# Tranexamic Acid for Traumatic Injury in the Emergency Setting: A Systematic Review and Bias-Adjusted Meta-Analysis of Randomized Controlled Trials

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**Study objective:** Traumatic injury causes a significant number of deaths due to bleeding. Tranexamic acid (TXA), an antifibrinolytic agent, can reduce bleeding in traumatic injuries and potentially enhance outcomes. Previous reviews suggested potential TXA benefits but did not consider the latest trials.

**Methods:** A systematic review and bias-adjusted meta-analysis were performed to assess TXA's effectiveness in emergency traumatic injury settings by pooling estimates from randomized controlled trials. Researchers searched Medline, Embase, and Cochrane Central for randomized controlled trials comparing TXA's effects to a placebo in emergency trauma cases. The primary endpoint was 1-month mortality. The methodological quality of the trials underwent assessment using the MASTER scale, and the meta-analysis applied the quality-effects method to adjust for methodological quality.

**Results:** Seven randomized controlled trials met the set criteria. This meta-analysis indicated an 11% decrease in the death risk at 1 month after TXA use (odds ratio [OR] 0.89, 95% confidence interval [CI] 0.84 to 0.95) with a number needed to treat of 61 to avoid 1 additional death. The meta-analysis also revealed reduced 24-hour mortality (OR 0.76, 95% CI 0.65 to 0.88) for TXA. No compelling evidence of increased vascular occlusive events emerged (OR 0.96, 95% CI 0.73 to 1.27). Subgroup analyses highlighted TXA's effectiveness in general trauma versus traumatic brain injury and survival advantages when administered out-of-hospital versus inhospital.

**Conclusions:** This synthesis demonstrates that TXA use for trauma in emergencies leads to a reduction in 1-month mortality, with no significant evidence of problematic vascular occlusive events. Administering TXA in the out-of-hospital setting is associated with reduced mortality compared to inhospital administration, and less mortality with TXA in systemic trauma is noted compared with traumatic brain injury specifically. [Ann Emerg Med. 2024;83:435-445.]

Please see page 436 for the Editor's Capsule Summary of this article.

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## INTRODUCTION

### Background

Traumatic injury is a leading cause of death and disability with approximately 4.4 million deaths worldwide each year, accounting for nearly 8% of the total global mortality rate.[1,2] Major trauma includes traumatic brain injury, spinal cord injury, and multiple organ damage, which can lead to significant and life-threatening blood loss. Uncontrolled hemorrhage from traumatic injuries is the primary cause of death for approximately one third of inhospital trauma admissions.[3] A normal physiologic response in trauma bleeding is clot breakdown. Occasionally, this can progress to pathological hyperfibrinolysis, which could result in further bleeding and worsen mortality.[4] Tranexamic acid (TXA) is a synthetic lysine analog that inhibits the activation of plasminogen to plasmin. Plasmin is an autologous serum protease that breaks down fibrin.[5] TXA may reduce bleeding by inhibiting the activation of plasmin and maintaining clot stability and integrity.[6,7] Systematic reviews have shown that TXA is likely to be effective in reducing bleeding and improving outcomes in patients

**Editor's Capsule Summary**

*What is already known on this topic*

Previous reviews suggest that tranexamic acid (TXA) decreases mortality in emergency trauma patients but have not included the most recent data and employed the most rigorous designs.

*What question this study addressed*

Do updated data and more selective analysis support previous data on the benefit of TXA?

*What this study adds to our knowledge*

Analysis of 7 current randomized and controlled trials showed decreased 1-month and 24-hour mortality compared to placebo, with no indication of increased occlusive events. Out-of-hospital administration of TXA was associated with decreased mortality compared to inhospital administration.

*How this is relevant to clinical practice*

These results strengthen the evidence for the use of TXA and suggest a potential benefit with earlier administration.

with traumatic injury.[6,7] A Cochrane review published in 2015 found benefit, but the estimates from that meta-analysis did not include any of the randomized trials published after 2015.[7] Further, these results are based predominantly on one large trial.[7] Another systematic review included these subsequent trials,[6] but did not include the results from recent large-scale out-of-hospital trial published in 2023.[8,9] Moreover, that meta-analysis included observational studies that might have been the cause of sizable heterogeneity, limiting the pooling of some study estimates, including 24-hour mortality.

### Importance

This systematic review and meta-analysis reviews all recent randomized trials conducted in the emergency setting. Additionally, including the latest trial data in the meta-analysis of 24-hour survival and out-of-hospital TXA aims to achieve more precise and consistent estimates.

