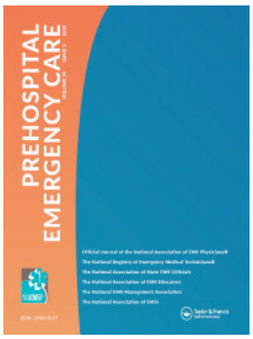

Prehospital Emergency Care

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ipec20

Prehospital Trauma Compendium: Tranexamic Acid in Trauma– a joint position statement and resource document of NAEMSP, ACEP, and ACS-COT

Whitney J Barrett, Kevin A Kaucher, Ross E Orpet, Eric M Campion, Jeffrey M Goodloe, Peter Fischer, Christopher B Colwell & John W Lyng

To cite this article: Whitney J Barrett, Kevin A Kaucher, Ross E Orpet, Eric M Campion, Jeffrey M Goodloe, Peter Fischer, Christopher B Colwell & John W Lyng (05 May 2025): Prehospital Trauma Compendium: Tranexamic Acid in Trauma– a joint position statement and resource document of NAEMSP, ACEP, and ACS-COT, Prehospital Emergency Care, DOI: 10.1080/10903127.2025.2497056

To link to this article: https://doi.org/10.1080/10903127.2025.2497056

Prehospital Trauma Compendium: Tranexamic Acid in Trauma– a joint position statement and resource document of NAEMSP, ACEP, and ACS-COT.

Whitney J Barrett[a,*] 0000-0002-7714-5342, Kevin A Kaucher[b] 0000-0002-0563-4569, Ross E Orpet[c], Eric M Campion[d] 0000-0002-4563-7748, Jeffrey M Goodloe[e] 0000-0001-6024-8436, Peter Fischer[f], Christopher B Colwell[g] 0000-0003-1375-7056, John W Lyng[h] 0000-0001-5191-5700

[a]University of New Mexico School of Medicine, Department of Emergency Medicine, Albuquerque, NM. National Association of EMS Physicians
[b]University of New Mexico Health Sciences Center, Department of Pharmacy Practice, Albuquerque, NM. National Association of EMS Physicians
[c]First Contact Medical Specialists, Montrose Regional Health, Department of Emergency Medicine, Montrose, CO. National Association of EMS Physicians
[d]Denver Health Medical Center, Department of Surgery, Denver, CO American College of Surgeons
[e]University of Oklahoma School of Community Medicine, Department of Emergency Medicine, Tulsa, OK. American College of Emergency Physicians
[f]University of Tennessee Health Science Center, Department of Surgery, Memphis, TN. American College of Surgeons Committee on Trauma
[g]University of California at San Francisco School of Medicine, Department of Emergency Medicine, San Francisco, CA National Association of EMS Physicians
[h]North Memorial Health Level I Trauma Center, Department of Emergency Medicine, Minneapolis, MN National Association of EMS Physicians

***Corresponding Author:** Whitney, J, Barrett, Department of Emergency Medicine, University of New Mexico School of Medicine, UNM School of Medicine MSC08 4720 1 UNM Albuquerque, NM 87131-0001, wjbarrett@salud.unm.edu

ABSTRACT

Prehospital use of tranexamic acid (TXA) has grown substantially over the past decade despite contradictory evidence supporting its widespread use. Since the previous guidance document on the prehospital use of TXA for injured patients was published by the National Association of Emergency Medical Services Physicians (NAEMSP), the American College of Surgeons Committee on Trauma (ACS-COT), and the American College of Emergency Physicians (ACEP) in 2016, new research has investigated outcomes of patients who receive TXA in the prehospital setting. To provide updated evidence-based guidance on the use of intravenous TXA for injured patients in the EMS setting, we performed a structured literature review and developed the following recommendations supported by the evidence summarized in the accompanying resource document.

