Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

SUPPLEMENTARY APPENDIX

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2 SUPPLEMENTARY METHODS

2.1 Supplementary Appendix Methods Section S1. Eligibility criteria

<u>Inclusion criteria</u> – patients had to fulfill the following inclusion criteria:

1. ≥45 years of age;
2. undergoing noncardiac surgery;
3. expected to require at least one overnight hospital admission after surgery;
4. fulfilled ≥1 of the following 6 criteria (A-F):
    - A. N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥200 ng/L;
    - B. history of coronary artery disease as defined by any one of the following 7 criteria:
        - I. history of angina,
        - II. history of myocardial infarction or acute coronary syndrome,
        - III. history of a regional cardiac wall motion abnormality on echocardiography or a segmental fixed defect on radionuclide imaging,
        - IV. history of a radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test demonstrating cardiac ischemia,
        - V. history of a coronary angiographic or computer tomography coronary angiographic evidence of atherosclerotic stenosis ≥50% of the diameter of any coronary artery,
        - VI. electrocardiogram with pathological Q waves in two contiguous leads, or
        - VII. previous coronary artery revascularization (i.e. percutaneous coronary intervention or coronary artery bypass graft surgery);
    - C. history of peripheral arterial disease as defined by a physician diagnosis of a current, or prior, history of any one of the following 4 criteria:
        - I. intermittent claudication,
        - II. vascular surgery for atherosclerotic disease,
        - III. an ankle/arm systolic blood pressure ratio ≤0.90 in either leg at rest, or
        - IV. angiographic or doppler study demonstrating ≥70% stenosis in a noncardiac artery;
    - D. history of stroke as defined by any one of the following 2 criteria
        - I. a physician diagnosis of stroke, or
        - II. computed tomography or magnetic resonance imaging evidence of a prior stroke;
    - E. undergoing major vascular surgery defined as all vascular surgery except arteriovenous shunt, vein stripping procedures, carotid endarterectomies, and endovascular abdominal aortic aneurysm repair; or
    - F. any 3 of the following 9 risk criteria:

I. undergoing major surgery defined as intraperitoneal, intrathoracic, retroperitoneal, or major orthopedic surgery (i.e., hip arthroplasty, internal fixation of hip or femur, pelvic arthroplasty, knee arthroplasty, above-knee amputation, or amputation below the knee but above the foot),
II. history of congestive heart failure defined as a physician diagnosis of a current or prior episode of congestive heart failure or prior radiographic evidence of vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema,
III. history of a transient ischemic attack,
IV. diabetes and currently taking an oral hypoglycemic agent or insulin,
V. age $\geq$70 years,
VI. history of hypertension,
VII. serum creatinine >175 µmol/L (>2.0 mg/dL) based on most recent measurement before randomization,
VIII. history of smoking within 2 years of surgery, or
IX. undergoing emergent/urgent surgery defined as surgery that a surgeon schedules to go to the operating room within 48 hours of an acute presentation to the hospital; and

5. provided written informed consent to participate in the POISE-3 Trial.

Exclusion criteria – patients fulfilling any of the following criteria were excluded:

1. undergoing cardiac surgery or intracranial neurosurgery;
2. planned use of systemic tranexamic acid during surgery;
3. low-risk surgical procedure, based on individual physician's judgment;
4. hypersensitivity or known allergy to tranexamic acid;
5. creatinine clearance <30 mL/min (Cockcroft-Gault equation) or on chronic dialysis;
6. history of seizure disorder;
7. recent (<3 months) stroke, myocardial infarction, acute arterial thrombosis, or venous thromboembolism;
8. fibrinolytic condition following consumption coagulopathy;
9. subarachnoid hemorrhage within the past 30 days;
10. women of childbearing potential who are not taking effective contraception, pregnant or breast-feeding; or

11. previously enrolled in the POISE-3 trial.

POISE = PeriOperative ISchemic Evaluation

2.2 Supplementary Appendix Methods Section S2. Follow-up process

Patients had troponin measurements in hospital 6-12 hours after surgery and on postoperative days 1, 2, and 3, or up until hospital discharge. If a troponin measurement was elevated, we recommended obtaining an electrocardiogram. Research personnel followed patients throughout their time in hospital evaluating the patients and reviewing their medical records and recording any outcomes. Study personnel contacted all patients by telephone at 30 days after randomization, collected data, and submitted case report forms and supporting event documentation directly into the data management system. These processes were followed before and during the COVID-19 pandemic.

2.3 Supplemental Appendix Methods Section S3. Secondary and tertiary outcomes

Secondary 30-day outcomes were time to occurrence of: 1. bleeding independently associated with mortality after noncardiac surgery (BIMS); 2. life-threatening bleeding; 3. major bleeding; 4. critical organ bleeding; 5. myocardial injury after noncardiac surgery (MINS); 6. MINS not fulfilling the universal definition of myocardial infarction; 7. myocardial infarction; and 8. a net risk-benefit outcome – a composite of cardiovascular death, and non-fatal life-threatening, major bleeding, critical organ bleeding, MINS, stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism.

Tertiary 30-day outcomes were time to occurrence of: 1. all-cause mortality; 2. cardiovascular mortality; 3. International Society on Thrombosis and Haemostasis (ISTH) major bleeding; 4. non-hemorrhagic stroke; 5. peripheral arterial thrombosis; 6. symptomatic proximal venous thromboembolism; 7. hemorrhagic stroke; 8. cardiac revascularization; 9. amputation; 10. symptomatic pulmonary embolism; 11. symptomatic proximal deep vein thrombosis; 12. any symptomatic or asymptomatic proximal venous thromboembolism; 13. acute kidney injury; 14. new renal replacement therapy; 15. re-hospitalization for cardiovascular reasons; 16. seizures; 17. infection; and 18. sepsis. Other tertiary 30-day outcomes included: 19. transfusions (i.e., proportion of patients transfused); 20. length of hospital stay; and 21. number of days alive at home.

2.4 Supplemental Appendix Methods Section S4. Outcome definitions

Outcome	Definition
Life-threatening bleeding	Life-threatening bleeding was bleeding that was fatal, or led to: significant hypotension that requires inotrope therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.
Major bleeding	Major bleeding was defined as bleeding that was not specified under "life- threatening bleeding" above, and required one of the following criteria: resulted in a postoperative hemoglobin ≤70 g/L; a transfusion of ≥1 unit of red blood cells; or led to an intervention (i.e., embolization, superficial vascular repair, or nasal packing).
Critical organ bleeding	A critical organ bleeding event was bleeding that was intracranial, intraocular, intraspinal, pericardial, retroperitoneal, or intramuscular with compartment syndrome.
Bleeding independently associated with mortality after noncardiac surgery (BIMS)	BIMS was bleeding meeting any of the following 3 criteria: 1. associated with a postoperative hemoglobin <70 g/L; 2. resulting in transfusion of one or more units of red blood cells; or 3. judged to be the immediate cause of death.
International Society on Thrombosis and Haemostasis (ISTH) major bleeding	ISTH major bleeding was bleeding that met any of the following criteria: 1. fatal bleeding; 2. bleeding that was symptomatic and occurred in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon; 3. extra-surgical site bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 hours to the bleeding;

	4. surgical site bleeding that required a second intervention - open, arthroscopic, endovascular - or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection; or 5. surgical site bleeding that was unexpected and prolonged or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associated fall in hemoglobin level of 20 g/L (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 hours to the bleeding.
Myocardial injury after noncardiac surgery (MINS)	MINS was defined as any myocardial infarction (as defined below), and any elevated troponin (i.e., a value higher than the local laboratory threshold) judged to be due to myocardial ischemia (i.e., without evidence of a nonischemic etiology [e.g., chronic elevation, pulmonary embolism, sepsis, cardioversion]) that occurred within the first 30 days after the initiation of surgery. The only exceptions to the definition of an elevated troponin was to use a higher threshold for troponin T (TnT) of ≥30 ng/L, and for high-sensitivity troponin T (hsTnT) of 20 to <65 ng/L with an absolute change of at least 5 ng/L or an hsTnT level ≥65 ng/L. These threshold for TnT and hsTnT are based upon data from a large international prospective perioperative cohort study that established troponin thresholds that were independently associated with 30-day mortality after non-cardiac surgery.[1,2]
Myocardial infarction	If the diagnostic criteria for myocardial infarction included an elevated troponin, then the definition of MINS must have been met to fulfill the diagnostic criteria for myocardial infarction (universal definition). The diagnosis of myocardial infarction required any one of the following criteria. 1. Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following: A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort, shortness of breath, or pulmonary edema);