### Goals of This Study

This systematic review and meta-analysis aims to combine the results from all randomized controlled trials conducted to date comparing TXA to placebo for hemorrhage control in the emergency setting in terms of 1-month survival.

## MATERIALS AND METHODS

### Design

This systematic review is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses format and was registered with the PROSPERO registry (registration no. CRD42022350456).[10]

### Data Sources, Search Strategy and Study Selection

Two researchers (BM and PF) independently completed a comprehensive search of Medline, EMBASE, and the Cochrane Central Register of Controlled Trials from the inception of these databases up to May 1, 2023 (search terms in Appendix E1, available at http://www.annemergmed.com). Once published, the researchers tracked any trials for which protocols were available but remained unreported and subsequently included these. An author (PF) supplemented the search by examining the reference lists of all identified trials and relevant systematic reviews. Two authors (BM and PF) screened abstracts and full-text articles for applicability.

### Eligibility Criteria

Eligible studies comprised randomized controlled trials that compared TXA to placebo. Selected studies were not limited to a specific time frame. Trials were included if they were in a setting where emergency trauma management occurs, such as an emergency department and out-of-hospital settings. Therefore, this review only included studies where the TXA is given in the context of the initial emergency treatment of trauma in the hospital or out-of-hospital setting. Trials had to report (at least) 1-month (28 to 30 days follow-up) mortality or 24-hour mortality. This analysis excluded studies published exclusively as an abstract, and those which did not allow for the assessment of methodological quality (mQ). Furthermore, we excluded studies that reported surgical, obstetric, or other nonemergency inhospital admissions, studies that reported on patients less than 15 years old, and trials that reported results from which it was impossible to extract effect size statistics. Trials on animals were also excluded.

### Data Abstraction

Three authors (CS, BM, and PF) independently conducted a review of each included trial. Two authors (CS and PF) identified and extracted the following characteristics: study and year, inhospital or out-of-hospital setting, dosage and actual timing of TXA and placebo, type of trauma (intracranial or generalized trauma), age range of patients, number of thrombo-embolic events at 1 month and mortality at 1 month or 24 hours. In cases where a trial

only provided relative risk without raw data, we used the baseline death risk to convert this into odds ratios (ORs) for meta-analysis.[11] All authors resolved disagreements in extracted data by arbitration and consensus.

### Methodological Quality Assessment

Researchers quantified the credibility of each randomized controlled trial by assessing its mQ using the MASTER scale to determine the relative probability.[12] Two researchers (CS and FF) rated trials for mQ, and any disagreement was adjudicated by a third person (SD). Interrater agreement was assessed with an intraclass correlation coefficient.[13,14] Analysts used relative study ranks derived from mQ assessment to bias-adjust the meta-analytical estimate as previously described.[15,16] The summary count of the safeguards is on a numerical scale, and we did not set thresholds for high- and low-quality studies because stratifying studies by mQ should be avoided, as it may introduce selection bias into the systematic review.[17]

### Analysis

The primary outcome was 1-month mortality, defined as the number of patients who received a trial drug and died at 28 or 30 days. The secondary outcomes included 24-hour mortality and vascular occlusive events at 1 month, including all or any of the following events: myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. The researchers computed all outcome estimates of effect as ORs in the meta-analysis, as synthesizing relative risks has questionable utility.[11,18] The meta-analysis of relative risk presents problems because it varies for reasons beyond the magnitude of the effect, as it is a ratio of 2 posterior probabilities, both dependent on the baseline prevalence of an outcome.[11] Furthermore, relative risk shifts toward its null value with increasing outcome prevalence.[11] For these reasons we report pooled results as OR. To calculate the number needed to treat, the analyst used a specified baseline risk and the pooled OR.[11]

Heterogeneity was considered present when $I^2$ exceeded 50% or when the value of $\tau^2$ was $> 0$. The authors considered mQ of the included trials, which is one of the key contributors to systematic error-related heterogeneity, in addition to random error (the variance of the study estimate) through the use of Doi and Thalib's[19] quality-effects model for bias adjustment.[19-21] Simulation studies have shown that this method outperforms other meta-analytic estimators.[19,22-24] This estimator resolves several problems inherent in the use of random effects model estimators in meta-analysis, including estimates that may not always be conservative, confidence intervals (CIs) being too narrow resulting in spuriously overconfident results, and exacerbation of small study effects.[23,25-28]

