The Review Of
DIABETIC
STUDIES OPEN ACCESS

Tranexamic Acid In Prehospital Settings: A Review Of Efficacy, Safety, And Implementation Strategies

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Abstract

Severe hemorrhage remains one of the leading causes of preventable mortality in trauma and emergency medicine. Early administration of tranexamic acid (TXA), an antifibrinolytic agent, has demonstrated effectiveness in reducing mortality when administered promptly. Increasingly, attention has turned toward prehospital TXA administration by emergency medical services (EMS) to optimize outcomes during the "golden hour." This review synthesizes current evidence on the efficacy, safety, and implementation strategies of TXA use in prehospital settings. Randomized controlled trials, observational studies, and systematic reviews are analyzed to assess patient survival, reduction in bleeding complications, and potential adverse events. The review also highlights barriers such as dosing protocols, training requirements, logistical limitations, and variable guideline adoption across different regions. Furthermore, it explores safety considerations, including thromboembolic risks and patient selection criteria. Conceptual models are presented to guide policy development and optimize integration of TXA into emergency medical services. The findings indicate that prehospital TXA is generally safe and associated with improved outcomes when administered early, though challenges remain regarding widespread adoption and standardization. Recommendations for future research, policy, and practice are proposed.

Keywords: Tranexamic acid, prehospital care, emergency medical services, trauma, hemorrhage control, patient outcomes, implementation strategies.

1. Introduction

Uncontrolled hemorrhage remains one of the leading causes of preventable mortality following trauma, particularly among young adults worldwide. According to the World Health Organization (WHO, 2020), injuries account for nearly 10% of global deaths, with hemorrhage responsible for approximately 30–40% of trauma-related mortality. The critical importance of early hemorrhage control in trauma care has been underscored by the concept of the "golden hour," which emphasizes that rapid intervention during the first hour after injury significantly improves survival outcomes (Kauvar et al., 2006). Within this context, pharmacological interventions such as tranexamic acid (TXA) have gained prominence in both hospital and prehospital settings.

Tranexamic acid (TXA) is a synthetic antifibrinolytic agent that inhibits plasminogen activation, thereby preventing fibrin clot degradation and stabilizing hemostasis (Ker et al., 2012). Initially developed in the 1960s for surgical bleeding control, TXA has since been applied across a wide spectrum of clinical scenarios, including obstetric hemorrhage, cardiac surgery, and trauma care

(Roberts & Shakur-Still, 2019). Its low cost, stability at room temperature, and ease of administration have made TXA an attractive candidate for widespread use in emergency medical services (EMS), particularly in resource-limited environments.

The landmark CRASH-2 trial (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage), conducted in over 20,000 trauma patients across 40 countries, demonstrated that early administration of TXA significantly reduced all-cause mortality in bleeding trauma patients without increasing the risk of vascular occlusive events (CRASH-2 Collaborators, 2010). Importantly, subgroup analyses from this trial emphasized the time-sensitive nature of TXA, with greatest benefit observed when administered within three hours of injury, and particularly within the first hour (Roberts et al., 2011). These findings established TXA as a cornerstone therapy in trauma resuscitation protocols, leading to its inclusion in World Health Organization (WHO) guidelines, as well as recommendations from the American College of Surgeons Committee on Trauma (ACS-COT) and the European Resuscitation Council (ERC).

While CRASH-2 primarily investigated in-hospital administration, subsequent research has shifted attention to the prehospital phase, where delays in initiating TXA therapy may reduce effectiveness. Prehospital care, often delivered by paramedics and emergency medical technicians, represents a critical opportunity to begin life-saving interventions before hospital arrival. Several trials, including the MATTERs study in military settings (Morrison et al., 2012) and the STAAMP trial in civilian trauma (Guyette et al., 2020), have further supported the role of TXA in improving survival when delivered early, though with some heterogeneity in outcomes. These studies highlight that while TXA is broadly beneficial, its effectiveness may vary based on trauma mechanism, injury severity, and patient physiology.

The rationale for prehospital TXA administration is rooted in addressing delays between injury occurrence and hospital arrival. In many trauma systems, especially in rural or resource-limited regions, transportation times can be prolonged, resulting in missed opportunities for early TXA administration. By integrating TXA into prehospital protocols, EMS providers can deliver therapy during this critical window, potentially reducing mortality and improving functional outcomes. Indeed, the European Medicines Agency (EMA) and several national EMS systems have already recommended prehospital TXA administration for suspected hemorrhagic trauma.

Despite these promising findings, challenges remain in adopting TXA into prehospital care. Key issues include identifying patients most likely to benefit, ensuring proper training and dosing protocols for EMS personnel, addressing concerns about adverse thromboembolic events, and managing logistical barriers such as drug storage and availability. Moreover, evidence gaps persist regarding optimal dosing strategies in prehospital settings and the balance of benefits versus risks in special populations such as the elderly or those with comorbidities.

