ORIGINAL ARTICLE

Hospital Policy of Tranexamic Acid to Reduce Transfusion in Major Noncardiac Surgery

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ABSTRACT

BACKGROUND

Whether a hospital policy of tranexamic acid administration for patients undergoing major noncardiac surgery safely reduces the need for red-cell transfusion is uncertain.

METHODS

We conducted a multicenter, double-blind, cluster-randomized, placebo-controlled trial involving patients undergoing noncardiac surgery who were at high risk for red-cell transfusion. Hospitals were randomly assigned at 4-week intervals to a hospital-wide policy of intraoperative tranexamic acid or placebo. The coprimary effectiveness and safety outcomes were transfusion of red cells during the index hospitalization and diagnosis of venous thromboembolism within 90 days, respectively. The safety outcome was assessed for noninferiority, with a prespecified noninferiority margin defined as an upper boundary of 1.46 for the 95% confidence interval of the relative risk. Analyses used mixed-effects models that accounted for the cluster-crossover design.

RESULTS

A total of 8273 patients enrolled across 10 Canadian hospitals could be evaluated for the coprimary outcomes. Oncologic surgery accounted for 60.5% of the surgical procedures (5002 of 8273). The percentage of patients who received a red-cell transfusion during hospitalization was 7.4% (306 of 4156) in the tranexamic acid group and 9.8% (403 of 4117) in the placebo group (relative risk, 0.73; 95% confidence interval [CI], 0.61 to 0.86; adjusted difference, −2.7 percentage points; 95% CI, −4.2 to −1.4). Venous thromboembolism within 90 days occurred in 2.1% of patients (86 of 4128) in the tranexamic acid group and 2.1% of patients (85 of 4052) in the placebo group (relative risk, 0.96; 95% CI, 0.65 to 1.38; adjusted difference, −0.1 percentage points; 95% CI, −0.9 to 0.7), which met the criterion for noninferiority.

CONCLUSIONS

Among patients undergoing major noncardiac surgery, a hospital policy of tranexamic acid administration resulted in a lower incidence of red-cell transfusion than placebo administration, and tranexamic acid was noninferior to placebo with regard to diagnosis of venous thromboembolism. (Funded by the Canadian Institutes of Health Research and others; TRACTION ClinicalTrials.gov number, NCT04803747.)

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Perioperative bleeding is a leading indication for red-cell transfusion among hospitalized patients.[1] The supply of blood components is increasingly constrained owing to rising demand and declining donor pools, which underscores the need for strategies that reduce the demand for transfusion.[2-4] Tranexamic acid is an inexpensive and widely available antifibrinolytic medication that reduces blood loss and the incidence of red-cell transfusion in cardiac and orthopedic surgeries.[5-7]

In the Perioperative Ischemic Evaluation–3 (POISE-3) trial that evaluated tranexamic acid in a selected population of adult patients undergoing noncardiac surgery who were at risk for bleeding or cardiovascular complications, the incidence of a composite of life-threatening bleeding, major bleeding, or bleeding into a critical organ at 30 days was significantly lower with tranexamic acid than with placebo.[6] Noninferiority was not established for the primary safety outcome of 30-day major cardiovascular complications. Adoption of tranexamic acid across and within hospitals has been variable, in part because of unresolved concerns about potential thrombotic complications, particularly in patients with cancer or other prothrombotic conditions.[8,9]

We conducted the Tranexamic Acid to Reduce Transfusion in Major Noncardiac Surgery (TRACTION) trial to determine whether a hospital policy of tranexamic acid administration in patients undergoing major noncardiac surgeries would reduce the incidence of red-cell transfusion without a clinically important increase in the incidence of venous thromboembolism.

Methods

Trial Design and Oversight

In this multicenter, randomized, placebo-controlled, cluster-crossover trial, we evaluated whether a hospital policy of routine tranexamic acid use in patients undergoing major noncardiac surgeries would safely reduce the incidence of red-cell transfusion. Details of the trial design have been published previously[10] and are provided in the protocol, available with the full text of this article at NEJM.org.