B. development of pathologic Q waves present in any two contiguous leads that are ≥30 milliseconds;

C. new or presumed electrocardiography (ECG) changes indicative of ischemia (i.e., ST segment elevation [≥2 mm in leads V_1, V_2, or V_3 OR ≥1 mm in the other leads], ST segment depression [≥1 mm], or symmetric inversion of T waves ≥1 mm) in at least two contiguous leads;

D. new left bundle branch block (LBBB);

E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or

F. identification of intracoronary thrombus on angiography or autopsy;

2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased;

3. Percutaneous coronary intervention (PCI) related myocardial infarction was defined by elevation of a troponin value (>5 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL) or a rise of a troponin measurement >20% if the baseline values were elevated and were stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality were required;

4. Stent thrombosis associated with myocardial infarction when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL;

5. Coronary artery bypass grafting (CABG) related myocardial infarction was defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery

	occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; or 6. For patients who were believed to have suffered a myocardial infarction within 28 days of a MINS event or within 28 days of a prior myocardial infarction, the following criteria for myocardial infarction was required: Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) and 20% higher than the last troponin measurement related to the preceding event together with evidence of myocardial ischemia with at least one of the following: A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort, shortness of breath, pulmonary edema); B. development of pathologic Q waves present in any two contiguous leads that are ≥30 milliseconds; C. new or presumed new ECG changes indicative of ischemia (i.e., ST segment elevation [>2 mm in leads V_1, V_2, or V_3 OR >1 mm in the other leads], ST segment depression [>1 mm], or symmetric inversion of T waves >1 mm) in at least two contiguous leads; D. new LBBB; E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or F. identification of intracoronary thrombus on angiography or autopsy.
MINS not fulfilling the universal definition of myocardial infarction	Any elevated troponin (higher than the local lab threshold) judged to be due to myocardial ischemia (i.e., without evidence of a non-ischemic etiology [e.g., chronic elevation, pulmonary embolism, sepsis, cardioversion]) that occurred with the first 30 days after surgery, and not fulfilling the definition of MI (as defined above).

Stroke	Stroke was defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death. Stroke was sub-classified into hemorrhagic and non-hemorrhagic stroke. Non-hemorrhagic stroke was sub-classified into ischemic, ischemic with secondary transformation, or stroke of uncertain classification. Hemorrhagic stroke was sub-classified into primary intracerebral hemorrhage and primary subarachnoid hemorrhage. 1. Ischemic stroke was a focal brain infarction caused by an arterial (or rarely venous) obstruction and as documented by computed tomography / magnetic resonance imaging (CT/MRI) that is normal or shows an infarct in the clinically expected area. 2. Secondary hemorrhagic transformation of ischemic stroke was a hemorrhagic transformation of ischemic stroke that was symptomatic or asymptomatic. A. Symptomatic transformation of ischemic stroke was defined as a hematoma occupying 30% or more of the infarcted tissue associated with a significant neurologic deterioration (consistent with a decrease of 4 points in the National Institutes of Health Stroke Scale/Score [NIHSS]) compared to immediately before the worsening and an absence of an alternative explanation for deterioration. B. Asymptomatic transformation of ischemic stroke was defined as a hemorrhagic transformation not meeting the criteria for symptomatic transformation. 3. Undetermined stroke was a definite stroke that did not meet the criteria for ischemic or hemorrhagic stroke because CT or MRI were not done and there were no autopsy data. Rarely it cannot be determined with confidence whether the stroke was ischemic versus hemorrhagic, even after review of CT/MRI images (e.g., primary intracerebral hemorrhage versus severe hemorrhagic transformation); these stroke events were classified as undetermined. 4. Hemorrhagic stroke was a hemorrhagic stroke required neuroimaging or autopsy confirmation and includes two subcategories: primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage. Intracranial bleeding caused by head trauma, bleeding associated with tumors, hemorrhagic transformation of ischemic stroke and

	subdural/epidural hematomas were not considered as hemorrhagic strokes (but these were counted separately as major hemorrhages). Microbleeds are not considered intracranial hemorrhage. A. Primary intracerebral hemorrhage was a symptomatic hemorrhagic stroke with CT/MRI or autopsy evidence of bleeding into the substance of the brain or ventricular spaces. Large or superficial intracerebral hemorrhages often are associated with minor amounts of subarachnoid hemorrhage, but these should be classified as intracerebral hemorrhages. Does not include secondary hemorrhage into cerebral infarct (i.e. hemorrhagic transformation which was defined separately), or intracerebral bleeding (i.e. contusions) due to trauma, or microbleeds detected by MRI. B. Primary subarachnoid hemorrhage: Typical clinical syndrome of sudden onset headache, with or without focal signs (subarachnoid hemorrhage may not have focal deficits), and CT or cerebrospinal fluid evidence of bleeding primarily into the subarachnoid space. Subarachnoid bleeding due to ruptured intracranial aneurysms and vascular malformation were counted as hemorrhagic strokes, but traumatic subarachnoid hemorrhage was not.
Peripheral arterial thrombosis	We consider peripheral arterial thrombosis to have occurred when there was clear evidence of abrupt occlusion of a peripheral artery (i.e., not a stroke related to an intracranial artery or myocardial infarction) consistent with either an acute local thrombotic event or a peripheral arterial embolism. To fulfill this definition, we required at least one of the following objective findings of peripheral arterial thrombosis: 1. surgical report indicating evidence of arterial thrombosis/ peripheral arterial embolism, 2. pathological specimen demonstrating arterial thrombosis/ peripheral arterial embolism, 3. imaging evidence consistent with arterial thrombosis/ peripheral arterial embolism, or 4. autopsy reports documenting arterial thrombosis/ peripheral arterial embolism

Symptomatic proximal venous thromboembolism	Venous thromboembolism that includes symptomatic pulmonary embolism or symptomatic proximal deep vein thrombosis.
Symptomatic pulmonary embolism	The diagnosis of symptomatic pulmonary embolism required symptoms (e.g., dyspnea, pleuritic chest pain) or signs (e.g., hypoxia, increased work of breathing) and any one of the following: 1. A high probability ventilation/perfusion lung scan; 2. An intraluminal filling defect of segmental or larger artery on a helical CT scan; 3. An intraluminal filling defect on pulmonary angiography; or 4. A positive diagnostic test for deep venous thrombosis (e.g., positive compression ultrasound) and one of the following: A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan; or B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan.
Symptomatic proximal deep venous thrombosis	The diagnosis of symptomatic proximal deep venous thrombosis (DVT) required: 1. symptoms or signs that suggested DVT (e.g., leg pain or swelling); and 2. thrombosis involving the popliteal vein or more proximal veins for leg DVT or axillary or more proximal veins for arm DVTs. Any of the following defined evidence of vein thrombosis: A. a persistent intraluminal filling defect on contrast venography (including on CT); B. noncompressibility of one or more venous segments on B mode compression ultrasonography; or C. a clearly defined intraluminal filling defect on doppler imaging in a vein that cannot have compressibility assessed (e.g., iliac, inferior vena cava, subclavian).

Subclassification of death	Cardiovascular death was defined as any death with a cardiovascular cause and included those deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG] surgery), pulmonary embolism, hemorrhage, or deaths due to an unknown cause. Non-cardiovascular death was defined as any death due to a clearly documented non-cardiovascular cause (e.g. trauma, infection, malignancy).
Cardiac revascularization procedure	Cardiac revascularization procedure was defined as PCI or CABG surgery.
Amputation	Amputation was defined as an amputation procedure, or auto amputation subsequent to the initial surgery.
Acute kidney injury	Acute kidney injury was defined as an increase in serum creatinine concentration from the preoperative (pre-randomization) concentration by either an increase of ≥26.5 μmol/L (≥0.3 mg/dL) within 48 hours of surgery or an increase of 50% or greater within 7 days of surgery.
New requirement of renal replacement therapy (dialysis)	Dialysis was defined as the use of a hemodialysis machine or peritoneal dialysis apparatus.
Rehospitalization for cardiovascular reasons	Rehospitalization for cardiovascular reasons was defined as re-hospitalization for myocardial infarction, cardiac arrest, stroke, congestive heart failure, ischemic symptoms with ST or T wave changes on an ECG, cardiac arrhythmia, cardiac revascularization procedure, amputation, peripheral arterial thrombosis, deep venous thrombosis, pulmonary embolism, any vascular surgery, or bleeding.
Seizure	Seizure was defined as the abrupt onset of focal or generalized experiential, motor, sensory or cognitive phenomena, in absence of another etiology for the event (e.g., movement or psychiatric disorder).
Infection	Infection was defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms.

