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Effect of tranexamic acid in the treatment of angiotensin-converting enzyme inhibitor-induced angioedema: A systematic review and meta-analysis

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Abstract:

OBJECTIVE: To assess the effectiveness of tranexamic acid (TXA) in the treatment of angiotensin-converting enzyme inhibitor-induced angioedema.

METHODS: A systematic review was conducted using PubMed, Scopus, Embase, and ProQuest databases from inception to January 2025, following PROSPERO registration (CRD42025524300). We included observational studies that evaluated the use of TXA in angiotensin-converting enzyme inhibitor-induced angioedema. Proportion meta-analyses were performed on the data obtained from the selected studies.

RESULTS: Only four retrospective studies met the inclusion criteria, including two cohort studies, one retrospective study, and one case series, encompassing a limited sample size of 133 patients. Meta-analysis showed that approximately 98% of patients treated with TXA did not require intubation, and 76% avoided intensive care unit admission. However, the absence of randomized controlled trials and the retrospective nature of the studies substantially limit the strength and generalizability of these results.

CONCLUSION: TXA may be a potential treatment option for angiotensin-converting enzyme inhibitor-induced angioedema by lowering intensive care unit admission and intubation; however, current evidence is limited and primarily retrospective. Robust prospective, randomized controlled trials are needed to draw definitive conclusions.

Keywords:

Angioedema, angiotensin-converting enzyme inhibitor, tranexamic acid

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Introduction

Angiotensin-converting enzyme inhibitors (ACEIs) are commonly used for hypertension, heart failure, and chronic kidney disease, but a major side effect is angioedema. Unlike histamine-mediated angioedema, ACEI-induced angioedema

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Box-ED section

What is already known on the study topic?

- Angiotensin-converting enzyme (ACE) inhibitor-induced angioedema is bradykinin-mediated, making standard treatments (corticosteroids, antihistamines, and epinephrine) ineffective, especially with airway obstruction risk. Tranexamic acid (TXA) has emerged as a potential therapy, but current supporting evidence is limited and mainly anecdotal. There are no Food and Drug Administration-approved treatments.

What is the conflict on the issue? Has it importance for readers?

- The conflict stems from TXA's growing use despite a lack of robust, high-quality evidence, particularly the absence of randomized controlled trials. This gap is critical for clinicians, as it creates uncertainty regarding TXA's definitive efficacy and safety, underscoring the urgent need for further research to guide clinical practice.

How is this study structured?

- This research is a systematic review and meta-analysis, registered with PROSPERO and adhering to PRISMA guidelines. It involved extensive searches across major databases (PubMed, Scopus, Embase, and ProQuest). Two independent reviewers screened articles and extracted data, while the risk of bias was assessed using ROBINS-I and JBI tools. Proportion meta-analyses were conducted using a random-effects model.

What does this study tell us?

- The study suggests TXA may be beneficial, showing high rates of avoiding intubation (98%) and avoiding intensive care unit admission (76%), with low adverse events and mortality. However, the certainty of this evidence is low to very low due to the retrospective nature, risk of bias, confounders, and inconsistency of the included studies. Therefore, further prospective, randomized trials are essential for definitive conclusions.

is mediated by bradykinin, which does not respond to corticosteroids, antihistamines, or epinephrine.[1,2] Angiotensin-converting enzyme (ACE) inhibition leads to bradykinin accumulation, which results in swelling, most often involving the lips, face, tongue, pharynx, and larynx. Airway involvement can lead to life-threatening obstruction, sometimes requiring intubation or intensive care unit (ICU) care.[1-3] Despite ACEIs being widely prescribed, there are no Food and Drug Administration-approved treatments for ACEi angioedema. Management typically involves discontinuing the ACEI and airway support, while conventional therapies provide limited benefit. For severe cases, options such as tranexamic acid (TXA), icatibant, and ecallantide have been explored. TXA, an anti-fibrinolytic agent, may reduce bradykinin production, but evidence is limited to retrospective studies. This review aims to assess TXA's effectiveness and safety for ACEI-induced angioedema. By synthesizing existing data, this review aims to provide clinicians with a clearer understanding of TXA's role in managing this challenging condition and to highlight the need for further high-quality research.