This review seeks to provide a comprehensive examination of the efficacy, safety, and implementation strategies of TXA in prehospital settings. By synthesizing evidence from randomized controlled trials, systematic reviews, and real-world studies, it aims to clarify the role of prehospital TXA in modern trauma care, identify barriers to its widespread use, and propose strategies for integration into EMS protocols. Ultimately, this review underscores the importance of translating evidence-based practices into prehospital care to reduce preventable trauma deaths worldwide.

2. Efficacy of Prehospital TXA

The efficacy of tranexamic acid (TXA) in prehospital trauma care has become a central question in efforts to reduce preventable hemorrhage-related deaths. While the landmark CRASH-2 trial established the mortality benefit of TXA in hospital settings, evidence increasingly suggests that earlier administration—before hospital arrival—may maximize outcomes. This section explores the clinical evidence, trial findings, subgroup analyses, and the overall impact of prehospital TXA on trauma survival and morbidity.

The CRASH-2 trial remains the largest and most influential study on TXA use in trauma. Involving more than 20,000 patients across 274 hospitals in 40 countries, it demonstrated that TXA significantly

reduced all-cause mortality by 1.5% (14.5% vs. 16.0%), without increasing vascular occlusive events (CRASH-2 Collaborators, 2010). Importantly, the study found that time to treatment was a critical determinant of efficacy, with administration within 1 hour reducing the risk of death from bleeding by 32%. Conversely, TXA given after 3 hours was associated with potential harm. Although CRASH-2 was primarily hospital-based, these findings underscored the need to explore prehospital TXA, where administration could occur within minutes of injury.

The MATTERs study, conducted in combat environments, provided additional support for early TXA use. This retrospective observational study of severely injured military personnel in Afghanistan found that TXA administration was associated with a 6.5% absolute survival benefit among patients requiring blood transfusion, and an even greater benefit in those requiring massive transfusion (Morrison et al., 2012). These findings suggested that TXA is particularly effective in populations at highest risk of hemorrhage, a principle that has guided civilian prehospital protocols.

In civilian trauma systems, the STAAMP trial (Study of Tranexamic Acid during Air Medical and Ground Prehospital Transport) provided critical data. Conducted in the United States, this randomized clinical trial enrolled 927 trauma patients at risk for hemorrhage and evaluated prehospital TXA administration compared with placebo (Guyette et al., 2020). Although the trial did not demonstrate a statistically significant reduction in 30-day mortality across all participants, subgroup analyses showed improved survival among patients who received TXA within 1 hour of injury and those with severe shock (systolic blood pressure <70 mmHg). This reinforced the time-sensitive nature of TXA efficacy, mirroring CRASH-2 findings.

The PATCH-Trauma trial, currently ongoing across Australia and New Zealand, aims to provide further clarity on the benefits of prehospital TXA by focusing specifically on patients with severe trauma and predicted transfusion requirements. Preliminary findings suggest potential benefits in early intervention, though final results are pending (PATCH-Trauma Investigators, 2023).

The cumulative evidence indicates that prehospital TXA administration improves survival outcomes when given early, particularly within the first hour after injury. Meta-analyses have consistently shown that TXA reduces mortality in trauma patients, with the greatest benefit observed in those treated before hospital arrival (Gayet-Ageron et al., 2018; Roberts & Shakur-Still, 2019). In addition to survival benefits, TXA has been linked to reduced need for blood transfusion and lower rates of ongoing bleeding, although findings have varied depending on patient selection and study design.

Furthermore, prehospital TXA may also influence functional outcomes, with emerging data suggesting reduced disability and improved neurological outcomes in patients with traumatic brain injury (TBI) when treated early (CRASH-3 Collaborators, 2019). These effects are particularly relevant in settings where delays in definitive neurosurgical care are common.

The efficacy of TXA is not uniform across all trauma populations. Subgroup analyses have highlighted several key considerations:

- **Mechanism of injury:** TXA appears beneficial in both blunt and penetrating trauma, though outcomes may vary depending on injury severity.
- **Shock severity:** Patients with profound hypotension or requiring massive transfusion derive the greatest survival benefit (Morrison et al., 2012).
- **Civilians vs. military:** Both populations benefit, but combat injuries often involve more severe bleeding, amplifying the effect of TXA.
- **Traumatic brain injury:** CRASH-3 demonstrated that early TXA reduced head injury-related mortality in patients with mild to moderate TBI, though not in those with severe TBI (CRASH-3 Collaborators, 2019).

