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Safety and Efficacy of Tranexamic Acid in General Surgery

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IMPORTANCE Perioperative bleeding is common in general surgery. The POISE-3 (Perioperative Ischemic Evaluation-3) trial demonstrated efficacy of prophylactic tranexamic acid (TXA) compared with placebo in preventing major bleeding without increasing vascular outcomes in noncardiac surgery.

OBJECTIVE To determine the safety and efficacy of prophylactic TXA, specifically in general surgery.

DESIGN, SETTING, AND PARTICIPANTS Subgroup analyses were conducted that compared randomized treatment with TXA vs placebo according to whether patients underwent general surgery or nongeneral surgery in the POISE-3 blinded, international, multicenter randomized clinical trial. Participants were 45 years or older, were undergoing noncardiac surgery, had increased cardiovascular risk, and were expected to require at least an overnight hospital admission after surgery. Among 26 581 eligible patients identified, 17 046 were excluded, resulting in 9535 patients randomized to the POISE-3 trial. Participants were enrolled from June 2018 through July 2021. The data were analyzed during December 2023.

INTERVENTION Prophylactic, 1-g bolus of intravenous TXA or placebo at the start and end of surgery.

MAIN OUTCOMES AND MEASURES The primary efficacy outcome was a composite of life-threatening bleeding, major bleeding, or bleeding into a critical organ. The primary safety outcome was a composite of myocardial injury after noncardiac surgery, nonhemorrhagic stroke, peripheral arterial thrombosis, or symptomatic proximal venous thromboembolism at 30 days. Cox proportional hazards models were conducted, incorporating tests of interaction.

RESULTS Among 9535 POISE-3 participants, 3260 underwent a general surgery procedure. Mean age was 68.6 (SD, 9.6) years, 1740 were male (53.4%), and 1520 were female (46.6%). Among general surgery patients, 8.0% and 10.5% in the TXA and placebo groups, respectively, had the primary efficacy outcome (hazard ratio [HR], 0.74; 95% CI, 0.59-0.93; *P* = .01) and 11.9% and 12.5% in the TXA and placebo groups, respectively, had the primary safety outcome (HR, 0.95; 95% CI, 0.78-1.16; *P* = .63). There was no significant interaction by type of surgery (general surgery vs nongeneral surgery) on the primary efficacy (*P* for interaction = .81) and safety (*P* for interaction = .37) outcomes. Across subtypes of general surgery, TXA decreased the composite bleeding outcome in hepatopancreaticobiliary surgery (HR, 0.55; 95% CI, 0.34-0.91 [n = 332]) and colorectal surgery (HR, 0.67; 95% CI, 0.45-0.98 [n = 940]). There was no significant interaction across subtypes of general surgery (*P* for interaction = .68).

CONCLUSIONS AND RELEVANCE In this study, TXA significantly reduced the risk of perioperative bleeding without increasing cardiovascular risk in patients undergoing general surgery procedures.

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General surgery encompasses a wide range of surgical procedures with varying propensities for bleeding.[1] A large prospective cohort study involving over 40 004 patients having noncardiac surgery demonstrated that major bleeding was significantly associated with 30-day postoperative mortality and had the largest attributable fraction for death, among other major postoperative complications.[2] A substudy confirmed these findings among patients who underwent general surgery.[3] Major perioperative bleeding also increases transfusion need and is associated with reinterventions, reoperations, and longer length of hospital stay.[4]

