ORIGINAL ARTICLE

Prehospital Tranexamic Acid for Severe Trauma

The PATCH-Trauma Investigators and the ANZICS Clinical Trials Group*

ABSTRACT

BACKGROUND

Whether prehospital administration of tranexamic acid increases the likelihood of survival with a favorable functional outcome among patients with major trauma and suspected trauma-induced coagulopathy who are being treated in advanced trauma systems is uncertain.

METHODS

We randomly assigned adults with major trauma who were at risk for trauma-induced coagulopathy to receive tranexamic acid (administered intravenously as a bolus dose of 1 g before hospital admission, followed by a 1-g infusion over a period of 8 hours after arrival at the hospital) or matched placebo. The primary outcome was survival with a favorable functional outcome at 6 months after injury, as assessed with the use of the Glasgow Outcome Scale–Extended (GOS-E). Levels on the GOS-E range from 1 (death) to 8 ("upper good recovery" [no injury-related problems]). We defined survival with a favorable functional outcome as a GOS-E level of 5 ("lower moderate disability") or higher. Secondary outcomes included death from any cause within 28 days and within 6 months after injury.

RESULTS

A total of 1310 patients were recruited by 15 emergency medical services in Australia, New Zealand, and Germany. Of these patients, 661 were assigned to receive tranexamic acid, and 646 were assigned to receive placebo; the trial-group assignment was unknown for 3 patients. Survival with a favorable functional outcome at 6 months occurred in 307 of 572 patients (53.7%) in the tranexamic acid group and in 299 of 559 (53.5%) in the placebo group (risk ratio, 1.00; 95% confidence interval [CI], 0.90 to 1.12; P=0.95). At 28 days after injury, 113 of 653 patients (17.3%) in the tranexamic acid group and 139 of 637 (21.8%) in the placebo group had died (risk ratio, 0.79; 95% CI, 0.63 to 0.99). By 6 months, 123 of 648 patients (19.0%) in the tranexamic acid group and 144 of 629 (22.9%) in the placebo group had died (risk ratio, 0.83; 95% CI, 0.67 to 1.03). The number of serious adverse events, including vascular occlusive events, did not differ meaningfully between the groups.

CONCLUSIONS

Among adults with major trauma and suspected trauma-induced coagulopathy who were being treated in advanced trauma systems, prehospital administration of tranexamic acid followed by an infusion over 8 hours did not result in a greater number of patients surviving with a favorable functional outcome at 6 months than placebo. (Funded by the Australian National Health and Medical Research Council and others; PATCH-Trauma ClinicalTrials.gov number, NCT02187120.)

The members of the writing committee (Russell L. Gruen, M.B., B.S., Ph.D., Biswadev Mitra, M.B., B.S., Ph.D., Stephen A. Bernard, M.B., B.S., M.D., Colin J. McArthur, M.B., Ch.B., Brian Burns, M.B., B.Ch., B.A.O., Dashiell C. Gantner, M.B., B.S., Ph.D., Marc Maegele, M.D., Ph.D., Peter A. Cameron, M.B., B.S., M.D., Bridget Dicker, B.H.Sc., Ph.D., Andrew B. Forbes, Ph.D., Sally Hurford, R.N., Catherine A. Martin, Ph.D., Stefan M. Mazur, M.B., Ch.B., Robert L. Medcalf, Ph.D., Lynnette J. Murray, B. App.Sci., Paul S. Myles, M.P.H., D.Sc., Sze J. Ng, M.B., B.S., Veronica Pitt, Ph.D., Stephen Rashford, M.B., B.S., Michael C. Reade, M.B., B.S., D.Phil., Andrew H. Swain, M.B., B.S., Ph.D., Tony Trapani, B.Ed., and Paul J. Young, M.B., Ch.B., Ph.D.) assume responsibility for the overall content and integrity of this article.

The affiliations of the members of the writing committee are listed in the Appendix. Dr. Gruen can be contacted at russell.gruen@anu.edu.au or at the Office of the Dean, College of Health and Medicine, the Australian National University, 10 East Rd., Acton, ACT 2601, Australia.

*The PATCH-Trauma trial investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Trauma is the leading cause of death among young people.[1] Most of the preventable deaths are due to bleeding, which can be exacerbated by trauma-induced coagulopathy involving plasmin-mediated fibrinolysis resulting from tissue injury and hemorrhagic shock. Tranexamic acid, an antifibrinolytic drug, might be an effective treatment.[2]

