ORIGINAL ARTICLE

Protective Effects of Tranexamic Acid on Clopidogrel Before Coronary Artery Bypass Grafting

A Multicenter Randomized Trial

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Importance: Excessive bleeding and transfusion increase morbidity and mortality in patients receiving coronary artery bypass grafting (CABG), especially in those exposed to antiplatelet agents.

Objective: To evaluate the influence and interaction of clopidogrel bisulfate and tranexamic acid on bleeding and transfusion outcomes.

Design: A multicenter randomized and blinded trial.

Setting: Seven medical centers across China.

Participants: Patients eligible for randomization were 1173 men and women aged 18 to 85 years undergoing primary and isolated on-pump CABG; 570 adults were randomized and 552 were analyzed. Patients were recruited and stratified into 3 levels according to preoperative clopidogrel exposure (clopidogrel ingestion ≤7 days, clopidogrel discontinuation >7 days, and nonexposure).

Intervention: Patients were randomized to receive tranexamic acid (10–mg/kg^{-1} bolus and 10–mg/kg^{-1}/h^{-1} maintenance dose) or placebo.

Main Outcome Measure: The primary outcomes included blood loss, major bleeding, and red blood cell (RBC) transfusion volume and exposure.

Results: As compared with controls, clopidogrel increased blood loss (mean difference [MD], 270 mL; 95% CI, 135 to 404 mL), major bleeding (risk difference [RD], 18.5; 95% CI, 7.85 to 29.2), volume of RBCs transfused (MD, 2.97 U; 95% CI, 1.51 to 4.43 U), and RBC transfusion exposure (RD, 17.9; 95% CI, 8.51 to 27.2). As compared with placebo, tranexamic acid reduced blood loss (MD, −278 mL; 95% CI, −380 mL to −176 mL), major bleeding (RD, −19.5; 95% CI, −27.7 to −11.4), volume of RBCs transfused (MD, −2.58 U; 95% CI −3.61 U to −1.55 U), and RBC transfusion exposure (RD, −18.9; 95% CI, −26.4 to −11.4). Subgroup analysis demonstrated a significantly enhanced effect of tranexamic acid especially in patients with impaired platelet function.

Conclusions and Relevance: Preoperative clopidogrel exposure increased bleeding and transfusion requirements in patients receiving on-pump CABG. Tranexamic acid reduced this risk and provided extra protection selectively in the patients with persistent clopidogrel exposure within 7 days before surgery.

Trial Registration: clinicaltrials.gov Identifier: NCT01060163.

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Current American College of Cardiology/American Heart Association guidelines recommend dual antiplatelet therapy with aspirin and either clopidogrel bisulfate or a glycoprotein IIb/IIIa inhibitor for the treatment of patients with non–ST-segment elevation acute coronary syndrome[1,2] and patients with coronary artery stents.[3,4] In the approximately 10% of this population who require coronary artery bypass grafting (CABG), potential hemorrhagic complications arising from the use of antiplatelet agents in proximity to the operation have become a major issue.[5,6] Excessive bleeding and transfusion contribute to overall morbidity and mortality in cardiac surgery, especially in CABG involving cardiopulmonary bypass.[7,8]

See Invited Critique at end of article

Fortunately, several pharmacological agents are available to reduce perioperative bleeding and transfusion, including tranexamic acid. Despite the extensive research focused on clopidogrel and tranex-

amic acid, little is known about their interaction in the balance between ischemia and hemorrhage in CABG patients,[9-11] which has generated the enthusiasm for the present study. The aim of the study was to evaluate the influence and interaction of clopidogrel and tranexamic acid on bleeding and transfusion outcomes in patients receiving primary isolated on-pump CABG.

METHODS

OVERVIEW AND PATIENTS

The study was sponsored by the National Center for Cardiovascular Diseases in China and was conducted as a randomized, blinded trial in 7 medical centers across China. Patients eligible for randomization were men and women aged 18 to 85 years undergoing primary and isolated on-pump CABG. Exclusion criteria included previous cardiac surgery, hematocrit level less than 33% (to convert to proportion of 1.0, multiply by 0.01), platelet count less than 100 000 $\times 10^3/\mu L$ (to convert to $\times 10^9$/L, multiply by 1), allergy to tranexamic acid, and being recruited in other studies. Ethics approval was obtained from each center's institutional review board and written informed consent was provided by all participants.

STUDY PROTOCOL

In the first part of the study, patients were stratified into 3 observational groups according to preoperative clopidogrel exposure. The early CABG group (group E) included patients with clopidogrel ingestion within 7 days before surgery, the late CABG group (group L) included those with clopidogrel discontinuation for more than 7 days, and the blank group (group B) included those without clopidogrel exposure. In the second part of the study, patients were randomized into 2 interventional groups in a double-blind fashion to receive tranexamic acid (group T) or placebo (group P). There were consequently 6 subgroups in the present study, early group tranexamic acid (ET), early group placebo (EP), late group tranexamic acid (LT), late group placebo (LP), blank group tranexamic acid (BT), and blank group placebo (BP).

Patient recruitment, stratification, randomization, and blinding were conducted and supervised by an independent committee. Participants were requested to conceal their clopidogrel exposure after enrollment. The randomization sequence was generated by computer in permuted blocks by a 1:1 ratio and masked in sealed, sequentially numbered, and opaque envelopes. Participants, medical staff, and the investigators were unaware of the treatment allocation until the discharge of the last patient. Study and placebo medication were prepared by the hospital pharmacy of each center. Identical syringes of 50 mL labeled with the randomization number contained transparent solution, either 50 mg/mL^{-1} of tranexamic acid or saline. The medication was pumped intravenously with a bolus of 0.2 mL/kg^{-1} after induction over 10 minutes followed by a maintenance dose of 0.2 mL/kg^{-1}/h^{-1} throughout the surgery, fulfilling the dosage regimen of tranexamic acid as a bolus of 10 mg/kg^{-1} and a maintenance dose of 10 mg/kg^{-1}/h^{-1}. Perioperative management of patients followed institutional routines by fixed medical teams in each center.

END POINTS

There were 3 coprimary end points assessed in the present analyses: postoperative blood loss, major bleeding, and red blood cell (RBC) transfusion volume and exposure. Postoperative blood loss was recorded as the total volume of chest and mediastinal tube drainage until removal. Major bleeding was evaluated according to the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events Trial[12] definition: substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 4 U of blood. Allogeneic RBCs were transfused if the hemoglobin level was less than 6 g/dL (to convert to grams per liter, multiply by 10) during cardiopulmonary bypass, less than 8 g/dL postoperatively, or less than 9 g/dL for elderly people (>70 years). Indication for fresh frozen plasma was excessive bleeding of more than 2 mL/kg^{-1} for 2 consecutive hours with a thromboelastography result implying low clotting factors (estimated percentage of lysis <15% or percentage of lysis at 30 minutes <7.5%; coagulation index <3.0; and reaction time >10 minutes). Concentrated platelets were given at the discretion of the attending physician. Surgical reexploration for hemostasis was performed when chest tube drainage exceeded 500 mL in the first hour or 1000 mL in 4 consecutive hours.