Tranexamic acid (TXA) is an antifibrinolytic medication that was shown to reduce bleeding risk in patients undergoing noncardiac surgery.[5,6] Given its mechanism of action of supporting physiologic hemostasis, there is a theoretical risk of thrombotic complications, like venous thromboembolism (VTE), with TXA use. The Perioperative Ischemic Evaluation-3 (POISE-3) trial was an international, randomized clinical trial (RCT) that included 9535 patients having noncardiac surgery who were at risk for bleeding and cardiovascular events.[5] In this trial, TXA proved to be superior to placebo for the primary efficacy outcome, which was a composite of major bleeding events (hazard ratio [HR], 0.76; 95% CI, 0.67-0.87; absolute difference, −2.6%; 95% CI, −3.8 to −1.4). TXA did not meet noninferiority for the composite cardiovascular safety outcome, which was a composite of thromboembolic and cardiovascular events (HR, 1.02; 95% CI, 0.92-1.14; noninferiority margin 1.125; absolute difference, 0.3%; 95% CI, −1.1 to 1.7).[5] An updated meta-analysis that includes 191 RCTs (40 621 patients) has provided updated findings, which report that the POISE-3 noninferiority margin has been met for perioperative cardiovascular thromboembolic events (risk ratio [RR], 1.02; 95% CI, 0.94-1.11). This suggests that TXA use is not worse than placebo with regard to the safety outcome.[7]

Although the evidence to support the use of TXA in noncardiac surgery is strong, data specific to general surgery are lacking.[8] In a survey among oncologic surgeons in a Canadian tertiary center, 63% of respondents stated that they felt a trial was needed in their own surgical field to determine the efficacy and safety of TXA.[9] This highlights the importance of context-specific evidence for TXA use, particularly in general surgery.

In the POISE-3 trial, 3542 participants underwent a general surgery procedure.[5] This represents, to our knowledge, the largest population of general surgery patients to date in which the effect of TXA has been evaluated. In this POISE-3 substudy, the objective was to determine whether perioperative TXA affected the risk of a composite bleeding or major cardiovascular outcome at 30 days among patients who underwent general surgery and whether this effect differed from the effect in other types of surgery. The primary efficacy and safety outcomes for this substudy are the same outcomes used in the overall trial.

Key Points

Question What is the safety and efficacy profile of prophylactic tranexamic acid (TXA) use in general surgery?

Findings In this substudy of a randomized clinical trial that included 9535 participants, among whom 3260 underwent a general surgery procedure, prophylactic TXA significantly reduced major bleeding events (8.0% vs 10.5%) without significant differences in safety events (11.9% vs 12.5%) compared with placebo. There were no subgroup effects according to whether patients underwent general surgery vs nongeneral surgery procedures.

Meaning In this study, prophylactic TXA reduced bleeding without increasing cardiovascular risk for both general surgery and nongeneral surgery patients.

Methods

Study Design

Details of the POISE-3 trial have been previously reported.[10] This article was written in adherence to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.[10] In summary, the POISE-3 trial was an international multicenter RCT that compared the efficacy and safety of prophylactic TXA vs placebo among adult patients undergoing noncardiac surgery. Participants, health care professionals, data collectors, and adjudicators were blinded to treatment allocation. Local ethics board approval was provided by all participating centers before patient recruitment.

Participants and Setting

Patients were enrolled if they were 45 years or older, planned to undergo noncardiac surgery, were expected to require at least an overnight hospital admission after surgery, and were deemed to be at risk of perioperative bleeding and cardiovascular complications. Patients undergoing cardiac surgery or intracranial neurosurgery were excluded. Full details of the trial, including the eligibility criteria for POISE-3, are reported elsewhere and provided in eAppendix 1 in Supplement 1.

Intervention and Placebo

Once informed consent was obtained, participants were randomized by means of a central computerized system in a 1:1 ratio to receive a 1-g intravenous bolus of tranexamic acid or placebo at the start and end of surgery.

Study Outcomes

eAppendix 2 in Supplement 1 reports all outcome definitions. The primary efficacy outcome was a composite of life-threatening bleeding (bleeding that was fatal or required inotrope therapy, reoperation, or intracranial hemorrhage), major bleeding (bleeding associated with postoperative hemoglobin 70 g/L or less, transfusion of 1 or more unit of red blood cells, or led to a nonoperative intervention), and critical organ bleeding (bleeding that was intracranial, intraocular, pericardial, intraspinal, retroperitoneal, or intramuscular with compartment syndrome) at 30 days after randomization. The primary safety outcome was a composite of myocardial injury after noncardiac surgery (MINS) (myocardial infarction or any elevated troponin judged to be due to myocardial ischemia), nonhemorrhagic stroke, peripheral arterial thrombosis (clear evidence of abrupt occlusion of a peripheral artery), and symptomatic proximal VTE (inclusive of

pulmonary embolism or proximal deep vein thrombosis) at 30 days after randomization.

