ORIGINAL ARTICLE

Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery

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ABSTRACT

BACKGROUND

Tranexamic acid reduces the risk of bleeding among patients undergoing cardiac surgery, but it is unclear whether this leads to improved outcomes. Furthermore, there are concerns that tranexamic acid may have prothrombotic and proconvulsant effects.

METHODS

In a trial with a 2-by-2 factorial design, we randomly assigned patients who were scheduled to undergo coronary-artery surgery and were at risk for perioperative complications to receive aspirin or placebo and tranexamic acid or placebo. The results of the tranexamic acid comparison are reported here. The primary outcome was a composite of death and thrombotic complications (nonfatal myocardial infarction, stroke, pulmonary embolism, renal failure, or bowel infarction) within 30 days after surgery.

RESULTS

Of the 4662 patients who were enrolled and provided consent, 4631 underwent surgery and had available outcomes data; 2311 were assigned to the tranexamic acid group and 2320 to the placebo group. A primary outcome event occurred in 386 patients (16.7%) in the tranexamic acid group and in 420 patients (18.1%) in the placebo group (relative risk, 0.92; 95% confidence interval, 0.81 to 1.05; P=0.22). The total number of units of blood products that were transfused during hospitalization was 4331 in the tranexamic acid group and 7994 in the placebo group (P<0.001). Major hemorrhage or cardiac tamponade leading to reoperation occurred in 1.4% of the patients in the tranexamic acid group and in 2.8% of the patients in the placebo group (P=0.001), and seizures occurred in 0.7% and 0.1%, respectively (P=0.002 by Fisher's exact test).

CONCLUSIONS

Among patients undergoing coronary-artery surgery, tranexamic acid was associated with a lower risk of bleeding than was placebo, without a higher risk of death or thrombotic complications within 30 days after surgery. Tranexamic acid was associated with a higher risk of postoperative seizures. (Funded by the Australian National Health and Medical Research Council and others; ATACAS Australia New Zealand Clinical Trials Registry number, ACTRN12605000557639.)

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Excessive bleeding and blood transfusions are common in patients undergoing cardiac surgery,[1] and in some of these patients, there is a need for reoperation because of life-threatening bleeding.[2] Both blood transfusion and reoperation are strongly associated with poor outcomes after cardiac surgery.[2,3] Antifibrinolytic therapy reduces the risk of blood loss and transfusion among patients undergoing cardiac surgery,[4,5] but it is unclear whether such therapy reduces the risk of reoperation for bleeding.[4]

Antifibrinolytic agents that have been used in patients undergoing cardiac surgery include aprotinin[6,7] and the lysine analogues tranexamic acid and aminocaproic acid.[8-11] These agents may have prothrombotic effects, and their use may potentially increase the risk of myocardial infarction, stroke, and other thrombotic complications after cardiac surgery. Tranexamic acid in particular seems to be associated with an increased risk of postoperative neurologic events,[12] including seizures.[13] Some studies have shown that tranexamic acid reduces cerebral blood flow[14] and increases the risk of cerebral infarction.[15] This raises the possibility that seizures induced by tranexamic acid may have a thromboembolic basis. We investigated whether tranexamic acid increases the risk of death and thrombotic complications among at-risk patients undergoing coronary-artery surgery.

Methods

Trial Design

The Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial was a multicenter, double-blind trial with a 2-by-2 factorial design in which patients who were scheduled to undergo coronary-artery surgery and were at increased risk for complications were randomly assigned to receive tranexamic acid or placebo and aspirin or placebo. The rationale for and design of the ATACAS trial[16] and the results of the aspirin comparison[17] have been published previously. The results of the tranexamic acid comparison are reported here.

The trial protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at each site. The members of the steering committee (see the Supplementary Appendix, available at NEJM.org) designed the trial, gathered and analyzed the data, prepared the manuscript, and together with their coauthors made the decision to submit the manuscript for publication. The members of the steering committee vouch for the accuracy and completeness of the data set and for adherence of the study to the protocol and statistical analysis plan. There was no commercial involvement in the trial.

Participants

Eligible participants included adults who were at increased risk for major complications related to age or coexisting conditions and who were about to undergo on-pump (with cardiopulmonary bypass) or off-pump (without cardiopulmonary bypass) coronary-artery surgery, with or without cardiac-valve replacement or other procedures. Details regarding eligibility criteria are provided in the Supplementary Appendix. The first 2127 participants who were enrolled in the trial had not been taking aspirin regularly before the trial or had stopped taking aspirin at least 4 days before surgery, and half of these participants were randomly assigned to receive aspirin (100 mg) before surgery[17]; participants who were subsequently enrolled may or may not have been previously exposed to aspirin therapy. All participants provided written informed consent.

Trial Drug

Tranexamic acid at a dose of 100 mg per kilogram of body weight or 0.9% saline (placebo) was administered intravenously more than 30 minutes after the induction of anesthesia; in the tranexamic acid group, we aimed to maintain an effective plasma concentration of the drug for approximately 6 to 8 hours.[4,18] We encouraged blinding of the trial drug preparation but allowed the attending anesthesiologist to prepare the drug if research personnel were not available, and this information was recorded.