The secondary end points included major morbidity and mortality. Major morbidity was defined as permanent disability caused by stroke, postoperative myocardial infarction, renal failure, and respiratory failure. Stroke was defined as a new focal neurologic deficit lasting more than 24 hours confirmed by cerebral computed tomography and an attending neurologic consultant. Postoperative myocardial infarction was diagnosed by 2 of the following: prolonged (>20 minutes) chest pain not relieved by rest or nitrates, new pathological Q waves in more than 2 contiguous electrocardiograph leads, elevated enzyme level (creatine kinase–myoglobin test result >5% of total creatine kinase level or troponin T level ≥0.05 ng/mL [to convert to micrograms per liter, multiply by 1]), new wall motion abnormalities, or the need for revascularization. Renal failure was defined as first-time dependency on renal dialysis, an increase in postoperative creatinine level of 0.2 mg/dL or more (to convert to micromoles per liter, multiply by 88.4), or a difference of 0.07 mg/dL or more between the baseline value and the maximal postoperative plasma creatinine concentration. Respiratory failure was defined as prolonged mechanical ventilation (>48 hours), the need for continuous positive airway pressure therapy, reintubation, or tracheostomy. Furthermore, we evaluated the following adverse outcomes: seizures, sudden cardiac arrest, readmission to the intensive care unit, reoperation for surgical cause, intra-aortic balloon pumping, extracorporeal membrane oxygenation, and deep sternal wound infection. Randomized patients were followed up by means of questionnaire and telephone at 1 year after the operation.

STATISTICAL ANALYSES

Sample size was calculated based on the volume and exposure of allogeneic RBC transfusion using 2-tailed tests at an α level of .05 with 80% power. In group E, 60 patients in each interventional subgroup were sufficient to detect a difference of 1.3 U with an SD of 2.5 U or 59 patients to detect a 20% increase of the exposure if 70% of patients required transfusion. In groups L and B, 100 patients in each interventional subgroup were sufficient to detect a difference of 1.0 U with an SD of 2.5 U or 80 patients to detect a 20% increase of the exposure if 60% of patients required transfusion. Assuming a dropout rate of 10%, the total sample size estimated was 572 patients. Continuous variables were summarized by mean (standard deviation) and median with interquartile range. Categorical variables were presented by frequencies and percentages. Intention-to-treat analysis was performed among the groups, together with a per-protocol analysis. For continuous variables, differences between groups were assessed by a between-subject *t* test or analysis of

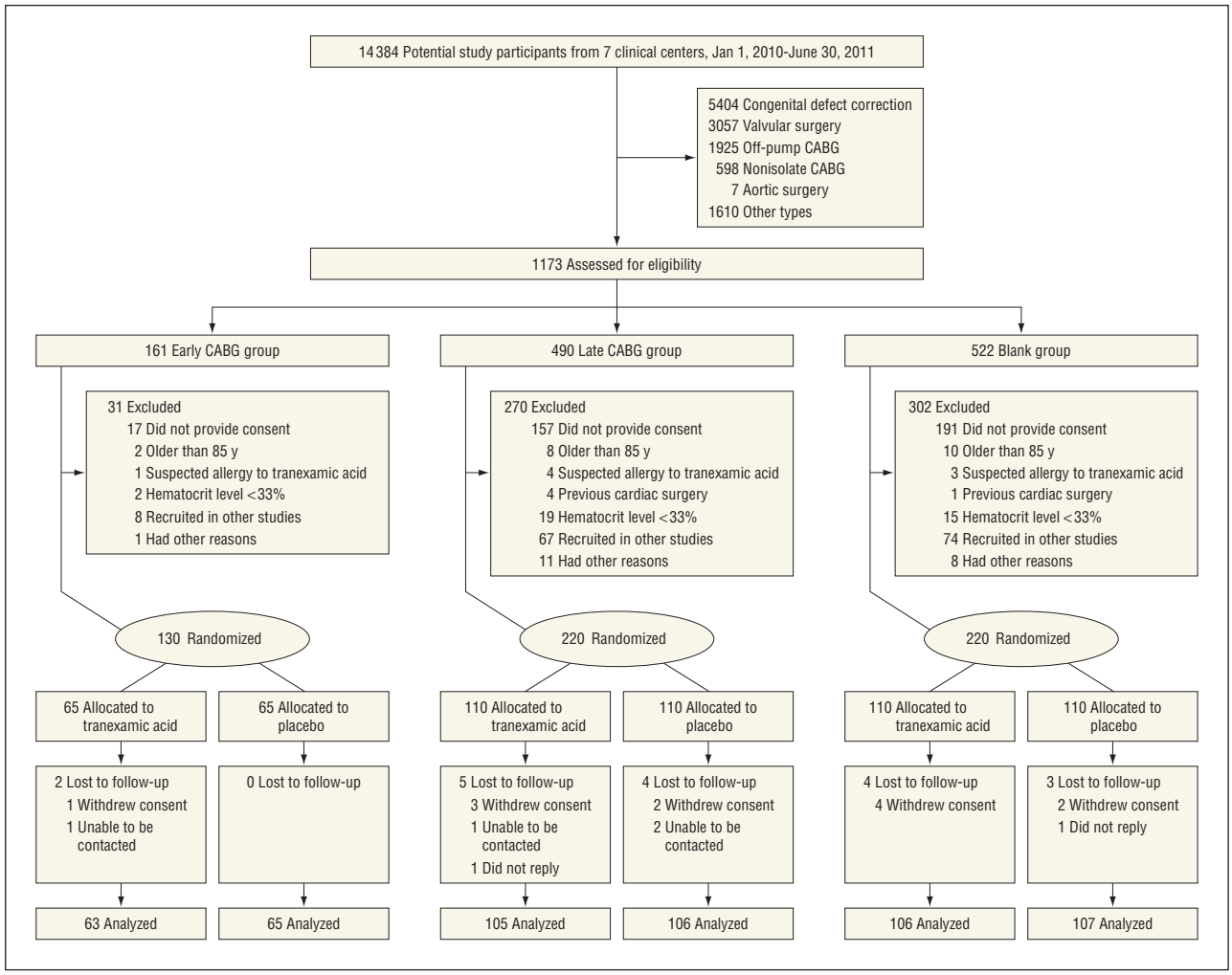

Figure 1. Consolidated Standards of Reporting Trials flowchart. Numbers for recruitment, randomization, follow-up, and analysis are presented. CABG indicates coronary artery bypass grafting.

variance for normally distributed variables and a Wilcoxon Mann-Whitney test or Kruskal-Wallis H test for nonnormally distributed variables. Mean difference and 95% confidence interval were calculated. Categorical variables were compared by a χ^2 test or Fisher exact test as appropriate. The estimated effect size and its precision were presented by the absolute risk difference and relative risk with their 95% confidence intervals. The Mantel-Haenszel method was applied in the calculation of relative risk. All tests were 2-sided and a *P* value less than .05 was considered statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc).