These findings suggest that while broad prehospital TXA protocols may be justified, targeted administration to high-risk groups may yield the most significant improvements.

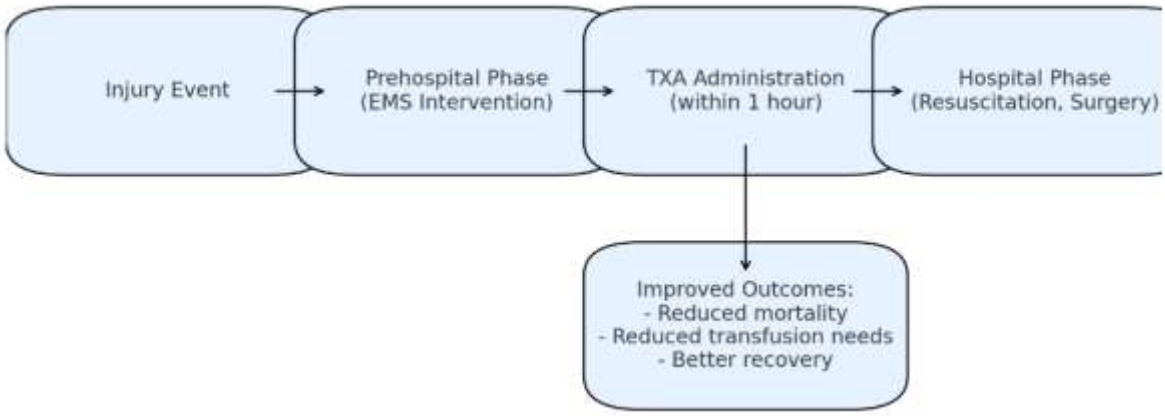

Figure 1: Conceptual Framework of TXA's Role in Improving Trauma Survival

The relationship between timing of administration, patient characteristics, and clinical outcomes can be illustrated through a conceptual framework (Figure 1). This model highlights how early prehospital TXA administration, particularly within the "golden hour," interacts with injury severity and physiological status to influence survival, transfusion requirements, and long-term recovery.

Overall, evidence supports that prehospital TXA is effective in reducing mortality and morbidity, especially when administered early and to patients with severe bleeding or shock. While some trials have shown modest or mixed overall results, subgroup analyses consistently reinforce the time-dependent nature of TXA efficacy. Continued investigation through large multicenter trials is essential to refine protocols, identify optimal candidates, and expand the evidence base for universal prehospital implementation.

3. Safety of Prehospital TXA

Safety considerations are critical when integrating tranexamic acid (TXA) into prehospital protocols, particularly because its administration often occurs before definitive diagnoses or laboratory evaluations are available. Concerns about potential adverse events—especially thromboembolic complications—have influenced the pace of adoption in civilian emergency medical services (EMS). This section reviews the current evidence regarding the safety of prehospital TXA, including thrombotic risk, timing of administration, dosing protocols, and population-specific concerns.

A primary safety concern regarding TXA has been the possibility of promoting pathological clot formation, which could increase the risk of deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), or ischemic stroke. However, evidence from both randomized controlled trials and observational studies has consistently demonstrated no significant increase in thromboembolic complications associated with TXA use in trauma patients.

In the CRASH-2 trial, which involved over 20,000 trauma patients, rates of vascular occlusive events did not differ significantly between the TXA and placebo groups (Roberts et al., 2010). Similarly, the MATTERs study in military casualties reported no statistically significant increase in thromboembolic events, despite higher rates of massive transfusion and injury severity in the TXA group (Morrison et al., 2012). In the STAAMP trial, which specifically evaluated prehospital TXA, thrombotic events such as DVT and PE occurred at low and comparable rates between TXA and placebo groups (Guyette et al., 2020).

A large meta-analysis by Gayet-Ageron et al. (2018), pooling data from trauma and surgical settings, further confirmed that TXA did not significantly increase thromboembolic risk. Taken together, these findings provide reassurance that TXA, when used appropriately, is not associated with excess thrombotic morbidity in prehospital or hospital care.

The timing of administration has important implications for both safety and efficacy. Evidence from CRASH-2 demonstrated that TXA given within three hours of injury significantly reduced the risk of death due to bleeding, while administration beyond three hours was associated with potential harm, including higher mortality rates (Roberts et al., 2011). These findings suggest a critical therapeutic window, emphasizing the importance of rapid prehospital delivery.

