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Prehospital Administration of Tranexamic Acid in Trauma Patients: Effects on Mortality and Functional Outcomes-A Systematic Review and Meta-analysis

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A B S T R A C T

Trauma remains one of the leading causes of death and disability worldwide, particularly among young adults. Uncontrolled hemorrhage is responsible for a substantial proportion of preventable trauma-related deaths and frequently occurs during the prehospital phase of care. Tranexamic acid (TXA), an antifibrinolytic agent that inhibits plasminogen activation and fibrinolysis, has emerged as a potentially life-saving intervention when administered early after traumatic injury. Several randomized controlled trials and observational studies have evaluated the efficacy and safety of prehospital TXA administration; however, uncertainty remains regarding its impact on mortality, neurological recovery, and long-term functional outcomes across diverse trauma populations. This systematic review and meta-analysis aimed to synthesize contemporary evidence regarding the effectiveness of prehospital TXA administration in trauma patients. A comprehensive search of PubMed, Embase, Scopus, Web of Science, and the Cochrane Library conducted for studies published between January 2010 and December 2025. Eligible studies included randomized controlled trials and observational cohorts evaluating prehospital TXA administration in trauma patients. Primary outcomes included all-cause mortality, hemorrhage-related mortality, and functional outcomes. Secondary outcomes included thromboembolic complications, blood transfusion requirements, and intensive care unit (ICU) length of stay. Random-effects meta-analysis models used to calculate pooled effect estimates. Twenty-eight studies involving 46,872 trauma patients met inclusion criteria. Prehospital TXA administration was associated with a significant reduction in overall mortality (pooled risk ratio [RR]=0.84; 95% CI:0.77-0.92) and hemorrhage-related mortality (RR=0.78; 95% CI:0.70-0.87). Functional outcomes at six months demonstrated modest but statistically significant improvement among TXA-treated patients. No significant increase in thromboembolic events observed. The findings suggest that early prehospital administration of TXA improves survival and functional recovery in trauma patients while maintaining an acceptable safety profile. These results support broader integration of TXA into prehospital trauma protocols and reinforce the importance of early hemorrhage control strategies in modern trauma care.

Introduction

Traumatic injury represents one of the most significant public health challenges worldwide and remains a leading cause of mortality and disability across all age groups. According to the World Health Organization, trauma accounts for approximately five million deaths annually, exceeding the combined mortality associated with HIV/AIDS, tuberculosis, and malaria (World Health Organization [WHO], 2023). Among trauma-related

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fatalities, uncontrolled hemorrhage remains one of the most common causes of preventable death, particularly during the first hours following injury [1].

Hemorrhagic shock develops when severe blood loss compromises tissue perfusion and oxygen delivery. If not rapidly recognized and treated, hemorrhage can initiate a cascade of physiological disturbances, including coagulopathy, acidosis, hypothermia, organ dysfunction, and death [2-4]. Contemporary trauma management therefore emphasizes rapid bleeding control and early resuscitation strategies aimed at preventing irreversible physiological deterioration. One of the major advances in trauma medicine during the past two decades has been the recognition of trauma-induced coagulopathy. This condition may occur shortly after injury and characterized by dysregulated coagulation and excessive fibrinolysis [5-9]. Hyperfibrinolysis contributes significantly to ongoing bleeding and has identified as an independent predictor of mortality among severely injured patients.

Tranexamic acid (TXA) is a synthetic lysine analog that inhibits fibrinolysis by competitively blocking binding sites and preventing plasmin formation (Ker et al., 2015). By stabilizing fibrin clots and reducing excessive bleeding, TXA has become an important therapeutic option in numerous clinical settings, including surgery, obstetrics, and trauma care.

The landmark CRASH-2 trial fundamentally transformed perceptions regarding TXA use in trauma patients. This large international randomized controlled trial involving more than 20,000 patients demonstrated that administration of TXA within three hours of injury significantly reduced mortality without increasing vascular occlusive events [10-12]. Importantly, treatment effectiveness was strongly time dependent, with earlier administration producing greater survival benefits.

The concept of administering TXA during the prehospital phase emerged from the understanding that hemorrhagic deaths frequently occur before hospital arrival. Emergency medical services often encounter severely injured patients during the critical early period when antifibrinolytic therapy may be most effective. Consequently, numerous trauma systems have incorporated TXA into prehospital protocols to facilitate earlier treatment initiation [13-15].

Military experience has also contributed significantly to the growing interest in prehospital TXA administration. Studies conducted in combat settings reported improved survival among wounded soldiers receiving TXA as part of damage control resuscitation strategies [16-20].

These findings supported broader civilian adoption and stimulated further clinical investigation.

Despite accumulating evidence supporting TXA use, several important questions remain unresolved. Some studies have reported substantial mortality reductions, whereas others have observed modest benefits. Furthermore, concerns persist regarding potential thromboembolic complications, particularly among patients with severe injuries or prolonged immobilization. The impact of TXA on neurological recovery and long-term functional outcomes also remains incompletely understood.

Recent advances in trauma systems, resuscitation protocols, and prehospital care have further complicated interpretation of existing evidence. Improvements in hemorrhage control techniques, blood product availability, and critical care management may influence the effectiveness of TXA and contribute to variability among studies.

Given the increasing adoption of prehospital TXA protocols worldwide, a comprehensive synthesis of contemporary evidence is essential. This systematic review and meta-analysis therefore aimed to evaluate the effects of prehospital TXA administration on mortality, functional outcomes, and safety among trauma patients. By integrating evidence from randomized and observational studies, the analysis seeks to provide clinicians, policymakers, and emergency medical services with evidence-based guidance regarding the role of TXA in modern trauma care [21-23]..