RESULTS

STUDY PARTICIPANTS

Of the 14 384 potential study participants from January 1, 2010, to June 30, 2011, in the 7 medical centers, 1173 patients received on-pump CABG and were assessed for eligibility. The numbers of patients randomized were 130, 220, and 220 in groups E, L, and B, respectively, of whom 128, 211, and 213 in each group were included in the final analysis (total: 274 treated with tranexamic acid and 278 treated with placebo) (**Figure 1**). The reasons for the failure of treatment or follow-up were consent withdrawal (n=12), unable to be contacted (n=4), or no reply (n=2). Baseline characteristics were well balanced among the groups (**Table 1**). The interval between the cessation of clopidogrel and the operation was well matched between the interventional subgroups in group E (mean [SD], 128.0 [57.2] vs 124.4 [56.1] hours; *P*=.35) and group L (mean [SD], 315.4 [130.3] vs 315.9 [132.9] hours; *P*=.65). All the participants received subcutaneous low-molecular-weight heparin within 24 hours preoperatively.

PERIOPERATIVE DATA

There were more urgent cases in group E (n = 14; 10.9%) than group L (n = 5; 2.37%) and group B (n = 2; 0.94%; $P < .001$) (**Table 2**). After operation, patients in group E had longer mechanical ventilation (mean [SD], 19.2 [3.90] vs 17.9 [3.76] and 17.5 [3.67] hours, respectively; $P < .001$) and intensive care unit stay (mean [SD], 50.4 [20.0] vs 43.7 [17.2] and 43.5 [16.5] hours, respectively; *P* = .005) as compared with those in groups L and

Table 1. Baseline Characteristics

	No. (%)				
	Observational Groups			Interventional Groups	
	Early	Late	Blank	TA	Placebo
Baseline demographics					
Male	102 (79.7)	153 (72.5)	169 (79.3)	210 (76.6)	214 (77.0)
Age, y, mean (SD)	59.9 (9.12)	61.5 (9.19)	58.0 (8.80)	60.0 (9.41)	59.6 (9.02)
Weight, kg, mean (SD)	72.8 (12.2)	71.8 (11.1)	73.1 (10.4)	72.5 (11.5)	72.6 (10.7)
Body mass index,[a] mean (SD)	26.4 (3.01)	26.2 (2.79)	26.3 (2.83)	26.2 (2.91)	26.3 (2.68)
Clinical history					
Hypertension	80 (62.5)	131 (62.1)	135 (63.4)	175 (63.9)	171 (61.5)
Diabetes mellitus	20 (15.6)	33 (15.6)	35 (16.4)	41 (15.0)	47 (16.9)
Hyperlipidemia	78 (60.9)	102 (48.3)	120 (56.3)	147 (53.7)	153 (55.0)
COPD	0	1 (0.47)	2 (0.94)	2 (0.73)	1 (0.36)
Previous stroke	6 (4.69)	15 (7.11)	6 (2.82)	16 (5.84)	11 (3.96)
Previous MI	29 (22.7)	47 (22.3)	47 (22.1)	65 (23.7)	58 (20.9)
Previous PCI	42 (32.8)	67 (31.8)	27 (12.7)	68 (24.8)	68 (24.5)
Current smoker	46 (35.9)	82 (38.9)	77 (36.2)	102 (37.2)	103 (37.1)
Alcohol abuse	23 (18.0)	26 (12.3)	21 (9.86)	34 (12.4)	36 (13.0)
Liver dysfunction	0	1 (0.47)	0	1 (0.36)	0
Renal dysfunction	0	0	1 (0.47)	1 (0.36)	0
Ejection fraction, %, mean (SD)	52.6 (8.41)	52.9 (8.19)	52.9 (8.48)	52.86 (8.17)	52.79 (8.52)
NYHA class					
I	28 (21.9)	55 (26.1)	52 (24.4)	64 (23.4)	71 (25.5)
II	81 (63.3)	126 (59.7)	125 (58.7)	166 (60.6)	166 (59.7)
III	18 (14.1)	28 (13.3)	32 (15.0)	42 (15.3)	36 (13.0)
IV	1 (0.78)	2 (0.95)	4 (1.88)	2 (0.73)	5 (1.80)
Euroscore II, mean (SD)	2.91 (2.23)	2.72 (1.86)	2.45 (1.61)	2.77 (1.95)	2.55 (1.78)
APACHE II, mean (SD)	4.62 (2.02)	4.84 (1.87)	4.42 (1.82)	4.58 (1.80)	4.67 (1.98)
Risk factors					
Left main disease	93 (72.7)	149 (70.6)	149 (70.0)	187 (68.3)	204 (73.4)
Three-vessel disease	119 (93.0)	190 (90.1)	194 (91.1)	252 (92.0)	251 (90.3)
Acute coronary syndrome	94 (73.4)	154 (73.0)	67 (31.5)	156 (56.9)	159 (57.2)
Ventricular aneurysm	16 (12.5)	31 (14.7)	19 (8.92)	28 (10.2)	38 (13.7)
Preoperative IABP	2 (1.56)	1 (0.47)	0	2 (0.73)	1 (0.36)
Medication					
Nitrates	125 (97.7)	210 (99.5)	211 (99.1)	272 (99.3)	274 (98.6)
β-Blocker	110 (85.9)	184 (87.2)	185 (86.9)	238 (86.9)	241 (86.7)
ACEI	49 (38.3)	79 (37.4)	84 (39.4)	106 (38.7)	106 (38.1)
Diuretics	73 (57.0)	114 (54.0)	122 (57.3)	154 (56.2)	155 (55.8)
Calcium channel blockers	55 (43.0)	75 (35.6)	74 (34.7)	112 (40.9)	92 (33.1)
Statins	67 (52.3)	94 (44.6)	112 (52.6)	137 (50.0)	136 (48.9)
LMWH <24 h preoperatively	128 (100.0)	211 (100.0)	213 (100.0)	274 (100.0)	278 (100.0)
Clopidogrel[b] free, h, mean (SD)	126.2 (56.4)	315.7 (131.2)	. . .	245.4 (142.6)	243.2 (144.0)

Abbreviations: ACEI, angiotension-converting enzyme inhibitors; APACHE, acute physiology and chronic health evaluation; COPD, chronic obstructive pulmonary disease; IABP, intra-aortic balloon pumping; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TA, tranexamic acid.

