Tranexamic acid in trauma: How should we use it?

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The CRASH-2 trial results have prompted trauma centers to contemplate whether tranexamic acid (TXA) should be added to their armamentarium for the treatment of bleeding trauma patients. Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma (ACOT).[1–5] Furthermore, some studies have documented that the risk of death in trauma correlates significantly with fibrinolysis. The presence of hyperfibrinolysis (HF) in patients with severe traumatic injuries is associated with a high mortality rate (70–100%).[6–9] The use of antifibrinolytic agents in the treatment of the ACOT therefore has significant biologic plausibility. We will review the current knowledge of fibrinolysis in trauma and studies of antifibrinolytic agents to make evidence-based recommendations regarding TXA use in trauma systems with mature hemostatic resuscitation protocols for the treatment of hemorrhagic shock patients.

PATIENTS AND METHODS

A comprehensive literature search was undertaken through PubMed and MEDLINE, using the following keywords: *tranexamic acid, antifibrinolytic agents, trauma, injury, surgery, fibrinolysis, hemorrhage.* Articles were selected if the topic was relevant to "tranexamic acid use in hemorrhage." Additional articles were identified by a careful review of reference lists. Ongoing clinical research studies for TXA and hemorrhage were identified by search of www.clinicaltrials.gov/.

Postinjury Fibrinolysis and Coagulation

Coagulopathy, strictly defined as any perturbation of coagulation, occurs in nearly all patients after significant injury.[10] Impaired clotting after injury initially was thought to be caused by iatrogenic causes (hypothermia, acidosis, hemodilution), which are sequelae of resuscitation. Impaired thrombin production occurs secondary to hypothermia and acidosis. The deleterious effects of hemodilution and resulting factor depletion include impaired protease cascade activation, impaired

thrombin production, reduced platelet function, and dysfunctional fibrinogen bioavailability.[11,12]

ACOT, initially described in 2003,[13–15] occurs in approximately 25% to 40% of patients nearly immediately when severe injury is combined with tissue hypoperfusion (shock), independent of iatrogenic causes. ACOT is associated with increased blood product requirements, increased morbidity, and mortality.[16,17]

Additional studies suggest that ACOT occurs owing to of activation of the protein C system.[18] Protein C is a serine protease, which when activated (in a mechanism that involves thrombin, endothelial protein C receptor, and thrombomodulin) results in a proteolytic deactivation of clotting factors Va and VIIIa and enhanced fibrinolysis by a mechanism mediated through a reduction in plasminogen activator inhibitor 1 (PAI-1, which normally inhibits t-PA), which in turn results in an increase in t-PA activity and increased fibrinolysis.[19] As a result, thrombin is bound, less clot is formed, and existing clot is more efficiently lysed by existing fibrinolytic mechanisms. Blood coagulation has evolved into a highly tuned system capable of dynamically balancing effective coagulation to prevent bleeding while preventing excessive thrombosis and fibrin deposition.[20] Fibrinolysis is essential to this normal homeostasis and occurs primarily through the proteolytic effects of plasmin. Plasmin is formed by the cleavage of its inactive zymogen (plasminogen) by either tissue plasminogen activator (t-PA) or by urokinase (UPA). t-PA and UPA are both effectively cleaved by plasmin, resulting in increased activity. Fibrin also works in a positive feedback role: in the presence of fibrin, t-PA and UPA possess increased affinity and activity on plasminogen.

Negative control of the fibrinolytic system comes from direct inhibition of plasmin by PAI-1 and thrombin activatable fibrinolysis inhibitor (TAFI), which block the conversion of plasminogen to plasmin, thus inhibiting fibrinolysis. α_2-plasmin inhibitor directly inhibits plasmin. Plasmin is protected from α_2-plasmin inhibitor while bound to fibrin. Thrombin activatable fibrinolysis inhibitor serves to break this bond, rendering plasmin susceptible to inhibition. While the mechanisms of trauma-induced fibrinolysis remain speculative, the activated protein C system is implicated. Activated protein C (APC) directly inhibits PAI-1, thereby limiting the negative control of t-PA, allowing plasmin inhibition.

How to Determine Postinjury Fibrinolysis: Role of Thromboelastography and Thromboelastometry

Identification of postinjury fibrinolysis can be challenging. The traditional laboratory test for pathologic fibrinolysis has been the euglobulin lysis time (ELT). In brief, the euglobulin fraction (prepared by acidification) of citrated,

platelet-poor, diluted plasma is allowed to clot. The ELT is the time for spontaneous lysis of the clot (normal range, 60–300 minutes). Unfortunately, the obligatory laboratory time to prepare the ELT exceeds 4 hours. Moreover, the ELT does not assess fibrinolysis in whole blood. In contrast, thromboelastography (TEG) (Haemonetics, Braintree, MA) and thromboelastometry (ROTEM) (Tem International, Munich Germany) provide a rapid assessment of fibrinolysis in whole blood.[21–24]

In the TEG system, fibrinolysis is typically recorded as the percent lysis at 30 minutes (LY30) after reaching the maximum amplitude. The% lysis represents the reduction of the area under the curve. The range in healthy adults is reported to be 0% to 7.5%, although in the Denver experience, it has always been less than 3% in normal individuals.[25] Estimated percent lysis (EPL) is available 2 minutes after maximum amplitude and recalculated every 30 seconds thereafter to project the ultimate LY30. In general, EPL underestimates LY30. A small early increase in LY30 unrelated to fibrinolysis may occur owing to clot retraction from hyperactive platelets.[26] A new TXA-inhibitable assay has been developed to obviate this artifact.

