

# Effects of tranexamic acid treatment in severely and non-severely injured trauma patients

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## Abstract

**Background:** Urgent treatment with tranexamic acid (TXA) reduces bleeding deaths but there is disagreement about which patients should be treated. We examine the effects of TXA treatment in severely and non-severely injured trauma patients.

**Study Design and Methods:** We did an individual patient data meta-analysis of randomized trials with over 1000 trauma patients that assessed the effects of TXA on survival. We defined the severity of injury according to characteristics at first assessment: systolic blood pressure of less than 90 mm Hg and a heart rate greater than 120 beats per minute or Glasgow Coma Scale score of less than nine or any GCS with one or more fixed dilated pupils. The primary measure was survival on the day of the injury. We examined the effect of TXA on survival in severely and non-severely injured patients and how these effects vary with the time from injury to treatment.

**Results:** We obtained data for 32,944 patients from two randomized trials. Tranexamic acid significantly increased survival on the day of the injury (OR = 1.22, 95% CI 1.11–1.34;  $p < .01$ ). The effect of tranexamic acid on survival in non-severely injured patients (OR = 1.25, 1.03–1.50) was similar to that in severely injured patients (OR = 1.22, 1.09–1.37) with no significant heterogeneity ( $p = .87$ ). In severely and non-severely injured patients, treatment within the first hour after injury was the most effective.

**Discussion:** Early tranexamic acid treatment improves survival in both severely and non-severely injured trauma patients. Its use should not be restricted to the severely injured.

## KEYWORDS

blood management, hemostasis

## 1 | INTRODUCTION

Bleeding is a leading cause of death after injury. Timely tranexamic acid (TXA) treatment reduces bleeding deaths

and all-cause mortality, without increasing the risk of thrombotic adverse events.<sup>1,2,3</sup> However, there is uncertainty about which trauma patients benefit from TXA treatment. Some authors recommend the selective use of

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TXA, depending on injury severity and results from viscoelastic haemostatic assays (VHA).<sup>4,5</sup> They argue that TXA should only be used if patients have VHA evidence of “hyperfibrinolysis.” In the pre-hospital setting, they advocate limiting TXA use to severely injured patients, based on the belief that hemorrhagic shock is the main driver of “fibrinolytic dysregulation.”<sup>4</sup> Others contend that TXA is safe and effective in a wide range of trauma patients. They are skeptical about the ability of VHA to identify patients who will benefit from TXA treatment and are concerned that restricting TXA use to severely injured patients will deny many patients a lifesaving drug with an excellent safety profile.<sup>5,6</sup> We examine data from large randomized trials to explore the effects of TXA treatment in severely injured and non-severely injured trauma patients.

## 2 | METHODS

### 2.1 | Study design, eligibility criteria, and patients

We conducted an individual patient data meta-analysis of randomized placebo-controlled trials with over 1000 patients that assessed the effects of tranexamic acid in trauma patients. We selected only trials that enrolled at least 1000 patients because small trials contribute very little evidence and could increase the risk of selection bias. We identified trials from a register of trials maintained by the LSHTM Clinical Trials Unit. The register is based on searches of the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, PubMed, Popline, and the WHO International Clinical Trials Registry Platform (Appendix S1). Abstracts were screened for relevant trials and the selection criteria were applied. Reasons for exclusion were discussed, and discrepancies were solved by consensus. Two reviewers (I.R., F.-X.A.) independently extracted the data. We analyzed individual patient data for baseline, outcome, and predictor variables (e.g., time from injury to the start of TXA treatment) from the selected trials. Ethical committee approval was not required for this study although all the included trials had been approved.

### 2.2 | Outcomes

The primary measure of treatment benefit was survival on the day of the injury (i.e., survival for at least 24 h from the time of injury). Because TXA improves outcome by reducing bleeding and most bleeding deaths are in the first 24 h, survival over this period is an objective measure of the effect of TXA.<sup>7</sup> Although some authors believe that

tranexamic acid decreases trauma mortality by reducing inflammation, the main effect of tranexamic acid appears to be a reduced risk of exsanguination on the day of injury.<sup>8</sup> However, we present survival at 28 days as secondary outcome. Safety outcomes were fatal and non-fatal thrombotic events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis).