Methods

Study design

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO ID-CRD42025524300) and conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency.[4]

Eligibility criteria

Studies were selected for inclusion based on the following predefined criteria:

Participants

Studies involving patients of any age, sex, or clinical setting diagnosed clinically with angioedema attributed to ACEI use.

Intervention

Studies that used TXA, regardless of dose, route (intravenous or oral), frequency, or formulation, as part of the therapeutic approach for ACE inhibitor-induced angioedema.

Comparator

Studies that compared TXA to standard care (e.g., supportive management, corticosteroids, antihistamines, epinephrine, or fresh frozen plasma [FFP]), placebo, or those with no comparator or control arm were considered eligible.

Outcomes

Studies that reported on the need for intubation, ICU admission, length of hospital stay, symptom resolution time, adverse events, or mortality following TXA administration.

Study design

Randomized controlled trials (RCTs) and any form of observational studies (prospective, retrospective, case control studies, cohort studies, and case series) were included.

Search strategy

We conducted extensive searches across multiple databases (PubMed, EMBASE, Scopus, and ProQuest).

Two independent reviewers (KIC and SP) utilized a variety of search terms, such as ("tranexamic acid," "antifibrinolytic agent"), ("angiotensin converting enzyme inhibitor," "ACE inhibitor," "enalapril," "captopril"), and ("angioedema"), applying different field codes (e.g., "TITLE-ABS-KEY," "ti-ab-kw," "noft") and Boolean operators (AND, OR, NOT). No restrictions were imposed based on publication date, country, or language. In addition, we reviewed the references of the selected articles for further relevant studies. Gray literature, preprints, or conference abstracts were not included. The initial database search was conducted on January 25, 2025 and reconfirmed on February 28, 2025.

Study selection

To enhance methodological rigor, a two-stage screening process was employed for study selection, where two reviewers (KIC and SP) independently screened titles, abstracts, and full texts for eligibility.[5] Interrater agreement was assessed using Cohen's kappa, which yielded a value of 0.80, indicating good agreement between reviewers and supporting the reliability of the selection process. Discrepancies between reviewers were finally resolved by a third reviewer (SM).

Data extraction and management

Two reviewers (KIC and SP) independently extracted data on study characteristics, baseline details, and outcomes in ACEI-induced angioedema patients treated with TXA, focusing on the proportion of patients not requiring intubation or ICU admission. A third reviewer (SM) verified data accuracy.

Risk of bias assessment of the studies

The methodological quality and risk of bias of all included studies were assessed by two reviewers (KIC and SM) using validated tools as per Cochrane guidelines. The Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool was used for nonrandomized studies, evaluating seven key bias domains. Each domain was rated as low, moderate, serious, or critical risk of bias, and an overall judgment was assigned accordingly. The Joanna Briggs Institute (JBI) checklist was used for case series. Disagreements were resolved by discussion and consultation with a third reviewer (SP).

Statistical analysis

Analyses were performed using Stata MP version 17. The Freeman–Tukey double arcsine transformation was used to stabilize variance in proportions, particularly for studies with skewed/extreme values (near 0 or 1), which can otherwise lead to biased/imprecise pooled estimates. This method reduces the influence of such studies and improves the distribution's normality, enhancing the robustness of the analysis, especially in the context of small sample sizes or rare events, as seen in our review. A random-effects model with restricted maximum likelihood (REML) estimation assumes inherent heterogeneity across the study population/design, which was used to account for between-study variability, providing a more conservative estimate. Pooled estimates were reported with 95% confidence intervals (CIs) and visually represented using forest plots. Heterogeneity was assessed using Cochran's Q test, I^2 statistic (interpreted as: 0%–40% = low, 30%–60% = moderate, 50%–90% = substantial, and 75%–100% = considerable heterogeneity), between-study variance (τ^2), and H2. A Galbraith plot was used to explore heterogeneity and detect outliers. If ≥10 studies were available, sensitivity analyses and publication bias assessments (e.g., funnel plot) were planned.