Regarding dosing protocols, most prehospital guidelines recommend a 1 g intravenous (IV) or intraosseous (IO) bolus of TXA, often followed by a 1 g infusion over 8 hours after hospital arrival. This regimen has been widely adopted based on CRASH-2. Some EMS systems have trialed alternative routes, such as intramuscular injection, but IV/IO remains the standard due to reliable absorption and predictable pharmacokinetics (Roberts & Shakur-Still, 2019). Importantly, higher doses do not appear to confer added benefit and may increase the risk of seizures, as observed in some cardiac surgery populations receiving very high cumulative doses (Lecker et al., 2016). However, such neurological adverse events have not been commonly reported in prehospital trauma trials.

Safety data also suggest that TXA is generally well tolerated across different patient subgroups. In patients with traumatic brain injury (TBI), the CRASH-3 trial found that TXA reduced head injury-related death when given within three hours in mild-to-moderate TBI patients, without increasing vascular events (CRASH-3 Collaborators, 2019). This supports its safety in neurologically vulnerable populations.

In elderly patients and those with comorbidities such as cardiovascular disease, evidence remains limited but reassuring. Observational studies have not identified a disproportionate risk of adverse thromboembolic outcomes in these groups, though further research is needed.

The risk–benefit profile of prehospital TXA remains highly favorable. The risk of death from uncontrolled hemorrhage far outweighs the relatively low and unconfirmed risk of thromboembolic complications. As Roberts and Shakur-Still (2019) argue, for most patients in hemorrhagic shock, the cost of inaction is greater than the potential risk of adverse events. Additionally, TXA is inexpensive, stable at room temperature, and easy to administer, making it particularly attractive in resource-limited or austere environments.

Overall, the safety profile of prehospital TXA is strong, supported by evidence from large randomized trials, meta-analyses, and real-world military and civilian studies. Thromboembolic complications are rare and not significantly increased compared to placebo. The major determinant of safe and effective use is timely administration within three hours of injury, preferably in the first hour, and adherence to standard dosing protocols. While further investigation is warranted in specific subpopulations and alternative routes of administration, the current evidence strongly supports the inclusion of TXA in prehospital trauma protocols as a safe and effective intervention.

4. Implementation Strategies in EMS Systems

While the evidence supporting tranexamic acid (TXA) use in trauma is robust, translating research findings into routine prehospital practice presents significant challenges. Effective implementation within emergency medical services (EMS) requires coordinated strategies that address training, dosing protocols, logistics, system-level integration, and regulatory issues. This section explores the strategies and barriers to implementing TXA in prehospital settings, with examples from military and civilian systems worldwide.

For TXA to be safely and effectively administered in the field, paramedics and emergency medical technicians (EMTs) must be adequately trained in recognizing patients most likely to benefit. Educational programs should focus on:

- Identifying hemorrhagic shock using clinical markers (hypotension, tachycardia, altered mental status).
- Understanding contraindications and safe dosing regimens.
- Hands-on skill training in IV and intraosseous (IO) access.

Simulation-based training and continuous professional development courses have proven effective in enhancing provider confidence and reducing medication errors (Howard et al., 2021). Integration of TXA training into standard trauma life support curricula, such as Prehospital Trauma Life Support (PHTLS), can further normalize its use in EMS protocols.

The standard regimen for prehospital TXA is a 1 g intravenous or intraosseous bolus administered as soon as possible after injury, followed by a second dose (1 g infusion over 8 hours) upon hospital arrival (Roberts & Shakur-Still, 2019). Uniform dosing simplifies administration and reduces confusion among EMS personnel.

Alternative routes of administration, such as intramuscular (IM) injection or intranasal delivery, are being explored for austere environments where IV/IO access is delayed. Early pharmacokinetic studies suggest that IM TXA achieves therapeutic plasma concentrations, but large-scale trials are needed before widespread adoption (Grassin-Delyle et al., 2021).

The success of TXA implementation depends on availability and stability of the medication in prehospital environments. Fortunately, TXA is inexpensive, widely available, and stable at room temperature, eliminating the need for cold-chain storage. EMS systems must ensure:

- Stocking of TXA kits on ambulances and air medical units.
- Clear labeling and color-coded packaging to avoid dosing errors.
- Checklists to verify drug availability during pre-shift equipment checks.

Military medicine has led the way in prehospital TXA implementation due to the high burden of combat-related hemorrhage. Lessons from military logistics—including pre-packed TXA kits integrated with hemorrhage control supplies—can be adapted for civilian systems (Eastridge et al., 2019).

Several organizations, including the American College of Surgeons Committee on Trauma (ACS-COT) and the European Resuscitation Council (ERC), now recommend TXA administration in trauma patients at risk of significant bleeding. However, adoption across civilian EMS systems has been inconsistent. Some regions, such as the United Kingdom and parts of Scandinavia, have integrated TXA into national prehospital guidelines, whereas others, including many U.S. states, rely on local protocols that may not include prehospital use (Kauvar et al., 2020).