The trial was designed by the investigators and approved by research ethics committees at each participating site with the use of either altered or waived consent. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation. The trial was funded by the Canadian Institutes of Health Research; the Health Sciences Centre Foundation; the Government of Manitoba through the Ministry of Health, Seniors, and Long-Term Care; and the Innovation Fund of the Ontario Ministry of Health. The University of Manitoba served as the regulatory sponsor and multicenter coordinating site. The Ottawa Hospital Research Institute was responsible for generating the randomization scheme, hosting Web-based enrollment, and managing and validating the data. Individual-site principal investigators were responsible for trial conduct at their respective sites. The steering committee provided clinical and methodologic guidance pertaining to trial design and execution, data analysis, and publication of the trial results. An independent data and safety monitoring board oversaw participant safety. The statistical analysis plan, available with the protocol, was finalized before investigators were aware of any trial results. The first author and last author wrote the first draft of the manuscript. The first two authors and last two authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The funders had no role in trial design, data collection, trial management, data analysis, interpretation of data, writing of the manuscript, or the decision to submit the manuscript for publication.

Patients

We recruited patients from 10 hospitals (clusters) in Canada. Hospitals were included if the site performed at least 100 noncardiac surgeries per month and if anesthesia, surgical, and hospital leadership agreed to manage the care of patients according to the policy implemented and evaluated in the trial (Table S1 in the Supplementary Appendix, available at NEJM.org). Eligible patients were adults (≥18 years of age) undergoing major noncardiac surgery, defined as an inpatient surgery with an estimated risk of red-cell transfusion of 5% or more; such surgeries broadly included open surgeries or laparoscopic surgeries with an estimated duration of at least 3 hours (Table S2).[5,11] Estimates of bleeding risk were informed by an observational study of approximately 75,000 surgical procedures conducted at four participating TRACTION sites.[11] Exclusion criteria were active thromboembolic disease, car-

diac and hip or knee total arthroplasty surgeries (in which tranexamic acid administration is standard practice), surgeries involving a free flap, trauma surgery in which tranexamic acid was administered within the previous 3 hours, and pregnancy.

PROCEDURES

Participating sites were randomly assigned in a 1:1 ratio at 4-week intervals to provide either tranexamic acid or matching placebo (0.9% sodium chloride) to patients undergoing surgery who were at high risk for transfusion. Randomization was performed with the use of a central, secure, Web-based randomization system. Tranexamic acid was administered as a 1-g bolus (2-g bolus for patients with a weight of >100 kg) intravenously at the start of surgery, followed by 1 additional gram before skin closure, with the timing of the additional dose at the discretion of the anesthesiologist. The dose regimen reflected clinical use and was supported by pharmacokinetic studies.[12,13] To decrease the effect of secular changes in tranexamic acid use over time and to preserve valid inferences of our superiority and safety outcomes, patients, health care providers, research staff, investigators, and the trial statistician were unaware of the randomization schemes and the investigational product administered. Cointerventions including, but not limited to, cell salvage, topical tranexamic acid, and intraoperative thromboprophylaxis were documented but not protocolized. In the event of life-threatening hemorrhage in which the surgical team believed that confirmation of tranexamic acid administration was required, blinded emergency investigational product was available that contained the opposite of the site's randomization. Given the cluster trial design, this procedure abrogated the need for emergency unblinding. Outcomes were ascertained centrally and electronically by means of validated clinical and administrative data, as described in the Supplementary Appendix.

OUTCOME MEASURES

The coprimary outcomes evaluated effectiveness in the context of safety. The coprimary outcomes were transfusion of red cells during the index hospitalization (effectiveness) and diagnosis of deep-vein thrombosis or pulmonary embolism, collectively referred to as venous thromboembolism, within 90 days after surgery (safety). Venous thromboembolic outcomes were obtained from provincial administrative sources with the use of a validated combination of physician billing and imaging codes or reports (Table S3).[14,15] Secondary outcomes included the number of red-cell units transfused up to hospital discharge, evaluated at the patient and cluster level; in-hospital diagnoses of myocardial infarction, stroke, deep-vein thrombosis, or pulmonary embolism; hospital length of stay (from surgery to hospital discharge); intensive care unit admission; hospital survival; overall survival to day 90; and the number of days alive and out of hospital to day 30. Adherence was measured as the proportion of enrolled patients who received a minimum of one dose of the trial intervention.