In the ROTEM system, fibrinolysis is usually reported as LI30 (Lysis Index after 30 minutes), which, in contrast to LY30, is the percentage of maximum clot firmness (amplitude) remaining 30 minutes after the initiation of clotting. The normal LI is 94% to 100%. The previously reported ROTEM parameter maximum lysis is the percent reduction of maximum clot firmness at 60 minutes. Thus, it is difficult to interpret studies of fibrinolysis in comparing TEG versus ROTEM. Interestingly, the TEG functional fibrinogen assay and the ROTEM FIBTEM are more sensitive in detecting fibrinolysis than LY30 or LI30.[22]

Although TEG and ROTEM provide more rapid data for fibrinolysis compared with previous techniques, there are significant limitations with these techniques since the ACOT is a dynamic process and frequent changes may occur.[27] Both tests can be performed as point of care, and the faster availability of results may assist clinical decisions of TXA use as well as what, when, and how much blood products to transfuse.[28] Preliminary test results are obtained as early as 5 minutes, with full results available within 20 minutes after starting the analysis.[29] We believe that viscoelastic studies should have a role in the clinical care of patients with ACOT and ongoing hemorrhage.

We also recognize that there may be occult HF in trauma that is not diagnosed by viscoelastic studies. In a prospective study of 303 trauma patients, thromboelastometry (TEM) HF was defined as maximum clot lysis of greater than 15%, and fibrinolytic activation was determined according to plasmin-antiplasmin (PAP) complex and D-dimer levels.[30] Only 5% of patients had severe fibrinolysis on TEM, but 57% of patients had evidence of "moderate" fibrinolysis, with PAP complex levels elevated to more than twice normal without lysis on TEM. At present, we do not know what is pathologic "hyperfibrinolysis." PAP complexes and D-dimer levels signify that clotting (fibrin cross-linking) has occurred, and the innate response to control clot progression is plasmin degradation.[31] Whether this HF is clinically significant and warrants treatment has yet to be determined. The criterion standard for measurement of HF remains ELT. As stated previously, the TEG functional fibrinogen assay and the ROTEM FIBTEM may be more sensitive in detecting fibrinolysis compared with maximum clot lysis by TEM. Additional research is required in this important area, and in particular, development of a standardized measurement of HF in trauma is needed.

HF in Trauma: How Common?

The incidence of HF ranges from 2% to 34% and seems to vary based on the instrument measuring fibrinolysis, how soon after injury the sample is drawn, the threshold selected, and the severity of injury. The Denver study of 61 trauma patients requiring transfusion during the resuscitative phase reported that HF (defined as EPL > 15% by r-TEG) occurred in 11 patients (18%). However, this finding was present in 34% of those patients requiring massive transfusion (MT) compared with only 2% of the remainder. HF was associated with significantly increased mortality, and with a depressed fibrinogen and prolonged partial thromboplastin time values.[1]

A single-center study of 1996 highest-level trauma activations admitted directly from the scene demonstrated that HF (defined as >7.5% LY30 by r-TEG) was present in only 41 patients (2%) on arrival.[32] More importantly, this group found that mortality doubled when the admission LY30 is more than 3%, which occurred in 7% of the severely injured. Based on these data, the Memorial Hermann Hospital clinical guideline recommends TXA infusion only in bleeding trauma patients if r-TEG confirms LY30 of more than 3%.[33] The Denver group now uses the same threshold of LY30 of more than 3% for TXA administration because of a similar observation.[25]

Investigators from LA County identified HF (defined as EPL > 15%) in 10% of their patients (n = 118) through serial TEG on admission and 1, 2, and 6 hours. Of note, 62% of the HF patients died of hemorrhage by 6 hours. Of those who survived 6 hours, 92% eventually died of either hemorrhage or head injury. HF was a strong independent predictor of need for MT and mortality.[34]

Looking at a more critically injured cohort, the San Francisco group noted that 20% of 115 patients had HF, defined as an admission maximal clot lysis of 10% or higher. As with other studies, this group found that HF was associated with multiorgan failure (63.2% vs. 24.6%, p = 0.004) and mortality (52.2% vs. 12.9%, p < 0.001).[17] In evaluating the published work on this lethal presentation, several key risk factors for HF have been identified (Table 1).

The LA County and Houston groups noted that increasing Injury Severity Score (ISS) was associated with significantly increasing likelihood of presenting with HF, contrary to studies from Denver and San Francisco. Shock on arrival and admission hypothermia were strong predictors of HF at all 4 centers. Base deficit was confirmed as an independent predictor of HF by Ives et al.[34], Cotton et al.[32], and Kashuk et al.[1], but not by Kutcher et al.[17]

Tranexamic Acid

TXA, a synthetic derivative of the amino acid lysine, is an antifibrinolytic agent that acts by binding to plasminogen and blocking the interaction of plasminogen with fibrin, thereby preventing dissolution of the fibrin clot.[35] TXA has been available

TABLE 1. Mortality and Risk Factors Associated With Development of HF

	No. Patients	Prevalence of HF	Diagnostic Measure and Criteria for HF	Mortality Rate for HF	Risk Factors for HF
Cotton et al.[32]	1,996	2%	LY30 > 7.5% by admission r-TEG	76%	Increasing base deficit
					SBP < 90 mm Hg
					Increasing ISS
					Prehospital fluids
Ives et al.[34]	118	11%	EPL > 15% by serial TEG	92%	Increasing lactate
					Increasing base deficit
					SBP < 90 mm Hg
					ISS > 16
Kashuk et al.[1]	61	18%	EPL > 15% by serial r-TEG	64%	Increasing base deficit
					Increasing lactate
					SBP < 90 mm Hg
					Increasing ISS
Kutcher et al.[17]	115	20%	MCL ≥ 10% by ROTEM	52%	Hypothermia (≤36.0°C)
					Acidosis (pH ≤ 7.2)
					INR ≥ 1.3
					aPTT ≥ 30
					Platelet count < 200,000
Schochl et al.[8]	33	N/A	Maximal lysis of 100% by ROTEM	88%	ISS > 25

aPTT, activated partial thromboplastin time; INR, international normalized ratio; MCL, maximal clot lysis N/A, not applicable.

for more than 20 years. It was first approved by the US Food and Drug Administration (FDA) in 1986 for short-term use (2–8 days) as an injection to reduce or prevent bleeding during tooth extraction in hemophilia patients.[36] In November 2009, the FDA approved the oral form of TXA to treat menorrhagia.[37,38] All other uses of TXA, including trauma use, are considered "off-label" uses.

