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Safety of Preoperative Use of Ticagrelor With or Without Aspirin Compared With Aspirin Alone in Patients With Acute Coronary Syndromes Undergoing Coronary Artery Bypass Grafting

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IMPORTANCE The optimal timing of discontinuation of ticagrelor before cardiac surgery is controversial.

OBJECTIVE To evaluate the safety of preoperative use of ticagrelor with or without aspirin in patients with acute coronary syndromes (ACS) undergoing isolated coronary artery bypass grafting (CABG) compared with aspirin alone.

DESIGN, SETTING, AND PARTICIPANTS This prospective, multicenter clinical trial was performed at 15 European centers of cardiac surgery. Participants were patients with ACS undergoing isolated CABG from the European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG) registry between January and September 2015.

EXPOSURES Before surgery, patients received ticagrelor with or without aspirin or aspirin alone.

MAIN OUTCOMES AND MEASURES Severe bleeding as defined by the Universal Definition of Perioperative Bleeding (UDPB) and E-CABG bleeding classification criteria. A propensity score–matched analysis was performed to adjust for differences in baseline and operative covariates.

RESULTS Of 2482 patients from the E-CABG registry, the study cohort included 786 (31.7%) consecutive patients with ACS (mean [SD] age, 67.1 [9.3] years; range, 32-88 years), and 132 (16.8%) were female. One-to-one propensity score matching provided 215 pairs, whose baseline and operative covariates had a standardized difference of less than 10%. Preoperative use of ticagrelor was associated with a similar risk of bleeding according to the UDPB and E-CABG bleeding classifications, but the incidence of platelet transfusion was higher in the ticagrelor group (13.5% [29 of 215] vs 6.0% [13 of 215]. Compared with those receiving aspirin alone, continuing ticagrelor up to the time of surgery or discontinuing its use less than 2 days before surgery was associated with a higher risk of platelet transfusion (22.7% [5 of 22] vs 6.4% [12 of 187]) and E-CABG bleeding grades 2 and 3 (18.2% [4 of 22] vs 5.9% [11 of 187]) and tended to have an increased risk of UDPB grades 3 and 4 (22.7% [5 of 22] vs 9.6% [18 of 187]). Among patients in whom antiplatelet drug use was discontinued at least 2 days before surgery, the incidence of platelet transfusion was 12.4% (24 of 193) in the ticagrelor group and 3.6% (1 of 28) in the aspirin-alone group.

CONCLUSIONS AND RELEVANCE In propensity score–matched analyses among patients with ACS undergoing CABG, the use of preoperative ticagrelor with or without aspirin compared with aspirin alone was associated with more platelet transfusion but similar degree of bleeding; in patients receiving ticagrelor 1 day before or up until surgery, there was an increased rate of severe bleeding.

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Supplemental content

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Approximately 10% of patients with non-ST-segment elevation and acute coronary syndromes (ACS) require coronary artery bypass grafting (CABG) during the same hospitalization.[1] Irrespective of the revascularization strategy, P_2Y_{12} inhibitor agents are recommended in addition to aspirin (class of recommendation 1 and level of evidence A) in patients with ACS.[2,3] Ticagrelor is a newer P_2Y_{12} inhibitor that has been demonstrated to significantly reduce the risk of a composite end point of death from vascular causes, myocardial infarction, and stroke.[4] In this scenario, patients requiring CABG represent a challenging group of individuals because of the difficulties in balancing thrombosis and bleeding risks in relation to the timing of surgery and optimal antithrombotic therapy management. Current revascularization guidelines and the US Food and Drug Administration–approved patient labeling recommend discontinuation of ticagrelor therapy 5 days before surgery.[5-7] This recommendation is substantiated by the lack of difference between clopidogrel bisulfate and ticagrelor in terms of major bleeding in subgroups with different intervals between cessation of study treatment and CABG and the observation of a reduction in bleeding risk when use of these drugs were discontinued for at least 5 days before surgery.[8] Concern exists that a discontinuation of several days may be associated with an increased risk of cardiovascular events while awaiting surgery.[9,10] Indeed, in the Platelet Inhibition and Patient Outcomes (PLATO) trial,[3] it was recommended that, in patients undergoing CABG, administration of ticagrelor should be withheld for 24 to 72 hours, and prior guidelines suggested a shorter discontinuation of treatment in patients requiring urgent CABG.[10,11] The absence of randomized studies makes it difficult to establish the exact risk of bleeding complications after perioperative ticagrelor administration and its optimal timing of discontinuation before surgery.[12-15] To our knowledge, no data exist on any possible increased risk of bleeding associated with exposure to ticagrelor with or without aspirin compared with aspirin alone among patients with ACS undergoing CABG. The prospective European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG) registry[16] aims to investigate the association of the use of ticagrelor vs aspirin alone with the risk of major bleeding and blood product requirement after surgery.