NAEMSP, ACEP, and ACS-COT recommends:

- Prehospital TXA administration may reduce mortality in adult trauma patients with hemorrhagic shock when administered after lifesaving interventions.
- Prehospital TXA administration appears safe, with low risk of thromboembolic events or seizure.
- The ideal dose, rate, and route of prehospital administration of TXA for adult trauma patients with hemorrhagic shock has not been determined. Current evidence suggest EMS agencies may administer either a 1-gram IV/IO dose (followed by a hospital-based 1-gram infusion over 8 hours), or a 2-gram IV/IO dose as an infusion or slow push.
- Prehospital TXA administration, if used for adult trauma patients, should be given to those with clinical signs of hemorrhagic shock and no later than 3 hours post-injury.

There is no evidence to date to suggest improved clinical outcomes from TXA initiation beyond this time or in those without clinically significant bleeding.

- The role of prehospital TXA in pediatric trauma patients with clinical signs of hemorrhagic shock has not been studied and standardized dosing has not been established. If used, it should be given within 3 hours of injury.
- Prehospital TXA administration, if used, should be clearly communicated to receiving healthcare professionals to promote appropriate monitoring and to avoid duplicate administration(s).
- A multidisciplinary team, led by EMS physicians, that includes EMS clinicians, emergency physicians, and trauma surgeons should be responsible for developing a quality improvement program to assess prehospital TXA administration for protocol compliance and identification of clinical complications.

INTRODUCTION

Tranexamic acid (TXA) has been variably introduced into prehospital trauma resuscitation protocols following the publication of the CRASH-2 and MATTERs trials based on its potential lifesaving effect (1,2). The beneficial findings of CRASH-2 and MATTERs were predicated on TXA dosing in-hospital and in forward battlefield hospitals respectively. Since the publication of those trials, much attention has been focused on further clarifying the efficacy and safety of TXA use in prehospital settings.

The impact of EMS-administered TXA on early survival (e.g., 24-hr), 30-day survival, long-term functional neurologic outcomes, the need for blood product transfusion, and iatrogenic complications are of interest to multiple stakeholders in the continuum of acute trauma care. Also, the impact of prehospital TXA on specific trauma populations needs to be explored to determine if treatment effect varies by injury type or location. In an effort to explore these topics National Association of Emergency Medical Services Physicians (NAEMSP), American College of Surgeons- Committee on Trauma (ACS-COT), and American College of Emergency Physicians (ACEP) collaborated to conduct a structured review of the literature to develop evidence-based recommendations.

METHODS

In collaboration with the trauma compendium editorial board, our author team identified several content areas of interest regarding the role of prehospital administration of intravenous TXA for trauma patients:

1. Safety and effectiveness for suspected hemorrhagic shock.
2. Identification of patient populations with the greatest benefit.
3. System development, implementation, and evaluation of clinical protocol(s).

Search strategy

A PubMed search was performed on 23 December 2022 for all existing literature following the preestablished NAEMSP trauma compendium methodology and using additional terms relevant to EMS-administration of TXA (Supplemental File Table 1) (3).

Evidence evaluation

Two authors (WJB and KAK) independently reviewed titles and abstracts of all citations identified in our initial search to determine each paper's relevance. We also performed bibliography searches of retained articles to identify additional relevant articles. The two authors adjudicated disagreements regarding relevance by advancing any involved abstracts to full manuscript review. All citations deemed relevant at this point underwent full text review by two authors (REO and KAK) who retained and categorized articles by content focus areas. Two authors (REO and KAK) abstracted the data using a structured data abstraction form, collating them by content focus areas and summarizing the data.

Development of guidelines

Authors REO, WJB, KAK, and EMC representing the specialties of emergency medicine, EMS, pharmacy, and trauma surgery met, reviewed the summarized literature, and developed the initial position statements. Authors CBC and JWL provided a secondary review and additional recommendations. Authors JMG and PF representing ACEP and ACS-COT respectively, then reviewed these position statements and associated resource document and provided comment and further discussion. The final statements went through the formal review processes for the National Association of EMS Physicians (NAEMSP), ACEP, and ACS-COT and received endorsement prior to submission.

