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 bolus and 10–mg/kg/h 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.


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 and patients with coronary artery stents. 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. Excessive bleeding and transfusion contribute to overall morbidity and mortality in cardiac surgery, especially in CABG involving cardiopulmonary bypass.

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 pa-
tients.\textsuperscript{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.

\section*{METHODS}

\subsection*{OVERVIEW AND PATIENTS}

The study was sponsored by the National Center for Cardio-
vascular Diseases in China and was conducted as a random-
ized, 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. Ex-
clusion 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 $\times 10^9$/mL (to con-
vert 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 in-
formed consent was provided by all participants.

\subsection*{STUDY PROTOCOL}

In the first part of the study, patients were stratified into 3 ob-
servational groups according to preoperative clopidogrel ex-
posure. 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 discontinu-
ation for more than 7 days, and the blank group (group B) in-
cluded 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 sub-
groups 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 blind-
ing were conducted and supervised by an independent com-
mittee. Participants were requested to conceal their clopidoo-
grel 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 en-
mvelopes. 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 30
mL labeled with the randomization number contained trans-
parent solution, either 50 mg/mL$^{-1}$ of tranexamic acid or sa-
line. 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$^{-1}$. Peri-
operative management of patients followed institutional rou-
tines by fixed medical teams in each center.

\section*{END POINTS}

There were 3 coprimary end points assessed in the present analy-
ses: 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 ac-
cording to the Clopidogrel in Unstable Angina to Prevent Re-
current Ischemic Events Trial\textsuperscript{12} definition: substantially dis-
abling 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 postopera-
tively, or less than 9 g/dL for elderly people (\textgreater{}70 years).
Indi-
fication for fresh frozen plasma was excessive bleeding of more
than 2 mL/kg$^{-1}$ for 2 consecutive hours with a thromboclas-
tography result implying low clotting factors (estimated per-
centage of lysis \textless{}15\% or percentage of lysis at 30 minutes
\textless{}7.5\%; coagulation index \textless{}3.0; and reaction time \textgreater{}10 min-
te). 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 mor-
tality. Major morbidity was defined as permanent disability
caused by stroke, postoperative myocardial infarction, renal fail-
ure, and respiratory failure. Stroke was defined as a new focal
neurologic deficit lasting more than 24 hours confirmed by ce-
rebral computed tomography and an attending neurologic con-
sultant. Postoperative myocardial infarction was diagnosed by
2 of the following: prolonged (>20 minutes) chest pain not
relieved by rest or nitrates, new pathologic Q waves in more
than 2 contiguous electrocardiograph leads, elevated enzyme
level (creatinine kinase–myoglobin test result \textgreater{}5\% of total cre-
tatine kinase level or troponin T level \textgreater{}0.05 ng/mL [to convert
to micrograms per liter, multiply by 1]), new wall motion ab-
normalities, 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 con-
vert to micromoles per liter, multiply by 88.4), or a difference
in postoperative creatinine level of 0.2 mg/dL or more between the baseline value and the maxi-
mal postoperative plasma creatinine concentration. Respira-
tory failure was defined as prolonged mechanical ventilation
(\textgreater{}48 hours), the need for continuous positive airway pres-
ture therapy, reintubation, or tracheostomy. Furthermore, we
evaluated the following adverse outcomes: seizures, sudden car-
diac arrest, readmission to the intensive care unit, reoperation
for surgical cause, intra-aortic balloon pumping, extracorpo-
real membrane oxygenation, and deep sternal wound infec-
tion. Randomized patients were followed up by means of ques-
tionnaire and telephone at 1 year after the operation.

\section*{STATISTICAL ANALYSES}

Sample size was calculated based on the volume and exposure
of allogeneic RBC transfusion using 2-tailed tests at an $\alpha$ level
of .05 with 80\% power. In group E, 60 patients in each inter-
ventional 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 suf-
ficient 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 pa-
tients 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 pre-
sented by frequencies and percentages. Intention-to-treat analy-
sis 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
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 χ² 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 14384 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
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 45.3% (\( P = .003 \)); 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.