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

[b] Clopidogrel bisulfate.

B. Tranexamic acid shortened time to chest tube removal (mean [SD], 52.1 [13.7] vs 54.9 [15.3] hours, respectively; $P = .04$) and postoperative length of stay (mean [SD], 7.85 [1.72] vs 8.28 [2.28] days, respectively; $P = .03$) as compared with placebo.

BLEEDING AND TRANSFUSION OUTCOMES

Analysis of Clopidogrel

Analysis among the 3 observational groups demonstrated a significant increase in bleeding and transfusion requirements due to clopidogrel exposure. In groups E, L, and B, the mean (SD) total blood loss was 1262 (791) mL, 1107 (627) mL, and 993 (474) mL ($P = .01$); the incidence of major bleeding was 64.1%, 55.5%, and 45.5% ($P = .003$); the mean (SD) volume of RBCs transfused was 7.12 (9.14) U, 5.16 (5.40) U, and 4.15 (4.51) U ($P = .002$), and the exposure to RBC transfusion was 81.3%, 70.1%, and 63.4% ($P = .002$), respectively. Between-group analysis is shown in **Table 3** and **Figure 2**.

Analysis of Tranexamic Acid

Analysis between the 2 interventional groups presented an obvious reduction in bleeding and transfusion requirements due to tranexamic acid (Table 3 and Figure 2). As compared with placebo, tranexamic acid reduced blood loss (mean [SD], 959 [515] vs 1237 [691] mL; mean difference [MD], −278 mL; 95% CI, −380 to −176 mL; $P < .001$), major bleeding (43.8% vs 63.3%; absolute risk difference [RD] in percentage points, −19.5; 95% CI, −27.7 to −11.4; relative risk [RR], 0.69; 95% CI, 0.59 to 0.81; $P < .001$), volume of RBCs transfused (mean [SD], 3.93 [4.66] vs 6.51 [7.33] U; MD, −2.58 U; 95% CI, −3.61 to −1.55 U; $P < .001$), and RBC transfusion

Table 2. Perioperative Data

	No. (%)						
	Observational Groups				Interventional Groups		
	Early	Late	Blank	*P* Value	TA	Placebo	*P* Value
Operative data							
Urgent case	14 (10.9)	5 (2.37)	2 (0.94)	<.001	11 (4.01)	10 (3.60)	.80
Left internal mammary artery	125 (97.7)	206 (97.6)	208 (97.7)	.99	268 (97.8)	271 (97.5)	.80
Distal anastomoses							
1	4 (3.13)	9 (4.27)	6 (2.82)	.70	8 (2.92)	11 (3.96)	.50
2	17 (13.3)	37 (17.5)	31 (14.6)	.52	44 (16.1)	41 (14.8)	.67
3	72 (56.3)	113 (53.6)	121 (56.8)	.78	156 (56.9)	150 (54.0)	.48
4	29 (22.7)	44 (20.9)	43 (20.2)	.86	54 (19.7)	62 (22.3)	.45
5	6 (4.69)	8 (3.79)	12 (5.63)	.67	12 (4.38)	14 (5.04)	.72
Total dose of heparin, IU/kg, mean (SD)	491 (44.5)	486 (25.6)	482 (22.0)	.16	484 (25.3)	487 (34.1)	.49
Total dose of protamine, mg, mean (SD)	338 (104)	343 (97.0)	328 (75.1)	.32	339 (93.7)	333 (88.8)	.58
Heparin neutralization ratio, mean (SD)[a]	0.94 (0.22)	0.99 (0.26)	0.94 (0.19)	.07	0.97 (0.23)	0.95 (0.22)	.27
Aortic cross-clamp time, min, mean (SD)	94.1 (30.1)	94.4 (24.6)	93.6 (19.6)	.33	94.1 (20.7)	94.0 (27.2)	.15
CPB time, min, mean (SD)	134 (45.6)	138 (35.9)	136 (28.0)	.08	136 (31.2)	136 (39.7)	.22
Chest closure time, min, mean (SD)	101 (37.1)	99.3 (39.2)	94.6 (26.3)	.46	94.6 (28.7)	101 (38.8)	.12
Operation time, min, mean (SD)	334 (96.9)	322 (79.1)	311 (55.4)	.28	312 (57.3)	329 (90.4)	.07
Inotropic support	126 (98.4)	210 (99.5)	209 (98.1)	.41	269 (98.2)	276 (99.3)	.25
Operative mortality	0	0	0	.99	0	0	.99
Postoperative time course, mean (SD)							
Mechanical ventilation, h	19.2 (3.90)	17.9 (3.76)	17.5 (3.67)	<.001	18.3 (3.71)	17.8 (3.91)	.10
ICU stay, h	50.4 (20.0)	43.7 (17.2)	43.5 (16.5)	.005	45.8 (17.9)	44.5 (17.8)	.33
Chest tube removal, h	56.4 (15.4)	53.1 (15.0)	52.2 (13.6)	.07	52.1 (13.7)	54.9 (15.3)	.04
Hospital length of stay, d	8.47 (2.50)	7.94 (1.82)	7.95 (1.91)	.09	7.85 (1.72)	8.28 (2.28)	.03

Abbreviations: CPB, cardiopulmonary bypass; ICU, intensive care unit; TA, tranexamic acid.
[a]A 1:1 neutralization ratio means 1 mg of protamine for 100 IU of heparin.

exposure (60.6% vs 79.5%; RD, −18.9; 95% CI, −26.4 to −11.4; RR, 0.76; 95% CI, 0.68 to 0.85; $P < .001$). The overall incidence of reoperation for bleeding was cut down from 6.83% to 1.82% (RD, −5.01; 95% CI, −8.37 to −1.65; RR, 0.27; 95% CI, 0.10 to 0.71; $P = .004$).