Secondary outcomes included individual components of the safety and efficacy composite outcomes, bleeding independently associated with mortality after noncardiac surgery (BIMS),[11] transfusions (ie, proportion of patients who received a transfusion of 1 or more units of packed red blood cells [pRBCs] transfusion), transfusion of 2 or more units of pRBCs, and transfusion of 2 to 4 units of pRBCs.

Tertiary outcomes included a net risk-benefit outcome as a composite of vascular death, nonfatal life-threatening, major, or critical organ bleeding, MINS, stroke, peripheral arterial thrombosis, symptomatic proximal VTE, all-cause mortality, vascular mortality, International Society on Thrombosis and Hemostasis major bleeding, and infection/sepsis.

Analysis Population and General Surgery Definitions

The overall POISE-3 trial categorized participants into 9 surgery categories (ie, general, orthopedic, vascular, urologic, spinal, gynecologic, thoracic, plastic, and low risk). The focus of this article is patients undergoing general surgery, as defined by the original study protocol (eTable 1 in Supplement 1). The POISE-3 trial reported that 3542 participants had undergone a general surgery procedure (TXA, 1769; placebo, 1773) and 73 participants (TXA, 39; placebo, 24) who underwent a low-risk surgery procedure (eTable 2 in Supplement 1).

For the original POISE-3 trial, study personnel had recorded the category of surgery the participant underwent (eg, general surgery, orthopedic surgery) but not the specific procedure each patient underwent (eg, cholecystectomy, anterior resection, lumpectomy). To conduct the current substudy, all centers that enrolled participants undergoing either general surgery or low-risk surgeries were contacted to obtain the specific name of the procedure that each participant underwent.

Subcategories of General Surgery

We defined, a priori, broad subcategories of general surgery (hepatopancreaticobiliary, colorectal, upper gastrointestinal, head and neck procedures, other major general, and other minor general) (eTable 2 in Supplement 1). These subcategories were developed in consultation with practicing subspecialty general surgeons. Each procedure was subcategorized independently and in duplicate by 2 senior general surgery residents (L.P and C. T. B. K.). Disagreements were resolved through consultation of independent practicing general surgeons.

Statistical Analysis

A statistical analysis plan was finalized on November 16, 2023, before undertaking the analyses. For all analyses, the TXA group was compared with the placebo group. For the primary efficacy and safety outcomes, we followed the modified intention-to-treat principle, where patients who did not undergo surgery or underwent a surgery that was not categorized (ie, not general surgery or nongeneral surgery) were omitted from analyses (n = 67; **Figure 1**). Otherwise, all recruited participants were analyzed in the treatment groups to which they were randomized, regardless of treatments received or duration of trial participation. Any participants lost to follow-up were right censored.

Cox proportional hazards models incorporating tests of interaction were used. The POISE-3 trial had a partial factorial design for which a subset of the patients were also randomized in a blood pressure management trial. Therefore, we adjusted the Cox models for the allocation to the blood pressure strategy. Tests for interaction were conducted between TXA allocation and general surgery status (yes vs no), as well as cancer status, and prespecified subcategories of general surgery. An interaction *P* value <.05 was considered statistically significant for a subgroup effect.

In the original POISE-3 trial, a sample of 9500 patients provided 90% power to detect an HR of 0.80 or less (2-sided α = .05) for TXA vs placebo, assuming a 9.0% incidence of composite bleeding events in the placebo group. This sample also gave 98% power for noninferiority, with a margin of 1.125 (1-sided α = .025), assuming a 14.0% incidence of composite cardiovascular events. This main trial was not powered for the subgroup analyses conducted in the present work.