Sepsis	The Third International Consensus Definitions Task Force defined sepsis as a "life-threatening organ dysfunction due to a dysregulated host response to infection." Based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria, sepsis required a quick Sequential Organ Failure Assessment (qSOFA) Score ≥2 points due to infection. The qSOFA included the following items and scoring system: 1. Glasgow Coma Scale (GCS) score of 13 or less (1 point) 2. systolic blood pressure of 100 mm Hg or less (1 point), and 3. respiratory rate of 22 breaths/min or more (1 point).

2.5 Supplemental Appendix Methods Section S5. Monitoring

Monitoring in POISE-3 consisted of central data consistency checks, statistical data monitoring, and site monitoring (either on-site or virtually). Site monitoring occurred at hospitals that randomized ≥150 patients or stood out on central data consistency checks or statistical data monitoring. For site monitoring, the study statistician randomly selected participants with and without primary outcomes, and independent monitors audited their hospital charts and supporting documents. Study personnel corrected any data errors identified through central data consistency checks or site monitoring. Site monitoring did not indicate any major discrepancies between the submitted data and site monitoring findings. Our approach to monitoring was consistent before and during the COVID-19 pandemic.

2.6 Supplemental Appendix Methods Section S6. Adjudication process

The Event Adjudication Committee consisted of clinicians with expertise in perioperative outcomes who were blinded to treatment allocation and adjudicated the following outcomes: life-threatening bleeding, major bleeding, critical organ bleeding, bleeding independently associated with mortality after noncardiac surgery (BIMS), International Society on Thrombosis and Haemostasis (ISTH) major bleeding, myocardial injury after noncardiac surgery (MINS), myocardial infarction, stroke, peripheral arterial thrombosis, symptomatic pulmonary embolism, and symptomatic proximal deep vein thrombosis. Outcome events that remained unrefuted after the adjudication process were used in the analyses.

2.7 Supplemental Appendix Methods Section S7. Original sample size calculation

POISE-3 was initially designed to randomize 10,000 patients to tranexamic acid or placebo. This sample size would provide 95% power to demonstrate that the upper bound of the one-sided 97.5% CI for a HR was <1.125, assuming a placebo event rate of 11% and an actual HR of 0.9. This sample size would also provide >90% power to detect a HR <0.75 for the primary efficacy outcome, assuming a placebo event rate of 7%.

2.8 Supplemental Appendix Methods Section S8. Details of the interim analyses

For the tranexamic acid trial, three interim analyses based on the primary safety outcome occurred when 25%, 50% and 75% of the 30-day data were available. The Data Monitoring Committee (DMC) employed the modified Haybittle-Peto rule of 3.5 standard deviations (SDs) ($\alpha = 0.00047$).[3,4] To trigger discussion about stopping the trial early for harm, the point estimate of the hazard ratio for tranexamic acid versus placebo needed to exceed 1.0 by more than 3.5 SDs at any of the interim analyses.

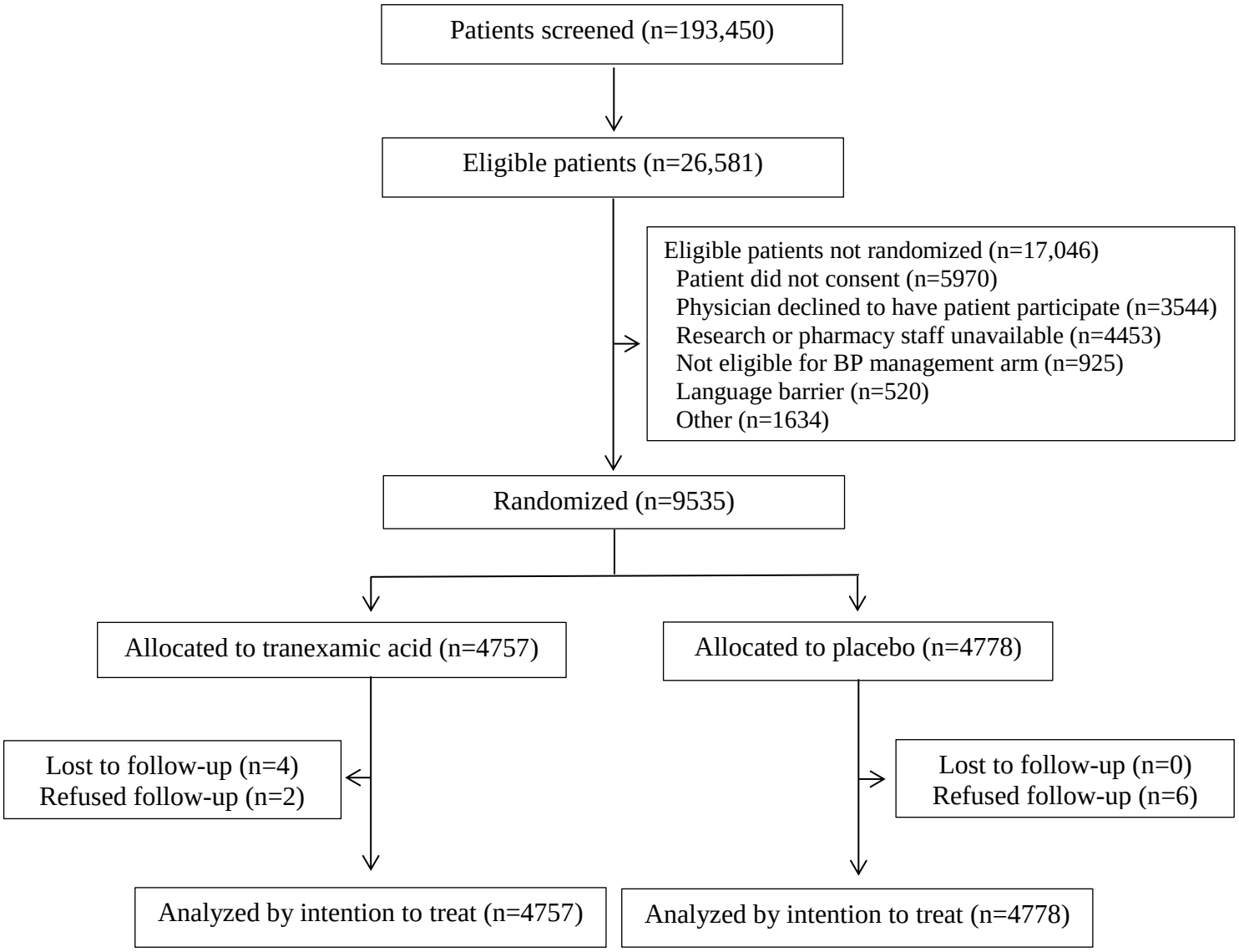
Two interim analyses for efficacy of tranexamic acid occurred when 50% and 75% of the 30-day data were available. These analyses were based on a net risk-benefit outcome defined as the composite of cardiovascular death, bleeding (i.e., non-fatal life-threatening, major, or critical organ bleeding), myocardial injury after noncardiac surgery, stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism. The DMC employed the modified Haybittle-Peto rules[3,4] of 4 SDs ($\alpha = 0.000067$) for the interim analysis on the 50% subset, and of 3.5 SDs ($\alpha = 0.00047$) for the 75% subset analysis. For the results of the interim analyses to be considered significant to trigger discussions about stopping the trial for greater than expected efficacy, these predefined boundaries had to be exceeded in at least 2 consecutive analyses, 3 or more months apart. The α-level for the final efficacy analysis remained the conventional $\alpha = 0.05$ given the infrequent interim analyses, their extremely low α levels, and the requirement for confirmation with subsequent analyses.