The effect of in-hospital administration of tranexamic acid in patients with trauma was evaluated in the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH)–2 and CRASH-3 trials.[3,4] Tranexamic acid, administered within 3 hours after injury, was shown to reduce 28-day mortality among patients with suspected bleeding (CRASH-2 trial)[3] and among patients with mild-to-moderate traumatic brain injury (CRASH-3 trial).[4] Most of the participants in these trials were recruited in countries that were yet to implement organized regionwide systems of trauma care. Advanced trauma systems facilitate timely access to lifesaving critical care, blood products, surgery, and interventional radiology, thereby reducing preventable trauma deaths.[5] Unlike the CRASH-2 and CRASH-3 trials, subsequent trials of prehospital tranexamic acid therapy in advanced trauma systems did not show benefits in trauma patients with suspected bleeding[6] or isolated traumatic brain injury,[7] and another trial showed a dose-dependent increase in thromboembolism with tranexamic acid therapy.[8] Overall, the balance of benefits and risks of tranexamic acid in advanced trauma systems with multiple prehospital and in-hospital hemorrhage control strategies is uncertain, and uptake has varied across the world. Moreover, because patients in the CRASH trials were not followed beyond 28 days and functional outcomes were not reported, the effect of tranexamic acid on quality of survival is unclear.

We undertook the Pre-hospital Antifibrinolytics for Traumatic Coagulopathy and Hemorrhage (PATCH-Trauma) trial to evaluate the efficacy and safety of tranexamic acid therapy in patients with severe trauma who were at risk for trauma-induced coagulopathy. Our hypothesis was that tranexamic acid initiated before hospital admission in advanced trauma systems would result in a greater percentage of patients surviving with a favorable functional outcome at 6 months than placebo.

Methods

Trial Design and Oversight

The protocol for this international, double-blind, randomized, placebo-controlled trial was designed by the trial management committee, endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group, and approved by the human research ethics committee responsible for each participating site.[9] The protocol is available with the full text of this article at NEJM.org. Each ethics committee approved a waiver of the requirement to seek informed consent on the basis that the intervention was already used in some regions and needed to be administered as early as possible. Patients or their legally authorized representatives were notified as soon as feasible and asked to consent to continued participation and data collection.

An independent data and safety monitoring committee oversaw the trial and reviewed the results of planned interim analyses after 296 patients and 592 patients had completed 28 days of follow-up. The writing committee vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All the members of the writing committee contributed to the writing of the manuscript and agreed to submit the manuscript for publication. No commercial support was provided.

Patients

Eligible patients were adults (≥18 years of age) with suspected severe traumatic injuries who were treated at the scene by paramedics or physicians and transported by road or air ambulance to participating trauma centers. Patients were eligible for inclusion if they were assessed as being at high risk for trauma-induced coagulopathy and if the first dose of tranexamic acid or placebo could be administered within 3 hours after injury and before hospital admission. Prehospital assessment of coagulopathy risk was performed with the use of the Coagulopathy of Severe Trauma (COAST) score. COAST scores range from 0 to 7, with 1 point assigned for each of the following variables: entrapment in a vehicle, systolic blood pressure of less than 100 mm Hg, body temperature of less than 35°C, suspected pneumothorax, and suspected intraabdominal or pelvic injury. Additional points are assigned if the

systolic blood pressure is less than 90 mm Hg or if the body temperature is less than 32°C.[10] Patients with a COAST score of 3 or greater are considered to be at high risk for coagulopathy. Patients were excluded if they were known or suspected to be pregnant or if they resided in a facility for older persons. Prespecified subgroups were defined according to age (<50 years or ≥50 years), initial score on the Glasgow Coma Scale (<9 or ≥9; on a scale of 3 to 15, with higher scores indicating a greater level of consciousness), initial systolic blood pressure (≤75 mm Hg, 76 to 89 mm Hg, or ≥90 mm Hg), mechanism of injury (blunt, penetrating, or burn), and time from injury to first dose of tranexamic acid or placebo (<1 hour, 1 to <2 hours, or ≥2 hours).

RANDOMIZATION AND PROCEDURES

We randomly assigned patients in a 1:1 ratio to receive tranexamic acid or placebo. The trial statisticians generated the randomization sequence with the use of computer-generated random numbers stratified according to national or state jurisdiction and initial score on the Glasgow Coma Scale (<9 or ≥9). Two independent pharmaceutical packaging companies used the sequence to prepare trial packs as consecutively numbered, opaque, foil parcels with a tamper-proof seal. Each pack included two identical 10-ml glass ampules containing either 1 g of tranexamic acid in water for injection or 0.9% sodium chloride solution. All trial personnel — including the participants, treating clinicians, and follow-up assessors — were unaware of the trial-group assignments.

Clinicians administered one dose of tranexamic acid or placebo intravenously as a bolus (by means of a slow-push method over 10 minutes) as soon as practicable at the scene or en route to the receiving hospital. After hospital arrival, the second 10-ml ampule in the trial pack was added to 1 liter of 0.9% sodium chloride solution and infused over a period of 8 hours. In addition to tranexamic acid or placebo, patients received usual prehospital, in-hospital, and posthospital care. Tranexamic acid or placebo could be discontinued in the event of suspected allergy, if a reason for exclusion became apparent (e.g., a positive pregnancy test), if the patient was transitioned to palliative care, or if further participation in the trial was declined. Inpatients were screened for deep venous thrombosis in the legs with the use of Doppler ultrasonography on or around day 7.