We provided the effects of TXA vs placebo within each subgroup as HRs and associated 2-sided 95% CIs, and absolute risk differences with the associated 95% CI. The outcome of transfusion rates was analyzed using a logistic regression model and, therefore, was reported as odds ratio (OR). All analyses were conducted using SAS version 9.4 (SAS Institute).

Results

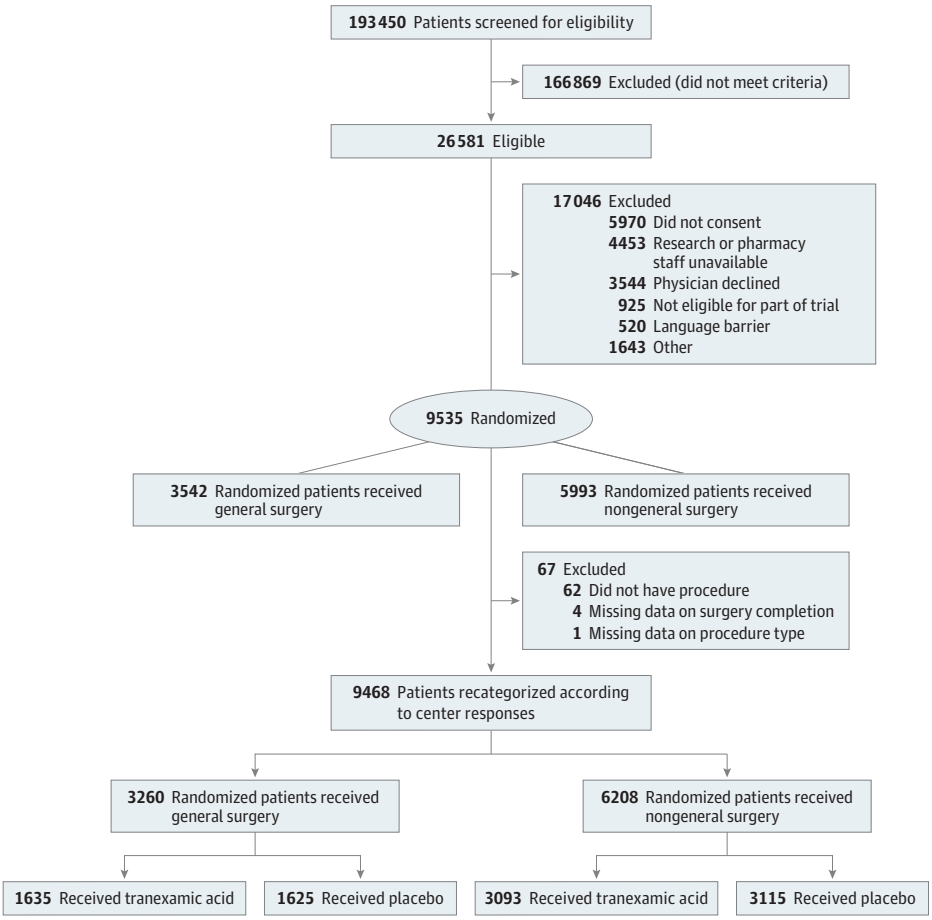
To obtain information on the specific procedure, all participating sites were contacted that enrolled according to the initial coding, 3542 patients who had undergone general surgery, and 73 patients who had undergone low-risk surgery (which could potentially be general surgery procedures). These patients were enrolled from June 2018 to July 2021. Following this data collection, there were 326 procedures originally coded as general surgery for which information was not obtained and were assumed to be correctly categorized to general surgery. There were 282 participants who were originally categorized as general surgery who were recategorized to a nongeneral surgery procedure, and 23 low-risk surgery procedures were identified to be low-risk general surgery procedures.

After this reclassification, the study population included 3260 patients who underwent general surgery procedures (TXA, 1635; placebo, 1625), 6208 who underwent nongeneral surgery procedures (TXA, 3093; placebo, 3115), and 67 who underwent an unknown category of noncardiac surgery. Figure 1 demonstrates the flow of patient inclusion.

