The Effect of Tranexamic Acid on Functional Outcomes: An Exploratory Analysis of the CRASH-2 Randomized Controlled Trial

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Study objective: Tranexamic acid improves survival in severely injured adults. However, its effectiveness on overall functional outcome is unknown. We hypothesized that tranexamic acid improves overall functional outcome compared with placebo in severely injured adults and conduct an exploratory analysis of the Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) data to investigate this hypothesis.

Methods: We included injured adults from the CRASH-2 trial who were randomized 3 hours or less from injury. The primary outcome measure was functional status at hospital discharge or on day 28 if the subject was still in the hospital. Functional status was measured with the modified Oxford Handicap Scale, a 6-category ordinal functional outcome scale. We conducted 3 separate analyses using 3 different outcome measures to evaluate the effectiveness of tranexamic acid versus placebo on functional outcomes, including the mean utility-weighted modified Oxford Handicap Scale score (overall functional outcome), the area under the curve (based on functional outcome and rate of recovery), and a sliding dichotomy analysis (favorable versus unfavorable functional outcome) stratified by baseline mortality risk (stratified analysis).

Results: There were 13,432 patients (6,679 randomized to placebo and 6,753 to tranexamic acid) included in the study cohort. The mean utility-weighted modified Oxford Handicap Scale score was 0.66 (SD 0.33) for patients randomized to tranexamic acid compared with a mean of 0.64 (SD 0.34) for those randomized to placebo (mean difference 0.02; 95% confidence interval [CI] 0.01 to 0.03). The area under the curve analysis demonstrated that patients randomized to tranexamic acid had a higher 28-day mean utility-weighted modified Oxford Handicap Scale score compared with those randomized to placebo (mean score 0.55 [SD 0.30] versus 0.53 [SD 0.31]; mean difference 0.02 [95% CI 0.01 to 0.03]). The sliding dichotomy analysis demonstrated heterogeneity of treatment effects across risk groups. The overall proportion of patients with favorable functional outcomes was higher in the tranexamic acid group (5,360/6,753 [79.4%]; 95% CI 78.4% to 80.3%) compared with the placebo group (5,174/6,679 [77.5%]; 95% CI 76.5% to 78.5%; difference 1.9% [95% CI 0.5% to 3.3%]; number needed to treat=52). When each risk group was tested separately, only the lowest-risk group (<6% baseline mortality risk) demonstrated a statistically significant effect of tranexamic acid toward favorable functional outcomes (tranexamic acid versus placebo adjusted odds ratio 0.78; 95% CI 0.67 to 0.90). There were no differences between tranexamic acid and placebo in the other risk groups.

Conclusion: Across 3 exploratory analyses, severely injured adult patients randomized within 3 hours from injury demonstrated better functional outcomes with tranexamic acid compared with placebo. When heterogeneity of treatment effects across risk groups was evaluated, only the lowest-risk group demonstrated a significant effect of tranexamic acid toward favorable outcomes. Given the overall safety and cost-effectiveness of tranexamic acid use in injured adults, our results further support the use of tranexamic acid for this population. Future trauma trials that evaluate tranexamic acid use should also consider functional status as an important outcome. [Ann Emerg Med. 2019;74:79-87.]

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INTRODUCTION

Background

Tranexamic acid is an antifibrinolytic drug that blocks plasmin-mediated fibrin clot breakdown and attenuates bleeding. It is extensively used in surgery to decrease blood product transfusion requirements.[1,2] The success of its use in the surgical setting led to the Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial, an international randomized controlled trial of the early administration of tranexamic acid to bleeding adult

Editor's Capsule Summary

What is already known on this topic

Tranexamic acid is used to reduce mortality in severely injured patients.

What question this study addressed

Does tranexamic acid use in severely injured patients improve overall functional capacity?

What this study adds to our knowledge

This secondary and exploratory analysis of patients randomized to placebo (n=6,679) or tranexamic acid (n=6,753) suggests that the use of tranexamic acid in injured patients is associated with improved patient function as measured up to 28 days postinjury. This improvement was mainly noted among individuals with the lowest mortality risk (<6%).

How this is relevant to clinical practice

Routine use of tranexamic acid in selected trauma patients may improve functional status as determined early in the postinjury phase of recovery, but the long-term effects are unknown and prospective studies would be required to confirm this finding.

trauma patients. In the trial, tranexamic acid reduced mortality with no increase in adverse events compared with placebo.[3] All-cause 28-day mortality was 1,463 (14.5%) in the tranexamic acid group and 1,613 (16.0%) in the placebo group (relative risk 0.91; 95% confidence interval [CI] 0.85 to 0.97).

