Revised manuscript

Variation in Preoperative Antithrombotic Strategy, Severe Bleeding and Use of Blood Products in Coronary Artery Bypass Grafting: Results from the Multicenter E-CABG Registry

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Abstract

Background: No data exists on inter-institutional differences in terms of adherence to international guidelines regarding the discontinuation of antithrombotics and rates of severe bleeding in coronary artery bypass grafting (CABG).

Methods and Results: This is an analysis of 7118 patients from the prospective multicenter E-CABG registry who underwent isolated CABG in 15 European centers. Preoperative pause of P2Y12 receptor antagonists shorter than that suggested by the 2017 ESC guidelines (overall, 11.6%) ranged from 0.7% to 24.8% between centers (adjusted p<0.0001) and increased the rate of severe-massive bleeding (E-CABG bleeding grades 2-3, OR 1.66, 95%CI 1.27-2.17; UDPB bleeding grades 3-4, OR 1.50, 95%CI 1.16-1.93). The incidence of resternotomy for bleeding (overall, 2.6%) ranged from 0% to 6.9% (adjusted p<0.0001) and surgical site bleeding (overall, 59.6%) ranged from 0% to 84.6% (adjusted p=0.003). The rate of the UDPB bleeding grades 3-4 (overall, 8.4%) ranged from 3.7% to 22.3% (p<0.0001) and of the E-CABG bleeding grades 2-3 (overall, 6.5%) ranged from 0.4% to 16.4% between centers (p<0.0001). Resternotomy for bleeding (adjusted OR 5.04, 95%CI 2.85-8.92), UDPB bleeding grades 3-4 (adjusted OR 6.61, 95%CI 4.42-9.88) and E-CABG bleeding grades 2-3 (adjusted OR 8.71, 95%CI 5.76-13.15) were associated with an increased risk of hospital/30-day mortality.

Conclusions: Adherence to the current guidelines on the early discontinuation of P2Y12 receptor antagonists is of utmost importance to reduce excessive bleeding and early mortality after CABG. Inter-institutional variation should be considered for a correct interpretation of the results in multicentre studies evaluating perioperative bleeding and use of blood products.

Key words: Bleeding; P2Y12; Antithrombotic; Coronary artery bypass grafting; Cardiac Surgery; Blood transfusion.

Introduction

Patients undergoing isolated coronary artery bypass grafting (CABG) are often at risk of severe bleeding because of recent exposure to potent antithrombotics (1). Excessive bleeding and exposure to blood products are known to vary significantly between institutions, likely because of different patient-blood management strategies (2-5). However, there is no data on the possible impact of the individual patient risk of bleeding, late discontinuation of potent antiplatelets and differences in the rate and nature of excessive bleeding requiring reoperation as the main determinants of such inter-institutional differences. We sought to investigate any inter-institutional variation in the adherence to early discontinuation of antithrombotics, perioperative bleeding and use of blood products from the prospective, multicenter European Coronary Artery Bypass Grafting (E-CABG) registry.

Methods

The E-CABG registry is a prospective, multicenter observational study that enrolled patients undergoing isolated CABG at 16 European centers of cardiac surgery from Finland, France, Italy, Germany, Sweden and United Kingdom. The detailed protocol and definition criteria have been published earlier (6). Out of 7352 patients enrolled in the E-CABG registry, 181 were operated after the recruitment period. Further 53 patients were excluded because they were recruited from one center only at the end of the study period. Overall, 7118 patients operated in 15 centers from January 2015 to December 2016 had complete data on the covariates and outcomes of interest and were included in the present analysis. Data were collected prospectively and underwent robust validation and checking of its quality. Only data on timing of resternotomy and sources of bleeding were retrieved retrospectively. The study was approved by the Regional or Institutional Review Board of the participating centers. Informed consent was obtained when required by the Review Board, otherwise it was waived. The study is registered with the Clinical Trials Identifier NCT02319083 and was not supported financially. The participating centers did not adopt a common strategy of patient-blood management and the indication for blood transfusion varied between centers.

Point-of-care testing of coagulation was performed in all centers only in case of excessive intra- or postoperative bleeding.

The risk of postoperative bleeding was estimated by the WILL-BLEED (8), CRUSADE (9), Papworth (10), TRUST (11), TRACK (12) and CathPCI bleeding risk scores (13).

Outcomes

The main outcome measures were reoperation for bleeding, severe-massive bleeding defined as the Universal Definition of Perioperative Bleeding (UDPB) classes 3-4 (7) and E-CABG bleeding classes 2-3 (6). Secondary outcomes were chest drain output at 12 hours after surgery, nadir hematocrit, red blood cell (RBC) transfusions, plasma transfusion, platelets transfusion, use of procoagulants, hospital/30-day death, length of stay in the intensive care unit, stroke, prolonged inotropic support, deep sternal wound infection/mediastinitis, acute kidney injury, renal replacement therapy, and postoperative atrial fibrillation.

Reoperation for bleeding was defined as any resternotomy for excessive bleeding performed during the index hospitalization. According to the E-CABG bleeding classification, severe-massive bleeding was defined as any reoperation for excessive bleeding and/or transfusion >4 units of red blood cells (6). According to the UDPB bleeding classification, severe-massive bleeding was defined as chest tube blood loss within 12 hours >1000 mL and/or reoperation for excessive bleeding and/or transfusion >4 units of red blood cells and/or transfusion >4 units of fresh frozen plasma after closure of the chest (7). Use of procoagulants was defined as any administration of fibrinogen, prothrombin complex concentrate, cryoprecipitate and recombinant factor VIIa intraoperatively during the index hospitalization. Nadir levels of hematocrit were defined as the lowest value measured on the day of surgery. Hospital/30-day mortality was defined as all-cause death occurring during the index hospitalization or within 30 days after CABG. Intensive care unit length of stay was defined as the number of days of treatment in the intensive care unit considering also any readmission during the same index hospitalization. Stroke was defined as any focal or global neurological syndrome occurring during the index hospitalization not resolving within 24 h. The diagnosis and nature of stroke was based on findings at computed tomography and/or magnetic resonance imaging of the brain and confirmed by a

neurologist. Need of intra-aortic balloon pump and/or extra-corporeal membrane oxygenation refers to the use of these mechanical circulatory supports method any time after surgery and during the index hospitalization. Deep sternal wound and mediastinitis were defined as a surgical site infection occurring within 3 months after surgery involving deep soft tissues, sternum and/or mediastinum with purulent drainage or abscess, with or without fever (>38°C), detected at direct examination, during reoperation, or radiologic examination and requiring antibiotic treatment with or without reoperation. Postoperative atrial fibrillation was defined as any new event of atrial fibrillation occurred after CABG and detected at electrocardiogram, requiring or not pharmacological/electrical cardioversion. Acute kidney injury was defined as an increase in serum creatinine ≥1.5 times the baseline level or serum creatinine increase ≥26.5 µmol/l within seven days after surgery and/or de novo renal replacement therapy. Patients with baseline estimated glomerular filtration rate <15 mL/min/1.73 m^2 or on chronic dialysis were excluded from the analysis on postoperative acute kidney injury.