OUTCOMES

The primary outcome was survival with a favorable functional outcome at 6 months, as assessed with the use of the Glasgow Outcome Scale–Extended (GOS-E), administered as a standardized questionnaire by trained telephone interviewers.[11] Although developed for traumatic brain injury, the GOS-E is widely used to assess functional outcomes in major trauma registries because it also performs favorably in populations without traumatic brain injury, can be administered by proxy, and includes most domains from the International Classification of Functioning, Disability, and Health by the World Health Organization.[12,13] Levels on the GOS-E range from 1 (death) to 8 ("upper good recovery" [no injury-related problems]). Categories were dichotomized into "death or survival with an unfavorable functional outcome" (which included "death," "vegetative state," "lower severe disability," and "upper severe disability" [GOS-E levels of 1 to 4]) and "survival with a favorable functional outcome" (which included "lower moderate disability," "upper moderate disability," "lower good recovery," and "upper good recovery" [GOS-E levels of 5 to 8]).

Secondary outcomes included death within 24 hours, 28 days, and 6 months after injury, as determined through follow-up contact and medical records. The treating clinician categorized the cause of death as bleeding, vascular occlusion, multiorgan failure, traumatic brain injury, or other. Vascular occlusive events (deep venous thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, or other arterial events) and sepsis that occurred up to the time of death, hospital discharge, or 28 days after injury (whichever occurred first) were also defined as secondary outcomes. A full list of outcomes is provided in the protocol.

STATISTICAL ANALYSIS

The statistical analysis plan was posted publicly on the PATCH-Trauma trial website (http://www.patchtrauma.org) on August 19, 2022, before unblinding of the trial-group assignments. For the sample-size calculation, the percentage of patients who were expected to have a favorable GOS-E level at 6 months and the anticipated treatment effect were based on previous work.[3,5]

We calculated that enrollment of 1184 patients would provide 90% power to detect a between-group difference of 9 percentage points in the percentage of patients who survived with a favorable functional outcome, with a two-sided alpha level of 0.05. In February 2020, with an observed loss to follow-up of 10%, the target sample size was increased to 1316. Recruitment was stopped when 1310 patients had been enrolled because of expiration of the trial agents.

The primary outcome was assessed in the intention-to-treat population (the primary analysis) and the per-protocol population. The intention-to-treat population included all the patients who had undergone randomization and excluded patients with unknown trial-group assignment or who withdrew consent for any data to be used. The per-protocol population included the patients in the intention-to-treat population, with the exclusion of those who were later found not to have met the inclusion criteria, who were later found to have met the exclusion criteria, who did not receive both doses of tranexamic acid or placebo, or who received open-label tranexamic acid.

The analysis of the primary outcome used log-binomial regression to estimate the risk ratio and 95% confidence interval. Supplementary analyses were adjusted for the randomization stratification variables and restricted the use of GOS-E assessments to those available within 4 to 8 months after injury. Planned subgroup analyses used regression models that included interaction terms between the subgroup and trial group.

For secondary outcomes, comparisons between trial groups were estimated as risk ratios for binary outcomes and differences in medians (determined with the use of quantile regression) for continuous outcomes, with 95% confidence intervals. The comparison between groups for each cause of death within 6 months was expressed as a cause-specific hazard ratio with 95% confidence interval.

Additional analyses that were performed to account for missing primary and secondary outcome data (and for 3 patients whose trial-group assignments were unknown) used multiple imputation with chained equations to create 30 imputed data sets. To account for the competing risk of death, supplementary analyses of sepsis and vascular occlusive events were performed with the use of cumulative incidence functions to estimate the risk ratio at 28 days. To assess whether the effect of tranexamic acid on the primary outcome differed between patients with or without a traumatic brain injury of more than moderate severity, we conducted a post hoc analysis with an interaction term between trial group and whether the score on the Abbreviated Injury Scale for the head or neck region was greater than 2 (on a scale of 0 to 6, with higher scores indicating more severe injury).

Additional information on statistical analyses is provided in the statistical analysis plan (available with the protocol) and the Supplementary Appendix, available at NEJM.org. All analyses were conducted with the use of Stata software, version 16.1 (StataCorp). Because there was no correction for multiple comparisons in the analyses of secondary outcomes, P values are not reported, 95% confidence intervals should not be used in place of hypothesis testing, and the results should be considered to be exploratory.

RESULTS

PATIENTS

From July 28, 2014, to September 28, 2021, a total of 1310 patients were enrolled and treated by 15 emergency medical services and at 21 hospitals in Australia, New Zealand, and Germany. The trial packs for 3 patients were lost in the field, so the trial-group assignment was known for 1307 patients (661 assigned to the tranexamic acid group and 646 assigned to the placebo group) (Fig. 1). Consent for participation was withdrawn by 4 patients in the tranexamic acid group and 3 patients in the placebo group; therefore, the intention-to-treat population included 657 patients in the tranexamic acid group and 643 in the placebo group. Primary outcome data were available for 1131 patients (572 in the tranexamic acid group and 559 in the placebo group [87.0%]). Primary outcome data were not available for 50 patients who declined to participate in follow-up and for 119 patients who could not be contacted.