CRASH-2 Trial

The CRASH-2 Trial was a large pragmatic international randomized placebo-controlled trial of the effects of the early administration of TXA (1 g over 10 minutes intravenously administered, then intravenous infusion of 1 g over 8 hours) on 28-day hospital mortality, vascular events, and transfusions in adult trauma patients.[39] The trial enrolled 20,211 patients with, or at risk of, significant bleeding from 274 hospitals across 40 countries, with no significant difference in baseline characteristics. The inclusion criteria were as follows:

- Adult trauma patients with significant hemorrhage
- Systolic blood pressure (SBP) less than 90 mm Hg, heart rate of more than > 110 beats per minute, or both
- Within 8 hours of injury

The fundamental eligibility criterion was whether the responsible doctor was "substantially uncertain" as to whether to use an antifibrinolytic in the trauma patient.[40] The authors have disclosed that 20,225 patients were screened, and 20,211 patients were randomized, leaving only 14 patients who were excluded.[41]

All-cause 28-day mortality was 1,463 (14.5%) in TXA and 1,613 (16.0%) in placebo patients (relative risk [RR], 0.91; 95% confidence interval [CI], 0.85–0.97; *p* = 0.0035). All-cause mortality reduction was 1.5%, giving a number needed to treat (NNT) of 67 to save one life over 28 days. Considering

the mortality benefit and the absence of evidence in the study to suggest a risk of harm, this is a significant result. On the basis of the CRASH-2 Trial results, it has been estimated that TXA use could save between 70,000 and 100,000 lives per year worldwide.[42]

Since TXA is an antifibrinolytic agent whose primary mechanism of action is reduction in clot lysis, the potential for increased thromboembolic events was evaluated. Secondary outcomes were vascular occlusive events (myocardial infarction, stroke, pulmonary embolism [PE] and deep vein thrombosis [DVT], surgical intervention [neurosurgery as well as thoracic, abdominal, and pelvic surgery]), receipt of blood transfusion, and units of blood products transfused. There was no difference in the rate of vascular occlusive events between groups: no difference in venous thrombotic events (PE 72 [0.7%] for the TXA group vs. 71 [0.7%] for the control group; DVT 40 [0.4%] for the TXA group vs. 41 [0.4%] for the control group) or risk of stroke (57 [0.6%] for the TXA group vs. 66 [0.5%] for the control group). There was a reduced risk of myocardial infarction in the TXA group (35 [0.3%] for the TXA group vs. 55 [0.55%] for the control group).

Closer Look at Mortality in CRASH-2 Trial

Only approximately 5% of patients had bleeding as a cause of death, and these were early deaths, with most occurring within the first 48 hours after injury. Mortality caused by bleeding was 489 (4.9%) in the TXA group and 574 (5.7%) in the control group (RR, 0.85; 95% CI, 0.76–0.96; *p* = 0.0077). There were no significant differences in mortality due to any other cause (cause of death was defined by the following categories: bleeding, vascular occlusion [myocardial infarction, stroke, and PE], multiorgan failure, head injury, and other). Traumatic brain injury (TBI) was the leading

cause of death (6.0% for the TXA group vs. 6.2% for the placebo group; RR, 0.97; 95% CI, 0.87–1.08; $p = 0.60$).

Evaluation of all-cause 28-day mortality by subgroups confirmed that the signal for benefit of TXA was in the most severe shock group as defined by admission SBP. In the subgroup of trauma patients presenting with SBP of 75 mm Hg or less, all-cause 28-day mortality was 30.6% (478 of 1,562) for the TXA group versus 35.1% (562 of 1,599) for the placebo group (RR, 0.87; 99% CI 0.76–0.99).

Data Limitations in CRASH-2 Trial

Red blood cell (RBC) transfusion was administered to approximately 50% of patients enrolled in the CRASH-2 Trial (50.4% for the TXA group vs. 51.3% for the placebo group), with mean (SD) units transfused 6.06 (9.98) for the TXA group versus 6.29 (10.31) for the placebo group. No standardized RBC transfusion protocol was used in the trial. Most of the study sites were in low- and middle-income countries where MT protocols and hemostatic resuscitation are not routinely available.

No data are available from this trial regarding additional blood products (plasma, platelets) administered, number and outcome of patients requiring MT, whether MT protocols were used, or specific information regarding coagulopathy and injury severity. Furthermore, time to cessation of hemorrhage and information regarding thrombotic events were not captured in this trial. These are significant limitations of the CRASH-2 Trial (Table 2).

TXA Added to World Health Organization List of Essential Medicines

Based on the results of the CRASH-2 Trial, TXA was recently added to the World Health Organization list of essential medicines in March 2011:

- "Section 10: addition of TXA injection for the treatment of adult patients with trauma and significant risk of ongoing haemorrhage. On the basis of the results of a very large trial of the use of TXA specifically for trauma patients—including those who have been in road traffic accidents, the Committee concluded that there is sufficient evidence to support the proposal that listing TXA may contribute to a reduction in this cause of death."[43,44]

Cochrane Systematic Reviews—Antifibrinolytics

Antifibrinolytics for Acute Traumatic Injury

The Cochrane systematic review regarding antifibrinolytic drugs for acute traumatic injury[45] included all randomized controlled trials (4 trials, n = 20,548 patients) of antifibrinolytic agents (aprotinin and TXA) following acute traumatic injury. Two of these trials studied TXA in 20,451 patients, and one of the trials was the CRASH-2 Trial. TXA reduced the risk of death by 10% (RR, 0.90; 95% CI, 0.85–0.97; $p = 0.0035$). No additional information concerning vascular occlusive events beyond the data from CRASH-2 was provided. The two aprotinin trials provided no reliable data according to the authors of the Cochrane systematic review.