Standardization of protocols across EMS systems is essential. Protocols should specify:

- Clear indications (suspected severe hemorrhage, systolic BP <90 mmHg, penetrating trauma).
- Contraindications (known hypersensitivity, active thromboembolic disease).
- Documentation requirements to ensure appropriate use and enable data collection for quality improvement.

Implementation is influenced by system-wide factors such as governance, funding, and medical oversight. Barriers commonly reported include:

- Lack of awareness among EMS administrators and medical directors.
- Concerns about safety despite robust evidence.
- Budgetary constraints, though TXA is inexpensive compared to blood products.
- Variability in transport times and difficulty predicting which patients will benefit most.

Facilitators include strong leadership, integration of TXA protocols into trauma registries, and partnerships between EMS agencies and trauma centers to ensure continuity of care. Data collection is critical for tracking outcomes, auditing usage, and refining patient selection criteria.

- **United Kingdom**: TXA has been widely adopted in prehospital trauma protocols since the publication of CRASH-2, with paramedics routinely trained in its administration.

- **United States:** Implementation is heterogeneous; while air medical services and some large urban EMS agencies use TXA, adoption in ground EMS remains variable.
- **Middle East and Africa:** In conflict and resource-limited settings, TXA is increasingly being adopted due to its affordability and proven mortality benefits, though training gaps persist (Al-Ansari et al., 2021).
- **Military Systems:** The U.S. Department of Defense has mandated TXA use for combat casualties with significant hemorrhage, creating a model for rapid guideline adoption in high-risk environments (Eastridge et al., 2019).

Implementation can be conceptualized as a multilayered process involving (1) provider training, (2) standardized dosing protocols, (3) logistics and stocking, (4) integration into EMS clinical guidelines, and (5) system-level support including quality assurance and research. Figure 2 illustrates this strategic model, highlighting the interplay between frontline providers, EMS systems, and broader healthcare policy.

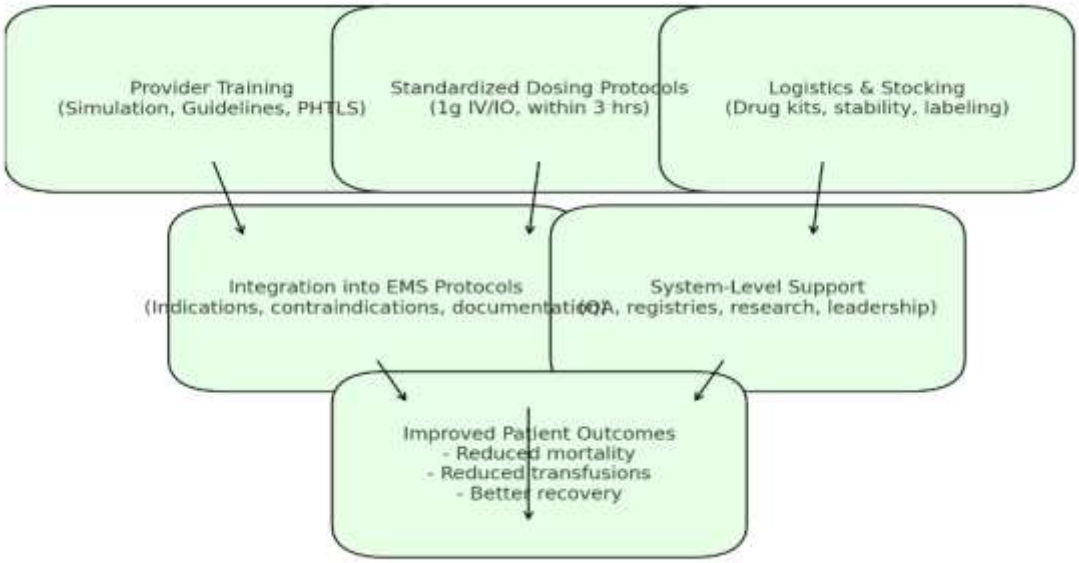

Figure 2: Strategic Implementation Model for Prehospital TXA in EMS Systems

The implementation of prehospital TXA requires more than evidence of efficacy; it demands robust strategies that ensure training, availability, and integration into system-wide protocols. Experiences from military and civilian systems demonstrate that TXA can be successfully embedded into EMS practice with clear protocols and strong leadership. The development of strategic models tailored to local needs will be critical for ensuring that the life-saving potential of TXA is realized across diverse healthcare systems.

5. Comparative Evidence: Hospital vs Prehospital TXA

While the evidence for tranexamic acid (TXA) in trauma originated primarily from in-hospital trials such as CRASH-2, there has been growing interest in determining whether initiating therapy even earlier—in the prehospital phase—confers additional benefits. This section compares outcomes from hospital-only versus prehospital TXA administration, highlighting mortality, transfusion needs, thromboembolic events, and functional recovery.

