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Perioperative Bleeding In Patients With Acute Coronary Syndrome Treated With Fondaparinux Versus Low-Molecular-Weight Heparin Before Coronary Artery Bypass Grafting

Short title: Fondaparinux versus LMWH before CABG

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Abstract

The perioperative bleeding risk in patients receiving fondaparinux versus low-molecular weight heparin before coronary artery bypass grafting has not been reported. We evaluated perioperative coronary artery bypass grafting -related bleeding in patients with acute coronary syndrome preoperatively treated with fondaparinux or low-molecular weight heparin. All patients with acute coronary syndrome from the prospective, European multicenter registry on Coronary Artery Bypass Grafting (E-CABG) preoperatively treated with fondaparinux or low-molecular weight heparin undergoing isolated primary CABG were eligible. The primary outcome measure was severe or massive bleeding defined according to the Universal Definition of Perioperative Bleeding stratified by $P2Y_{12}$ inhibitor discontinuation. Secondary outcome measures included three additional definitions of major bleeding used in cardiac surgery trials. Propensity score matching was performed to adjust for differences in pre- and perioperative covariates. 1525 patients were included, of whom 276 (18.1%) received fondaparinux and 1249 (81.9%) low-molecular weight heparin preoperatively. In the propensity score-matched cohort (245 pairs), the risk of major bleeding according to the Universal Definition of Perioperative Bleeding severe or massive bleeding (11.8 versus 9.0%, p = 0.285) and the three other major bleeding definitions was similar between the fondaparinux and low-molecular weight heparin cohorts. In conclusion, preoperative treatment with fondaparinux compared to low-molecular weight heparin was associated with similar incidence of perioperative bleeding in patients with acute coronary syndrome undergoing coronary artery bypass grafting.

Clinical Trial Registration: http://www.clinicaltrials.gov. Unique identifier: NCT02319083; European multicenter registry on Coronary Artery Bypass Grafting (E-CABG) registry.

Key words: Bleeding complications; Coronary artery bypass; Fondaparinux; Low-molecular weight heparin.

Introduction

The factor Xa inhibitor fondaparinux has been found to be noninferior to low-molecular-weight heparin (LMWH) in reducing ischemic outcomes in patients with non-ST-segment elevation myocardial infarction (NSTEMI) [1]. Patients treated with fondaparinux had fewer severe in-hospital bleeding events which was associated with a reduction of short- and long-term mortality [1]. In patients who underwent percutaneous coronary intervention, fondaparinux patients had a lower incidence of major bleeding complications, including access site-related bleeding [2]. These findings were confirmed in a non-trial setting, where fondaparinux was associated with a lower risk for major bleeding events and death compared with LMWH [3]. European guidelines therefore recommend fondaparinux as the anticoagulant of choice in patients with NSTEMI regardless of the management strategy, unless the patient is scheduled for immediate coronary angiography [4]. The implementation of these guidelines differs between countries and patients with NSTEMI planned to undergo urgent coronary artery bypass grafting (CABG) might have received either fondaparinux or LMWH preoperatively. The risk for CABG-related bleeding in this setting has not been studied before and is of interest since severe bleeding has been shown to be associated with increased morbidity and mortality [5]. In a prospective, multicenter registry, we sought to evaluate perioperative CABG-related bleeding in patients with acute coronary syndrome (ACS) preoperatively treated with fondaparinux or LMWH.

Methods

This is a post-hoc study from the European multicenter registry on Coronary Artery Bypass Grafting (E-CABG), which is a prospective observational, multicenter study including patients undergoing isolated CABG. The detailed study protocol for the E-CABG registry has been published previously [6]. The study was approved by the local regional or

institutional review board according to national guidelines for approval of registry studies. Patient informed consent was collected in institutions where it was required by the Institutional Review Board.

Data were collected consecutively from 16 cardiac surgery centers in six European countries (Finland, France, Germany, Italy, Sweden, and United Kingdom). All adult patients with acute coronary syndrome who were preoperatively treated with fondaparinux or LMWH and underwent isolated primary CABG in one of the participating centers from January 2015 to May 2017 were eligible. Preoperative dose and type of LMWH were not recorded. Exclusion criteria were (1) patients with discontinuation of fondaparinux or LMWH >24 hours prior to surgery and (2) patients treated with both fondaparinux and LMWH within 24 hours prior to surgery.