2.9 Supplemental Appendix Methods Section S9. Planned subgroup analyses

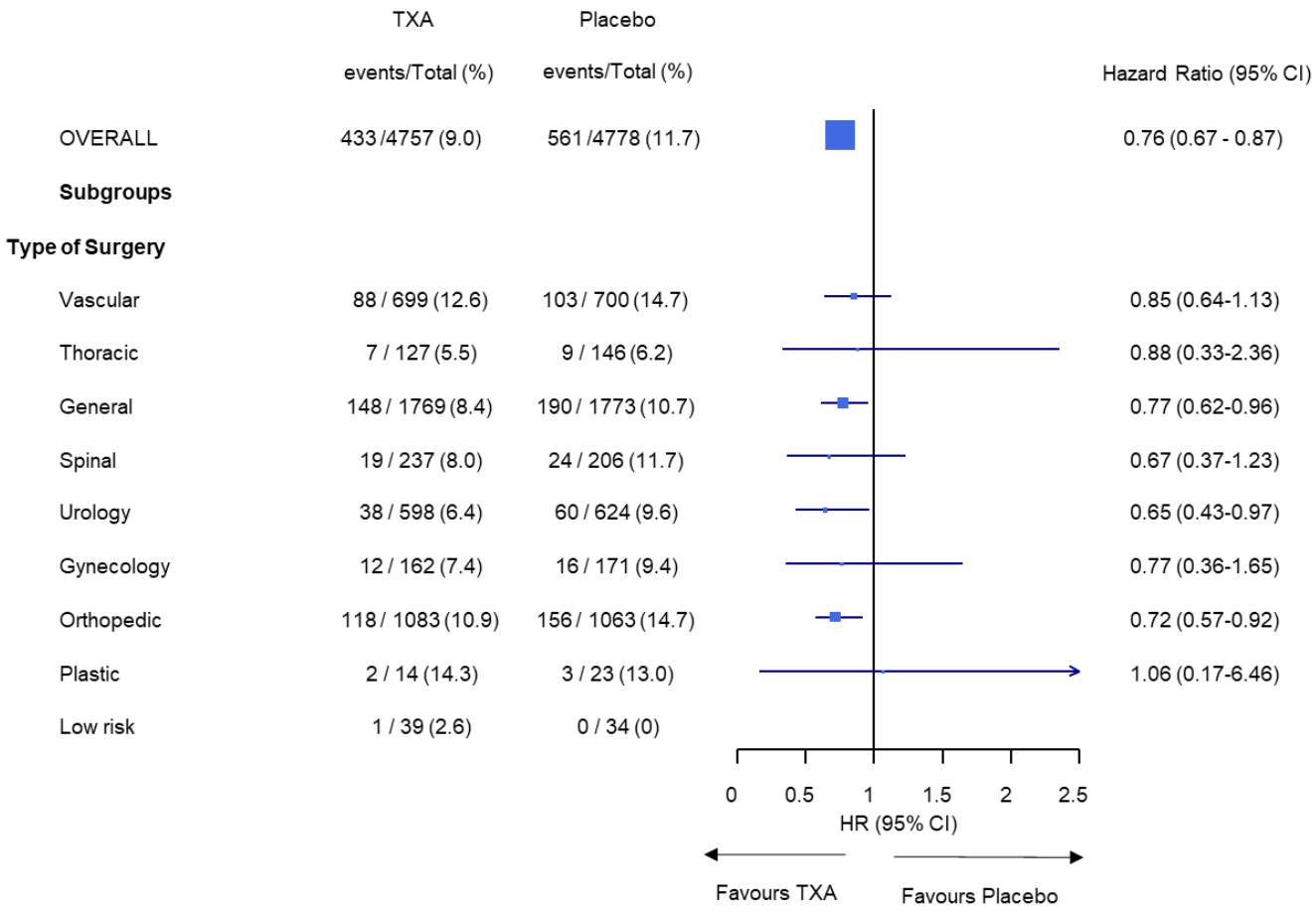
For the primary efficacy and safety outcomes, we evaluated the following subgroups: orthopedic versus non-orthopedic surgery; preoperative hemoglobin <120 g/L versus ≥120 g/L; preoperative estimated glomerular filtration rate (eGFR) <45, 45-<60, and ≥60 ml min^{-1} 1.73 m^2; and preoperative N-terminal pro–B-type natriuretic peptide (NT-proBNP) <200, 200-<1500, and ≥1500 ng/L. We expected tranexamic acid to have greater benefit and safety in patients having orthopedic surgery, with a preoperative hemoglobin <120 g/L, a lower preoperative eGFR, and higher preoperative NT-proBNP values.

3 SUPPLEMENTARY FIGURES AND TABLES

3.1 Supplementary Appendix Figure S1. Patient flow diagram

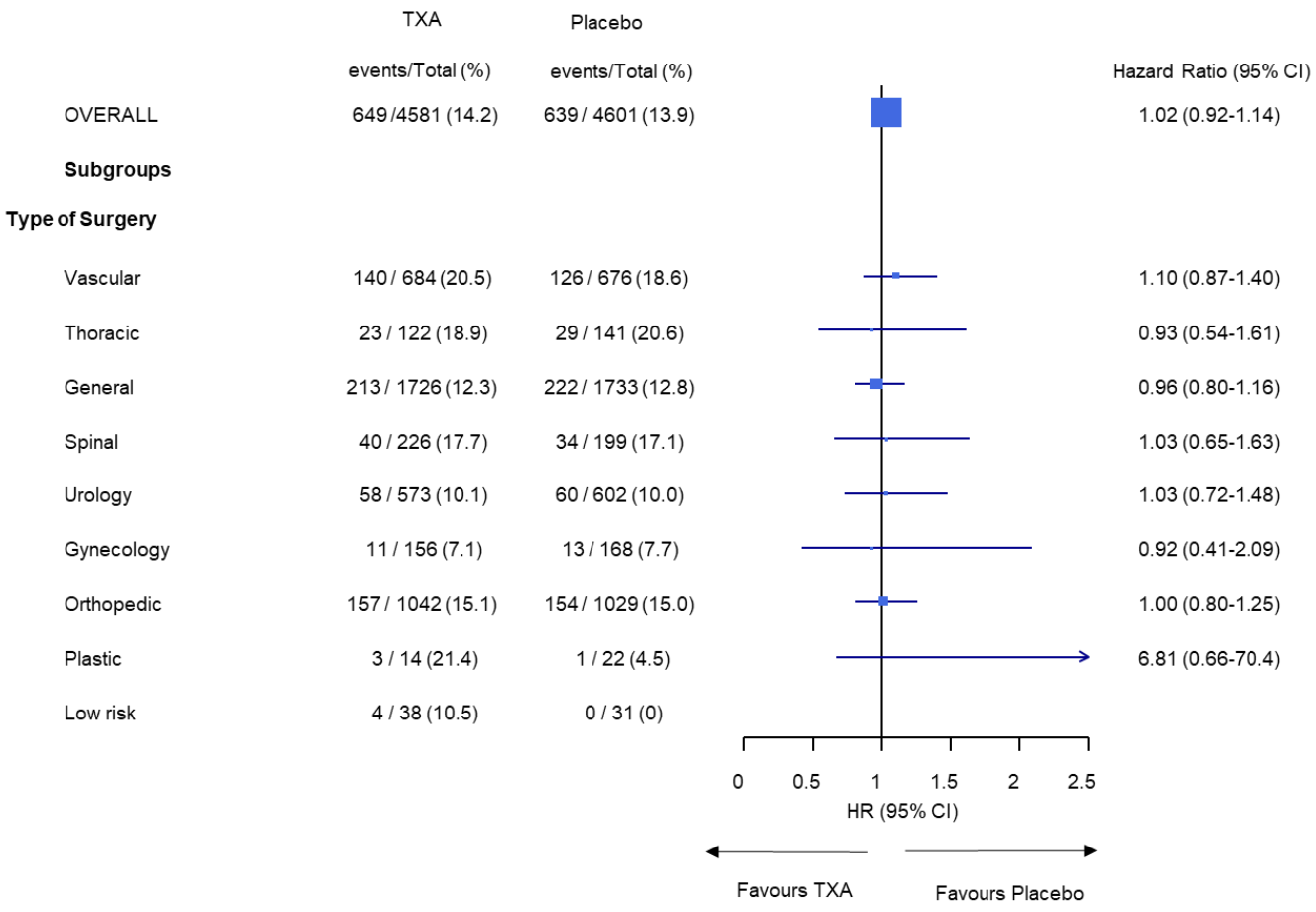


3.2 Supplementary Appendix Figure S2. Panel A: Post hoc subgroup analysis of the primary efficacy outcome*



CI = confidence interval; TXA = tranexamic acid
* composite of life-threatening, major, and critical organ bleeding

3.3 Supplementary Appendix Figure S2. Panel B: Post hoc subgroup analysis of the primary safety outcome*



CI = confidence interval; TXA = tranexamic acid
* composite of myocardial injury after noncardiac surgery, non-hemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism

3.4 Supplementary Appendix Table S1. Region, ethnicity, and baseline measurements

Characteristics	Tranexamic acid group (N=4757)	Placebo group (N=4778)
Region – no. (%)		
North America	1475 (31.0)	1486 (31.1)
Europe	1895 (39.8)	1898 (39.7)
Asia-Pacific	1284 (27.0)	1294 (27.1)
South America	90 (1.9)	88 (1.8)
Africa	13 (0.3)	12 (0.3)
Ethnicity – no. (%)		
White/Caucasian	3618 (76.1)	3621 (75.8)
Asian	929 (19.5)	950 (19.9)
Hispanic/Latino	84 (1.8)	90 (1.9)
Black/African	76 (1.6)	71 (1.5)
Aboriginal	27 (0.6)	25 (0.5)
Middle Eastern descent	15 (0.3)	10 (0.2)
Pacific Islander	5 (0.1)	10 (0.2)
Preoperative laboratory measurements		
hemoglobin (g/L) (mean [± SD])	131 ± 19	131 ± 19
creatinine (μmol/L) (mean [± SD])	87 ± 29	87 ± 31

no. = number; % = percentage; SD = standard deviation.

