13 (1.11)	31 (2.8)	0.010
Ventilation time >24 h, *n* (%)	71 (3.12)	24 (2.06)	47 (4.2)	0.0061
ICU time (h), mean (SD)	88.8 (101.1)	86.4 (90.3)	91.3 (111.4)	0.301
Total hospitalization time (days), mean (SD)	10.3 (6.6)	9.8 (5.1)	10.8 (7.8)	0.0069

Wound infection defined as requiring surgical re-exploration of the wound for septic signs within 30 days of the procedure.
AKI: acute kidney insufficiency (defined as an increase of serum creatinine level 3× greater than baseline/new requirement for dialysis in postoperative); ASA: aspirin group; DAPT: dual antiplatelet therapy group; ICU: intensive care unit; TIA: transient ischaemic attack.

with RGDA did not increase the occurrence of mortality or postoperative ischaemic events.

While we encourage the adoption of multiple arterial grafting in the context of increased use of DAPT, we consider OpECC associated with RGDA a helpful approach to achieve myocardial revascularization in this population.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Conflict of interest: none declared.

DATA AVAILABILITY

The data underlying this research will be shared upon reasonable request to the corresponding author.

Author contributions

Maroua Eid: Conceptualization; Data curation; Methodology; Writing—original draft; Writing—review & editing. **Simon Dang Van:** Writing—review & editing. **Yveline Hamon:** Data curation. **Emmanuel Rineau:** Writing—review & editing. **Jérémie Riou:** Data curation; Formal analysis; Writing—review & editing. **Christophe Baufreton:** Conceptualization; Formal analysis; Methodology; Supervision; Validation; Writing—original draft; Writing—review & editing.