During the course of the trial, reports of seizures occurring after the administration of tranexamic acid were published, and the seizures were considered to be most likely dose-related.[13,19] Given evidence that a dose of tranexamic acid of 100 mg per kilogram was probably not required to achieve effective antifibrinolysis,[4,20,21] we halved the dose to 50 mg per kilogram in January 2012, after 1392 patients had been enrolled.

Procedures

Randomization was performed with the use of a computer-generated code. Treatment assignments were stratified with the use of permuted blocks according to trial site and on-pump or off-pump

surgery. The surgical team and postoperative interviewers were unaware of the group assignments. The attending anesthesiologists were sometimes aware of the group assignments. Details regarding data and safety monitoring are provided in the Supplementary Appendix.

All patients received routine surgical and other perioperative care with respect to selection of vein and artery conduit harvesting, determination of the extent of grafting needed according to results of coronary angiography, surgical hemostasis, and blood transfusion. We provided a guideline for the use of heparin and protamine, a guideline for the management of excessive bleeding during surgery, and a guideline and recommended hemoglobin thresholds for autologous transfusion (see the Supplementary Appendix). Open-label tranexamic acid or other antifibrinolytic therapy could not be used before or during cardiopulmonary bypass but was allowed if clinically significant bleeding occurred after the reversal of heparin treatment with protamine or postoperatively.

Patient demographic and perioperative characteristics were recorded. A 12-lead electrocardiogram was obtained preoperatively; on the first, second, and third days after surgery; and at the time of hospital discharge. Blood samples were collected at 12 to 24 hours and 48 to 72 hours after surgery to assess levels of troponin or, if unavailable, creatine kinase–myocardial band.

OUTCOMES

The primary outcome of the trial was a composite of death and thrombotic events (nonfatal myocardial infarction, stroke, pulmonary embolism, renal failure, or bowel infarction) during the initial 30 postoperative days. Postoperative myocardial infarction was defined according to the third universal definition.[22] In addition, we defined non–Q-wave myocardial infarction as the presence of markedly elevated levels of cardiac biomarkers in a patient recovering from isolated coronary-artery bypass grafting (see the Supplementary Appendix).[23-25] All primary outcome events were reviewed by an independent adjudication committee whose members were unaware of the group assignments.

The prespecified secondary outcomes were death, nonfatal myocardial infarction, stroke, pulmonary embolism, renal failure, bowel infarction, reoperation due to major hemorrhage or cardiac tamponade, and a requirement for transfusion. In January 2012, the occurrence of seizures was added as a safety outcome. The diagnosis of a seizure was based only on clinical observation.

SUBGROUPS

Prespecified subgroups were defined according to the following characteristics: sex, age, presence or absence of diabetes, previous or no previous myocardial infarction, presence or absence of unstable angina, surgical risk (calculated with the use of the European System for Cardiac Operative Risk Evaluation [EuroSCORE], on which scores are calculated by means of a logistic-regression equation and range from 0 to 100%, with higher scores indicating greater risk), left ventricular function, risk of bleeding during surgery, on-pump or off-pump surgery, and aortic cross-clamp time (the time from placement of the aortic cross-clamp to removal). Our list of risk factors for bleeding during surgery has been published previously and is included in the Supplementary Appendix.[17] A post hoc subgroup was defined according to open-chamber surgery or isolated coronary-artery surgery; open-chamber surgery includes concomitant cardiac-valve replacement, repair of a ventricular aneurysm, or repair of an ascending aortic aneurysm. This post hoc subgroup was used in analyses of the risk of seizures associated with tranexamic acid. We computed differences in the primary outcome across subgroups by adding the appropriate interaction terms to the regression models. All reported P values are two-sided and have not been adjusted for multiple comparisons.

STATISTICAL ANALYSIS

The trial was initially planned to have 90% power to detect a clinically significant difference (10% vs. 7%) between the tranexamic acid group and the placebo group and between the aspirin group and the placebo group in the primary outcome of death or thrombotic events when the effect of each trial drug was considered separately; this difference would translate into a difference of 8.50% versus 5.95% between the pooled tranexamic acid groups and the placebo groups. Using a chi-square test with a two-sided type I error rate of 5%,[16] we calculated that a sample size of 4484 patients would be required; we aimed to recruit a total of 4600 patients. The aspirin comparison was discontinued after 2127 patients had been enrolled,[17] but the tranexamic acid comparison was continued until full enrollment was reached.

The trial protocol specified that all analyses would be performed with data from all patients who underwent randomization, regardless of whether they underwent surgery or received a trial drug. However, after the protocol and statistical analysis plan were written, the decision was made to perform all primary and secondary analyses only with data from patients who underwent randomization and underwent surgery.