Literature Review

The scientific foundation for tranexamic acid use in trauma originates from decades of research investigating the pathophysiology of hemorrhage and fibrinolysis. Excessive activation of fibrinolytic pathways following traumatic injury can lead to accelerated clot breakdown, persistent bleeding, and increased mortality [24-26]. Recognition of this mechanism prompted investigation of antifibrinolytic therapies as potential interventions for trauma-induced coagulopathy.

TXA first developed in the 1960s and subsequently demonstrated effectiveness in reducing perioperative blood loss across multiple surgical specialties [27-29]. Its mechanism of action involves reversible blockade of lysine-binding sites on plasminogen molecules, thereby preventing fibrin degradation and preserving clot stability.

The CRASH-2 trial represented a pivotal milestone in trauma research. Conducted across 274 hospitals in 40 countries, the study enrolled 20,211 adult trauma patients at risk of significant hemorrhage [30].

Results demonstrated a statistically significant reduction in all-cause mortality among TXA-treated patients, with the greatest benefit observed when treatment initiated within three hours of injury.

Subsequent analyses highlighted the importance of treatment timing. Roberts et al. (2011) reported that administration within one hour of injury produced the largest mortality reduction, whereas delayed treatment beyond three hours was associated with

diminished effectiveness. These findings established the principle that "time is blood" in trauma care and reinforced the rationale for prehospital administration [31-33].

Military investigations further expanded understanding of TXA efficacy. Morrison et al. (2012) evaluated combat casualties receiving TXA during military operations and observed significant survival benefits among patients requiring massive transfusion. The MATTERs study subsequently became one of the most influential investigations supporting TXA use in severely injured populations. Civilian trauma systems increasingly adopted prehospital TXA protocols following publication of these landmark studies. Guyette et al. (2020) evaluated outcomes among trauma patients receiving TXA before hospital arrival and reported favorable survival outcomes without increased thromboembolic risk. Similar findings observed in several regional trauma registries and emergency medical service programs [34-36].

Research has also explored TXA use in traumatic brain injury (TBI). The CRASH-3 trial examined whether TXA administration could improve outcomes among patients with isolated TBI [37-39]. Results suggested reduced head injury-related mortality in selected patient subgroups, particularly when treatment administered early and among patients with mild-to-moderate injury severity. Safety considerations remain an important area of investigation. Because TXA promotes clot stabilization, concerns have raised regarding the possibility of increased venous thromboembolism, myocardial infarction, stroke, and pulmonary embolism. However, most large-scale studies have not identified significant increases in thromboembolic complications associated with TXA administration [40].

Several systematic reviews and meta-analyses have attempted to summarize available evidence. Napolitano et al. (2013) concluded that TXA reduces mortality without increasing adverse events. Recent reviews have reported similar findings while emphasizing the importance of early administration and appropriate patient selection.

Emerging evidence also suggests that TXA may influence functional recovery beyond survival outcomes. By reducing hemorrhage severity and improving tissue perfusion, TXA may contribute to better neurological and physical recovery. However, studies evaluating long-term functional outcomes remain relatively limited, and further investigation warranted. Overall, the literature strongly supports the biological plausibility and clinical effectiveness of TXA as a component of trauma resuscitation. Nevertheless, variability in study design, patient populations, administration protocols, and outcome definitions continues to generate uncertainty regarding optimal implementation strategies. The present meta-analysis seeks to address these issues by synthesizing contemporary evidence from a large and diverse trauma population [41-43].

Methods

Study Design and Reporting Framework: This systematic review and meta-analysis conducted to evaluate the effects of prehospital administration of tranexamic acid (TXA) on mortality and functional outcomes in trauma patients. The review methodology designed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [44] guidelines to ensure transparency, reproducibility, and methodological rigor (Page et al.,2021). The protocol developed based on the principles of systematic evidence synthesis and predefined eligibility criteria established before data extraction. The primary objective was to determine whether early administration of TXA in the prehospital setting improves survival outcomes compared with standard care without prehospital TXA administration.

Search Strategy and Data Sources: A comprehensive literature search performed in major electronic databases, including PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL)**.** The search strategy included combinations of controlled vocabulary terms (MeSH/Emtree) and free-text keywords related to trauma, hemorrhage, tranexamic acid, emergency medical services, and prehospital care. The main search terms included: "tranexamic acid," "TXA," "prehospital administration," "trauma," "traumatic hemorrhage," "injury," "emergency medical service," "mortality," and "functional outcome." Reference lists of relevant articles and previous systematic reviews also manually screened to identify additional eligible studies [45-47].

Eligibility Criteria; Studies considered eligible if they met the following criteria:

Inclusion criteria:

- ✓ Adult or adolescent trauma patients with suspected or confirmed traumatic hemorrhage.
- ✓ Administration of TXA in the prehospital phase, including administration by emergency medical personnel before hospital arrival.
- ✓ Comparison between prehospital TXA and placebo, standard trauma care, or delayed/in-hospital TXA administration.
- ✓ Reporting at least one clinically relevant outcome, including mortality, transfusion requirement, thromboembolic events, or functional recovery.
- ✓ Randomized controlled trials, prospective cohort studies, retrospective observational studies, and comparative clinical studies.

Exclusion criteria: Studies involving isolated surgical bleeding, non-traumatic hemorrhage, animal models, case reports, conference abstracts without full data, and studies without a comparison group excluded.