Statistical Analysis

Statistical analysis was performed using SPSS statistical software v. 24.0 (IBM Corporation, New York, USA), and Stata v. 14.2 (StataCorp LLC, Texas, USA). Covariates and outcomes were reported as counts and percentages, and as mean and standard deviation. The Mann-Whitney, Kruskall-Wallis, Chi-square, Fisher Exact tests were used to compare baseline and operative covariates between the study cohorts. Predictive ability of bleeding risk scores were evaluated by the area under the receiver operating (ROC) curves and these were compared by the de Long's test. Since the study cohorts had a significantly different distribution of baseline and operative covariates, logistic regression models evaluating the primary outcomes were adjusted using the enter method for the following covariates: age, gender, baseline hemoglobin, baseline platelets count <150 10^9/L, estimated glomerular filtration rate, P2Y12 receptor inhibitors pause shorter than that suggested by the 2017 European Society for Cardiology (ESC) guidelines, aspirin administered within 7 days from surgery, oral anticoagulants administered within 2 days from surgery, diabetes, stroke or transient ischemic attack, atrial fibrillation, pulmonary disease, extracardiac arteriopathy, emergency procedure, left

ventricular ejection fraction ≤50%, critical preoperative state, prior cardiac surgery, prior percutaneous coronary intervention, off-pump surgery, bilateral internal mammary artery grafting and number of distal anastomoses. Continuous variables were left untransformed. We did not include the duration of cross-clamping and cardiopulmonary bypass in to regression models because a significant number of patients in this series underwent off-pump CABG. The goodness of fit of regression models were tested with the Hosmer-Lemeshow's test. The anonymized center codes were ranked in descending order of center volume and was included in the regression models as a factor covariate. The risk-adjusted rate of adverse binary events was calculated by dividing, for each participating center, the observed number of events by the expected number of events, and by multiplying this ratio by the average event rate of the entire series. The expected numbers of events were estimated using logistic regression. The estimated risk-adjusted rates of adverse events with 95% confidence intervals (CI) were summarized in caterpillar plots with the x-axis ordered for increasing adjusted rates. All tests were two-sided with the alpha level set at 0.05 for statistical significance.

Results

Baseline risk factors

Their baseline characteristics, operative data, preoperative antithrombotic regimen as well as bleeding risk are summarized in Tables 1 and 2.

Univariate analysis showed that participating centers differed in all baseline risk factors. In particular, the prevalence of recent myocardial infarction ranged from 17.9% to 62.5%, left ventricular ejection fraction ≤50% from 16.9% to 48.7% and critical preoperative state from 1.5% to 21.8% (Tab. 1). Such imbalances in baseline risk factors translated in marked inter-institutional differences in the operative risk as shown by the mean EuroSCORE II, which ranged from 1.6±1.3% to 5.2±6.8% ($p<0.0001$, Tab. 1). Similarly, also the surgical approach differed markedly between centers as the proportion of bilateral internal mammary artery grafting ranged from 0.9% to 88.5% and of off-pump surgery from 0.9% to 57.6% (Tab. 1).

Preoperative antithrombotic regimen

Aspirin were discontinued less than seven days before CABG in 88.4% of patients (range between centers, 67.3-98.6%, p<0.0001) (Tab. 2). When adjusted for multiple covariates and participating centers, aspirin discontinued less than seven days was not associated with an increased risk of resternotomy for bleeding (p=0.898) as well as severe-massive bleeding defined as E-CABG bleeding grades 2-3 (p=0.251) and UDPB bleeding grades 3-4 (p=0.997).

Low molecular weight heparin, unfractionated heparin and fondaparinux were administered preoperatively in 41.8% of patients (range between centers, 4.4-97.4%, p<0.0001) (Tab. 2). When adjusted for multiple covariates and participating centers, preoperative exposure to low molecular weight heparin, unfractionated heparin and fondaparinux showed was not associated with an increased risk of resternotomy for bleeding (p=0.264). However, these drugs increased significantly the risk of severe-massive bleeding defined as E-CABG bleeding grades 2-3 (p=0.001, OR 1.51, 95%CI 1.17-1.95) and UDPB bleeding grades 3-4 (p=0.016, OR 1.34, 95%CI 1.05-1.69).

Overall, 14.6% of patients were operated on with a pause of P2Y12 receptor antagonists of <5 days from surgery (range between centers, 0.7-25.0%, p<0.0001) (Fig. 1). Similarly, 11.6% of patients were operated on with a pause of P2Y12 receptor antagonists shorter than recently suggested by the 2017 ESC guidelines, i.e. ticagrelor <3 days, clopidogrel <5 days and prasugrel <7 days before CABG (range between centers, 0.7-24.8%, p<0.0001) (Fig. 1).

When adjusted for recent myocardial infarction, left ventricular ejection fraction ≤50%, critical preoperative state and emergency operation, the proportion of patients with pause of P2Y12 receptor antagonists <5 days from surgery (p<0.0001) and pause of P2Y12 receptor antagonists shorter than recently suggested by the 2017 ESC guidelines (p<0.0001) significantly differed between centers.

Logistic regression adjusted for multiple covariates and participating centers showed that patients operated on with a pause of P2Y12 receptor antagonists shorter than those recently suggested by the 2017 ESC guidelines had a significantly increased risk of E-CABG bleeding grades 2-3 (OR 1.66, 95%CI 1.27-2.17) and UDPB bleeding grades 3-4 (OR 1.50, 95%CI 1.16-1.93), but not of resternotomy for bleeding (adjusted OR 1.22, 95%CI 0.80-1.87). Similarly, logistic regression adjusted for multiple covariates and participating

centers showed that patients operated on with a pause of P2Y12 receptor antagonists <5 days had a significantly increased risk of E-CABG bleeding grades 2-3 (OR 1.78, 95%CI 1.38-2.29) and UDPB bleeding grades 3-4 (OR 1.43, 95%CI 1.12-1.83), whilst a trend toward increased risk of resternotomy for bleeding was observed as well (adjusted OR 1.36, 95%CI 0.92-2.01).

Estimated bleeding risk

The bleeding risk estimated by the WILL-BLEED, CRUSADE, Papworth, TRUST, TRACK and CathPCI risk scores were significantly different between centers (all scores, p<0.0001, Tab. 2). Among these bleeding risk scoring methods, the WILL-BLEED and the CathPCI bleeding scores had the largest area under the curve to predict resternotomy for bleeding, E-CABG bleeding grades 2-3 and UDPB bleeding grades 3-4 (Tab. 3). Similar results were observed among patients with and without preoperative pause of P2Y12 receptor antagonists according to the 2017 ESC guidelines (Tab. 3). The WILL-BLEED score had a significantly larger area under the curve to predict E-CABG bleeding grades 2-3 (p=0.024) than the CathPCI bleeding score, but not for resternotomy for bleeding (p=0.456) and UDPB bleeding grades 3-4 (p=0.483). The mean WILL-BLEED score ranged from 2.3±3.0 to 5.6±4.6 and the mean CathPCI score ranged from 36±17 to 52±20 between participating centers (Tab. 2).

Resternotomy for bleeding

Overall, 186 patients (2.6%) underwent resternotomy for excessive bleeding with significant variation between centers (p<0.0001, Tab. 4). One-hundred and forty five patients (75.7%) underwent resternotomy for bleeding within 12 hours from surgery and their mean chest drainage output was 845±376 mL (median, 800 mL, IQR 400, range 200-2000 mL). Among these patients, the amount of blood loss until reoperation significantly differed between centers (range, mean 607±257 mL to 1073±505 mL, p<0.0001). A significant difference between centers was observed also in terms of incidence of late resternotomies (later than 12 hours after surgery: range, 0-87.5%, p<0.0001, Tab. 4).

Surgical site bleeding was identified in 89 patients (48.6%), diffuse bleeding in 74 patients (40.4%), whilst both diffuse and surgical site bleeding was identified in 20 patients (10.8%). No specific data on the site of bleeding was reported in three patients. Surgical site bleeding was detected in 59.6% of these patients with significant variation between centers (range, 0% to 84.6%, adjusted p=0.003, Tab. 4, Fig. 2). Details on the sources of bleeding are reported in Table 5. Two or more sources of surgical bleeding were observed in 12 patients. Patients with diffuse bleeding had a higher risk of hospital/30-day mortality compared to patients with any surgical site bleeding (13.5% vs. 9.1%, adjusted OR 3.195, 95%CI 0.870-11.730), but the difference did not reach statistical significance.