Key Points

Question What is the normal timing of discontinuation of antiplatelet drug use in acute coronary syndromes before coronary artery bypass grafting?

Findings In this multicenter clinical trial that included 786 adult patients, administration of ticagrelor with or without aspirin was associated with the same risk of bleeding and major complication after cardiac surgery compared with aspirin alone. However, the risk was significantly increased among patients in whom ticagrelor was administered 1 day before or up until surgery.

Meaning The use of ticagrelor is safe before coronary artery bypass grafting, particularly if its use is discontinued more than 24 hours before surgery.

Methods

Ethical Considerations

This study was approved by the institutional review boards of 15 participating centers (listed below). Written informed consent was obtained from participants at institutions where it was required by the internal institutional review board but otherwise was waived.

Patient Population and Data Collection

The E-CABG registry is a prospective, multicenter study enrolling patients undergoing isolated CABG at 15 European centers of cardiac surgery (San Camillo Forlanini Hospital, Rome, Italy; Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; Verona University Hospital, Verona, Italy; University Hospital Jean Minjoz, Besançon, France; Pontchaillou University Hospital, Rennes, France; Hamburg University Heart Center, Hamburg, Germany; Paracelsus Medical University, Nuremberg, Germany; St Anna Hospital, Catanzaro, Italy; Centro Cuore Morgagni, Pedara, Italy; Second University of Naples, Naples, Italy; Ospedali Riuniti, Trieste, Italy; University of Genoa, Genoa, Italy; University of Parma, Parma, Italy; Centro Cardiologico–Fondazione Monzino Istituto di Ricovero e Cura a Carattere Scientifico, University of Milan, Milan, Italy; and Oulu University Hospital, Oulu, Finland). Participants were patients with ACS undergoing isolated CABG from the E-CABG registry between January and September 2015. This study is registered at clinicaltrials.gov (identifier NCT02319083), and its detailed protocol and definition criteria have been previously published.[16] For the present analysis, all consecutive patients with unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction exposed to ticagrelor with or without aspirin or to aspirin alone within 14 days of surgery were considered. Patients exposed to other antiplatelet agents (clopidogrel or prasugrel) were excluded from the analysis. Data on preoperative antithrombotic agents, preoperative and perioperative hemoglobin levels, postoperative blood loss, and use of any type of blood products were collected prospectively to stratify the severity of bleeding according to the E-CABG bleeding severity definition (eTable 1 in the Supplement)[16,17] and Universal Definition of Perioperative Bleeding (UDPB) criteria.[18]

Clinical Management

Antiplatelet drugs were administered according to guidelines by the European Society of Cardiology for ACS.[5,6] Treatment with fondaparinux sodium, low-molecular-weight heparin, and unfractionated heparin were generally discontinued 12 hours before nonacute surgery, whereas aspirin and oral anticoagulant (warfarin sodium) treatments were discontinued 24 to 48 hours before surgery. When feasible, ticagrelor use was discontinued 5 days before the scheduled operation. Finally, perioperative need for blood products, including fresh frozen plasma, pooled plasma, and platelets, was determined on an individual patient basis. The amount of blood products transfused refers to those blood-derived products administered during surgery and during the subsequent

in-hospital stay. In general, red blood cells (RBCs) were administered during surgery to maintain a hemoglobin level exceeding 7 g/dL (to convert to grams per liter, multiply by 10.0) or a hematocrit exceeding 20% (to convert to proportion of 1.0, multiply by 0.01) during cardiopulmonary bypass or were administered after surgery if the hemoglobin level was less than 8 g/dL. Interinstitutional differences in patient blood management and transfusion strategy may exist.

Outcome End Points

The primary outcome of this study was severe bleeding as defined by the UDPB[18] and E-CABG bleeding classification criteria.[16] Secondary end points were chest drain output 12 hours after surgery, reexploration for excessive bleeding or tamponade, use of blood products, length of stay in the intensive care unit, sternal wound infection, and in-hospital mortality, as well as postoperative neurological, renal, and cardiac complications. We did not consider the length of in-hospital stay as an outcome measure because the timing of discharge in these patients could have been influenced by the availability of beds in rehabilitation clinics.