The primary outcome measure was severe or massive bleeding defined according to the Universal Definition of Perioperative Bleeding (UDPB) in adult cardiac surgery [7]. UDPB severe or massive bleeding is defined as including one or more of the following criteria: delayed sternal closure for bleeding, postoperative blood loss more than 1000 ml within 12 hours, 5 or more red blood cell (RBC) units transfused, 5 or more plasma units transfused, the use of recombinant factor VIIa, or reoperation due to excessive bleeding. In the UDPB classification only RBC transfusions administered after chest closure are counted.

Secondary outcome measures included four additional definitions of major bleeding previously used in cardiac surgery trials. Some of the definitions of major bleeding were slightly modified so that they could be employed in the current study. The three secondary definitions of major bleeding were: (1) Bleeding Academic Research Consortium (BARC) CABG-related bleeding [8] defined by one or more of the following criteria: postoperative chest tube output more than 1000 ml within 12 hours, transfusion of 5 or more units of RBC, reoperation for bleeding, or death due to bleeding; (2) Blood conservation using Antifibrinolytics Randomized Trial (BART) massive bleeding [9] defined by one or more of the following criteria: postoperative chest tube output more than 1500 ml within 12 hours, transfusion of 11 or more

units of RBCs, reoperation for bleeding, or death secondary to bleeding; (3) E-CABG severe or massive bleeding [10] defined by one or more of the following criteria: transfusion of 5 or more RBC units during hospital stay and/or reoperation for excessive bleeding. Other secondary outcome measures of this study were reoperation for bleeding, 12-hour postoperative chest tube output, decline in hemoglobin during the operation day, number of RBC units transfused per- and postopoperatively, as well as plasma and platelet transfusion.

Variables are described using frequencies and percentages for categorical variables, and means and standard deviations or medians and interquartile range for continuous variables. In the overall cohort, outcomes were compared by independent samples t-test and χ^2 test for binary and categorical variables, and analysis of variance for continuous variables. To reduce selection bias, a propensity score was calculated with fondaparinux/LMWH as the dependent variable. In the propensity score-matched cohort, outcomes were compared by univariate conditional logistic regression for binary and categorical variables and by paired samples t-test for continuous variables. The propensity score-matched cohort was constructed by matching of 1 fondaparinux patient to 1 LMWH patient, with a caliper of 0.2 of the standard deviation of the logit of the propensity score (logit standard deviation 0.098, caliper width 0.02) without replacement and giving priority to exact matching. The following variables were included as covariates: age, gender, preoperative hemoglobin level, preoperative platelet count, estimated glomerular filtration rate, days since discontinuation of $P2Y_{12}$ receptor inhibitor, acetylsalicylic acid use within 7 days before surgery, oral anticoagulant paused <2 days before surgery, use of unfractionated heparin, stroke, extracardiac arteriopathy, diabetes, dialysis, chronic lung disease, atrial fibrillation, prior percutaneous coronary intervention, left ventricular ejection fraction ≤50%, emergency procedure, critical preoperative state, off-pump surgery, bilateral internal mammary artery grafting, and number of distal coronary artery anastomoses. We calculated standardized differences for variables to investigate post-match balance. A standardized difference <0.1 was considered to indicate adequate balance between

variables of the intervention cohorts. A 2-sided p value of <0.05 was considered to indicate statistical significance. Analyses were performed using Stata v.15.1 statistical software (StataCorp LP, College Station, TX, USA) and SPSS v.25.0 (IBM Corporation, New York, USA).

Results

Of 7 352 patients included in the E-CABG prospective, multicenter registry, 5 687 patients were not eligible. Of the remaining 1665 patients, 139 were excluded owing to discontinuation of fondaparinux or LMWH >24 hours prior to surgery and 1 was excluded owing to treatment with both fondaparinux and LMWH within 24 hours prior to surgery (Figure 1). Thus, 1525 patients with ACS who underwent isolated primary CABG and were treated with fondaparinux or LMWH within 24 hours prior to surgery were included in the present analysis. Of these, 276 (18.1%) had received fondaparinux and 1249 (81.9%) LMWH preoperatively.

Patient and procedural characteristics are listed in Table 1. Comorbidities differed between the two groups with preoperative extracardiac arteriopathy, chronic pulmonary disease, percutaneous coronary intervention, atrial fibrillation, and dialysis being more common in the LMWH group. Predicted high risk of severe bleeding estimated with the WILL-BLEED risk score [11] was higher in the LMWH group (53.6 vs. 46.0%).