Analysis of the primary and dichotomous secondary outcomes was performed with the use of chi-square tests constructed from binomial regression with a logarithmic link; the results are expressed as risk ratios with 95% confidence

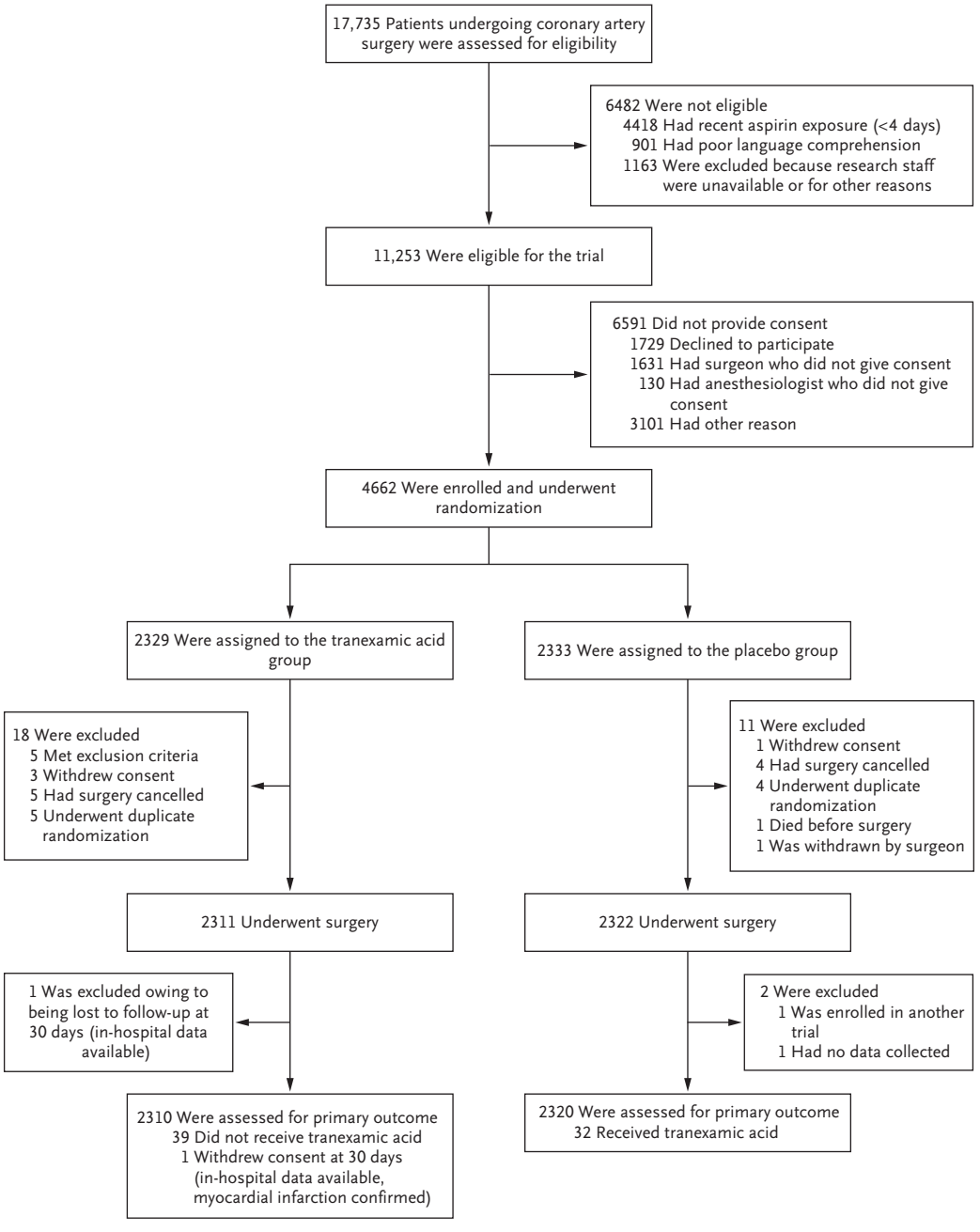

Figure 1. Enrollment, Randomization, and Assessment.