Analysis of Subgroups

Analysis within the 3 observational groups (Table 3 andFigure 2) suggested the stratified action of tranexamic acid in the context of different preoperative clopidogrel exposures, which was the most effective in group E and the least effective in group L. Between the 2 interventional subgroups in groups E, L, and B, the mean difference in blood loss was −366 mL (95% CI, −636 to −95.8 mL), −170 mL (95% CI, −339 to −1.05 mL), and −330 mL (95% CI, −450 to −210 mL); the absolute RD for major bleeding was −26.1 (95% CI, −42.2 to −10.1), −13.7 (95% CI, −27.0 to −0.41), and −21.2 (95% CI, −34.2 to −8.10); the MD for volume of RBCs transfused was −4.07 U (95% CI, −7.20 to −0.94 U), −1.76 U (95% CI, −3.21 to −0.31 U), and −2.48 U (95% CI, −3.65 to −1.30 U); and the RD for RBC transfusion exposure was −16.2 (95% CI, −29.5 to −2.91), −12.6 (95% CI, −24.8 to −0.37), and −26.6 (95% CI, −39.1 to −14.2), respectively. Furthermore, tranexamic acid sharply reduced the incidence of reoperation for bleeding in group E (1.59% vs 9.23%; RD, −7.64; 95% CI, −15.3 to 0.04; RR, 0.17; 95% CI, 0.02 to 1.39; $P = .06$) and group B (0.94% vs 6.54%; RD, −5.60; 95% CI, −10.6 to −0.57; RR, 0.14; 95% CI, 0.02 to 1.15; $P = .03$).

Analysis within the placebo group (Table 3 andFigure 2) demonstrated the negative impact of clopidogrel exposure within 7 days before surgery and the advantage of a washout period. As compared with group L (subgroup LP), clopidogrel exposure within 7 days before surgery (subgroup EP) increased blood loss (MD, 251 mL; 95% CI, 18.3 to 484 mL; $P = .04$), major bleeding (RD, 14.7; 95% CI, 0.87 to 28.5; RR, 1.24; 95% CI, 1.01 to 1.51; $P = .05$), volume of RBCs transfused (MD, 3.09 U; 95% CI, 0.50 to 5.67 U; $P = .03$), and RBC transfusion exposure (RD, 12.8; 95% CI, 1.77 to 23.9; RR, 1.17; 95% CI, 1.02 to 1.33; $P = .04$). As compared with group B (subgroup BP), clopidogrel exposure within 7 days before surgery (subgroup EP) increased blood loss (MD, 285 mL; 95% CI, 67.0 to 504 mL; $P = .04$), major bleeding (RD, 20.9; 95% CI, 6.94 to 34.8; RR, 1.37; 95% CI, 1.11 to 1.70; $P = .006$), volume of RBCs transfused (MD, 3.74 U; 95% CI, 1.31 to 6.17 U; $P = .007$), and RBC transfusion exposure (RD, 12.6; 95% CI, 1.59 to 23.6; RR, 1.16; 95% CI, 1.02 to 1.33; $P = .04$). Comparison between subgroup LP and subgroup BP revealed similar bleeding and transfusion outcomes and confirmed the advantage of a 7-day washout period.

Analysis within the tranexamic acid group (Table 3 and Figure 2) demonstrated a modified impact of clopidogrel exposure on the outcomes in the context of an antifibrinolytic agent. The interval between the cessation of clopidogrel and the operation was no longer crucial. Comparison between subgroup ET and subgroup LT proved the ineffectiveness of a 7-day waiting period, with similar results in blood loss (MD, 55.1 mL; 95% CI, −136 to 246 mL; $P = .73$), major bleeding (RD, 2.22; 95% CI, −13.4 to 17.8; RR, 1.05; 95% CI, 0.76 to 1.43; $P = .78$), volume of RBCs transfused (MD, 0.78 U; 95% CI, −0.84

Table 3. Bleeding and Transfusion Outcomes

	Bleeding			RBC Transfusion		Plasma Transfusion	
	Blood Loss, mL, Mean (SD)	No. (%)					
		Major Bleeding	Reoperation	Volume, U, Mean (SD)	Exposure, No. (%)	Volume, U, Mean (SD)	Exposure, No. (%)
Analysis of Clopidogrel[a]							
Group							
Early	1262 (791)	82 (64.1)	7 (5.47)	7.12 (9.14)	104 (81.3)	2.69 (3.94)	91 (71.1)
Late	1107 (627)	117 (55.5)	9 (4.27)	5.16 (5.40)	148 (70.1)	2.21 (3.02)	131 (62.1)
Blank	993 (474)	97 (45.5)	8 (3.76)	4.15 (4.51)	135 (63.4)	1.65 (2.20)	112 (52.6)
P value among groups	.01	.003	.75	.002	.002	.002	.003
Between-group analysis							
Early vs late							
P value	.10	.12	.61	.05	.02	.08	.09
RD or MD	156	8.61	1.20	1.96	11.1	0.48	9.01
(95% CI)	(2.87 to 308)	(−2.07 to 19.3)	(−3.59 to 5.99)	(0.41 to 3.51)	(1.95 to 20.2)	(−0.27 to 1.23)	(−1.22 to 19.2)
RR (95% CI)	. . .	1.16 (0.97 to 1.38)	1.28 (0.49 to 3.36)	. . .	1.16 (1.03 to 1.31)	. . .	1.14 (0.98 to 1.33)
Early vs blank							
P value	.002	<.001	.46	<.001	<.001	<.001	<.001
RD or MD	270	18.5	1.71	2.97	17.9	1.04	18.5
(95% CI)	(135 to 404)	(7.85 to 29.2)	(−2.98 to 6.41)	(1.51 to 4.43)	(8.51 to 27.2)	(0.39 to 1.70)	(8.18 to 28.8)
RR (95% CI)	. . .	1.41 (1.16 to 1.71)	1.46 (0.54 to 3.92)	. . .	1.28 (1.12 to 1.46)	. . .	1.35 (1.14 to 1.60)
Late vs blank							
P value	.13	.04	.79	.08	.14	.05	.05
RD or MD	114	9.91	0.51	1.01	6.76	0.56	9.50
(95% CI)	(8.05 to 220)	(0.44 to 19.4)	(−3.23 to 4.24)	(0.06 to 1.96)	(−2.18 to 15.7)	(0.06 to 1.07)	(0.13 to 18.9)
RR (95% CI)	. . .	1.22 (1.00 to 1.47)	1.14 (0.45 to 2.89)	. . .	1.11 (0.97 to 1.27)	. . .	1.18 (1.00 to 1.39)
Analysis of TA							
Group							
TA	959 (515)	120 (43.8)	5 (1.82)	3.93 (4.66)	166 (60.6)	1.43 (2.02)	132 (48.2)
Placebo	1237 (691)	176 (63.3)	19 (6.83)	6.51 (7.33)	221 (79.5)	2.77 (3.62)	202 (72.7)
Between-group analysis							
P value	<.001	<.001	.004	<.001	<.001	<.001	<.001
RD or MD	−278	−19.5	−5.01	−2.58	−18.9	−1.34	−24.5
(95% CI)	(−380 to −176)	(−27.7 to −11.4)	(−8.37 to −1.65)	(−3.61 to −1.55)	(−26.4 to −11.4)	(−1.83 to −0.85)	(−32.4 to −16.6)
RR (95% CI)	. . .	0.69 (0.59 to 0.81)	0.27 (0.10 to 0.71)	. . .	0.76 (0.68 to 0.85)	. . .	0.66 (0.58 to 0.76)
Analysis of Subgroups							
Subgroup							
ET	1076 (632)	32 (50.8)	1 (1.59)	5.06 (6.01)	46 (73.0)	1.68 (1.70)	36 (57.1)
EP	1442 (887)	50 (76.9)	6 (9.23)	9.12 (11.1)	58 (89.2)	3.66 (5.11)	55 (84.6)
LT	1022 (593)	51 (48.6)	3 (2.86)	4.28 (4.53)	67 (63.8)	1.78 (2.56)	56 (53.3)
LP	1191 (650)	66 (62.3)	6 (5.66)	6.04 (6.05)	81 (76.4)	2.63 (3.37)	75 (70.8)
BT	827 (276)	37 (34.9)	1 (0.94)	2.91 (3.61)	53 (50.0)	0.92 (1.39)	40 (37.7)
BP	1157 (565)	60 (56.1)	7 (6.54)	5.38 (4.97)	82 (76.6)	2.36 (2.59)	72 (67.3)
Analysis Within the 3 Observational Groups							
Subgroup ET vs EP							
P value	.003	.002	.06	.001	.02	.002	<.001
RD or MD	−366	−26.1	−7.64	−4.07	−16.2	−1.98	−27.5
(95% CI)	(−636 to −95.8)	(−42.2 to −10.1)	(−15.3 to 0.04)	(−7.20 to −0.94)	(−29.5 to −2.91)	(−3.32 to −0.64)	(−42.5 to −12.4)
RR (95% CI)	. . .	0.66 (0.50 to 0.87)	0.17 (0.02 to 1.39)	. . .	0.82 (0.69 to 0.97)	. . .	0.68 (0.53 to 0.86)
Subgroup LT vs LP							
P value	.02	.05	.31	.03	.05	.01	.009
RD or MD	−170	−13.7	−2.80	−1.76	−12.6	−0.85	−17.4
(95% CI)	(−339 to −1.05)	(−27.0 to −0.41)	(−8.24 to 2.63)	(−3.21 to −0.31)	(−24.8 to −0.37)	(−1.66 to −0.04)	(−30.3 to −4.54)
RR (95% CI)	. . .	0.78 (0.61 to 1.00)	0.50 (0.13 to 1.97)	. . .	0.84 (0.70 to 1.00)	. . .	0.75 (0.61 to 0.94)
Subgroup BT vs BP							
P value	<.001	.002	.03	<.001	<.001	<.001	<.001
RD or MD	−330	−21.2	−5.60	−2.48	−26.6	−1.44	−29.6
(95% CI)	(−450 to −210)	(−34.2 to −8.10)	(−10.6 to −0.57)	(−3.65 to −1.30)	(−39.1 to −14.2)	(−2.00 to −0.87)	(−42.4 to −16.7)
RR (95% CI)	. . .	0.62 (0.46 to 0.85)	0.14 (0.02 to 1.15)	. . .	0.65 (0.53 to 0.81)	. . .	0.56 (0.42 to 0.74)