In the propensity score-matched cohort (245 pairs), baseline characteristics, including predicted risk of severe bleeding, as well as procedural characteristics were well balanced as shown in Table 1. Fondaparinux dose was 2.5 mg once daily in all patients but one who received 5 mg once daily. Patients who received fondaparinux preoperatively were switched to receive LMWH postoperatively.

In the overall cohort, the LMWH-treated patients had a higher incidence of UDPB severe or massive bleeding, as well as the 3 other definitions of major bleeding (BARC CABG-

related bleeding, BART massive bleeding, E-CABG severe or massive bleeding), compared with fondaparinux-treated patients (Table 2 and Figure 2).

In the propensity score-matched cohort, the risk of major bleeding according to UDPB severe or massive bleeding and other major bleeding definitions was similar between the fondaparinux and LMWH cohorts (Table 2 and Figure 2). Chest tube output and resternotomy rate for bleeding were similar between the two groups.

In patients with UDPB severe or massive bleeding, in-hospital mortality was higher compared with patients without UDPB sever or massive bleeding (11.1% vs. 1.9%, p<0.001).

Discussion

In this prospective, multicenter registry, after propensity score matching we found that preoperative treatment with fondaparinux compared to LMWH was associated with similar incidence of perioperative bleeding in ACS patients undergoing CABG.

To study the effects of antithrombotic drugs in patients undergoing cardiac surgery is a topic of interest since severe bleeding has been shown to be associated with increased morbidity and mortality in these patients [5]. In contrast to antiplatelet drugs, the effect of fondaparinux versus LMWH on CABG-related bleeding has not been evaluated. A few previous studies investigated the bleeding-related effects of LMWH and unfractionated heparin [12], but none included patients preoperatively treated with fondaparinux. Although European guidelines recommend fondaparinux as the anticoagulant of choice in patients with NSTEMI regardless of the management strategy [4], the implementation of these guidelines differs between countries and patients with NSTEMI planned to undergo urgent CABG might have received either fondaparinux or LMWH preoperatively. This could be owing to that these guidelines are based on studies conducted in populations of general NSTEMI patients [1], not only NSTEMI patients undergoing CABG. A possible concern for increased CABG-related bleeding

in patients receiving fondaparinux could therefore prevent physicians of using this medication in patients accepted for urgent CABG. Another reason why the implementation of fondaparinux in patients with NSTEMI has differed between European countries could be that it has been argued that the study on fondaprinux versus enoxaparin in ACS patients used a higher enoxaparin dose than the one used currently [1]. Also, fondaparinux in that study was associated with a higher incidence of catheter-related thrombosis which necessitated unfractionated heparin during angiography and PCI [1].

Although bleeding associated with fondaparinux versus LMWH has not been investigated in patients undergoing CABG previously, it has been studied in patients undergoing percutaneous coronary intervention [2]. In these patients, fondaparinux patients had a lower incidence of major bleeding complications, including access site-related bleeding [2]. These are findings from a different clinical setting but still somewhat contrast to the results of the present study, supporting similar periprocedural bleeding in patients receiving fondaparinux or LMWH.

This study has limitations that need to be considered. By using propensity score matching we adjusted for differences in baseline characteristics between patients who had preoperatively received either fondaparinux or LMWH. Still, residual confounding might be present even after adjustment. Preoperative treatment with fondaparinux or LMWH was known by the treating physicians, which may have influenced their decision to use blood transfusions and hemostatic drugs. This could be why red blood cell and platelet transfusions, as well as use of hemostatic drugs differed between the two groups. Furthermore, the type and dose of LMWH administered were not registered. However, the study was prospectively conducted in a multicenter setting with a large number or pre- peri- and postoperative variables. The use of multiple definitions of major perioperative bleeding may more accurately describe major bleeding as incidence differs significantly depending on the bleeding definition used [8].

Preoperative treatment with fondaparinux compared to LMWH was associated with similar incidence of perioperative bleeding in ACS patients undergoing CABG. These

findings support that the choice between fondaparinux and LMWH in ACS patients considered to be at high probability to undergo CABG do not need to be influenced by the concern about possible risk for perioperative CABG-related bleeding.