Statistical Analysis

Statistical analysis was performed using software programs (SPSS, version 23.0; IBM Corporation and SAS, version 9.2; SAS Institute Inc). No attempt was made to replace missing values. The only variables with missing data were SYNTAX score (11.5% [90 of 786]), length of operation (8.8% [69 of 786]), body mass index (0.8% [6 of 786]), preoperative atrial fibrillation (0.6% [5 of 786]), and left ventricular ejection fraction (0.3% [2 of 786]). The Fisher exact test, χ^2 test, Mann-Whitney test, and Kruskal-Wallis test were used for univariate analysis. Correlation between continuous and ordinal variables was estimated by the Spearman rank correlation test. C statistics were calculated to assess the predictive ability of continuous variables on outcome end points. Because observational studies lack randomization, propensity score matching was used to select 2 groups of patients receiving ticagrelor with or without aspirin or aspirin alone with similar baseline characteristics. The propensity score was estimated using a nonparsimonious logistic regression model with aspirin alone as the reference treatment group and ticagrelor with or without aspirin as the outcome treatment group.[19] The following variables were included as covariates: age, sex, body mass index, hemoglobin level, estimated glomerular filtration rate, pulmonary disease, diabetes, stroke, poor mobility, extracardiac arteriopathy, atrial fibrillation, previous percutaneous coronary intervention, previous cardiac surgery, left ventricular ejection fraction less than 50%, diagnosis (stable or unstable angina, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction), critical preoperative status, preoperative intra-aortic balloon pump, ventricular arrhythmias, out-of-hospital cardiac arrest, left main coronary artery stenosis or equivalent, number of diseased vessels, use of low-molecular-weight heparin or fondaparinux, use of vitamin K antagonists, glycoprotein IIb/IIIa inhibitors, unfractionated heparin, operative technique, use of bilateral mammary arteries, and number of distal anastomoses.

One-to-one propensity score matching was performed using the nearest neighbor method and a caliper of 0.2 of the SD of the logit of the propensity score.[20] To evaluate the balance between the matched groups, the *t* test for paired samples for continuous variables, McNemar test for dichotomous variables, Stuart-Maxwell test for categorical variables, and analysis of the standardized differences after matching were used. The same tests were used to test differences in the early adverse events of propensity score–matched groups. All tests were 2 sided, with $\alpha = .05$ indicating statistical significance.

Results

Baseline Characteristics

The study cohort included 786 (31.7%) consecutive patients with ACS among 2482 patients from the E-CABG registry. Their mean (SD) age was 67.1 (9.3) years (age range, 32-88 years), and 132 (16.8%) were female. Preoperative antiplatelet regimens were administration of ticagrelor with or without aspirin in 290 (36.9%) patients and aspirin alone in 496 (63.1%) patients. In addition, 270 (93.1%) patients in the ticagrelor group were receiving dual antiplatelet therapy with aspirin. Patient characteristics in the study groups are listed in **Table 1**. Briefly, patients in the aspirin-alone group were older (mean [SD] age, 68.3 [9.1] vs 65.1 [9.4] years; $P < .001$) and had higher operative risk (mean [SD] European System for Cardiac Operative Risk Evaluation II [EuroSCORE II], 3.6% [5.0%] vs 3.1% [5.2%]; $P < .001$). Patients receiving ticagrelor more frequently required CABG performed in an urgent and emergency setting. Operative data are listed in **Table 2**.

Outcome in the Overall Series

No differences were observed between the 2 study groups on univariate analysis in chest tube output (mean [SD], 470 [389] vs 454 [273] mL; $P = .08$), RBC transfusion (43.8% [217 of 496] vs 39.0% [113 of 290]; $P = .19$), and fresh frozen plasma or pooled plasma administration (5.4% [27 of 496] vs 7.2% [21 of 290]; $P = .31$). Compared with those in the aspirin-alone group, patients in the ticagrelor group required more platelet transfusion (13.1% [28 of 290] vs 5.6% [38 of 496], receiving a mean [SD] of 0.7 [3.7] vs 0.2 [1.3] U) ($P < .001$ for both). Bleeding and postoperative outcomes in the overall series are summarized in eTable 2, eTable 3, eFigure 1, and eFigure 2 in the Supplement. No significant differences were observed in terms of bleeding-related and other outcomes on multivariable analysis (eResults in the Supplement).

Outcome Among Propensity Score–Matched Pairs

Because of baseline differences in the study groups, a propensity score was estimated, and its distribution between the study groups is shown in eFigure 3 in the Supplement. One-to-one propensity score matching provided 215 pairs. All baseline and operative covariates had a standardized difference of less than 10% after matching (eFigure 4 in the Supplement), which suggests a balance between the baseline risk factors of the study groups.