Patient Characteristics

Table 1 describes the general surgery participant characteristics based on whether they were in the TXA or placebo group. Among the 3260 general surgery participants, the mean age was 68.6 (SD, 9.6) years, 53.4% were male, 46.6% were female, and 40.8% had active cancer. There were 940 colorectal surgery procedures (28.8%), 793 other low-risk general sur-

Figure 1. Patient Flowchart for Inclusion of Participants in Perioperative Ischemic Evaluation-3 General Surgery Substudy



gery (24.3%), 433 head and neck procedures (13.3%), 332 hepatopancreaticobiliary procedures (10.2%), 275 upper gastrointestinal procedures (8.4%), and 161 other major general surgery procedures (4.9%) (Table 1; eTable 2 in Supplement 1).

Primary Efficacy Outcome

Table 2 and **Figure 2** summarize the primary efficacy and safety outcome analyses. Among general surgery participants, 130 of 1635 in the intervention group (8.0%) and 171 of 1625 in the placebo group (10.5%) experienced the composite bleeding outcome (HR, 0.74; 95% CI, 0.59-0.93; *P* = .01). Among the individual component end points of the composite outcome, major bleeding occurred in 110 of 1635 in the TXA group (6.7%) and 152 of 1625 in the placebo group (9.4%) (HR, 0.71; 95% CI, 0.55-0.90; *P* < .01). The *P* value for interaction was not significant between participants in the general surgery and nongeneral surgery cohorts across the composite efficacy outcome (*P* = .81).

Primary Safety Outcome

In the general surgery cohort, 195 of 1635 in the TXA group (11.9%) and 203 of 1625 in the placebo group (12.5%) experienced the primary composite safety outcome (HR, 0.95; 95% CI, 0.78-1.16; Table 2). There were no differences across the components of the composite outcome (Table 2). The *P* value for interaction between general surgery and nongeneral surgery participants was not statistically significant across the composite safety outcome (*P* = .37).

Subgroup Analyses by Subcategories of General Surgery

Among the subcategories of general surgery, a statistically significant lower risk of the composite bleeding outcome with TXA use was seen among those undergoing hepatopancreaticobiliary surgery (15.0% vs 25.0%; HR, 0.55; 95% CI, 0.34-0.91; *P* = .02) and colorectal surgery (9.3% vs 13.6%; HR, 0.67; 95% CI, 0.45-0.98; *P* = .04). The *P* value for interaction was not significant. Regarding the composite safety outcome, those who underwent head and neck procedures in the TXA group had a lower risk of experiencing an event (4.2% vs 10.4%; HR, 0.39; 95% CI, 0.18-0.84; *P* = .02), which likely drove the *P* value for interaction to be significant for the safety outcome. eTable 3 in Supplement 1 provides further details.

Subgroup Analyses by Cancer Status

The effects of TXA vs placebo on the primary efficacy and safety outcomes were not modified by cancer status within the gen-

eral surgery cohort (*P* values for interaction of .21 and .48, respectively). The treatment effect on VTE was not statistically significantly different between those with and without cancer. See eTable 4 in Supplement 1 for details.

Other Secondary and Tertiary Outcomes

Participants who received TXA in the general surgery subgroup demonstrated reduced risk of BIMS (7.7% vs 9.8%; HR, 0.77; 95% CI, 0.61-0.97; *P* = .03) and receipt of 1 or more units of pRBCs (8.6% vs 10.8%; OR, 0.77; 95% CI, 0.61-0.97; *P* = .03). The *P* values for interaction were .84 and .86, respectively. Within the general surgery subgroup, there were no differences between the TXA and placebo groups regarding the need for transfusion of 2 or more pRBC units or 2 to 4 pRBC units. Details are provided in eTable 5 in Supplement 1.

General surgery participants in the TXA group experienced less bleeding, according to the International Society on Thrombosis and Hemostasis definition for major bleeding (6.9% vs 9.0%; HR, 0.76; 95% CI, 0.59-0.97; *P* = .03). There were no statistically significant differences among subgroups in the general surgery cohort regarding other tertiary outcomes, including all-cause mortality, vascular mortality, infection, and sepsis. None of the *P* value for interactions were statistically significant. eTable 6 in Supplement 1 provides further details.