The demographic and clinical characteristics of the patients at baseline were similar in the two trial groups (Table 1 and Tables S1 through S3 in the Supplementary Appendix). The representativeness of the trial population is described in Table S4. A total of 24.1% of the patients had laboratory evidence of early coagulopathy, and 39.3% subsequently received a diagnosis of a head

or neck injury of more than moderate severity (Abbreviated Injury Scale score >2) (Table 1). Protocol deviations occurred in 215 patients (32.7%) in the tranexamic acid group and in 238 patients (37.0%) in the placebo group, including 104 (15.8%) and 106 (16.5%), respectively, who received open-label tranexamic acid in the hospital (Table S5).

PRIMARY OUTCOME

In the intention-to-treat analysis, a favorable functional outcome (a GOS-E level of ≥5) was recorded for 307 of 572 patients (53.7%) in the tranexamic acid group and 299 of 559 patients (53.5%) in the placebo group (absolute risk difference, 0.2 percentage points; 95% confidence interval [CI], −5.6 to 6.0; risk ratio, 1.00; 95% CI, 0.90 to 1.12; P=0.95) (Fig. 2). There was no evidence of heterogeneity in the effect of tranexamic acid on the primary outcome in any prespecified subgroups (Fig. 3).

In the post hoc assessment of patients with a score of greater than 2 on the Abbreviated Injury Scale (head or neck region), a favorable functional outcome occurred in 86 of 243 patients (35.4%) in the tranexamic acid group and in 83 of 217 patients (38.2%) in the placebo group (risk ratio, 0.93; 95% CI, 0.73 to 1.18). Among patients with a score of 2 or less on the Abbreviated Injury Scale (head or neck region), a favorable functional outcome occurred in 221 of 315 patients (70.2%) in the tranexamic acid group and in 216 of 327 (66.1%) in the placebo group (risk ratio, 1.06; 95% CI, 0.96 to 1.18) (Fig. S1).

Between-group differences in the primary outcome after imputation of missing data and after adjustment for randomization stratification variables are presented in Tables S10 and S14 and in Figure S3. Sensitivity analyses that excluded primary outcome data that were assessed outside a window of 4 to 8 months after injury are presented in Table S16, and the results of the analysis of the primary outcome in the per-protocol population are provided in Table S22 and Figure S6. These analyses yielded findings that were consistent with those of the primary analysis.

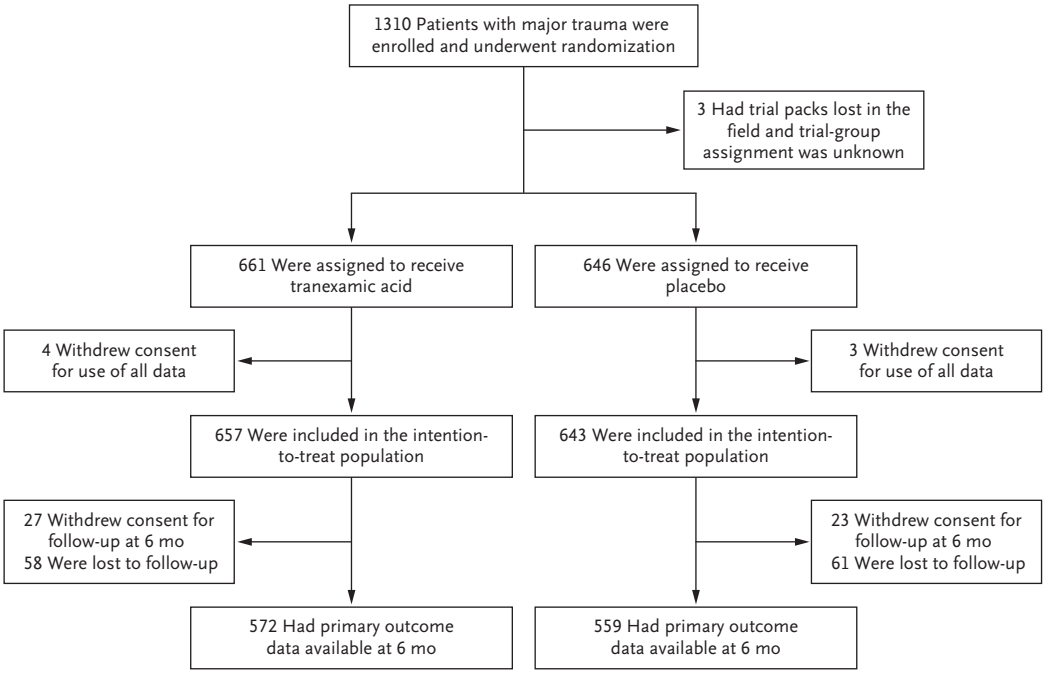

Figure 1. Randomization and Follow-up.