TABLE 2. Significant Limitations of the CRASH-2 Trial

Study Limitation	Comment
Approach to randomization: "Doctor is reasonably certain that antifibrinolytic agents are indicated or contraindicated—do not randomize"	Concern regarding selection bias
No data regarding injury severity of the patient cohort (ISS, RTS)	Unable to determine if cohorts are similar
No data regarding shock in the patient cohort (lactate, base deficit)	Unable to determine if cohorts are similar
Small sample size of hypotensive patients (SBP ≤ 90 mm Hg), which is target population	SBP < 90 mm Hg in only 31.5% of study patients
Small sample size of tachycardic patients (HR > 107), which is target population	HR > 107 in only 48% of patients
No data regarding fibrinolysis on admission, no coagulation testing	Rate of fibrinolysis at admission in North American trauma centers is ≤5%
Only 1,063 deaths (35%) were caused by bleeding	The most common cause of death was traumatic brain injury
TXA did not reduce blood transfusions	Only 50% of study cohort received blood transfusion; Median (IQR) units of blood product transfused 3 (2–6) in total cohort. In transfused cohort, mean (SD) 6.06 (9.98) for the TXA group vs. 6.29 (10.31) for the placebo group.
No adverse events regarded as serious, unexpected, or suspected to be related to the study treatment	Concern about possible inadequate reporting
Patient follow-up reported as 100%	Difficult to believe
Effect size small. Statistically significant but not clinically meaningful finding?	Study determined a 0.8% absolute reduction in "death caused by bleeding" in 20,000 patients.
Absolute increase in mortality if TXA given 3 h after injury	TXA treatment given after 3 h after injury was associated with an increased risk of death caused by bleeding (4.4% vs. 3.1%; RR, 1.44; 95% CI, 1.12–1.84; $p = 0.004$).

The aim of the CRASH-2 trial was to assess the effects of early administration of TXA on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage.

Inclusion criteria include trauma patients judged to be 16 years or older, with significant hemorrhage (SBP < 90 mm Hg and/or heart rate > 110 beats per minute), or considered to be at risk of significant hemorrhage, within 8 hours of injury.

HR, heart rate; IQR, interquartile range; RTS, Revised Trauma Score.

Antifibrinolytics for Minimizing Perioperative RBC Transfusion

The Cochrane systematic review regarding antifibrinolytic (TXA, aprotinin and epsilon aminocaproic acid [EACA]) use for minimizing perioperative allogeneic blood transfusion in adult surgical patients supports its use. This review included 252 randomized controlled trials with more than 25,000 participants and concluded that antifibrinolytic drugs provide worthwhile reductions in blood loss and receipt of RBC transfusion and seem to be free of serious adverse effects.[46]

TXA reduced the risk of blood transfusion by 39% (RR, 0.61; 95% CI, 0.53–0.70), but it did not reduce the need for reoperation due to bleeding (RR, 0.80; 95% CI, 0.55–1.17) and mortality (RR, 0.60; 95% CI, 0.33–1.10). Aprotinin reduced the need for reoperation due to bleeding by 54% (RR, 0.46; 95% CI, 0.81–0.99), and a similar trend was seen with EACA (RR, 0.32; 95% CI, 0.11–0.99). Aprotinin (vs. TXA and EACA) was associated with a significant increase in the risk of death (RR, 1.39) and myocardial infarction (RR, 1.11). Sixty-five of the trials (n = 4,842) specifically compared TXA with a control arm. An evaluation of these trials reveals that there was no increased incidence of DVT, PE, myocardial infarction or stroke in the patients who received TXA.

However, this review did not include trials assessing the effect of TXA in emergency surgery. A systematic review of randomized trials in adults undergoing emergency or urgent surgery identified 5 trials with 372 patients. TXA reduced the probability of receiving a blood transfusion by 30% (RR, 0.70; 95% CI, 0.52–0.94), but there was no impact on mortality (RR, 1.01; 95% CI, 0.14–0.73).[47]

Effect of TXA on Surgical Bleeding

The Cochrane systematic review on the effect of TXA on surgical bleeding included 129 trials (n = 10,488), with studies performed between 1972 and 2011. TXA reduced the probability of receiving a blood transfusion by a third (RR, 0.62; 95% CI, 0.58–0.65; p < 0.001). This effect remained when the analysis was restricted to trials using adequate allocation concealment (RR, 0.68; 95% CI, 0.62–0.74; p < 0.001). The effect of TXA on myocardial infarction (RR, 0.68; 95% CI, 0.43–1.09; p = 0.11), stroke (RR, 1.14; 95% CI, 0.65–2.00; p = 0.65), DVT (RR, 0.86; 95% CI, 0.53–1.39; p = 0.54), and PE (RR, 0.61; 95% CI, 0.25–1.47; p = 0.27) was uncertain. Fewer deaths occurred in the TXA group (RR, 0.61;

95% CI, 0.38–0.98; p = 0.04), although, when the analysis was restricted to trials using adequate concealment there was considerable uncertainty (RR, 0.67; 95% CI, 0.33–1.34; p = 0.25). The evidence is strong that TXA reduces blood transfusion in surgery, but the effect on thromboembolic events and mortality remains uncertain.[48]

Exploratory Analysis of CRASH-2: Early Versus Late TXA

The effect of TXA treatment on death caused by bleeding, rather than all-cause 28-day mortality, was examined. This subgroup analysis examined four baseline characteristics as follows: (1) time from injury to treatment (≤1, >1–3, and >3 h); (2) severity of hemorrhage as assessed by SBP (≤75, 76–89, and >89 mm Hg); (3) Glasgow Coma Scale (GCS) score (severe, 3–8; moderate, 9–12; mild, 13–15); and (4) type of injury (penetrating only, blunt only, and blunt plus penetrating). These were the same subgroup analyses that were reported previously but for the outcome of death caused by bleeding rather than for all-cause mortality.[49]

Of the 3,076 deaths from all causes, 1,063 deaths (35%) were caused by bleeding. The risk of death caused by bleeding was significantly reduced with TXA (4.9% vs. 5.7%; RR, 0.85; 95% CI, 0.76–0.96; p = 0.0077). There was no significant effect of TXA on the risk of death for all other (nonbleeding) causes combined (Table 3). Subgroup analysis confirmed a significant reduction (19%) in deaths caused by bleeding (14.9% vs. 18.4%; RR, 0.81; 95% CI, 0.69–0.95) in the most severe hemorrhagic shock patients with SBP of 75 mm Hg or less (Table 4).