Discussion

In this POISE-3 substudy, TXA resulted in a significant reduction in major bleeding without an increase in the primary safety outcome within the general surgery subgroup. There was no subgroup effect for TXA vs placebo in the general surgery subpopulation when compared with the nongeneral surgery subpopulation. Within the subcategories of general surgery, TXA demonstrated an efficacy in bleeding reduction in the hepatopancreaticobiliary (HR, 0.55; 95% CI, 0.34-0.91) and colorectal (HR, 0.67; 95% CI, 0.45-0.98) groups without differences in the safety outcome. Subgroup analyses by cancer status also demonstrated no subgroup effect, suggesting that TXA is equally effective among participants undergoing general surgery vs nongeneral surgery and in participants with or without cancer.

The use of TXA has been supported by literature in specific perioperative and acute care settings, namely in postpartum hemorrhage following cesarean deliveries, cardiac surgery, major orthopedic and spine surgical procedures, and trauma.[12-17] Existing studies on TXA use outside of these contexts are commonly limited by small sample sizes.[18,19] The POISE-3 trial addressed the knowledge gap for TXA use in noncardiac surgery.[5]

To our knowledge, the present study provides results for the largest general surgery population to date in the evaluation of prophylactic TXA use. The specific subcategory of general surgery that each participant underwent was collected from participating sites and this added granularity of data redemonstrated TXA efficacy and safety without subgroup effect by general surgery. This bolsters external validity to encourage clinical practice uptake in general surgery contexts, where routine prophylactic TXA is rarely used.

TXA is an antifibrinolytic that inhibits the interaction of plasminogen with plasmin and fibrin, thereby supporting physiologic hemostasis.[20,21] In essence, TXA slows the breakdown of physiologic fibrinolysis.[20,21] Considering this mechanism of action, TXA is limited in the management of profuse, brisk bleeding, as there would not be formed clots for stabilization. For instance, in the CRASH-2 trial (n = 20 211),[17] TXA

Table 1. Baseline Characteristics of Participants Included in the Perioperative Ischemic Evaluation-3 General Surgery Substudy

Characteristic	General surgery (n = 3260), mean (SD)	
	TXA (n = 1635)	Placebo (n = 1625)
Physical measurements/preoperative laboratory assessments, No. (%)		
Age, y	68.8 (9.6)	68.4 (9.5)
Weight, kg	78.3 (20.1)	78.4 (20.6)
Height, cm	165.6 (9.9)	165.7 (9.9)
Body mass index[a]	28.4 (6.3)	28.4 (6.6)
Heart rate, bpm	76.3 (13.1)	76.1 (13.5)
Serum creatinine, μmol/L	84.7 (27.0)	85.6 (32.5)
Hemoglobin, g/L	128.3 (19.0)	128.9 (19.3)
Baseline history, No. (%)		
Sex		
Male	867 (53.0)	873 (53.7)
Female	768 (47.0)	752 (46.3)
History		
Hypertension	1473 (90.1)	1464 (90.1)
Myocardial infarction	151 (9.2)	188 (11.6)
Stroke	123 (7.5)	124 (7.6)
Atrial fibrillation	163 (10.0)	139 (8.6)
Dementia	7 (0.4)	4 (0.2)
Receiving ongoing dialysis	1 (<0.1)	0 (0)
Angiography only	119 (7.3)	123 (7.6)
Coronary revascularization	227 (13.9)	220 (13.5)
Active cancer	666 (40.7)	664 (40.9)
PCI		
BMS	70 (4.3)	62 (3.8)
DES	98 (6.0)	112 (6.9)
CABG surgery	84 (5.1)	69 (4.2)
Previous tobacco use	603 (36.9)	634 (39.0)
Subcategory of general surgery, No. (%)		
Hepatopancreaticobiliary	332 (10.2)	
Colorectal	940 (28.8)	
Upper gastrointestinal	275 (8.4)	
Low-risk general surgery	793 (24.3)	
Other major general surgery	161(4.9)	
Head and neck	433 (13.3)	
Uncategorized general surgery	326 (10.0)	

Abbreviations: BMS, bare metal stent; bpm, beats per minute; CABG, coronary artery bypass graft; DES, drug-eluting stent; PCI, percutaneous coronary intervention; TXA, tranexamic acid.