Assessment of the quality of evidence

The certainty of evidence for primary outcomes was assessed independently by two reviewers (KIC and SM) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, with disagreements resolved by a third reviewer (SP). GRADE is applicable across various study designs, and it evaluates evidence quality based on study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias, overall grading it as high, moderate, low, or very low certainty, reflecting the reviewers' overall confidence in the effect estimates. Although observational studies typically start as low-quality evidence, GRADE allows downgrading for limitations (high risk of bias [e.g., lack of blinding or poor allocation concealment], inconsistency across study findings [I^2 > 50% heterogeneity], indirectness [e.g., differences in population, intervention, or outcomes], imprecision [e.g., wide CIs due to small sample sizes], and suspected publication bias) or upgrading for factors such as strong effect size, clear dose-response, or minimal confounding. These principles enable a nuanced evaluation of observational data, which, although often rated as low or very low quality, may still yield meaningful insights when rigorously assessed. This structured approach supports transparent, evidence-based conclusions about TXA in ACEI-induced angioedema.

Results

Study selection

A total of 81 studies were identified through PubMed, Scopus, Embase, and ProQuest. After removing 17 duplicates, 64 were screened. Only four studies met the inclusion criteria, all of which were retrospective study (two cohort studies, one retrospective study, and one case series) involving a limited sample size of 133 patients treated with TXA for ACEI-induced

angioedema.[6-9] The selection process is shown in the PRISMA flow diagram [Figure 1].

Baseline characteristics of the studies

Three of the four included studies were conducted in the United States. Baseline patient details are shown in Table 1. The face was the most common site of angioedema. In addition to TXA, patients also received H1 and H2 blockers, epinephrine, corticosteroids, FFP, and C1 esterase inhibitor (C1-INH), either prior to or following TXA administration. Lisinopril was used by 79.8% of total patients (257/322) and accounted for 69.2% (92/133) of angioedema cases in the TXA group. The common outcomes assessed in all studies were intubation and ICU admission after TXA treatment.

Methodological quality of the included studies

The ROBINS-I tool [Figure 2a] showed moderate risk of bias for the observational and cohort studies, whereas the JBI tool [Figure 2b] indicated low risk of bias for the case series. However, both study types are generally considered low or very low quality of evidence.

Narrative synthesis of tranexamic acid in the treatment of angiotensin-converting enzyme inhibitors angioedema

TXA was used to treat ACEI-induced angioedema in 133 patients, with doses ranging from 100 mg to 4 g, administered either intravenously (124 patients) or orally (8 patients); the route was unspecified in one case. Fifteen patients out of 133 were intubated, including 8 before TXA administration. In the TXA group, intubation rates were 5.6% (7/125 patients), ICU admission rate was 31.6% (42/133 patients), the mortality rate was 0.75% (1/133 patients), and adverse effects were 0%. Detailed outcomes are presented in Table 1.

