Tranexamic Acid in Patients Undergoing Noncardiac Surgery

P.J. Devereaux, M. Marcucci, T.W. Painter, D. Conen, V. Lomivorotov, D.I. Sessler, M.T.V. Chan, F.K. Borges, M.J. Martínez-Zapata, C.Y. Wang, D. Xavier, S.N. Ofori, M.K. Wang, S. Efremov, G. Landoni, Y.V. Kleinlugtenbelt, W. Szczeklik, D. Schmartz, A.X. Garg, T.G. Short, M. Wittmann, C.S. Meyhoff, M. Amir, D. Torres, A. Patel, E. Duceppe, K. Ruetzler, J.L. Parlow, V. Tandon, E. Fleischmann, C.A. Polanczyk, A. Lamy, S.V. Astrakov, M. Rao, W.K.K. Wu, K. Bhatt, M. de Nadal, V.V. Likhvantsev, P. Paniagua, H.J. Aguado, R.P. Whitlock, M.H. McGillion, M. Prystajecky, J. Vincent, J. Eikelboom, I. Copland, K. Balasubramanian, A. Turan, S.I. Bangdiwala, D. Stillo, P.L. Gross, T. Cafaro, P. Alfonsi, P.S. Roshanov, E.P. Belley-Côté, J. Spence, T. Richards, T. VanHelder, W. McIntyre, G. Guyatt, S. Yusuf, and K. Leslie, for the POISE-3 Investigators*

ABSTRACT

BACKGROUND

Perioperative bleeding is common in patients undergoing noncardiac surgery. Tranexamic acid is an antifibrinolytic drug that may safely decrease such bleeding.

METHODS

We conducted a trial involving patients undergoing noncardiac surgery. Patients were randomly assigned to receive tranexamic acid (1-g intravenous bolus) or placebo at the start and end of surgery (reported here) and, with the use of a partial factorial design, a hypotension-avoidance or hypertension-avoidance strategy (not reported here). The primary efficacy outcome was life-threatening bleeding, major bleeding, or bleeding into a critical organ (composite bleeding outcome) at 30 days. The primary safety outcome was myocardial injury after noncardiac surgery, nonhemorrhagic stroke, peripheral arterial thrombosis, or symptomatic proximal venous thromboembolism (composite cardiovascular outcome) at 30 days. To establish the noninferiority of tranexamic acid to placebo for the composite cardiovascular outcome, the upper boundary of the one-sided 97.5% confidence interval for the hazard ratio had to be below 1.125, and the one-sided P value had to be less than 0.025.

RESULTS

A total of 9535 patients underwent randomization. A composite bleeding outcome event occurred in 433 of 4757 patients (9.1%) in the tranexamic acid group and in 561 of 4778 patients (11.7%) in the placebo group (hazard ratio, 0.76 ; 95% confidence interval [CI], 0.67 to 0.87 ; absolute difference, -2.6 percentage points; 95%CI, -3.8 to -1.4 ; two-sided P<0.001 for superiority). A composite cardiovascular outcome event occurred in 649 of 4581 patients (14.2%) in the tranexamic acid group and in 639 of 4601 patients (13.9%) in the placebo group (hazard ratio, 1.02; 95% CI, 0.92 to 1.14 ; upper boundary of the

one-sided 97.5%CI, 1.14; absolute difference, 0.3 percentage points; 95%CI,-1.1 to 1.7 ; one-sided P=0.04 for noninferiority).

CONCLUSIONS

Among patients undergoing noncardiac surgery, the incidence of the composite bleeding outcome was significantly lower with tranexamic acid than with placebo. Although the between-group difference in the composite cardiovascular outcome was small, the noninferiority of tranexamic acid was not established. (Funded by the Canadian Institutes of Health Research and others; POISE-3 ClinicalTrials.gov number, NCT03505723.)

PERIOPERATIVE BLEEDING, A COMMON complication in patients undergoing noncardiac surgery, is associated with increased morbidity and mortality. [1−4] Large surgical trials have shown that tranexamic acid reduces the incidence and severity of bleeding in patients undergoing cesarean section or cardiac surgery. [5,6] Encouraging evidence from small trials suggests that tranexamic acid may reduce the incidence and severity of bleeding in patients undergoing orthopedic surgery [7]; there are limited data on its use in patients undergoing nonorthopedic noncardiac surgeries. [8] Tranexamic acid is an antifibrinolytic drug, [9] and trials have not been large enough to establish whether tranexamic acid increases the risk of thrombotic events in noncardiac surgery.

We undertook the Perioperative Ischemic Evaluation-3 (POISE-3) trial to answer the following questions. In patients undergoing noncardiac surgery who are at risk for bleeding and cardiovascular events, does tranexamic acid result in a lower incidence of life-threatening bleeding, major bleeding, or bleeding into a critical organ than placebo, and is it noninferior to placebo with respect to the incidence of major cardiovascular complications within 30 days?

METHODS

TRIAL DESIGN

In this international, randomized, controlled trial, we evaluated the effects of tranexamic acid as compared with placebo in patients undergoing noncardiac surgery. We used a partial factorial design in patients who were receiving at least one long-term antihypertensive medication to evaluate a hypotension-avoidance strategy as compared with a hypertension-avoidance strategy. We report the results of the trial of tranexamic acid here. Details of the trial design have been published previously.[10] Trial centers obtained ethics approval before commencing recruitment.

TRIAL OVERSIGHT

The trial was funded by the Canadian Institutes of Health Research and others. The Population Health Research Institute was the trial coordinating center and was responsible for the randomization scheme, database, data validation, analyses, and trial

coordination. No external funder had a role in the design or conduct of the trial, collection or analysis of the data, or preparation of the manuscript. The steering committee designed the trial and vouches for the accuracy and completeness of the data and for the adherence of the trial to the protocol, available with the full text of this article at NEJM.org. Investigators and trial personnel collected the data. The writing committee finalized the statistical analysis plan, available with the protocol, before any investigator was made aware of the trial results. The first author wrote the first draft of the manuscript, and the writing committee made revisions and made the decision to submit the manuscript for publication. There were no agreements concerning confidentiality of the data between the sponsors (i.e., funders) and the authors or their institutions.