3.5 Supplementary Appendix Table S2: Representativeness of study participants

Category	Considerations
Disease, problem or condition under investigation	Patients ≥45 years of age, undergoing inpatient noncardiac surgery, and at increased risk of bleeding and cardiovascular complications.
Sex and gender	Among adults undergoing different types of noncardiac surgery worldwide, the proportion of women and men tends to be similar.[5,6] In the subpopulation of patients undergoing noncardiac surgery at increased risk of cardiovascular complications, the proportion of men is expected to be higher than women.[1]
Age	The annual hospitalizations for noncardiac surgery increase with age, until age 65 years, and then the number starts to decline.[5] In the subpopulation of patients undergoing noncardiac surgery at increased risk of bleeding and cardiovascular complications, older patients are expected to be more represented than in the overall noncardiac surgical population.[1,7]
Race or ethnic group	Studies suggest non-white patients represent up to 25% of patients undergoing noncardiac surgery, in the United States.[8,9]
Geography	Patients undergoing noncardiac surgery in low and middle-income countries tend to be younger and with less comorbidities than in high-income countries.[6]
Other considerations	Of the >300 million surgeries that occur annually, only 6% occur in the poorest third of the world.[10] Geography, race, and socioeconomic status influence access to surgery, type of surgery (e.g., elective versus emergency, invasive versus minimally invasive), and outcomes after noncardiac surgery.[6,10]

Category	Considerations
Overall representativeness of this trial	The participants in POISE-3 demonstrated the expected ratio of male to female. Data on gender were not collected. The mean age in the study population is consistent with prior international and United States noncardiac surgery cohort studies, especially considering the inclusion in the present trial of patients at increased risk of bleeding and cardiovascular complications. The proportion of non-white patients was consistent with the proportion of non-white patients undergoing noncardiac surgery in the United States. We included patients from all inhabited regions of the world.

3.6 Supplementary Appendix Table S3. Study drug compliance

Compliance	Tranexamic acid (N=4757) no. (%)	Placebo (N=4778) no. (%)
Received the first dose of study drug	4612 (97.0)	4619 (96.7)
Received the second dose of the study drug	4586 (96.4)	4612 (96.5)
Received both doses of the study drug	4581 (96.3)	4601 (96.3)

no. = number; % = percentage

3.7 Supplementary Appendix Table S4. Non-study antifibrinolytic drug administration*

Non-study antifibrinolytic drug administration	Tranexamic acid (N=4729) no. (%)	Placebo (N=4740) no. (%)
Topical tranexamic acid	168 (3.6)	183 (3.9)
Intravenous tranexamic acid	69 (1.5)	78 (1.6)
Other antifibrinolytic drug	23 (0.5)	24 (0.5)

no. = number; % = percentage

***** among patients who had surgery

3.8 Supplementary Appendix Table S5. Medications taken after surgery while in the hospital*

	Tranexamic acid group (N=4729)	Placebo group (N=4740)
Medications taken after surgery while in the hospital – no. (%)		
therapeutic thrombin/factor Xa inhibitor	338 (7.1)	306 (6.5)
therapeutic dose vitamin K antagonist	81 (1.7)	65 (1.4)
therapeutic dose intravenous or subcutaneous antithrombotic	428 (9.1)	431 (9.1)
prophylactic dose anticoagulant	2353 (49.8)	2373 (50.1)
aspirin	1375 (29.1)	1362 (28.7)
venous thromboembolism prophylactic medication†	3037 (64.2)	3015 (63.6)
$P2Y_{12}$ inhibitor	254 (5.4)	254 (5.4)
non-steroidal anti-inflammatory drug	1524 (32.2)	1598 (33.7)
cox-2 inhibitor	377 (8.0)	358 (7.6)

* among patients who had surgery

† prophylactic dose anticoagulant or aspirin

3.9 Supplementary Appendix Table S6. Serious adverse events

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Number of patients with ≥1 SAE	263 (5.5)	242 (5.1)	0.5 (-0.4 to 1.4)	0.16
Blood and lymphatic system disorders	**4 (0.1)**	**4 (0.1)**	0 (-0.1 to 0.1)	>0.99
Anemia	2 (<0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.56
Disseminated intravascular coagulation	0 (0)	1 (<0.1)	NA	NA
Febrile neutropenia	1 (<0.1)	0 (0)	NA	NA
Iron deficiency anemia	0 (0)	1 (<0.1)	NA	NA
Lymphadenopathy	1 (<0.1)	0 (0)	NA	NA
Pancytopenia	0 (0)	1 (<0.1)	NA	NA
Cardiac disorders	**8 (0.2)**	**6 (0.1)**	<0.1 (-0.1 to 0.2)	0.59
Atrial fibrillation	2 (<0.1)	0 (0)	NA	NA
Bradycardia	0 (0)	2 (<0.1)	NA	NA
Cardiac arrest	0 (0)	1 (<0.1)	NA	NA
Cardiac failure congestive	1 (<0.1)	0 (0)	NA	NA
Mitral valve incompetence	1 (<0.1)	0 (0)	NA	NA
Nodal arrhythmia	1 (<0.1)	0 (0)	NA	NA
Pericarditis	1 (<0.1)	0 (0)	NA	NA
Sinus tachycardia	0 (0)	1 (<0.1)	NA	NA
Supraventricular tachycardia	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Ventricular tachycardia	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Congenital, familial and genetic disorders	**1 (<0.1)**	**2 (<0.1)**	>-0.1 (-0.1 to 0.1)	0.57
11-beta-hydroxylase deficiency	1 (<0.1)	0 (0)	NA	NA
Tracheo-esophageal fistula	0 (0)	1 (<0.1)	NA	NA
Hyperglycinemia	0 (0)	1 (<0.1)	NA	NA
Ear and labyrinth disorders	**0 (0)**	**1 (<0.1)**	NA	NA
Vertigo	0 (0)	1 (<0.1)	NA	NA

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Endocrine disorders	**1 (<0.1)**	**0 (0)**	NA	NA
Inappropriate antidiuretic hormone secretion	1 (<0.1)	0 (0)	NA	NA
Eye disorders	**2 (<0.1)**	0 (0)	NA	NA
Amaurosis fugax	1 (<0.1)	0 (0)	NA	NA
Blindness transient	1 (<0.1)	0 (0)	NA	NA
Gastrointestinal disorders	**68 (1.4)**	**42 (0.9)**	0.6 (0.1 to 1.0)	0.01
Abdominal pain	6 (.1)	5 (0.1)	<0.1 (-0.1 to 0.2)	0.76
Anal stenosis	1 (<0.1)	0 (0)	NA	NA
Ascites	0 (0)	1 (<0.1)	NA	NA
Colitis	0 (0)	1 (<0.1)	NA	NA
Constipation	4 (0.1)	2 (<0.1)	<0.1 (-0.1 to 0.2)	0.41
Diarrhea	2 (<0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.56
Diverticulum intestinal	0 (0)	1 (<0.1)	NA	NA
Duodenal obstruction	0 (0)	1 (<0.1)	NA	NA
Dysphagia	1 (<0.1)	0 (0)	NA	NA
Enteritis	1 (<0.1)	0 (0)	NA	NA
Enterocele	1 (<0.1)	0 (0)	NA	NA
Enterocolitis	1 (<0.1)	0 (0)	NA	NA
Food poisoning	1 (<0.1)	0 (0)	NA	NA
Gastric polyps	1 (<0.1)	0 (0)	NA	NA
Gastric ulcer	1 (<0.1)	0 (0)	NA	NA
Gastric ulcer perforation	0 (0)	1 (<0.1)	NA	NA
Gastrointestinal fistula	0 (0)	1 (<0.1)	NA	NA
Gastrointestinal hemorrhage	2 (<0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.56
Hematemesis	1 (<0.1)	0 (0)	NA	NA
Ileal stenosis	1 (<0.1)	0 (0)	NA	NA
Ileus	1 (<0.1)	3 (0.1)	>-0.1 (-0.1 to 0.1)	0.32