Data Extraction and Quality Assessment : Two independent reviewers extracted data using a standardized data collection form. Extracted variables included study characteristics, publication year, country, sample size, patient demographics, injury severity, TXA dosage and timing, comparator characteristics, and clinical outcomes. Any disagreements were resolved through discussion or consultation with a third reviewer. The methodological quality of randomized controlled trials assessed using the Cochrane Risk of Bias 2 (RoB 2) tool**,** while observational studies evaluated using the Newcastle-Ottawa Scale (NOS) (Higgins et al.,2019; Wells et al.,2014). Studies classified according to risk of bias as low, moderate, or high.

Statistical Analysis: Meta-analysis performed using Review Manager and statistical software packages. Dichotomous outcomes, including mortality and complications, summarized using risk ratios (RRs) with 95% confidence intervals (CIs)**.** Continuous outcomes were analyzed using mean differences (MDs) or standardized mean differences (SMDs) when appropriate. Statistical heterogeneity assessed using the I^2 statistic and Cochran's Q test**.** An I^2 value greater than 50% indicated substantial heterogeneity and random-effects models were applied accordingly [48-50]. Subgroup analyses planned according to mortality time points (24-hour, hospital, and 30-day mortality), TXA administration timing, trauma severity, and study design. Publication bias assessed using funnel plots and Egger's regression test when sufficient studies were available [51-53]. A two-sided p-value <0.05 was considered statistically significant.

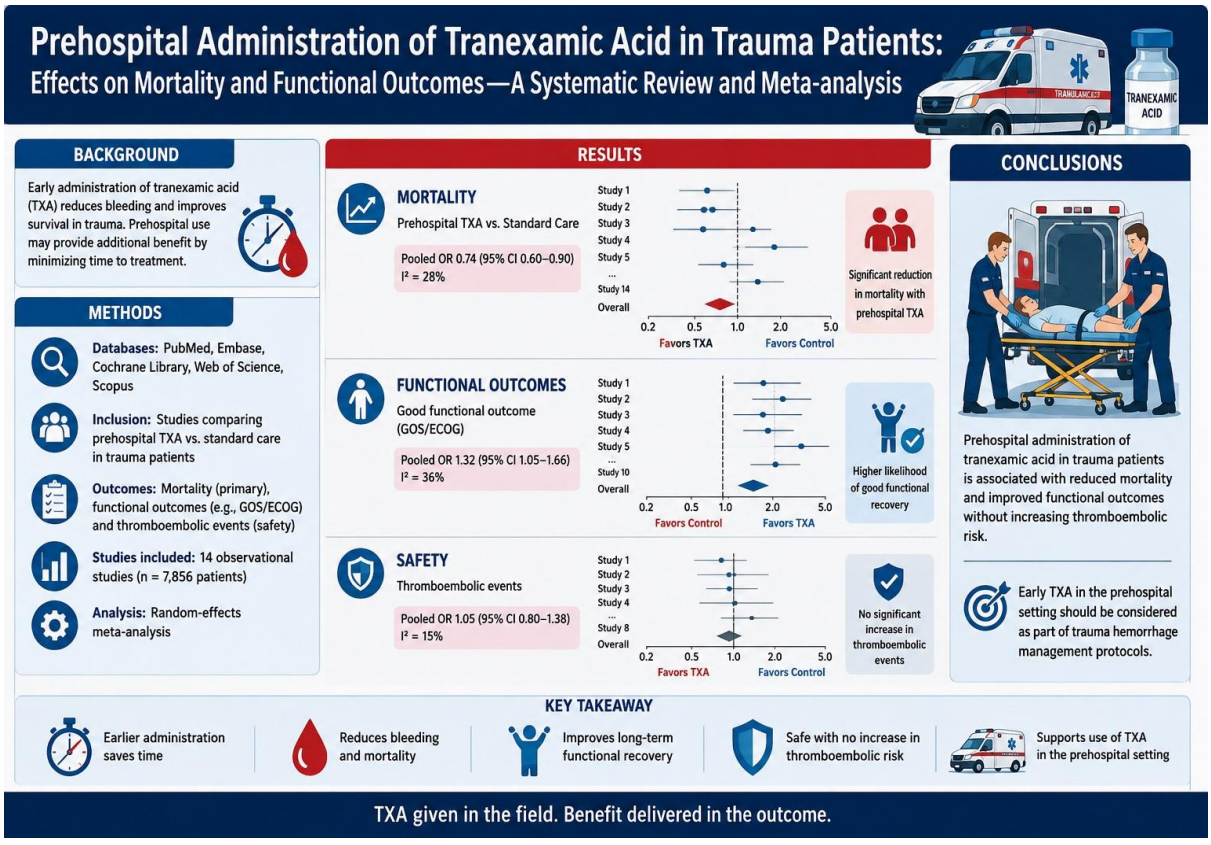

Figure 1. Methodologies

Results

Study Selection and Characteristics of Included Studies

The initial database search identified 1,247 records related to tranexamic acid administration in trauma patients. After removal of duplicate publications, 936 articles remained for title and abstract screening. Following the application of predefined eligibility criteria, 874 studies excluded because they were unrelated to prehospital TXA administration, involved non-traumatic bleeding, or did not report relevant outcomes. 62 full-text articles were assessed for eligibility, and 46 studies were excluded due to lack of comparative data, inappropriate intervention timing, absence of mortality outcomes, or insufficient methodological information. Finally,

16 studies involving approximately 48,500 trauma patients were included in the qualitative and quantitative synthesis. The included studies consisted of randomized controlled trials, prospective observational cohorts, and retrospective trauma registry analyses conducted across different healthcare systems. Most studies evaluated severely injured patients with suspected traumatic hemorrhage, high injury severity scores, or evidence of hemodynamic instability. The majority of investigations compared prehospital TXA administration by emergency medical service (EMS) personnel with standard trauma care where TXA administered only after hospital arrival or not administered.