### 2.3 | Assessment of risk of bias of included trials

We evaluated trial quality by assessing sequence generation, allocation concealment, blinding, data completeness and risk of selective reporting. Two reviewers (F.-X.A., I.R.)

TABLE 1 Main characteristics

	Tranexamic acid N = 16,499	Placebo N = 16,445
Age, mean (SD)	38 (17)	38 (17)
Age, median [IQR]	34 [24–48]	33 [24–48]
<25	4145 (25)	4181 (25)
25–44	7272 (44)	7186 (44)
45–64	3474 (21)	3452 (21)
≥65	1606 (10)	1624 (10)
Unknown	2 (0)	2 (0)
Sex, N (%)		
Women	2955 (18)	2935 (18)
Men	13,543 (82)	13,509 (82)
Unknown	1 (0)	1 (0)
Time since injury, N (%)		
0–1 h	4633 (28)	4592 (28)
2–3 h	6817 (41)	6690 (41)
>3 h	5049 (31)	5163 (31)
Systolic blood pressure, N (%)		
<90 mmHg	3296 (20)	3419 (21)
Unknown	26 (0)	30 (0)
Glasgow coma scale, N (%)		
≤8	4083 (25)	4112 (25)
9–13	4437 (27)	4409 (27)
14–15	7943 (48)	7972 (48)
Unknown	36 (0)	52 (0)
Severity, N (%)		
Severely injured	5009 (30)	5014 (31)
Non-severely injured	11,484 (70)	11,418 (69)
Unknown	6 (0)	13 (0)

Abbreviations: IQR, Interquartile range; SD, standard deviation.

independently rated the risk of bias according to established criteria.

## 2.4 | Data analysis

### 2.4.1 | Patient characteristics and presentation of outcome measures

All analyses were by intention to treat. Data analysis was based on individual patient data. For continuous variables, we reported the mean, standard deviation, and median. For categorical variables, we reported numbers and proportions. We reported survival and thrombotic events by treatment allocation for each trial and overall.

### 2.4.2 | Treatment effect overall and by time since injury

We examined the effects of TXA on binary outcomes using logistic regression. We reported treatment effects using odds ratios (OR) and 95% confidence intervals (95% CI). We expressed the effect of TXA on survival as the OR for survival for the 24 h after injury (relative treatment benefit). We first assessed the homogeneity of the treatment effects between trials by including an interaction term between the treatment and the trial variable and reporting the *p*-value (see model-1 in Appendix S2). We anticipated that treatment effect may be impacted