(continued)

Table 3. Bleeding and Transfusion Outcomes (continued)

	Bleeding			RBC Transfusion		Plasma Transfusion	
	Blood Loss, mL, Mean (SD)	No. (%)		Volume, U, Mean (SD)	Exposure, No. (%)	Volume, U, Mean (SD)	Exposure, No. (%)
		Major Bleeding	Reoperation				
Analysis Within the Placebo Group							
Subgroup EP vs LP							
P value	.04	.05	.38	.03	.04	.06	.04
RD or MD	251	14.7	3.57	3.09	12.8	1.03	13.9
(95% CI)	(18.3 to 484)	(0.87 to 28.5)	(−4.73 to 11.9)	(0.50 to 5.67)	(1.77 to 23.9)	(−0.25 to 2.31)	(1.53 to 26.2)
RR (95% CI)	. . .	1.24 (1.01 to 1.51)	1.63 (0.55 to 4.84)	. . .	1.17 (1.02 to 1.33)	. . .	1.20 (1.02 to 1.40)
Subgroup EP vs BP							
P value	.04	.006	.52	.007	.04	.05	.01
RD or MD	285	20.9	2.69	3.74	12.6	1.30	17.3
(95% CI)	(67.0 to 504)	(6.94 to 34.8)	(−5.77 to 11.1)	(1.31 to 6.17)	(1.59 to 23.6)	(0.14 to 2.46)	(4.84 to 29.8)
RR (95% CI)	. . .	1.37 (1.11 to 1.70)	1.41 (0.50 to 4.02)	. . .	1.16 (1.02 to 1.33)	. . .	1.26 (1.06 to 1.49)
Subgroup LP vs BP							
P value	.95	.36	.79	.66	.97	.90	.58
RD or MD	34.3	6.19	−0.88	0.65	−0.22	0.27	3.46
(95% CI)	(−130 to 199)	(−6.99 to 19.4)	(−7.31 to 5.55)	(−0.84 to 2.15)	(−11.6 to 11.2)	(−0.54 to 1.08)	(−8.95 to 15.9)
RR (95% CI)	. . .	1.11 (0.89 to 1.39)	0.87 (0.30 to 2.49)	. . .	1.00 (0.86 to 1.16)	. . .	1.05 (0.88 to 1.26)
Analysis Within the TA Group							
Subgroup ET vs LT							
P value	.73	.78	.60	.55	.22	.55	.63
RD or MD	55.1	2.22	−1.27	0.78	9.21	−0.10	3.81
(95% CI)	(−136 to 246)	(−13.4 to 17.8)	(−5.71 to 3.17)	(−0.84 to 2.39)	(−5.10 to 23.5)	(−0.82 to 0.62)	(−11.7 to 19.3)
RR (95% CI)	. . .	1.05 (0.76 to 1.43)	0.56 (0.06 to 5.23)	. . .	1.14 (0.93 to 1.41)	. . .	1.07 (0.81 to 1.42)
Subgroup ET vs BT							
P value	.05	.04	.71	.008	.003	.003	.01
RD or MD	250	15.9	0.64	2.15	23.0	0.76	19.4
(95% CI)	(111 to 389)	(0.57 to 31.2)	(−2.95 to 4.24)	(0.69 to 3.61)	(8.50 to 37.5)	(0.28 to 1.23)	(4.09 to 34.7)
RR (95% CI)	. . .	1.46 (1.02 to 2.08)	1.68 (0.11 to 26.4)	. . .	1.46 (1.15 to 1.86)	. . .	1.51 (1.09 to 2.10)
Subgroup LT vs BT							
P value	.04	.04	.31	.03	.04	.009	.02
RD or MD	194	13.7	1.91	1.37	13.8	0.87	15.6
(95% CI)	(69.2 to 320)	(0.49 to 26.9)	(−1.77 to 5.59)	(0.26 to 2.48)	(0.58 to 27.0)	(0.30 to 1.42)	(2.32 to 28.9)
RR (95% CI)	. . .	1.39 (1.00 to 1.92)	3.03 (0.32 to 28.7)	. . .	1.28 (1.00 to 1.62)	. . .	1.41 (1.04 to 1.91)