STATISTICAL ANALYSIS

The primary effectiveness hypothesis tested whether tranexamic acid reduced the percentage of patients who received a red-cell transfusion during the index hospitalization. The safety hypothesis tested whether tranexamic acid was noninferior to placebo with respect to venous thromboembolism within 90 days, with the use of a noninferiority margin defined as an upper boundary of 1.46 for the 95% confidence interval of the relative risk, equal to a 1-percentage-point difference in 90-day venous thromboembolism under the assumption of a baseline incidence of 2.2%. Effectiveness and safety were jointly assessed because both coprimary outcomes were required to be satisfied to declare a hospital policy of tranexamic acid to be beneficial, so no adjustment for multiplicity was required.

All the analyses followed a prespecified statistical analysis plan finalized before unblinding. The primary superiority analysis for effectiveness was performed in the intention-to-treat population, and the noninferiority analysis was performed in both the per-protocol (primary) and intention-to-treat populations. The intention-to-treat population included all the patients who underwent randomization. The per-protocol population included all the patients except those assigned to the tranexamic acid group who did not receive at least one dose of tranexamic acid and those assigned to the placebo group who received open-label tranexamic acid. Between-group comparisons for binary outcomes were estimated with mixed-effects logistic-regression models that accounted for clustering and period effects. Con-

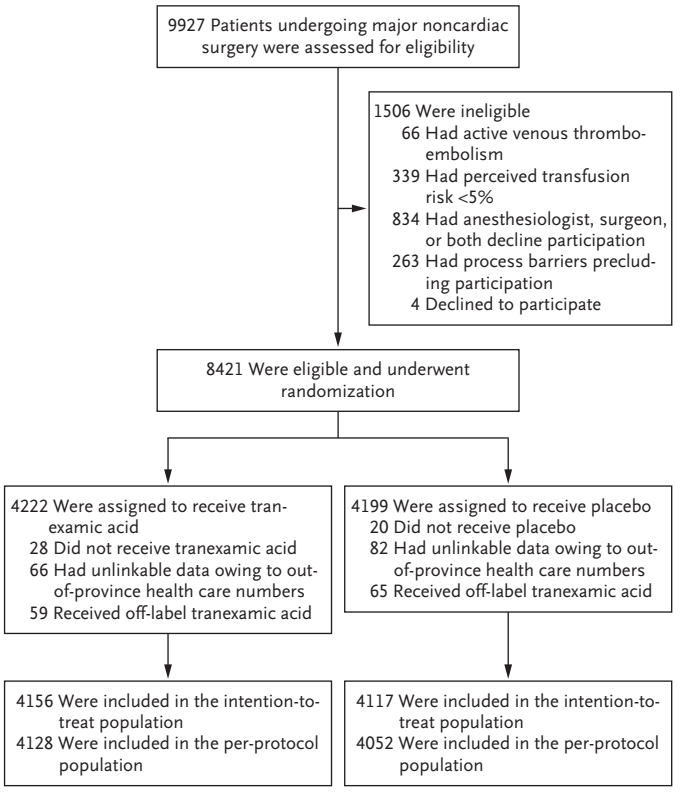


Figure 1. Screening and Randomization.

During screening, process barriers precluding participation included drug unavailability, coordinator unavailability, high surgical volumes, and surgical understaffing. The primary superiority analysis for effectiveness was performed in the intention-to-treat population.

tinuous outcomes were analyzed with linear or negative-binomial regression, and time-to-event outcomes were analyzed with Cox proportional-hazards models. Results are presented as relative and absolute risk differences, mean differences, or hazard ratios with 95% confidence intervals. Missing outcome data were expected to be minimal given electronic ascertainment; therefore, we performed complete-case analyses, implicitly assuming that any missing data would have been missing completely at random, with no evidence of differential missingness according to intervention group.

Prespecified sensitivity analyses of the coprimary outcomes were adjusted for age, sex, surgery type, surgical urgency, and preoperative hemoglobin concentration. Effect modification was explored through interaction terms for prespecified subgroups. Detailed modeling specifications and sample-size calculations are provided in the Supplementary Appendix.