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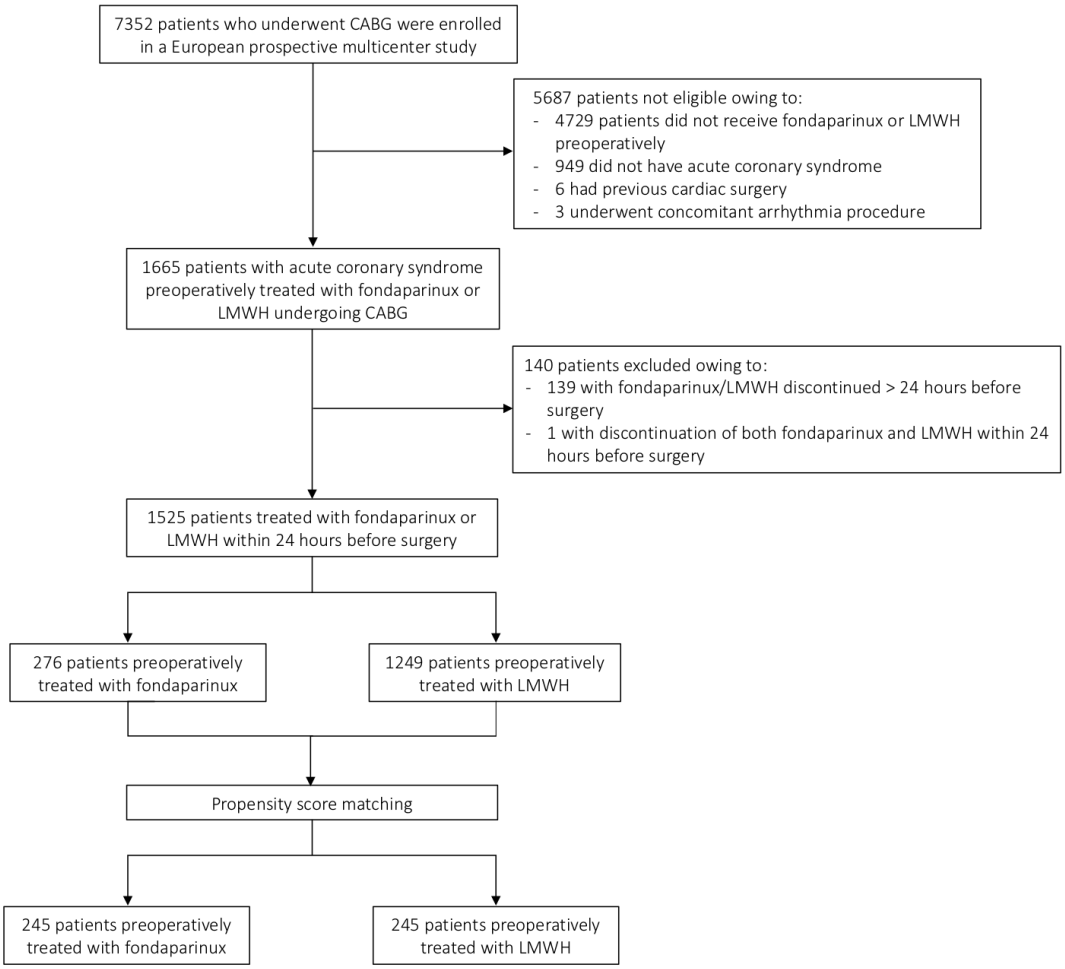

Figure 1

Study flow chart. ACS = acute coronary syndrome, CABG = coronary artery bypass grafting, LMWH = low molecular weight heparin.