PATIENTS

We recruited patients from June 2018 through July 2021 at 114 hospitals in 22 countries. Eligible patients were 45 years of age or older, were undergoing inpatient noncardiac surgery, and were at risk for bleeding and cardiovascular complications according to criteria previously associated with perioperative bleeding and cardiovascular complications (e.g., known atherosclerotic disease, undergoing major surgery, an age of ≥ 70 years, and a serum creatinine level of $> 175\mu$ mol per liter [2.0 mg per deciliter]). [11,12] Patients were excluded if they were undergoing cardiac surgery or intracranial neurosurgery, if a physician planned to administer systemic tranexamic acid during surgery, or if the patient had a creatinine clearance of less than 30 ml per minute (CockcroftGault equation) or was receiving long-term dialysis. All eligibility criteria are presented in Section S1 in the Methods section in the Supplementary Appendix, available at NEJM.org.

PROCEDURES

After written informed consent was obtained from all the patients or a patient-designated decision maker, randomization was performed by means of a central computerized system with the use of block randomization, with stratification according to center. Patients were assigned in a 1:1 ratio to receive tranexamic acid (1-g intravenous bolus) or placebo at the start and end of surgery and, in a 1:1 ratio with the use of a partial factorial design, to a hypotension-avoidance strategy or a hyper-tension-avoidance strategy. Patients, health care providers, data collectors, and outcome adjudicators were unaware of the trial-group assignments. The follow-up process is described in Section S2.

TRIAL OUTCOMES

The primary efficacy outcome was a composite of life-threatening bleeding, major bleeding, and bleeding into a critical organ - henceforth referred to as the composite bleeding outcome at 30 days after randomization. The primary safety outcome was a composite of myocardial injury after noncardiac surgery (i.e., myocardial infarction or isolated ischemic troponin elevation), nonhemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism - henceforth referred to as the composite cardiovascular outcome - at 30 days after randomization.

Secondary and tertiary outcomes (Section S3) included the individual components of the composite bleeding outcome and the composite cardiovascular outcome, bleeding independently associated with death after noncardiac surgery, [4] myocardial infarction, a net risk-benefit outcome (death from cardiovascular causes, nonfatal lifethreatening bleeding, major bleeding, bleeding into a critical organ, myocardial injury after noncardiac surgery, stroke, peripheral arterial thrombosis, or symptomatic proximal venous thromboembolism), major bleeding according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH) [13], transfusion of at least 1 unit of packed red cells, amputation, any symptomatic or asymptomatic proximal venous thromboembolism, and seizure. Outcome definitions, monitoring, and the adjudication process are described in Sections S4, S5, and S6, respectively.

STATISTICAL ANALYSIS

The primary efficacy hypothesis was that tranexamic acid would be superior to placebo with respect to the composite bleeding outcome. The primary safety hypothesis was that tranexamic acid would be noninferior to placebo with respect to the composite cardiovascular outcome. To satisfy the noninferiority hypothesis, the upper boundary of the one-sided 97.5% confidence interval for the hazard ratio of the composite cardiovascular outcome - which corresponds to the upper boundary of the two-sided 95% confidence interval - had to be below 1.125, and the one-sided P value had to be less than 0.025 . The noninferiority margin corresponds to a relative increase in risk of 12.5%, which is half the relative decrease in risk of 25% that we looked for to establish the superiority of aspirin to placebo in the POISE-2 trial. [1,14] To inform our primary hypotheses, the POISE-3 trial was initially designed to randomly assign 10,000 patients to receive tranexamic acid or placebo (Section S7).

Owing to a financial deficit resulting from slowed recruitment during the coronavirus disease 2019 (Covid-19) pandemic, the steering committee stopped recruitment on July 15, 2021, after at least 9500 patients had undergone randomization. This decision was made without knowledge of the trial results but with knowledge that the incidences of the aggregate composite bleeding and composite cardiovascular outcome events were higher than originally estimated. We estimated that a sample of 9500 patients would provide the trial with 90% power to detect a hazard ratio of 0.80 or less (two-sided alpha level of 0.05) for tranexamic acid as compared with placebo, assuming an incidence of composite bleeding outcome events of 9.0% in the placebo group. Stopping the trial at 9500 patients also provided the trial with 98% power for a noninferiority margin, expressed as a hazard ratio of 1.125 (one-sided alpha level of 0.025), under the assumption of an incidence of composite cardiovascular outcome events of 14.0% in the placebo group and an expected hazard ratio of 0.90 and with adjustment for the partial factorial design.

The noninferiority hypothesis was evaluated in the per-protocol population (i.e., patients who received both planned doses of tranexamic acid or placebo). For all the other analyses, data were analyzed in the intention-to-treat population (i.e., patients evaluated in the trial group to which they had been randomly assigned). Data for patients who were lost to follow-up were censored on the last day that their status was known. An independent data and safety monitoring committee reviewed interim analyses when

25%, 50%, and 75% of the 30-day data were available. Details of the interim analyses are provided in Section S8.

Most outcomes were analyzed with the use of Cox proportional-hazards models, with stratification according to trial group in the blood-pressure management factorial. For the Cox models, we calculated the hazard ratio, corresponding 95% confidence interval, and associated P value. A two-sided *P* value of less than 0.05 was considered to indicate statistical significance. For the primary efficacy and safety outcomes, we assessed whether the blood-pressure management factorial affected the results of tranexamic acid as compared with placebo using Cox proportionalhazards models that incorporated tests of interaction.

We analyzed the binary outcome of transfusion using a two-by-two table and analyzed length of hospital stay and days alive at home using quantile regression. Because we did not correct for multiplicity when conducting tests for secondary or tertiary outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for the secondary or tertiary outcomes.

We performed four prespecified subgroup analyses of the primary outcomes; subgroups were defined according to type of surgery, hemoglobin level, estimated glomerular filtration rate, and N-terminal pro-brain natriuretic peptide level (Section S9). For the composite cardiovascular outcome, we performed a sensitivity analysis according to the intention-to-treat principle. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS, FOLLOW-UP, AND ADHERENCE

We randomly assigned 9535 patients to receive tranexamic acid (4757 patients) or placebo (4778 patients) (Fig. S1). The 30-day follow-up visit was completed for 99.9% of the patients. The baseline characteristics of the patients, type of noncardiac surgeries, and preoperative medications were similar in the two groups (Table 1). The mean age of the patients was 69.4 years, and 4183 were women (43.9%). Most patients underwent nonorthopedic noncardiac surgery (76.8%). Most patients were enrolled in North America (31.1%), Europe (39.8%), and the Asia-Pacific region (27.0%) (Table S1). A total of 75.9% of the patients were White (Table S2).

