Prehospital Tranexamic Acid for Severe Trauma

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

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Trauma is the leading cause of death among young people.

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.

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

Tranexamic acid, administered within 3 hours after injury, was shown to reduce 28-day mortality among patients with suspected bleeding (CRASH-2 trial) and among patients with mild-to-moderate traumatic brain injury (CRASH-3 trial).

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.

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 or isolated traumatic brain injury, and another trial showed a dose dependent increase in thromboembolism with tranexamic acid therapy.

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.

Trial Design and Oversight

international, double-blind, randomized, placebo-controlled trial

Designed by the trial management committee

Endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group
Approved by the human research ethics committee responsible for each participating site.

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.

Patients

Eligible patients : adults (≥18 years of age)
suspected severe traumatic injuries who were
treated at the scene by paramedics or physicians
transported by road or air ambulance to participating trauma centers

Inclusion criteria : high risk for trauma-induced coagulopathy and
first dose of tranexamic acid or placebo could be administered within 3 hours after injury and before hospital admission.

Prehospital assessment of coagulopathy risk : the Coagulopathy of Severe Trauma (COAST) score ,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 SBP 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.

Exclusion criteria : pregnancy
residence 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 SBP (≤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

Patients were randomly assigned in a 1:1 ratio to receive tranexamic acid or placebo.

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 in 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.

The primary outcome

survival with a favorable functional outcome at 6 months, as assessed with the use of the Glasgow Outcome Scale–Extended (GOS-E)

GOS-E range from 1 (death) to 8 (“upper good recovery”).

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])

“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

death within 24 hours, 28 days, and 6 months after injury

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.

Patients

From July 28, 2014, to September 28, 2021

1310 patients were enrolled and treated

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 tranexamicnacid group and 646 assigned to the placebo group).

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

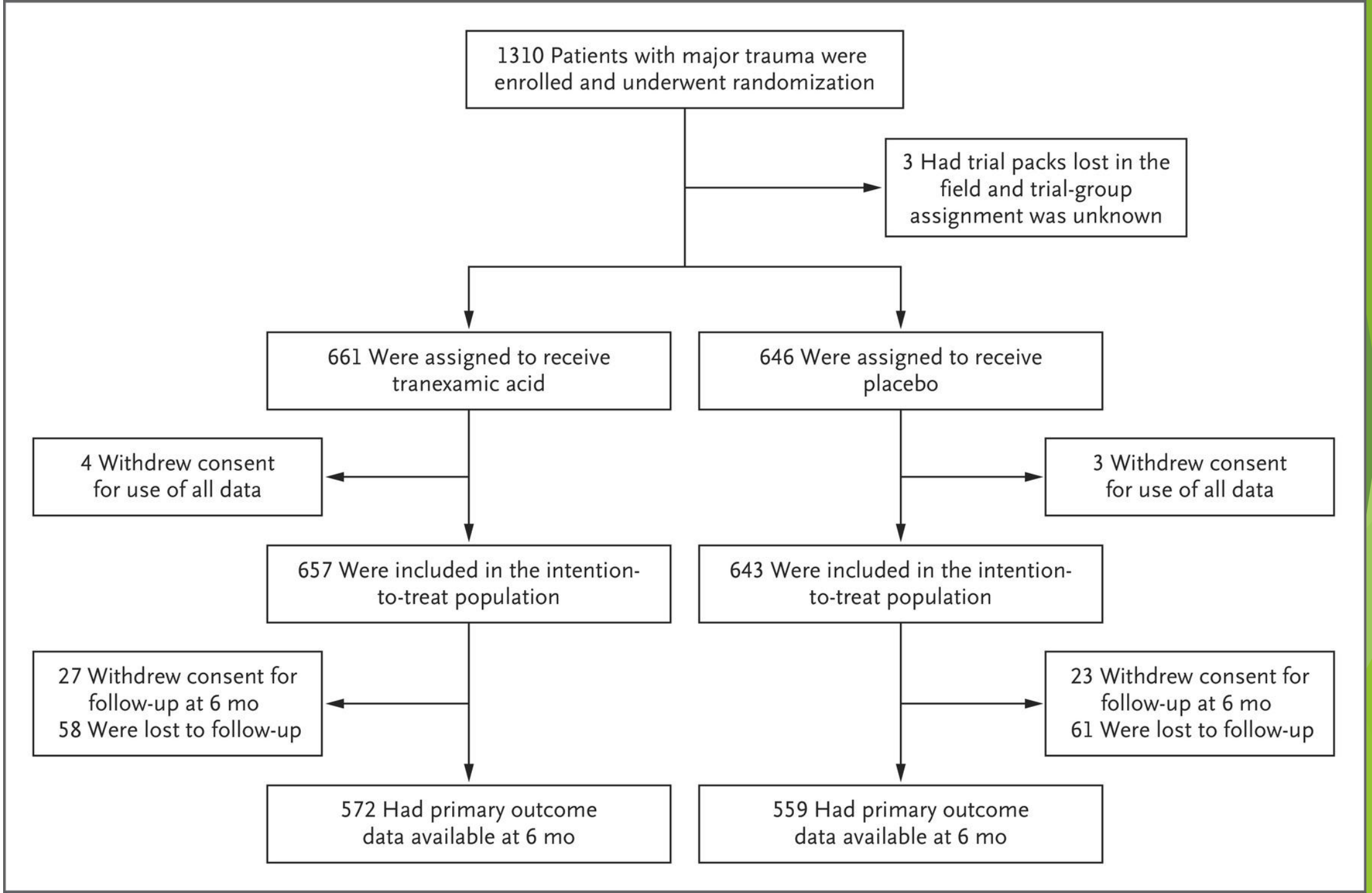
1310 Patients with major trauma were enrolled and underwent randomization
3 Had trial packs lost in the field and trial-group assignment was unknown
661 Were assigned to receive tranexamic acid
646 Were assigned to receive placebo
4 Withdrew consent for use of all data
3 Withdrew consent for use of all data
657 Were included in the intention-to-treat population
643 Were included in the intention-to-treat population
27 Withdrew consent for follow-up at 6 mo
58 Were lost to follow-up
23 Withdrew consent for follow-up at 6 mo
61 Were lost to follow-up
572 Had primary outcome data available at 6 mo
559 Had primary outcome data available at 6 mo

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.

Survival with a favorable functional outcome at 6 months occurred
307 of 572 patients (53.7%) in the tranexamic acid group
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).

Death by 24 hours after injury
64 of 657 patients (9.7%) in the tranexamic acid group
90 of 640 patients (14.1%) in the placebo group
(risk ratio, 0.69; 95% CI, 0.51 to 0.94)

At 28 days after injury : death :
113 of 653 patients (17.3%) in the tranexamic acid group
139 of 637 (21.8%) in the placebo group
(risk ratio, 0.79; 95% CI, 0.63 to 0.99).

6 months : death :
123 of 648 patients (19.0%) in the tranexamic acid group
144 of 629 (22.9%) in the placebo group
(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.

36 (29.3%) and 52 (36.1%) deaths, respectively, were attributed to bleeding.

One or more vascular occlusive events occurred in :

155 of 657 patients (23.6%) in the tranexamic acid group

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 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).

Conclusion :

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