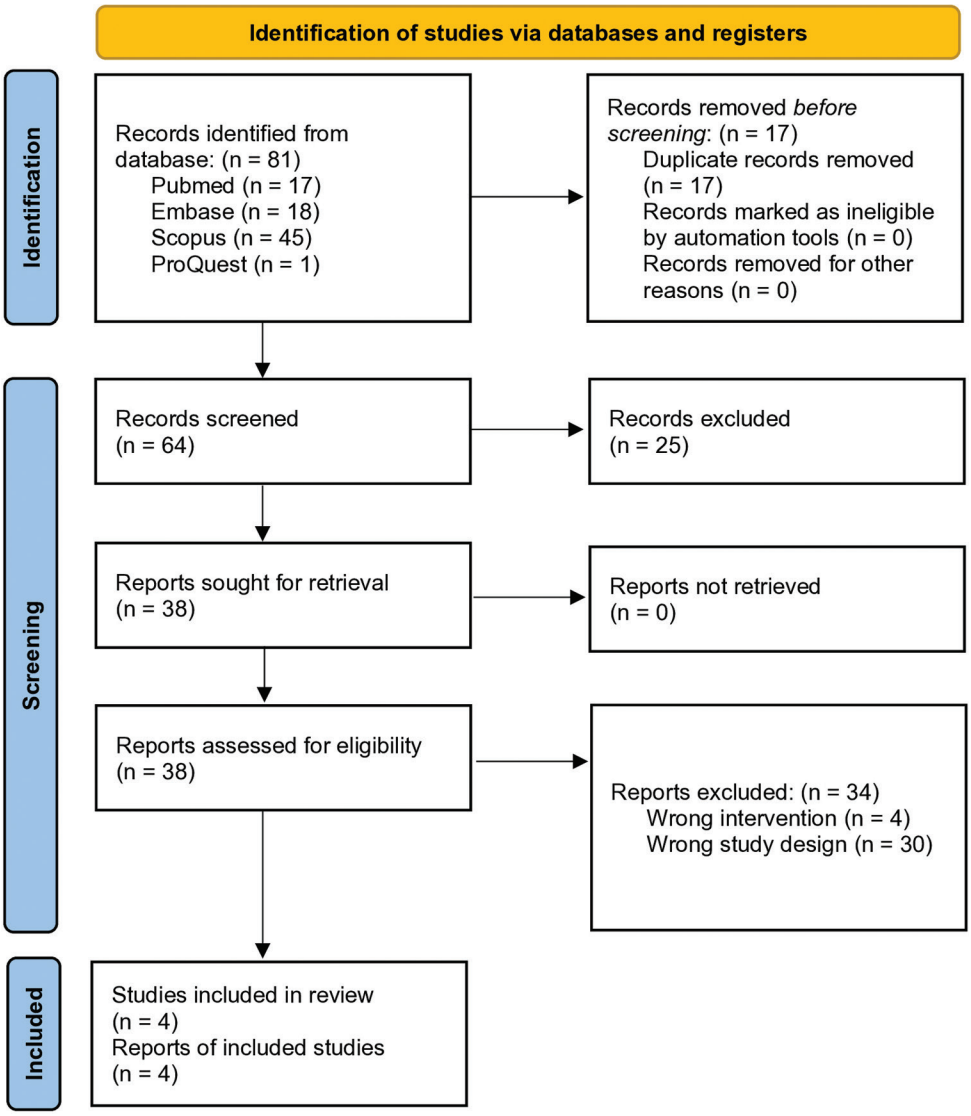

Figure 1: PRISMA flowchart for the study selection process

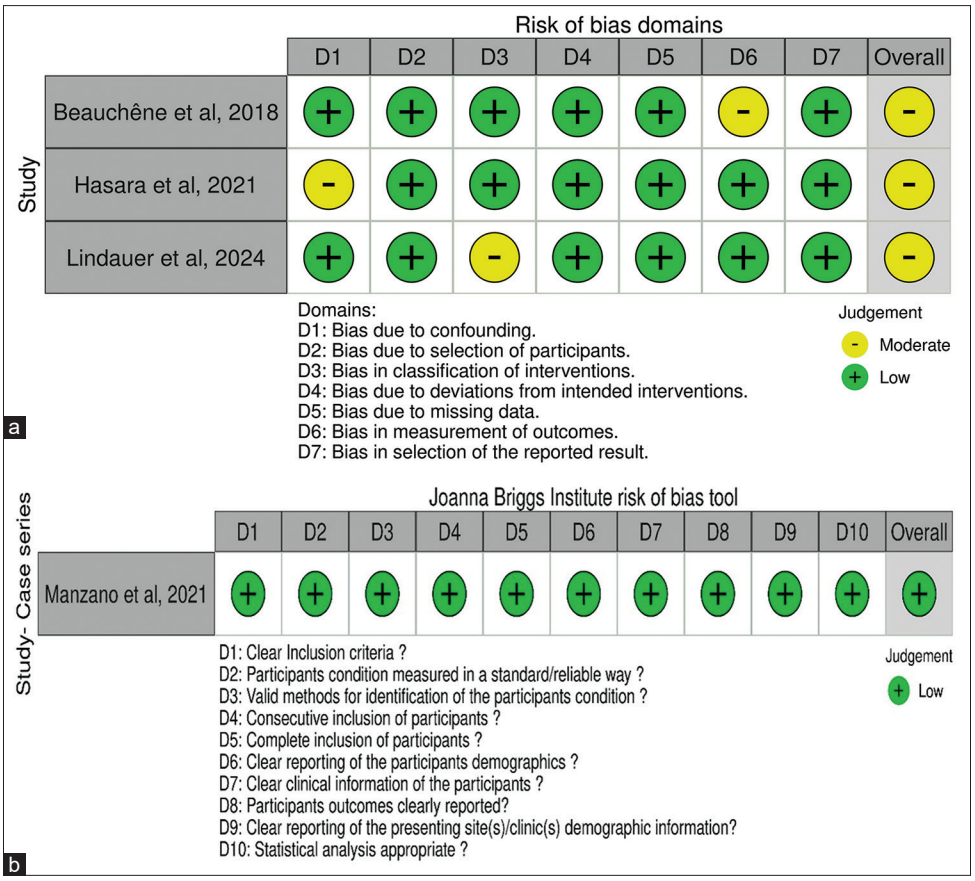

Figure 2: (a) Risk of bias assessment for observational studies using ROBINS-I tool (b) Risk of bias assessment for the case series using Joanna Briggs Institute risk of bias tool

Meta-analysis

Proportion of patients not requiring intubation post-tranexamic acid treatment

This forest plot presents a proportional meta-analysis of TXA effectiveness in preventing intubation in ACEI-induced angioedema, based on data from four studies [Figure 3a and b]. Using Freeman–Tukey transformation and a random-effects REML model, each study's effect size (transformed proportion) is shown with 95% CIs. Number of successes denotes patients not requiring intubation, total denotes TXA-treated patients, blue squares represent point estimates, and the horizontal line represents 95% CI. The green diamond represents the overall pooled proportion, with its center and width indicating the estimate (0.98) and 95% CI (0.91–1.00), suggesting 98% of TXA-treated patients did not require intubation.

Meta-analysis showed moderate heterogeneity (I^2 = 50.17%, τ^2 = 0.04, H^2 =2.01) [Supplementary Table 1]. Although Cochran's Q test was not statistically significant (Q = 6.03, P = 0.11), the Galbraith plot showed precision-dependent heterogeneity. The upward slope suggests studies with greater precision reported a stronger effect size, indicating the possible influence of study-level factors, which may explain the variability and should be further explored.

Proportion of patients not requiring intensive care unit admission posttranexamic acid treatment

This forest plot presents a proportional meta-analysis of TXA effectiveness in preventing ICU admission in ACEI-induced angioedema, based on data from four studies [Figure 3c and d]. Using Freeman–Tukey transformation and a random-effects REML model, each study's effect size (transformed proportion) is shown with 95% CIs. Number of successes denotes patients not requiring ICU admission, total denotes TXA-treated patients, blue squares represent point estimates, and the horizontal line represents 95% CI. The green diamond represents the overall pooled proportion, with its center and width indicating the estimate (0.76) and 95% CI (0.58–0.90), suggesting 76% of TXA-treated patients did not require ICU admission.

The meta-analysis showed significant heterogeneity (I^2 = 73.15%, τ^2 = 0.10, H^2 = 3.72; Q = 14.41, df = 3, P < 0.00), indicating notable variation across studies [Supplementary Table 2]. The Galbraith plot revealed a positive association between study precision and effect