Table 1. Baseline Characteristics in the Overall Series and in Propensity Score–Matched Pairs[a]

Variable	Overall Series			Propensity Score–Matched Pairs		
	Aspirin Alone (n = 496)	Ticagrelor With or Without Aspirin (n = 290)	*P* Value	Aspirin Alone (n = 215)	Ticagrelor With or Without Aspirin (n = 215)	*P* Value
Age, mean (SD), y	68.3 (9.1)	65.1 (9.4)	<.001	65.5 (9.5)	66.1 (9.1)	.41
Female, No. (%)	80 (16.1)	52 (17.9)	.51	29 (13.5)	32 (14.9)	.67
Body mass index, mean (SD)[b]	27.8 (4.3)	27.0 (4.1)	.02	27.2 (3.8)	27.2 (4.2)	.87
Hemoglobin level, mean (SD), g/dL	13.4 (1.6)	13.6 (1.6)	.08	13.7 (1.6)	13.6 (1.6)	.58
Platelet count, mean (SD), $\times 10^3/\mu L$	227 (64)	226 (63)	.97	232 (59)	224 (64)	.20
eGFR, mean (SD), mL·min·1.73 m^2	79 (26)	86 (27)	.003	85.8 (26.5)	84.0 (23.6)	.44
Dialysis, No. (%)	9 (1.8)	0	.03	0	0	NA
Functioning kidney transplant, No. (%)	3 (0.6)	0	.30	0	0	NA
Pulmonary disease, No. (%)	57 (11.5)	23 (7.9)	.11	18 (8.4)	20 (9.3)	.74
Diabetes, No. (%)	164 (33.1)	83 (28.6)	.20	54 (25.1)	58 (27.0)	.66
Stroke, No. (%)	25 (5.0)	12 (4.1)	.56	7 (3.3)	7 (3.3)	>.99
Poor mobility, No. (%)	21 (4.2)	3 (1.0)	.01	0	0	NA
Extracardiac arteriopathy, No. (%)	112 (22.6)	36 (12.4)	<.001	33 (15.3)	32 (14.9)	.89
Atrial fibrillation, No. (%)	52 (10.5)	12 (4.1)	.002	12 (5.6)	10 (4.7)	.66
Previous PCI, No. (%)	86 (17.3)	64 (22.1)	.10	41 (19.1)	42 (19.5)	.89
Previous cardiac surgery, No. (%)	6 (1.2)	1 (0.3)	.27	1 (0.5)	1 (0.5)	>.99
Left ventricular ejection fraction <50%, No. (%)	162 (32.7)	108 (37.2)	.21	70 (32.6)	75 (34.9)	.61
Diagnosis, No. (%)						
Unstable angina	218 (44.0)	85 (29.3)	<.001	71 (33.0)	74 (34.4)	.83
NSTEMI	230 (46.4)	163 (56.2)		118 (54.9)	112 (52.1)	
STEMI	48 (9.7)	42 (14.5)		26 (12.1)	29 (13.5)	
Critical preoperative status, No. (%)	28 (5.6)	11 (3.8)	.25	10 (4.7)	7 (3.3)	.44
Preoperative IABP, No. (%)	25 (5.0)	7 (2.4)	.07	8 (3.7)	5 (2.3)	.37
Ventricular arrhythmias, No. (%)	13 (2.6)	10 (3.4)	.52	6 (2.8)	4 (1.9)	.53
Out-of-hospital cardiac arrest, No. (%)	5 (1.0)	6 (2.1)	.23	3 (1.4)	3 (1.4)	>.99
Coronary artery status						
Left main stenosis or equivalent, No. (%)	298 (60.1)	152 (52.4)	.04	119 (55.3)	118 (54.9)	.92
No. of diseased vessels, mean (SD)	2.7 (0.5)	2.6 (0.6)	.20	2.6 (0.6)	2.6 (0.6)	.92
Antithrombotic drugs before surgery						
Aspirin, No. (%)	496 (100.0)	270 (93.1)	<.001	215 (100.0)	201 (93.5)	<.001
Aspirin therapy discontinuation, mean (SD), d	1.1 (2.5)	1.2 (1.8)	.02	1.1 (1.6)	1.1 (1.8)	.17
Aspirin therapy discontinuation 0-1 d, No. (%)	427 (86.1)	222 (76.6)	.001	107 (49.8)	63 (29.3)	<.001
Ticagrelor therapy discontinuation, mean (SD), d	NA	5.4 (3.0)	NA	NA	5.3 (3.9)	NA
Clopidogrel bisulfate, No. (%)	0	0	NA	0	0	NA
Prasugrel, No. (%)	0	0	NA	0	0	NA
Warfarin sodium, No. (%)	20 (4.0)	1 (0.3)	.002	2 (0.9)	1 (0.5)	.56
New oral anticoagulants, No. (%)	4 (0.8)	0	.13	0	0	NA
Ticlopidin hydrochloride, No. (%)	0	0	NA	0	0	NA
Low-molecular-weight heparin or fondaparinux sodium, No. (%)	194 (39.1)	173 (59.7)	<.001	112 (52.1)	113 (52.6)	.92
Unfractionated heparin, No. (%)	67 (13.5)	27 (9.3)	.08	26 (12.1)	24 (11.2)	.76
Glycoprotein IIb/IIIa inhibitors, No. (%)	11 (2.2)	1 (0.3)	.04	1 (0.5)	1 (0.5)	>.99
Thrombolysis, No. (%)	0	0	NA	0	0	NA
CRUSADE bleeding score, mean (SD)	27 (13)	23 (13)	<.001	23 (13)	23 (12)	.87
Papworth bleeding score, mean (SD)	1.3 (0.8)	1.3 (0.7)	.56	1.3 (0.8)	1.2 (0.7)	.52
GRACE score, mean (SD)	138 (30)	137 (30)	.58	137 (30)	136 (30)	.76
EuroSCORE II, mean (SD), %	3.6 (5.0)	3.1 (5.2)	<.001	2.6 (3.4)	2.8 (4.2)	.65