Table 1. Characteristics of the Patients at Trial Entry.*

Characteristic	Tranexamic Acid Group (N=2311)	Placebo Group (N=2320)
Age — yr	66.8±9.8	67.0±9.6
Weight — kg	86.5±17.4	85.8±16.6
Male sex — no. (%)	1930 (83.5)	1930 (83.2)
ASA physical status classification — no. (%)†		
1	0	0
2	90 (3.9)	87 (3.8)
3	1215 (52.6)	1213 (52.3)
4	1006 (43.5)	1020 (44.0)
Left ventricular ejection fraction — no. (%)		
>50%	1709 (74.0)	1737 (74.9)
35–50%	491 (21.2)	468 (20.2)
20–34%	94 (4.1)	100 (4.3)
<20%	16 (0.7)	15 (0.6)
NYHA classification — no. (%)		
1	422 (18.3)	467 (20.1)
2	1207 (52.2)	1162 (50.1)
3	622 (26.9)	632 (27.2)
4	59 (2.6)	59 (2.5)
EuroSCORE for operative risk — %‡	4.7±3.0	4.7±2.9
Location		
Australia	1385	1387
Canada	193	197
Hong Kong	132	131
Europe other than United Kingdom	80	82
New Zealand	288	289
United Kingdom	233	234
Preexisting medical conditions — no. (%)		
Diabetes	799 (34.6)	806 (34.7)
Renal impairment	173 (7.5)	170 (7.3)
Hypertension	1812 (78.4)	1856 (80.0)
Angina	1582 (68.5)	1581 (68.1)
Heart failure	240 (10.4)	244 (10.5)
Myocardial infarction within 90 days	914 (39.5)	910 (39.2)
Endocarditis	7 (0.3)	1 (<0.1)
Cerebrovascular disease	218 (9.4)	229 (9.9)
Peripheral vascular disease	230 (10.0)	236 (10.2)
Pulmonary hypertension	134 (5.8)	105 (4.5)
Previous angioplasty or stenting	57 (2.5)	57 (2.5)
Previous cardiac surgery	37 (1.6)	27 (1.2)
Thrombolysis	14 (0.6)	22 (0.9)
Smoking history	1482 (64.1)	1575 (67.9)
Respiratory disease	320 (13.8)	348 (15.0)
Chronic obstructive pulmonary disease	223 (9.6)	241 (10.4)

Table 1. (Continued.)

Characteristic	Tranexamic Acid Group (N=2311)	Placebo Group (N=2320)
Preoperative medications — no. (%)		
ACE inhibitor or angiotensin-receptor blocker	1542 (66.7)	1570 (67.7)
Beta-blocker	1566 (67.8)	1550 (66.8)
Calcium-channel blocker	704 (30.5)	779 (33.6)
Nitrate	909 (39.3)	890 (38.4)
Statin	2016 (87.2)	2050 (88.4)
Amiodarone	24 (1.0)	43 (1.9)
Digoxin	55 (2.4)	46 (2.0)
Diuretic	581 (25.1)	526 (22.7)
Aspirin within 3 days	1662 (71.9)	1667 (71.9)
Other NSAID or cyclooxygenase-2 inhibitor	34 (1.5)	33 (1.4)
Clopidogrel within 7 days	64 (2.8)	67 (2.9)
Warfarin within 7 days	27 (1.2)	24 (1.0)
Heparin within 24 hours	172 (7.4)	182 (7.8)
Most recent platelet count ($\times 10^{-6}$/liter)	234±64	235±68
Most recent activated partial-thromboplastin time — sec	32.9±13.5	32.8±13.8
Most recent international normalized ratio	1.0±0.1	1.0±0.1
Most recent serum creatinine level — μmol/liter	92.9±40.8	92.8±33.1
Assignment to aspirin group — no. (%)	529 (22.9)	533 (22.9)

* Plus–minus values are means ±SD. There were no significant differences between groups at baseline. ACE denotes angiotensin-converting enzyme, NYHA New York Heart Association, and NSAID nonsteroidal antiinflammatory drug.
† An American Society of Anesthesiologists (ASA) physical status classification score of 1 equates to no disease, 2 mild disease, 3 severe disease, and 4 severe disease that is a constant threat to life.
‡ The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is calculated by means of a logistic-regression equation and ranges from 0 to 100%, with higher scores indicating greater risk.

intervals. Continuous secondary outcomes were assessed with the use of the Student's t-test or the Wilcoxon rank-sum test. Time-to-event outcomes were assessed with the use of the Wilcoxon–Breslow–Gehan test, with data on length of stay in the hospital and intensive care unit censored at 30 days and in-hospital deaths assigned the highest length of stay. Analyses were repeated with adjustment for the stratification factors of trial site and on-pump or off-pump surgery with the use of linear or generalized linear mixed models, with site as a random effect. Results differed negligibly and only the unadjusted results are reported here.

RESULTS

PATIENT CHARACTERISTICS

Between March 2006 and October 2015, a total of 4662 patients at 31 sites in seven countries were randomly assigned to receive tranexamic acid (2329 patients) or placebo (2333 patients); 18 patients in the tranexamic acid group and 11 patients in the placebo group were excluded for a variety of reasons (Fig. 1). A total of 2311 patients in the tranexamic acid group and 2322 patients in the placebo group underwent surgery. After surgery, 2 additional patients in the placebo group were excluded; the remaining 2320 patients in that group were included in the outcome analyses.