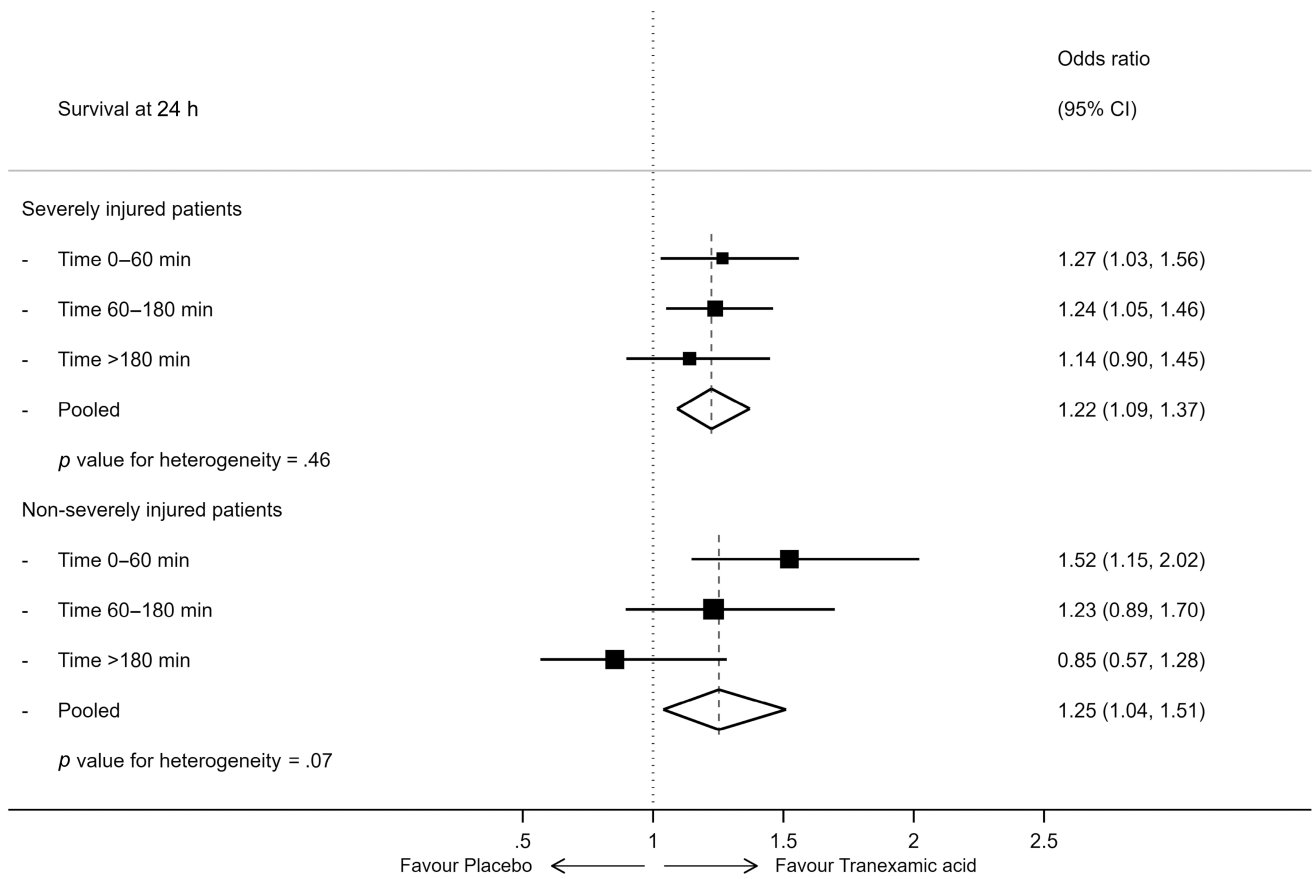
negatively by treatment delay and explored the impact of treatment delay on treatment effect by including terms for minutes of treatment delay and its square (because of non-linearity of the treatment effect), and interactions between these two variables with treatment group. To check the homogeneity of the effect of treatment delay across trials, we ran a second model with a triple interaction between the terms for treatment delay, the treatment group, and the trial (see model-2 in Appendix S2). Once homogeneity of the effect of treatment delay across trials was verified, we reported results from a third model including the two interaction terms (see model-3 in Appendix S2).