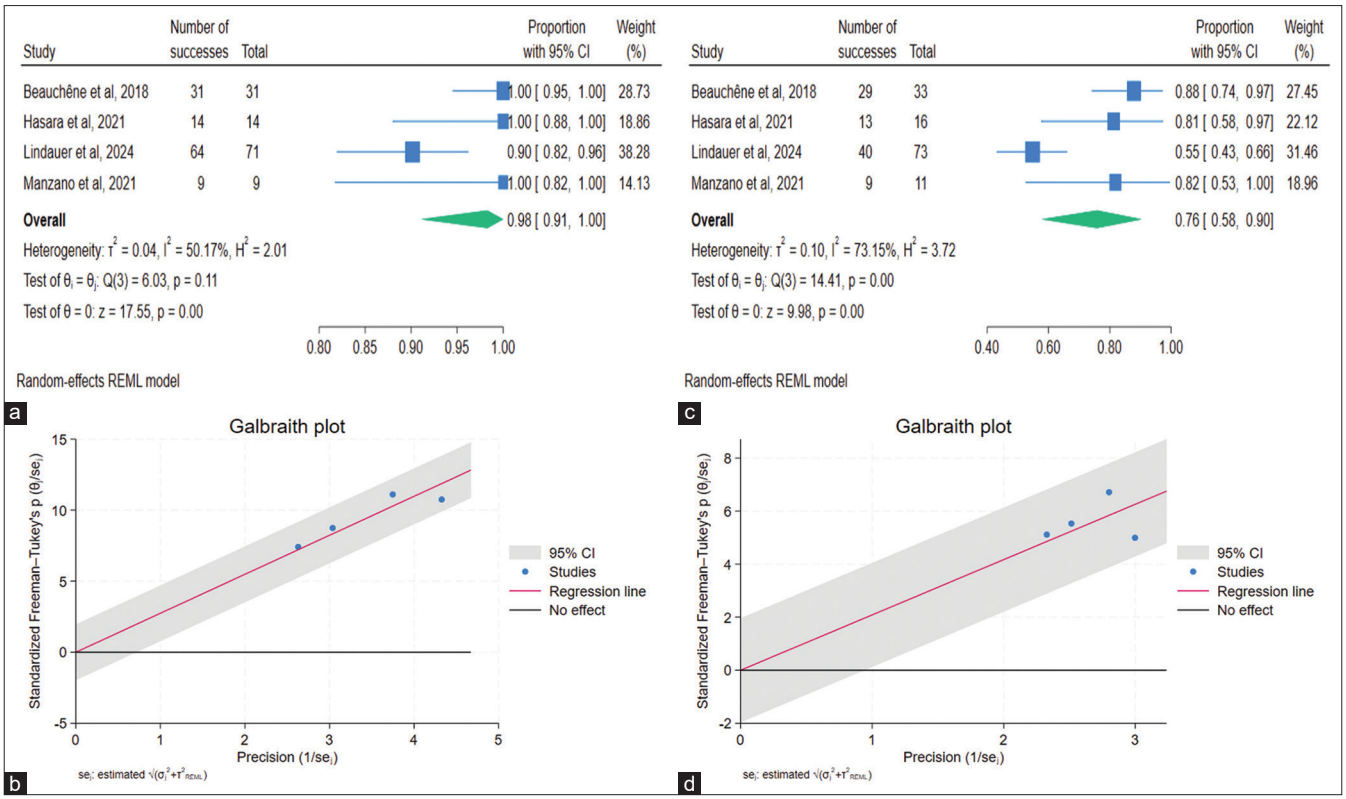

Figure 3: (a) Proportional meta-analysis Forest plot on "intubation prevention among angiotensin-converting enzyme inhibitor (ACEI) induced angioedema post tranexamic acid treatment" (b) Galbraith heterogeneity plot for meta-analysis assessing the effect of Tranexamic acid (TXA) on prevention of intubation in ACEI-induced angioedema (c) Proportional meta-analysis Forest plot on "Non requirement of intensive care unit (ICU) admission post tranexamic acid treatment" (d) Galbraith heterogeneity plot for meta-analysis assessing the effect of TXA on prevention of ICU admission in ACEI-induced angioedema

size. The upward slope of the regression line implies higher-precision studies reported a stronger effect size. This pattern, along with the significant heterogeneity, highlights the need for cautious interpretation and further investigation into variability, such as differences in study populations or methods.

Grade evidence profile and summary of finding table

The meta-analysis suggests a potential benefit of TXA in increasing the likelihood of avoiding intubation (118/125; estimated pooled effect 0.98, 95% CI: 0.91–1.00) and avoiding intensive care admission (91/133; estimated pooled effect 0.76, 95% CI: 0.58–0.90). However, it is crucial to acknowledge the limitations in the available evidence. The certainty of this evidence, assessed using the GRADE system [Table 2], was determined to be low for avoiding intubation and very low for avoiding intensive care admission, reflecting concerns about serious risk of bias in the included nonrandomized studies, inconsistency in results (heterogeneity), and imprecision.