RESULTS

PATIENTS, FOLLOW-UP, AND ADHERENCE

Patients were enrolled from February 2022 through March 2024 across 25 consecutive 4-week periods at 10 hospitals (Tables S4 and S5). Of the 8421 patients enrolled, data linkages were successfully established for 8273 (98.2%), comprising the primary intention-to-treat population. The per-protocol population included 8180 patients (98.9%) (Fig. 1). Open-label tranexamic acid use was uncommon (1.5%; 124 patients), as was use of blinded emergency investigational product (4.0%; 334 patients). Administration of cointerventions is included in Table S6.

Baseline characteristics were similar in the two groups (Table 1). The median age of the patients was 64 years (interquartile range, 54 to 72), and 47.1% were men. The most common surgeries performed according to specialty were general surgery (2742 surgeries; 33.1%), gynecologic surgery (1540; 18.6%), urologic surgery (1434; 17.3%), vascular surgery (582; 7.0%), and spine surgery (461; 5.6%). Oncologic surgery accounted for 60.5% of the surgical procedures performed (5002 surgeries). There were no missing data for primary or secondary outcomes.

PRIMARY OUTCOMES

The percentage of patients who received a red-cell transfusion during hospitalization was 7.4% (306 of 4156) in the tranexamic acid group and 9.8% (403 of 4117) in the placebo group (relative risk, 0.73; 95% confidence interval [CI], 0.61 to 0.86; adjusted difference, −2.7 percentage points; 95% CI, −4.2 to −1.4; number needed to treat, 37 patients) (Table 2). The treatment effect was insensitive to differential follow-up in a time-to-event analysis (Table S7).

The percentage of patients who received a diagnosis of thromboembolism within 90 days was 2.1% (86 of 4128) in the tranexamic acid group and 2.1% (85 of 4052) in the placebo group (relative risk, 0.96; 95% CI, 0.65 to 1.38; adjusted difference, −0.1 percentage points; 95% CI, −0.9 to 0.7), which met the prespecified criterion for noninferiority in the per-protocol population. In the intention-to-treat population, the percentage of patients who received a diagnosis of venous

Table 1. Baseline Characteristics of the Patients and Types of Surgeries.*

Characteristic	Tranexamic Acid (N=4156)	Placebo (N=4117)
Median age (IQR) — yr	64 (54–72)	64 (54–73)
Male sex — no. (%)	1985 (47.8)	1908 (46.3)
Median weight (IQR) — kg	80 (68–95)	80 (68–94)
Median Charlson Comorbidity Index score (IQR)†	2 (0–2)	2 (0–2)
Type of surgery — no./total no. (%)		
General surgery	1358/4107 (33.1)	1384/4058 (34.1)
Orthopedic surgery	87/4107 (2.1)	78/4058 (1.9)
Spine surgery	244/4107 (5.9)	217/4058 (5.3)
Otolaryngologic surgery	16/4107 (0.4)	21/4058 (0.5)
Thoracic surgery	451/4107 (11.0)	466/4058 (11.5)
Vascular surgery	286/4107 (7.0)	296/4058 (7.3)
Gynecologic surgery	799/4107 (19.5)	741/4058 (18.3)
Urologic surgery	735/4107 (17.9)	699/4058 (17.2)
Neurosurgery	126/4107 (3.1)	140/4058 (3.4)
Other	5/4107 (0.1)	16/4058 (0.4)
Surgical urgency — no./total no. (%)	4093/4156 (98.5)	4052/4117 (98.4)
Elective	3806/4093 (93.0)	3753/4052 (92.6)
Urgent or emergency	287/4093 (7.0)	299/4052 (7.4)
Surgical indication — no./total no. (%)	4072/4156 (98.0)	4027/4117 (97.8)
Oncologic	2536/4072 (62.3)	2466/4027 (61.2)
Nononcologic	1536/4072 (37.7)	1561/4027 (38.8)
Surgical method — no./total no. (%)	3583/4156 (86.2)	3402/4117 (82.6)
Open	1969/3583 (55.0)	1848/3402 (54.3)
Laparoscopic or endoscopic	1614/3583 (45.0)	1554/3402 (45.7)
Preoperative red-cell transfusion — no. (%)	56 (1.3)	64 (1.6)
Preoperative investigations‡		
Median hemoglobin level (IQR) — g/dl	13.4 (12.1–14.5)	13.4 (12.2–14.5)
Median platelet count (IQR) — $\times 10^{-9}$/liter	248 (205–303)	255 (205–311)
Median creatinine level (IQR) — mg/dl	0.96 (0.81–1.18)	0.96 (0.81–1.15)
Median international normalized ratio (IQR)	1 (1–1)	1 (1–1)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† The Charlson Comorbidity Index categorizes a patient's coexisting conditions on the basis of International Classification of Disease diagnoses in administrative data. Each of the 17 categories of coexisting conditions is assigned a weight (from 1 to 6, with higher scores indicating a greater burden of illness), and the sum of all weights results in the patient comorbidity score.
‡ For hemoglobin level, data were available for 2835 patients in the tranexamic acid group and 2819 patients in the placebo group. For platelet count, data were available for 2812 patients and 2783 patients, respectively. For creatinine level, data were available for 2641 patients and 2629 patients. For international normalized ratio, data were available for 444 patients and 455 patients.