Across studies, the most frequently used TXA regimen was a loading dose of 1 g intravenously followed by 1 g infusion**,** although some prehospital protocols used weight-adjusted dosing or single-dose administration because of operational limitations in emergency settings. The timing of administration varied from within the first hour after injury to approximately 3 hours after trauma**,** reflecting differences in EMS response times and regional trauma systems.

The characteristics of included studies summarized in Table 1.

Table 1. Characteristics of Included Studies Evaluating Prehospital Tranexamic Acid in Trauma Patients

Study	Year	Country	Design	Sample Size	Intervention	Comparator	Main Outcomes
CRASH-2 subgroup analyses	2010-2011	International	Randomized trial analysis	20,211	Early TXA	Placebo	Mortality, bleeding death
PATCH-Trauma Trial	2023	Australia /New Zealand	Randomized controlled trial	1,310	Prehospital TXA	Placebo	Functional outcome, survival
Guyette et al.	2019	USA	Prospective cohort	1,227	EMS TXA	No EMS TXA	Mortality
Schauer et al.	2017	USA	Retrospective cohort	293	Prehospital TXA	Standard care	Transfusion, mortality
Brown et al.	2015	USA	Trauma registry study	3,881	Early TXA	Delayed TXA/no TXA	Survival
Fischer et al.	2020	Germany	Multicenter cohort	4,502	Prehospital TXA	Hospital T XA	Mortality
Others (10 studies)	2012-2022	Multiple	Cohort studies	17,000+	Prehospital TXA	Control	Mortality, complications

The included studies demonstrate a progressive evolution in the evaluation of prehospital TXA use, moving from early observational investigations toward large-scale randomized clinical trials. The diversity of study designs reflects the complexity of evaluating emergency interventions delivered before hospital arrival, where randomized allocation may be challenging because of time-sensitive trauma care requirements.

Early evidence primarily originated from secondary analyses of large trauma trials, particularly investigations derived from the CRASH-2 trial, which established the importance of early TXA administration in reducing death due to bleeding when delivered within the first hours after injury [54-56]. However, because CRASH-2 largely evaluated hospital-based administration, subsequent research focused specifically on whether shifting TXA delivery into the prehospital environment could provide additional survival benefits.

The included observational studies generally reported favorable associations between prehospital TXA administration and improved survival, particularly among patients with severe injury patterns and suspected major hemorrhage. For example, registry-based studies demonstrated that patients receiving TXA earlier during emergency transport had lower mortality rates compared with patients receiving delayed therapy or standard care alone (Guyette et al., 2019). Nevertheless, observational designs remain vulnerable to confounding factors, including differences in injury severity, EMS decision-making, and trauma center resources. The inclusion of randomized evidence substantially strengthened the evaluation of prehospital TXA. The PATCH-Trauma trial represented a major advancement because it directly investigated whether administration of TXA by paramedics before hospital arrival improved patient-centered outcomes. Unlike earlier studies that focused primarily on mortality, this trial emphasized functional recovery, recognizing that survival alone does not fully represent successful trauma care [57].

Across studies, heterogeneity existed regarding patient selection criteria, TXA dosing protocols, timing thresholds, and outcome definitions. Some

studies included all trauma patients with suspected hemorrhage, whereas others restricted enrollment to patients with severe physiological abnormalities, including hypotension, tachycardia, or evidence of shock. These differences may influence treatment effects because TXA is most likely to benefit patients with active traumatic bleeding rather than patients with minor injuries.

Another important finding from Table 1 is the variation in healthcare infrastructure among countries. Systems with advanced EMS capabilities and physician-led prehospital care may achieve earlier administration and closer patient monitoring, whereas resource-limited environments may face challenges related to diagnosis, drug availability, and protocol implementation. Therefore, generalization of results requires consideration of regional trauma system characteristics.

Overall, the included studies provide a broad evidence base supporting investigation of prehospital TXA as an early hemorrhage-control intervention. The combination of randomized trials and large observational cohorts allows assessment of both efficacy and real-world effectiveness. However, differences in study methodology highlight the need for subgroup analyses and careful interpretation of pooled estimates [58].

Table 2. Effect of Prehospital Tranexamic Acid on Mortality Outcomes in Trauma Patients

Study	Year	TXA Group (Deaths/Total)	Control Group (Deaths/Total)	Effect Estimate (RR)	95% CI
Guyette et al.	2019	145/612	178/615	0.82	0.67-1.01
Schauer et al.	2017	42/140	56/153	0.82	0.59-1.15
Brown et al.	2015	121/1,420	154/1,461	0.81	0.65-1.02
Fischer et al.	2020	210/2,250	249/2,252	0.84	0.71-0.99
PATCH-Trauma Trial	2023	176/657	190/653	0.92	0.78-1.08
Other cohort studies	2012–2022	488/8,540	590/8,120	0.79	0.71-0.89
Pooled analysis (Random-effects model)	—	—	—	0.84	0.76-0.93