In both the tranexamic acid group and the placebo group, 96.3% of the patients received both doses of the trial agent (Table S3). Administration of nontrial antifibrinolytic drugs was uncommon (Table S4), and the postoperative use of drugs during the hospital stay that can increase the risk of bleeding was similar in the two groups (Table S5). After surgery, 64.2% of the patients in the tranexamic acid group and 63.6% of those in the placebo group received prophylactic medication against venous thromboembolism.

PRIMARY OUTCOMES

A composite bleeding outcome event occurred in 433 patients (9.1%) in the tranexamic acid group and in 561 patients (11.7%) in the placebo group (hazard ratio, 0.76; 95% confidence interval [CI], 0.67 to 0.87 ; absolute difference, -2.6 percentage points; 95% CI, -3.8 to -1.4 ; two-sided P<0.001 for superiority) (Table 2 and Fig. 1). A composite cardiovascular outcome event occurred in 649 of 4581 patients (14.2%) in the tranexamic acid group and in 639 of 4601 patients (13.9%) in the placebo group (hazard ratio, 1.02; 95% CI, 0.92 to 1.14; upper boundary of the one-sided 97.5% CI, 1.14; absolute difference, 0.3 percentage points; 95% CI, -1.1 to 1.7; one-sided $P = 0.04$ for noninferiority); the sensitivity analysis performed according to the intention-to-treat principle produced a similar result (hazard ratio, 1.03; 95%CI, 0.92 to 1.14).

The interaction term of log-time according to trial group in the models indicated that the assumptions of proportional hazards were not violated ($P = 0.75$ for interaction in the analysis of the primary efficacy outcome and $P = 0.48$ for interaction in the analysis of the primary safety outcome). The blood-pressure management factorial had no significant effect on the results of the comparison between tranexamic acid and placebo for the primary efficacy outcome ($P = 0.67$ for interaction) and the primary safety outcome ($P = 0.74$ for interaction).

SECONDARY AND TERTIARY OUTCOMES AND SERIOUS ADVERSE EVENTS

With respect to secondary outcomes (Table 2), bleeding independently associated with death after noncardiac surgery occurred in 416 patients in the tranexamic acid group (8.7%) and in 541 patients (11.3%) in the placebo group (hazard ratio, 0.76; 95%CI, 0.67 to 0.87); major bleeding occurred in 363 patients (7.6%) and in 496 patients (10.4%), respectively (hazard ratio, 0.72; 95%CI, 0.63 to 0.83); and a net risk-benefit outcome event occurred in 983 patients (20.7%) and in 1046 patients (21.9%), respectively (hazard ratio, 0.94; 95% CI, 0.86 to 1.02). With respect to tertiary outcomes (Table 3), major bleeding according to ISTH criteria occurred in 315 patients (6.6%) in the tranexamic acid group and in 415 patients Hazard ratios for selected secondary and tertiary outcomes in the tranexamic acid group as compared with the placebo group are as follows: for myocardial infarction, 1.27 (95%CI, 0.89 to 1.82); for nonhemorrhagic stroke, 1.51 (95%CI, 0.80 to 2.84); for peripheral arterial thrombosis, 0.96 (95%CI, 0.53 to 1.72); for amputation, 0.67 (95% CI, 0.34 to 1.31); and for any symptomatic or asymptomatic proximal venous thromboembolism, 1.15 (95% CI, 0.69 to 1.91) (Tables 2 and 3). Serious adverse events occurred in 263 patients (5.5%) in the tranexamic acid group and in 242 patients (5.1%) in the placebo group ($P = 0.16$) (Table S6).

Table 1. Baseline Characteristics of the Patients, Type of Surgery, and Medications.*

Characteristics	**Tranexamic Acid (N = 4757)**	**Placebo (N = 4778)**
Age - yr	69.5 ± 9.5	69.3 ± 9.4
Male sex - no./total no. (%)	2669/4755 (56.1)	2681/4778 (56.1)
Eligibility criteria met - no. (%)	4742 (99.7)	4766 (99.7)
NT-proBNP $\geq \frac{200\text{ng}}{\text{liter}}$	574 (12.1)	552 (11.6)
History of coronary artery disease	1410 (29.6)	1466 (30.7)
History of peripheral artery disease	714 (15.0)	722 (15.1)
History of stroke	400 (8.4)	388 (8.1)
Undergoing major vascular surgery	541 (11.4)	544 (11.4)
Risk criteria		
Met ≥ 3 of 9 criteria	3988 (83.8)	4003 (83.8)
Undergoing major surgery †	3741 (78.6)	3798 (79.5)
Undergoing urgent or emergency surgery	555 (11.7)	540 (11.3)
Age ≥ 70yr	2611 (54.9)	2588 (54.2)
Current diabetes for which medication is taken	1749 (36.8)	1812 (37.9)
Preoperative serum creatinine level $> \frac{175\mu\text{ mol}}{\text{liter}}$	57 (1.2)	73 (1.5)
History of congestive heart failure	674 (14.2)	671 (14.0)
History of transient ischemic attack	282 (5.9)	247 (5.2)
History of hypertension	4293 (90.2)	4321 (90.4)
History of smoking within 2 yr before surgery	1131 (23.8)	1128 (23.6)
Other medical history - no. (%)		
Atrial fibrillation	478 (10.0)	445 (9.3)
Active cancer	1311 (27.6)	1360 (28.5)
Surgery - no./total no. (%)		
Any procedure	4729/4757 (99.4)	4740/4778 (99.2)
General ‡	1769/4729 (37.4)	1773/4740 (37.4)
Orthopedic	1083/4729 (22.9)	1063/4740 (22.4)