Early TXA treatment (≤1 hour from injury) was associated with the greatest reduction (32% reduction) in deaths caused by bleeding (198 [5.3%] of 3,747 for the TXA group vs. 286 [7.7%] of 3,704 for the placebo group; RR, 0.68; 95% CI, 0.57–0.82; p < 0.0001). Treatment given between 1 hours and 3 hours after injury also reduced the risk of death caused by bleeding (147 [4.8%] of 3,037 vs. 184 [6.1%] of 2,996; RR, 0.79; 95% CI, 0.64–0.97; p = 0.03) (Tables 3 and 4).

In contrast, TXA treatment given after 3 hours after injury was associated with an increased risk of death caused by bleeding (144 [4.4%] of 3,272 vs. 103 [3.1%] of 3,362; RR, 1.44; 95% CI, 1.12–1.84; p = 0.004). In patients given TXA 3 hours after injury, no effect of TXA on death caused by bleeding was identified in the SBP, GCS, or type of injury groups. The authors

TABLE 3. RR (95% CI) of Death With TXA, Overall and by Time to Treatment in CRASH-2 Trial

	n	All Causes of Death	Bleeding Death	Nonbleeding Death
Overall	20,127	0.91 (0.85–0.97), p = 0.0035	0.85 (0.76–0.96), p = 0.0077	0.94 (0.86–1.02), p = 0.13
Time to treatment, h				
≤1	7,451	0.87 (0.76–0.97)	0.68 (0.57–0.82)	1.04 (0.89–1.21)
>13	6,033	0.87 (0.77–0.97)	0.79 (0.64–0.97)	0.91 (0.78–1.05)
>3	6,634	1.00 (0.90–1.13)	1.44 (1.12–1.84)	0.89 (0.78–1.02)
χ^2 test of homogeneity	—	4.411 (p = 0.11)	23.516 (p = 0.0000)	2.537 (p = 0.28)

Primary outcome was 28-day all-cause mortality with cause of death described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke, and PE), multiorgan failure, head injury, and other.
Adapted from CRASH-2 collaborators.[49]

TABLE 4. Mortality Caused by Bleeding, by Subgroup Analysis in CRASH-2 Trial

	TXA	Placebo	RR (95% CI)
Time to treatment, h			
≤1	198/3,747 (5.3%)	286/3,704 (7.7%)	0.68 (0.57–0.82)
>1–3	147/3,037 (4.8%)	184/2,996 (6.1%)	0.79 (0.64–0.97)
>3	144/3,272 (4.4%)	103/3,362 (3.1%)	1.44 (1.12–1.84)
$\chi^2 = 23.516$, $p < 0.0000$			
SBP, mm Hg			
>89	146/6,878 (2.1%)	163/6,761 (2.4%)	0.88 (0.71–1.10)
76–89	110/1,609 (6.8%)	114/1,689 (6.7%)	1.01 (0.79–1.30)
≤75	233/1,562 (14.9%)	295/1,599 (18.4%)	0.81 (0.69–0.95)
$\chi^2 = 2.235$, $p = 0.33$			
GCS score			
Severe (3–8)	168/1,789 (9.4%)	186/1,830 (10.2%)	0.92 (0.76–1.13)
Moderate (9–12)	93/1,349 (6.9%)	121/1,344 (9.0%)	0.77 (0.59–0.99)
Mild (13–15)	228/6,915 (3.3%)	265/6,877 (3.8%)	0.86 (0.72–1.02)
$\chi^2 = 1.275$, $p = 0.53$			
Type of injury			
Blunt	308/6,788 (4.5%)	347/6,817 (5.1%)	0.89 (0.77–1.04)
Penetrating	181/3,272 (5.5%)	227/3,250 (7.0%)	0.79 (0.66–0.96)
$\chi^2 = 0.923$, $p = 0.34$			
All deaths	489/10,060 (4.9%)	574/10,067 (5.7%)	0.85 (0.76–0.96)
Two-sided $p = 0.0077$			

Adapted from CRASH-2 collaborators.[49]

concluded that TXA should be given as early as possible to bleeding trauma patients. For trauma patients admitted late after injury, TXA treatment was harmful.

CRASH-2 Intracranial Bleeding Study (IBS)

CRASH-2 IBS was a prospective randomized controlled trial nested within the CRASH-2 Trial[50] in patients (n = 270) who fulfilled the inclusion criteria for the CRASH-2 Trial and also had TBI (defined as GCS ≤ 14 and brain computed tomographic [CT] scan compatible with TBI). The primary outcome was increase of intracranial hemorrhage size between a CT scan at hospital admission and a second CT scan 24 hours to 48 hours later.

TXA was associated with a nonsignificant reduction in hemorrhage growth (adjusted difference, −3.8 mL, 95% credibility interval [CrI], −11.5 mL to 3.9 mL), fewer focal ischemic lesions (adjusted odds ratio [OR], 0.54, 95% CrI, 0.20–1.46) and fewer deaths (adjusted OR, 0.49, 95% CrI, 0.22–1.06) (Table 5). In the CRASH-2 IBS study, the majority (85%) of the observed deaths were caused by TBI, not bleeding. Inadequate sample size (n = 270) prohibits definitive conclusions from this study.[51]

MATTERs Study

The Military Application of TXA in Trauma Emergency Resuscitation (MATTERs) study is a retrospective observational study comparing TXA to no TXA in combat casualty patients (n = 896; 293 TXA) treated in a Role 3 surgical hospital in southern Afghanistan. Trauma patients were identified from UK and US trauma registries.[52]

The TXA group had lower unadjusted mortality than the no-TXA group (17.4% vs. 23.9%, respectively; $p = 0.03$) despite being more severely injured (mean [SD] ISS, 25.2 [16.6] vs. 22.5 [18.5]; $p < 0.001$). This benefit was greatest in MT patients (14.4% vs. 28.1%, respectively; $p = 0.004$), where TXA was also independently associated with survival (OR, 7.228; 95% CI, 3.016–17.322) and less coagulopathy ($p = 0.003$).