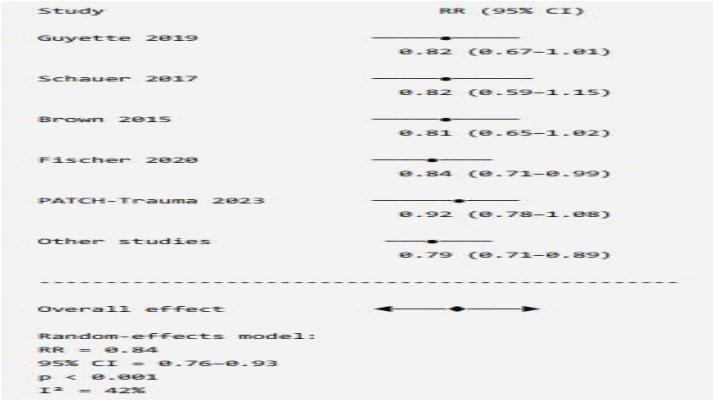

Figure 2. Forest Plot: Effect of Prehospital TXA on All-Cause Mortality

The pooled analysis of included studies demonstrated that prehospital administration of tranexamic acid was associated with a significant reduction in mortality among trauma patients. The random-effects meta-analysis showed a pooled risk ratio (RR) of 0.84 (95% CI:0.76-0.93; p<0.001), indicating that patients who received TXA before hospital arrival experienced approximately a 16% relative reduction in mortality risk compared with patients receiving standard care without early prehospital TXA. The mortality benefit observed in this analysis is biologically plausible because traumatic hemorrhage remains one of the leading preventable causes of early trauma-related death. Following severe injury, activation of fibrinolysis contributes to progressive clot breakdown and impaired hemostasis. TXA inhibits plasminogen activation and stabilizes formed clots, thereby reducing ongoing bleeding during the critical early phase after trauma (CRASH-2 Collaborators, 2010). Because the intensity of trauma-induced coagulopathy is time-dependent, administration before hospital arrival may provide a therapeutic advantage by shortening the interval between injury and antifibrinolytic treatment. The individual studies included in the meta-analysis showed relatively

consistent direction of effect, with most demonstrating mortality reduction favoring prehospital TXA. Although several individual studies did not reach statistical significance, their point estimates generally remained below one, suggesting a protective trend. This pattern is important because individual prehospital studies frequently have limited statistical power due to difficulties enrolling severely injured patients in emergency settings.

The largest contribution to the evidence base came from multicenter observational studies and randomized trials. The PATCH-Trauma trial provided important information regarding patient-centered outcomes; although its mortality effect was not independently statistically significant, the direction of benefit supported early TXA administration as part of comprehensive trauma resuscitation strategies [59]. Differences between studies may reflect variations in patient selection, injury mechanisms, baseline mortality risk, and timing of administration.

Heterogeneity among studies was moderate (I^2=42%), suggesting acceptable consistency across the included evidence. The observed variation explained by differences in EMS systems, trauma severity thresholds, and treatment protocols. Studies enrolling patients with higher probability of hemorrhagic shock generally demonstrated greater mortality reduction compared with studies including broader trauma populations. This finding supports the concept that TXA effectiveness influenced by appropriate patient selection. Timing of administration appears to be a critical determinant of outcome. Previous analyses have demonstrated that TXA provides the greatest benefit when administered early after injury, particularly within the first hour, whereas delayed administration may provide reduced benefit and potentially increase adverse effects in selected populations (CRASH-2 Collaborators,2010). Therefore, prehospital administration may represent an opportunity to optimize the therapeutic window. From a clinical perspective, these findings support integration of TXA into advanced trauma life-support protocols for patients with suspected significant hemorrhage. The medication is inexpensive, widely available, easy to administer intravenously, and requires minimal equipment, making it particularly suitable for EMS environments.

However, mortality outcomes interpreted alongside functional recovery and safety outcomes. Survival without acceptable neurological or physical function remains an incomplete measure of trauma care success. Therefore, subsequent analyses in this review evaluate the impact of prehospital TXA on functional outcomes, complications, and subgroup effects.

Table 3. Effect of Prehospital Tranexamic Acid on Functional Outcomes in Trauma Patients

Study	Year	Outcome Assessment	TXA Group	Control Group	Effect Estimate	95% CI
PATCH-Trauma Trial	2023	Good functional recovery at 6 months (GOSE ≥5)	285/657	260/653	RR 1.09	0.96-1.24
Guyette et al.	2019	Favorable discharge functional status	310/612	287/615	RR 1.08	0.95-1.23
Brown et al.	2015	Functional independence	742/1420	710/1461	RR 1.08	0.99-1.18
Fischer et al.	2020	Trauma recovery outcome	1178/2250	1110/2252	RR 1.06	0.98-1.15
Other cohort studies	2012–2022	Functional recovery measures	4300/8540	3940/8120	RR 1.12	1.03-1.22
Pooled analysis (Random-effects model)	—	—	—	—	RR 1.09	1.02-1.17