Importance

The mortality outcome measure is patient centered, not prone to the subjectivity of outcome assessors, and not affected by the methodological problem of competing risks.[4] However, other clinically important patient-centered benefits (or harms) associated with tranexamic acid use are unknown. In the CRASH-2 trial, 28-day functional status as measured by the modified Oxford Handicap Scale was collected but not analyzed in detail.[3,5]

Goals of This Investigation

The goal of this study was to evaluate whether tranexamic acid was associated with improved functional outcomes and, if so, which patients benefitted from tranexamic acid use. The results of this study may inform future trauma trials about the use of functional status as an outcome measure, as well as potential analytic methods. We hypothesized that tranexamic acid use compared with placebo improves overall functional outcome in severely injured adults as measured by the modified Oxford Handicap Scale. We conducted an exploratory analysis of the CRASH-2 data to investigate this hypothesis.

MATERIALS AND METHODS

Study Design and Selection of Participants

The overall study design and protocol of the CRASH-2 trial have been previously reported.[3,6] In summary, 20,111 adults with or at risk of significant traumatic bleeding within 8 hours of injury were randomized to tranexamic acid (loading dose 1 g during 10 minutes, followed by a 1-g infusion during 8 hours) or placebo. Both patients and study staff were blinded to treatment allocation. A secondary analysis demonstrated that, compared with placebo, tranexamic acid given at 1 hour or sooner (relative risk 0.87; 95 CI% 0.76 to 0.97) and at 1 to 3 hours from injury (relative risk 0.87; 95% CI 0.77 to 0.97) decreased death caused by bleeding. There was no statistically significant difference when tranexamic acid was given more than 3 hours from injury (relative risk 1.00; 95% CI 0.90 to 1.13).[7] Thus, for this study, we included only patients randomized 3 hours or less from the time of injury. We also excluded patients who did not have modified Oxford Handicap Scale scores reported.

Outcome Measures

The primary outcome measure was functional status at hospital discharge or on day 28 after injury if the subject was still in the hospital. Functional status was measured with the modified Oxford Handicap Scale, an ordinal scale with the following functional categories (best to worst): no symptoms, minor symptoms, some restriction, dependent (not requiring constant attention), fully dependent, and dead. We converted the ordinal modified Oxford Handicap Scale score to a utility-weighted score. This conversion was based on previous measurements of health-related quality-of-life in patients with different functional outcome scores after acute neurologic injuries (Table 1).[8] The modified Oxford Handicap Scale score measured at hospital discharge has been shown to be highly correlated with 6-month functional outcomes.[5] The scale is very similar to the modified Rankin Scale, which has been shown to be a valid and reliable measure of functional outcomes.[5]

Primary Data Analysis

We developed a statistical analysis plan (Appendix E1, available online at http://www.annemergmed.com) that was approved by the Free Bank of Injury and Emergency Research Data investigators (http://freebird.lshtm.ac.uk)

Table 1. Modified Oxford Handicap Scale conversion to quality of life.

Modified Oxford Handicap Scale	Quality of Life*
No symptoms	1.00
Minor symptoms	0.84
Some restriction	0.78
Dependent†	0.58
Fully dependent	0.18
Dead	0

*Based on a 3-month quality-of-life index from Rangaraju et al.[8]
†Because the dependent category collapses the moderate and moderate-to-severe handicap categories, the score of 0.58 is an average of the moderate (0.71) and the moderate-to-severe (0.44) categories.

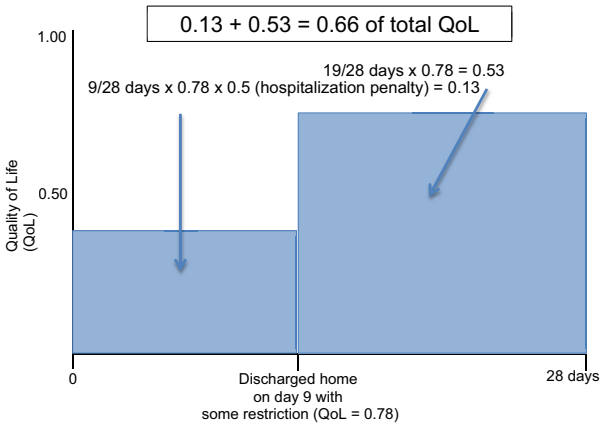


Figure 1. Example of total quality-of-life for an individual using the area under the curve calculation. In this example, the patient was discharged home on hospital day 9 with a Modified Oxford Handicap scale of "some restriction." This equates to a quality of life score of 0.78. For the days during hospitalization, the quality of life is calculated by the length of time of hospitalization (9 of 28 days) x the discharge quality of life (0.78) x hospitalization penalty (0.5). For the days after hospital discharge, the quality of life is calculated by the length of time out of hospital (19 of 28 days) x the discharge quality of life (0.78).