In this pragmatic trial involving patients with major trauma, treating clinicians determined enrollment eligibility in the field, often under adverse conditions. Information on the numbers or reasons for nonenrollment was not collected.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Tranexamic Acid (N=657)	Placebo (N=643)
Age — yr	44.1±19.7	44.2±18.9
Male sex — no. (%)	459 (69.9)	459 (71.4)
Mechanism of injury — no. (%)		
Blunt	610 (92.8)	588 (91.4)
Penetrating	44 (6.7)	55 (8.6)
Burn	3 (0.5)	0
Median initial heart rate (IQR) — beats/min†	110.0 (88.0–130.0)	109.0 (88.0–128.0)
Initial systolic blood pressure — no./total no. (%)		
≤75 mm Hg	246/639 (38.5)	248/626 (39.6)
76–89 mm Hg	218/639 (34.1)	197/626 (31.5)
≥90 mm Hg	175/639 (27.4)	181/626 (28.9)
Initial body temperature — °C‡	35.5±1.2	35.5±1.3
Initial Glasgow Coma Scale score — no./total no. (%)§		
<9	229/655 (35.0)	211/642 (32.9)
9 to 12	51/655 (7.8)	73/642 (11.4)
13 to 15	375/655 (57.3)	358/642 (55.8)
COAST score — no. (%)¶		
<3	4 (0.6)	4 (0.6)
3	247 (37.6)	268 (41.7)
4	251 (38.2)	237 (36.9)
5	122 (18.6)	106 (16.5)
6	33 (5.0)	28 (4.4)
Median Injury Severity Score (IQR)‖	29.0 (18.0–41.0)	29.0 (17.0–38.0)
Score >2 on the Abbreviated Injury Scale for head or neck — no./total no. (%)‖	263/643 (40.9)	236/626 (37.7)
Previous anticoagulant use — no./total no. (%)	15/584 (2.6)	17/545 (3.1)
Previous antiplatelet use — no./total no. (%)	46/581 (7.9)	36/546 (6.6)
Prerandomization red-cell transfusion — no./total no. (%)	230/655 (35.1)	238/642 (37.1)
Prerandomization plasma transfusion — no./total no. (%)	17/493 (3.4)	24/493 (4.9)
Time from injury to first dose of tranexamic acid or placebo — no./total no. (%)		
<1 hr	214/656 (32.6)	176/641 (27.5)
1 to <2 hr	297/656 (45.3)	329/641 (51.3)
≥2 hr	145/656 (22.1)	136/641 (21.2)

* Plus–minus values are means ±SD. Data are shown for the intention-to-treat population, which included all the patients who had undergone randomization and excluded patients with unknown trial-group assignments or who withdrew consent for any data to be used. A total of 7 patients (4 in the tranexamic acid group and 3 in the placebo group) withdrew consent for use of all data and were not included in the intention-to-treat population. IQR denotes interquartile range.

† Data were available for 655 patients in the tranexamic acid group and 641 in the placebo group.

‡ Data were available for 569 patients in the tranexamic acid group and 572 in the placebo group.

§ Scores on the Glasgow Coma Scale range from 3 to 15, with higher scores indicating a greater level of consciousness.

¶ Coagulopathy of Severe Trauma (COAST) scores range from 0 to 7, with 1 point assigned for each of the following variables: entrapment in a vehicle, systolic blood pressure of less than 100 mm Hg, body temperature of less than 35°C, suspected pneumothorax, and suspected intraabdominal or pelvic injury. Additional points are assigned if the systolic blood pressure is less than 90 mm Hg or if the body temperature is less than 32°C. Patients with a COAST score of 3 or greater are considered to be at high risk for coagulopathy.

‖ Injury Severity Scores range from 1 to 75, with higher scores indicating more severe injury. Each of six regions of the body (head or neck, face, chest, abdomen, extremities [including the pelvis], and external) is assigned a score of 1 to 6 on the Abbreviated Injury Scale (with a score of 1 indicating a mild injury and a score of 6 indicating an unsurvivable injury), and the Injury Severity Score is calculated as the sum of the squares of the highest scores on the Abbreviated Injury Scale for each of the three most severely injured body regions. If a score of 6 on the Abbreviated Injury Scale is assigned for any region, an Injury Severity Score of 75 is automatically assigned. Major trauma is usually defined as an Injury Severity Score of 12 or greater or 15 or greater. Data for Injury Severity Scores were available for 644 patients in the tranexamic acid group and 627 patients in the placebo group.