Red blood cell transfusion

The rate of RBC transfusion in the overall series was 40.9% and ranged from 24.1% to 71.3% between centers (p<0.0001, Tab. 4). Caterpillar plot showed that three centers (F, K, I) had a significantly higher adjusted rates and four centers (B,C,D,M) had significantly lower adjusted rates of RBC transfusion.

Severe-massive perioperative bleeding

The rate of UDPB bleeding grades 3-4 in the overall series was 8.4% and ranged from 3.7% to 22.3% between centers (p<0.0001, Tab. 4). The rate of E-CABG bleeding grades 2-3 in the overall series was 6.5% and ranged from 0.4% to 16.4% between centers (p<0.0001, Tab. 4). Caterpillar plot showed that a number of centers had a significantly lower and higher risk of severe-massive bleeding, respectively (Fig. 3). However, centers performed differently in terms of UDPB and E-CABG severe-massive bleeding. When UDPB bleeding grades 3-4 were chosen as an endpoint for its more comprehensive bleeding- and blood products-related parameters, three centers (C,K,I) had significantly higher risk-adjusted rates of severe-massive bleeding, while six centers (B,E,H,J,M,N) had a significantly lower risk-adjusted rates of severe-massive bleeding (Fig. 3). Three centers (C,F,I) had significantly higher and three centers (G,K,M) significantly lower risk-adjusted rates of E-CABG bleeding grades 2-3 (Fig. 3).

Clinical implications of severe perioperative bleeding

When adjusted by multiple covariates, resternotomy for bleeding (adjusted OR 5.042, 95%CI 2.85-8.92), UDPB bleeding grades 3-4 (adjusted OR 6.61, 95%CI 4.42-9.88) and E-CABG bleeding grades 2-3 (adjusted OR 8.71, 95%CI 5.76-13.15) were associated with an increased risk of hospital/30-day mortality.

Reoperation for bleeding and severe-massive bleeding were predictive of hospital/30-day mortality also in patients undergoing elective CABG without prior myocardial infarction and with preserved left ventricular function (2621 patients included in the analysis, resternotomy for bleeding: adjusted OR 11.57, 95%CI 2.91-45.95, UDPB bleeding grades 3-4, OR 15.90, 95%CI 5.83-43.36; E-CABG bleeding grades 2-3, adjusted OR 21.87, 95%CI 7.96-60.06).

Discussion

This study showed that: 1) the risk of postoperative bleeding as assessed by several risk scores significantly varied between centers; 2) adherence to the currently recommended discontinuation period for P2Y12 receptor antagonists varied significantly between centers and this had a significant impact on the occurrence of postoperative major bleeding; 3) the rate of resternotomy for excessive bleeding was different between centers and was independent of any recent exposure to P2Y12 receptor antagonists or individual bleeding risk; 4) surgical site bleeding significantly varied between centers and was observed in two thirds of patients undergoing resternotomy; 5) the rate of severe-massive bleeding differed significantly between centers; 6) resternotomy for bleeding and severe-massive bleeding according to the UDPB and E-CABG definition criteria were associated with an excessive risk of early mortality.

Goodnough et al. (14) in 1991 provided evidence of a significant inter-institutional variability of the use of blood products after CABG. The present analysis along with a few previous studies (2-5) confirm that such inter-institutional differences persisted during the last three decades most likely because of a lack of common, effective patient-blood management strategy. The uncertainty about the safety of a liberal threshold for hemoglobin level in RBC transfusion is one of the key factors underlying these differences. A recent study by Murphy et al. (15) failed to demonstrate the superiority of a restrictive over a liberal policy

of blood transfusion in patients undergoing adult cardiac surgery. This means that strategies aiming to improve the outcomes by preventing perioperative blood loss may be more efficacious than targeting only a reduction of the exposure to allogenic blood. Indeed, the present findings demonstrate a large heterogeneity in the estimated risk of bleeding, prevalence of early discontinuation of potent antiplatelets and rates of severe-massive bleeding, which had a significant impact on the outcome of patients undergoing isolated CABG. In this regard, our decision to investigate severe bleeding rather than the exposure to any amount of RBC transfusion as in previous studies (2-5) was substantiated by the evidence of a formidable risk of early mortality in patients undergoing reoperation for bleeding (16) and/or transfusion of more than four units of RBCs (7,17).

This study showed that the measures to counteract increased bleeding risk, of early discontinuation of potent antiplatelets and to reduce of the risk of surgical bleeding should be implemented in centers with high rates of severe bleeding. The combined evidence of an individual surgeon's impact on perioperative blood loss (18) and a high rate of surgical sources of bleeding detected at reoperation (19) suggests that meticulous surgical technique could be an important issue in preventing significant bleeding. In fact, the individual patient's risk of bleeding and recent exposure to potent antiplatelets were not associated with an increased risk of reoperation for bleeding. This finding further confirm that excessive bleeding requiring reoperation is most often due to factors related to surgical technique rather than perioperative coagulopathy. Furthermore, these findings may explain why the discrimination ability of current bleeding risk scores in predicting severe-massive bleeding is limited (Tab. 3).

One of the main findings of this analysis is the significant heterogeneity of preoperative exposure to P2Y12 receptor antagonists, which ranged from 7% to 63% in the participating centers (Tab. 2). Even more striking is the inter-institutional difference in the incidence of preoperative discontinuation of P2Y12 receptor antagonists <5 days from surgery or with a pause a suggested by the 2017 ESC guidelines, i.e. ticagrelor <3 days, clopidogrel <5 days and prasugrel <7 days before CABG (range between centers, 0.7-24.8%, p<0.0001) (Fig. 1). The attention to the currently recommended washout period for P2Y12 receptor antagonists to minimize postoperative bleeding markedly varied between institutions and, when these guidelines were not

followed, this resulted in an increased risk of severe-massive defined according to the E-CABG and UDPB criteria. When UDPB bleeding grades 3-4 were chosen as an endpoint for its more comprehensive parameters, i.e. chest drainage output, resternotomy for bleeding, transfusion of >4units of RBC and/ fresh frozen plasm and use of procoagulants, three centers had significantly higher and six centers significantly lower rates of severe-massive bleeding compared to the results of overall series also when adjusted for multiple baseline risk factors (Fig. 3). These findings confirm that a few centers adopted effective strategies to prevent significant blood loss after CABG and this effect was evident when adjusted for potential confounders.

A few limitations may affect the results of this study. First, we do not have preoperative data on platelet reactivity, fibrinogen level, thrombin generation and other coagulation parameters for a detailed inter-institutional analysis of baseline coagulopathies in these patients. Second, the lack of specific data on point-of-care testing of postoperative coagulopathy prevents a more in depth analysis of the causes of excessive postoperative bleeding. Third, we do not have data on individual surgeons, which prevents conclusive results on the impact of individual surgical skills on postoperative bleeding end-points. Fourth, stratification of the severity of perioperative bleeding in cardiac surgery has been based mainly on the evaluation of RBC transfusion, but this fails to identify those patients with significant bleeding and high risk of other adverse events. The UDPB and E-CABG bleeding classifications are more detailed and specific tools for stratification of the severity of perioperative bleeding and its prognostic implications (20), but they differ significantly in their characteristics. Therefore, participating centers to this study behaved somewhat differently in terms of rates of severe-massive bleeding as defined by the UDPB and E-CABG bleeding classifications. Such heterogeneity makes these findings generalizable.