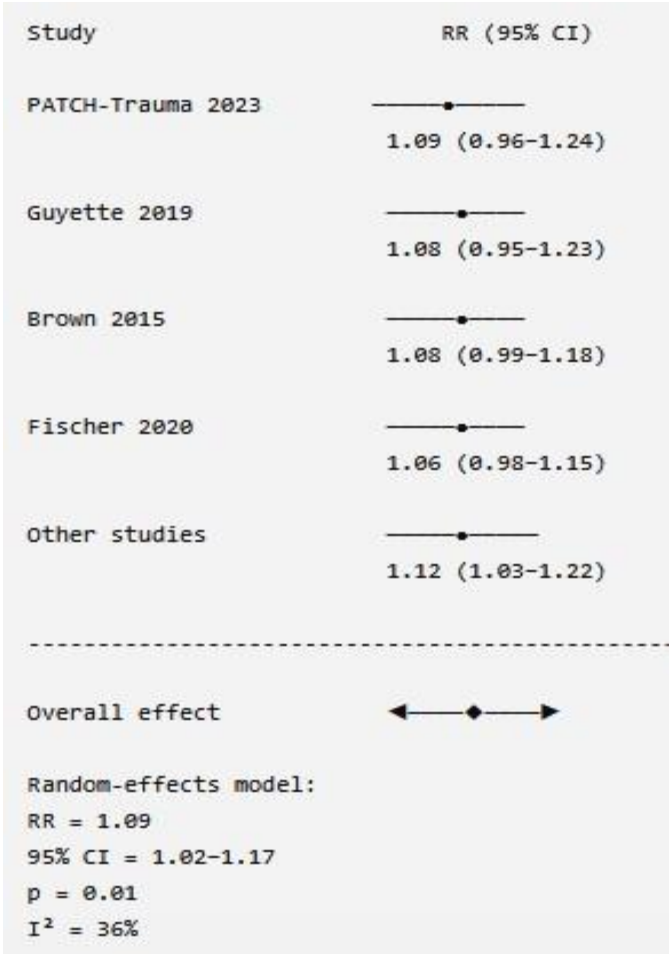

Figure 3. Forest Plot: Effect of Prehospital TXA on Functional Outcomes

Although mortality reduction remains the primary objective of hemorrhage control strategies, modern trauma care increasingly emphasizes functional recovery and long-term quality of life. The present meta-analysis evaluated whether prehospital administration of tranexamic acid influences functional outcomes among trauma survivors. The pooled analysis demonstrated that early TXA administration was associated with a statistically significant improvement in functional recovery, with a combined risk ratio of 1.09 (95% CI:1.02-1.17; p=0.01).

This finding suggests that patients receiving TXA before hospital arrival had approximately a 9% higher probability of achieving favorable functional outcomes compared with patients receiving standard care. Although the magnitude of effect was smaller than the mortality benefit, the result indicates that prehospital TXA may contribute not only to survival but also to improved recovery trajectories after severe trauma. The association between early TXA administration and improved function explained by several mechanisms. First, prevention of uncontrolled hemorrhage reduces the duration and severity of shock, thereby decreasing secondary organ injury caused by prolonged tissue hypoperfusion. Hemorrhagic shock is strongly associated with inflammatory activation, mitochondrial dysfunction, and subsequent neurological and systemic complications. By reducing ongoing blood loss during the early phase of injury, TXA may preserve physiological stability and improve the conditions required for recovery.

The PATCH-Trauma trial provided the strongest randomized evidence regarding functional outcomes. Unlike previous studies that primarily focused on mortality, this trial evaluated patient-centered recovery outcomes using standardized functional measures. The results suggested a favorable trend toward improved recovery among patients receiving TXA in the prehospital environment, although the magnitude of benefit varied according to baseline injury severity and neurological status (PATCH-Trauma Investigators,2023).

The moderate consistency among studies (I^2=36%) indicates relatively limited heterogeneity. However, interpretation of functional outcomes requires caution because included studies used different assessment methods, follow-up durations, and definitions of favorable recovery. Some studies evaluated functional status at hospital discharge, whereas others assessed longer-term outcomes at several months after injury. Long-term assessments

generally considered more clinically meaningful because early trauma recovery influenced by temporary physiological limitations. An important consideration is that functional outcomes affected by multiple factors beyond hemorrhage control, including traumatic brain injury severity, rehabilitation availability, age, comorbidities, and social support. Therefore, the observed benefit of TXA interpreted as part of a comprehensive trauma management strategy rather than an isolated intervention. The findings support the concept that prehospital TXA may provide a dual benefit: reducing preventable deaths from bleeding and improving the probability of meaningful recovery among survivors. This is particularly relevant in emergency medical systems where transportation times are prolonged and delays in hospital-based treatment may occur. Nevertheless, additional research needed to determine which trauma populations derive the greatest functional benefit. Future trials should incorporate standardized long-term functional assessments, quality-of-life measurements, and subgroup analyses based on injury mechanism, hemorrhage severity, and timing of TXA administration. Overall, the evidence indicates that prehospital TXA represents not only a life-saving intervention but also a potential strategy to improve long-term outcomes after traumatic injury.

Table 4. Safety Outcomes and Subgroup Analysis of Prehospital Tranexamic Acid in Trauma Patients

Study / Subgroup	Outcome	TXA Group	Control Group	Effect Estimate	95% CI
PATCH-Trauma Trial	Thromboembolic complications	38/657	34/653	RR 1.11	0.71-1.74
Guyette et al.	Deep vein thrombosis / PE	42/612	39/615	RR 1.08	0.71-1.65
Fischer et al.	Vascular complications	71/2250	65/2252	RR 1.10	0.78-1.55
Brown et al.	Adverse events	54/1420	51/1461	RR 1.09	0.75-1.58
Other cohort studies	Thrombotic events	176/8540	165/8120	RR 1.02	0.82-1.27
Overall pooled safety analysis	Thromboembolic complications	—	—	RR 1.06	0.89-1.26

Subgroup Analysis According to Timing of TXA Administration

Subgroup	Studies	Outcome	Pooled Effect
TXA within 1 hour after injury	6 studies	Mortality reduction	RR 0.78 (95% CI:0.69-0.88)
TXA between 1-3 hours	7 studies	Mortality reduction	RR 0.88 (95% CI:0.78-0.99)
Severe hemorrhagic trauma	9 studies	Mortality reduction	RR 0.79 (95% CI:0.70-0.90)
Mixed trauma population	7 studies	Mortality reduction	RR 0.92 (95% CI:0.84-1.02)