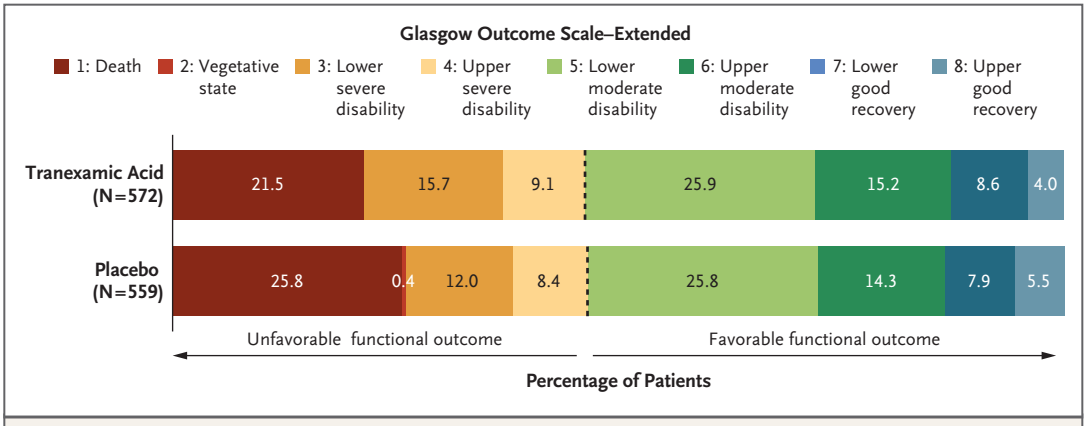

Figure 2. Levels on the Glasgow Outcome Scale–Extended (GOS-E) at 6 Months.

The GOS-E ranges from 1 to 8, with higher levels indicating better outcomes. The percentages represent the percentage of patients with each level. No patients in the tranexamic acid group had a GOS-E level of 2. The dotted line indicates the demarcation between death or survival with an unfavorable functional outcome (GOS-E levels of 1 to 4) and survival with a favorable functional outcome (GOS-E levels of 5 to 8). Results are shown without imputation; the results of an analysis that used imputation are provided in Figure S3 in the Supplementary Appendix. Percentages may not total 100 because of rounding.

SECONDARY OUTCOMES

Secondary outcomes are shown in Table 2 and in Tables S6 through S8. By 24 hours after injury, 64 of 657 patients (9.7%) in the tranexamic acid group and 90 of 640 patients (14.1%) in the placebo group had died (risk ratio, 0.69; 95% CI, 0.51 to 0.94). By 28 days, 113 of 653 patients (17.3%) in the tranexamic acid group and 139 of 637 (21.8%) in the placebo group had died (risk ratio, 0.79; 95% CI, 0.63 to 0.99). By 6 months, 123 of 648 patients (19.0%) in the tranexamic acid group and 144 of 629 (22.9%) in the placebo group had died (risk ratio, 0.83; 95% CI, 0.67 to 1.03), among whom 36 (29.3%) and 52 (36.1%) deaths, respectively, were attributed to bleeding. The GOS-E levels at 6 months are shown in Figure 2.

One or more vascular occlusive events occurred in 155 of 657 patients (23.6%) in the tranexamic acid group and in 126 of 641 (19.7%) in the placebo group (risk ratio, 1.20; 95% CI, 0.97 to 1.48). The incidences of other adverse events were similar in the two trial groups (Table S9).

DISCUSSION

In this international trial involving adults with major trauma who were at risk for acute traumatic coagulopathy, there was no significant between-group difference in the percentage of patients surviving with a favorable functional outcome at 6 months. In our trial, for every 100 patients assigned to receive tranexamic acid rather than placebo, there were approximately 4 extra patients alive at 6 months; however, approximately 4 extra patients were also categorized as having severe disability.

We studied patients who were treated in advanced trauma systems, and we found that the effect of tranexamic acid on early death and death due to bleeding was consistent with that observed in the CRASH-2 trial, which predominantly enrolled patients who were treated in less-developed trauma systems.[3] The effect of tranexamic acid on functional and long-term outcomes was not reported in the CRASH-2 trial, and our trial provides new information on the quality of survival after severe trauma that is treated with tranexamic acid.

Our finding of no between-group difference in survival with a favorable functional outcome at 6 months is consistent with outcomes reported in a previous trial of tranexamic acid in patients with isolated traumatic brain injury.[7] Longitudinal studies of trauma patients in equivalent populations have shown that some patients have functional improvement beyond 6 months.[14] Our data do not preclude the possibility that tranexamic acid can prevent early death from bleeding in some patients who will go on to make a good recovery. However, because we did not find evi-