SI conversion factor: To convert to mg/dL, multiply by 88.4.

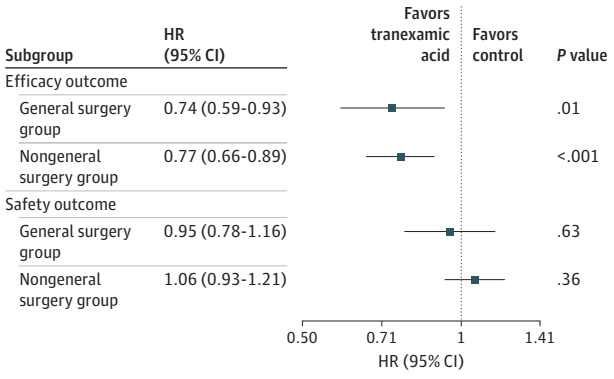
[a] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Primary Safety and Efficacy Outcomes at 30 Days Comparing General Surgery vs Nongeneral Surgery Subgroups

Outcome	No./total No.		TXA vs placebo		
	TXA (n = 4728)	Placebo (n = 4740)	HR (95% CI)	*P* value	*P* value for interaction
Coprimary efficacy outcomes					
Composite					
General surgery	130/1635 (8.0)	171/1625 (10.5)	0.74 (0.59-0.93)	.01	.81
Nongeneral surgery	304/3093 (9.8)	393/3115 (12.6)	0.77 (0.66-0.89)	.001	
Life-threatening bleeding					
General surgery	25/1635 (1.5)	25/1625 (1.5)	0.99 (0.57-1.73)	.98	.91
Nongeneral surgery	53/3093 (1.7)	56/3115 (1.8)	0.95 (0.66-1.39)	.81	
Major bleeding					
General surgery	110/1635 (6.7)	152/1625 (9.4)	0.71 (0.55-0.90)	.01	.85
Nongeneral surgery	254/3093 (8.2)	347/3115 (11.1)	0.73 (0.62-0.85)	<.001	
Critical organ bleeding					
General surgery	4/1635 (0.2)	2/1625 (0.1)	1.98 (0.36-10.8)	.43	.11
Nongeneral surgery	8/3093 (0.3)	19/3115 (0.6)	0.42 (0.19-0.97)	.04	
Coprimary safety outcomes					
Surgery type					
General surgery	195/1635 (11.9)	203/1625 (12.5)	0.95 (0.78-1.16)	.63	.37
Nongeneral surgery	476/3093 (15.4)	454/3115 (14.6)	1.06 (0.93-1.21)	.36	
MINS					
General surgery	184/1635 (11.3)	186/1625 (11.4)	0.98 (0.80-1.20)	.85	.67
Nongeneral surgery	424/3093 (13.7)	415/3115 (13.3)	1.04 (0.90-1.19)	.62	
Nonhemorraghic stroke					
General surgery	4/1635 (0.2)	5/1625 (0.3)	0.80 (0.22-2.98)	.74	.28
Nongeneral surgery	20/3093 (0.6)	11/3115 (0.4)	1.83 (0.88-3.82)	.11	
PAT					
General surgery	2/1635 (0.1)	1/1625 (<0.1)	1.97 (0.18-21.8)	.58	.54
Nongeneral surgery	20/3093 (0.6)	22/3115 (0.7)	0.91 (0.50-1.68)	.77	
VTE					
General surgery	9/1635 (0.6)	12/1625 (0.7)	0.75 (0.32-1.78)	.51	.23
Nongeneral surgery	23/3093 (0.7)	16/3115 (0.5)	1.45 (0.76-2.74)	.26	
Amputation					
General surgery	0/1635 (0)	0/1625 (0)	NA	NA	>.99
Nongeneral surgery	14/3093 (0.5)	22/3115 (0.7)	0.64 (0.33-1.25)	.19	
Seizure					
General surgery	2/1635 (0.1)	2/1625 (0.1)	0.99 (0.14-7.00)	.99	.15
Nongeneral surgery	8/3093 (0.3)	1/3115 (<0.1)	8.11 (1.01-64.8)	.05	

Abbreviations: HR, hazard ratio; MINS, myocardial injury after noncardiac surgery; PAT, peripheral arterial thrombosis; TXA, tranexamic acid; VTE, venous thromboembolism.