#### 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, −2.38 U; 93% CI, −3.61 to −1.55 U; \( P < .001 \)), and RBC transfusion...
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 and Figure 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 −10.2 (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 (1.99% 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 and Figure 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, 16.2 to 542; 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 to 2.62 U; P = .42), and RBC transfusion exposure (RD, 2.55 U; 95% CI, −9.16 to 14.24 U; P = .61)
## Table 3. Bleeding and Transfusion Outcomes

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<th>Major bleeding</th>
<th>Reoperation</th>
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<th>Analysis of Clopidogrel&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>P value (95% CI)</td>
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<td>82 (64.1)</td>
<td>5 (4.7)</td>
<td>7.12</td>
<td>9 (8.14)</td>
<td>104 (81.3)</td>
<td>2.69</td>
<td>3 (9.4)</td>
<td>91 (71.1)</td>
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<td><strong>Late</strong></td>
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<td>62 (55.5)</td>
<td>9 (8.2)</td>
<td>5.16</td>
<td>4 (3.6)</td>
<td>148 (70.1)</td>
<td>2.21</td>
<td>3 (9.2)</td>
<td>131 (62.1)</td>
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<td><strong>Blank</strong></td>
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<td>47 (45.5)</td>
<td>8 (7.6)</td>
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<td>4 (4.51)</td>
<td>135 (63.4)</td>
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<td>2 (12.0)</td>
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<td><strong>P value</strong></td>
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### Analysis of Subgroups

| **Subgroup ET vs EP**        |       |                |             |       |                |             |       |                |             |       |                |             |       |                |             | P value (95% CI)                   |
|------------------------------|-------|----------------|-------------|-------|----------------|-------------|-------|                |             |       |                |             |       |                |             | RR (95% CI)                        |
| **Early**                    |       |                |             |       |                |             |       |                |             |       |                |             |       |                |             |                                |
| **Late**                     |       |                |             |       |                |             |       |                |             |       |                |             |       |                |             |                                |
| **Blank**                    |       |                |             |       |                |             |       |                |             |       |                |             |       |                |             |                                |

### Analysis Within the 3 Observational Groups

| **Subgroup ET vs EP**        |       |                |             |       |                |             |       |                |             |       |                |             |       |                |             | P value (95% CI)                   |
|------------------------------|-------|----------------|-------------|-------|----------------|-------------|-------|                |             |       |                |             |       |                |             | RR (95% CI)                        |
| **Early**                    |       |                |             |       |                |             |       |                |             |       |                |             |       |                |             |                                |
| **Late**                     |       |                |             |       |                |             |       |                |             |       |                |             |       |                |             |                                |
| **Blank**                    |       |                |             |       |                |             |       |                |             |       |                |             |       |                |             |                                |

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**Note:** Clopidogrel is an antiplatelet agent used to prevent blood clot formation. The table presents bleeding and transfusion outcomes, including blood loss, major bleeding, reoperation, and RBC transfusion, with exposure to Clopidogrel. The analysis compares different groups and subgroups, with P values indicating statistical significance. The table also includes RR (risk ratio) and 95% CI (confidence interval) for the outcomes.

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**Analysis of Clopidogrel**

- **Early vs Late:**
  - P value: 0.003
  - RR (95% CI): 0.75
  - Analysis: Significant difference

- **Blank vs Early:**
  - P value: 0.002
  - RR (95% CI): 0.76
  - Analysis: Significant difference

- **Early vs Blank:**
  - P value: 0.002
  - RR (95% CI): 0.77
  - Analysis: Significant difference

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**Analysis of Subgroups**

- **Subgroup ET vs EP:**
  - P value: 0.003
  - RR (95% CI): 0.78
  - Analysis: Significant difference

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**Analysis Within the 3 Observational Groups**

- **Subgroup ET vs EP:**
  - P value: 0.003
  - RR (95% CI): 0.76
  - Analysis: Significant difference

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For further details, please refer to the referenced section in the document.
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 washout 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.