before receiving the CRASH-2 data. We planned 3 separate analyses to evaluate the effectiveness of tranexamic acid on functional outcomes. First, in unadjusted (Student's *t* test) and adjusted (multiple linear regression) analyses, we compared the mean utility-weighted modified Oxford Handicap Scale scores between patients randomized to tranexamic acid versus placebo within 3 hours of injury. For the unadjusted analysis, we reported the results as means and SDs for both groups and the absolute difference in means with 95% CIs. The modified Oxford Handicap Scale score was measured at hospital discharge or routinely at 28 days if the patient was still in the hospital. It was not measured routinely at any other follow-up points. For the adjusted analysis, we included in the regression model a parsimonious set of covariates, composed of age, male sex, income level of country, hours since injury, initial systolic blood pressure (millimeters of mercury), initial pulse rate (beats/minute), initial Glasgow Coma Scale (GCS) score, and study intervention. Income level of country was categorized as low, middle, and high and was based on previous definitions.[9] These were all the potentially relevant clinical variables that were collected in the CRASH-2 trial and were selected for their simplicity and availability, as well as their ability to improve the precision of our effect size estimates by removing explainable variation in the outcome. To account for heteroskedasticity or other violations of modeling assumptions (which may arise from errors in the dependent variable not having a Gaussian distribution), we used a robust standard error estimator for regression test statistics and CIs.

Second, to estimate the rate of functional recovery, we calculated the area under the curve according to utility-weighted functional outcome and length of hospitalization (Figure 1). The area under the curve represents the total amount of quality of life during the first 28 days after injury. This calculation was based on the following assumptions: the discharge functional outcome score (and resultant quality-of-life conversion) remained the same until day 28; hospitalization inferred a quality penalty, and thus the discharge functional outcome score was multiplied by 0.5 for days spent in the hospital; and death before 28 days equated to an area under the curve of 0. We used a linear regression model to estimate the adjusted mean difference in the quality of life between patients receiving tranexamic acid and those receiving placebo. We included the same covariates as in the previously described multiple regression model. We also analyzed models using hospitalization quality penalties of 0.25 and 0.75 for days spent in the hospital to evaluate this analysis under different parameter assumptions.

Third, to further explore differences across the functional outcome spectrum while incorporating baseline risk of mortality, we conducted a sliding dichotomy analysis. Patients within the CRASH-2 cohort were classified into 4 mortality risk strata (<6%, 6% to 20%, 21% to 50%, and >50%) based on a previously developed risk score.[9] This risk score was developed with the CRASH-2 data and externally validated with a separate trauma registry (the Trauma Audit and Research Network). Favorable versus unfavorable outcomes were defined separately for each risk stratum. For example, for a patient with a baseline risk of mortality stratum of less than 6%, a favorable outcome would be no symptoms and an unfavorable one would be minor symptoms or worse.

On the other hand, for a patient with a baseline risk of mortality stratum of greater than 50%, a favorable outcome would be dependent or better and an unfavorable one would be fully dependent or death. We analyzed each of these strata by using a multiple logistic regression model with favorable outcome as the dependent outcome. We included the same covariates as in the previously described linear regression model. We compared models with and without baseline risk stratum as an independent categorical variable and selected the model with the better Akaike information criteria.[10] We also used the χ^2 test to compare the overall proportion of patients with favorable functional outcomes between the tranexamic acid and placebo groups. We calculated a number-needed-to-treat based on the absolute risk reduction of tranexamic acid use compared with placebo (1/absolute risk reduction).

We conducted a sensitivity analysis to evaluate for the potential of inaccurate functional outcome data collection by sites. Specifically, we calculated the proportion of patients with significant head injuries and Glasgow Coma Scale scores of 3 to 8 who had modified Oxford Handicap Scale scores of 1 (no symptoms) by site (limited to sites that enrolled ≥100 patients). Because these patients are expected to have poor functional outcomes, a high proportion of patients with functional outcomes of no symptoms might suggest inaccurate data collection. We used complete case analysis to handle missing data because of the small numbers of patients with missing data in the CRASH-2 trial (<1%).[11]

RESULTS

Characteristics of Study Subjects

After exclusion of 6,667 patients with times of presentation more than 3 hours after injury, 11 patients with missing times of injury, and 97 patients with missing modified Oxford Handicap Scale scores, there were 13,432 patients (6,679 randomized to placebo and 6,753 randomized to tranexamic acid) included in the study cohort (Figure 2). Patients were aged a mean of 34 years