thromboembolism within 90 days was 2.1% (86 of 4156) in the tranexamic acid group and 2.2% (90 of 4117) in the placebo group (relative risk, 0.92; 95% CI, 0.62 to 1.30). The results of post hoc sensitivity analyses of venous thromboembolism within 90 days that used varying definitions for the per-protocol and as-treated populations are shown in Table S8.

Table 2. Primary and Secondary Outcomes.*

Outcome	Tranexamic Acid (N=4156)	Placebo (N=4117)	Effect Estimate (95% CI)
Primary effectiveness outcome: red-cell transfusion during index hospitalization — no. (%)	306 (7.4)	403 (9.8)	0.73 (0.61 to 0.86)†‡
Primary safety outcome: diagnosis of venous thromboembolism within 90 days — no./total no. (%)			
Per-protocol population	86/4128 (2.1)	85/4052 (2.1)	0.96 (0.65 to 1.38)†§
Intention-to-treat population	86/4156 (2.1)	90/4117 (2.2)	0.92 (0.62 to 1.30)†
Secondary outcomes¶			
Red-cell units transfused			
Patient level per 100 patients	24.7±3.6	34.2±2.6	−9.5 (−19.2 to −0.2)‖
Hospital level per 100 patients	23.5±27.2	39.6±80.6	−16.2 (−33.5 to 1.1)‖
Myocardial infarction — no. (%)	29 (0.7)	34 (0.8)	NA
Stroke — no. (%)	9 (0.2)	9 (0.2)	NA
Deep-vein thrombosis — no.	<6**	<6**	NA
Pulmonary embolism — no. (%)	8 (0.2)	6 (0.1)	NA
Hospital length of stay — days	6.20±8.89	6.26±9.42	−0.15 (−0.69 to 0.29)‖
Intensive care unit admission — no. (%)	693 (16.7)	721 (17.5)	−0.01 (−0.03 to 0.02)††
Hospital survival — no. (%)	4112 (98.9)	4076 (99.0)	NA
Overall survival at 90 days — no. (%)	4066 (97.8)	4017 (97.6)	0.95 (0.71 to 1.28)‡‡
Median days alive and out of hospital to day 30 (IQR)	26 (22 to 27)	26 (22 to 27)	0.03 (−0.33 to 0.39)‖

* Plus–minus values are means ±SD. NA denotes not analyzed (the limited number of events precluded reliable between-group comparison).
† Shown is the relative risk.
‡ The intracluster correlation was 0.68, and the cluster autocorrelation coefficient was −0.13.
§ The intracluster correlation was 0.03, and the cluster autocorrelation coefficient was 0.05. The upper boundary of the 95% confidence interval of the risk ratio was 1.38, which did not cross the prespecified noninferiority margin of 1.46.
¶ These outcomes were evaluated at hospital discharge, unless otherwise specified.
‖ Shown is the mean difference.
** The Ontario Personal Health Information Protection Act precludes the reporting of cell sizes with fewer than six persons to minimize the risk of patient identification.
†† Shown is the difference in the proportion of patients (maximum, 1.00).
‡‡ Shown is the hazard ratio for death. The proportional-hazards assumption was satisfied; owing to the nonconvergence of the model used to compute the marginal estimate for overall survival at 90 days, the conditional estimate is provided.