Vascular	699/4729 (14.8)	700/4740 (14.8)
Urologic	598/4729 (12.6)	624/4740 (13.2)
Spinal	237/4729 (5.0)	206/4740 (4.3)
Gynecologic	162/4729 (3.4)	171/4740 (3.6)
Thoracic	127/4729 (2.7)	146/4740 (3.1)
Low-risk	39/4729 (0.8)	34/4740 (0.7)
Plastic	14/4729 (0.3)	23/4740 (0.5)
Data missing on type of procedure performed	1/4729 (<0.1)	0/4740
No procedure performed	27/4757 (0.6)	35/4778 (0.7)
Data missing on whether patient underwent surgery	1/4757 (<0.1)	3/4778 (0.1)
Medication taken within 24 hr before surgery - no. (%)		
Therapeutic-dose thrombin or factor Xa inhibitor	22 (0.5)	28 (0.6)
Therapeutic-dose vitamin K antagonist	6 (0.1)	8 (0.2)
Therapeutic-dose intravenous or subcutaneous antithrombotic agent	58 (1.2)	44 (0.9)
Prophylactic-dose anticoagulant	753 (15.8)	757 (15.8)
Aspirin	638 (13.4)	634 (13.3)
P2Y12 inhibitor	88 (1.8)	84 (1.8)
Nonsteroidal antiinflammatory drug	266 (5.6)	267 (5.6)
Cyclooxygenase-2 inhibitor	132 (2.8)	158 .3)

* Plus-minus values are means ± SD. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. NT-proBNP denotes N-terminal probrain natriuretic peptide.
† Major surgery was defined as intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery.
‡ General surgery was defined as complex visceral resection (i.e., surgery involving the liver, esophagus, pancreas, or multiple organs); partial or total colectomy, stomach surgery, or small-bowel resection; major head and neck resection for nonthyroid tumor; or other intraabdominal surgery (e.g., dissection of the gallbladder, appendix, adrenal glands, spleen, or regional lymph nodes).

Table 2. Effects of Tranexamic Acid on 30-Day Outcomes*

Outcome	Tranexamic Acid (N = 4757)	Placebo (N = 4778)	Hazard Ratio (95% CI) †	P Value
Primary efficacy outcome: composite bleeding outcome - no. (%) ‡	433 (9.1)	561 (11.7)	0.76 (0.67-0.87)	<0.001 【
Individual components of composite bleeding outcome - no. (%)				
Life-threatening bleeding ¶	78 (1.6)	79 (1.7)	0.99 (0.73-1.36)	
Major bleeding **I**	363 (7.6)	496 (10.4)	0.72 (0.63-0.83)	
Bleeding into a critical organ |	12 (0.3)	21 (0.4)	0.57 (0.28-1.16)	
Primary safety outcome: composite cardiovascular outcome - no./total no. (%)‖	649/4581 (14.2)	639/4601 (13.9)	1.02 (0.92-1.14)	0.04**
Individual components of composite cardiovascular outcome - no. (%)				
MINS |	608 (12.8)	602 (12.6)	1.02 (0.91-1.14)	
Nonhemorrhagic stroke ††	24 (0.5)	16 (0.3)	1.51 (0.80-2.84)	
Peripheral arterial thrombosis † †	22 (0.5)	23 (0.5)	0.96 (0.53-1.72)	
Symptomatic proximal venous thromboembolism ††	32 (0.7)	28 (0.6)	1.15 (0.69-1.91)	
Other secondary outcomes - no. (%)				
Bleeding independently associated with death after noncardiac surgery	416 (8.7)	541 (11.3)	0.76 (0.67-0.87)	
MINS not fulfilling the universal definition of myocardial infarction	549 (11.5)	549 (11.5)	1.01 (0.89-1.13)	
Myocardial infarction	67 (1.4)	53 (1.1)	1.27 (0.89-1.82)	
Net risk-benefit outcome ‡ ‡	983 (20.7)	1046 (21.9)	0.94 (0.86-1.02)	

* MINS denotes myocardial injury after noncardiac surgery.
† The widths of the confidence intervals for the secondary and tertiary outcomes have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for these outcomes.
‡ The composite bleeding outcome was a composite of life-threatening bleeding, major bleeding, and bleeding into a critical organ.
∫ Shown is the two-sided P value for superiority.
| This is a secondary outcome.
|| The composite cardiovascular outcome was a composite of myocardial injury after noncardiac surgery, nonhemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism.
** Shown is the one-sided P value for noninferiority. To show statistical significance, this P value had to be less than 0.025 .
帧 This is a tertiary outcome.
† The net risk-benefit outcome was a composite of death from cardiovascular causes, nonfatal life-threatening bleeding, major bleeding, bleeding into a critical organ, MINS, stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism

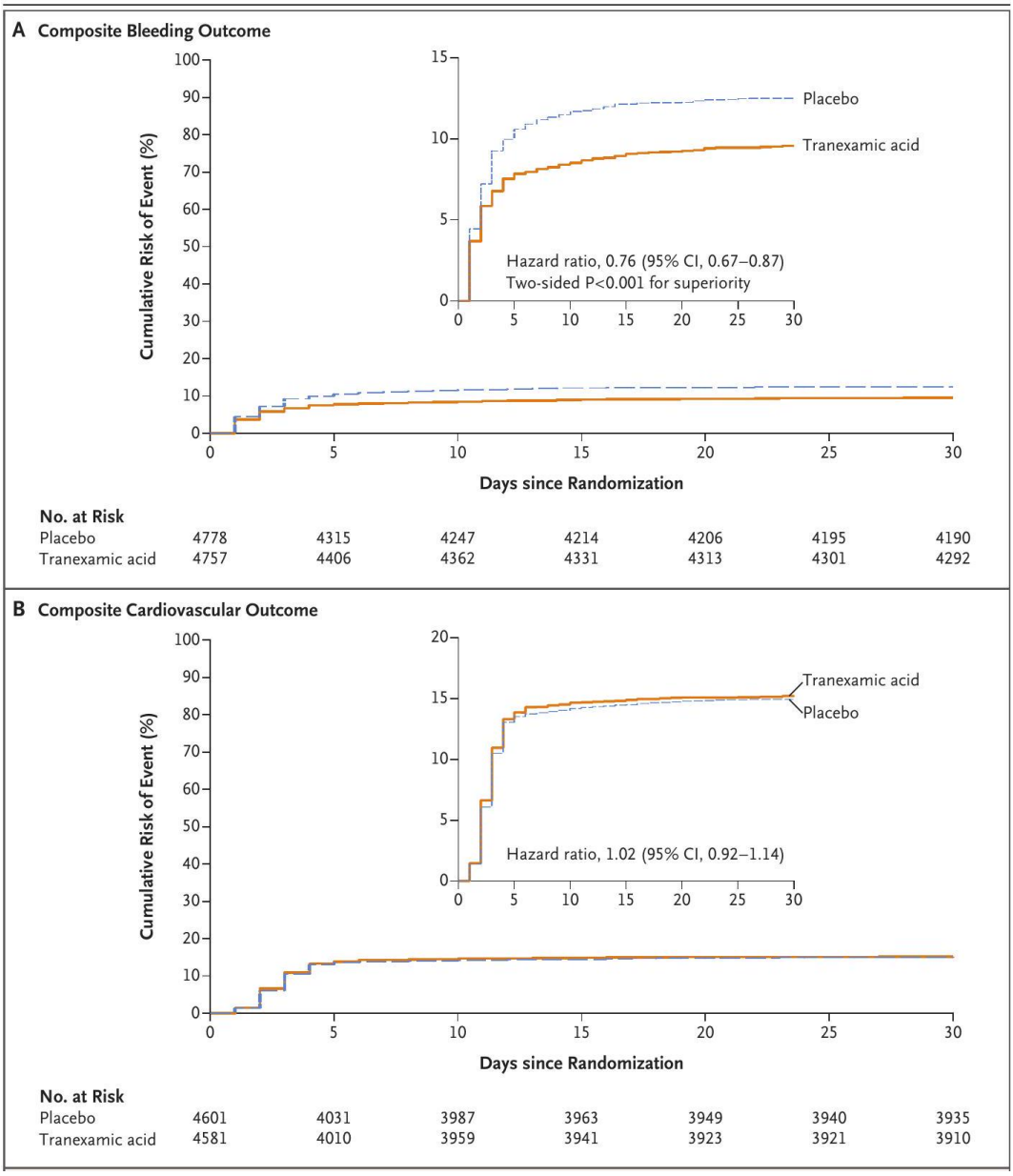


Figure 1. Kaplan-Meier Estimates of the Primary Outcomes.

The composite bleeding outcome (Panel A) was a composite of life-threatening bleeding, major bleeding, and bleeding into a critical organ at 30 days. The composite cardiovascular outcome (Panel B) was a composite of myocardial injury after noncardiac surgery, nonhemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism at 30 days. The insets show the same data on an expanded *y* axis. (8.7%) in the placebo group (hazard ratio, 0.75; 95%CI, 0.65 to 0.87), and transfusion of at least 1 unit of packed red cells occurred in 449 patients (9.4%) and in 574 patients (12.0%), respectively (odds ratio, 0.77; 95%CI, 0.68 to 0.88).

Table 3. Effects of Tranexamic Acid on 30-Day Tertiary Outcomes.*

Outcome	Tranexamic Acid (N = 4757)	Placebo (N = 4778)	Hazard Ratio (95% CI) †
Major bleeding according to ISTH criteria - no. (%)	315 (6.6)	415 (8.7)	0.75 (0.65 to 0.87)
Transfusion of ≥ 1 unit of packed red cells - no. (%)	449 (9.4)	574 (12.0)	0.77 (0.68 to 0.88) ‡
Death from any cause - no. (%)	52 (1.1)	57 (1.2)	0.92 (0.63 to 1.33)
Death from cardiovascular cause - no. (%)	25 (0.5)	30 (0.6)	0.84 (0.49 to 1.42)
Hemorrhagic stroke - no. (%)	2 (<0.1)	0	-
Amputation - no. (%)	14 (0.3)	21 (0.4)	0.67 (0.34 to 1.31)
Symptomatic pulmonary embolism - no. (%)	24 (0.5)	17 (0.4)	1.42 (0.76 to 2.64)
Symptomatic proximal deep venous thrombosis - no. (%)	11 (0.2)	13 (0.3)	0.85 (0.38 to 1.90)
Any symptomatic or asymptomatic proximal venous thromboembolism - no. (%)	32 (0.7)	28 (0.6)	1.15 (0.69 to 1.91)
Cardiac revascularization - no. (%)	12 (0.3)	13 (0.3)	0.93 (0.42 to 2.03)
Acute kidney injury - no. (%)/J	672 (14.1)	655 (13.7)	1.03 (0.93 to 1.15)
New renal-replacement therapy - no. (%)	19 (0.4)	16 (0.3)	1.19 (0.61 to 2.32)
Rehospitalization for cardiovascular reasons - no. (%)	84 (1.8)	75 (1.6)	1.13 (0.82 to 1.54)
Seizure - no. (%)	10 (0.2)	3 (0.1)	3.35 (0.92 to 12.20)
Infection - no. (%)	499 (10.5)	487 (10.2)	1.03 (0.91 to 1.17)
Sepsis - no. (%)	68 (1.4)	63 (1.3)	1.08 (0.77 to 1.53)
Median length of hospital stay (IQR) - days	4.0 (2.1 to 7.1)	4.0 (2.1 to 7.1)	0 (-0.1 to 0.1) 【
Median no. of days alive at home (IQR)	25 (22 to 28)	25 (21 to 28)	0 (-0.4 to <0.1) 【
Disability - no. (%)	1408 (31.9)	1407 (31.6)	1.02 (0.92 to 1.13) ‖

* IQR denotes interquartile range, and ISTH International Society on Thrombosis and Haemostasis. † The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.
‡ Shown is the odds ratio.
/ Acute kidney injury was defined as an increase in the serum creatinine concentration from the preoperative (prerandomization) concentration either by 26.5μ mol or more per liter (0.3 mg per deciliter) within 48 hours after surgery or by 50% or more within 7 days after surgery.
| Shown is the median difference.
‖ Shown is the odds ratio from logistic regression with a score on the 12-item World Health Organization Disability Schedule 2.0 (WHODAS 2.0) of 12 or higher at 30 days as the dependent variable, with

adjustment for the WHODAS 2.0 score at baseline. WHODAS 2.0 scores range from 0 to 48 , with higher scores indicating greater disability. A score of 12 or higher represents a disability level of 25% or higher. A total of 4416 patients in the tranexamic acid group and 4459 in the placebo group had baseline and follow-up data available and were included in the analyses.