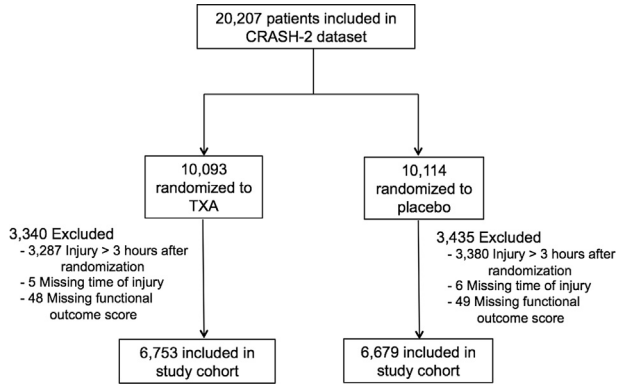


Figure 2. Flowchart of the study cohort (n=13,432). *TXA*, Tranexamic acid.

Table 2. Characteristics of subjects included in the analysis (n=13,432).

Characteristics	Intervention, No. (%)	
	TXA, n=6,753	Placebo, n=6,679
Men	5,605 (83.0)	5,606 (84.0)
Age, mean (SD), y	34.1 (13.8)	34.1 (14.2)
Time since injury, mean (SD), h	1.53 (0.84)	1.53 (0.84)
≤1	3,731 (55.3)	3,689 (55.2)
>1–3	3,022 (44.7)	2,990 (44.8)
Type of injury		
Blunt*	3,292 (48.8)	3,305 (49.5)
Penetrating	2,583 (38.2)	2,516 (37.7)
Blunt and penetrating	878 (13.0)	858 (12.8)
Initial systolic blood pressure, mean (SD), mm Hg	95.5 (30.2)	94.6 (27.9)
Initial pulse, mean (SD), beats/min	104.7 (20.9)	104.9 (21.0)
Initial respiratory rate, mean (IQR), breaths/min	23.1 (6.5)	23.3 (7.8)
Initial GCS score, median (IQR)	12.7 (3.6)	12.7 (3.6)
Baseline risk of mortality stratum, %†		
<6	2,415 (35.8)	2,325 (34.9)
6–20	2,410 (35.7)	2,391 (35.9)
21–50	1,171 (17.4)	1,201 (18.0)
>50	753 (11.2)	752 (11.3)
Any vascular occlusive event‡	95 (1.4)	137 (2.1)
Blood products transfused	3,218 (47.7)	3,263 (48.9)
Units of blood products transfused, median (IQR)§	3 (2–6)	3 (2–6)
Any surgery‖	3,304 (49.5)	3,290 (48.7)
Days in hospital, median (IQR)¶	7 (3–14)	7 (3–14)
Days in the ICU, median (IQR)¶	0 (0–2)	0 (0–2)
Country income level		
Low	91 (1.4)	91 (1.4)
Middle	6,548 (97.0)	6,467 (96.8)
High	114 (1.7)	121 (1.8)

IQR, Interquartile range.
*Includes patients with both blunt and penetrating injuries and those with only blunt injuries.
†Baseline risk strata were derived from Perel et al.[10]
‡Includes deep venous thrombosis, pulmonary embolism, stroke, and myocardial infarction.
§Includes packed RBCs, plasma, platelets, and cryoprecipitate.
‖Includes neurologic, chest, abdominal, and pelvic surgery.
¶Hospital and ICU length of stay recorded up to 28 days.

Table 3. Modified Oxford Handicap Scale score by intervention (n=13,432).

	Intervention, No. (%)	
Category	**TXA, n=6,753**	**Placebo, n=6,679**
No symptoms	1,052 (15.6)	941 (13.9)
Minor symptoms	2,190 (32.4)	2,140 (32.0)
Some restrictions	1,311 (19.4)	1,324 (19.8)
Dependent	807 (11.9)	779 (11.7)
Fully dependent	421 (6.2)	396 (5.9)
Dead	972 (14.4)	1,109 (16.6)

(SD 14 years), 11,211 (83.5%) were men, and 6,835 (50.9%) had penetrating traumatic injuries. Characteristics of the study population are described in Table 2.

Main Results

The modified Oxford Handicap Scale scores stratified by intervention are reported in Table 3. The mean utility-weighted score was 0.66 (SD 0.33) for patients randomized to tranexamic acid compared with a mean of 0.64 (SD 0.34) for those randomized to placebo (mean difference 0.02; 95% CI 0.01 to 0.03; P=.001). Adjusted analysis demonstrated that tranexamic acid use was significantly associated with higher utility-weighted modified Oxford Handicap Scale scores (coefficient 0.02; 95% CI 0.01 to 0.03) (Table E1, available online at http://www.annemergmed.com).