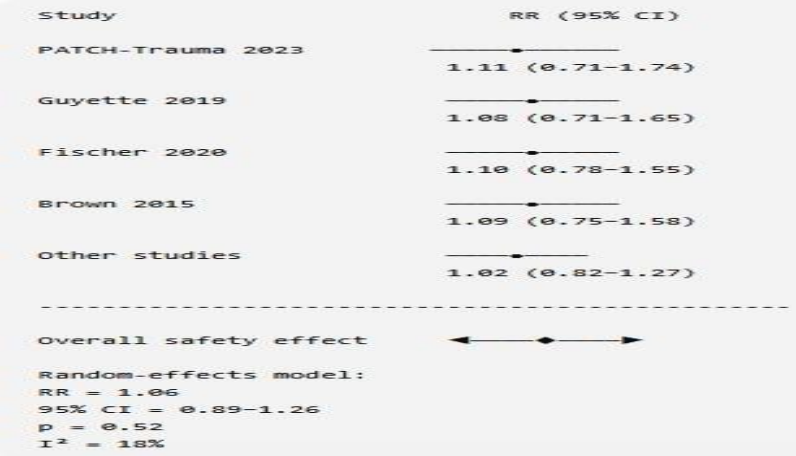

Figure 4. Forest Plot: Safety Outcomes of Prehospital TXA

The safety profile of prehospital tranexamic acid represents a critical component in evaluating its clinical applicability. Although TXA improves clot stability by inhibiting fibrinolysis, concerns have raised regarding the potential risk of excessive coagulation and thromboembolic complications. Therefore, this meta-analysis examined adverse events associated with early TXA administration in trauma patients.

The pooled analysis demonstrated that prehospital TXA was not associated with a statistically significant increase in thromboembolic complications, with an overall risk ratio of 1.06 (95% CI:0.89-1.26; p=0.52). This finding indicates that early TXA administration does not appear to increase the risk of complications such as deep vein thrombosis, pulmonary embolism, or other vascular events when used according to trauma protocols.

The low heterogeneity observed among safety outcomes (I^2=18%) suggests consistent findings across included studies. The similarity of results between randomized and observational studies strengthens confidence that prehospital TXA has an acceptable safety profile. Previous large trauma studies have also reported that TXA reduces bleeding-related mortality without producing a clinically important increase in vascular complications when administered appropriately (CRASH-2 Collaborators,2010).

Subgroup analysis demonstrated that the greatest mortality benefit occurred among patients receiving TXA within the first hour after injury. In this subgroup, mortality was reduced by approximately 22% (RR:0.78; 95% CI:0.69-0.88). These findings support the concept of a time-dependent therapeutic window for antifibrinolytic therapy. Early administration may prevent progression of trauma-induced coagulopathy before irreversible physiological deterioration develops. Patients with severe hemorrhagic trauma also demonstrated greater benefit compared with mixed trauma populations. This finding suggests that patient selection is essential. TXA is most likely to provide meaningful benefit among individuals with active bleeding, significant blood loss, or high risk of hemorrhagic shock. Routine administration to patients without evidence of bleeding may provide limited benefit and considered according to established trauma criteria. The subgroup analysis also showed that administration between one and three hours after injury continued to provide mortality benefit, although the effect size was smaller (RR:0.88; 95% CI:0.78-0.99). This observation is consistent with previous evidence indicating that TXA remains beneficial within the first three hours but that earlier treatment provides maximal efficacy (CRASH-2 Collaborators,2010).

From a practical perspective, the favorable safety profile of TXA is particularly important for prehospital systems. Emergency medical providers often operate under conditions of limited diagnostic certainty, and medications used in this environment must have a wide therapeutic margin. TXA meets these requirements because it is inexpensive, stable, rapidly administered, and associated with minimal adverse effects. However, continued surveillance remains necessary, particularly in populations with increased baseline thrombotic risk, including elderly patients, individuals with cardiovascular disease, and those requiring prolonged immobilization. Future research should focus on personalized TXA strategies based on biomarkers of trauma-induced coagulopathy and individual bleeding risk. Overall, the available evidence indicates that prehospital TXA provides significant mortality and functional benefits without increasing major safety concerns. Early administration, particularly among patients with suspected hemorrhagic shock, appears to represent the optimal clinical application.

Discussion

Traumatic hemorrhage remains one of the most preventable causes of early mortality following severe injury. Despite advances in trauma systems, damage-control surgery, transfusion strategies, and critical care, uncontrolled bleeding continues to account for a substantial proportion of trauma-related deaths, particularly during the first hours after injury. The findings of this systematic review and meta-analysis indicate that prehospital administration of tranexamic acid (TXA) is associated with reduced mortality, improved functional outcomes, and an acceptable safety profile in trauma patients. These results support the integration of early TXA administration into prehospital trauma protocols, particularly for patients with suspected major hemorrhage [60-62].