Abbreviations: BP, blank group placebo; BT, blank group tranexamic acid; EP, early group placebo; ET, early group tranexamic acid; LP, late group placebo; LT, late group tranexamic acid; MD, mean difference; RBC, red blood cell; RD, risk difference (absolute percentage points); RR, relative risk; TA, tranexamic acid.
[a] Clopidogrel bisulfate.

to 2.39 U; *P* = .55), and RBC transfusion exposure (RD, 9.21; 95% CI, −5.10 to 23.5; RR, 1.14; 95% CI, 0.93 to 1.41; *P* = .22). As compared with patients in group B (subgroup BT), clopidogrel recipients with (subgroup LT) or without (subgroup ET) a washing-out period more than 7 days demonstrated similar bleeding and transfusion results.

MORTALITY, MORBIDITY, AND FOLLOW-UP

In-hospital mortality and morbidity were similar among the groups (**Table 4**). Three patients (2.34%) in group E, 1 patient (0.47%) in group L, and 1 patient (0.47%) in group B died (*P* = .15) of postoperative myocardial infarction (2 cases), cardiac failure (1 case), and multiple organ dysfunction syndrome (2 cases). Among them, 2 patients (0.73%) were treated with tranexamic acid and 3 patients (1.08%) were treated with placebo (*P* = .67). As for adverse outcomes, similar results were found among the groups except for a higher incidence of postoperative sudden cardiac arrest in group B (n = 4; 1.88%) as compared with none in the other 2 observational groups (*P* = .04). Follow-up at 1 year was achieved in 552 randomized patients (96.8%). Mortality and morbidity at 1-year follow-up were comparable among the groups though the incidence of myocardial infarction and renal failure was slightly higher in group E than in the other 2 observational groups.

COMMENT

The main findings of the present study were that (1) preoperative clopidogrel exposure increased bleeding and transfusion requirements in patients receiving on-pump CABG, (2) tranexamic acid reduced this risk, and (3) tranexamic acid provided extra protection in patients with impaired platelet function. Overall analysis revealed the benefit of tranexamic acid regardless of preoperative clopidogrel exposure and its cessation time. There was a significantly enhanced effect of tranexamic acid selectively in the patients with persistent clopidogrel exposure within 7 days before surgery.