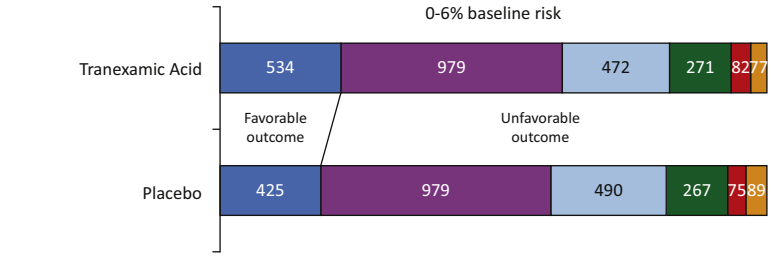
The area under the curve analysis demonstrated that patients randomized to tranexamic acid had a higher 28-day mean utility-weighted modified Oxford Handicap Scale score compared with those randomized to placebo (mean score 0.55 [SD 0.30] versus 0.53 [SD 0.31]; mean difference 0.02; 95% CI 0.01 to 0.03). Multiple regression analysis demonstrated that tranexamic acid was significantly associated with higher 28-day utility-weighted modified Oxford Handicap Scale scores (coefficient 0.01; 95% CI 0.01 to 0.02) (Table E2, available online at http://www.annemergmed.com). The results were similar when we used different hospitalization quality penalties (ie, 0.25 and 0.75) for days spent in the hospital (Table E2, available online at http://www.annemergmed.com).

The relative frequencies of the undichotomized and dichotomized outcomes for the sliding dichotomy analysis are presented in Figure 3, grouped by risk stratum and treatment arm. For the dichotomized outcome, the logistic regression model with the interaction term for risk score and tranexamic acid fit the data better than the "main effects only" model, according to the Akaike information criteria. Statistical significance testing of the risk stratum×tranexamic acid interaction term also demonstrated evidence of heterogeneity of treatment effects across risk groups (P=.04). Therefore, for each risk group, we report separate adjusted odds ratios (ORs) for the tranexamic acid versus placebo effect. When each risk group was tested separately, only the group with less than 6% baseline risk of mortality demonstrated a statistically significant effect of tranexamic acid for favorable outcomes (tranexamic acid versus placebo adjusted OR 1.28, 95% CI 1.11 to 1.48). The 6 to 20% risk group (adjusted OR 0.99, 95% CI 0.88 to 1.11), 21 to 50% risk group (adjusted OR 1.15; 95% CI 0.97 to 1.37), and the greater than 50% risk group (adjusted OR 1.24, 95% CI 0.97 to 1.57) did not demonstrate a statistically significant effect of tranexamic acid for favorable outcomes. The overall proportion of patients with favorable functional outcomes was higher in the tranexamic acid group (5,360/6,753 [79.4%]; 95% CI 78.4% to 80.3%) compared with the placebo group (5,174/6,679 [77.5%], 95% CI 76.5% to 78.5%; difference 1.9%, 95% CI 0.5% to 3.3%; number-needed-to-treat=52, 95% CI 30 to 196).

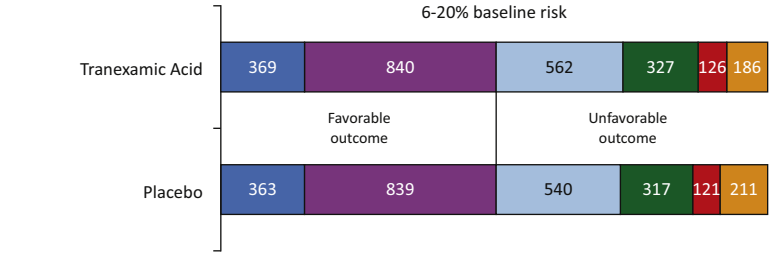
The sensitivity analysis demonstrated no evidence of gross inaccuracies in functional outcomes scores across sites (Table E3, available online at http://www.annemergmed.com).