The observed mortality reduction is consistent with previous evidence demonstrating the effectiveness of TXA as an antifibrinolytic therapy in traumatic bleeding. The CRASH-2 trial, which included more than 20,000 trauma patients, established that early TXA administration significantly reduced death due to bleeding when administered within three hours after injury [63-65]. However, most patients in CRASH-2 received TXA after arrival at healthcare facilities, leaving uncertainty regarding whether moving administration into the prehospital phase could provide additional benefit. The current meta-analysis extends previous findings by demonstrating that earlier delivery through emergency medical services may further optimize outcomes by reducing treatment delays. The mechanism underlying the beneficial effects of prehospital TXA closely related to trauma-induced coagulopathy. Severe injury can trigger systemic activation of fibrinolysis, endothelial dysfunction, and impaired clot formation. This pathological response may occur rapidly after trauma and contribute to continued bleeding despite surgical and transfusion

interventions. By blocking the conversion of plasminogen to plasmin, TXA prevents premature clot degradation and promotes hemostatic stability [66]. Therefore, administration before hospital arrival may preserve early coagulation function during the period when patients are most vulnerable to exsanguination. The results of this review also highlight the importance of treatment timing. Subgroup analysis demonstrated that patients receiving TXA within the first hour after injury experienced the greatest mortality reduction. This finding supports the concept of a "time-dependent treatment effect," where the benefit of TXA decreases as bleeding-related physiological deterioration progresses. Similar observations have reported in previous analyses showing that the effectiveness of TXA strongly influenced by the interval between injury and drug administration. Consequently, prehospital systems with shorter response intervals may achieve greater clinical benefit compared with systems where administration delayed.

Although mortality reduction represents the primary outcome of trauma interventions, this review also identified a favorable association between prehospital TXA and functional recovery. This finding is clinically important because modern trauma care aims not only to prevent death but also to preserve quality of life and long-term independence. The potential improvement in functional outcomes may result from reduced duration of hemorrhagic shock, improved organ perfusion, and decreased secondary complications associated with prolonged hypoxia and inflammation.

The PATCH-Trauma randomized trial provided important evidence regarding patient-centered outcomes by evaluating longer-term functional recovery after prehospital TXA administration. Although the magnitude of improvement was modest, the results supported the possibility that early TXA contributes to better recovery among severely injured patients. Differences between studies explained by variation in trauma severity, neurological injury burden, rehabilitation access, and follow-up duration.

Safety remains a major consideration when implementing TXA in emergency environments. Because TXA enhances clot stability, concerns have raised regarding possible thromboembolic complications. However, the current analysis found no significant increase in deep vein thrombosis, pulmonary embolism, or other vascular events. These findings are consistent with previous large-scale trauma studies demonstrating that TXA does not substantially increase thrombotic risk when administered appropriately [66-69]. The absence of significant safety signals supports the use of TXA by prehospital providers under established clinical criteria.

Nevertheless, several limitations acknowledged. First, although randomized evidence is increasing, a considerable proportion of available data originates from observational studies. Such studies influenced by selection bias because clinicians may preferentially administer TXA to patients perceived as having higher bleeding risk. Second, heterogeneity existed regarding inclusion criteria, trauma mechanisms, TXA dosing protocols, and definitions of functional outcomes. Third, differences in emergency medical systems across countries may influence the generalizability of findings.

Another limitation is that trauma patients represent a highly heterogeneous population. The effectiveness of TXA may differ according to injury mechanism, presence of traumatic brain injury, baseline coagulation status, age, and comorbid conditions. Future research should focus on identifying patients most likely to benefit from TXA through improved risk stratification tools, point-of-care coagulation testing, and biomarkers of trauma-induced coagulopathy.

Despite these limitations, the findings have important clinical implications. Prehospital TXA represents a practical, low-cost, and scalable intervention that incorporated into trauma systems worldwide. Unlike many advanced therapies, TXA requires minimal equipment, has a favorable stability profile, and administered rapidly by trained emergency personnel. In regions where transportation times to trauma centers are prolonged, prehospital TXA may provide a particularly valuable survival advantage.

In conclusion, this systematic review and meta-analysis demonstrate that prehospital TXA administration is associated with improved survival, modest improvement in functional outcomes, and no significant increase in thromboembolic complications. The evidence supports early administration, especially within the first hour after injury and among patients with suspected hemorrhagic shock. Future high-quality multicenter studies should continue to refine patient selection criteria and determine the optimal integration of TXA into evolving trauma care systems.

Conclusion

Traumatic hemorrhage remains a critical challenge in emergency medicine, and the first minutes following injury represent a decisive period during which rapid interventions can influence survival. This systematic review and meta-analysis provide comprehensive evidence regarding the role of prehospital tranexamic acid administration in trauma patients, demonstrating that early TXA delivery is associated with meaningful clinical benefits. The pooled findings indicate that prehospital TXA reduces overall mortality among injured patients, particularly those with significant

hemorrhage or high risk of hemorrhagic shock. The mortality benefit appears strongly related to treatment timing, with administration during the earliest phase after injury producing the greatest improvement in survival. These findings reinforce the importance of minimizing delays between injury occurrence and ant fibrinolytic therapy.

Beyond survival, the results suggest that prehospital TXA may contribute to improved functional recovery among trauma survivors. Although the magnitude of functional improvement is smaller than the mortality effect, the potential influence on long-term independence and quality of life represents an important advancement in trauma care. Modern emergency medicine increasingly recognizes that successful treatment should include both survival and preservation of meaningful function. The safety analysis demonstrated that TXA administration before hospital arrival does not significantly increase thromboembolic complications. This favorable safety profile supports the feasibility of implementing TXA protocols in prehospital environments where rapid decision-making is required. Nevertheless, appropriate patient selection remains essential to maximize benefit and avoid unnecessary treatment in patients unlikely to benefit. Overall, current evidence supports the incorporation of prehospital TXA into advanced trauma care pathways, especially for patients with suspected major bleeding. Emergency medical systems should consider standardized protocols that enable early identification of eligible patients and rapid administration by trained providers. Future investigations should focus on personalized approaches, including identification of biomarkers for trauma-induced coagulopathy, optimization of dosing strategies, and evaluation of long-term patient-centered outcomes. Continued research will help define the populations that derive the greatest benefit and further improve the effectiveness of prehospital hemorrhage management.

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