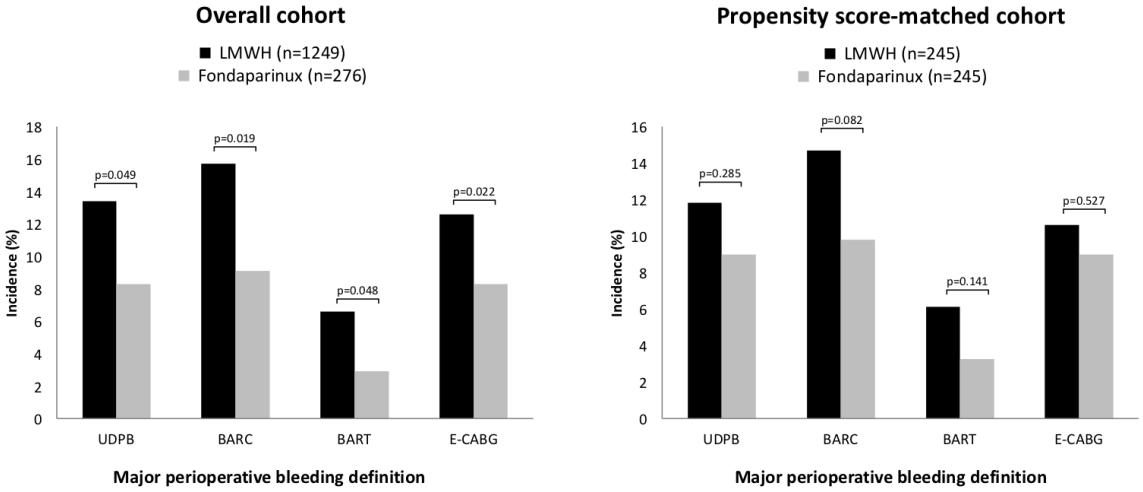

Figure 2

Incidence of major perioperative bleeding between patients preoperatively treated with fondaparinux versus low-molecular weight heparin according to 4 definitions: UDPB severe or massive bleeding, BARC CABG-related bleeding, BART massive bleeding, and E-CABG severe or massive bleeding. Left panels: Overall cohort. Right panels: Propensity score-matched cohort. BARC CABG = Bleeding Academic Research Consortium, BART = Blood conservation using Antifibrinolytics Randomized Trial, E-CABG = European multicenter study on Coronary Artery Bypass Grafting, UDPB = Universal Definition of Perioperative Bleeding.

Table 1 Patient and procedural characteristics

	Overall cohort	Propensity score-matched cohort				
Variable	Fondaparinux n=276	LMWH n=1249	Standardized difference	Fondaparinux n=245	LMWH n=245	Standardized difference
Age (years) mean ± SD	66.1 ± 9.9	66.9 ± 9.7	-0.0835	66.1 ± 9.8	66.2 ± 10.4	-0.0081
Women	48 (17.4%)	249 (19.9%)	-0.0653	44 (18.0%)	44 (18.0%)	0
Stroke	11 (4.0%)	64 (5.1%)	-0.0546	9 (3.7%)	13 (5.3%)	-0.0787
Extracardiac arteriopathy	40 (14.5%)	314 (25.1%)	-0.2693	40 (16.3%)	45 (18.4%)	-0.0538
Diabetes mellitus	83 (30.1%)	436 (34.9%)	-0.1033	72 (29.4%)	81 (33.1%)	-0.0792
Dialysis	0	23 (1.8%)	-0.1936	0	0	-
Chronic lung disease	16 (5.8%)	176 (14.1%)	-0.2796	15 (6.1%)	14 (5.7%)	0.0173
Atrial fibrillation	12 (4.3)	129 (10.3)	-0.2309	12 (4.9%)	13 (5.3%)	-0.0185
Prior percutaneous coronary intervention	40 (14.5%)	291 (23.3%)	-0.2262	40 (16.3%)	38 (15.5%)	0.0223
Left ventricular ejection fraction ≤50%	103 (37.3%)	488 (39.1%)	-0.0367	91 (37.1%)	101 (41.2%)	-0.0835
Emergent or salvage procedure	21 (7.6%)	108 (8.6%)	-0.0380	19 (7.8%)	18 (7.3%)	0.0154
Critical preoperative state	14 (5.1%)	128 (10.2%)	-0.1954	14 (5.7%)	12 (4.9%)	0.0364
Preoperative laboratory parameters						
Hemoglobin (g/L) mean ± SD	137 ± 17	133 ± 18	0.2193	137 ± 17	136 ± 17	0.0712
Platelets ($x10^9$/L) mean ± SD	235 ± 70	233 ± 74	0.0210	235 ± 71	235 ± 86	0.0050