LIMITATIONS

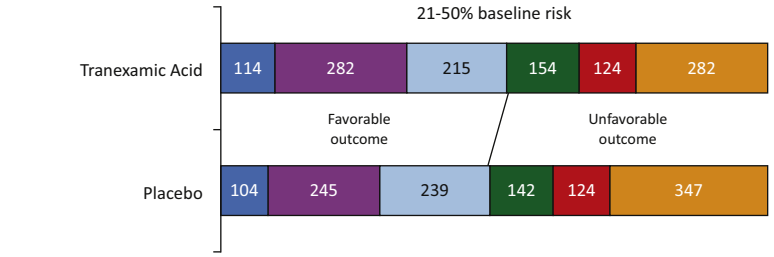
Our results should be interpreted in the context of some limitations. First, this was an exploratory analysis of a previously completed clinical trial, and the results of this study should be considered hypothesis generating rather than confirmatory.[12] However, we developed the statistical analysis plan before receiving the data, thereby limiting the potential for data dredging.[13] Second, there may be unknown variables associated with the outcomes of interest that would have altered the results of our adjusted analyses. The CRASH-2 trial was a pragmatic trial and did not collect prognostic clinical variables requiring extensive training such as the Injury Severity Score.[14,15] However, we included all potentially relevant clinical variables that were collected in the CRASH-2 trial. Third, functional outcome was measured at hospital discharge or 28 days, whichever came first. It is possible that functional outcome measured at a longer follow-up point (eg, 3 or 6 months after injury) is more predictive of long-term functional outcome. However, a previous trauma study demonstrated that the modified Oxford Handicap Scale score measured at



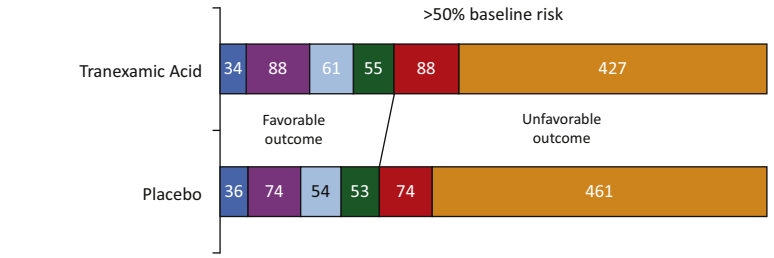
Overall favorable outcome: TXA 534/2415 (22.1%, 95% CI 20.5 to 23.8%), Placebo 425/2325 (18.3%, 95% CI 16.7 to 19.9%), TXA vs. placebo adjusted odds ratio (AOR) for favorable outcome 1.28, 95% CI 1.11 to 1.48)



Overall favorable outcome: TXA 1209/2410 (50.2%, 95% CI 48.1 to 52.2%), Placebo 1202/2391 (50.3%, 95% CI 48.2 to 52.3%), AOR 0.99, 95% CI 0.88 to 1.11



Overall favorable outcome: TXA 611/1171 (52.2%, 95% CI 49.3 to 55.1%), Placebo 588/1201 (49.0%, 95% CI 46.1% to 51.8%), AOR 1.15; 95% CI 0.97 to 1.37



Overall favorable outcome: TXA 238/753 (31.6%, 95% CI 28.3 to 35.1%), Placebo 217/752 (28.9%, 95% CI 25.6 to 32.2%), AOR 1.24, 95% CI 0.97 to 1.57

Figure 3. Sliding dichotomy analysis comparing functional outcomes in patients receiving tranexamic acid versus placebo, stratified by CRASH-2 prognostic score.* *Patients were classified into 4 mortality risk strata (<6%, 6% to 20%, 21% to 50%, and >50%) based on a previously developed risk score.[9] Favorable versus unfavorable outcomes were defined separately for each risk stratum. For example, for a patient with a baseline risk of mortality stratum of less than 6%, a favorable outcome would be no symptoms and an unfavorable one would be minor symptoms or worse. On the other hand, for a patient with a baseline risk stratum of greater than 50%, a favorable outcome would be dependent or better and an unfavorable one would be fully dependent or death.

hospital discharge was highly correlated with 6-month functional outcomes.[5] Fourth, in calculating the area under the curve functional outcome, we made certain assumptions (eg, quality-of-life penalty for hospitalization) that were based on clinical intuition but were not validated. Fifth, it is difficult to know whether the functional

outcome benefit of tranexamic acid in our study is driven only by a survival benefit. Unfortunately, conducting a sensitivity analysis by including only survivors would be flawed because it would bias against tranexamic acid as a result of survivors' likely being sicker compared with the placebo group (survivor bias).

DISCUSSION

In this exploratory analysis of the CRASH-2 study, we found that adult trauma patients randomized to tranexamic acid within 3 hours of injury had better functional outcomes compared with patients randomized to placebo. The effect of tranexamic acid was consistent across different analyses, including overall functional outcome (mean utility-weighted functional outcome analysis), an estimation of the rate of functional outcome improvement (area under the curve analysis), and an analysis stratifying by level of baseline mortality risk (sliding dichotomy analysis).