Demographic, medical, and perioperative characteristics of the patients were similar in the two groups (Tables 1 and 2). In the tranexamic acid group, 758 patients received the drug at a dose of 100 mg per kilogram and 1553 patients received the drug at a dose of 50 mg per kilogram. Two patients in the tranexamic acid group did not have complete follow-up data, but in-hospital data were available for both patients, and data on

Table 2. Surgical and Other Perioperative Characteristics of the Patients.*

Characteristic	Tranexamic Acid Group (N=2311)	Placebo Group (N=2320)
Received propofol — no. (%)	1250 (54.1)	1289 (55.6)
Received inhalational anesthetic agent — no. (%)	1990 (86.1)	1975 (85.1)
Underwent pulmonary-artery catheterization — no. (%)	1171 (50.7)	1171 (50.5)
Underwent intraoperative TEE — no. (%)	1931 (83.6)	1889 (81.4)
Total heparin dose — mg	394±138	386±138
Minimum temperature during bypass — °C	34±1.7	34±1.7
Previous cardiac surgery — no. (%)	37 (1.6)	27 (1.2)
No. of risk factors for bleeding — no. (%)†		
0 or 1	1004 (43.4)	991 (42.7)
2 or 3	1138 (49.2)	1171 (50.5)
4 or 5	169 (7.3)	158 (6.8)
Surgery type — no. (%)‡		
Nonelective	1657 (71.7)	1647 (71.0)
Isolated CABG	1752 (75.8)	1802 (77.7)
Combined CABG and cardiac-valve replacement	484 (20.9)	484 (20.9)
On-pump	2241 (97.0)	2245 (96.8)
Off-pump	68 (2.9)	74 (3.2)
Open-chamber	511 (22.1)	471 (20.3)
No. of distal grafts		
Median	3	3
Interquartile range	2–4	2–4
Received internal thoracic-artery graft — no. (%)	2082 (90.1)	2099 (90.5)
Cross-clamp time — min§		
Median	69	64
Interquartile range	50–90	48–88
Duration of anesthesia — hr	4.5±1.2	4.5±1.2
Duration of surgery — hr		
Median	3.7	3.7
Interquartile range	3.1–4.4	3.1–4.5
Postoperative aspirin within 24 hr — no. (%)	1935 (83.7)	1852 (79.8)

* Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, and TEE transesophageal echocardiography.
† Prespecified risk factors for bleeding were an age of older than 70 years, female sex, use of low-molecular-weight heparin or an antiplatelet drug less than 5 days before surgery, renal impairment (estimated glomerular filtration rate, <60 ml per minute), and insulin-dependent diabetes.
‡ "Off-pump" refers to surgery without cardiopulmonary bypass, and "on-pump" to surgery with cardiopulmonary bypass.
§ Cross-clamp time refers to the time from placement of the aortic cross-clamp to removal.

postoperative myocardial infarction were available for one of them (Fig. 1).

PRIMARY OUTCOME

Death or thrombotic complications occurred within the first 30 days after surgery in 386 patients (16.7%) in the tranexamic acid group and in 420 patients (18.1%) in the placebo group (relative risk, 0.92; 95% confidence interval [CI], 0.81 to 1.05; P=0.22) (Table 3). Myocardial infarction was detected within the first 30 days after surgery in 269 patients (11.6%) in the tranexamic

acid group and in 300 patients (12.9%) in the placebo group (Table 3), including 58 patients (2.5%) and 47 patients (1.9%), respectively, who were recovering from isolated coronary-artery bypass grafting and were identified as having a non–Q-wave myocardial infarction, a classification that was based solely on the presence of a markedly elevated troponin or cardiac enzyme level. In a post hoc analysis in which myocardial infarction was defined only according to the third universal definition,[22] the relative risk of myocardial infarction with tranexamic acid versus placebo was 0.84 (95% CI, 0.70 to 1.00; P=0.045). The rates of death, stroke, pulmonary embolism, renal failure, and bowel infarction were similar in the two groups (Table 3).

BLEEDING-RELATED OUTCOMES

The tranexamic acid group had lower rates than the placebo group for the following bleeding-related outcomes: the number of patients who had blood loss during surgery (P<0.001), the number of units of red cells and other blood products that were transfused (P<0.001 for all comparisons), and the number of patients who underwent blood transfusion (P<0.001) (Table 3, and Table S1 in the Supplementary Appendix). The total number of units of any blood products (red cells, platelets, or fresh frozen plasma) that were transfused during hospitalization in all patients was 4331 in the tranexamic acid group and 7994 in the placebo group. Open-label tranexamic acid was administered during the postoperative period to control ongoing bleeding in 8 patients in the tranexamic acid group and in 26 patients in the placebo group (P<0.001); a small percentage of patients (<0.3%) received aprotinin or recombinant factor VIIa after the reversal of heparin treatment with protamine or postoperatively (Table S1 in the Supplementary Appendix).

Major hemorrhage or cardiac tamponade leading to reoperation occurred in 1.4% of the patients in the tranexamic acid group and in 2.8% of the patients in the placebo group (P=0.001) (Table 3). The number needed to treat with tranexamic acid to prevent one reoperation within 30 days after surgery was 71 patients (95% CI, 45 to 167). In a post hoc analysis, patients who underwent reoperation were more likely than those who did not undergo reoperation to die or have thrombotic complications within 30 days after surgery (relative risk, 2.13; 95% CI, 1.62 to 2.80; P<0.001) (Table S2 in the Supplementary Appendix).