Conclusions

This study documented a significant inter-institutional heterogeneity in the estimated risk of bleeding, preoperative antithrombotic policy and discontinuation of antiplatelet drugs, incidence of severe-massive bleeding as well as in the use of blood products. The present findings suggest that inter-institutional variation

of perioperative bleeding and use of blood products should be considered for a correct interpretation of the results of multicentre studies. Adherence to the current guidelines on the early discontinuation of P2Y12 receptor antagonists and meticulous surgical technique aimed to reduce surgical site bleeding seems to be of utmost importance to prevent excessive bleeding, exposure to blood products and improve the outcome after CABG.

Conflict of interest

None.

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Table 1. Baseline characteristics and operative data of patients undergoing coronary surgery in the participating centers.

		Participating centers															
Covariates	*Overall*	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*N*	*O*	*p-value*
	no. 7118	*no. 1045*	*no. 763*	*no. 659*	*no. 613*	*no. 523*	*no. 503*	*no. 494*	*no. 444*	*no. 433*	*no. 415*	*no. 404*	*no. 226*	*no. 224*	*no. 205*	*no. 167*	
Baseline risk factors																	
Age (years)	67.4±9.4	67.8±9.6	67.6±9.2	66.6±9.0	66.1±8.9	69.3±9.8	67.9±9.5	64.8±9.0	68.1±9.6	68.3±8.5	66.1±9.1	68.1±9.7	66.1±9.0	67.4±9.3	67.9±10.2	68.3±8.7	<0.0001
Female	1160 (16)	153 (15)	126 (17)	79 (12)	93 (15)	102 (20)	88 (18)	90 (18)	80 (18)	90 (21)	67 (16)	55 (14)	42 (19)	37 (17)	32 (16)	26 (16)	0.014
Body mass index	27.5±4.2	27.9±4.4	28.0±4.4	26.7±3.6	27.7±4.3	27.3±4.5	27.2±4.1	27.4±3.9	27.4±4.0	28.1±4.4	27.7±4.0	27.4±4.2	27.6±4.1	26.6±3.5	26.8±3.5	26.8±3.7	<0.0001
eGFR (mL/min/1.73 m^2)	76±20	73±20	80±19	78±17	77±19	73±21	72±21	85±22	73±23	78±20	76±20	76±20	77±20	76±22	72±20	75±20	<0.0001
Anemia	1615 (23)	179 (17)	168 (22)	70 (11)	136 (22)	93 (18)	156 (31)	138 (28)	129 (29)	117 (27)	90 (22)	139 (34)	54 (24)	51 (23)	67 (33)	28 (17)	<0.0001
Platelets count <150 10^9/L	588 (8)	54 (5)	83 (11)	52 (8)	39 (7)	26 85)	51 (10)	50 (10)	42 (10)	39 (9)	32 (8)	62 (15)	15 (7)	10 (5)	20 (10)	13 (8)	<0.0001
Dialysis	78 (1)	14 (1)	3 (0)	3 (0)	4 (1)	4 (1)	6 (1)	7 (1)	17 (4)	4 (1)	4 (1)	3 81)	1 (0)	4 (2)	4 (2)	0	<0.0001
Diabetes	2215 (31)	269 (26)	235 (31)	123 (19)	184 (30)	196 (38)	160 (32)	187 (38)	143 (32)	142 (33)	195 (47)	58 (14)	107 (47)	82 (37)	74 (36)	60 (36)	<0.0001
Recent MI	2291 (32)	247 (24)	158 (21)	172 (26)	149 (24)	143 (27)	145 (29)	222 (45)	201 (45)	230 (53)	171 (41)	98 (24)	95 (42)	140 (63)	90 (44)	30 (18)	<0.0001
Prior stroke/TIA	430 (6)	93 (9)	32 (4)	30 (5)	48 (8)	16 (3)	35 (7)	25 (5)	11 (3)	41 (10)	27 (7)	9 (2)	16 (2)	16 (7)	11 (5)	20 (12)	<0.0001
Atrial fibrillation	566 (8)	116 (11)	54 (7)	31 (5)	43 (7)	57 (11)	50 (10)	23 (5)	33 (7)	47 (11)	25 (6)	29 (7)	16 (7)	11 (5)	16 (8)	15 (9)	<0.0001
Pulmonary disease	738 (10)	138 (13)	58 (8)	41 (6)	41 (7)	39 (8)	26 (5)	120 (24)	11 (3)	54 (13)	25 (6)	28 (7)	30 (13)	47 (21)	60 (29)	20 (12)	<0.0001
Extracardiac arteriopathy	1637 (23)	272 (26)	117 (15)	118 (18)	52 (9)	163 (31)	153 (30)	142 (29)	101 (23)	44 (10)	101 (25)	84 (21)	73 (32)	75 (34)	72 (35)	70 (42)	<0.0001
LVEF ≤50%	2059 (29)	339 (32)	140 (18)	102 (16)	237 (39)	132 (25)	131 (26)	194 (39)	154 (35)	112 (26)	202 (49)	86 (21)	68 (30)	38 (17)	82 (40)	42 (25)	<0.0001
Prior PCI	1490 (21)	253 (24)	126 (17)	161 (24)	115 (19)	130 (25)	89 (18)	109 (22)	70 (16)	91 (21)	91 (22)	44 (11)	72 (32)	52 (23)	43 (21)	44 (26)	<0.0001
Prior cardiac surgery	39 (1)	4 (0)	5 (1)	1 (0)	2 (0)	1 (0)	2 (0)	1 (0)	8 (2)	7 (2)	1 (0)	4 (1)	0	2 (1)	0	1 (1)	<0.0001
Critical preoperative state	450 (6)	35 (3)	52 (7)	18 (3)	9 (2)	14 (3)	70 (13)	12 (2)	12 (3)	44 (10)	36 (9)	88 (22)	14 (6)	7 (3)	26 (13)	13 (8)	<0.0001
Emergency procedure	334 (5)	106 (10)	24 (3)	9 (1)	5 (1)	59 (11)	19 (4)	19 (4)	11 (3)	43 (10)	2 (1)	11 (3)	12 (5)	1 (0)	10 (5)	3 (2)	<0.0001
EuroSCORE II (%)	2.8±4.1	2.8±4.3	2.1±3.0	1.6±1.3	1.9±2.4	3.0±4.6	3.4±3.8	2.3±3.0	3.1±4.1	4.1±6.3	2.6±3.2	4.1±5.8	3.7±5.1	2.5±3.5	5.2±6.8	2.8±4.7	<0.0001
Operative data																	
Off-pump surgery	1470 (21)	517 (50)	5 (1)	84 (13)	6 (1)	171 (33)	10 (2)	92 (19)	4 (1)	241 (56)	239 (58)	14 (4)	34 (15)	23 (10)	9 (4)	21 (13)	<0.0001
No. of distal anastomoses	2.7±0.9	2.3±0.8	2.7±0.7	2.4±0.8	3.0±0.8	3.1±1.0	2.4±0.7	2.3±0.8	2.8±0.8	3.6±1.0	2.4±0.8	3.5±1.0	2.4±1.0	2.6±0.8	2.7±0.9	2.9±1.0	<0.0001
BIMA grafting	2578 (36)	582 (56)	78 (10)	466 (71)	243 (40)	463 (89)	5 (1)	5 (1)	47 (11)	17 (4)	245 (59)	273 (68)	35 (16)	49 (22)	50 (24)	20 (12)	<0.0001

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. Percentages are rounded to nearest integer. Anemia is defined as <12.0g/L in women and <13.0 g/L in men. eGFR indicates estimated glomerular filtration rate according to the MDRD equation; MI, myocardial infarction; TIA, transient ischemic attack; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; EuroSCORE, European System for Cardiac Operative Risk Evaluation; BIMA bilateral internal mammary artery. Clinical variables are according to the EuroSCORE II definition criteria.