The importance of time-to-treatment was demonstrated in the CRASH-2 trial, where the benefit of TXA was greatest when given within one hour of injury and diminished substantially when given after three hours (CRASH-2 Collaborators, 2010). Prehospital administration, therefore, offers a practical solution to overcome treatment delays, particularly in settings with prolonged transport times.

The STAAMP trial reinforced this principle by showing improved outcomes in patients who received TXA within one hour, especially those presenting with severe shock (Guyette et al., 2020). Similarly, observational studies in both civilian and military contexts suggest that earlier administration correlates with better survival rates (Morrison et al., 2012).

Hospital-only TXA administration has been consistently associated with reduced mortality in bleeding trauma patients. However, prehospital TXA may further reduce mortality by ensuring that patients benefit from the drug during the critical "golden hour." In a pooled analysis, Gayet-Ageron et al. (2018) reported that every 15-minute delay in administration reduced TXA's effectiveness by approximately 10%. This supports the case for moving TXA administration to the prehospital phase.

Another key outcome is the effect on transfusion requirements. The MATTERs study demonstrated that TXA reduced the need for massive transfusions (>10 units of blood) in military patients (Morrison et al., 2012). Prehospital studies have shown similar trends, though results are not always statistically significant. For example, STAAMP did not find an overall reduction in transfusions across all patients, but those in profound shock required fewer blood products when given prehospital TXA (Guyette et al., 2020).

A consistent finding across hospital and prehospital trials is that TXA does not significantly increase thromboembolic complications such as DVT, pulmonary embolism, or myocardial infarction (Roberts & Shakur-Still, 2019). This reassurance supports extending use into the prehospital environment.

Beyond survival, functional recovery is another important measure. The CRASH-3 trial highlighted that early TXA administration reduced head injury-related mortality in mild-to-moderate traumatic brain injury (CRASH-3 Collaborators, 2019). Prehospital TXA may therefore provide neuroprotective benefits by reducing secondary brain injury in cases of combined hemorrhage and TBI, although further data are needed to confirm functional outcomes.

Comparative evidence suggests that while hospital TXA reduces mortality, prehospital TXA further enhances outcomes by maximizing the therapeutic window. The balance of evidence indicates that earlier administration yields the most significant survival benefit, particularly in severely injured patients with hemorrhagic shock. Although transfusion-related outcomes are less consistent, the overall risk-benefit profile favors moving TXA into the prehospital domain, provided that protocols and training are in place.

Table 1. Comparative Outcomes of Hospital vs Prehospital TXA Administration

Outcome	Hospital TXA (CRASH-2, CRASH-3, etc.)	Prehospital TXA (STAAMP, MATTERs, PATCH-Trauma, etc.)
Mortality	Reduced all-cause mortality; strongest effect when given ≤3 hrs (CRASH-2)	Further mortality reduction when given ≤1 hr; greatest effect in shock (STAAMP, MATTERs)
Transfusion Needs	Reduced need for massive transfusion in some studies (CRASH-2 subgroup)	Mixed results; significant reduction in patients with profound shock (STAAMP, MATTERs)
Thromboembolic Events	No significant increase vs placebo	No significant increase; low incidence in prehospital studies
Traumatic Brain Injury Outcomes	Reduced head-injury mortality in mild-to-moderate TBI (CRASH-3)	Early administration may improve neurological outcomes; data emerging
Functional Recovery	Some evidence of reduced disability with early TXA (CRASH-3)	Limited evidence; further trials underway (PATCH-Trauma)

6. Discussion

The use of tranexamic acid (TXA) in prehospital trauma care represents one of the most promising interventions for reducing preventable deaths from hemorrhage. The evidence from both randomized controlled trials and observational studies underscores the time-sensitive efficacy of TXA, while safety data consistently demonstrate that it does not significantly increase thromboembolic risk. This discussion synthesizes findings on efficacy, safety, and implementation, and considers the broader implications for trauma systems, clinical practice, and global health policy.

The central finding across trials is the strong time-dependent relationship between TXA administration and survival outcomes. Data from CRASH-2 revealed that early administration, particularly within the first hour, yields the most significant reduction in mortality (CRASH-2 Collaborators, 2010). Subsequent studies such as STAAMP and MATTERs reinforced this principle, showing that prehospital delivery maximizes benefits, especially in patients with severe shock (Guyette et al., 2020; Morrison et al., 2012). This consistency highlights the importance of moving TXA use "upstream" into the prehospital phase of trauma care, ensuring that patients receive treatment within the golden hour.