In this report, the results sections provide CIs and interpret them as either indicating no, weak, moderate, strong, or very strong evidence for a certain finding or effect. This interpretation depends on approximate ranges within which the actual *P* value falls, following the reasoning of Muff et al.[29] Additionally, publication bias was examined visually using Doi plots and the Luis Furuya-Kanamori index that allow interpretation for meta-analysis with fewer than 10 studies, the minimum now being 5.[14,30] The Doi plot uses a folded variant of the normal quantile-versus-effect plot to assess study asymmetry, where a symmetrical triangle is created with a z-score close to 0 at its peak. If the studies in the analysis are asymmetric in effect size, then this implies that small study effects and related biases may have affected the pooled effect estimate.[14] The Luis Furuya-Kanamori index quantifies the level of asymmetry of the Doi plot and indicates no asymmetry if within $\pm 1$ unit. Values that are more extreme than $\pm 1$ unit imply asymmetry, but only if the asymmetry is in the same direction as the *a priori* judgment of the direction of suspected bias.[30]

This analysis used Stata version 18 (Stata Corp, College Station, Texas, USA), employing the *metan* and *doiplot* commands to implement the quality-effects model and assess publication bias, respectively. This review reported statistical significance in terms of the strength of evidence against the model hypothesis (which is the null hypothesis of the relevant study or meta-analysis). Although not explicitly stated in the text, this assessment is specific to the sample size of the relevant study or meta-analysis.[29]

## RESULTS

### Identification of Trials

The literature search identified 363 articles. After abstract screening and duplicate removal, 7 trials were included in the systematic review and meta-analysis (Figure 1). The Table shows the study characteristics of included trials.

### Characteristics of Included Trials

The 7 trials included were all randomized and double blinded (Table). Of the 7 trials, 3 were conducted in the out-of-hospital setting, and none included pediatrics (children). Three studies were on general trauma, and 4 focused on traumatic brain injury. Only 2 trials had TXA (or placebo) administered more than 3 hours from injury, and TXA doses aligned with the dosing schedule from the

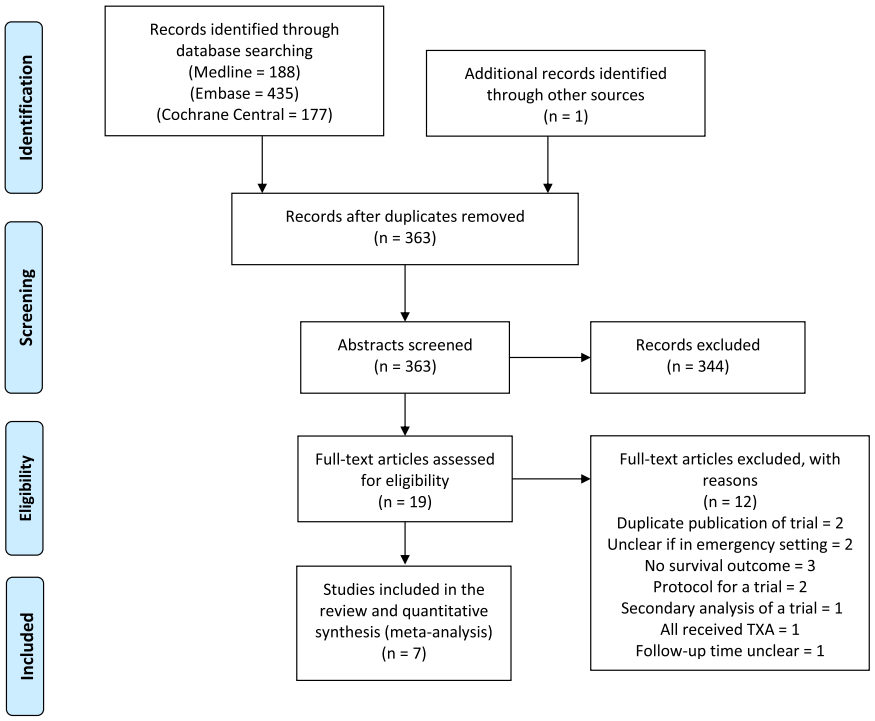


**Figure 1.** Study selection flow diagram. *TXA*, tranexamic acid.

Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) study (1 g bolus initially, with mostly 1 g infusion doses thereafter).[31]

## Study Quality

Two reviewers rated each trial for mQ, and the average intraclass correlation coefficient for agreement between the 2 raters was 0.90 (95% CI 0.40 to 0.98), indicating a high level of agreement when considering both raters as a group. The mQ of the included trials was mostly very similar and of higher quality, with the Chakroun-Walha trial scoring the lowest (Table). Some safeguard items consistently emerged as problematic across trials. The safeguard assessing if the analyst was blinded was notably prominent, obtaining the highest number of 0 ratings. Adjustments in exposure or poststudy commencement withdrawals also often raised concerns. Additionally, aspects concerning caregiver blinding, participant random allocation, and the thoroughness of the randomization process were occasionally highlighted as possible shortcomings.