Table 2. Preoperative antithrombotics and bleeding risk scores in patients undergoing coronary surgery.

		Participating centers															
Covariates	*Overall* no. 7118	*A* no. 1045	*B* no. 763	*C* no. 659	*D* no. 613	*E* no. 523	*F* no. 503	*G* no. 494	*H* no. 444	*I* no. 433	*J* no. 415	*K* no. 404	*L* no. 226	*M* no. 224	*N* no. 205	*O* no. 167	*p-value*
Antithrombotics																	
Aspirin	6364 (89)	883 (85)	710 (93)	616 (94)	565 (92)	474 (91)	422 (84)	473 (96)	441 (99)	394 (91)	349 (84)	272 (67)	186 (82)	216 (97)	199 (97)	163 (98)	<0.0001
Aspirin pause<7 days	6285 (88)	881 (84)	705 (93)	613 (93)	565 (92)	475 (91)	407 (82)	463 (94)	438 (99)	392 (91)	329 (79)	272 (67)	173 (77)	210 (94)	199 (97)	163 (98)	<0.0001
P2Y12 receptor antagonists	2405 (34)	278 (27)	53 (7)	220 (33)	360 (59)	186 (36)	179 (36)	309 (63)	89 (49)	210 (49)	204 (49)	32 (8)	94 (42)	72 (32)	75 (37)	44 (26)	<0.0001
Ticagrelor	1038 (15)	95 (9)	22 (3)	76 (12)	278 (45)	85 (16)	43 (9)	123 (25)	30 (7)	78 (18)	75 (18)	10 (3)	49 (22)	24 (11)	38 (19)	12 (7)	<0.0001
Ticagrelor pause<3 days	212 (3)	90 (9)	3 (0)	4 (1)	23 (4)	27 (5)	7 (1)	6 (1)	3 (1)	27 (6)	6 (1)	0	2 (1)	2 (1)	9 (4)	2 (1)	<0.0001
Clopidogrel	1329 (19)	186 (18)	26 (3)	140 (21)	84 (14)	104 (20)	135 (27)	181 (37)	57 (13)	135 (31)	111 (27)	23 (6)	43 (19)	46 (21)	27 (13)	31 (19)	<0.0001
Clopidogrel pause<5 days	573 (8)	166 (16)	12 (2)	25 (4)	34 (6)	71 (14)	62 (12)	28 (6)	12 (3)	65 (15)	62 (15)	3 (1)	4 (2)	7 (3)	13 (6)	9 (5)	<0.0001
Prasugrel	66 (1)	2 (0)	5 (1)	8 (1)	1 (0)	0	4 (1)	7 (1)	3 (1)	1 (0)	19 (5)	0	2 (1)	2 (1)	11 (5)	1 (1)	<0.0001
Prasugrel pause<7 days	46 (1)	2 (0)	4 (1)	2 (0)	1 (0)	0	3 (1)	3 (1)	2 (1)	1 (0)	13 (3)	0	2 (1)	1 (0)	11 (5)	1 (1)	<0.0001
P2Y12 rec. antagonists pause<5 days	1041 (15)	258 (25)	26 (3)	37 (6)	134 (22)	127 (24)	81 (16)	47 (10)	31 (7)	113 (26)	92 (22)	3 (1)	11 (5)	20 (9)	45 (22)	16 (10)	<0.0001
P2Y12 rec. antagonists pause shorter than 2017 ESC guidelines*	826 (12)	256 (25)	19 (3)	31 (5)	56 (9)	98 (19)	71 (14)	37 (8)	17 (4)	93 (22)	81 (20)	3 (1)	9 (4)	10 (5)	33 (16)	12 (7)	<0.0001
Oral anticoagulants		47 (5)	8 (1)	25 (4)	25 (4)	3 (1)	18 (4)	5 (1)	12 (3)	39 (9)	6 (1)	13 (3)	3 (1)	7 (3)	4 (2)	8 (5)	<0.0001
Warfarin/coumadin	162 (2)	28 (3)	5 (1)	14 (2)	14 (2)	3 (1)	17 (3)	4 (1)	11 (3)	33 (8)	2 (1)	12 (3)	3 (1)	6 (3)	3 (2)	7 (4)	<0.0001
Rivaroxaban	32 (0)	14 (1)	1 (0)	7 (1)	3 (1)	0	0	0	0	4 (1)	2 (1)	0	0	1 (0)	0	0	<0.0001
Dabigatran	15 (0)	2 (0)	0	2 (0)	4 (1)	0	1 (0)	0	0	3 (1)	1 (0)	1 (0)	0	0	0	1 (1)	0.203
Apixaban	20 (0)	3 (0)	2 (0)	2 (0)	4 (1)	0	0	1 (0)	1 (0)	1 (0)	1 (0)	0	0	0	1 (0)	0	0.712
Oral anticoagulants within 2 days	52 (1)	10 (1)	0	0	5 (1)	1 (0)	6 (1)	1 (0)	0	26 (6)	0	1 (0)	0	2 (1)	0	0	<0.0001
LMWH / Fondaparinux / Unfractionated	2974 (42)	939 (90)	115 (15)	32 (5)	278 (45)	49 (9)	320 (64)	481 (97)	101 (23)	224 (52)	125 (30)	36 (9)	123 (54)	22 (10)	106 (52)	23 (14)	<0.0001
LMWH	2187 (31)	652 (62)	1 (0)	24 (4)	14 (2)	6 (1)	286 (57)	480 (97)	100 (23)	223 (52)	125 (30)	36 (9)	93 (41)	22 (10)	104 (51)	21 (13)	<0.0001
Fondaparinux	352 (5)	4 (0)	0	8 (2)	266 (43)	43 (8)	28 (6)	0	0	0	0	0	0	0	1 (1)	2 (1)	<0.0001
Unfractionated heparin	476 (7)	311 (30)	114 (15)	0	0	0	15 (3)	1 (0)	1 (0)	1 (0)	0	0	32 (14)	0	1 (1)	0	<0.0001
Thrombolysis	20 (0)	0	1 (0)	1 (0)	0	0	0	6 (1)	1 (0)	6 (1)	5 (1)	0	0	0	0	0	<0.0001
Bivaluridin	5 (0)	0	0	0	1 (0)	0	0	0	0	4 (1)	0	0	0	0	0	0	<0.0001
Tirofiban	80 (1)	1 (0)	13 (2)	1 (0)	2 (0)	0	2 (0)	20 (4)	13 (3)	1 (0)	0	0	1 (0)	6 (3)	16 (8)	4 (2)	<0.0001
Cangrelor	1 (0)	0	0	0	1 (0)	0	0	0	0	0	0	0	0	0	0	0	0.716
Eptifibatide	19 (0)	0	0	0	0	0	0	0	0	13 (3)	1 (0)	0	1 (0)	0	0	0	<0.0001
Bleeding risk scores																	
WILL-BLEED score	4.0±3.6	3.7±3.2	2.7±3.2	2.3±3.0	3.7±3.2	3.4±3.6	5.2±3.8	5.5±3.2	4.3±3.5	5.6±4.6	4.2±3.7	4.2±3.7	4.2±3.7	4.6±3.0	5.9±3.6	3.0±3.7	<0.0001
CRUSADE score	26±14	25±13	24±13	23±11	23±12	28±14	28±14	25±14	30±15	26±15	29±14	24±13	28±14	27±14	30±14	27±14	<0.0001
Papworth score	1.0±1.2	0.9±0.8	0.8±1.2	0.8±0.8	1.0±0.8	1.0±0.9	1.4±1.4	1.0±0.8	1.4±1.4	1.2±1.5	0.6±0.7	1.5±1.9	1.2±1.8	0.6±0.6	1.4±0.8	0.8±2.1	<0.0001
TRUST score	2.2±1.3	1.9±1.3	1.9±1.3	1.8±1.2	2.1±1.3	2.3±1.4	2.6±1.4	2.3±1.4	2.7±1.4	2.4±1.4	1.8±1.2	2.6±1.3	2.4±1.4	1.9±1.3	2.8±1.3	1.9±1.3	<0.0001
TRACK score	6.7±5.1	6.3±4.7	6.8±5.1	5.8±4.2	5.7±4.5	7.3±5.1	6.8±5.3	6.4±5.2	8.6±6.0	7.6±5.5	5.8±4.8	7.5±5.2	6.5±5.1	7.0±4.8	7.2±4.9	6.4±4.4	<0.0001
CathPCI score	43±21	42±22	38±19	36±17	43±18	47±24	51±20	46±22	52±20	49±22	36±17	50±20	45±23	35±17	52±20	36±19	<0.0001