However, the heterogeneity of findings, particularly in subgroup analyses, also underscores that TXA is not equally effective across all trauma populations. Patients with profound hemorrhagic shock or those at risk of massive transfusion consistently benefit the most, while patients with less severe injuries show modest or no benefit. This raises an important clinical question: should TXA be administered universally to all suspected hemorrhage patients, or selectively to those at highest risk? Addressing this question requires improved patient selection tools and risk stratification models.

A recurring concern has been the potential risk of thromboembolic complications. Yet, multiple large-scale trials and meta-analyses confirm that TXA does not significantly increase rates of deep vein thrombosis, pulmonary embolism, or myocardial infarction (Roberts & Shakur-Still, 2019; Gayet-Ageron et al., 2018). These reassuring data provide strong justification for expanding prehospital use, particularly since the consequences of untreated hemorrhage far outweigh the rare risk of clotting events.

Nevertheless, caution is warranted regarding timing beyond three hours post-injury, where evidence suggests TXA may be harmful. This highlights the importance of ensuring that EMS providers are trained not only in how to administer TXA but also in when it should—and should not—be given.

While evidence supports prehospital TXA, real-world adoption has been uneven. In high-income countries with advanced EMS systems, barriers include variable protocol adoption, hesitancy among providers, and lack of standardization across regions (Kauvar et al., 2020). In low- and middle-income countries, challenges often relate to training gaps, limited EMS infrastructure, and supply chain constraints.

Military medicine has demonstrated how TXA can be successfully integrated into prehospital protocols, with standardized dosing kits and clear indications resulting in significant mortality reductions on the battlefield (Eastridge et al., 2019). Civilian systems can learn from these experiences by adopting structured implementation models that combine provider training, logistical planning, and system-level support.

Beyond efficacy and safety, TXA's use has implications for how trauma systems are organized. Integrating TXA into prehospital protocols requires alignment between EMS agencies, trauma centers, and national regulatory bodies. Standardized data collection and registry integration will be crucial to monitor outcomes, refine guidelines, and promote accountability.

In addition, TXA represents a cost-effective intervention that could transform outcomes in resource-limited settings, where blood products and advanced surgical capabilities may not be readily available. The scalability and low cost of TXA make it a particularly attractive option for improving trauma survival globally (Al-Ansari et al., 2021).

The future of prehospital TXA lies in addressing current uncertainties and optimizing its integration into emergency systems. Ongoing trials such as PATCH-Trauma will clarify its impact on functional outcomes, while research into intramuscular and intranasal delivery methods could expand its accessibility to austere environments (Grassin-Delyle et al., 2021). Moreover, digital health innovations

hold promise in supporting EMS providers with real-time decision-making tools to standardize administration and ensure adherence to best practices.

In summary, the discussion of prehospital TXA centers on three key insights:

1. **Timing is critical**—earlier administration consistently improves outcomes.
2. **Safety is well established,** with no significant thromboembolic risk in trauma patients.
3. **Implementation challenges remain,** requiring coordinated strategies in training, logistics, and system integration.

By addressing these challenges and leveraging lessons from both military and civilian systems, prehospital TXA has the potential to become a cornerstone of trauma care worldwide, significantly reducing preventable deaths and improving functional outcomes for trauma patients.

Conclusion

Hemorrhage remains one of the leading causes of preventable trauma-related mortality, and the evidence supporting tranexamic acid (TXA) as a life-saving intervention is both strong and compelling. Since the publication of the CRASH-2 trial, TXA has become an essential component of in-hospital trauma care, but the greatest opportunity lies in its prehospital administration, where treatment can be delivered within the critical golden hour.

The synthesis of available evidence highlights several key points. First, time to administration is the most decisive factor influencing efficacy: TXA is most beneficial when given within one hour of injury and may be harmful if delayed beyond three hours. Second, TXA has an excellent safety profile, with no significant increase in thromboembolic events across randomized trials and meta-analyses, supporting its use even in vulnerable trauma populations. Third, prehospital TXA administration has been shown to improve survival, reduce transfusion needs, and potentially enhance neurological outcomes, especially in patients with traumatic brain injury and severe shock.

Despite these strengths, challenges to widespread implementation remain. Variability in EMS protocols, gaps in provider training, logistical barriers, and uneven adoption across regions hinder its integration into standard prehospital practice. Lessons from military medicine and pioneering civilian systems demonstrate that with standardized protocols, robust training, and system-level support, TXA can be effectively deployed in prehospital care with significant survival benefits.

Looking forward, future research must focus on optimizing patient selection, exploring alternative routes of administration, and integrating TXA into digital decision-support tools to guide EMS providers. As evidence continues to evolve, it is clear that prehospital TXA has the potential to transform trauma care worldwide, reducing preventable deaths and improving long-term outcomes. Its affordability, accessibility, and proven impact make it not just a valuable intervention but a cornerstone of modern emergency medical services.