Estimated glomerular filtration rate (ml/min/1,73m^2) mean ± SD	84 ± 26	84 ± 29	0.0039	84 ± 26	84 ± 27	-0.0050
Preoperative antithrombotic medications						
Acetylsalicylic acid	261 (94.6%)	1119 (89.6%)	0.1848	231 (94.3%)	232 (94.7%)	-0.0179
Unfractionated heparin	0	6 (0.5%)	-0.0982	0	1 (0.4%)	-0.0904
Warfarin	1 (0.4%)	21 (1.7%)	-0.1314	1 (0.4%)	0	0.0904
Novel oral anticoagulant	0	4 (0.3%)	-0.0801	0	1 (0.4%)	-0.0904
Days since discontinuation of ticagrelor, clopidogrel, or prasugrel			0.0547			0.0884
0-3	77 (57.5%)	196 (54.7%)		69 (57.0%)	40 (52.6%)	
4-5	57 (42.5%)	162 (45.3%)		52 (43.0%)	36 (47.4%)	
WILL-BLEED bleeding risk score			0.1658			0.0447
Low risk (<4)	44 (15.9%)	197 (15.8%)		36 (14.7%)	36 (14.7%)	
Medium risk (4-6)	105 (38.0%)	383 (30.7%)		91 (37.1%)	86 (35.1%)	
High risk (>6)	127 (46.0%)	669 (53.6%)		118 (48.2%)	123 (50.2%)	
Off-pump surgery	16 (5.8%)	285 (22.8%)	-0.5008	16 (6.5%)	10 (4.1%)	0.1092
Bilateral internal mammary grafting	123 (44.6%)	187 (15.0%)	0.6831	101 (41.2%)	97 (39.6%)	0.0332
Number of distal anastomoses	3.0 ± 0.8	2.6 ± 1.0	0.3894	2.9 ± 0.8	2.8 ± 0.9	0.1525

Data are n (%) unless otherwise noted. LMWH = low molecular weight heparin, SD = standard deviation.

Table 2 Postoperative outcomes

	Overall cohort	Propensity score-matched cohort				
Variable	Fondaparinux n=276	LMWH n=1249	p-value	Fondaparinux n=245	LMWH n=245	p-value
Definitions of major bleeding						
UDPB severe or massive bleeding	24 (8.7%)	168 (13.5%)	0.031	22 (9.0%)	29 (11.8%)	0.285
BARC CABG-related bleeding	26 (9.4%)	197 (15.8%)	0.007	24 (9.8%)	36 (14.7%)	0.082
BART massive bleeding	9 (3.3%)	85 (6.8%)	0.027	8 (3.3%)	15 (6.1%)	0.141
E-CABG severe or massive bleeding	23 (8.3%)	157 (12.6%)	0.048	22 (9.0%)	26 (10.6%)	0.527
12 hours chest tube output (mL) mean ± SD	470 ± 230	500 ± 370	0.16	470 ± 230	510 ± 330	0.143
Resternotomy for bleeding	8 (2.9%)	56 (4.5%)	0.23	7 (2.9%)	8 (3.3%)	0.796
Decline in hemoglobin during the operation day (g/L) mean ± SD	37 ± 15	35 ± 20	0.31	36 ± 16	39 ± 21	0.145
Transfusions						
Units of RBC transfused per- and postoperative, mean ± SD	1.1 ± 2.5	1.9 ± 3.3	<0.001	1.2 ± 2.5	1.8 ± 2.7	0.008
Plasma transfused	17 (6.2%)	125 (10.0%)	0.046	16 (6.5%)	24 (9.8%)	0.193
Platelets transfused	40 (14.5%)	119 (9.5%)	0.015	38 (15.5%)	19 (7.8%)	0.006
Any hemostatic drug administered	6 (2.2%)	65 (5.2%)	0.031	6 (2.4%)	17 (6.9%)	0.009
Atrial fibrillation	71 (25.7%)	385 (30.8%)	0.094	60 (24.5%)	60 (24.5%)	0.833
Maximum postoperative creatinine (µmol/L) mean ± SD	109 ± 63	119 ± 106	0.13	108 ± 65	109 ± 51	0.838
Dialysis	5 (1.8%)	48 (3.8%)	0.19	4 (1.6%)	2 (0.8%)	0.410
Stroke	2 (0.7%)	21 (1.7%)	0.24	2 (0.8%)	4 (1.6%)	0.306

Intensive care unit stay (days) mean ± SD	2.3 ± 2.4	3.2 ± 5.2	0.005	2.3 ± 2.4	3.1 ± 5.8	0.052
In-hospital death	4 (1.4%)	43 (3.4%)	0.083	4 (1.6%)	4 (1.6%)	1.0

Data are n (%) unless otherwise noted. BARC CABG = Bleeding Academic Research Consortium, BART = Blood conservation using Antifibrinolytics Randomized Trial, E-CABG = European multicenter study on Coronary Artery Bypass Grafting, LMWH = low molecular weight heparin, RBC = red blood cells, SD = standard deviation, UDPB = Universal Definition of Perioperative Bleeding.