## Main Results

***One-month and 24-hour mortality.*** A bias-adjusted meta-analysis of all trials that report 1-month mortality yielded an estimated effect that suggested moderate benefit for TXA (OR 0.89) with strong evidence (95% CI, 0.84 to 0.95) against the model hypothesis and very little heterogeneity (Figure 2). For a baseline risk for 1-month mortality of 18%, the risk difference (derived from the pooled OR) is −1.7% (95% CI 0.7% to 2.4%) and the number needed to treat with TXA to prevent 1 additional death at 1 month is 61 patients (95% CI 42 to 135). There was no evidence of asymmetry to suggest publication bias for studies that report 1-month mortality, with a largely symmetrical Doi plot and a Luis Furuya-Kanamori index of -0.63 (Figure E1, available at http://www.annemergmed.com). A synthesis of the 4 trials that report 24-hour mortality also found that TXA administration had a similar moderate benefit (OR 0.76) with strong evidence (95% CI 0.65 to 0.88) against the model hypothesis and very little heterogeneity (Figure E2, available at http://www.annemergmed.com).

***Vascular occlusive events.*** A pooling of trial estimates did not demonstrate evidence of an increase in vascular occlusive events (OR 0.96, 95% CI 0.73 to 1.27); however, there was substantial heterogeneity (Figure E3, available at http://www.annemergmed.com).

## Subgroups

***Timing of TXA administration.*** There were insufficient studies reporting TXA administration at more than 3 hours to permit meta-analysis for the main outcome. Even so, the CRASH-2 trial shows a 11% reduced risk of death for general trauma patients having received TXA less than 3 hours

**Table.** Description of tranexamic acid trials.

| Study | Description of Study (Trial Design and Important Inclusion Criteria) | Location | Indication | Age Range | TXA Dosage | Timing of Study Drugs | Total Number of Patients in Intention to Treat Population for Stated Main Outcome (TXA vs Placebo) | Methodological Quality (Out of Possible Total of 36) |
|---|---|---|---|---|---|---|---|---|
| PATCH 2023[9] | Multicenter double-blinded randomized controlled trial of adult patients with general trauma with coagulopathy (severe trauma score $\geq$ 3) | Out-of-hospital | General trauma | 18 years or older | 1 g over 10 min then infusion of 1 g over 8 h | < 3 hours | 1,300 (657 vs 643) | 34 |
| Guyette 2020[33] | Multicenter, double-blind superiority randomized controlled trial of general trauma with out-of-hospital hypotension (SBP < 90 mmHg) or tachycardia (heart rate > 110/min) | Out-of-hospital | General trauma | 18 to 90 years | 1 g over 10 min then infusion of either 1 g, 2 g, or 3 g over 8 hours | < 3 hours | 903 (447 vs 456) | 34 |
| Rowell 2020[37] | Multicenter, double-blinded randomized controlled trial in patients with moderate or severe TBI with a GCS of 12 or less and systolic blood pressure of 90 mmHg or higher | Out-of-hospital | Traumatic brain injury | 15 years or older | 1 g or 2 g over 10 min then infusion of 1 g or placebo over 8 h | < 3 hours | 966 (657 vs 309) | 33 |
| CRASH-3 2019[32] | Multicenter, double-blinded randomized controlled trial in adults with TBI within 3 hours of injury with a GCS score of 12 or lower or any intracranial bleeding on CT scan, and no major extracranial bleeding | Inhospital | Traumatic brain injury | 16 years or older | 1 g over 10 min then infusion of 1 g over 8 h | | 9,127 (4,613 vs 4,514) | 34 |