### 2.4.3 | Treatment effect stratified by severity of injury

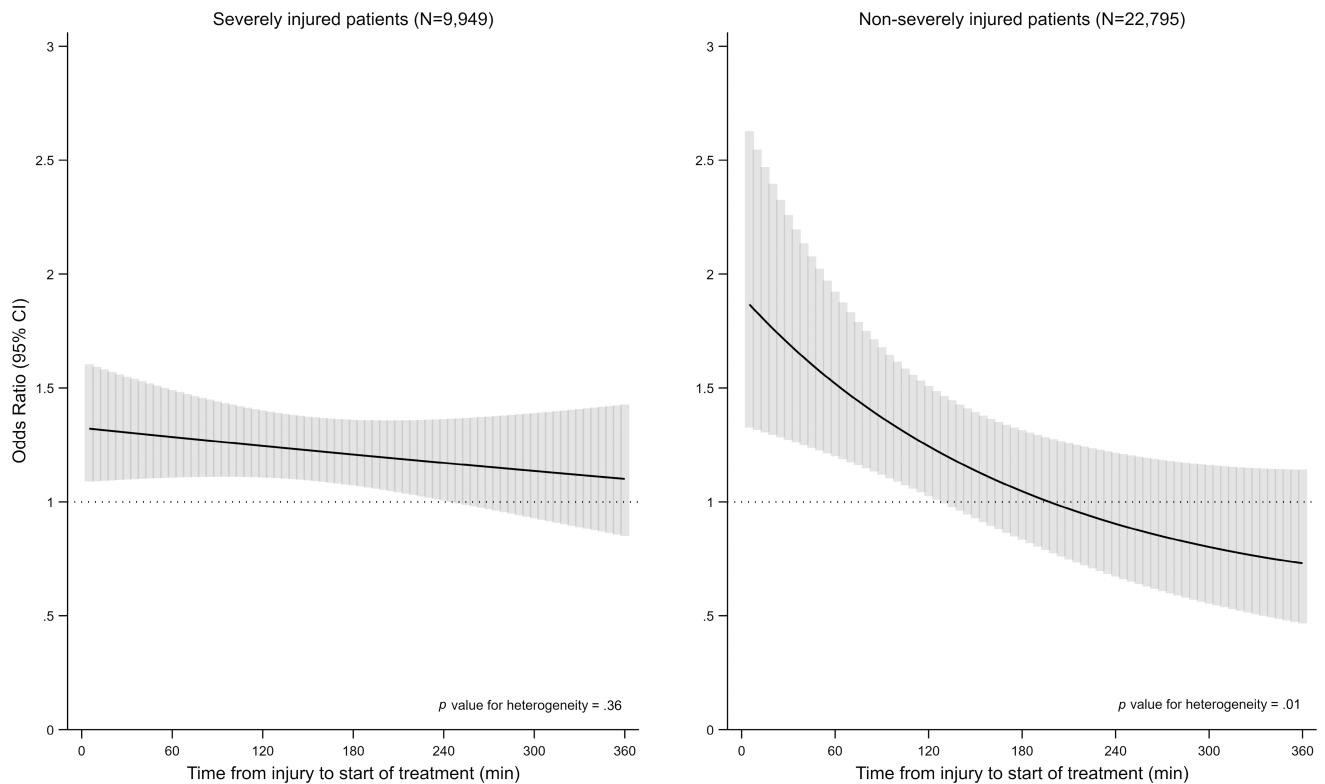
To explore the effects of TXA treatment in severely injured and non-severely injured patients, we defined the severity of injury according to baseline characteristics at first assessment. For polytrauma patients, severe injury was defined as systolic blood pressure of less than 90 mm Hg and a heart rate greater than 120 beats per minute. For isolated traumatic brain injury, we defined severe injury as a Glasgow Coma Scale score of less than nine or any GCS with one or more fixed dilated pupils. Because the decision of treatment has to be made as soon as possible in the prehospital setting or at hospital admission, we choose a clinical definition of severely injured patient

**TABLE 2** Effect of tranexamic treated within 3 h from injury on early death by severity

	Tranexamic acid N (%)	Placebo N (%)	Odds ratio (95% CI)
Survival at 24 h			
All	15,572/16,418 (94.9)	15,330/16,345 (93.8)	1.22 (1.11–1.34)
Severely injured	4334/4976 (87.1)	4210/4973 (84.7)	1.22 (1.09–1.37)
Not severely injured	11,233/11,436 (98.2)	11,109/11,359 (97.8)	1.25 (1.03–1.50)
Survival at 24 h (treated within 3 h from injury)			
All	10,741/11,396 (94.3)	10,401/11,213 (92.8)	1.28 (1.15–1.42)
Severely injured	2968/3470 (85.5)	2858/3463 (82.5)	1.25 (1.10–1.42)
Not severely injured	7773/7926 (98.1)	7540/7746 (97.3)	1.39 (1.12–1.72)
Survival at 28 days			
All	13,685/16,448 (83.4)	13,429/16,345 (82.2)	1.09 (1.02–1.15)
Severely injured	3052/4976 (61.3)	2961/4973 (59.5)	1.08 (0.99–1.17)
Not severely injured	10,629/11,436 (92.9)	10,457/11,359 (92.0)	1.14 (1.02–1.25)
Survival at 28 h (treated within 3 h from injury)			
All	9490/11,396 (83.3)	9153/11,213 (81.6)	1.12 (1.05–1.20)
Severely injured	2085/3470 (60.1)	2018/3463 (58.3)	1.08 (0.98–1.19)
Not severely injured	7405/7926 (93.4)	7132/7746 (92.1)	1.22 (1.08–1.38)



**FIGURE 1** Effect of tranexamic acid on survival at 24 h in severely and non-severely injured patients



**FIGURE 2** Effect of tranexamic acid on survival at 24 h by treatment delay in severely and non-severely injured patients

based on usual admitted severity criteria. This clinical definition has been used in the guidance for TXA treatment endorsed by the American College of Surgeons–Committee on Trauma, the American College of Emergency Physicians, and the National Association of EMS Physicians.<sup>9</sup> We examined the effect of TXA on survival in severely injured and non-severely injured patients. We also examined the effect of treatment delay in severely injured and non-severely injured patients using the models described above. We plotted the effect of TXA by treatment delay using model 3 in severely and non-severely injured patients.