Reviewer information

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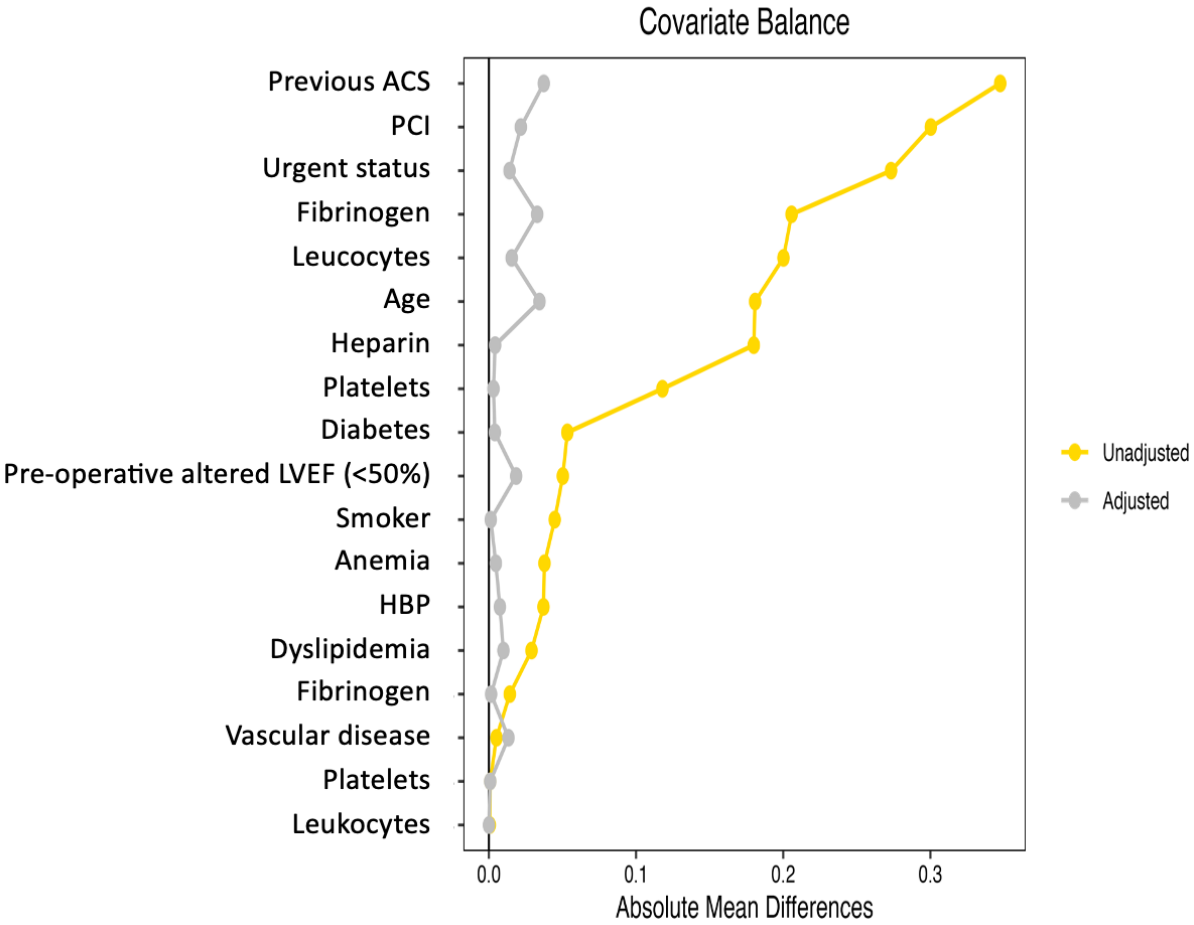
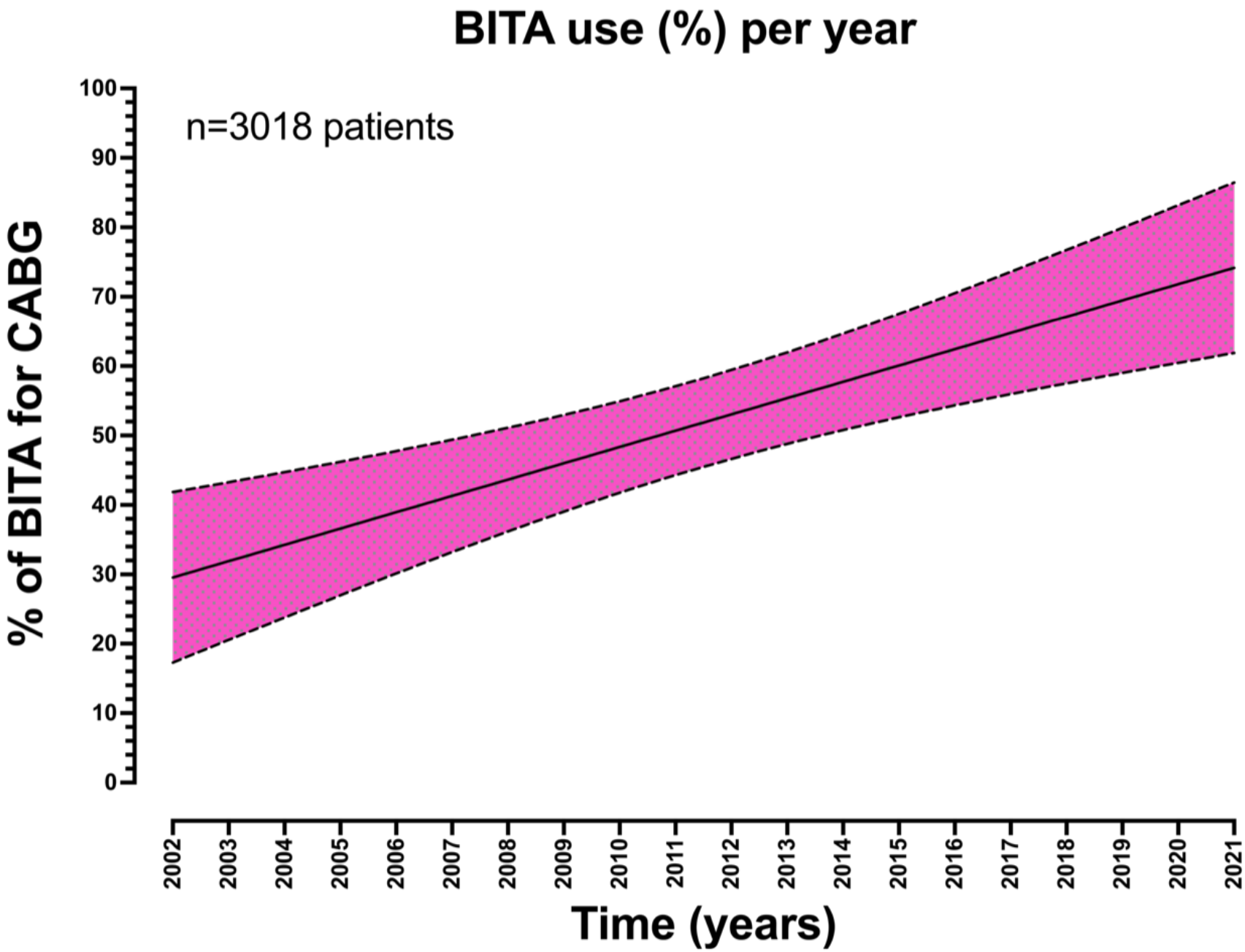
Supplementary Figure 1. Standardized mean differences before and after matching. ASA: aspirin. DAPT: dual antiplatelet therapy.