Abbreviations: CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA [American College of Cardiology/American Heart Association] Guidelines; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Event; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; IABP, intra-aortic balloon pump; NA, not applicable; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

SI conversion factors: To convert hemoglobin level to grams per liter, multiply by 10.0; platelet count to $\times 10^9$/L, multiply by 1.0.

[a] Clinical variables are reported according to the EuroSCORE II definition criteria.

[b] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Operative Data in the Overall Series and in Propensity Score–Matched Pairs

Variable	Overall Series			Propensity Score–Matched Pairs		
	Aspirin Alone (n = 496)	Ticagrelor With or Without Aspirin (n = 290)	*P* Value	Aspirin Alone (n = 215)	Ticagrelor With or Without Aspirin (n = 215)	*P* Value
Urgency status, No. (%)[a]						
Elective	118 (23.8)	53 (18.3)	.03	45 (20.9)	43 (20.0)	.99
Urgent	339 (68.3)	211 (72.8)		152 (70.7)	153 (71.2)	
Emergency class 1	27 (5.4)	18 (6.2)		15 (7.0)	16 (7.4)	
Emergency class 2	10 (2.0)	2 (0.7)		3 (1.4)	3 (1.4)	
Emergency class 3	2 (0.4)	2 (0.7)		0	0	
Emergency class 4	0	4 (1.4)		0	0	
Revascularization technique, No. (%)						
On pump with arrest	406 (81.9)	237 (81.7)	.51	178 (82.8)	179 (83.3)	.99
Off pump	79 (15.9)	48 (16.6)		33 (15.3)	32 (14.9)	
Heart beating on perfusion	5 (1.0)	3 (1.0)		4 (1.9)	4 (1.9)	
Conversion to heart beating on perfusion	6 (1.2)	1 (0.3)		0	0	
Conversion to on pump with arrest	0	1 (0.3)		0	0	
Bilateral mammary artery graft, No. (%)	170 (34.3)	115 (39.7)	.13	86 (40.0)	80 (37.2)	.55
No. of distal anastomoses, mean (SD)	2.7 (0.9)	2.8 (1.0)	.32	2.8 (0.9)	2.8 (0.9)	>.99
Cross-clamping time, mean (SD), min	60 (27)	57 (24)	.23	62 (29)	57 (24)	.04
Cardiopulmonary bypass time, mean (SD), min	88 (40)	82 (37)	.03	91 (45)	82 (40)	.049
Length of operation, mean (SD), min	240 (73)	233 (69)	.21	249 (75)	233 (70)	.04

[a] Emergency class 1 is persistent angina, electrocardiogram changes, or increasing levels of cardiac enzymes, despite best medical treatment, without need of inotropes. Emergency class 2 is hemodynamic instability responsive to inotropes. Emergency class 3 is hemodynamic instability unresponsive to inotropes or requiring preoperative insertion of an intra-aortic balloon pump. Emergency class 4 is salvage coronary artery bypass grafting, including patients requiring cardiopulmonary resuscitation (external cardiac massage) en route to the operating theater and excluding cardiopulmonary resuscitation after induction of anesthesia.