Figure 2. Forest Plot of Primary Efficacy and Safety Outcomes



HR indicates hazard ratio.

demonstrated reduced mortality when administered within 3 hours of injury in a trauma population with low injury severity and low rates of penetrating trauma (14.5% vs 16.0%; RR, 0.91; 95% CI, 0.85-0.97; *P* = .004). However, in the HALT-IT trial,[22] which randomized 12 009 patients with significant upper and lower gastrointestinal bleeding, there were no differences in death from bleeding within 5 days of randomization (4% in both groups; RR, 0.99; 95% CI, 0.82-1.18). Rather than being contradictory, these trials suggest that TXA efficacy may vary depending on context. These contextual nuances may introduce variability that obscures TXA effectiveness, underscoring the importance of large-scale studies. Although TXA likely cannot address all forms of bleeding, our work demonstrates it is able to reduce the risk of clinically important bleeding in general surgery contexts.

The mechanism of action of TXA also raises the theoretical concern for increased thromboembolic events. In the overall

POISE-3 trial, it was concluded that there was a low probability of a small increase in the incidence of composite cardiovascular outcome events with an absolute difference of 0.3% (95% CI, −1.1 to 1.7).[5] A large meta-analysis, including 191 RCTs and 40 621 patients in total, has since demonstrated that the noninferiority margin was met (RR, 1.02; 95% CI, 0.94-1.11; P = .65; I^2 = 0; n = 37 512) but demonstrated through trial sequential analysis that the diversity adjusted required information size was 58 036 patients.[7] Although this suggests more trials are needed to definitively determine the effect of TXA on composite cardiovascular thromboembolic outcomes, it also suggests that VTE events are rarer compared with bleeding events.[3,5] In a recent prospective cohort study, including 7950 contemporary general surgery patients, major bleeding was found to be the most common postoperative complication (18.3%) with greatest attributable fraction of death in the cohort.[3] However, any VTE was comparatively uncommon (0.9%) and did not show association with 30-day mortality.[3] Altogether, this demonstrates the urgent need to reduce perioperative bleeding, prompting careful consideration of the clear beneficial reduction in composite bleeding against the low probability of a small increase in cardiovascular events with prophylactic TXA use.[5]

Limitations

The major limitation is that this was a subgroup analysis of the POISE-3 trial, and as such, the study was not powered for the subgroups and subcategories explored. However, there was biological rationale underpinning the subgroups and subcategories, which were determined a priori. We also used P values for interactions to investigate for subgroup effects. Moreover, for the general surgery cohort there were over 300 primary efficacy outcomes and approximately 400 primary safety outcomes. Another limitation is that there are variations in bleeding risk across the subcategories of general surgery. Lastly, hemostatic management, including transfusion triggers, may have varied between surgeons and institutions across this pragmatic multicenter trial.[23-25] Nonetheless, this remains the largest general surgery population to date in which the safety and efficacy of TXA have been investigated.

Conclusions

The POISE-3 trial provides the optimal estimate of effect for TXA in noncardiac surgery, including general surgery. In POISE-3, TXA reduced the risk of a composite bleeding outcome without increasing the risk of a composite cardiovascular risk outcome. There were no significant interactions between the effects of TXA vs placebo and the type of surgery (general surgery or nongeneral surgery, and across subcategories of general surgery) or cancer status. The absence of subgroup effects suggests that TXA reduces bleeding without increasing cardiovascular risk for both general surgery and nongeneral surgery patients.

ARTICLE INFORMATION

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