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. Percentages are rounded to nearest integer. *, Ticagrelor paused at least 3 days, clopidogrel at least 5 days and prasugrel at least 7 days before surgery according to the 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease (); LMWH: low molecular weight heparin.

Table 3. C-statistics of bleeding risk scoring methods in predicting resternotomy for bleeding, UDPB bleeding grades 3-4 and E-CABG bleeding grades 2-3.

Bleeding risk scores	*Resternotomy for bleeding*	*UDPB bleeding grades 3-4*	*E-CABG bleeding grades 2-3*
Overall series			
WILL-BLEED score	0.595 (0.551-0.640)	0.608 (0.584-0.633)	0.706 (0.679-0.732)
CRUSADE score	0.541 (0.500-0.583)	0.555 (0.530-0.580)	0.657 (0.629-0.685)
Papworth score	0.531 (0.489-0.573)	0.556 (0.532-0.580)	0.582 (0.556-0.608)
TRUST score	0.535 (0.492-0.578)	0.571 (0.546-0.595)	0.654 (0.627-0.681)
TRACK score	0.515 (0.471-0.558)	0.553 (0.527-0.578)	0.625 (0.596-0.655)
CathPCI score	0.582 (0.539-0.625)	0.603 (0.579-0.627)	0.683 (0.656-0.710)
P2Y12 rec. antagonists pause shorter than suggested by 2017 ESC guidelines			
WILL-BLEED score	0.592 (0.494-0.690)	0.624 (0.564-0.684)	0.707 (0.651-0.763)
CRUSADE score	0.561 (0.470-0.652)	0.583 (0.525-0.641)	0.640 (0.582-0.699)
Papworth score	0.486 (0.381-0.591)	0.523 (0.464-0.581)	0.578 (0.521-0.634)
TRUST score	0.497 (0.399-0.595)	0.554 (0.492-0.615)	0.643 (0.584-0.7019
TRACK score	0.484 (0.384-0.584)	0.535 (0.469-0.600)	0.617 (0.584-0.701)
CathPCI score	0.558 (0.460-0.656)	0.611 (0.552-0.670)	0.675 (0.620-0.730)
P2Y12 rec. antagonists paused according to the 2017 ESC guidelines			
WILL-BLEED score	0.581 (0.531-0.631)	0.593 (0.566-0.621)	0.687 (0.656-0.718)
CRUSADE score	0.534 (0.487-0.580)	0.546 (0.519-0.574)	0.657 (0.626-0.689)
Papworth score	0.536 (0.490-0.682)	0.557 (0.531-0.584)	0.573 (0.544-0.603)
TRUST score	0.539 (0.491-0.587)	0.572 (0.545-0.598)	0.653 (0.622-0.684)
TRACK score	0.520 (0.472-0.568)	0.556 (0.529-0.583)	0.627 (0.594-0.660)
CathPCI score	0.582 (0.534-0.630)	0.597 (0.570-0.624)	0.676 (0.645-0.707)
WILL-BLEED score	0.581 (0.531-0.631)	0.593 (0.566-0.621)	0.687 (0.656-0.718)

Values are areas under the receiver operating characteristics curve with 95% confidence intervals.

Table 4. Outcomes.