Analysis of the outcome in these propensity score–matched pairs showed that preoperative use of ticagrelor was associated with a similar risk of bleeding according to the UDPB and E-CABG but with a significantly higher risk of platelet transfusion in the ticagrelor group (incidence, 13.5% [29 of 215] vs 6.0% [13 of 215]; *P* = .009), receiving a mean (SD) of 0.5 (1.8) vs 0.1 (0.4) U (*P* = .006) (**Table 3**). The risk of reoperation for bleeding was similar in the ticagrelor and aspirin-alone groups (2.8% [6 of 215] vs 2.3% [5 of 215]; *P* = .76).

Analysis of severe bleeding according to the timing of discontinuation of use of aspirin and ticagrelor showed that continuing ticagrelor up to the time of surgery or discontinuing it less than 2 days before surgery was associated with a significantly higher risk of E-CABG bleeding grades 2 and 3 (18.2% [4 of 22] vs 5.9% [11 of 187]; *P* = .03) and tended to have an increased risk of UDPB grades 3 and 4 (22.7% [5 of 22] vs 9.6% [18 of 187]; *P* = .06) (**Figure**). The risk of severe bleeding was similar in subsets of patients in whom antiplatelet drug regimens were discontinued 2 to 3 days or 4 to 14 days before surgery.

Among the secondary end points, continuing use of ticagrelor up to the time of surgery vs discontinuing it less than 2 days before surgery was associated with a significantly higher risk of platelet transfusion in the ticagrelor group compared with the aspirin-alone group (incidence, 22.7% [5 of 22] vs 6.4% [12 of 187]; *P* = .008), receiving a mean (SD) of 1.2 (3.7) vs 0.1 (0.5) U (*P* = .007), but with a similar risk of reoperation for bleeding (0% [0 of 22] vs 2.1% [4 of 187]; *P* > .99). In patients with discontinuation of use of antiplatelet drugs of at least 2 days before surgery, the incidence of platelet transfusion was 12.4% (24 of 193) in the ticagrelor group vs 3.6% (1 of 28) in the aspirin-alone group (*P* = .22), receiving a mean (SD) of 0.4 (1.4) vs 0.1 (0.2) U (*P* = .16), and the incidence of reoperation for bleeding was 3.1% (6 of 193) vs 3.6% (1 of 28) (*P* = .90).

Preoperative use of ticagrelor with or without aspirin was associated with similar early outcomes compared with aspirin alone. These results are summarized in eTable 4 in the Supplement.

Discussion

The present study demonstrated that patients with ACS receiving ticagrelor with or without aspirin before CABG do not have an overall increased risk of major bleeding compared with patients receiving aspirin alone. Significant differences between the groups were observed for platelet transfusion but not for RBC transfusion. The incidence of severe bleeding as defined by UDPB grades 3 and 4 and E-CABG bleeding grades 2 and 3 was significantly increased only when ticagrelor was administered less than 2 days before or up to the time of surgery. Similarly, the risk of platelet transfusion was significantly higher in the ticagrelor group. However, the risk of reoperation for excessive bleeding in this subset of patients was similar between the study groups.

Unstable patients with high-risk coronary anatomy, ongoing ischemia, or hemodynamic instability who are suitable

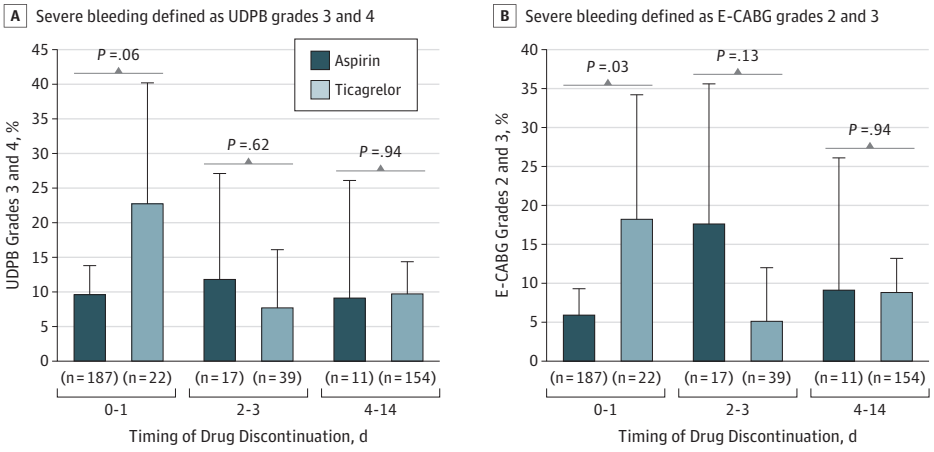
Table 3. Outcomes in Propensity Score–Matched Pairs