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Ileus paralytic		1 (<0.1)	NA	NA
Impaired gastric emptying	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Inguinal hernia	1 (<0.1)	0 (0)	NA	NA
Intestinal ischemia	2 (<0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.56
Intestinal obstruction	10 (0.2)	2 (<0.1)	0.2 (<0.1 to 0.3)	0.02
Intestinal perforation	0 (0)	1 (<0.1)	NA	NA
Intestinal pseudo-obstruction	0 (0)	1 (<0.1)	NA	NA
Intestinal stenosis	0 (0)	1 (<0.1)	NA	NA
Malabsorption	1 (<0.1)	0 (0)	NA	NA
Melaena	0 (0)	1 (<0.1)	NA	NA
Mesenteric artery thrombosis	0 (0)	1 (<0.1)	NA	NA
Nausea	1 (<0.1)	0 (0)	NA	NA
Obstruction gastric	0 (0)	1 (<0.1)	NA	NA
Esophageal stenosis	1 (<0.1)	0 (0)	NA	NA
Esophagitis	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Pancreatitis	1 (<0.1)	0 (0)	NA	NA
Pancreatitis acute	2 (<0.1)	0 (0)	NA	NA
Rectal hemorrhage	1 (<0.1)	2 (<0.1)	>-0.1 (-0.1 to 0.1)	0.57
Rectal prolapse	0 (0)	1 (<0.1)	NA	NA
Small intestinal obstruction	13 (0.3)	3 (0.1)	0.2 (<0.1 to 0.4)	0.01
Small intestinal perforation	1 (<0.1)	0 (0)	NA	NA
Upper gastrointestinal hemorrhage	0 (0)	1 (<0.1)	NA	NA
Vomiting	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Pneumoperitoneum	1 (<0.1)	0 (0)	NA	NA
Duodenal stenosis	1 (<0.1)	0 (0)	NA	NA
Enterocutaneous fistula	0 (0)	1 (<0.1)	NA	NA
Large intestine polyp	1 (<0.1)	0 (0)	NA	NA

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Gastrointestinal edema	1 (<0.1)	0 (0)	NA	NA
Abdominal hernia	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Incarcerated umbilical hernia	0 (0)	1 (<0.1)	NA	NA
Pharyngo-esophageal diverticulum	1 (<0.1)	0 (0)	NA	NA
Intra-abdominal fluid collection	0 (0)	1 (<0.1)	NA	NA
General disorders and administration site conditions	**13 (0.3)**	**13 (0.3)**	<0.1 (-0.1 to 0.1)	0.99
Asthenia	1 (<0.1)	0 (0)	NA	NA
Chest pain	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Generalized edema	0 (0)	1 (<0.1)	NA	NA
Hernia	0 (0)	1 (<0.1)	NA	NA
Edema	1 (<0.1)	0 (0)	NA	NA
Edema peripheral	2 (<0.1)	0 (0)	NA	NA
Pain	4 (0.1)	5 (0.1)	>-0.1 (-0.1 to 0.1)	0.74
Swelling	0 (0)	2 (<0.1)	NA	NA
General physical health deterioration	0 (0)	1 (<0.1)	NA	NA
Polyp	0 (0)	1 (<0.1)	NA	NA
Non-cardiac chest pain	0 (0)	1 (<0.1)	NA	NA
Medical device site discharge	1 (<0.1)	0 (0)	NA	NA
Stenosis	1 (<0.1)	0 (0)	NA	NA
Dehiscence	2 (<0.1)	0 (0)	NA	NA
Hepatobiliary disorders	**9 (0.2)**	**5 (0.1)**	0.1 (-0.1 to 0.3)	0.28
Autoimmune hepatitis	1 (<0.1)	0 (0)	NA	NA
Bile duct stone	0 (0)	1 (<0.1)	NA	NA
Biliary colic	1 (<0.1)	0 (0)	NA	NA
Cholecystitis	0 (0)	1 (<0.1)	NA	NA
Cholecystitis acute	4 (0.1)	0 (0)	NA	NA

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Hepatitis	1 (<0.1)	0 (0)	NA	NA
Hepatitis alcoholic	1 (<0.1)	0 (0)	NA	NA
Portal vein thrombosis	1 (<0.1)	0 (0)	NA	NA
Liver injury	0 (0)	1 (<0.1)	NA	NA
Biliary obstruction	0 (0)	2 (<0.1)	NA	NA
Immune system disorders	**0 (0)**	**1 (<0.1)**	NA	NA
Hypersensitivity	0 (0)	1 (<0.1)	NA	NA
Infections and infestations	**5 (0.1)**	**6 (0.1)**	>-0.1 (-0.1 to 0.1)	0.77
Abscess	0 (0)	1 (<0.1)	NA	NA
Diverticulitis	3 (0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.32
Empyema	0 (0)	1 (<0.1)	NA	NA
Gastroenteritis	0 (0)	2	NA	NA
Herpes simplex encephalitis	1 (<0.1)	0 (0)	NA	NA
Peritonitis	1 (<0.1)	0 (0)	NA	NA
Coronavirus infection	0 (0)	1 (<0.1)	NA	NA
Injury, poisoning and procedural complications	**76 (1.6)**	**75 (1.6)**	<0.1 (-0.5 to 0.6)	0.91
Ankle fracture	0 (0)	1 (<0.1)	NA	NA
Burns third degree	1 (<0.1)	0 (0)	NA	NA
Clavicle fracture	0 (0)	1 (<0.1)	NA	NA
Fall	5 (0.1)	3 (0.1)	<0.1 (-0.1 to 0.2)	0.48
Femur fracture	2 (0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.56
Fibula fracture	1 (<0.1)	0 (0)	NA	NA
Foot fracture	0 (0)	1 (<0.1)	NA	NA
Head injury	1 (<0.1)	0 (0)	NA	NA
Hip fracture	2 (<0.1)	3 (0.1)	>-0.1 (-0.1 to 0.1)	0.66
Humerus fracture	0 (0)	1 (<0.1)	NA	NA
Incisional hernia	0 (0)	1 (<0.1)	NA	NA