		Participating centers															
Outcomes	*Overall*	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*N*	*O*	*p-value*
	no. 7118	no. 1045	no. 763	no. 659	no. 613	no. 523	no. 503	no. 494	no. 444	no. 433	no. 415	no. 404	no. 226	no. 224	no. 205	no. 167	
Hospital/30-day mortality	275 (3.9)	23 (2.2)	7 (0.9)	6 (0.9)	10 (1.6)	22 (4.2)	6 (1.2)	21 (4.3)	8 (1.8)	8 (1.8)	3 (0.7)	5 (1.2)	14 (5.2)	1 (0.4)	7 (3.4)	0	<0.0001
De novo IABP/ECMO[a]	188 (2.6)	31 (3.0)	9 (1.2)	6 (0.9)	5 (0.8)	17 (3.3)	21 (4.8)	29 (5.9)	12 (2.7)	6 (1.4)	3 (0.8)	19 (5.4)	14 (6.5)	1 (0.5)	9 (4.7)	6 (3.6)	<0.0001
Stroke	84 (1.2)	21 (2.0)	14 (1.8)	5 (0.8)	5 (0.8)	4 (0.1)	11 (2.2)	3 (0.7)	6 (1.4)	1 (0)	0	1 (0.2)	5 (2.2)	1 (0.4)	1 (0.5)	2 (1.2)	0.010
DSWI / mediastinitis	177 (2.5)	26 (2.5)	17 (2.2)	30 (4.6)	14 (2.3)	5 (1.0)	16 (3.2)	10 (2.0)	4 (0.9)	13 (3.0)	7 (1.7)	14 (3.5)	13 (5.8)	3 (1.3)	4 (2.0)	1 (0.6)	<0.0001
Acute kidney injury, stage 3[a]	181 (2.5)	44 (4.3)	15 (2.0)	7 (1.1)	22 (3.6)	16 (3.1)	5 (1.0)	12 (2.5)	7 (1.7)	9 (2.1)	6 (1.5)	13 (3.3)	12 (5.4)	2 (0.9)	6 (3.0)	5 (3.0)	<0.0001
Bleeding-related outcomes																	
Nadir hematocrit, op. day	30±5	29±4	30±4	34±4	31±5	29±4	33±3	29±5	31±5	30±4	28±4	26±4	28±5	26±4	30±3	28±4	<0.0001
Drainage output, 12 h (mL)	464±311	505±332	360±172	585±268	493±230	339±141	385±301	554±296	327±193	644±490	317±136	751±502	368±222	288±91	373±211	526±247	<0.0001
RBC transfusion,	1180 (16.6)	178 (17.0)	96 (12.6)	67 (10.2)	39 (6.4)	30 (5.7)	124 (24.8)	38 (7.7)	95 (21.4)	149 (34.4)	76 (18.3)	131 (32.4)	29 (12.8)	39 (17.4)	63 (30.7)	26 (15.6)	<0.0001
RBC units, intraoperatively	0.2±0.4	0.4±1.1	0.2±0.7	0.2±0.7	1±0.6	0.1±0.4	0.5±0.9	0.1±0.6	0.4±0.9	0.8±01.7	0.3±0.7	0.5±0.7	0.2±0.5	0.3±0.6	0.6±1.0	0.3±0.9	<0.0001
RBC transfusion, overall	2908 (40.9)	397 (38.0)	236 (31.0)	159 (24.1)	160 (26.1)	179 (34.2)	323 (64.5)	239 (48.4)	172 (38.7)	241 (55.7)	151 (36.4)	288 (71.3)	118 (52.2)	67 (29.9)	113 (55.1)	65 (38.9)	<0.0001
RBC units, overall	1.2±2.5	1.3±2.7	0.8±1.5	0.6±1.4	1.1±3.3	0.8±1.9	2.3±3.3	1.1±1.7	1.1±2.0	2.3±3.7	1.0±3.3	1.3±1.1	1.1±1.0	0.6±1.0	1.6±2.5	1.0±1.4	<0.0001
Fresh frozen plasma	443 (6.2)	40 (3.8)	43 (5.6)	40 (6.1)	33 (5.4)	17 (3.3)	80 (16.0)	2 (0.4)	21 (4.7)	102 (23.6)	8 (1.9)	16 (4.0)	26 (11.5)	1 (0.4)	9 (4.4)	5 (3.0)	<0.0001
Platelets transfusion	544 (7.6)	34 (3.3)	39 (5.1)	30 (4.6)	66 (10.8)	138 (26.4)	29 (5.8)	3 (0.8)	15 (3.4)	138 (31.9)	5 (1.2)	24 (5.9)	7 (3.1)	2 (0.9)	5 (2.4)	9 (5.4)	<0.0001
rFVIIa	11 (0.2)	3 (0.3)	0	0	0	0	1 (0.2)	0	1 (0.2)	0	2 (0.5)	0	0	1 (0.4)	0	3 (1.8)	<0.0001
Cryoprecipitate	18 (0.3)	12 (1.1)	1 (0.1)	0	1 (0.2)	0	0	3 (0.6)	0	0	1 (0.2)	0	0	0	0	0	<0.0001
Fibrinogen	258 (3.6)	98 (9.4)	25 (3.3)	31 (4.7)	13 (2.1)	0	20 (4.0)	18 (3.6)	0	3 (0.7)	13 (3.2)	0	0	35 (15.6)	0	2 (1.2)	<0.0001
PCC	119 (1.7)	34 (3.3)	4 (0.5)	0	0	0	3 (0.6)	15 (3.0)	0	1 (0.2)	14 (3.4)	0	31 (13.7)	16 (7.1)	1 (0.5)	0	<0.0001
Resternotomy for bleeding	186 (2.6)	34 (3.3)	16 (2.1)	16 (2.4)	16 (2.6)	9 (1.7)	10 (2.0)	8 (1.6)	4 (0.9)	30 (6.9)	12 (2.9)	13 (3.2)	9 (4.0)	0	2 (1.0)	7 (4.2)	<0.0001
Surgical bleeding[c]	89 (48.6)	18 (56.2)	9 (56.3)	8 (50.0)	9 (56.3)	6 (66.7)	5 (50.0)	1 (12.5)	0	21 (72.4)	0	7 (53.8)	5 (55.6)	0	0	0	<0.0001
Diffuse bleeding[c]	74 (40.4)	12 (36.4)	6 (37.5)	8 (50.0)	3 (18.8)	3 (33.3)	5 (50.0)	7 (87.5)	2 (50.0)	6 (20.7)	11 (91.7)	2 (15.4)	3 (33.3)	0	2 (100)	4 (57.1)	<0.0001
Surgical and diffuse bleeding[c]	20 (10.8)	2 (6.1)	1 (6.3)	0	4 (25.0)	0	0	0	2 (50.0)	2 (6.9)	1 (8.3)	4 (30.8)	1 (11.1)	0	0	3 (42.9)	<0.0001
Resternotomy > 12 hours	45 (24.3)	6 (18.2)	5 (31.3)	0	4 (25.0)	4 (44.4)	1 (10.0)	7 (87.5)	0	12 (40.0)	4 (33.3)	0	2 (22.2)	-	0	0	<0.0001
UDPB bleeding grades 3-4	601 (8.4)	105 (10.2)	35 (4.6)	56 (8.5)	49 (8.0)	19 (3.7)	53 (10.6)	45 (9.2)	17 (3.8)	82 (20.0)	19 (4.6)	90 (22.3)	13 (5.8)	1 (0.4)	8 (3.9)	9 (5.4)	<0.0001
E-CABG bleeding grades 2-3	463 (6.5)	80 (7.7)	34 (4.5)	34 (5.2)	43 (7.0)	18 (3.4)	59 (11.8)	26 (5.3)	22 (5.0)	76 (16.4)	19 (4.6)	16 (4.0)	13 (5.8)	1 (0.4)	15 (7.3)	7 (4.2)	<0.0001

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. [a]: excluding patients with preoperative IABP; [b]: excluding patients with preoperative chronic kidney disease class V; [c]: proportion of among patients who underwent resternotomy for bleeding excluding three patients without data on the source of bleeding; IABP: intra-aortic balloon pump; ECMO: extra-corporeal membrane oxygenation; DSWI: deep sternal wound infection; KDIGO: Kidney Disease: Improving Global Outcomes; RBC: red blood cell; PCC: prothrombin complex concentrate.

Table 5. Surgical sources of bleeding detected at resternotomy in 109 patients.

Sources of bleeding	*No. (%)*
Coronary anastomosis	25 (20.5)
Int. mammary a. branch	24 (19.7)
Int. mammary a. harvesting site	22 (18.0)
Sternum	16 (13.1)
Vein graft branch	13 (10.7)
Neck, mediastinal and pericardial vessels	8 (6.6)
Pace-maker wire insertion site	3 (2.5)
Ventricular wall or epicardium	3 (2.5)
Atrial cannulation site	3 (2.5)
Aortic cannulation site	2 (1.6)
Ascending aorta	1 (0.8)
Coronary anastomosis after pacemaker wire removal	1 (0.8)
Radial a. graft branch	1 (0.8)

Legend to figures

Figure 1. Prevalence of patients with P2Y12 inhibitors pause shorter than five days as well as shorter than the period suggested by the 2017 ESC guidelines,

i.e. ticagrelor <3 days, clopidogrel <5 days and prasugrel <7 days before coronary artery bypass grafting in the participating centers (inter-istitutional difference, p<0.0001 for all P2Y12 inhibitors).

Figure 2. Risk-adjusted rates with 95% confidence intervals of resternotomy for bleeding and surgical site bleeding in participating centers. Red lines are the rates in the overall series, red dots indicate centers with significantly higher and blue dots indicate centers with significantly lower risk-adjusted rates.

Figure 3. Risk-adjusted rates with 95% confidence intervals of red blood cell (RBC) transfusion as well as severe-massive bleeding according to the Universal Definition of Perioperative Bleeding (UDPB) and E-CABG bleeding severity criteria in the participating centers. Red lines are the rates in the overall series, red dots indicate centers with significantly higher and blue dots indicate centers with significantly lower risk-adjusted rates.