SECONDARY OUTCOMES AND SERIOUS ADVERSE EVENTS

Patients in the tranexamic acid group received a mean (±SD) of 24.7±3.6 red-cell units, as compared with 34.2±2.6 red-cell units in patients in the placebo group (mean difference, −9.5 units; 95% CI, −19.2 to −0.2). When analyzed at a cluster level, the mean number of red-cell units transfused per 100 patients was 23.5±27.2 units in the tranexamic acid group and 39.6±80.6 units in the placebo group (mean difference, −16.2 units; 95% CI, −33.5 to 1.1) (Table 2). Among patients who received tranexamic acid as compared with those who received placebo, the incidence of in-hospital myocardial infarction, stroke, deep-vein thrombosis, pulmonary embolism, intensive care unit admission, hospital survival, and 90-day survival appeared to be similar. Prespecified serious adverse events (perioperative seizure and anaphylaxis) occurred in 2 patients, including perioperative seizure in 1 patient in the tranexamic acid group and perioperative anaphylaxis in 1 patient in the placebo group.

PRESPECIFIED SUBGROUP AND SENSITIVITY ANALYSES

The effectiveness and safety of tranexamic acid were largely similar across prespecified subgroups and are shown in Figure 2. The results of sensitivity analyses that evaluated the effectiveness

and safety of tranexamic acid with covariate adjustment are shown in Table S9.

DISCUSSION

In this pragmatic, cluster-crossover trial involving patients undergoing major noncardiac surgery, implementation of a hospital policy of tranexamic acid administration resulted in a lower percentage of patients who received red-cell transfusion than placebo administration (7.4% vs. 9.8%). Venous thromboembolism within 90 days occurred with the same frequency in the tranexamic acid and placebo groups (2.1% in each group).

Our results align with and extend previous evidence supporting antifibrinolytic therapy in surgery. Large trials such as the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2) trial,[16] the WOMAN (World Maternal Antifibrinolytic) trial,[17] BART (Blood Conservation Using Antifibrinolytics in a Randomized Trial),[18] and the ATACAS (Aspirin and Tranexamic Acid for Coronary Artery Surgery) trial[7] showed that tranexamic acid reduces bleeding and the incidence of transfusion across trauma, obstetric, and cardiac populations. Numerous modest-sized and heterogeneously designed trials highlighted the potential benefit of tranexamic acid in noncardiac surgery, but their individual and aggregate results were limited by the lack of generalizability when applied at a hospital level and the lack of systematically obtained long-term thrombotic outcomes.[5] The POISE-3 trial,[6] which enrolled 9535 patients at increased cardiovascular risk, showed a reduction in major bleeding. Although the trial did not meet its prespecified margin for noninferiority with respect to a composite thrombotic outcome at 30 days, the incidence of thrombosis was low in both trial groups. A recent meta-analysis evaluating tranexamic acid in noncardiac surgery suggested a reassuring thrombotic safety profile; however, its accompanying trial-sequential analysis reached only 65% of the required information size to definitively confirm safety.[19]

The TRACTION trial advances this evidence base by contributing a large proportion of the remaining information and providing the most precise, procedure-diverse estimates to date for risk of venous thromboembolism. As a prespecified tertiary outcome in the POISE-3 trial, red-cell transfusion occurred in 9.4% of the patients in the tranexamic acid group and in 12.0% of those in the placebo group. Our trial confirms the hemostatic effectiveness and relative safety of tranexamic acid with a similar dose regimen while addressing key limitations and enhancing generalizability. Whereas the POISE-3 trial targeted patients at risk for bleeding or ischemic events, our trial evaluated high-transfusion-risk surgeries while emphasizing pragmatic implementation at the hospital level. Moreover, approximately 22% of the patients in the POISE-3 trial underwent orthopedic surgery, a context in which tranexamic acid is now the standard of care. In contrast, the hospital-wide policy approach in our trial included a more diverse surgical population and a high percentage of oncologic surgeries (60.5%); patients undergoing such surgeries were often excluded or underrepresented in previous trials evaluating tranexamic acid.