Variable	Aspirin Alone (n = 215)	Ticagrelor With or Without Aspirin (n = 215)	Univariate Analysis *P* Value
In-hospital death, No. (%)	4 (1.9)	7 (3.3)	.36
Stroke, No. (%)	4 (1.9)	1 (0.5)	.18
Nadir hematocrit, mean (SD), %	29.7 (4.4)	29.9 (4.6)	.55
Nadir hemoglobin level, mean (SD), g/dL	9.8 (1.4)	9.9 (1.5)	.68
Chest tube output at 12 h, mean (SD), mL	482 (398)	445 (247)	.27
Use of blood products			
Transfused RBCs, No. (%)	80 (37.2)	87 (40.5)	.49
RBCs transfused during surgery, mean (SD), U	0.2 (0.7)	0.3 (0.8)	.50
RBCs transfused during and after surgery, mean (SD), U	1.2 (2.5)	1.2 (2.3)	.90
Transfused fresh frozen plasma, No. (%)	15 (7.0)	9 (4.2)	.22
Fresh frozen plasma, mean (SD), U	0.1 (0.7)	0.2 (0.9)	.24
Transfused platelets, No. (%)	13 (6.0)	29 (13.5)	.009
Platelets, mean (SD), U	0.1 (0.4)	0.5 (1.8)	.006
rFVII, No. (%)	0	0	NA
Cryoprecipitate, No. (%)	2 (0.9)	2 (0.9)	>.99
Fibrinogen, No. (%)	6 (2.8)	3 (1.4)	.32
Prothrombin complex, No. (%)	4 (1.9)	4 (1.9)	>.99
Delayed chest closure for bleeding, No. (%)	4 (1.9)	4 (1.9)	>.99
Resternotomy for bleeding, No. (%)	6 (2.8)	5 (2.3)	.76
Resternotomy for hemodynamic problems, No. (%)	0	4 (1.9)	.046
UDPB grade, No. (%)			
0	112 (52.1)	118 (54.9)	.56
1	27 (12.6)	24 (11.2)	
2	55 (25.6)	50 (23.3)	
3	19 (8.8)	23 (10.7)	
4	2 (0.9)	0	
E-CABG grade, No. (%)			
0	146 (67.9)	139 (64.7)	.85
1	54 (25.1)	57 (26.5)	
2	13 (6.0)	16 (7.4)	
3	2 (0.9)	3 (1.4)	

Abbreviations: E-CABG, European Multicenter Study on Coronary Artery Bypass Grafting; NA, not applicable; RBCs, red blood cells; rFVII, recombinant human coagulation factor VII; UDPB, Universal Definition of Perioperative Bleeding.

SI conversion factors: To convert hematocrit to proportion of 1.0, multiply by 0.01; hemoglobin level to grams per liter, multiply by 10.0.

Figure. Rates of Severe Bleeding in Propensity Score–Matched Pairs of Patients With Acute Coronary Syndromes Receiving Ticagrelor With or Without Aspirin or Aspirin Alone Before CABG According to the Timing of Drug Use Discontinuation



Whiskers are 95% CIs, and *P* values refer to the risk of severe bleeding of patients in whom the drug regimens were discontinued during the same interval. CABG indicates coronary artery bypass grafting; E-CABG, European Multicenter Study on Coronary Artery Bypass Grafting; and UDPB, Universal Definition of Perioperative Bleeding.

candidates for CABG should be treated with emergency surgery regardless of antiplatelet therapy, while urgent surgery (usually in the following days) should be reserved for stable patients.[10,11] In this context, surgeons are often faced with a potentially increased risk of bleeding associated with dual antiplatelet therapy, which is frequently exacerbated by the deleterious effect of cardiopulmonary bypass. Because of a lack of evidence, it is recommended that the heart team should estimate the individual risk of bleeding and cardiovascular events to guide the optimal antithrombotic management of patients receiving dual antiplatelet therapy.[5-7,11] Although current guidelines recommend that administration of ticagrelor should be withheld for at least 5 days before CABG, unstable conditions do not allow waiting for washout of this potent antiplatelet agent.[8,9,11] One of the most clinically important observations in this study was that discontinuation of ticagrelor therapy more than 24 hours before surgery in the group receiving ticagrelor with or without aspirin was not associated with an increased risk of major bleeding complications compared with patients receiving aspirin alone. These findings suggest that it may be safe to operate on patients treated with ticagrelor earlier after its discontinuation, leading to possible clinical and economic benefits. An earlier discontinuation reduces the risk of thrombotic events in patients waiting for CABG during the same hospitalization, while the decreased preoperative stay preserves hospital resources by reducing expenditures. Among patients in the PLATO study,[8] a subgroup of 1261 patients with ACS undergoing CABG demonstrated a reduction in mortality without an increased risk of bleeding when use of ticagrelor was discontinued 24 to 72 hours before surgery. Similar results have been recently reported by Hansson et al,[14] who demonstrated that discontinuation of ticagrelor use 3 days before surgery did not increase the risk of major bleeding after CABG. However, in their previous experience, the same group partially corroborates our observations, reporting a trend toward a higher incidence of major bleeding when ticagrelor use was discontinued 0 to 1 day before surgery.[12]