**Table.** Continued.

| Study | Description of Study (Trial Design and Important Inclusion Criteria) | Location | Indication | Age Range | TXA Dosage | Timing of Study Drugs | Total Number of Patients in Intention to Treat Population for Stated Main Outcome (TXA vs Placebo) | Methodological Quality (Out of Possible Total of 36) |
|---|---|---|---|---|---|---|---|---|
| Chakroun-Walha 2019[38] | Single center, double-blinded randomized controlled trial of TBI diagnosed in the first or the second brain CT scan and with a delay of management in the study center under 24 h and no major extracranial bleeding | Inhospital | Traumatic brain injury | 18 years or older | 1 g over 10 min then infusion of 1 g over 8 h | > 3 hours | 180 (96 vs 84) | 29 |
| Yutthakasemsunt 2013[39] | Single center, double-blinded randomized controlled trial in moderate to severe TBI (post-resuscitation GCS 4 to 12), CT brain scan within 8 hours of injury and with no immediate indication for surgery | Inhospital | Traumatic brain injury | 16 years or older | 1 g over 30 min then infusion of 1 g over 8 h | > 3 hours | 229 (115 vs 114) | 34 |
| CRASH-2 2010[31] | Multicenter, double-blinded randomized controlled trial in trauma patients with significant hemorrhage (SBP < 90 mmHg or heart rate >110 beats per min, or both) or who were at risk of significant hemorrhage and who were within 8 h of injury | Inhospital | General trauma | 16 years or older | 1 g over 10 min then infusion of 1 g over 8 h | < 3 hours | 20,127 (10,060 vs 10,067) | 34 |

*CI*, confidence interval; *CT*, computed tomography; *SBP*, systolic blood pressure; *TBI*, traumatic brain injury; *GCS*, Glascow Coma Score; *TXA*, tranexamic acid.

compared to those administered TXA at more than 3 hours (OR 0.89, 95% CI 0.78 to 1.00). In the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 3 (CRASH-3) trial on traumatic brain injury, a regression model indicated that early treatment was significantly more effective for patients with mild and moderate head injuries than later treatment.[32] However, the time to treatment did not significantly affect patients with severe head injuries. One trial revealed that 30-day mortality was lower when TXA was administered within 1 hour of injury compared to more than 1 hour (4.6% versus 7.6%; difference -3.0%; 95% CI −5.7% to−0.3%; $P < .002$).[33]

***Traumatic brain injury versus all other trauma.*** A meta-analysis of traumatic brain injury shows that in traumatic brain injury the odds of death at 1 month is 8% less for TXA compared to placebo (OR 0.92) though with weak evidence (95% CI 0.84 to 1.02) against the model hypothesis at this sample size (Figure 3). For a baseline risk of a 1-month mortality of 20%, the risk difference is −1.3% (95% CI 0.3% to 2.8%), and the number needed to treat with TXA is 78 patients (95% CI 36 to 317). The benefit of TXA in the setting of general trauma (that includes some traumatic brain injury) is similar (OR 0.88) to that noted exclusively for traumatic brain injury but with stronger evidence against the model hypothesis (95% CI 0.82 to 0.94). For a baseline risk of a 1-month mortality of 16%, the risk difference is −1.7% (95% CI −0.7% to 2.5%), and the number needed to treat with TXA is 61 patients (95% CI 40 to 147). Low heterogeneity is apparent in both subgroups.

***Out-of-hospital versus inhospital.*** The pooled estimates from trials of out-of-hospital TXA shows that the odds of death are 22% less compared to placebo (OR 0.78, 95% CI 0.64 to 0.95) (Figure 4). For a baseline risk of a 1-month mortality of 17%, the risk difference is -3.1% (95% CI −0.7% to 5.1%), and the number needed to treat with TXA is 33 patients (95% CI 20 to 148).The odds of death for inhospital trials are 9% less for TXA compared to placebo (OR 0.91, 95% CI, 0.85 to 0.96). For a baseline risk of a 1-month mortality of 20%, the risk difference is −1.4% (95% CI −0.6% to 2.4%), and the number needed to treat with TXA is 70 patients (95% CI 42 to 159). This analysis showed low heterogeneity in these 2 subgroups.

***Glasgow Coma Scale.*** Insufficient studies reported comparison of groups defined by the Glasgow Coma Scale (GCS) for pooling estimates. The CRASH-2 trial shows that TXA was associated with more pronounced reduction in all-cause mortality with mild and moderate reductions in GCS (OR 0.89, 95% CI 0.72 to 1.08) and (OR 0.90, 95% CI 0.79 to 1.03) compared to severe reductions (OR 0.97, 95% CI 0.92 to 1.02); however, in all cases, there was little strength of evidence against the model hypothesis.[31] Similarly, the CRASH-3 trial demonstrated that mild to moderate reductions in GCS had lower mortality with TXA (OR 0.79, 95% CI 0.66 to 0.95) compared to severe reductions in GCS (OR 0.99, 95% CI 0.94 to 1.04).[32] The Pre-hospital Antifibrinolytics for Traumatic Coagulopathy and Hemorrhage (PATCH) trial reported on the effect of GCS on outcomes, but only for survival with favorable neurologic outcome, and these data are not reported here.