Supplementary Figure 2. Yearly evolution of percentages of use of Bilateral Thoracic Internal Arteries (BITA). Regression line with 95% confidence interval. CABG: Coronary Artery Bypass Grafting.


Covariate Balance
Previous ACS
PCI
Urgent status
Fibrinogen
Leucocytes
Age
Heparin
Platelets
Diabetes
Pre-operative altered LVEF (<50%)
Smoker
Anemia
HBP
Dyslipidemia
Fibrinogen
Vascular disease
Platelets
Leukocytes
0.0
0.1
0.2
0.3
Absolute Mean Differences
Unadjusted
Adjusted


BITA use (%) per year
n=3018 patients
% of BITA for CABG
100
90
80
70
60
50
40
30
20
10
0
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Time (years)

Supplementary Table 1. Multivariate analyses of transfusion in the overall cohort (3018 patients)

Variable	Logistic regression of any transfusion		
	OR	95% CI	*p-value*
Female gender	3.015	(2.216-4.103)	< 0.001
Diabetes	1.076	(0.819-1.415)	ns
CKI	2.061	(1.517-2.799)	< 0.001
Hypertension	1.098	(0.819-1.472)	ns
Dyslipidemia	0.910	(0.612-1.354)	ns
Current smoker	0.932	(0.630-1.385)	ns
Anemia	4.557	(3.498-5.938)	< 0.001
Previous PCI	0.973	(0.744-1.271)	ns
Previous ACS	1.017	(0.778-1.329)	ns
DAPT	2.801	(2.078-3.775)	< 0.001
Preoperative heparin	1.411	(1.012-1.967)	0.042
Low LVEF (<50%)	1.661	(1.243-2.221)	< 0.001
Urgent status	1.085	(0.808-1.457)	ns
Age	1.020	(1.006-1.035)	0.005
BMI	0.948	(0.917-0.980)	0.002

Platelet count	1.003	(1.002-1.005)	< 0.001
Fibrinogen	0.974	(0.857-1.108)	ns
CPB time	1.012	(1.002-1.022)	0.015
Aortic cross clamp time	0.997	(0.985-1.009)	ns
Minimal CPB temperature	0.729	(0.602-0.883)	0.001
Total heparin dose on CPB	0.997	(0.993-1.000)	ns
Total protamine dose	0.992	(0.986-0.996)	0.013
Maximum ACT on pump	1.010	(1.007-1.013)	< 0.001
Minimum ACT on pump	1.001	(0.997-1.006)	ns
Baseline ACT before CPB	0.996	(0.985-1.007)	ns
Post-protamine ACT	1.009	(1.000-1.019)	ns
Nb of diseased vessels	1.352	(1.069-1.710)	0.012
BIMA use	0.892	(0.681-1.168)	ns

OR: odd-ratio; 95% CI: 95% confidence interval; SE: standard error; ns: not significant, CKI: chronic kidney insufficiency, PCI: percutaneous coronary intervention, ACS: acute coronary syndrome, DAPT: dual antiplatelet therapy; LVEF: left ventricular ejection fraction, BMI: body mass index, CPB: cardiopulmonary bypass, ACT: activated clotting time, BIMA: bilateral internal mammary artery. After assessment of normal probability by Q-Q plot, log-transformed for bleeding at H12 was applied.

Supplementary Table 2. Multivariate analyses of postoperative bleeding in the overall cohort (3018 patients)