RESULTS

Literature review

Our search strategy identified 138 articles. We retained 12 articles, found four additional articles through bibliography review, and added one article that was published after the search date. The additional article was identified by our writing committee in the original literature search but was only a methodological publication of the trial protocol. The final results were then published during the writing of this resource document. We included the resulting 17 articles in the final literature review (Figure 1).

Evidence synthesis

We found one systematic review, three prospective, randomized controlled trials, two subgroup analyses of randomized control trials, three prospective observational and four retrospective observational studies, that assessed the efficacy and safety of TXA use by prehospital clinicians in various trauma patients. Additionally, we reviewed one pharmacokinetic analysis, one survey-based analysis and two risk stratification model analyses for patient identification purposes. Evidence addressing each of our topic areas was sparse and primarily included indirect assessments and survey results. The articles used to develop the guidelines are summarized in the Evidence Table (Supplemental File Table 2).

DISCUSSION

Effectiveness and safety of prehospital tranexamic acid administration used for suspected hemorrhagic shock

Prehospital TXA administration may reduce mortality in adult trauma patients with hemorrhagic shock when administered after lifesaving interventions.

Patient outcomes of interest include prehospital TXA effects on short- and long-term survival, long-term neurological outcomes, and reduction in blood product use. Short-term (<24 hour) mortality was evaluated in a recent systematic review that included four studies (4–8). Their findings observed a 40% lower risk of 24-hour mortality in those who received prehospital TXA, influenced largely by one retrospective, observational, propensity-matched analysis. A large German prehospital trauma database assessed early survival in a propensity match control group and found lower 6- and 12-hour mortality rates, and absolute reductions of 2.3% and 2% at each timeframe, respectively, in those that received prehospital TXA (9). They did not, however, find any difference in mortality at 24-hours or later. An exploratory analysis of secondary outcomes assessed in a recently published, multicenter, randomized controlled trial suggested a benefit in 24-hour survival if TXA was administered in prehospital patients, but with limited certainty of the true effect (10). In aggregate, the current data suggests improved survival at 24 hours in patients who receive prehospital TXA.

Long-term survival was also assessed by previously mentioned studies (4–8). The Almuwallad meta-analysis did not show a reduction in mortality in those receiving prehospital TXA when assessing 28 or 30-day mortality (4). Similarly, Imach analysis did not find reduced mortality at 30-days with prehospital TXA administration (9). One secondary post-hoc analysis of the largest multicenter, randomized, controlled trial in trauma patients receiving prehospital TXA did show a 7.9% reduction in 30-day mortality if prehospital TXA was administered within an hour from time

of injury, but not between 1 and 3 hours. Additionally, no benefit was observed when TXA was given in combination with prehospital packed red blood cells (6,11,12). The most recent and largest, prospective, multicenter analysis which assessed 6-month functional outcomes in over 1300 prehospital injured patients did not observe improvement in 6-month favorable functional status with the administration of prehospital TXA compared to placebo (10).

Studies evaluating the potential blood product-sparing effects of TXA have not yielded consistent results (1,13,14). Two observational assessments of patients receiving prehospital TXA found that a higher proportion of these patients required blood product transfusions compared to those who did not receive TXA (9,15). A propensity-matched database analysis observed increased transfusions (absolute mean difference 3%), but a 1.7% absolute reduction in massive transfusion activation (9). Similarly, a prospective, observational assessment of prehospital TXA use also found an absolute increase in 2 units of blood products administered upon hospital arrival in the TXA group compared to a matched control (15). In contrast, two other analyses showed absolute reductions in blood product use in those receiving prehospital TXA by 2 units and 4.5 units, and a 30% reduction in those requiring activation of massive transfusion protocol (5,7). In a population of patients with traumatic brain injury (TBI), those receiving a 2-gram bolus of TXA compared to traditional 1-gram dosing or placebo were less likely to receive blood product transfusions (absolute mean proportion difference, 5%) and if they received blood, overall volume of blood products transfused was lower (median liter difference, 0.5 liters) (16).