The overall mean difference in functional outcomes between patients randomized to tranexamic acid compared with those randomized to placebo was a mean utility-weighted modified Oxford Handicap Scale score of 0.02 (95% CI 0.01 to 0.03). It is difficult to determine whether this difference represents a clinically important one because previous studies have used a wide range of methodological approaches to define the minimum clinically important difference, resulting in a wide range of values.[16] With use of a standardized instrument measuring health-related quality-of-life, a difference of 0.02 can equate to the difference between no pain or discomfort and moderate pain or discomfort.[17] A difference of 0.02 could also equate to the difference between no anxiety or depression and moderate anxiety or depression.[17] Our analysis also demonstrated a number-needed-to-treat of 52 for tranexamic acid to have 1 more patient with a favorable functional outcome. Depending on the level of baseline risk of mortality, this could equate to a patient's having no symptoms versus minor symptoms (or worse) or a patient's having some restriction versus dependent (or worse). Because the number-needed-to-treat is sensitive to several factors, such as the baseline risk, it is preferable to derive numbers needed to treat by applying the relative risk reductions from trials to estimates in prognosis in cohort studies (representing the groups for whom treatment decisions are to be made) rather than from the trials themselves.[18] Given the overall safety and cost-effectiveness of tranexamic acid in injured adults, our results further support its use for this population.[3,19]

Our study is important because it suggests that tranexamic acid may have additional clinically important benefits in a broad trauma population beyond the survival benefit as reported in the CRASH-2 trial.[3] It is also commonly thought that tranexamic acid should be reserved for patients with the greatest risk for death or massive transfusion.[20,21] However, in our sliding dichotomy analysis, tranexamic acid was most effective in the lowest-risk group (<6% baseline mortality risk). In this risk group, favorable functional outcome (defined as no symptoms) was 3.8% higher in patients randomized to tranexamic acid compared with placebo.

The mechanism by which tranexamic acid exerts potential benefit on functional outcomes, however, is unknown. It is an antifibrinolytic agent and confers benefit in bleeding patients by reducing excessive bleeding. Multiple previous studies in the controlled setting of elective surgery have demonstrated a reduction in the need and amount of blood transfusion products with tranexamic acid use.[1,22,23] A similar reduction of bleeding in severely injured trauma patients treated with tranexamic acid may translate to improved functional outcomes. Another possible explanation is that even slightly less bleeding into critical areas of the brain may result in improved functional outcomes. Patients with less bleeding are also less prone to complications with blood transfusions, may have shorter lengths of hospitalization, and may require surgical interventions less frequently.[24-26] Although the CRASH-2 trial did not show a reduction of blood transfusions with tranexamic acid use, this outcome is often difficult to measure in trauma trials. Blood loss, which may occur in the out-of-hospital setting or may be concealed (eg, in the chest, abdomen, pelvis), is notoriously difficult to estimate, leading to variability of assessing the need for blood transfusion. In addition, survivor bias (ie, patients surviving may need more blood transfusions or volume compared with those who die) may also skew blood transfusion requirements. Some authors have also suggested that tranexamic acid may have an anti-inflammatory mechanism, which may contribute to improved functional outcomes of patients treated with it, including those at low risk of mortality.[20,27,28]

Other studies have compared the effectiveness of tranexamic acid versus placebo on functional outcomes. The CRASH-2 trial demonstrated improved 28-day survival in patients randomized to tranexamic acid compared with placebo. In addition, there was a higher proportion of patients with no symptoms in the tranexamic acid group compared with the placebo group, meaning that fewer patients had residual deficits or other symptoms such as fatigue, headaches, or depression. There were no differences in other functional outcome scores.[3] Two previous randomized controlled trials

compared the effectiveness of tranexamic acid with placebo on functional outcomes in adults with traumatic brain injuries.[29,30] The CRASH-2 Intracranial Bleeding Study evaluated dependency at 28 days in survivors (dichotomized as dependent versus independent),[29] and a separate study evaluated the Glasgow Outcome Scale score (dichotomized as unfavorable [death, persistent vegetative state, or severe disability] or favorable) at hospital discharge.[30] A meta-analysis that combined these 2 studies suggested a trend toward favorable outcomes with tranexamic acid use (relative risk for unfavorable outcome, tranexamic acid versus placebo 0.77; 95% CI 0.59 to 1.02).[31] The results of our study are consistent with these previous studies and provide a more extensive evaluation of the effectiveness of tranexamic acid on functional outcomes.