PRESPECIFIED SUBGROUP ANALYSES AND POST HOC ANALYSES

The results in the tranexamic acid group as compared with the placebo group with respect to the primary efficacy and safety outcomes were consistent across the prespecified subgroups (Fig. 2) and, in post hoc analyses, were generally consistent across all major surgical subgroups (Fig. S2). The odds ratio for transfusion of at least 2 units of packed red cells in the tranexamic acid group as compared with the placebo group was 0.74 (95% CI, 0.64 to 0.86), and the odds ratio for transfusion of 2 to 4 units of packed red cells was 0.71 (95% CI, 0.60 to 0.84) (Table S7). Results of a competingrisks analysis that was adjusted for death that prevented observation of the primary outcome events were consistent with the results of the primary efficacy and safety analyses (Table S8).

DISCUSSION

In this trial involving patients undergoing noncardiac surgery who met criteria for increased risk of bleeding and cardiovascular events, composite bleeding outcome events (life-threatening bleeding, major bleeding, and bleeding into a critical organ) proved common (11.7% in the placebo group), and the likelihood of composite bleeding outcome events was lower with tranexamic acid than with placebo (hazard ratio, 0.76 ; 95% CI, 0.67 to 0.87). The noninferiority of tranexamic acid to placebo with respect to the composite cardiovascular outcome was not shown (hazard ratio, 1.02; 95% CI, 0.92 to 1.14).

Large trials have shown that tranexamic acid, as compared with placebo, is associated with a lower risk of death due to bleeding among patients with postpartum hemorrhage (relative risk, 0.81; 95% CI, 0.65 to 1.00) and a lower risk of death among patients with trauma (relative risk, 0.91; 95% CI, 0.85 to 0.97). [15,16] Large surgical trials have shown that tranexamic acid resulted in a lower incidence of postpartum hemorrhage among patients undergoing cesarean section and a lower incidence of hemorrhage resulting in reoperation among patients undergoing cardiac surgery than placebo. [5,6]

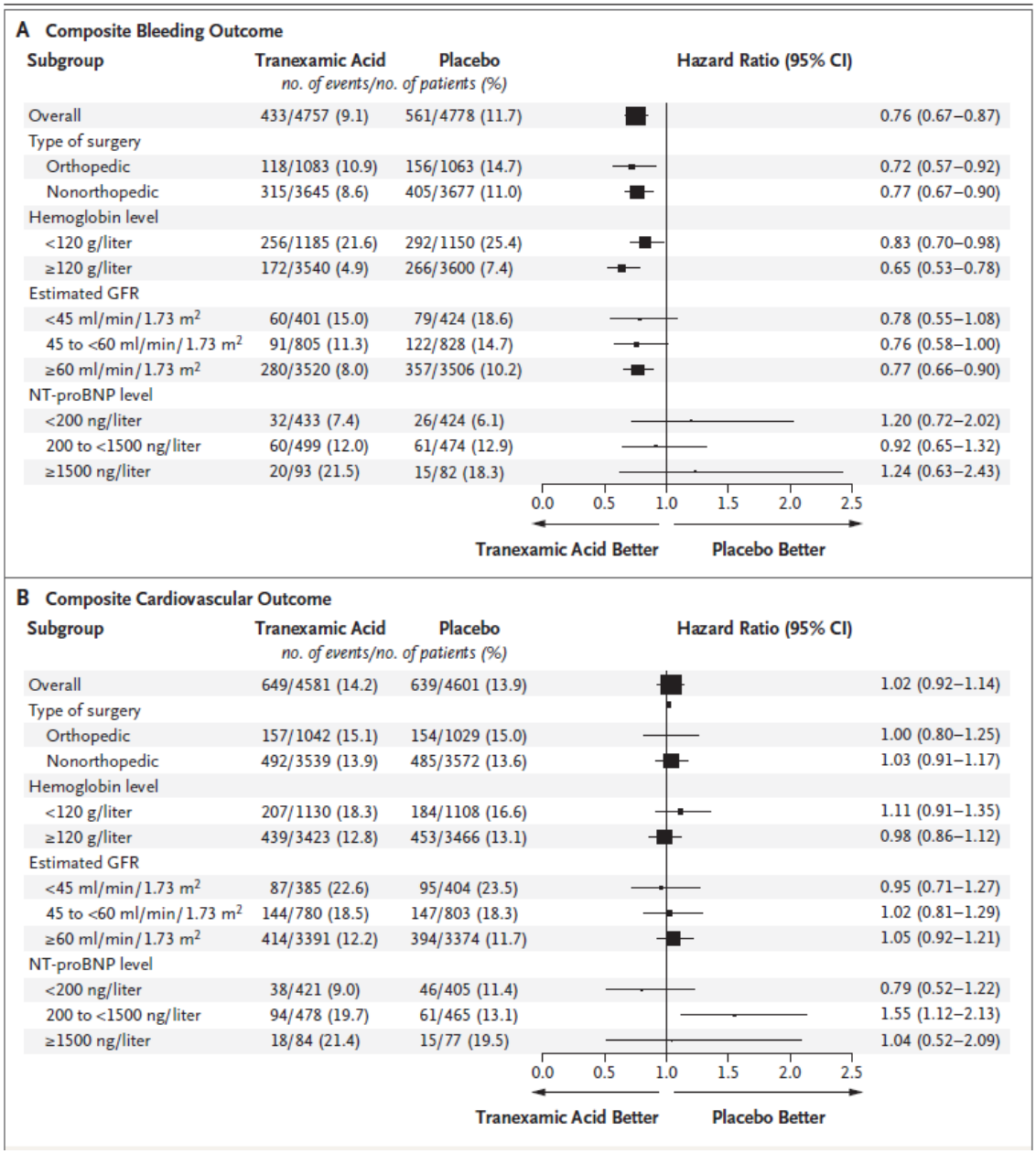


Figure 2. Prespecified Subgroup Analyses.

The size of the boxes is proportional to the number of patients with events. GFR denotes glomerular filtration rate, and NT-proBNP N-terminal pro-brain natriuretic peptide.