The efficacy of prehospital administration of TXA has not been consistently shown and is not widely reproducible. The significance of improved early survival must be balanced between the lack of evidence that TXA has a positive impact on long-term neurologic function and the mixed results of blood product resource use. Given the limitations of the available evidence, TXA

administration should not be prioritized above more evidence-based life-saving measures. If implemented, TXA should be incorporated into clinical care as early as possible with preference for < 1 hour but no more than 3 hours from the time of injury. These recommendations are based on relatively moderate to high quality evidence, but with mixed results and indirect assessment of outcome measures.

Prehospital TXA administration appears safe, with low risk of thromboembolic events or seizure.

Thrombotic complications after trauma are common and rates have been observed as high as 65% (17). There is theoretical concern that TXA may cause hypercoagulability by inhibiting clot breakdown. However, in-hospital use of TXA has not been associated with increased thromboembolic events (18). Thromboembolic complications and seizure rates are commonly examined only as secondary outcomes and may be influenced by reporting and recall biases (4,9,10,16,19). A meta-analysis by Almuwallad found no significant association between prehospital TXA administration and venous thromboembolic (VTE) events or seizures (4,15,16,19). We believe there is a benefit in future analyses identifying these adverse effects a priori to reduce reporting and recall bias. Based on limited available evidence, it appears that prehospital TXA administration is safe for trauma patients with hemorrhagic shock.

The ideal dose, rate, and route of prehospital administration of TXA for adult trauma patients with hemorrhagic shock has not been determined. Current evidence suggest EMS agencies may administer either a 1 gram IV/IO dose (followed by a hospital-based 1 gram infusion over 8 hours), or a 2 gram IV/IO dose as an infusion or slow push.

The TXA dosing strategy established by the CRASH-2 trial included a 1-gram bolus over 10 minutes followed by a 1-gram infusion over the following 8 hours. Faster and simpler rates of

administration are of interest to simplify prehospital care, but these dosing strategies have not yet been validated as safe or effective compared to the initial dosing strategies established by CRASH-2. Alternative dosing strategies using a more rapid and simplified dosing approach have been recommended, such as the single 2-gram dose by intravenous push only recommended for combat casualties by the Joint Trauma System Damage Control Resuscitation guideline (20).

Evidence assessing increased doses of TXA for prehospital use is sparse, including a well-designed multicenter, randomized controlled trial that found no evidence of harm, though no benefit (16). In this analysis of polytrauma patients with TBI (GCS < 12 without hypotension) who received a 1-gram bolus plus infusion, a 2-gram bolus alone, or placebo, no differences were observed in 28-day mortality or 6-month functional outcomes. In this same study, the proportion of patients requiring a blood transfusion and total volume of blood products administered within 24 hours showed a slight benefit in the 2-gram bolus dosing group (16). The 2-gram bolus-only dose was associated with a small increase in seizure rate compared to the 1-gram bolus and infusion dosing group. However, the seizure event rate across these groups was too small to determine if a true clinical difference exists.

In a pharmacokinetic assessment of trauma patients who received prehospital TXA, Grassin et al. observed that 21% of patients receiving a 1-gram bolus followed by 1-gram infusion over 8 hours did not reach serum TXA concentrations sufficient to inhibit fibrinolysis (21). Unfortunately, no correlation between serum concentration and patient outcomes has been established. We believe this is a needed focus in future research.

There is currently insufficient evidence to establish one optimal TXA dosing strategy. Either 1-gram bolus and 1-gram infusion over 8 hours OR 2-gram bolus can be specified by protocol for

civilian prehospital systems based upon local preferences established between EMS physicians, emergency physicians, and trauma surgeons.