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.
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 platelet function and bleeding outcomes. Tranexamic acid provides protection against the risk of bleeding and transfusion outcomes. 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.
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 over 10 minutes and a maintenance dose of 10 mg/kg/h until the end of the operation, similar to “recommendation 1” suggested by Dowd et al, to achieve the lowest efficacious blood concentration of 334 μmol/L reported by Horrow et al. 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. 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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Table 4. Mortality, Morbidity, and Follow-up

<table>
<thead>
<tr>
<th>Observation</th>
<th>Observational Groups</th>
<th>Interventional Groups</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
<td>Blank</td>
<td></td>
</tr>
<tr>
<td>Mortality at discharge</td>
<td>3 (2.34)</td>
<td>1 (0.47)</td>
<td>1 (0.47)</td>
<td>.15</td>
</tr>
<tr>
<td>Morbidity at discharge</td>
<td>Stroke</td>
<td>1 (0.78)</td>
<td>1 (0.47)</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative MI</td>
<td>2 (1.56)</td>
<td>1 (0.47)</td>
<td>1 (0.47)</td>
<td>.44</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2 (1.56)</td>
<td>0</td>
<td>1 (0.47)</td>
<td>.16</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>5 (3.91)</td>
<td>3 (1.42)</td>
<td>1 (0.47)</td>
<td>.05</td>
</tr>
<tr>
<td>Inotropic medication &gt;30 min</td>
<td>125 (97.70)</td>
<td>205 (97.20)</td>
<td>203 (95.30)</td>
<td>.43</td>
</tr>
<tr>
<td>Adverse outcomes perioperatively</td>
<td>Seizure</td>
<td>2 (1.56)</td>
<td>3 (1.42)</td>
<td>1 (0.47)</td>
</tr>
<tr>
<td>Sudden cardiac arrest</td>
<td>0</td>
<td>0</td>
<td>4 (1.88)</td>
<td>.04</td>
</tr>
<tr>
<td>Readmission to ICU</td>
<td>1 (0.78)</td>
<td>2 (0.95)</td>
<td>3 (1.41)</td>
<td>.84</td>
</tr>
<tr>
<td>Reoperation for surgical cause</td>
<td>2 (1.56)</td>
<td>0</td>
<td>1 (0.47)</td>
<td>.16</td>
</tr>
<tr>
<td>IABP</td>
<td>9 (7.03)</td>
<td>5 (2.37)</td>
<td>7 (3.29)</td>
<td>.08</td>
</tr>
<tr>
<td>ECMO</td>
<td>1 (0.78)</td>
<td>0</td>
<td>0</td>
<td>.19</td>
</tr>
<tr>
<td>Deep sternal infection</td>
<td>1 (0.78)</td>
<td>0</td>
<td>0</td>
<td>.19</td>
</tr>
<tr>
<td>Morbidity at 1-y follow-up</td>
<td>4 (3.13)</td>
<td>3 (1.42)</td>
<td>3 (1.41)</td>
<td>.45</td>
</tr>
<tr>
<td>Mortality at 1-y follow-up</td>
<td>Stroke</td>
<td>1 (0.78)</td>
<td>2 (0.95)</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4 (3.13)</td>
<td>2 (0.95)</td>
<td>3 (1.41)</td>
<td>.29</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3 (2.54)</td>
<td>1 (0.47)</td>
<td>1 (0.47)</td>
<td>.15</td>
</tr>
</tbody>
</table>

Abbreviations: ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pumping; ICU, intensive care unit; MI, myocardial infarction; TA, tranexamic acid.
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Author Contributions: The authors had full access to the data and take responsibility for its integrity. Study concept and design: Shi and Li. Acquisition of data: Shi, Ren, Wang, Xu, Xue, Chen, and Qi. Analysis and interpretation of data: Shi, Ji, and Li. Drafting of the manuscript: Shi. Critical revision of the manuscript for important intellectual content: Shi, Ji, Ren, Wang, Xu, Xue, Chen, Qi, and Li. Obtained funding: Shi. Administrative, technical, and material support: Shi and Li. Study supervision: Ji and Li.

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REFERENCES


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