***Blunt versus penetrating trauma.*** A meta-analysis of blunt versus penetrating trauma was not possible to conduct due to insufficient reporting. However, the CRASH-2 trial showed that TXA was associated with some improvement in all-cause mortality in penetrating trauma (OR 0.87, 95% CI 0.74 to 1.03) and blunt trauma (OR 0.93, 95% CI 0.86 to 1.02) although there was moderate to weak evidence against the model hypothesis in both cases.

## DISCUSSION

This systematic review of randomized trials demonstrated that patients receiving TXA had an 11% reduction in odds of death at 1 month than those of patients receiving placebo. When expressed as a difference in the risk of death at 1 month, the treated group would experience 1.7% fewer trauma deaths compared to the placebo group, resulting in 1 less death for every 61 patients treated with TXA. Despite the relatively small improvement, clinicians may consider even a slight enhancement to be significant from a clinical perspective, especially in patients with severe injuries, such as trauma and brain injuries. Some have argued that the use of TXA in trauma could potentially save around 100,000 lives annually worldwide.[34] Not only was 1-month mortality lower for the TXA arms of included trials, but reduced mortality at 24 hours is also apparent for TXA. These findings are consistent with previous meta-analyses and add to the growing body of evidence supporting the use of TXA in lowering mortality in patients with traumatic bleeding.[6,7]

This evidence synthesis primarily focuses on 1-month mortality as it is the most frequently reported outcome in TXA trials. Nevertheless, one could argue that measuring the quality of survival is preferable to exclusively assessing survival. To that end, the recently concluded PATCH trial measured survival with a favorable functional outcome at 6 months as a primary outcome. Surprisingly, the trial found no difference between TXA and placebo despite lower mortality at 24 hours, 1 month, and 6 months.[9] An editorial on the PATCH trial argued that for this group of

severely injured patients, it would not be surprising if patients saved by TXA treatment were incapacitated at 6 months, as these severely injured patients had disabling injuries, which are unlikely reversible with TXA.[35] Thus, uncertainty persists regarding whether the significant short-term advantages identified in this synthesis genuinely translate into meaningful benefits for patients. This raises additional ethical concerns often associated with interventions in cohorts of critically ill patients with high mortality rates.

To our knowledge, this analysis represents the most up-to-date meta-analysis of randomized trials in the out-of-hospital and emergency inhospital setting, as it incorporates the most recently published trials. Including randomized trials and using the OR effect size likely contributes to the homogeneity of effect sizes in this analysis and enhances the robustness of the pooled estimates. In a recent meta-analysis of TXA studies that included both randomized trials and observational studies, researchers identified a 17% reduction in relative risk in 1-month mortality. However, this reduction was accompanied by considerable heterogeneity in effect sizes.[6] We attribute the relatively modest effect found in this analysis to several factors, including the choice of effect size, the choice of model, and the low heterogeneity among the pooled trials. Similarly, the pooled estimates in this analysis are probably less biased not only because only randomized trials were included but also because these estimates underwent adjustment to account for the bias resulting from differences in mQ.[36]

One concern about using TXA is the potential risk of vascular occlusive events, such as deep venous thrombosis and pulmonary embolism. Nevertheless, this meta-analysis found limited evidence against the model hypothesis, which posits that the incidence of vascular occlusive events is similar between the TXA and placebo groups. Differences in the type and number of vascular occlusive events reported by each study may partially account for the significant heterogeneity.

Few studies reporting on some subgroups limited the intended subgroup meta-analyses. Nevertheless, we managed to combine some study estimates for subgroups, including traumatic brain injury versus general trauma and inhospital versus out-of-hospital. This analysis revealed that TXA offered greater benefits in the general trauma setting compared to traumatic brain injury. Karl et al[6] also reported the finding of improved mortality with TXA for patients with multiple injuries, including traumatic brain injury, as opposed to isolated traumatic brain injury in their recent review. Their findings indicated that benefits of TXA were more pronounced when the primary pathological finding was hemorrhage accompanied by clinical signs of shock.[15] Traumatic brain injuries, especially severe traumatic brain injury, have high injury severity and might be less responsive to any treatment, not just TXA.