POSTOPERATIVE SEIZURES AND OTHER ADVERSE EVENTS

Postoperative seizures occurred in 15 patients (0.7%) in the tranexamic acid group and in 2 patients (0.1%) in the placebo group (relative risk, 7.60; 95% CI, 1.80 to 68.70; P=0.002 by Fisher's exact test) (Table 3). The number needed to harm to cause 1 additional patient to have one or more seizures with tranexamic acid treatment within 30 days after surgery was 177 patients (95% CI, 17 to 1450). In a post hoc analysis, patients who had one or more postoperative seizures were more likely than those who did not have postoperative seizures to have a stroke (relative risk, 21.88; 95% CI, 10.06 to 47.58; P<0.001) or to die (relative risk, 9.52; 95% CI, 2.53 to 35.90; P=0.02) up to 30 days after surgery (Table S3 in the Supplementary Appendix).

A list of all postrandomization adverse events is provided in Table S4 in the Supplementary Appendix. Although the attending anesthesiologists were sometimes aware of the treatment assignments, this had no influence on the trial outcomes (Table S5 in the Supplementary Appendix). In a post hoc analysis, the duration of postoperative mechanical ventilation was slightly shorter in the tranexamic acid group than in the placebo group (5.0 hours [95% CI, 8.0 to 14.0] vs. 6.0 hours [95% CI, 9.0 to 16.0]; P<0.001) (Table 3).

SUBGROUP ANALYSES

With respect to primary outcome, there were no significant interactions between treatment group and patient demographic or perioperative characteristics (Fig. 2, and Fig. S1 in the Supplementary Appendix). There was no significant interaction between assignment to the tranexamic acid group and either assignment to the aspirin group or previous exposure to aspirin (Fig. 2, and Table S6 in the Supplementary Appendix). Study outcomes according to dose of tranexamic acid (50 mg per kilogram or 100 mg per kilogram) are shown in Table S7 in the Supplementary Appendix.

Among patients undergoing open-chamber surgery, the incidence of seizures was higher in the tranexamic acid group than in the placebo group (2.0% vs. 0%; relative risk, 13.27; 95% CI, 2.13 to infinity; P=0.003 by Fisher's exact test).

Table 3. Outcomes and Adverse Events.

Outcome or Event	Tranexamic Acid Group (N = 2311)	Placebo Group (N=2320)	Risk Ratio (95% CI)	P Value
Primary outcome: death, myocardial infarction, stroke, renal failure, pulmonary embolism, or bowel infarction — no./total no. (%)	386/2310 (16.7)	420/2320 (18.1)	0.92 (0.81–1.05)	0.22
Death	26/2310 (1.1)	33/2320 (1.4)	0.79 (0.47–1.32)	0.43
Myocardial infarction	269/2310 (11.6)	300/2320 (12.9)	0.90 (0.77–1.05)	0.19
Stroke	32/2309 (1.4)	35/2320 (1.5)	0.92 (0.57–1.48)	0.81
Renal failure	98/2309 (4.2)	96/2320 (4.1)	1.03 (0.78–1.35)	0.88
Pulmonary embolism	15/2309 (0.6)	15/2320 (0.6)	1.00 (0.49–2.05)	>0.99
Bowel infarction	8/2309 (0.3)	3/2320 (0.1)	2.68 (0.71–10.09)	0.15
Primary outcome not including renal failure — no./total no. (%)*	324/2310 (14.0)	362/2320 (15.6)	0.90 (0.78–1.03)	0.14
Reoperation — no./total no. (%)				
Due to any cause	32/2310 (1.4)	65/2320 (2.8)	0.49 (0.32–0.75)	0.001
Due to major hemorrhage	18/2310 (0.8)	48/2320 (2.1)	0.36 (0.21–0.62)	<0.001
Due to cardiac tamponade	16/2310 (0.7)	23/2320 (1.0)	0.61 (0.32–1.18)	0.19
Transfusion of red cells during hospitalization — no./total no. (%)	759/2311 (32.8)	1086/2320 (46.8)		
No. of units of red cells that were transfused during hospitalization				<0.001
Median	2	2		
Interquartile range	1–3	2–4		
Transfusion of any blood products during hospitalization — no./total no. (%)	876/2311 (37.9)	1269/2320 (54.7)		
No. of units of any blood products that were transfused during hospitalization				<0.001
Median	3	4		
Interquartile range	2–6	2–8		
Duration of mechanical ventilation — hr*†				<0.001
Median	8	9		
Interquartile range	5–14	6–16		
Length of stay in intensive care unit (initial admission) — hr†				0.04
Median	27	30		
Interquartile range	21–62	22–67		

Length of stay in intensive care unit (total) — hr†			0.07
Median	28	34	
Interquartile range	22–65	22–69	
Length of stay in hospital — days‡			0.08
Median	8.0	8.0	
Interquartile range	6.0–13.0	6.0–14.0	
Seizures — no./total no. (%)	15/2304 (0.7)§	2/2327 (0.1)	7.62 (1.77–68.71)	0.002§
Peptic ulceration — no./total no. (%)	13/2308 (0.6)	15/2319 (0.6)	0.87 (0.42–1.83)	0.85
Reintubation during hospitalization — no./total no. (%)*	62/2113 (2.9)	62/2122 (2.9)	1.00 (0.71–1.42)	>0.99

* Outcome was not prespecified in the trial protocol.
† Data were available for 2318 patients in the placebo group.
‡ Data were available for 2304 patients in the tranexamic acid group and 2308 patients in the placebo group.
§ Data include one patient who was randomly assigned to receive placebo and received tranexamic acid postoperatively.