Identification of patient populations that may benefit from prehospital administration of tranexamic acid for traumatic hemorrhagic shock.

Prehospital TXA administration, if used for adult trauma patients, should be given to those with clinical signs of hemorrhagic shock and no later than 3 hours post-injury. There is no evidence to date to suggest improved clinical outcomes from TXA initiation beyond this time or in those without clinically significant bleeding.

Patient selection criteria

Patient selection protocols that identify candidates for prehospital TXA administration should use clinical determinants easily and readily available to EMS clinicians. Simultaneously, such protocols should not distract from or hinder timeliness of richer evidence-based patient care priorities. There is agreement in research and current practice that prehospital TXA administration should not be indiscriminately given to all trauma patients, instead being reserved for those in hemorrhagic shock. Most civilian prehospital TXA inclusion criteria identify candidate patients based on the CRASH-2 criteria of systolic blood pressure (SBP) < 90mmHg and/or a heart rate > 110 who are < 3 hours from the time of injury.

Unfortunately, definitive, objective prehospital markers of patients who are in hemorrhagic shock, and therefore might benefit most from TXA, have not yet been well defined. Table 1 outlines the available prognostic tools derived from outcomes based on in-hospital TXA administration (10,22,23). There is limited certainty in extrapolating these to prehospital use. The recent multicenter, randomized controlled PATCH Trial used the Coagulopathy of Severe

Trauma (COAST) score and time less than 3 hours from injury as their initial patient inclusion criteria (10). The COAST score was developed in the hospital as a prognostic tool and its use to identify prehospital patients with risk of coagulopathy has not been validated. Tools or criteria to identify prehospital patients who would most benefit from TXA administration is a significant area for further research.

Head-injured patients

Our review included four articles that assessed survival and 6-month functional outcomes of TBI patients who received prehospital TXA (10,16,19,24). In patients with moderate to severe TBI with a GCS < 12 who were given prehospital TXA in various dosing regimens compared to placebo, there was no difference in 28-day survival or 6-month favorable neurologic function between the groups (16). In two retrospective analyses and another prospective, subgroup analysis, TXA did not affect 6-month functional outcomes (10,19,24). Mortality rates were higher in those with multi-system trauma with concomitant TBI who received TXA, but this is likely due to worse baseline injury severity (10,19,24). These four studies did not find an increased rate of VTE or other complications in TBI patients who received TXA. Importantly, only one of the studies evaluated isolated TBI while the others included multisystem trauma (24). While this limits the ability to generalize these findings to isolated TBI patients, it likely reflects the difficulty to definitively identify isolated head injuries in settings of polytrauma mechanisms.
Although TXA is likely safe in patients with moderate to severe TBI, prehospital TXA does not appear to confer any functional or survival benefit based on current evidence.

Viscoelastic Hemostatic Assays (VHAs)

Hyperfibrinolysis, which is inhibited by TXA administration, is prevalent in roughly 15% of trauma patients upon arrival to hospital and can be assessed with point-of-care viscoelastic testing (25). Hospital-based studies have used viscoelastic testing as a tool to identify targeted

resuscitation strategies in patients at-risk for or in hemorrhagic shock (26). Importantly, with respect to the use of viscoelastic testing, as stated in the article by Borgman, “While it seems logical that TXA may most benefit individuals who have a hyperfibrinolytic phenotype following trauma, there is no evidence to support this claim.” Our search did not identify any analysis that directly assessed prehospital use of viscoelastic testing to identify hyperfibrinolysis and guide prehospital use of TXA. Considering this significant lack of evidence, we cannot make an evidence-based recommendation regarding the utility of viscoelastic testing in the prehospital setting. We believe this is an area where future research can establish helpful guidance.

The role of prehospital TXA in pediatric trauma patients with clinical signs of hemorrhagic shock is unclear and standard dosing has not been established. If used, it should be given within 3 hours of injury.