In studies that investigated TXA for traumatic injuries while considering GCS scores, the CRASH-2 and CRASH-3 trials identified potential improvements in mortality odds among individuals with mild to moderate reductions in GCS. Nevertheless, the effect of TXA on severe reductions in GCS was less conclusive, implying variations in TXA effects depending on the severity of GCS reduction and highlighting the necessity for further research. In contrast, the PATCH trial uncovered a minor improvement in survival along with favorable neurologic outcomes when TXA was administered to patients with GCS scores below 9. Yet, this difference lacked statistical evidence, implying it might have been due to random error. Conversely, patients with GCS scores of 9 or greater did not experience reductions in mortality rates that were substantiated by statistical evidence when treated with TXA compared to placebo. The effect of GCS on mortality related to TXA involves a complex interplay among injury severity, patient physiology, and TXA's mechanism of action, necessitating further research for a comprehensive understanding of these nuances.

Furthermore, TXA appears to be more effective in preventing death in the out-of-hospital setting than in the inhospital setting, suggesting that early administration of TXA, preferably before hospital arrival, may be advisable. When combining out-of-hospital data, the number needed to treat was 33, which is less than half the number needed to treat within the hospital setting. This observation that earlier out-of-hospital administration yields better results than later inhospital administration aligns with the results of the CRASH-2 and CRASH-3 trials, which demonstrated a timing-response effect where early treatment had a more significant effect than later treatment.[31,32] It is interesting to note that although there is a clear pattern of improved mortality with shorter intervals to TXA administration, this pattern was not as apparent in the PATCH trial. In the PATCH trial, the best survival with favorable neurologic outcomes was observed in those who received TXA between 1 and 2 hours in contrast to those who received it in less than 1 hour or after 2 hours. It is unclear why this pattern is observed in the PATCH trial. In these subgroups, it is noteworthy there is large overlap of the CIs; therefore, the evidence against the model hypothesis is not compelling.

### Strengths and Limitations

In this systematic review and meta-analysis, the researchers employed rigorous methods to address bias arising from variations mQ. The credibility of these

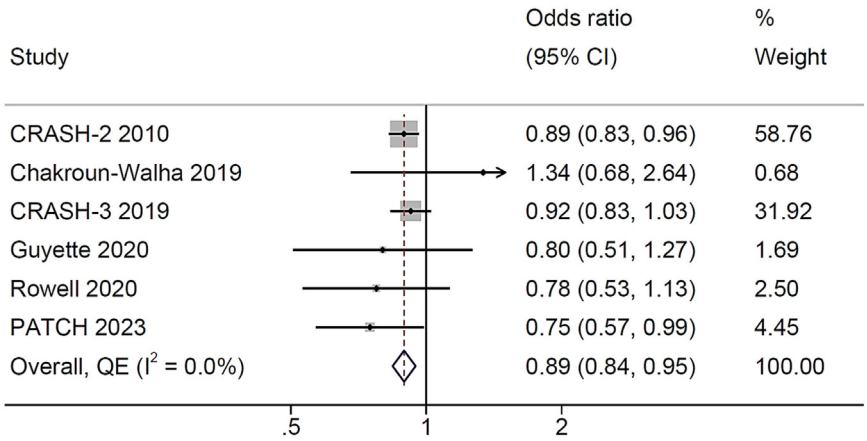


**Figure 2.** Forest plot depicting estimated effects of each trial and the meta-analytic effect. Odd ratios indicate the odds of mortality with tranexamic acid compared to placebo at one month. *CI*, confidence interval.

findings is strengthened by the remarkable homogeneity in estimates, which is further supported by the inclusion of randomized trials. However, a limitation arises from the inability to pool patient-centered outcomes, like favorable neurologic reporting, as the included trials did not report this outcome.

This evidence synthesis shows that early administration of TXA for trauma in the emergency setting leads to modest but perhaps clinically important 24-hour and 1-month mortality, with no evidence of problematic vascular occlusive events. In the out-of-hospital setting, TXA administration is associated with reduced mortality compared to inhospital administration, and the reduction in mortality with TXA is more pronounced in cases of systemic trauma than in cases of traumatic brain injury specifically. Ongoing research efforts should focus on exploring the optimal dosing regimens and identifying patient subgroups that could derive the greatest benefits from TXA treatment. Collaborative initiatives and further trials could strengthen the evidence base, addressing the remaining uncertainties surrounding TXA's efficacy and safety. Ultimately, integrating TXA into trauma care protocols has the potential to save lives for severely injured patients.