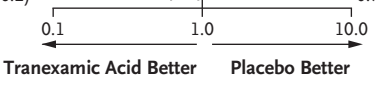
The inclusion of 5002 patients undergoing oncologic surgery is particularly relevant. Perioperative thrombosis risk in this population is well recognized[20] and has limited the use of antifibrinolytic agents owing to concerns about prothrombotic risk.[21,22] In our trial, the incidence of venous thromboembolism within 90 days among patients with cancer was low and not increased among those receiving tranexamic acid (2.4% in the tranexamic acid group and 2.6% in the placebo group; relative risk, 0.92; 95% CI, 0.68 to 1.48), which provides reassurance that tranexamic acid can be safely administered to patients with cancer undergoing major noncardiac surgery.

This trial also shows the feasibility and efficiency of modern, registry-based randomized evaluation within routine perioperative care. The trial used a risk-adapted consent approach, embedded placebo administration into the anesthetic workflow, and derived outcomes from linked clinical and administrative data sources. Once all the sites were active, enrollment exceeded 500 patients per month, which enabled rapid completion of a large multicenter trial at a fraction of the cost of a conventional trial. Such designs illustrate how integration of electronic health data and institutional policy randomization can accelerate evidence generation while maintaining rigor and generalizability.

The strengths of our trial include enrollment across a wide spectrum of high-transfusion-risk surgeries; a double-blind, placebo-controlled design; and coprimary outcomes selected to evalu-

A Red-Cell Transfusion during Hospitalization

Subgroup	Tranexamic Acid	Placebo	Relative Risk (95% CI)
	no. of patients with event/total no. (%)		
Overall	306/4156 (7.4)	403/4117 (9.8)	0.73 (0.61–0.86)
Age			
<40 yr	15/287 (5.2)	21/289 (7.3)	0.73 (0.31–1.39)
40–64 yr	111/1821 (6.1)	153/1814 (8.4)	0.69 (0.50–0.88)
65–74 yr	87/1282 (6.8)	125/1226 (10.2)	0.64 (0.47–0.83)
≥75 yr	93/766 (12.1)	104/788 (13.2)	0.86 (0.63–1.12)
Surgical specialty			
General surgery	102/1358 (7.5)	155/1384 (11.2)	0.65 (0.48–0.81)
Orthopedic surgery	10/87 (11.5)	9/78 (11.5)	0.85 (0.35–1.91)
Spine surgery	22/244 (9.0)	27/217 (12.4)	0.74 (0.34–1.49)
Neurosurgery	<6/126	11/140 (7.9)	0.47 (0.09–1.31)
Thoracic surgery	14/451 (3.1)	20/466 (4.3)	0.71 (0.30–1.47)
Vascular surgery	68/286 (23.8)	53/296 (17.9)	1.28 (0.83–1.95)
Gynecologic surgery	31/799 (3.9)	55/741 (7.4)	0.50 (0.25–0.84)
Urologic surgery	51/735 (6.9)	64/699 (9.2)	0.73 (0.48–1.09)
Surgical urgency			
Elective	243/3806 (6.4)	329/3753 (8.8)	0.70 (0.56–0.82)
Urgent or emergency	61/287 (21.3)	71/299 (23.7)	0.85 (0.61–1.16)
Surgical indication			
Oncologic	161/2536 (6.3)	241/2466 (9.8)	0.63 (0.49–0.77)
Nononcologic	139/1536 (9.0)	154/1561 (9.9)	0.87 (0.64–1.13)
Risk of red-cell transfusion			
<10%	98/2583 (3.8)	144/2523 (5.7)	0.64 (0.48–0.84)
≥10%	208/1573 (13.2)	259/1594 (16.2)	0.78 (0.62–0.95)