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Injury	0 (0)	1 (<0.1)	NA	NA
Joint dislocation	0 (0)	2 (<0.1)	NA	NA
Multiple fractures	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Peroneal nerve injury	1 (<0.1)	0 (0)	NA	NA
Rib fracture	0 (0)	1 (<0.1)	NA	NA
Seroma	1 (<0.1)	3 (0.1)	>-0.1 (-0.1 to 0.1)	0.32
Spinal compression fracture	1 (<0.1)	0 (0)	NA	NA
Spinal fracture	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Ulna fracture	1 (<0.1)	0 (0)	NA	NA
Ureteric injury	0 (0)	2 (<0.1)	NA	NA
Wound dehiscence	6 (0.1)	2 (<0.1)	0.1 (-0.1 to 0.2)	0.16
Wrist fracture	1 (<0.1)	0 (0)	NA	NA
Suture rupture	1 (<0.1)	0 (0)	NA	NA
Anastomotic leak	3 (0.1)	4 (0.1)	>-0.1 (-0.1 to 0.1)	0.71
Prescribed overdose	1 (<0.1)	0 (0)	NA	NA
Wound complication	0 (0)	1 (<0.1)	NA	NA
Postoperative ileus	37 (0.8)	30 (0.6)	0.2 (-0.2 to 0.5)	0.38
Post procedural diarrhea	0 (0)	1 (<0.1)	NA	NA
Pelvic fracture	0 (0)	1 (<0.1)	NA	NA
Postoperative wound complication	0 (0)	1 (<0.1)	NA	NA
Lower limb fracture	1 (<0.1)	2 (<0.1)	>-0.1 (-0.1 to 0.1)	0.56
Procedural hypotension	0 (0)	1 (<0.1)	NA	NA
Pancreatic leak	1 (<0.1)	0 (0)	NA	NA
Dural tear	0 (0)	1 (<0.1)	NA	NA
Procedural pain	0 (0)	1 (<0.1)	NA	NA
Incision site inflammation	0 (0)	1 (<0.1)	NA	NA
Gastrointestinal stoma complication	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Gastrointestinal anastomotic leak	0 (0)	1 (<0.1)	NA	NA
Radiation sickness syndrome	1 (<0.1)	0 (0)	NA	NA
Periprosthetic fracture	1 (<0.1)	0 (0)	NA	NA
Traumatic lung injury	1 (<0.1)	0 (0)	NA	NA
Fascial rupture	1 (<0.1)	0 (0)	NA	NA
Postoperative delirium	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Scrotal injury	0 (0)	1 (<0.1)	NA	NA
Incarcerated parastomal hernia	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Diversion colitis	0 (0)	1 (<0.1)	NA	NA
Investigations	**6 (0.1)**	**2 (<0.1)**	0.1 (-0.1 to 0.2)	0.16
Blood glucose increased	1 (<0.1)	0 (0)	NA	NA
Blood pressure abnormal	0 (0)	1 (<0.1)	NA	NA
Blood glucose fluctuation	1 (<0.1)	0 (0)	NA	NA
Ejection fraction decreased	1 (<0.1)	0 (0)	NA	NA
Coagulation test abnormal	1 (<0.1)	0 (0)	NA	NA
Nutritional condition abnormal	1 (<0.1)	0 (0)	NA	NA
SARS-CoV-2 test positive	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Metabolism and nutrition disorders	**17 (0.4)**	**24 (0.5)**	>-0.1 (>-0.1 to 0.1)	0.28
Abnormal loss of weight	1 (<0.1)	0 (0)	NA	NA
Dehydration	2 (<0.1)	6 (0.1)	-0.1 (-0.2 to 0.1)	0.16
Diabetes mellitus inadequate control	0 (0)	1 (<0.1)	NA	NA
Diabetic ketoacidosis	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Failure to thrive	2 (<0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.56
Gout	0 (0)	2 (<0.1)	NA	NA
Hypercalcemia	1 (<0.1)	0 (0)	NA	NA
Hyperglycemia	3 (0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.32
Hyperkalemia	1 (<0.1)	0 (0)	NA	NA

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Hypoglycemia	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Hypokalemia	1 (<0.1)	0 (0)	NA	NA
Hyponatremia	3 (0.1)	7 (0.1)	-0.1 (-0.2 to 0.1)	0.21
Hyperglycemic hyperosmolar nonketotic syndrome	0 (0)	1 (<0.1)	NA	NA
Diabetic metabolic decompensation	0 (0)	1 (<0.1)	NA	NA
Feeding intolerance	0 (0)	1 (<0.1)	NA	NA
Adult failure to thrive	1 (<0.1)		NA	NA
Starvation ketoacidosis	0 (0)	1 (<0.1)	NA	NA
Musculoskeletal and connective tissue disorders	**15 (0.3)**	**19 (0.4)**	-0.1 (-0.3 to 0.2)	0.50
Arthralgia	3 (0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.32
Back pain	3 (0.1)	5 (0.1)	>-0.1 (-0.2 to 0.1)	0.48
Bursitis	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Compartment syndrome	0 (0)	2 (<0.1)	NA	NA
Fistula	0 (0)	1 (<0.1)	NA	NA
Hemarthrosis	0 (0)	1 (<0.1)	NA	NA
Joint effusion	1 (<0.1)	0 (0)	NA	NA
Muscle atrophy	1 (<0.1)	0 (0)	NA	NA
Musculoskeletal pain	0 (0)	2 (<0.1)	NA	NA
Neck pain	1 (<0.1)	0 (0)	NA	NA
Osteoarthritis	2 (<0.1)	3 (0.1)	>-0.1 (-0.1 to 0.1)	0.66
Rhabdomyolysis	1 (<0.1)	0 (0)	NA	NA
Pseudarthrosis	0 (0)	1 (<0.1)	NA	NA
Intervertebral disc degeneration	0 (0)	1 (<0.1)	NA	NA
Spinal stenosis	2 (<0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.57
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**21 (0.4)**	**21 (0.4)**	<0.1 (-0.3 to 0.3)	>0.99

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Adenocarcinoma gastric	1 (<0.1)	0 (0)	NA	NA
Adenocarcinoma of colon	1 (<0.1)	0 (0)	NA	NA
B-cell lymphoma		1 (<0.1)	NA	NA
Bladder cancer	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Breast cancer	3 (0.1)	2 (<0.1)	<0.1 (-0.1 to 0.1)	0.65
Bronchial carcinoma	1 (<0.1)	0 (0)	NA	NA
Chronic myelomonocytic leukemia	1 (<0.1)	0 (0)	NA	NA
Colon cancer	1 (<0.1)	0 (0)	NA	NA
Endometrial cancer	0 (0)	1 (<0.1)	NA	NA
Laryngeal cancer	1 (<0.1)	0 (0)	NA	NA
Lung adenocarcinoma	0 (0)	1 (<0.1)	NA	NA
Metastases to liver	1 (<0.1)	3 (0.1)	>-0.1 (-0.1 to 0.1)	0.32
Metastases to lung	0 (0)	2 (<0.1)	NA	NA
Neoplasm	1 (<0.1)	0 (0)	NA	NA
Neoplasm malignant	0 (0)	1 (<0.1)	NA	NA
Rectal cancer	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Squamous cell carcinoma of the hypopharynx	1 (<0.1)	0 (0)	NA	NA
Adrenal gland cancer metastatic	0 (0)	1 (<0.1)	NA	NA
Lung neoplasm malignant	1 (<0.1)	0 (0)	NA	NA
Brain neoplasm	1 (<0.1)	0 (0)	NA	NA
Metastatic neoplasm	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Colorectal cancer	1 (<0.1)	0 (0)	NA	NA
Metastasis	1 (<0.1)	3 (0.1)	>-0.1 (-0.1 to 0.1)	0.32
Thyroid cancer stage I	1 (<0.1)	0 (0)	NA	NA
Hepatocellular carcinoma	0 (0)	1 (<0.1)	NA	NA
Intraductal proliferative breast lesion	0 (0)	1 (<0.1)	NA	NA
Papillary renal cell carcinoma	1 (<0.1)	0 (0)	NA	NA

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Adenocarcinoma metastatic	0 (0)	1 (<0.1)	NA	NA
Nervous system disorders	**16 (0.3)**	**10 (0.2)**	0.1 (-0.1 to 0.4)	0.23
Carotid artery thrombosis	1 (<0.1)	0 (0)	NA	NA
Cerebrospinal fluid leakage	1 (<0.1)	2 (<0.1)	>-0.1 (-0.1 to 0.1)	0.57
Dementia	1 (<0.1)	0 (0)	NA	NA
Dizziness	0 (0)	1 (<0.1)	NA	NA
Encephalopathy	0 (0)	1 (<0.1)	NA	NA
Hemiparesis	0 (0)	1 (<0.1)	NA	NA
Hypoglycemic encephalopathy	1 (<0.1)	0 (0)	NA	NA
Peroneal nerve palsy	1 (<0.1)	0 (0)	NA	NA
Presyncope	0 (0)	1 (<0.1)	NA	NA
Syncope	7 (0.1)	2 (<0.1)	0.1 (>-0.1 to 0.3)	0.09
Toxic encephalopathy	0 (0)	1 (<0.1)	NA	NA
Transient ischemic attack	1 (<0.1)	0 (0)	NA	NA
Visual field defect	1 (<0.1)	0 (0)	NA	NA
Vocal cord paralysis	1 (<0.1)	0 (0)	NA	NA
Cervical radiculopathy	1 (<0.1)	0 (0)	NA	NA
Metabolic encephalopathy	0 (0)	1 (<0.1)	NA	NA
Psychiatric disorders	**6 (0.1)**	**4 (0.1)**	<0.1 (-0.1 to 0.2)	0.52
Confusional state	0 (0)	1 (<0.1)	NA	NA
Delirium	4 (0.1)	2 (<0.1)	<0.1 (-0.1 to 0.2)	0.41
Suicidal ideation	1 (<0.1)	0 (0)	NA	NA
Suicide attempt	1 (<0.1)	0 (0)	NA	NA
Mental status changes	0 (0)	1 (<0.1)	NA	NA
Renal and urinary disorders	**30 (0.6)**	**20 (0.4)**	0.2 (-0.1 to 0.5)	0.15
Hematuria	2 (<0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.56
Hydronephrosis	0 (0)	1 (<0.1)	NA	NA