A 2011 trial[21] showed no increase in total major bleeding associated with clopidogrel and ticagrelor use defined according to PLATO, Thrombolysis in Myocardial Infarction (TIMI), and Global Utilization of Streptokinase and tPA for Occluded Arteries (GUSTO) criteria but demonstrated a higher rate of non-CABG and other procedure-related major bleeding. A reduction in mortality without an increased risk of bleeding was observed by Held and colleagues[8] in patients with ACS undergoing CABG who were receiving ticagrelor vs clopidogrel. The results of the present study suggest that preoperative administration of ticagrelor with or without aspirin compared with aspirin alone did not affect in-hospital death, major bleeding outcomes (eg, reexploration for bleeding or tamponade), or chest drainage output after CABG. In addition, the incidence of UDPB grades 3 and 4 and E-CABG bleeding grades 2 and 3 was not affected by the antiplatelet regimen. However, these findings are conditional on survival to CABG, and our data do not allow an assessment of the consequences of waiting for surgery for sufficient washout of this antiplatelet drug. Therefore, in this study, we assessed the safety of the 2 drug treatments under the assumption that no adverse events occurred after their discontinuation. The present results suggest that a shorter discontinuation before CABG is safe in patients with ACS who are receiving ticagrelor, which may reduce any potentially increased risk of cardiovascular events when this drug is withheld before surgery.

In this study, despite receiving ticagrelor within 24 hours before CABG, only a small proportion of patients required surgery, but these patients had a significantly higher risk of severe perioperative bleeding (Figure and eFigure 1 in the Supplement). Therefore, a potential risk of severe bleeding may be experienced by a small number of patients with ACS who receive ticagrelor. On the other hand, this multicenter registry demonstrated that a large number of patients with ACS are not treated with an P_2Y_{12} inhibitor. The present findings suggest that cardiologists are not comfortable with the use of ticagrelor in all patients with ACS because the use of this P_2Y_{12} inhibitor may still be associated with a higher risk of CABG-related bleeding and other adverse events when early discontinuation of drug use is not feasible. Indeed, the present study confirms that late discontinuation of ticagrelor use was not possible in 10.2% (22 of 215) of patients, and these individuals had a higher rate of severe bleeding.

Our study has several limitations. First, although the present data are from a prospective, multicenter registry investigation in which the study protocol and aims were planned before data collection,[13] a bias inherent to its observational nature is still possible. Second, the data set is conditional on survival after administration and, when feasible, discontinuation of the antiplatelet therapy before CABG, and our data do not allow an assessment of the consequences of waiting for surgery. Third, this study is limited by its small size. A post hoc sample size calculation based on the observed proportions of E-CABG bleeding grades 2 and 3 and UDPB grades 3 and 4 in the aspirin-alone group showed that we had 80% power to detect a difference of approximately 9%. In particular, the number of patients with late or no discontinuation of ticagrelor was small. Fourth, the treatment and time since discontinuation were known by the treating physicians, which may have influenced their decision to use blood products. Fifth, interinstitutional differences in patient blood management, transfusion policy, and indication for reoperation for bleeding may exist, which might have introduced a bias in the present analysis.

Conclusions

In propensity score–matched analyses among patients with ACS undergoing CABG, preoperative use of ticagrelor with or without aspirin compared with aspirin alone was associated with more platelet transfusion but with a similar degree of bleeding. However, in patients continuing use of ticagrelor up to the time of surgery or discontinuing its use less than 2 days before surgery, there was an increased rate of severe bleeding. Larger data sets and randomized clinical trials are needed to assess whether patients with ACS receiving ticagrelor are at higher risk of adverse events while waiting for CABG and whether they may safely undergo coronary surgery after such a short discontinuation of ticagrelor use.

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