Among patients undergoing isolated coronary-artery surgery, seizures occurred in 0.3% of the patients in the tranexamic acid group and in 0.1% of the patients in the placebo group (relative risk, 2.58; 95% CI, 0.42 to 27.14; P=0.43 by Fisher's exact test). However, the result of the test for interaction for this subgroup comparison was not significant (P=0.34 by Fisher's exact test).

DISCUSSION

In this trial, we found no evidence that the use of tranexamic acid resulted in a higher risk of death or thrombotic complications than that with placebo among patients undergoing coronary-artery surgery. We also found that the tranexamic acid group had a lower risk of blood loss, blood transfusion, and reoperation but a higher risk of postoperative seizures than did the placebo group. Subgroup analyses of the primary outcome showed no significant interactions. The results were consistent among patients who were being treated with aspirin and those who were not.

Patients in the tranexamic acid group received 46% fewer units of blood products than did those in the placebo group. In a cardiac surgical practice similar to the practices in which our trial population was treated, the use of tranexamic acid would save approximately 57 units of blood products for every 100 patients treated. The observed blood-sparing effects are consistent with those reported in meta-analyses.[4,5,12] The results of our trial have extended the reported findings by showing a significantly lower rate of reoperation with tranexamic acid than with placebo and robust estimates of the blood-sparing effects (including a lower risk of blood loss, decrement in hemoglobin levels, transfusions, and reoperations) associated with the use of tranexamic acid.

Although many observational studies have linked blood transfusion with poor outcomes after cardiac surgery, we did not identify a beneficial reduction in the risk of myocardial infarction, stroke, or death despite the blood-sparing effects of tranexamic acid. In addition, the lower risk of bleeding with tranexamic acid than with placebo did not translate into shorter surgery times, and the slightly shorter duration of mechanical ventilation did not translate into earlier discharge from the hospital.

Tranexamic acid is commonly administered at a dose of 30 to 100 mg per kilogram for a

Subgroup	Tranexamic Acid	Placebo	Relative Risk (95% CI)	P Value for Interaction
	no. of patients with events/total no. of patients (%)			
All patients	386/2310 (16.7)	420/2320 (18.1)	0.92 (0.81–1.05)	
Exposure to aspirin				0.48
Yes	273/1662 (16.4)	288/1667 (17.3)	0.95 (0.82–1.11)	
No	113/648 (17.4)	132/653 (20.2)	0.86 (0.69–1.08)	
Age				0.08
≤60 yr	91/604 (15.1)	74/590 (12.5)	1.20 (0.90–1.60)	
61–70 yr	127/806 (15.8)	161/815 (19.8)	0.80 (0.65–0.99)	
71–80 yr	129/743 (17.4)	150/750 (20.0)	0.87 (0.70–1.07)	
>80 yr	39/157 (24.8)	35/165 (21.2)	1.17 (0.78–1.75)	
Sex				0.60
Male	307/1929 (15.9)	338/1930 (17.5)	0.91 (0.79–1.05)	
Female	79/381 (20.7)	82/390 (21.0)	0.99 (0.75–1.30)	
Diabetes mellitus				0.48
Yes	151/798 (18.9)	156/806 (19.4)	0.98 (0.80–1.20)	
No	235/1512 (15.5)	264/1514 (17.4)	0.89 (0.76–1.05)	
Previous myocardial infarction				0.30
Yes	143/913 (15.7)	168/910 (18.5)	0.85 (0.69–1.04)	
No	243/1397 (17.4)	252/1410 (17.9)	0.97 (0.83–1.14)	
Unstable angina				0.12
Yes	17/137 (12.4)	27/128 (21.1)	0.59 (0.34–1.03)	
No	323/2026 (15.9)	354/2048 (17.3)	0.92 (0.80–1.06)	
EuroSCORE				0.89
≤4	149/1111 (13.4)	166/1125 (14.8)	0.91 (0.74–1.12)	
>4	190/1044 (18.2)	213/1044 (20.4)	0.89 (0.75–1.06)	
Open-chamber surgery				0.98
Yes	116/511 (22.7)	117/471 (24.8)	0.91 (0.73–1.14)	
No	270/1798 (15.0)	303/1849 (16.4)	0.92 (0.79–1.07)	
Surgical type				0.49
On-pump	375/2240 (16.7)	410/2245 (18.3)	0.92 (0.81–1.04)	
Off-pump	11/68 (16.2)	10/75 (13.3)	1.21 (0.55–2.68)	
Cross-clamp time				0.36
>150 min	16/48 (33.3)	14/49 (28.6)	1.17 (0.64–2.12)	
≤150 min	272/1816 (15.0)	312/1818 (17.2)	0.87 (0.75–1.01)	
No. of risk factors for bleeding				0.70
0 or 1	148/1004 (14.7)	166/991 (16.8)	0.88 (0.72–1.08)	
2 or 3	198/1137 (17.4)	210/1171 (17.9)	0.97 (0.81–1.16)	
4 or 5	40/169 (23.7)	44/158 (27.8)	0.85 (0.59–1.23)	
Left ventricular ejection fraction				0.10
>50%	270/1708 (15.8)	311/1737 (17.9)	0.88 (0.76–1.02)	
35–50%	100/491 (20.4)	82/468 (17.5)	1.16 (0.89–1.50)	
20–34%	13/94 (13.8)	25/100 (25.0)	0.55 (0.30–1.02)	
<20%	3/16 (18.8)	2/15 (13.3)	1.40 (0.27–7.28)	