Evidence guiding the use of prehospital TXA in pediatric trauma patients is scarce. Due to challenges with protocol design, pediatric patients were excluded from the large landmark in-hospital trials, CRASH-2 and CRASH-3. Further, the lowest age-cutoff identified in any of the studies reviewed for this manuscript was 15 years (16). The 2023 Pediatric Trauma Hemorrhagic Shock Consensus Conference reviewed evidence limited to four retrospective studies and one prospective observational trial (27). All these studies looked at patients who received TXA in the hospital and not prehospital so their application to the prehospital environment is unclear. The review included two retrospective studies in combat settings and one prospective civilian US study that found association with improved mortality, and two retrospective civilian studies found no benefit (27–32). There is clearly a need for further investigation of the role of TXA in pediatric trauma patients in general and in the prehospital environment to clarify appropriate timing, dose, and patient selection.

System development, implementation, and evaluation of clinical protocol(s)

Prehospital TXA administration, if used, should be clearly communicated to receiving healthcare professionals to promote appropriate monitoring and to avoid duplicate administration(s).

One widely used TXA dosing strategy involves the administration of a second dose by infusion. EMS clinicians must promote timely and effective communication of prehospital TXA administration, including timing and dose, upon transition of care to subsequent healthcare professionals. This will help the hospital-based trauma team to identify whether additional dose(s) are indicated and to trigger surveillance practices.

A multidisciplinary team, led by EMS physicians, that includes EMS clinicians, emergency physicians, and trauma surgeons should be responsible for developing a quality improvement program to assess prehospital TXA administration for protocol compliance and identification of clinical complications.

The original guidance document for prehospital use of TXA stated that collaboration and integration between prehospital and trauma center resources in protocol development and administration of quality assurance programs is imperative to successfully implement therapies that may impact patient care and outcomes (33). Our literature review did not yield any direct assessment of TXA use in general or effect on patient outcomes due to collaboration within trauma systems of care. However, one survey-based study found that 75% of trauma surgeons felt TXA had a role in prehospital trauma care, despite also being unsure whether TXA was available in their local EMS agencies (34).

Evidence regarding benefit of TXA for civilian trauma patients with hemorrhagic shock remains both limited and contradictory. In the absence of definitive guidance, it seems prudent for EMS physicians, emergency physicians, and trauma surgeons to collaborate on continuing education, quality improvement, and other evidence-based review practices to promote TXA administration according to local clinical protocols.

Considerations for implementation

TXA is likely safe; however, the available evidence is conflicting and the benefit of TXA remains unclear. Accordingly, there are some very important unknowns associated with its prehospital application. One glaring unknown is the lack of clear parameters (physiologic or injury) that identify patients who might benefit most or those who may possibly be harmed by receiving TXA. There is also limited understanding of the impact of the current variable dosing strategies. Future research should continue to investigate these critical questions. If TXA is used in the field there are a few important guiding principles. First, protocols should emphasize lifesaving interventions before consideration of the administration of TXA. Second, TXA should be administered as soon as possible after the traumatic injury in patients who meet criteria and should not be administered beyond 3 hours post-injury. Finally, the use of TXA should be part of a collaborative effort that includes local and regional trauma centers as part of guideline development and a thoughtful quality assurance program. Given the limited and conflicting data, agency leadership should carefully consider their unique characteristics including available resources such as training time and priorities, scope of available clinicians, proximity to trauma centers and usual patient population when deciding whether to implement TXA.