Thrombotic events were significantly increased in the TXA group for both PE (8 [2.7%] vs. 2 [0.3%], $p = 0.001$ in the overall cohort; 4[3.2%] vs. 0, $p = 0.001$ in the MT cohort) and DVT (7 [2.4%] vs. 1 [0.2%], $p = 0.001$ in the overall cohort; 2 [1.6%] vs. 1 [0.5%], $p = 0.32$ in the MT cohort). After correcting for severity of injury, there was no association of TXA use with an increased risk of DVT or PE.

TABLE 5. Effect of TXA on Outcomes in the CRASH-IBS

	Unadjusted OR (95% CrI) n = 270	Adjusted OR (95% CrI) n = 270	Probability of Benefit, %
Mortality	0.57 (0.28–1.14)	0.49 (0.22–1.06)	96
Mortality caused by head injury	0.59 (0.28–1.25)	0.54 (0.24–1.22)	93
Need for neurosurgery	0.98 (0.50–1.93)	0.98 (0.50–1.91)	53

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The authors concluded that treatment with TXA should be implemented into clinical practice as part of a resuscitation strategy following severe wartime injury and hemorrhage. This study is limited, however, because of its retrospective observational nature, lack of standardized indications and dosing of TXA, and no data regarding timing of TXA treatment or laboratory evaluation for fibrinolysis.[53]

MATTERs II Study

The MATTERs II study expanded the sample size of the MATTERs I study to further evaluate TXA and trauma outcomes. A review of 1,332 patients (identified from prospectively collected UK and US trauma registries) who required one or more RBC unit transfusion were analyzed to examine the impact of cryoprecipitate (CRYO) in addition to TXA on survival in combat injured patients.

Despite greater ISSs and RBC transfusion requirements, mortality was lowest in patients who received TXA (18.2%) or TXA/CRYO (11.6%) compared with CRYO alone (21.4%) or no-TXA/CRYO (23.6%). Logistic regression analysis confirmed that TXA and CRYO were independently associated with a similarly reduced mortality (OR, 0.61; 95% CI, 0.42–0.89; $p = 0.01$ and OR, 0.61; 95% CI, 0.40–0.94; $p = 0.02$, respectively). The combined TXA and CRYO effect versus neither in a synergy model had an OR of 0.34 (95% CI 0.20–0.58; $p < 0.001$), reflecting nonsignificant interaction ($p = 0.21$).[54]

Military Damage-Control Resuscitation Clinical Practice Guideline

The Joint Theater Trauma System Clinical Practice Guideline for Damage-Control Resuscitation at forward surgical hospitals and combat support hospitals includes evidence-based recommendations for TXA administration in combat casualty care:[55] "The early use of TXA (i.e., *as soon as possible after injury* but ideally not later than 3 hours post injury) should be strongly considered for any patient requiring blood products in the treatment of combat-related hemorrhage and is most strongly advocated in patients judged likely to require MT (e.g., significant injury and risk factors of MT)."

Potential Thrombotic Complications of Antifibrinolytics

When evaluating the therapeutic benefits of hemostatic drugs, we must also consider the risk of adverse events.[56] The frequency of thrombotic events among trauma patients who receive antifibrinolytic agents is not fully known from the clinical studies performed to date.

The MATTERs study documented no difference in thromboembolic events, but the retrospective nature of this study limits any conclusions regarding thrombotic complications related to TXA. The CRASH-2 Trial documented no difference in thromboembolic events (PE, DVT, stroke, myocardial infarction), but the event rates were very low, and no standard mechanism for diagnosis of these complications was mandated in the trial.

A systematic review of 57 studies of adults given antifibrinolytic drugs for spontaneous bleeding (n = 5,049, 3,616 [72%] had spontaneous subarachnoid hemorrhage) confirmed that the frequencies of limb ischemia and myocardial infarction were less than 1% for TXA and EACA. The frequency of DVT or PE was 1.9% for TXA versus 3.0% for EACA. A notable finding, however, was a cerebral infarction rate of 9.7% for TXA versus 7.7% for EACA in studies of subarachnoid hemorrhage. This study concluded that thrombotic events have occurred infrequently with antifibrinolytic drugs after spontaneous bleeding, apart from subarachnoid hemorrhage, so further exploration of their safety and efficacy after spontaneous bleeding is justified in randomized trials.[57]

TXA in Trauma: How Did It Reduce Mortality?

The CRASH-2 Trial documented no statistical difference in RBC transfusion between groups, so it is unclear whether the reduced mortality in the TXA group was caused by the prevention of clot lysis and improved coagulation with decreased bleeding after injury. TXA, as an antifibrinolytic agent, inhibits plasmin, which is known to induce proinflammatory effects by activation of monocytes, neutrophils, platelets, and endothelial cells and complement releasing lipid mediators and cytokines and by induction of proinflammatory genes.[58,59] Some have speculated that improved survival in TXA patients may be caused by an attenuated inflammatory response achieved in part through reduction of circulating plasmin levels.[60–63] It remains unclear whether the mortality benefit from TXA is from reversal of fibrinolysis or whether an inflammatory or immune modulation is the underlying mechanism.

Cost-Effectiveness Analysis of CRASH-2 Trial

The incremental cost per life years gained for TXA use in trauma was $48, $66, and $64 in Tanzania, India, and the United Kingdom, suggesting cost efficacy in low-, middle-, and high-income settings.[64] TXA cost ($5.70 per gram) was taken from the British National Formulary and converted into international dollars, but there is significant US variability.