In conclusion, across a number of exploratory analyses, severely injured adult patients randomized to tranexamic acid within 3 hours from injury had better functional outcomes than those randomized to placebo. When heterogeneity of treatment effects across risk groups was evaluated, only the lowest-risk group demonstrated a significant effect of tranexamic acid toward favorable outcomes. Given the overall safety and cost-effectiveness of tranexamic acid use in injured adults, our results further support its use for this population. Future trauma trials that evaluate tranexamic acid use should also consider functional status as an important outcome.

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REFERENCES

1. Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ*. 2012;344:e3054.
2. Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. *Br J Surg*. 2013;100:1271-1279.
3. CRASH-2 Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376:23-32.
4. Lauer MS, Blackstone EH, Young JB, et al. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol*. 1999;34:618-620.
5. Perel P, Edwards P, Shakur H, et al. Use of the Oxford Handicap Scale at hospital discharge to predict Glasgow Outcome Scale at 6 months in patients with traumatic brain injury. *BMC Med Res Methodol*. 2008;8:72.
6. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess*. 2013;17:1-79.
7. CRASH-2 Collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*. 2011;377:1096-1101, 1101.e1091-1092.
8. Rangaraju S, Haussen D, Nogueira RG, et al. Comparison of 3-month stroke disability and quality of life across modified Rankin Scale categories. *Interv Neurol*. 2017;6:36-41.
9. Perel P, Prieto-Merino D, Shakur H, et al. Development and validation of a prognostic model to predict death in patients with traumatic bleeding, and evaluation of the effect of tranexamic acid on mortality according to baseline risk: a secondary analysis of a randomised controlled trial. *Health Technol Assess*. 2013;17:1-45; v-vi.
10. Burnham KP, Anderson DR, Burnham KP. *Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach*. 2nd ed. New York, NY: Springer; 2002.
11. Newgard CD, Lewis RJ. Missing data: how to best account for what is not known. *JAMA*. 2015;314:940-941.

12. Moyé L. What can we do about exploratory analyses in clinical trials? *Contemp Clin Trials*. 2015;45(pt B):302-310.
13. Smith GD, Ebrahim S. Data dredging, bias, or confounding. *BMJ*. 2002;325:1437-1438.
14. Baker SP, O'Neill B, Haddon W Jr, et al. The Injury Severity Score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974;14:187-196.
15. Stevenson M, Segui-Gomez M, Lescohier I, et al. An overview of the Injury Severity Score and the new Injury Severity Score. *Inj Prev*. 2001;7:10-13.
16. Coretti S, Ruggeri M, McNamee P. The minimum clinically important difference for EQ-5D index: a critical review. *Expert Rev Pharmacoecon Outcomes Res*. 2014;14:221-233.
17. EuroQol. EQ-5D instrument. Available at: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/. Accessed September 18, 2018.
18. Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses—sometimes informative, usually misleading. *BMJ*. 1999;318:1548-1551.
19. Guerriero C, Cairns J, Perel P, et al. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PloS One*. 2011;6:e18987.
20. Napolitano LM, Cohen MJ, Cotton BA, et al. Tranexamic acid in trauma: how should we use it? *J Trauma Acute Care Surg*. 2013;74:1575-1586.
21. Valle EJ, Allen CJ, Van Haren RM, et al. Do all trauma patients benefit from tranexamic acid? *J Trauma Acute Care Surg*. 2014;76:1373-1378.
22. Faraoni D, Goobie SM. The efficacy of antifibrinolytic drugs in children undergoing noncardiac surgery: a systematic review of the literature. *Anesth Analg*. 2014;118:628-636.
23. Faraoni D, Willems A, Melot C, et al. Efficacy of tranexamic acid in paediatric cardiac surgery: a systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2012;42:781-786.
24. Galas FR, Almeida JP, Fukushima JT, et al. Blood transfusion in cardiac surgery is a risk factor for increased hospital length of stay in adult patients. *J Cardiothorac Surg*. 2013;8:54.
25. Goodnough LT, Levy JH, Murphy MF. Concepts of blood transfusion in adults. *Lancet*. 2013;381:1845-1854.
26. Goodnough LT, Maggio P, Hadhazy E, et al. Restrictive blood transfusion practices are associated with improved patient outcomes. *Transfusion*. 2014;54(10 pt 2):2753-2759.
27. Levy JH. Antifibrinolytic therapy: new data and new concepts. *Lancet*. 2010;376:3-4.
28. Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study. *Arch Surg*. 2012;147:113-119.
29. CRASH-2 Collaborators. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ*. 2011;343:d3795.
30. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, et al. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. *BMC Emerg Med*. 2013;13:20.
31. Zehtabchi S, Abdel Baki SG, Falzon L, et al. Tranexamic acid for traumatic brain injury: a systematic review and meta-analysis. *Am J Emerg Med*. 2014;32:1503-1509.