LIMITATIONS

Our literature review and development of recommendations was limited by the conflicting results of the available evidence. While some studies were moderate to high-quality evidence, the

inconsistent findings prevent drawing specific conclusions. Many limitations of the data itself have been specifically identified in the above discussion, however, a few are particularly worth highlighting to assist in identifying the research needed. Of the studies reviewed, there was significant variation in dosing strategies, patient identification, and outcomes evaluated. This heterogeneity makes drawing specific conclusions from available data as a whole very challenging. There are also potential limitations related to our search strategy and evaluation of the evidence. Our search was conducted in a single database (PubMed) and limited to the English language which limits results from other geographic regions and types of publications. Our search results did encompass several military-focused studies, potentially introducing bias and limiting external validity of the results. We focused on prehospital-based literature and excluded studies where TXA was administered in-hospital. Many more studies than reviewed here have evaluated in-hospital application of TXA. Some of these might be relevant or applicable to prehospital care but were excluded, given uncertainty of extrapolation accuracy. Further, our literature search strategy may have missed some articles related to our discussion. We do believe that the diversity of expertise we engaged in the editing and review of this publication mitigates several of the limitations related to the review and interpretation of the existing evidence while the limitations of the data itself persist.

CONCLUSIONS

Tranexamic acid has been widely adopted in civilian EMS systems and appears safe, but the beneficial effect of prehospital TXA for adult trauma patients with hemorrhagic shock remains uncertain despite earlier excitement about improving outcomes. In aggregate, evidence from a mix of military and civilian studies appears to show potential benefits in reducing early mortality when TXA is administered less than 3 hours from the time of injury. Considering the conflicting and uncertain evidence there is a need for high-quality studies to further define the role TXA for prehospital trauma. In the absence of clear evidence, local individual EMS agencies and trauma

systems must determine the feasibility of incorporating TXA into their prehospital traumatic hemorrhagic shock protocols, balancing potential clinical outcomes benefits with resource costs of implementation, education, training, and quality improvement programs.

ACKNOWLEDGEMENTS: none

EXTERNAL REVIEW: this document was created jointly by the National Association of EMS Physicians (NAEMSP), the American College of Surgeons Committee on Trauma (ACSCOT), and the American College of Emergency Physicians (ACEP). It has been independently reviewed and approved by each participating organization (NAEMSP 29 October 2024, ACSCOT 11 October 2024, ACEP 22 January 2025)

UPDATING PROCEDURE: this document will be reviewed and updated by NAEMSP, ACS COT, and ACEP five years after its publication. At a minimum the review process should include a search and synthesis of any new and relevant evidence that is published since the printing of this document.

FUNDING SOURCE: this document was developed by NAEMSP, ACEP and ACS-COT without external funding.

DECLARATION OF INTEREST STATEMENT: The authors report there are no competing interests to declare

DECLARATION OF GENERATIVE AI IN SCIENTIFIC WRITING: The authors did not use a generative artificial intelligence (AI) tool or service to assist with preparation or editing of this work. The author(s) take full responsibility for the content of this publication.

DATA SHARING STATEMENT: Not applicable.

AUTHORSHIP STATEMENT: REO, KAK, WJB, CBC, developed the plan for literature review and evidence extraction. All authors assume full responsibility for the collection and integrity of the data. REO, KAK, WJB and EMC participated in the evidence extraction, data analysis, development of the initial clinical practice guideline. All authors participated in editing. All authors assume full responsibility for the entire content of the manuscript.