Additional TXA Clinical Trials in Trauma and Hemorrhage
CRASH-3 Trial: TXA for TBI

CRASH-3 is an international, multicenter, pragmatic, randomized, double-blind, placebo-controlled trial to quantify the effects of the early TXA versus placebo on death and disability in adult TBI patients (n = 10,000)[65] who are within 8 hours of injury and have intracranial bleeding on CT scan or GCS score 12 or less if the responsible doctor is substantially uncertain as to whether to use TXA.[66,67]

World Maternal Antifibrinolytic (WOMAN) Trial: TXA for Postpartum Hemorrhage

This is an international, randomized, double-blind, placebo-controlled trial investigating TXA for the treatment of postpartum hemorrhage.[68,69] Obstetric hemorrhage is the leading cause of maternal mortality, accounting for up to one third of deaths, most in the postpartum period. As of January 2013, 5,657 women have been randomized (trial start, May 2009).

CRASH-2 Goes Viral

Despite the compelling findings of the CRASH-2 trial announced in 2010, an audit of UK hospitals in 2011 showed that, of 412 trauma patients who required blood transfusion

and were eligible for TXA treatment, only 12 (3%) received TXA. On November 19, 2011, the CRASH-2 research team rolled out an online brief video to assist in making clinicians aware of this lifesaving treatment.[70]

Despite this novel approach of disseminating research information from the CRASH-2 Trial, implementation of a TXA protocol for trauma has still not been initiated in most trauma centers in the United States. A recent survey of 24 member institutions of the Trauma Center Association of America documented that only 2 (one Level 1 and one Level 2 trauma center) were using TXA as part of an institutional protocol and 7 institutions were considering its use. Reasons reported for lack of TXA use included lack of availability, ineffectiveness, cost, and unfamiliarity with the drug.[71]

Analysis of TXA on Death/Thrombotic Events According to Baseline Risk of Death

A recent analysis examined the effect of TXA in trauma patients stratified by risk of death at baseline.[72] The baseline risk of death was calculated using a prognostic model that was derived from the CRASH-2 Trial.[73] The study cohort included 13,273 trauma patients in the CRASH-2 Trial who were treated with TXA or placebo within 3 hours of injury and trauma patients enrolled in the UK Trauma and Audit Research Network. TXA was associated with a significant reduction in all-cause mortality and deaths from bleeding in each stratum of baseline risk. Interestingly, TXA was associated with a significant reduction in the odds of fatal and nonfatal thrombotic events (OR, 0.69; 95% CI, 0.53–0.89; $p = 0.005$) and a significant reduction in arterial thrombotic events (OR, 0.58; 0.40–0.83; $p = 0.003$) but no significant reduction in venous thrombotic events (OR, 0.83; 95% CI, 0.59–1.17; $p = 0.295$) (Fig. 1).

Why the Delay in Implementing TXA in Trauma?

The significant delay in implementation of TXA administration in trauma is likely related to questions regarding which patients should receive it. Important knowledge gaps are present in the research to date, and additional research efforts are warranted about the TXA use in trauma.[74] We believe that a prospective randomized study performed in a controlled environment with laboratory monitoring of coagulation and standardized transfusion protocols is essential before TXA becomes standard of care in trauma. Based on the evidence to date, how should we implement TXA use in trauma?

One potential implementation strategy would be to use the inclusion criteria from the CRASH-2 Trial: use TXA in all patients with significant hemorrhage (SBP < 90 mm Hg and/or heart rate > 110 beats per minute) or considered to be at risk of significant hemorrhage within 8 hours of injury. This would result in a large number of patients being treated with TXA who would not be expected to have fibrinolysis, including those patients more than 3 hours from injury in which the post hoc analysis documented a significantly increased risk of death caused by bleeding with TXA, so we do not recommend this approach.

Another implementation strategy is to initiate TXA use in the trauma patient cohort most likely to derive benefit in mortality reduction, that is, those with significant injury and more severe hemorrhagic shock as identified by SBP 75 mm Hg or less and less than 3 hours from time of injury. This strategy will allow trauma centers to review their TXA use data and outcomes on a smaller cohort of patients in an initial implementation protocol for TXA use in trauma. A predictive model for mortality is being developed based on the CRASH-2 Trial data, and in the future, this may assist clinicians in the determination of which trauma patients would most benefit from TXA treatment. Another approach is to use TXA only in patients with documented HF by TEG or in those with risk factors for HF.

Summary: What Do We Know?

- TXA is associated with a 1.5% reduction in 28-day all-cause mortality in adult trauma patients with signs of bleeding (SBP < 90 mm Hg, heart rate > 110 beats per minute, or both, within 8 hours of injury) in a large pragmatic prospective randomized placebo-controlled trial.
- What is critical is the modest effect on the overall population: All-cause mortality was "significantly" reduced from 16.0% to 14·5% (NNT, 67). The risk of death caused by bleeding overall was "significantly" reduced from 5.7% to 4·9% (NNT, 121).
- TXA signal for benefit was in the most severe shock group (admission SBP ≤ 75 mm Hg), 28-day all-cause mortality of 30.6% for the TXA group versus 35.1% for the placebo group (RR, 0.87; 99% CI 0.76–0.99).
- 1,063 deaths (35%) were caused by bleeding in the CRASH-2 Trial.
- TXA had greatest impact on reduction of death caused by bleeding in the severe shock group (SBP ≤ 75 mm Hg) (14.9% vs. 18.4%; RR, 0.81; 95% CI, 0.69–0.95).
- Early TXA (≤1 hour from injury) was associated with the greatest reduction (32% reduction) in deaths caused by bleeding (5.3% vs. 7.7%; RR, 0.68; 95% CI, 0.57–0.82; $p < 0.0001$).
- TXA given between 1 hour and 3 hours after injury also reduced the risk of death caused by bleeding (4.8% vs. 6.1%; RR, 0.79; 95% CI, 0.64–0.97; $p = 0.03$).
- TXA given after 3 hours after injury was associated with an increased risk of death caused by bleeding (4.4% vs. 3.1%; RR, 1.44; 95% CI, 1.12–1.84; $p = 0.004$).
- TXA had no impact on TBI outcomes, but the study was limited by small sample size.
- TXA treatment is not associated with an increased risk of vascular occlusive events.