Figure 1

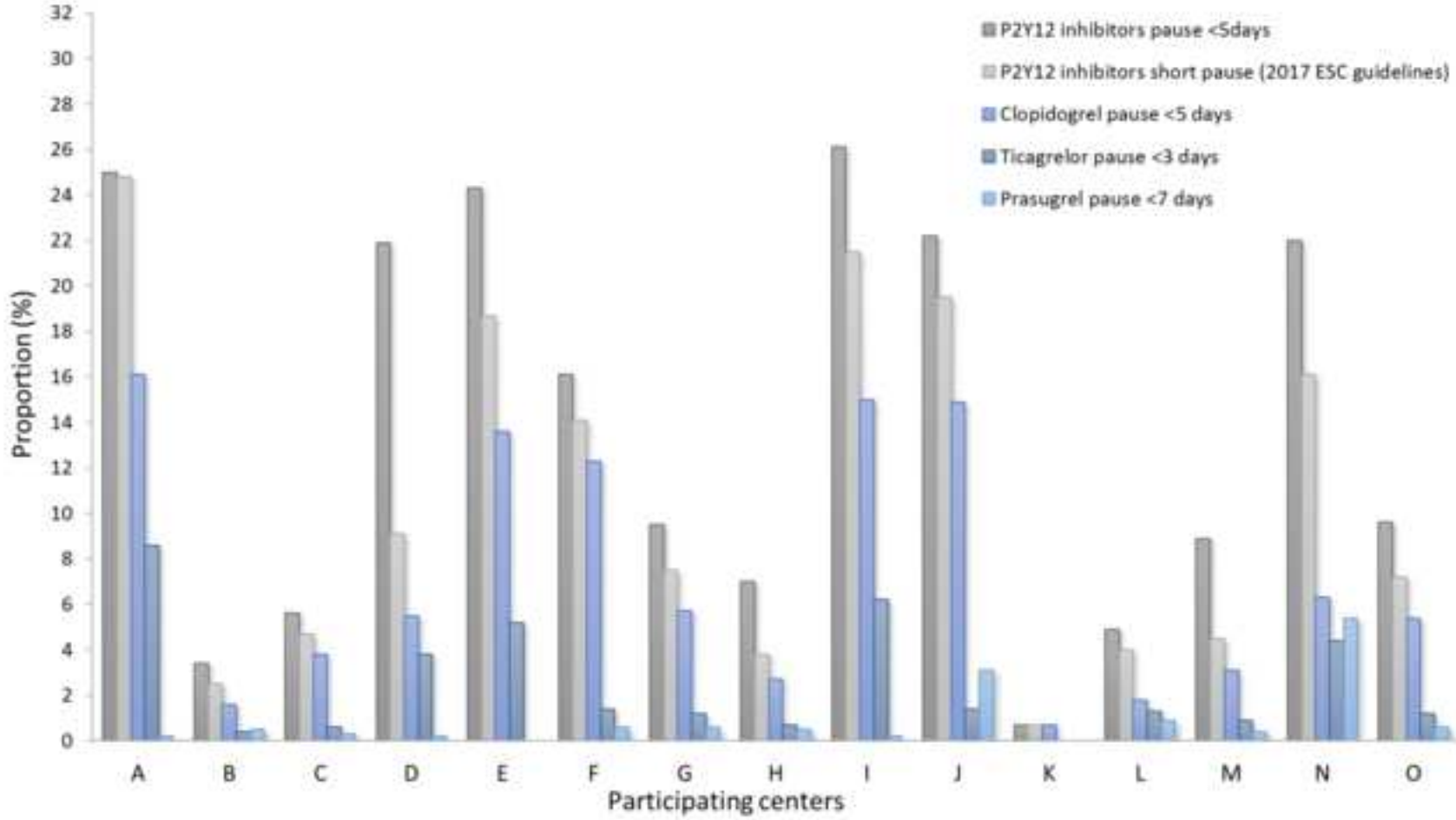
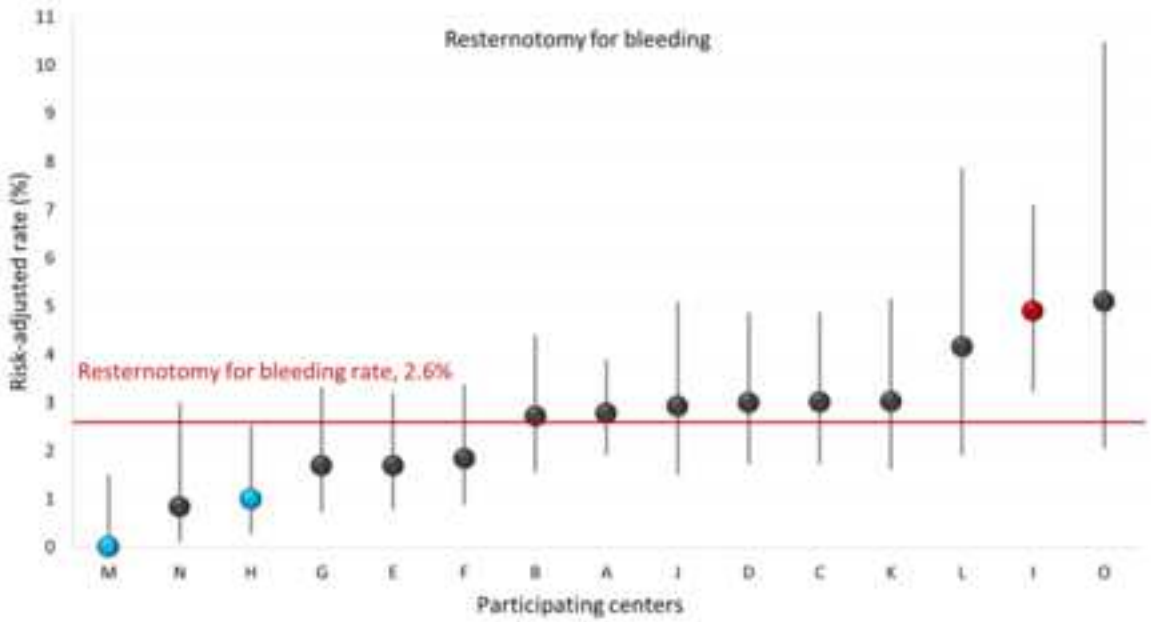


Figure 2



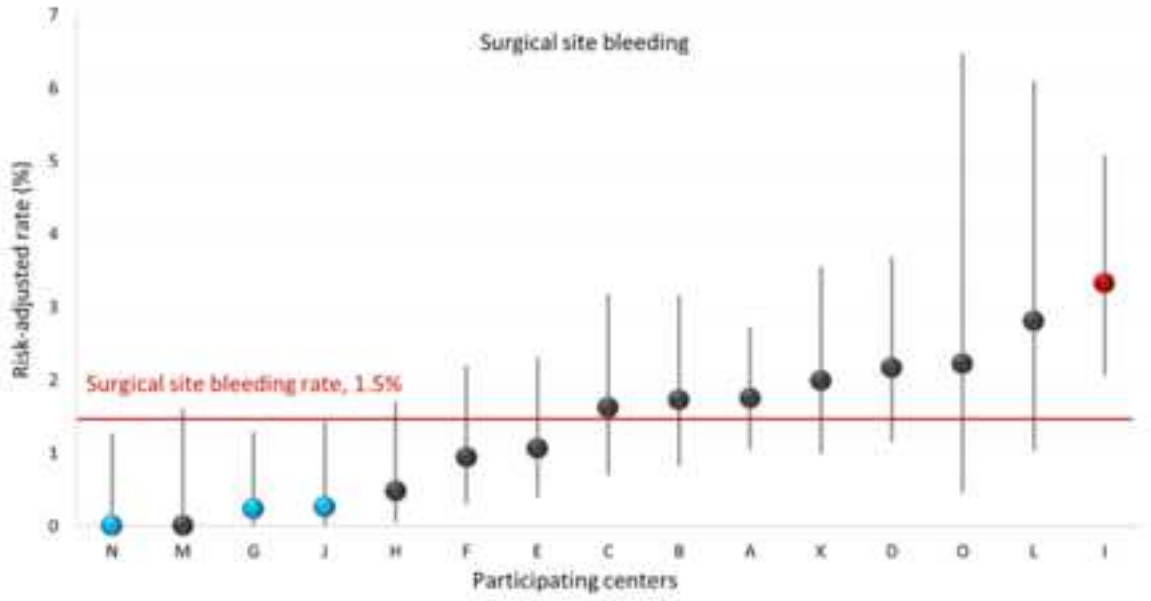


Figure 3