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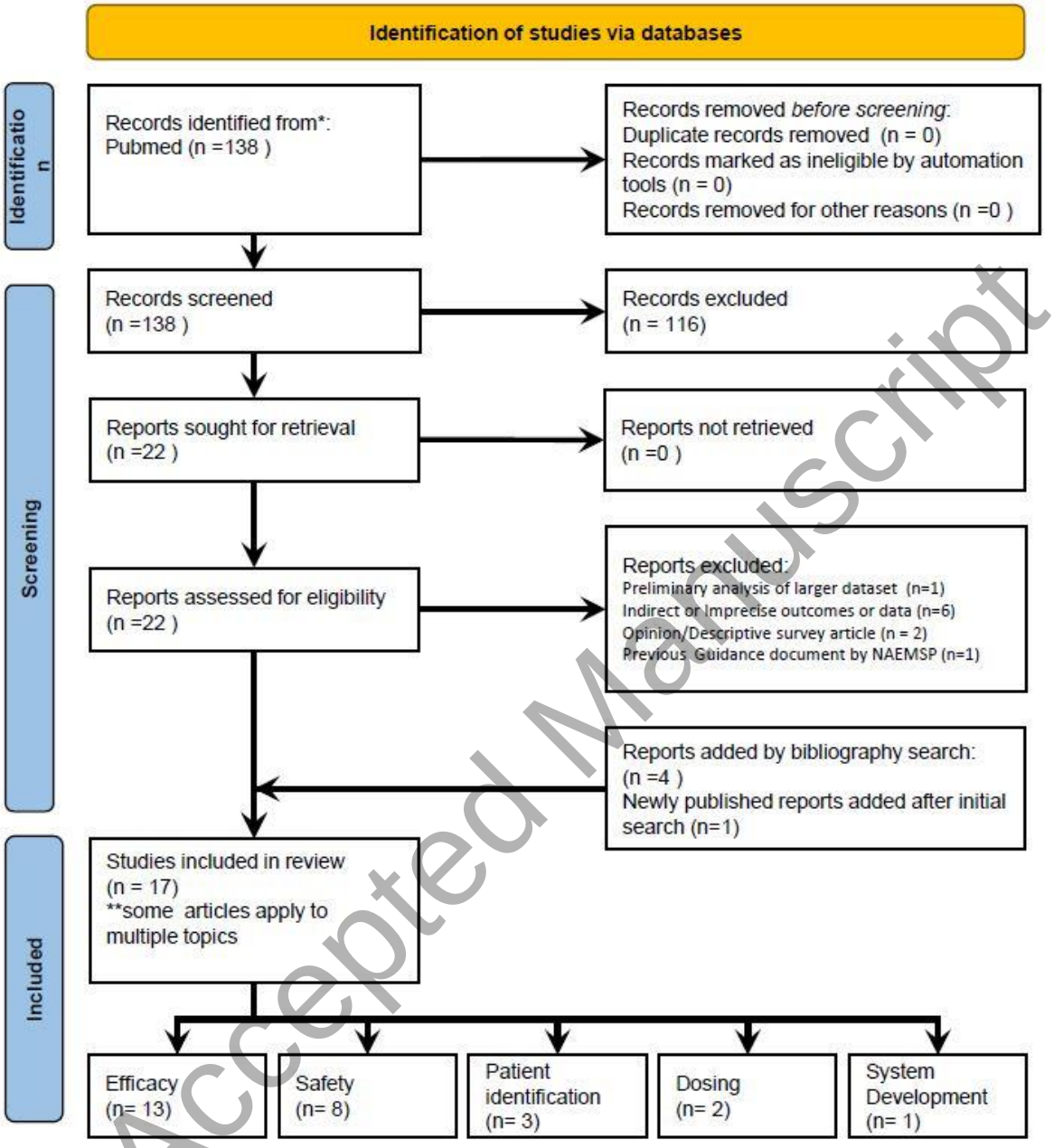
Figure 1: Literature search flow diagram



Database Searched: PubMed Dates: inception to December 22, 2022. See Supplemental Table for search strategy.

Table 1: Prognostic scoring systems

Score	Features	Reference
Bleeding Audit and Trauma Triage (BATT)	Age, mechanism, systolic blood pressure, respiratory rate, GCS	Ageron et al. 2021
Trauma Audit and Research Network (TARN) prognostic model	Based on a chart and a web-based calculator	Perel et al. 2013
Coagulopathy of Severe Trauma (COAST)	Entrapment, systolic blood pressure, temperature, major chest injury, likely intrabdominal or pelvic injury	Gruen et al. 2023

Prognostic tools to identify patients likely to be in hemorrhagic shock that have been used in the literature to identify patients.