Variable	Linear regression of log_{10} bleeding at 12 hours postoperatively			
	Estimate	SE	95% CI	*p-value*
Female gender	-0.077	0.013	(-0.103 ;-0.051)	< 0.001
Diabetes	-0.009	0.010	(-0.030 ;0.010)	ns
CKI	0.007	0.014	(-0.020 ;0.035)	ns
Hypertension	-0.002	0.010	(-0.021 ;0.019)	ns
Dyslipidemia	-0.030	0.014	(-0.058 ;-0.002)	0.034
Current smoker	-0.013	0.014	(-0.040 ;0.013)	ns
Anemia	-0.005	0.012	(-0.028 ;0.019)	ns
Previous PCI	-0.013	0.010	(-0.033 ;0.006)	ns
Previous ACS	0.025	0.010	(0.006 ;0.045)	0.011
DAPT	0.114	0.010	(0.094 ;0.134)	< 0.001
Preoperative heparin	-0.004	0.013	(-0.030 ;0.022)	ns
Low LVEF (<50%)	0.003	0.012	(0.005 ;0.050)	0.018
Urgent status	-0.023	0.011	(-0.044 ;-0.001)	0.039
Age	-0.343×10^{-3}	0.509×10^{-3}	(-0.001 ;0.654×10^{-3})	ns
BMI	-0.005	0.001	(-0.007 ;-0.003)	< 0.001

Platelet count	-0.720×10^{-4}	0.710×10^{-4}	$(-0.211 \times 10^{-3}$;$0.672 \times 10^{-4})$	ns
Fibrinogen	-0.037	0.005	(-0.047 ;-0.027)	< 0.001
CPB time	-0.905×10^{-3}	0.371×10^{-3}	$(-0.002$;$-0.178 \times 10^{-3})$	0.015
Aortic cross clamp time	0.002	0.475×10^{-3}	(0.001 ;0.003)	< 0.001
Minimal CPB temperature	-0.005	0.007	(-0.018 ;0.008)	ns
Total heparin dose on CPB	0.173×10^{-3}	0.126×10^{-3}	$(-0.742 \times 10^{-4}$;$0.421 \times 10^{-3})$	ns
Total protamine dose	0.836×10^{-4}	0.126×10^{-3}	$(-0.507 \times 10^{-3}$;$0.339 \times 10^{-3})$	ns
Maximum ACT on pump	0.670×10^{-3}	0.115×10^{-3}	$(0.444 \times 10^{-3}$;$0.895 \times 10^{-3})$	< 0.001
Minimum ACT on pump	0.386×10^{-3}	0.181×10^{-3}	$(0.321 \times 10^{-4}$;$0.740 \times 10^{-3})$	0.033
Baseline ACT before CPB	-0.001	0.409×10^{-3}	$(-0.002$;$-0.283 \times 10^{-3})$	0.008
Post-protamine ACT	0.002	0.361×10^{-3}	(0.002 ;0.003)	< 0.001
Nb of diseased vessels	0.007	0.008	(-0.009 ;0.022)	ns
BIMA use	-0.029	0.010	(-0.048 ;-0.009)	< 0.004

OR: odd-ratio; 95% CI: 95% confidence interval; SE: standard error; ns: not significant, CKI: chronic kidney insufficiency, PCI: percutaneous coronary intervention, ACS: acute coronary syndrome, DAPT: dual antiplatelet therapy; LVEF: left ventricular ejection fraction, BMI: body mass index, CPB: cardiopulmonary bypass, ACT: activated clotting time, BIMA: bilateral internal mammary artery. After assessment of normal probability by Q-Q plot, log-transformed for bleeding at H12 was applied

Supplementary Table 3. Post operative bleeding outcome with Average Treatment Effect (ATE)

Variables	ATE	Standard Error	95% CI
E-CABG score ≧2	0.024	0.009	[0.006;0.041]
UDPB score ≧3	0.018	0.008	[0.003;0.03]
BARC 4	0.017	0.009	[-0.001;0.03]
Reoperation for bleeding	0.017	0.008	[0.001;0.03]
Pleural effusion	0.019	0.009	[0.0007;0.04]
Units of RBC transfused	0.315	0.064	[0.19;0.44]
Units of FFP transfused	0.054	0.023	[0.007;0.1]
Units of PLT transfused	0.014	0.008	[-0.002;0.03]
Overall transfusion	0.119	0.016	[0.09;0.16]
Chest tube blood loss volume at 12H (mL)	66.2	7.21	[52.1;80.3]
Chest tube blood loss volume at 24H (mL)	76.9	9.4	[58.5;95.3]
Overall chest tube blood loss volume (mL)	97.3	13.3	[71.3;123]

E-CABG: European Coronary Artery Bypass Grafting bleeding classification; UDPB: Universal Definition of Perioperative Bleeding in cardiac surgery; BARC 4 Bleeding Academic Research Consortium; RBC: red blood cells; FFP: fresh frozen plasma; PLT: platelets.

ATE obtained using the CRAN module for R version 4.1 (https://cran.r-project.org/web/packages/targeted/vignettes/ate.html).