What Is Still Unknown?

- Whether TXA has any impact on trauma outcomes when damage-control resuscitation or MT protocols are used;
- The mechanism by which TXA reduced mortality in trauma in the CRASH-2 Trial. Fibrinolysis assessment and coagulation testing were not part of the study design, and determination of time to cessation of hemorrhage was not required in the study;
- Whether fibrinolysis testing should be performed before consideration of TXA treatment;
- What is the optimal dose and timing of TXA in trauma;
- Whether other antifibrinolytic agents could be substituted for TXA use in trauma;

• Whether TXA is associated with higher seizure rates in trauma or TBI patients. Increased postoperative seizures have been reported in cardiac surgery with TXA doses that are 2-fold to 10-fold higher than those used in CRASH-2.[75–80] These seizures have been associated with an increased incidence of neurologic complications (delirium and stroke), prolonged recovery, and higher mortality rates. A proposed mechanism for seizures is TXA-mediated inhibition of glycine receptors as a potential cause of neurotoxicity.[81,82] A recent warning has been added to the FDA drug label: "Convulsions have been reported in association with tranexamic acid treatment."[83]

A Rational Approach for TXA use in Trauma

• In adult trauma patients with severe hemorrhagic shock (SBP ≤ 75 mm Hg), with known predictors of fibrinolysis, or with known fibrinolysis by TEG (LY30 > 3%);
• Only administer TXA if less than 3 hours from time of injury;
• TXA administration: 1 g intravenously administered over 10 minutes, then 1 g intravenously administered over 8 hours.
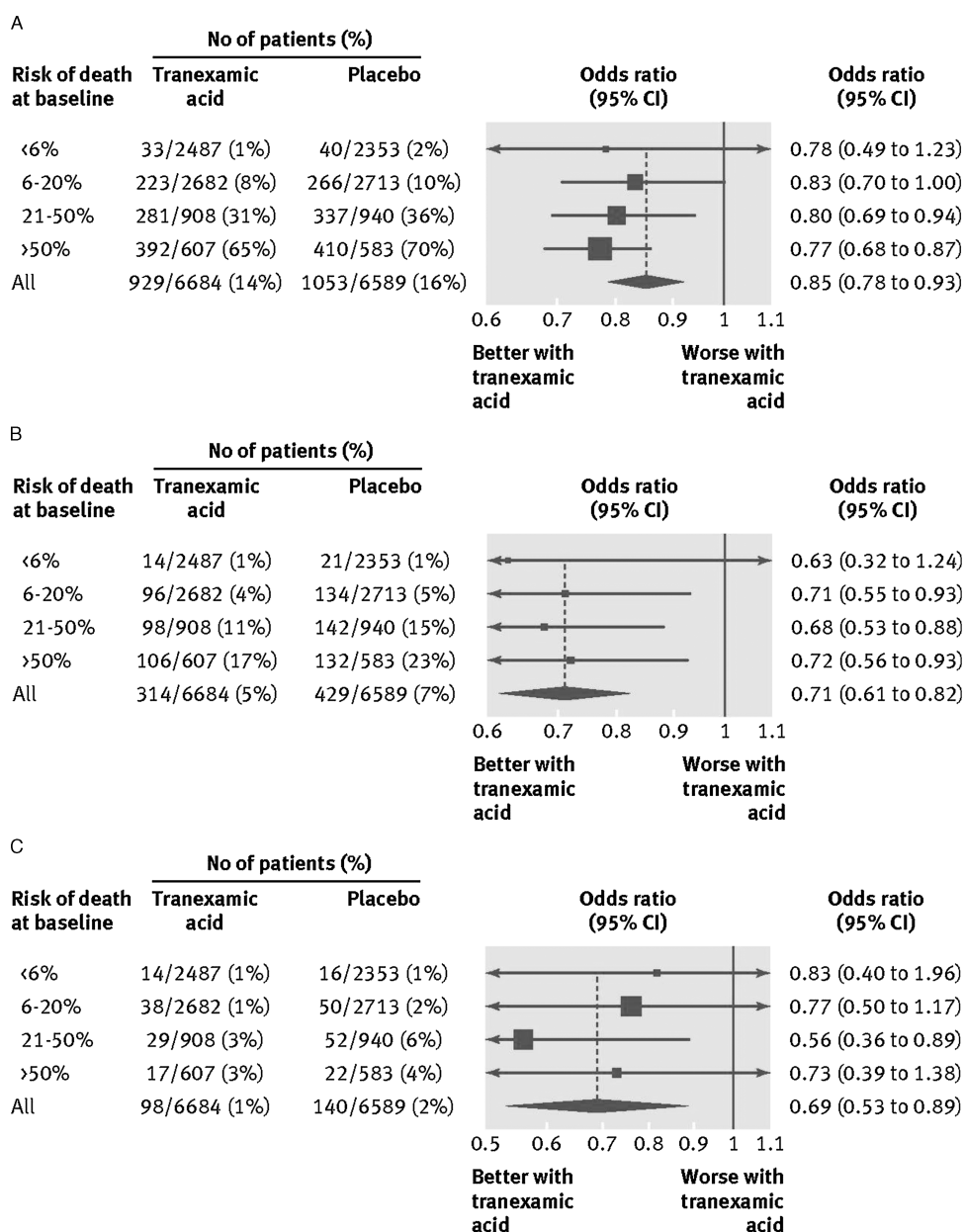

Figure 1. Prespecified analysis of TXA effect on mortality and thrombotic events based on risk of death at baseline in trauma patients. *A,* Deaths from all causes in patients with traumatic bleeding according to treatment with TXA (*p* = 0.96 for heterogeneity). *B,* Death from bleeding in patients with traumatic bleeding according to treatment with TXA (*p* = 0.98 for heterogeneity). *C,* Fatal and nonfatal thrombotic events in patients with traumatic bleeding according to treatment with TXA (*p* = 0.74 for heterogeneity) (reproduced with permission from BMJ Publishing Group Ltd. from Roberts et al.[72]).

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