Small trials suggest that tranexamic acid reduces the risk of bleeding among patients undergoing orthopedic surgery or nonorthopedic noncardiac surgery. [7,8] Although a recent meta-analysis of trials in diverse settings showed no increased risk of thromboembolic events with tranexamic acid, [17] the noncardiac surgery trials were small, which limits their reliability. [18] POISE-3 was a large trial addressing this knowledge gap in noncardiac surgery.

A recent meta-analysis of trials showed no dose response with tranexamic acid as compared with control for thrombotic events (2620 total events; relative risk, 1.00; 95% CI, 0.93 to 1.08); however, there was a dose response for seizures ($P = 0.01$). [19] Tranexamic acid doses of 2 g or less per day as compared with control were not associated with an increased risk of seizure (676 events; relative risk, 1.02 ; 95% CI, 0.88 to 1.19), whereas tranexamic acid doses of more than 2 g per day were associated with an increased risk of seizure (79 events; relative risk, 3.05 ; 95% CI, 1.01 to 9.02). In the POISE-3 trial, we evaluated a tranexamic acid dose of 2 g per day as compared with placebo, and seizures were uncommon (in 0.2% and <0.1% of the patients, respectively; hazard ratio, 3.35; 95% CI, 0.92 to 12.20).

A trial involving patients undergoing cesarean section showed that tranexamic acid was associated with a higher incidence of nausea and vomiting than placebo (relative risk, 1.19; 95% CI, 1.08 to 1.30). In the POISE-3 trial, we did not collect data on nausea and vomiting outcomes, but tranexamic acid was not associated with an increased risk of nausea or vomiting reported as a serious adverse event. We report significant between-group differences in serious adverse events for a few category outcomes (e.g., cardiovascular disorders); however, within these categories, the between-group differences in most individual serious adverse events were not significant, had contrasting results (e.g., hypertension and hypotension), and were not adjusted for multiplicity.

Bleeding was common in the placebo group in the POISE-3 trial irrespective of the definition used: the composite bleeding outcome (in 11.7% of the patients), bleeding independently associated with death after noncardiac surgery (in 11.3%), major bleeding (in 10.4%), major bleeding according to ISTH criteria (in 8.7%), and transfusion of packed red cells (in 12.0%). Tranexamic acid consistently lowered the relative risk by approximately 25% across these outcomes. Tranexamic acid yielded similar results for the composite bleeding outcome in patients undergoing orthopedic and nonorthopedic noncardiac surgery. Moreover, post hoc subgroup analyses showed a consistent result across all types of noncardiac surgery. We recently published a bleeding-risk calculator for patients undergoing noncardiac surgery that physicians can use to estimate the reduction in bleeding risk with tranexamic acid in individual patients. [11]

Noninferiority was not established for the primary safety outcome. Health care providers and patients will have to weigh a clear beneficial reduction in the incidence of composite bleeding outcome events (absolute difference, -2.6 percentage points; 95%CI, −3.8 to -1.4) against the low probability of a small increase in the incidence of composite cardiovascular outcome events (absolute difference, 0.3 percentage points; 95% CI, -1.1 to 1.7).

Patients prefer to avoid bleeding and transfusions. [20] Although tranexamic acid can facilitate these goals, only a small proportion of patients undergoing noncardiac surgery receive it. [21] There is an annual global shortage of 30 million bloodproduct units, [22] and surgical bleeding accounts for up to 40% of all transfusions. Given that 300 million surgeries occur annually worldwide, [23] the results of the POISE-3 trial indicate the potential for large public health and clinical benefits if tranexamic acid becomes standard practice in noncardiac surgery. [24,25]

Strengths of the trial include the participation of 114 hospitals across six continents, the blinding of trial-group assignments, high adherence to the trial agents, and follow-up of 99.9% of the patients. A limitation was that we stopped the trial early owing to a financial deficit resulting from slowed recruitment during the Covid-19 pandemic. We did, however, enroll more than 95% of our original planned sample size. Our decision to stop recruitment was made without knowledge of the trial results. There are limitations regarding our clinical ability to identify perioperative thrombotic complications [26]; however, tranexamic acid did not appear to increase the risk of any outcome known to result from thrombosis.

In our trial involving patients undergoing noncardiac surgery, the incidence of a composite of life-threatening bleeding, major bleeding, and bleeding into a critical organ was significantly lower with tranexamic acid than with placebo.

Although the difference in composite cardiovascular complications between the tranexamic acid group and the placebo group was small, the noninferiority of tranexamic acid was not established.

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APPENDIX

The authors' full names and academic degrees are as follows: P.J. Devereaux, M.D., Ph.D., Maura Marcucci, M.D., Thomas W. Painter, M.B., Ch.B., David Conen, M.D., M.P.H., Vladimir Lomivorotov, M.D., Daniel I. Sessler, M.D., Matthew T.V. Chan, M.B., B.S., Ph.D., Flavia K. Borges, M.D., Ph.D., María J. Martínez-Zapata, M.D., Ph.D., Chew Yin Wang, M.B., Ch.B., Denis Xavier, M.D., Sandra N. Ofori, F.W.A.C.P., Michael K. Wang, M.D., Sergey Efremov, M.D., Ph.D., Giovanni Landoni, M.D., Ydo V. Kleinlugtenbelt, M.D., Ph.D., Wojciech Szczeklik, M.D., Ph.D., Denis Schmartz, M.D., Amit X. Garg, M.D., Ph.D., Timothy G. Short, M.B., Ch.B., M.D., Maria Wittmann, M.D., Christian S. Meyhoff, M.D., Ph.D., Mohammed Amir, F.R.C.S.Ed., David Torres, M.D., Ameen Patel, M.D., M.A.C.P., Emmanuelle Duceppe, M.D., Ph.D., Kurt Ruetzler, M.D., Ph.D., Joel L. Parlow, M.D., Vikas Tandon, M.D., Edith Fleischmann, M.D., Carisi A. Polanczyk, M.D., Sc.D., Andre Lamy, M.D., Sergey V. Astrakov, M.D., Ph.D., Mangala Rao, M.D., William K.K. Wu, Ph.D., Keyur Bhatt, M.S., Miriam de Nadal, M.D., Ph.D., Valery V. Likhvantsev, M.D., Pilar Paniagua, M.D., Ph.D., Hector J. Aguado, M.D., Ph.D., Richard P. Whitlock, M.D., Ph.D., Michael H. McGillion, R.N., Ph.D., Michael Prystajecky, M.D., Jessica Vincent, M.Sc., John Eikelboom, M.B., B.S., Ingrid Copland, Kumar Balasubramanian, M.Sc., Alparslan Turan, M.D., Shrikant I. Bangdiwala, Ph.D., David Stillo, M.A.Sc., Peter L. Gross, M.D., Teresa Cafaro, M.D., Pascal Alfonsi, M.D., Ph.D., Pavel S. Roshanov, M.D., Emilie P. Belley-Côté, M.D., Ph.D., Jessica Spence, M.D., Ph.D., Toby Richards, M.D., Tomas