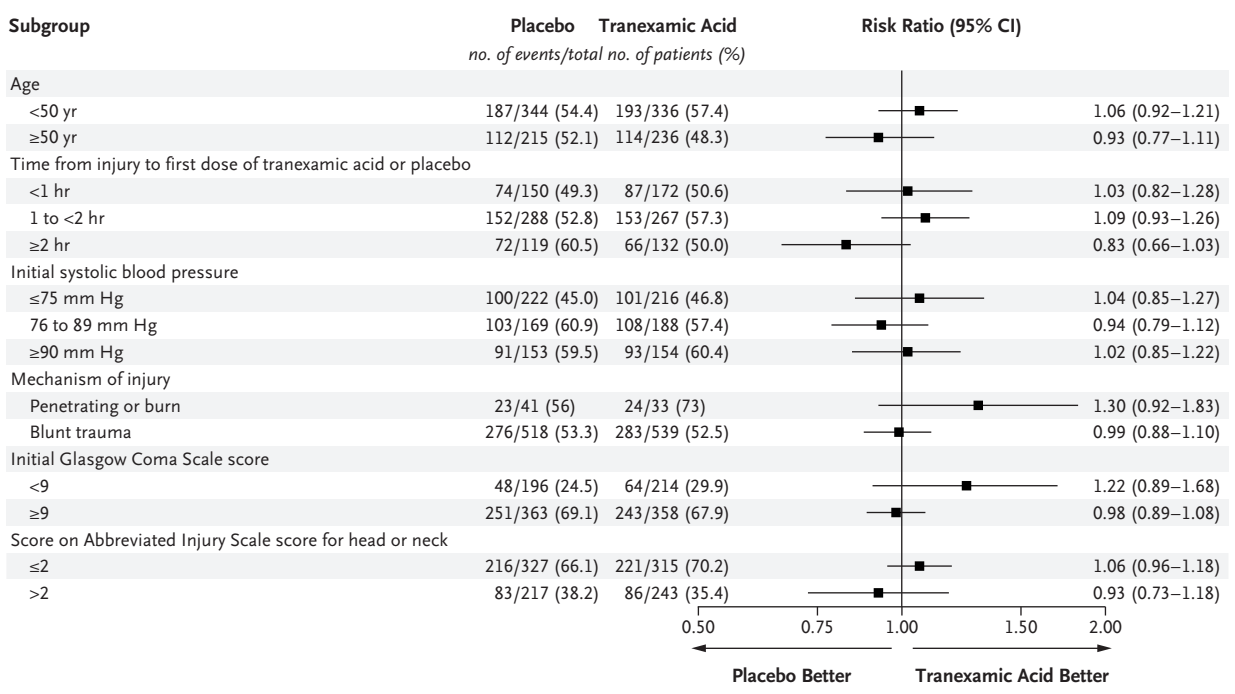

Figure 3. Subgroup Analyses of the Primary Outcome.

The primary outcome was survival with a favorable functional outcome at 6 months after injury, as assessed with the use of the GOS-E. Survival with a favorable functional outcome was defined as a GOS-E level of 5 ("lower moderate disability") or higher. Scores on the Abbreviated Injury Scale range from 0 to 6, with higher scores indicating more severe injury. The comparison of scores on the Abbreviated Injury Scale for the head or neck region was performed as a post hoc analysis.

dence of a between-group difference in subgroups according to age, mechanism of injury, systolic blood pressure, score on the Glasgow Coma Scale, or time to first dose of tranexamic acid or placebo, our findings do not provide a basis for identifying such patients in the prehospital setting.

A concern about tranexamic acid has been the potential risk of thrombotic complications, the prevention of which is a major focus of trauma care. We screened inpatients for deep venous thrombosis in the legs and, in contrast to a previous trial of tranexamic acid in major trauma patients[8] and another trial of tranexamic acid in nontraumatic gastrointestinal bleeding,[15] found little evidence that tranexamic acid increased the risk of such events.

We acknowledge some limitations. First, primary outcome data were missing for 13% of the patients, mostly because of loss to follow-up. Although the percentage was similar in the two trial groups and analyses that used multiple imputation to account for missing data yielded similar findings to a complete-case analysis, we cannot exclude the possibility that outcomes for patients with missing data differed in the two trial groups according to other factors. Second, some patients did not receive all the intended doses, and some received open-label tranexamic acid, in contravention of the protocol. Findings in the intention-to-treat and per-protocol analyses were similar, so it is unlikely that such protocol deviations meaningfully affected our findings. Third, the generalizability of our findings may be limited by the lack of information about patients who underwent screening but were not enrolled, by insufficient power to detect clinically important heterogeneity of treatment response in penetrating trauma and other subgroups with small numbers, and by the exclusive focus on severely injured patients at risk for trauma-induced coagulopathy who were being treated in advanced trauma systems. Fourth, we investigated a treatment regimen of tranexamic acid administered intravenously as a 1-g bolus before hospital admission, followed by a 1-g infusion over a period of 8 hours in the hospital,