### 2.5 | Role of the funding source

The funders of the included trials had no role in design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## 3 | RESULTS

We found two randomized trials that enrolled more than 1000 patients. Both trials had a low risk of bias (Web Appendix S3). The CRASH-2 trial assessed the effects of tranexamic acid on death and thrombotic events in 20,207 bleeding trauma patients. The CRASH-3 trial assessed the effects of tranexamic acid on death and thrombotic events in 12,737 patients with isolated traumatic brain injury. The characteristics of the included patients are shown in Table 1. TXA significantly increased survival on the day of the injury (OR = 1.22, 95% CI 1.11–1.34; *p* < .001). We found no heterogeneity in the treatment effect between trials (model 1: interaction *p* = .92). We found no heterogeneity in the treatment effect when considering treatment delay and trial (model 2: interaction *p* = .88). The effect of TXA on survival in non-severely injured patients (OR = 1.25, 95% CI 1.04–1.51) was similar to that in severely injured patients (OR = 1.22, 95% CI 1.09–1.37) with no significant heterogeneity (*p* = .87) (Table 2). Treatment effect on survival at 28 days were similar in severely and non-severely injured patients with no evidence of heterogeneity (*p* = .66).

Figure 1 shows the effect of TXA on survival in severely and non-severely injured patients stratified by time to treatment. The effect of TXA administered within 1 h from the injury was higher in non-severely injured patient (OR = 1.52, 95% CI 1.15–2.02) than in severely injured patient (OR = 1.27, 95% CI 1.03–1.56) with no

TABLE 3 Vascular occlusive events and complications

	All			Severely injured			Not severely injured		
	TXA N (%)	Placebo N (%)	OR (95% CI)	TXA N (%)	Placebo N (%)	OR (95% CI)	TXA N (%)	Placebo N (%)	OR (95% CI)
All vascular events	266 (1.6)	301 (1.8)	0.88 (0.74–1.04)	144 (2.9)	148 (3.0)	0.97 (0.77–1.23)	122 (1.1)	153 (1.3)	0.79 (0.62–1.00)
Fatal	58 (0.4)	61 (0.4)	0.95 (0.66–1.36)	25 (0.5)	30 (0.6)	0.83 (0.49–1.42)	33 (0.3)	31 (0.3)	1.06 (0.65–1.73)
Non-fatal	208 (1.3)	240 (1.5)	0.86 (0.71–1.04)	119 (2.4)	118 (2.4)	1.01 (0.78–1.30)	89 (0.8)	122 (1.1)	0.72 (0.55–0.95)
Pulmonary embolism	90 (0.5)	100 (0.6)	0.90 (0.67–1.19)	46 (0.9)	45 (0.9)	1.02 (0.68–1.54)	44 (0.4)	55 (0.5)	0.79 (0.53–1.18)
Deep venous thrombosis	59 (0.4)	57 (0.4)	1.03 (0.72–1.48)	32 (0.6)	31 (0.6)	1.03 (0.63–1.69)	27 (0.2)	26 (0.2)	1.03 (0.60–1.77)
Stroke	101 (0.6)	106 (0.6)	0.95 (0.72–1.25)	58 (1.2)	61 (1.2)	0.95 (0.66–1.36)	43 (0.4)	45 (0.4)	0.95 (0.62–1.44)
Myocardial infarction	53 (0.3)	72 (0.4)	0.73 (0.51–1.04)	28 (0.6)	35 (0.7)	0.80 (0.49–1.31)	25 (0.2)	37 (0.3)	0.67 (0.40–1.11)

Abbreviation: TXA, tranexamic acid.

significant heterogeneity ( $p = .30$ ). Figure 2 shows the modeled results. In severely and non-severely injured patients, treatment within the first hour after injury was the most effective. Thereafter, the survival benefit from TXA decreased with increasing treatment delay. There was heterogeneity in the treatment effect with treatment delay in non-severely injured patients ( $p = .01$ ) but not in severely injured patients ( $p = .36$ ).