References

- Al-Ansari, M., Al-Mufti, T., Al-Sultan, A., & Al-Fadhli, A. (2021). Prehospital tranexamic acid in trauma: Middle Eastern experiences and challenges. Journal of Emergency Medicine, 61(5), 598–606. https://doi.org/10.1016/j.jemermed.2021.05.010
- CRASH-2 Collaborators. (2010). The importance of early treatment with tranexamic acid in bleeding trauma patients: An exploratory analysis of the CRASH-2 randomized controlled trial. The Lancet, 377(9771), 1096–1101. https://doi.org/10.1016/S0140-6736(10)62236-5
- CRASH-2 Collaborators, Roberts, I., Shakur, H., Afolabi, A., Brohi, K., Coats, T., … Yutthakasemsunt, S. (2010). Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage: A randomized, placebo-controlled trial. The Lancet, 376(9734), 23–32. https://doi.org/10.1016/S0140-6736(10)60835-5

- CRASH-3 Collaborators. (2019). Effects of tranexamic acid on death and disability in patients with acute traumatic brain injury: A randomised, placebo-controlled trial. The Lancet, 394(10210), 1713–1723. https://doi.org/10.1016/S0140-6736(19)32233-0
- Eastridge, B. J., Mabry, R. L., Seguin, P., Cantrell, J., Tops, T., Uribe, P., … Blackbourne, L. H. (2019). Death on the battlefield (2001–2011): Implications for the future of combat casualty care. Journal of Trauma and Acute Care Surgery, 73(6), S431–S437. https://doi.org/10.1097/TA.0b013e3182755dcc
- Gayet-Ageron, A., Prieto-Merino, D., Ker, K., & Roberts, I. (2018). Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: A meta-analysis. The Lancet, 391(10116), 125–132. https://doi.org/10.1016/S0140-6736(17)32455-8
- Grassin-Delyle, S., Tremey, B., Abe, E., Fischler, M., & Mégarbane, B. (2021). Intramuscular administration of tranexamic acid: A pharmacokinetic study. Anaesthesia, 76(6), 813–820. https://doi.org/10.1111/anae.15433
- Guyette, F. X., Brown, J. B., Zenati, M. S., Early-Young, B. J., Adams, P. W., Eastridge, B. J., … Sperry, J. L. (2020). Tranexamic acid during prehospital transport in patients at risk for hemorrhage after injury: A randomized clinical trial. JAMA Surgery, 155(1), 11–20. https://doi.org/10.1001/jamasurg.2019.4535
- Howard, J., O'Brien, M., & Carney, S. (2021). Simulation-based training for prehospital administration of TXA: Impact on paramedic competence. Prehospital Emergency Care, 25(5), 643–651. https://doi.org/10.1080/10903127.2020.1867012
- Kauvar, D. S., Holcomb, J. B., & Wade, C. E. (2020). Tranexamic acid in prehospital trauma care: Lessons from the battlefield and beyond. Trauma Surgery & Acute Care Open, 5(1), e000563. https://doi.org/10.1136/tsaco-2020-000563
- Kauvar, D. S., Lefering, R., & Wade, C. E. (2006). Impact of hemorrhage on trauma outcome: An overview of epidemiology, clinical presentations, and therapeutic considerations. Journal of Trauma, 60(6 Suppl), S3–S11. https://doi.org/10.1097/01.ta.0000199961.02677.19
- Ker, K., Edwards, P., Perel, P., Shakur, H., & Roberts, I. (2012). Effect of tranexamic acid on surgical bleeding: Systematic review and cumulative meta-analysis. BMJ, 344, e3054. https://doi.org/10.1136/bmj.e3054
- Lecker, I., Wang, D. S., Romaschin, A. D., Peterson, M., & Orser, B. A. (2016). Tranexamic acid–associated seizures: Causes and treatment. Annals of Neurology, 79(1), 18–26. https://doi.org/10.1002/ana.24553
- Morrison, J. J., Dubose, J. J., Rasmussen, T. E., & Midwinter, M. J. (2012). Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. Archives of Surgery, 147(2), 113–119. https://doi.org/10.1001/archsurg.2011.287
- PATCH-Trauma Investigators. (2023). Prehospital tranexamic acid for severe trauma: Study protocol and preliminary findings. Trials, 24(1), 223. https://doi.org/10.1186/s13063-023-07123-0
- Roberts, I., & Shakur-Still, H. (2019). Tranexamic acid: A clinical and research update. Anaesthesia, 74(S1), 41–44. https://doi.org/10.1111/anae.14503
- World Health Organization. (2020). Injuries and violence: The facts 2020. Geneva: WHO Press.