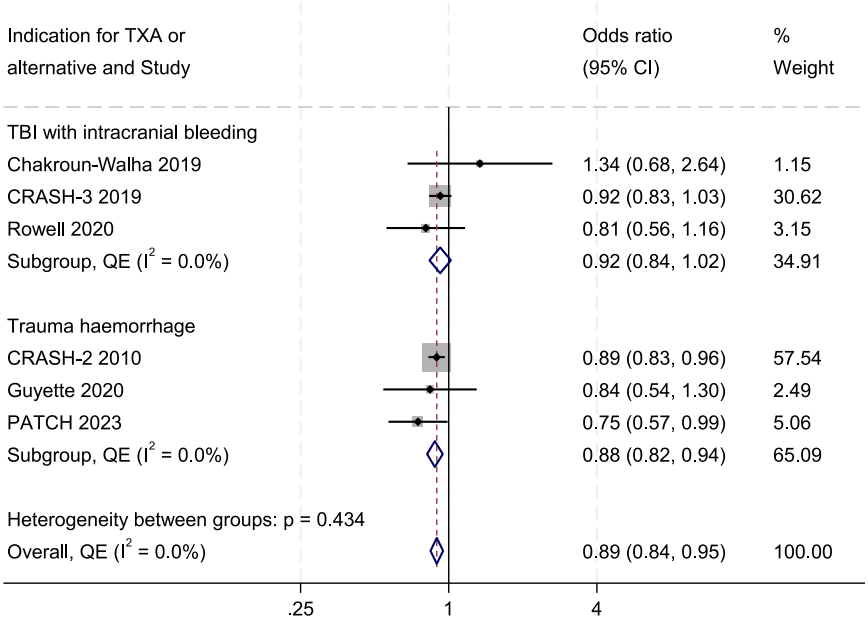


**Figure 3.** Forest plot depicting estimated effects of each trial and the meta-analytic effect. Odd ratios indicate the odds of mortality with tranexamic acid compared to placebo for traumatic brain injury versus general trauma. *CI*, confidence interval; *QE*, quality effect.

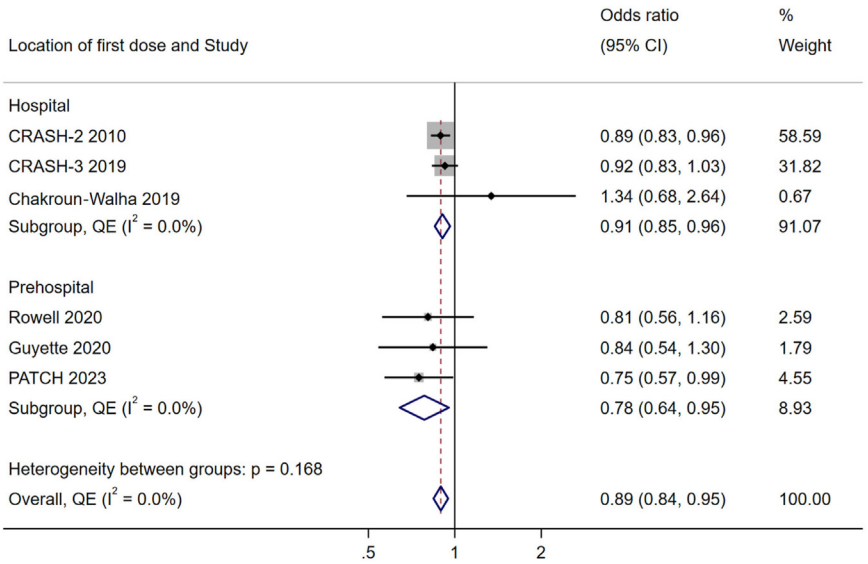


**Figure 4.** Forest plot depicting estimated effects of each trial and the meta-analytic effect. Odd ratios indicate the odds of mortality with tranexamic acid compared to placebo for hospital versus out-of-hospital administration. *CI*, confidence interval; *QE*, quality effect.

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*Author contributions:* PF conceived of the study, PF and BM searched databases, and PF and CS collated all data and rated trials for bias. PF and SD analyzed all data. All authors interpreted results and contributed to the manuscript. PF takes responsibility for the paper as a whole.

*Data sharing statement:* The authors affirm that this systematic review has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All data relevant to the study are included in the article or uploaded as supplementary information. Raw data used during the current study are available from the corresponding author on reasonable request. Any additional materials related to the study can be requested directly from the authors.

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