There was no increase in fatal or non-fatal thrombotic events with tranexamic acid (OR = 0.88, 95% CI 0.74–1.04;  $p = .12$ ). When the results were stratified by severity, there was no significant heterogeneity ( $p = .22$ ) (Table 3). Treatment delay did not modify the effect of TXA on thrombotic events ( $p = .42$ ) (Web Appendix S4).

## 4 | DISCUSSION

Tranexamic acid safely improves survival in severely injured and non-severely injured patients. Limiting the use of tranexamic acid to severely injured patients will deny many trauma patients a lifesaving treatment that has an excellent safety profile.

This analysis has several strengths. The CRASH-2 and CRASH-3 randomized trials were large international trials with good allocation concealment, rigorous blinding with placebo control and minimal loss to follow-up. Although sub-group analyses are often underpowered, with over 32,000 randomly assigned participants the chances of missing a clinically relevant sub-group difference in the survival benefit from TXA are much reduced. According to the inclusion criteria, we did not include two recent prehospital trials.<sup>9,10</sup> These trials includes less than 1000 patients and are unlikely to change the results. Moreover, these small trials could be at risk of selection bias. The STAAMP trial failed to recruit the planned sample size and presented underpowered results, although the direction and size of the treatment effect was similar to that observed in the CRASH-2 and CRASH-3 trials. The Trial for prehospital TXA in TBI had many protocol deviations. Over one-third of the included patients did not receive the complete infusion and there was more than 15% loss to follow-up. For ease of communication, we dichotomized the severity of injury into severely and non-severely injured. Although any such dichotomization is arbitrary, our definition of severe injury was based on the criteria for TXA treatment suggested in the “Guidance Document for the Prehospital Use of Tranexamic Acid in Injured Patients” which is endorsed by the American College of Surgeons–Committee on Trauma, the American College of Emergency Physicians, and the National Association of EMS Physicians.<sup>11</sup>

We have previously shown in an individual patient data meta-analysis including 28,333 patients with acute

severe bleeding (polytrauma and postpartum hemorrhage) that tranexamic acid is safe and effective regardless of baseline risk of death from bleeding.<sup>12</sup> Based on these results, we argued that because many deaths from bleeding occur in people who initially appear to have a low or intermediate risk of death, TXA should not be restricted to severe bleeding since this will deny large numbers of patients a lifesaving treatment. In this article, we build on our previous work but with a focus on trauma. The conclusions are essentially the same.

We can only speculate why some doctors are reluctant to treat patients with less severe injury. This view seems to arise from the belief that TXA should only be offered to trauma patients with biochemical or VHA evidence of “hyperfibrinolysis.”<sup>4</sup> Given the mechanism of action of TXA, if there was no fibrin breakdown at the bleeding site, there would be no theoretical basis for treatment with a fibrinolytic inhibitor. But beyond this extreme, it is conceivable that any degree of local fibrinolysis might worsen bleeding. We cannot be sure that the viscoelastic properties of peripheral venous blood accurately reflect fibrinolytic activity at the bleeding site. Randomized trials of TXA in elective surgery show that TXA reduces blood loss by about one-third regardless of the type of surgery.<sup>13</sup> None of these patients have “coagulopathy” or “hyperfibrinolysis” and because they are closely monitored by an anesthetist, few will have hypovolemia. TXA appears to reduce bleeding whether or not patients have overt “hyperfibrinolysis.” We found that the benefit of TXA treatment is highest when given within 1 h from injury, particularly in non-severely injured patients. The benefit of early treatment in non-severely injured patients is comparable to the prophylactic effect of TXA seen in elective surgery. Indeed, many of these patients will undergo surgery on the day of the injury. New evidence that TXA is well-tolerated and rapidly absorbed after intramuscular injection raise the possibility of pre-hospital TXA treatment by paramedics or lay responders.<sup>14,15</sup>

We argue that a treatment strategy based on results from randomized trials is more secure than one based on VHA testing. The available data show that TXA saves lives in less severely injured patients demonstrating that it should not be limited to the most severely injured. We previously developed a prognostic model to predict death from bleeding in trauma patients and proposed a threshold for pre-hospital tranexamic acid treatment.<sup>16</sup> However, the threshold used will also depend on local constraints such as feasibility and cost-effectiveness. Because TXA is safe and cheap, its prophylactic use should be highly cost-effective.<sup>17,18</sup>

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**CONFLICT OF INTEREST**

The authors have disclosed no conflicts of interest.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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