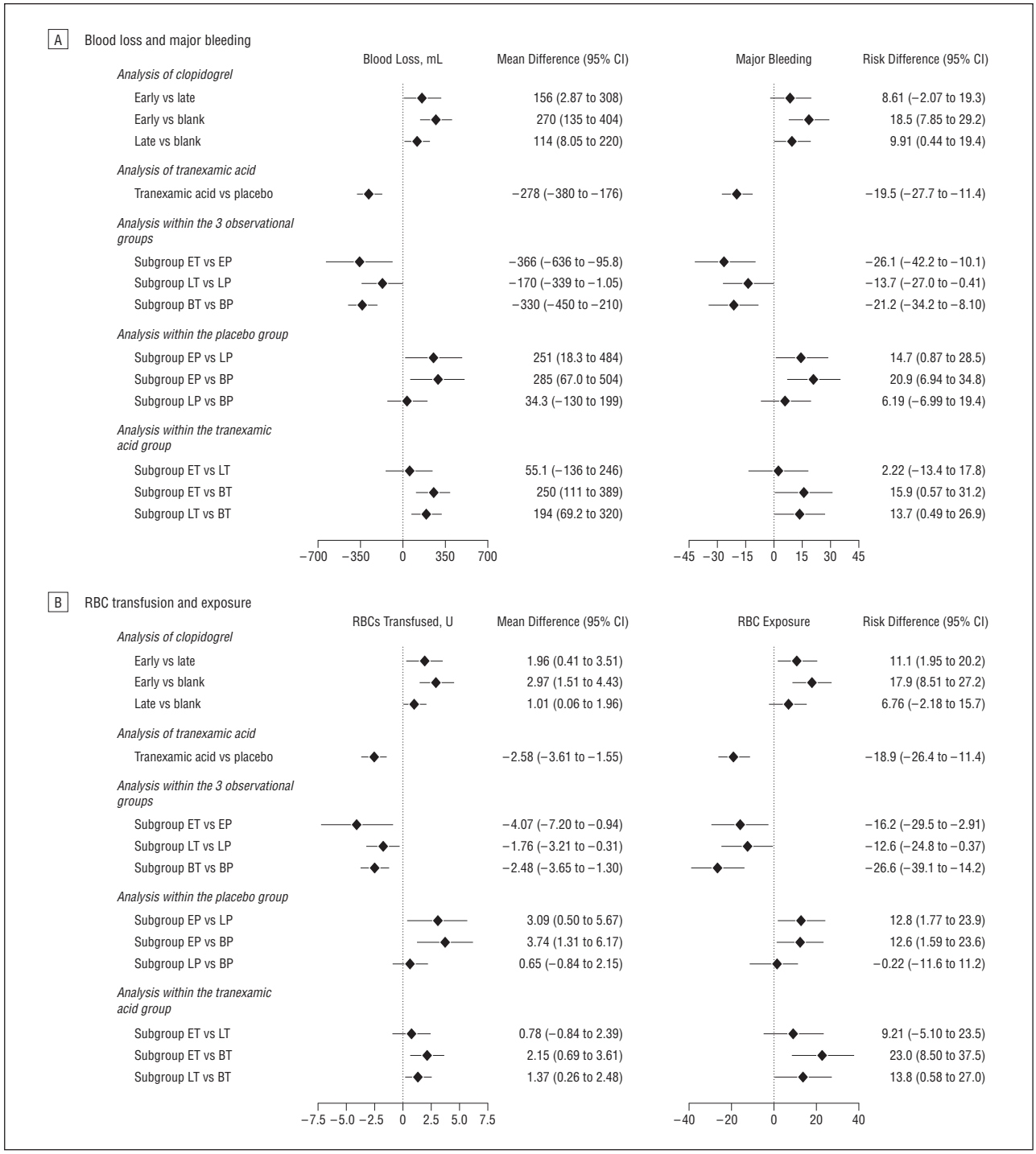

Figure 2. Estimated effect size and its precision of the bleeding and transfusion outcomes. The forest plot shows the mean difference and the absolute risk difference in percentage points (and their 95% confidence intervals) of the bleeding outcomes (A) and the transfusion outcomes (B). Preoperative clopidogrel bisulfate exposure deteriorated bleeding and transfusion outcomes and tranexamic acid provided protection against the risk. Analysis within the 3 observational groups suggested stratified efficacy of tranexamic acid, which was the most effective in the early group and the least effective in the late group. Analysis within the placebo group confirmed the advantage of a 7-day washout period on the outcomes. Analysis within the tranexamic acid group demonstrated that the interval between the cessation and the operation was no longer crucial with the presence of antifibrinolytics. BP indicates blank group placebo; BT, blank group tranexamic acid; EP, early group placebo; ET, early group tranexamic acid; LP, late group placebo; and LT, late group tranexamic acid.

This extra protection against impaired platelet function improved the bleeding and transfusion outcomes in patients with clopidogrel persistence (group ET) to a comparable level as that in patients with clopidogrel cessation (group LT). In light of the current study, the interval between the cessation and the operation is no longer a major determinant of the bleeding and transfusion outcomes in these patients and routine cessation of clopidogrel may not be necessary with the presence of antifibrinolytics, especially in urgent cases and patients with high thrombotic risk.

Despite the limited data, there has been some pilot research focused on the impact of tranexamic acid on plate-

Table 4. Mortality, Morbidity, and Follow-up

	No. (%)						
	Observational Groups				Interventional Groups		
	Early	Late	Blank	*P* Value	TA	Placebo	*P* Value
Mortality at discharge	3 (2.34)	1 (0.47)	1 (0.47)	.15	2 (0.73)	3 (1.08)	.67
Morbidity at discharge							
Stroke	1 (0.78)	1 (0.47)	0	.48	1 (0.36)	1 (0.36)	.99
Postoperative MI	2 (1.56)	1 (0.47)	1 (0.47)	.44	1 (0.36)	3 (1.08)	.32
Renal failure	2 (1.56)	0	1 (0.47)	.16	1 (0.36)	2 (0.72)	.57
Respiratory failure	5 (3.91)	3 (1.42)	1 (0.47)	.05	5 (1.82)	4 (1.44)	.72
Inotropic medication >30 min	125 (97.70)	205 (97.20)	203 (95.30)	.43	266 (97.10)	267 (96.00)	.50
Adverse outcomes perioperatively							
Seizure	2 (1.56)	3 (1.42)	1 (0.47)	.54	4 (1.46)	2 (0.72)	.40
Sudden cardiac arrest	0	0	4 (1.88)	.04	1 (0.36)	3 (1.00)	.32
Readmission to ICU	1 (0.78)	2 (0.95)	3 (1.41)	.84	4 (1.46)	2 (0.72)	.40
Reoperation for surgical cause	2 (1.56)	0	1 (0.47)	.16	2 (0.73)	1 (0.36)	.55
IABP	9 (7.03)	5 (2.37)	7 (3.29)	.08	6 (2.19)	15 (5.40)	.05
ECMO	1 (0.78)	0	0	.19	0	1 (0.36)	.32
Deep sternal infection	1 (0.78)	0	0	.19	1 (0.36)	0	.31
Mortality at 1-y follow-up	4 (3.13)	3 (1.42)	3 (1.41)	.45	6 (2.19)	4 (1.44)	.51
Morbidity at 1-y follow-up							
Stroke	1 (0.78)	2 (0.95)	0	.38	2 (0.73)	1 (0.36)	.55
Myocardial infarction	4 (3.13)	2 (0.95)	3 (1.41)	.29	3 (1.09)	6 (2.16)	.32
Renal failure	3 (2.34)	1 (0.47)	1 (0.47)	.15	3 (1.09)	2 (0.72)	.64

Abbreviations: ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pumping; ICU, intensive care unit; MI, myocardial infarction; TA, tranexamic acid.

let function.[11,13-16] As early as 1999, Mezzano and colleagues[14] found that the inhibition of plasmin activity with tranexamic acid shortened bleeding time and improved platelet function in patients with chronic renal failure. In a study published in 2005,[15] tranexamic acid improved platelet dysfunction in patients with substantially prolonged in vitro closure time. In 2011, Weber and colleagues[16] found that tranexamic acid significantly increased both arachidonic acid–induced and adenosine diphosphate–induced platelet aggregation selectively in the patients with persistent dual antiplatelet therapy until the day before surgery.

On the other hand, plasmin is a key substance in the effect of tranexamic acid on platelet function. Plasmin activates the complement cascade and generates C3a and C5a,[17] which impair platelet function.[18] Also, plasmin induces proteolytic degradation and redistribution of platelet Ib and IIb/IIIa receptors and thereby reduces platelet adhesion and aggregation.[19,20] Tranexamic acid reduces plasmin concentration by blocking the lysine-binding sites of plasminogen, preventing the binding of plasminogen to fibrin and the conversion of plasminogen to plasmin. Thus, tranexamic acid may preserve platelet function by a reduction of plasmin-induced platelet inhibition.

There is significant diversity in the dose regimens of tranexamic acid between trials. We followed the regimen of a loading dose of 10 mg/kg^{-1} over 10 minutes and a maintenance dose of 10 mg/kg^{-1}/h^{-1} until the end of the operation, similar to "recommendation 1" suggested by Dowd et al,[21] to achieve the lowest efficacious blood concentration of 334 μmol/L^{-1} reported by Horrow et al.[22] A recent report released by the Cochrane Collaboration including 252 randomized clinical trials and 25 000 participants demonstrated that tranexamic acid did not increase the risk of myocardial infarction, stroke, renal dysfunction, or overall mortality.[23] At 1-year follow-up in the current study, the mortality, morbidity, and adverse outcomes were fairly balanced among the groups. These results should be interpreted prudentially because of the relatively small sample size and the short follow-up period in the current study.

There was full randomization in the allocation of tranexamic acid and placebo but not of preoperative clopidogrel. There might be criticism on the possible bias in the selection of patients. However, full randomization of preoperative clopidogrel was unethical and impractical. Participants in the present study were consecutively recruited with definite inclusion and exclusion criteria in specific clinical sites and time. Also, identical demographic values and strict double-blinding could attenuate potential bias.

In summary, preoperative clopidogrel exposure increased bleeding and transfusion requirements in patients receiving on-pump CABG. Tranexamic acid reduced this risk and provided extra protection selectively in the patients with persistent clopidogrel exposure within 7 days before surgery.

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