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Nephrolithiasis	1 (<0.1)	0 (0)	NA	NA
Nephropathy	1 (<0.1)	0 (0)	NA	NA
Renal failure	1 (<0.1)	2 (<0.1)	>-0.1 (-0.1 to 0.1)	0.57
Ureteric stenosis	1 (<0.1)	1 (<0.1)	0 (-0.1 to 0.1)	>0.99
Urinary bladder hemorrhage	0 (0)	1 (<0.1)	NA	NA
Urinary retention	7 (0.1)	1 (<0.1)	0.1 (<0.1 to 0.3)	0.03
Tubulointerstitial nephritis	0 (0)	1 (<0.1)	NA	NA
Urinoma	1 (<0.1)	0 (0)	NA	NA
Renal mass	0 (0)	1 (<0.1)	NA	NA
Chronic kidney disease	0 (0)	1 (<0.1)	NA	NA
Acute kidney injury	16 (0.3)	9 (0.2)	0.1 (-0.1 to 0.4)	0.16
Ureterolithiasis	0 (0)	1 (<0.1)	NA	NA
Reproductive system and breast disorders	**1 (<0.1)**	**1 (<0.1)**	0 (-0.1 to 0.1)	>0.99
Ovarian cyst	1 (<0.1)	0 (0)	NA	NA
Female genital tract fistula	0 (0)	1 (<0.1)	NA	NA
Respiratory, thoracic and mediastinal disorders	**31 (0.7)**	**18 (0.4)**	0.3 (>-0.1 to 0.6)	0.06
Acute respiratory failure	2 (<0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1))	0.56
Asthma	1 (<0.1)	0 (0)	NA	NA
Atelectasis	0 (0)	1 (<0.1)	NA	NA
Chronic obstructive pulmonary disease	3 (0.1)	2 (<0.1)	<0.1 (-0.1 to 0.1)	0.65
Dyspnea	3 (0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.32
Hemoptysis	1 (<0.1)	0 (0)	NA	NA
Hypoxia	2 (<0.1)	0 (0)	NA	NA
Interstitial lung disease	0 (0)	2 (<0.1)	NA	NA
Laryngeal edema	1 (<0.1)	0 (0)	NA	NA
Pleural effusion	5 (0.1)	0 (0)	NA	NA
Pleurisy	1 (<0.1)	0 (0)	NA	NA

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Pneumonia aspiration	1 (<0.1)	0 (0)	NA	NA
Pneumothorax	4 (0.1)	4 (0.1)	0 (-0.1 to 0.1)	>0.99
Respiratory acidosis	1 (<0.1)	0 (0)	NA	NA
Respiratory depression	0 (0)	1 (<0.1)	NA	NA
Respiratory distress	1 (<0.1)	0 (0)	NA	NA
Respiratory failure	2 (<0.1)	5 (0.1)	>-0.1 (-0.2 to 0.1)	0.26
Pulmonary mass	2 (<0.1)	1 (<0.1)	<0.1 (-0.1 to 0.1)	0.56
Negative pressure pulmonary edema	1 (<0.1)	0 (0)	NA	NA
Skin and subcutaneous tissue disorders	**1 (<0.1)**	**2 (<0.1)**	>-0.1 (-0.2 to 0.1)	0.57
Decubitus ulcer	0 (0)	1 (<0.1)	NA	NA
Subcutaneous emphysema	0 (0)	1 (<0.1)	NA	NA
Transient acantholytic dermatosis	1 (<0.1)	0 (0)	NA	NA
Surgical and medical procedures	**4 (0.1)**	**12 (0.3)**	-0.2 (-0.4 to <0.1)	<0.05
Pituitary tumor removal	1 (<0.1)	0 (0)	NA	NA
Sarcoma excision	0 (0)	1 (<0.1)	NA	NA
Small intestinal anastomosis	0 (0)	1 (<0.1)	NA	NA
Small intestinal resection	1 (<0.1)	0 (0)	NA	NA
Transurethral prostatectomy	0 (0)	1 (<0.1)	NA	NA
Nephrostomy	0 (0)	1 (<0.1)	NA	NA
Ureteral stent removal	1 (<0.1)	0 (0)	NA	NA
Catheter placement	0 (0)	1 (<0.1)	NA	NA
Catheter removal	0 (0)	1 (<0.1)	NA	NA
Ileocolostomy	0 (0)	1 (<0.1)	NA	NA
Intestinal anastomosis	0 (0)	1 (<0.1)	NA	NA
Hernia repair	0 (0)	1 (<0.1)	NA	NA
Mitral valve repair	1 (<0.1)	0 (0)	NA	NA
Central venous catheter removal	0 (0)	1 (<0.1)	NA	NA

	TXA (N=4757) no. (%)	Placebo (N=4778) no. (%)	Absolute difference % (95% CI)	P value
Drain removal	0 (0)	1 (<0.1)	NA	NA
Eventration repair	0 (0)	1 (<0.1)	NA	NA
Cardiovascular disorders	**21 (0.4)**	**7 (0.1)**	0.3 (0.2 to 0.5)	0.01
Hematoma	1 (<0.1)	0 (0)	NA	NA
Hypertension	5 (0.1)	0 (0)	NA	NA
Hypertensive crisis	1 (<0.1)	2 (<0.1)	>-0.1 (-0.2 to 0.1)	0.57
Hypotension	4 (0.1)	1 (<0.1)	0.1 (-0.1 to 0.2)	0.20
Orthostatic hypotension	2 (<0.1)	0 (0)	NA	NA
Peripheral ischemia	0 (0)	1 (<0.1)	NA	NA
Vena cava thrombosis	0 (0)	1 (<0.1)	NA	NA
Dry gangrene	1 (<0.1)	0 (0)	NA	NA
Hemodynamic instability	1 (<0.1)	0 (0)	NA	NA
Aortic occlusion	0 (0)	1 (<0.1)	NA	NA
Brachiocephalic vein thrombosis	1 (<0.1)	0 (0)	NA	NA
Lymphatic fistula	2 (<0.1)	0 (0)	NA	NA
Granulomatosis with polyangiitis	1 (<0.1)	0 (0)	NA	NA
Peripheral venous disease	1 (<0.1)	0 (0)	NA	NA
Subclavian vein stenosis	0 (0)	1 (<0.1)	NA	NA
Atheroembolism	1 (<0.1)	0 (0)	NA	NA
Product issues	**3 (0.1)**	**1 (<0.1)**	<0.1 (-0.1 to 0.1)	0.32
Device leakage	1 (<0.1)	0 (0)	NA	NA
Device dislocation	0 (0)	1 (<0.1)	NA	NA
Device occlusion	1 (<0.1)	0 (0)	NA	NA
Device loosening	1 (<0.1)	0 (0)	NA	NA

3.10 Supplementary Appendix Table S7. Tranexamic acid versus placebo and the 30-day risk of transfusions of packed red blood cells and bleeding resulting in reoperation

Outcome	Tranexamic acid (N=4757) no. (%)	Placebo (N=4778) no. (%)	Odds Ratio (95% CI)
Transfusion ≥1 unit of packed red blood cells	449 (9.4)	574 (12.0)	0.77 (0.68-0.88)
Transfusion ≥2 units of packed red blood cells	296 (6.2)	396 (8.3)	0.74 (0.64-0.86)
Transfusion 2-4 units of packed red blood cells	223 (4.7)	312 (6.5)	0.71 (0.60-0.84)
Transfusion ≥5 units of packed red blood cells	73 (1.5)	84 (1.8)	0.87 (0.64-1.19)
Bleeding resulting in reoperation	61 (1.0)	74 (1.3)	0.83 (0.59-1.16)

no. = number; % = percentage; CI = confidence interval

3.11 Supplementary Appendix Table S8. Tranexamic acid versus placebo and the 30-day primary efficacy and safety outcomes based on competing outcomes analyses*

Outcome	Tranexamic acid (N=4757)	Placebo (N=4778)	Hazard Ratio (95% CI)	P Value
Primary efficacy bleeding outcome – no. (%)				
composite bleeding outcome	433 (9.1)	561 (11.7)	0.77 (0.68-0.87)	<0.0001†
Primary safety cardiovascular outcome – no. (%)				
composite cardiovascular outcome	649 (14.2)	639 (13.9)	1.023 (0.919-1.139)	0.042‡

* We undertook sensitivity competing outcomes analyses for the primary efficacy and safety outcomes[11]

† Two-sided P value for superiority.

‡ One-sided P value for noninferiority.

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