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INPLASY

Tranexamic Acid for the Management of Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema: A Systematic Review Protocol

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 October 2025 and was last updated on 25 October 2025.

INTRODUCTION

Review question / Objective In adults with ACE inhibitor–induced angioedema, how does tranexamic acid administration compare to standard supportive care or alternative pharmacologic treatments in reducing symptom severity, preventing airway compromise, and improving clinical outcomes?
This review seeks to investigate the efficacy and safety of tranexamic acid (TXA), via any route of administration (IV, oral, topical, or other), for angiotensin-converting enzyme inhibitor–induced angioedema (ACEI-AAE). It will also examine the role of treatment timing, evaluating whether early TXA use justifies consideration for prehospital protocols.

Rationale ACEI-AAE is a bradykinin-mediated emergency distinct from allergic reactions and often unresponsive to epinephrine or corticosteroids. TXA acts by attenuating plasmin activation and thereby reducing bradykinin generation. Current literature demonstrates TXA is safe, inexpensive, and potentially effective at reducing symptom progression and airway compromise. Although no prehospital studies currently exist, multiple hospital-based studies emphasize that early TXA administration yields improved outcomes. This finding provides a logical bridge for proposing prehospital use as a defensible research and implementation focus.

Condition being studied ACE inhibitor-induced angioedema, a non-allergic adverse drug reaction characterized by bradykinin-mediated swelling of facial and airway tissues.

METHODS

Search strategy Electronic searches will cover:
- CINAHL Ultimate, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, MEDLINE, Scopus, and PubMed.
- Search terms:

1. “ACE inhibitors” OR specific agents (Lisinopril, Enalapril, Ramipril) AND “Tranexamic Acid” OR “TXA” AND “angioedema”.
2. “Bradykinin angioedema” AND “Tranexamic Acid” OR “TXA”.
- (ACE inhibitors OR angiotensin converting enzyme inhibitors OR Lisinopril OR Ramipril OR Enalapril) AND (Tranexamic Acid OR TXA) AND angioedema
- (“ACE inhibitors” OR “angiotensin converting enzyme inhibitors” OR “Benazepril” OR “Captopril” OR “Enalapril” OR “Fosinopril” OR “Lisinopril” OR “Moexipril” OR “Perindopril” OR “Quinapril” OR “Ramipril” OR “Trandolapril”) AND (“bradykinin angioedema” OR “angioedema”) AND (“TXA” OR “tranexamic acid”)

- Filters: 2013–present, English-language publications.
- Grey literature and non-peer-reviewed sources will also be considered to minimize publication bias.

Participant or population Adults presenting with ACE inhibitor-induced angioedema.

Intervention Tranexamic acid (TXA) administr.

Comparator Standard supportive care or other pharmacologic therapies (e.g., icatibant, C1-inhibitor, FFP).

Study designs to be included Randomized controlled trials (RCTs), cohort studies, case-control studies, and case series (≥1 participant).

Eligibility criteria Inclusion: Human studies, English language, published ≥2013. Interventions involving TXA with reported clinical outcomes. Interventions involving TXA with at least one relevant clinical outcome (e.g., symptom resolution, intubation avoidance, ICU admission, recurrence). Exclusion: Non-human studies, reviews, commentaries, or case reports. Studies involving hereditary, allergic, or bradykinin-independent angioedema. Studies evaluating alternative therapies (e.g., icatibant, C1-INH, epinephrine) unless TXA was used concurrently or as a comparator.

Information sources Electronic databases as above, plus reference list searches of included studies and clinical trial registries (e.g., ClinicalTrials.gov).

Main outcome(s) Primary: Resolution time of angioedema symptoms, avoidance of intubation, and mortality.

Additional outcome(s) Secondary: ICU admission rates, adverse events, and recurrence of angioedema.
Improvement in clinical outcomes (symptom resolution, airway stabilization, need for intubation, recurrence rates, ICU admission).

Data management All records will be stored and managed using Covidence for screening, deduplication, and extraction. A shared spreadsheet will be used for data synthesis tracking.

Quality assessment / Risk of bias analysis The methodological quality of included observational studies was assessed using the Newcastle-Ottawa Scale (NOS), a validated tool for evaluating non-randomized studies in systematic reviews. The NOS evaluates studies across three domains: Selection (up to 4 points), Comparability (up to 2 points), and Outcome assessment (up to 3 points), with a maximum score of 9 points for comparative studies.

For studies with comparison groups (Loewe et al., Lindauer et al.), the full 9-point NOS cohort scale was applied. For single-arm studies without comparison groups (Stoldt et al., Wang-Geiger et al., Beauchêne et al., Hasara et al.), a modified 7-point version of the NOS was used, excluding the Comparability domain as this is not applicable to non-comparative study designs. This approach of adapting the NOS for single-arm studies has been previously validated and used in published systematic reviews.

Quality ratings were categorized as good quality (≥70% of maximum possible score: ≥6.3/9 for comparative studies, ≥5/7 for single-arm studies), moderate quality (35-70% of maximum score), or poor quality (<35% of maximum score). Two reviewers independently assessed risk of bias for each study, with discrepancies resolved through discussion or consultation with a third reviewer.

Strategy of data synthesis A narrative synthesis will be performed due to expected study heterogeneity.

Subgroup analysis If data permit, subgroup analyses will compare:
- TXA dosage (IV vs oral administration),
- Timing relative to symptom onset,
- Patient demographic factors (e.g., age, sex, comorbid conditions).

Sensitivity analysis If data permit, to test robustness, studies with a high risk of bias will be excluded to observe effect consistency.

Language restriction English only.

Country(ies) involved United States.

Other relevant information The review will give special consideration to TXA timing. Results will be discussed in the context of potential prehospital protocol translation, emphasizing safety, cost-effectiveness, and accessibility.

Keywords Angiotensin-converting enzyme inhibitors; ACEi-induced angioedema; Tranexamic acid; Bradykinin; Systematic review.

Dissemination plans Results will be reported according to PRISMA 2020 guidelines and submitted to INPLASY and a peer-reviewed journal such as Annals of Emergency Medicine or Clinical Therapeutics.

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