Table 2. Primary and Secondary Outcomes.*

Outcome	Tranexamic Acid (N=657)	Placebo (N=643)	Risk Ratio or Hazard Ratio (95% CI)†
Primary outcome			
Survival with a favorable functional outcome at 6 months — no./total no. (%)‡	307/572 (53.7)	299/559 (53.5)	1.00 (0.90–1.12)
Secondary outcomes			
Death — no./total no. (%)			
24 hr after injury	64/657 (9.7)	90/640 (14.1)	0.69 (0.51–0.94)
28 days after injury	113/653 (17.3)	139/637 (21.8)	0.79 (0.63–0.99)
6 mo after injury	123/648 (19.0)	144/629 (22.9)	0.83 (0.67–1.03)
Death within 6 mo after injury — no./total no. (%)§			
Due to bleeding	36/648 (5.6)	52/629 (8.3)	0.66 (0.43–1.01)
Due to vascular occlusion¶	2/648 (0.3)	0/629	—
Due to multiorgan failure	7/648 (1.1)	11/629 (1.7)	0.59 (0.23–1.52)
Due to traumatic brain injury	66/648 (10.2)	67/629 (10.7)	0.92 (0.65–1.29)
Due to other cause	7/648 (1.1)	10/629 (1.6)	0.65 (0.25–1.70)
Cause could not be classified	5/648 (0.8)	4/629 (0.6)	1.17 (0.31–4.37)
Vascular occlusive events — no./total no. (%)‖			
Deep venous thrombosis	100/657 (15.2)	80/641 (12.5)	1.22 (0.93–1.60)
Pulmonary embolism	43/657 (6.5)	45/641 (7.0)	0.93 (0.62–1.40)
Myocardial infarction	8/657 (1.2)	4/641 (0.6)	1.95 (0.59–6.45)
Ischemic stroke	19/657 (2.9)	14/641 (2.2)	1.32 (0.67–2.62)
Other arterial event	10/657 (1.5)	10/641 (1.6)	0.98 (0.41–2.33)
Any of the above	155/657 (23.6)	126/641 (19.7)	1.20 (0.97–1.48)
Sepsis — no./total no. (%)‖	226/657 (34.4)	198/641 (30.9)	1.11 (0.95–1.30)

* Data are shown for the intention-to-treat population, which included all the patients who had undergone randomization and excluded patients with unknown trial-group assignments or who withdrew consent for any data to be used.
† All values are risk ratios except those for death within 6 months after injury, which are hazard ratios.
‡ Functional outcomes were assessed with the use of the Glasgow Outcome Scale–Extended (GOS-E). Levels on the GOS-E range from 1 (death) to 8 ("upper good recovery" [no injury-related problems]). The primary outcome (survival with a favorable functional outcome at 6 months) was defined as a GOS-E level of 5 ("lower moderate disability") or higher. P=0.95 for the primary-outcome comparison.
§ The cause of death was classified by the treating clinician.
¶ The hazard ratio was not calculated because of the small number of events.
‖ Data on vascular occlusive events and episodes of sepsis were collected up to the time of death, hospital discharge, or 28 days after injury (whichever occurred first).

and our findings do not preclude the possibility of benefit or harm with other dosage regimens.

Among adults with major trauma who were at risk for trauma-induced coagulopathy and were receiving treatment in advanced trauma systems, 1 g of intravenous tranexamic acid initiated in the prehospital setting followed by an infusion of 1 g of tranexamic acid over a period of 8 hours in the hospital appeared to be associated with lower early mortality but did not result in a higher percentage of patients surviving with a favorable functional outcome at 6 months than placebo.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The writing committee members' affiliations are as follows: the College of Health and Medicine, Australian National University (R.L.G.), Canberra Health Services (R.L.G.), and Joint Health Command, Australian Defence Force (M.C.R.), Canberra, ACT, the Emergency and Trauma Centre (B.M., P.A.C.) and the Departments of Anaesthesiology and Perioperative Medicine (P.S.M.) and Intensive Care (S.A.B., D.C.G.), Alfred Hospital, the Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine (D.C.G., L.J.M., S.J.N., T.T., P.J.Y.), the School of Public Health and Preventive Medicine (B.M., S.A.B., C.J.M., P.A.C., A.B.F., C.A.M., V.P.), the Australian Centre for Blood Diseases (R.L.M.), and the Central Clinical School (P.S.M.), Monash University, Ambulance Victoria (S.A.B.), and the Department of Critical Care, University of Melbourne (P.J.Y.), Melbourne, Aeromedical Operations, NSW Ambulance, Trauma Service, Royal North Shore Hospital, and Sydney Medical School, University of Sydney, Sydney (B.B.), MedSTAR Emergency Medical Retrieval Services, South Australian Ambulance Service (S.M.M.), and the Emergency Department, Royal Adelaide Hospital (S.M.M.), Adelaide, SA, and Queensland Ambulance Service (S.R.) and the Faculty of Medicine, University of Queensland (M.C.R.), Brisbane — all in Australia; Te Toka Tumai Auckland City Hospital (C.J.M.), Hato Hone St. John, Mt. Wellington (B.D.), and the Department of Paramedicine, Faculty of Health and Environmental Sciences, Auckland University of Technology (B.D., A.H.S.), Auckland, and Medical Research Institute of New Zealand (C.J.M., S.H., P.J.Y.), Wellington Free Ambulance (A.H.S.), and the Intensive Care Unit, Wellington Hospital (P.J.Y.), Wellington — all in New Zealand; Cologne–Merheim Medical Center, Department of Traumatology, Orthopedic Surgery, and Sports Medicine, and the Institute for Research in Operative Medicine, Witten–Herdecke University — both in Cologne, Germany (M.M.).

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