VanHelder, M.D., Ph.D., William McIntyre, M.D., Ph.D., Gordon Guyatt, M.D., Salim Yusuf, M.D., D.Phil., and Kate Leslie, M.D.

The authors' affiliations are as follows: the Population Health Research Institute (P.J.D., M.M., D.C., F.K.B., S.N.O., M.K.W., A.L., R.P.W., M.H.M., J.V., J.E., I.C., K. Balasubramanian, S.I.B., D. Stillo, T.C., P.S.R., E.P.B.-C., J.S., W.M., S.Y.), the Departments of Health Research Methods, Evidence, and Impact (P.J.D., M.M., D.C., F.K.B., S.N.O., M.K.W., A.X.G., S.I.B., J.S., G.G.), Medicine (P.J.D., M.M., D.C., F.K.B., M.K.W., A.P., V.T., J.E., P.L.G., E.P.B.-C., W.M., G.G., S.Y.), Surgery (A.L., R.P.W.), and Anesthesia U.S., T.V.) and the School of Nursing (M.H.M.), McMaster University, Hamilton, the Departments of Medicine (A.X.G., P.S.R.) and Epidemiology and Biostatistics (A.X.G.), Western University, London, and the Department of Anesthesiology and Perioperative Medicine, Queen's University and Kingston Health Sciences Centre, Kingston U.L.P.), ON, the Department of Medicine, Centre Hospitalier de l'Université de Montréal (E.D.), and the Department of Medicine, Jewish General Hospital, McGill University (T.C.), Montreal, and the Department of Medicine, University of Saskatchewan, Saskatoon (M.P.) - all in Canada; the Discipline of Acute Care Medicine, University of Adelaide (T.W.P.), and the Department of Anaesthesia, Royal Adelaide Hospital (T.W.P.), Adelaide, SA, and the Department of Anaesthesia and Perioperative Medicine, Monash University (T.R.), and the Department of Critical Care Medicine, Melbourne Medical School, University of Melbourne (K.L.), Melbourne, VIC - all in Australia; the Department of Anesthesiology and Intensive Care, E. Meshalkin National Medical Research Center (V.L.), and the Department of Anesthesiology and Intensive Care (V.L.) and the Department of Anesthesiology, V. Zelman Institute of Medicine and Psychology (S.V.A.), Novosibirsk State University, Novosibirsk, Saint Petersburg State University Hospital, Saint Petersburg (S.E.), and V. Negovsky Reanimatology Research Institute, Anesthesia and Intensive Care Department, First Moscow State Medical University (Sechenov University), Moscow (V.V.L.) - all in Russia; the Departments of Outcomes Research (D.I.S., K.R., A.T.) and General Anesthesia (K.R., A.T.) and the Anesthesiology Institute (D.I.S., K.R., A.T.), Cleveland Clinic, Cleveland; Chinese University of Hong Kong, Shatin, China (M.T.V.C., W.K.K.W.); Iberoamerican Cochrane Center, Public Health and Clinical Epidemiology Service, Institut d'Investigació Biomèdica Sant Pau, Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (M.J.M.-Z.), the Department of Anesthesiology and Intensive Care, Hospital Vall d'Hebron, Universitat Autònoma de Barcelona (M.N.), and the Anesthesiology Department, Santa Creu i Sant Pau University Hospital (P.P.), Barcelona, and the Trauma and Orthopedic Surgery Department, Hospital Clínico Universitario de Valladolid, Valladolid (H.J.A.) - all in Spain; the Department of Anesthesiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia (C.Y.W.); St. John's Medical College, Bangalore (D.X., M.R.), and the Department of Gastrointestinal Surgery, Surat Institute of Digestive Sciences Hospital and Research Center, Surat (K. Bhatt) - both in India; the Department of Anesthesiology and Intensive Care, IRCCS San Raffaele Scientific Institute, Vita Salute San Raffaele University, Milan (G.L.); the Department of Orthopedic and Trauma Surgery, Deventer Ziekenhuis, Deventer, the Netherlands (Y.V.K.); Jagiellonian University Medical College, Center for Intensive Care and Perioperative Medicine, Krakow, Poland (W.S.); Centre Hospitalier Universitaire Brugmann, Université Libre de Bruxelles, Brussels (D. Schmartz); the

Department of Anesthesia, Auckland City Hospital, and the School of Health Sciences, University of Auckland, Auckland, New Zealand (T.G.S.); the Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany (M.W.); the Department of Anesthesia and Intensive Care, Copenhagen University Hospital-Bispebjerg and Frederiksberg, and the Department of Clinical Medicine, University of Copenhagen, Copenhagen (C.S.M.); Shifa International Hospital, Islamabad, Pakistan (M.A.); Departamento de Epidemiología y Estudios en Salud, Universidad de Los Andes, and Servicio de Anestesiología, Clínica Santa María, Santiago, Chile (D.T.); the Department of Anesthesia, General Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna (E.F.); Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, National Institute for Health Technology Assessment, and Hospital Moinhos de Vento, Porto Alegre, Brazil (C.A.P.); and the Department of Anesthesia, Hospital Paris Saint Joseph, University of Paris, Paris (P.A.).

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Devereaux can be contacted at pj.devereaux@phri.ca or at the David Braley Research Institute, Hamilton General Hospital, 237 Barton St. East, Hamilton, ON L8L 2X2, Canada.
*A complete list of the POISE-3 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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