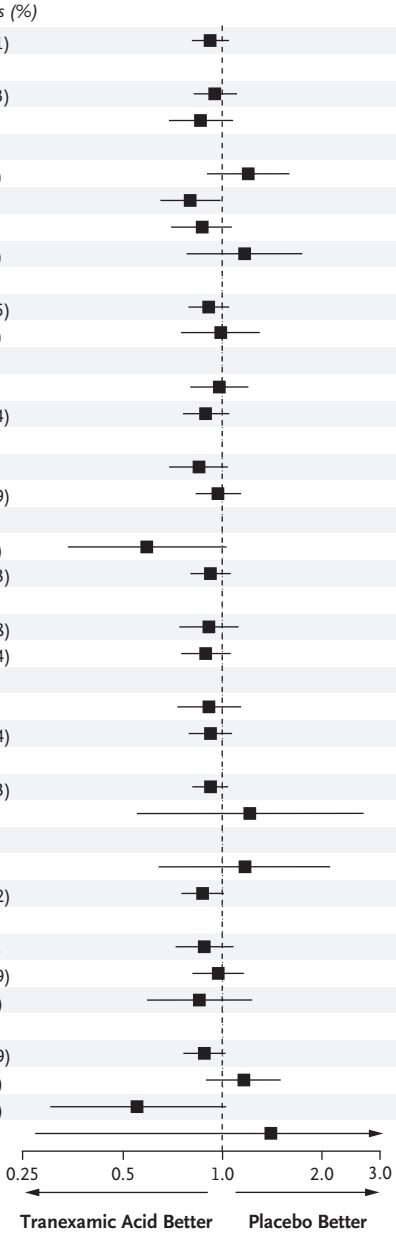

Figure 2. Subgroup Analysis of the Relative Risk of the Primary Outcome with Tranexamic Acid versus Placebo.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is calculated by means of a logistic-regression equation and ranges from 0 to 100%, with higher scores indicating greater risk. "Off-pump" refers to surgery without cardiopulmonary bypass, and "on-pump" to surgery with cardiopulmonary bypass. Cross-clamp time refers to the time from placement of the aortic cross-clamp to removal. Prespecified risk factors for bleeding were an age of older than 70 years, female sex, use of low-molecular-weight heparin or an antiplatelet drug less than 5 days before surgery, renal impairment (estimated glomerular filtration rate, <60 ml per minute), and insulin-dependent diabetes.

4-hour procedure.[4,26,27] We used a dose of 100 mg per kilogram at the beginning of the trial but later reduced this dose because of the growing number of reports of seizures associated with tranexamic acid that were believed to be dose-related.[13,20,21] The smaller dose (50 mg per kilogram) did not reduce the risk of seizure.[28] There is a strong association between seizures and stroke after cardiac surgery, even without the use of tranexamic acid.[20,29] The relationship of postoperative seizures with stroke and death observed in this trial suggests a possible underlying thromboembolic cause of the seizures.

Some limitations of our trial should be considered. First, although the reduction in the dose of tranexamic acid during the course of the trial provided an opportunity to test for a dose effect, this analysis was underpowered. Second, our trial included few patients who were at the highest risk for bleeding or thrombosis; however, we did not identify a subgroup effect that would suggest different findings among patients with overall higher risk. Third, in this trial, the attending anesthesiologists were sometimes aware of the treatment-group assignment; however, sensitivity analysis and the analysis of truly blinded data on postoperative blood loss and transfusion were consistent with the analysis of postoperative trial outcomes data. Finally, our trial included only a small proportion of patients undergoing off-pump surgery, and although the point estimates of effects among those patients were generally consistent with the point estimates of effects among patients undergoing on-pump surgery and although there were no significant interactions between subgroups, clinically important differences cannot be ruled out.

In summary, we found no evidence that tranexamic acid increases the risk of death and thrombotic complications after coronary-artery surgery. Tranexamic acid was associated with a lower risk of bleeding complications than placebo but also with a higher risk of postoperative seizures.

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