B Diagnosis of Venous Thromboembolism within 90 Days

Subgroup	Tranexamic Acid	Placebo	Relative Risk (95% CI)
	no. of patients with event/total no. (%)		
Overall	86/4128 (2.08)	85/4052 (2.10)	0.96 (0.65–1.38)
Age			
<40 yr	<6/286	<6/286	5.08 (0.44–8.37)
40–64 yr	41/1808 (2.3)	34/1792 (1.9)	1.21 (0.73–2.05)
65–74 yr	22/1271 (1.7)	27/1204 (2.2)	0.77 (0.45–1.58)
≥75 yr	18/763 (2.4)	23/770 (3.0)	0.79 (0.47–1.59)
Surgical specialty			
General surgery	32/1351 (2.4)	26/1367 (1.9)	1.24 (0.77–1.86)
Orthopedic surgery	<6/86	<6/77	2.76 (0.33–4.95)
Spine surgery	<6/242	<6/217	0.92 (0.21–3.67)
Neurosurgery	<6/126	6/135 (4.4)	0.84 (0.16–2.25)
Thoracic surgery	8/449 (1.8)	16/455 (3.5)	0.52 (0.28–2.04)
Vascular surgery	<6/284	<6/286	1.83 (0.50–10.75)
Gynecologic surgery	12/789 (1.5)	12/729 (1.6)	0.84 (0.42–1.83)
Urologic surgery	14/731 (1.9)	15/691 (2.2)	0.90 (0.39–1.92)
Surgical urgency			
Elective	70/3782 (1.9)	74/3692 (2.0)	0.93 (0.68–1.42)
Urgent or emergency	15/283 (5.3)	11/295 (3.7)	1.31 (0.71–2.59)
Surgical indication			
Oncologic	60/2526 (2.4)	64/2421 (2.6)	0.92 (0.68–1.48)
Nononcologic	25/1527 (1.6)	20/1541 (1.3)	1.26 (0.71–2.07)
Risk of red-cell transfusion			
<10%	45/2564 (1.8)	49/2482 (2.0)	0.89 (0.61–1.37)
≥10%	41/1564 (2.6)	36/1570 (2.3)	1.15 (0.73–1.95)

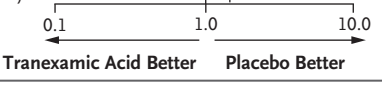


Figure 2 (facing page). Subgroup Analysis.
Panel A shows the relative risks for the effect of tranexamic acid on transfusion of red cells during the index hospitalization across prespecified subgroups in the intention-to-treat population. Panel B shows the relative risks for the effect of tranexamic acid on diagnosis of venous thromboembolism within 90 days after surgery across prespecified subgroups in the per-protocol population. The dashed vertical line indicates the prespecified noninferiority margin (defined as an upper boundary of 1.46 for the 95% confidence interval of the relative risk, representing an absolute risk increase of 1 percentage point given a baseline risk of 2.2%). The Ontario Personal Health Information Protection Act precludes the reporting of cell sizes with fewer than six persons to minimize the risk of patient identification.

ate effectiveness in the context of safety, thereby supporting informed clinical decision making. Patients and caregivers contributed to trial conception, consent processes, and outcome prioritization, which ensured patient-centered relevance. The dose of tranexamic acid paralleled usual clinical practice to maximize generalizability. Registry-based ascertainment enabled near-complete follow-up with efficient resource use. The trial achieved linkage for more than 98% of surgeries and highlights the infrastructure required to facilitate large-scale electronic randomized trials such as those exemplified by the FLUID trial[23] and Danish registry-based randomized, controlled trials.[24] The representativeness of the TRACTION trial population relative to patients undergoing major noncardiac surgery who were at risk for transfusion is summarized in Table S10 and supports the generalizability of our findings to routine perioperative practice in similar health care settings.

Several limitations are worth noting. First, participation was restricted to hospitals capable of linking clinical and administrative datasets. Nonetheless, enrolling hospitals reflected a broad range of case mixes from academic and community hospitals. Second, analyses relied on multisource data linkage; a small proportion of out-of-province patients could not be matched, although exclusion was balanced between the two groups. Third, although ascertainment of venous thromboembolism used validated diagnostic codes supplemented by imaging data, subclinical events may have been missed.[14,15]

In this trial, implementation of a hospital policy of tranexamic acid administration in patients undergoing major noncardiac surgeries resulted in a lower incidence of red-cell transfusion than placebo administration and was noninferior to placebo with regard to the incidence of venous thromboembolism. These findings support the use of tranexamic acid for hemostatic management in major noncardiac operations and illustrate the value of pragmatic, registry-based trials in evaluating widely available, low-cost interventions.

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