Discussion

TXA is a low-cost, widely available antifibrinolytic agent traditionally used to control bleeding in trauma, surgery, hemoptysis, and bleeding disorders. Its potential use in ACEI-induced angioedema has gained attention, driven by a deeper understanding of the pathophysiology, which, like hereditary angioedema, both driven by excess bradykinin. Given the bradykinin-mediated pathophysiology, TXA has emerged as a promising treatment option due to its safety, accessibility, and ease of administration. While initial evidence supporting TXA was based mainly on case reports and anecdotal evidence, recent retrospective studies have begun to investigate its efficacy. However, despite growing interest, only one comparative study has assessed TXA against a control group, and no RCTs have been conducted to date.

Mechanism and clinical application

ACE normally degrades bradykinin. Thus, ACEI leads to bradykinin accumulation, leading to angioedema.[10-13] TXA, an antifibrinolytic agent, has been proposed as a treatment option due to its ability to inhibit the conversion of plasminogen to plasmin formation.[14-16] Plasmin plays a role in the Kallikrein–Kinin system, contributing indirectly to bradykinin generation. Thus, TXA prevents activation of Kallikrein, a crucial enzyme in the bradykinin cascade. This ultimately leads to a reduction in bradykinin production. Bradykinin is a

Table 1: The baseline characteristics, outcome measures and conclusion of the included studies (*n*=4)

First author, year and study design	Country	Sample size	Age (mean) and race	Sex (male, female)	Site of angioedema	ACE inhibitor	Tranexamic dose	Epinephrine, FFP, C1 esterase inhibitor, Icatibant, Ecallantide use
Beauchêne, 2018[9] Retrospective Observational study	France	33	70.4	Male - 23 Female - 10	Face (33) and/or ENT region (11 had dyspnea on presentation)	Perindopril: 16 Enalapril: 7 Ramipril: 6 Lisinopril: 2 Captopril: 2 Trandolapril: 2	IV – 24 Oral - 8 NA - 1 Doses used: 0.5–4 g Most common 1 g IV	Five patients received icatibant One patient received C1INH concentrate
Hasara, 2021[7] Retrospective Cohort	USA	16	64.3 African Americans, Hispanic, whites	Male - 10 Female - 6	Face (16) (Tongue [11], lips [5])	Lisinopril 13 Benazepril 3	1 g IV - 15 patients 100 mg IV: 1 patient 1 patient required repeat dose of TXA	Five patient received epinephrine (3 - nebulized, 1 IM, 1 SC) Four patients received 2 units of FFP
Lindauer, 2024[8] Retrospective multicenter cohort study	USA	262 (73–189)	Rx group: 58.90 Control Group: 58.63 African Americans	Rx group: Male – 34, Female - 39 Control group: Male - 97 Female - 92	NA	Rx group Lisinopril - 66 Benazepril - 5 Ramipril - 2 Control group Lisinopril: 165 Benazepril: 15 Enalapril: 2 Ramipril: 3 Quinapril: 2	1–2 g IV – initial dose 1–3 g IV – total dose 64 out of 73 (87.7%) received initial TXA 1 g IV and 5 patients received additional dose	Epinephrine use in Rx versus Control group were 28 and 32 FFP use in Rx versus Control group were 17 and 18 C1 esterase inhibitor use in Rx versus Control group were 13 and 5
Martinez Manzano, 2021[6] Retrospective Case series	USA	11	62, African American	Male - 7 Female - 4	Face, neck, mouth, upper airway, with no systemic symptoms	Lisinopril 11	1 g IV single dose in all patients	Epinephrine was used in 4 patients

First author, year and study design	Other treatment taken	Outcomes measured	Outcomes – intubation, ICU admission and mortality	Other outcomes	Conclusion (favourable or not)
Beauchêne, 2018[9] Retrospective Observational study	Corticosteroids, antihistamines, adrenaline, icatibant, C1 INH concentrate	Intubation ICU admission Mortality Side effects of TXA Time to improvement	None of the patients were intubated following TXA therapy.(2 intubated nasotracheally before TXA) Four had ICU admission (all 4 were treated with TXA alone – Not treated with Icatibant or C1INH concentrate) No mortality reported	Most patients (13 out of 30) had improvement within 1 h	TXA can be used as a first line for ACEI induced angioedema (favourable)
Hasara, 2021[7] Retrospective Cohort	Diphenhydramine, Famotidine, Methylprednisolone, Nebulized racemic epinephrine IM epinephrine SC epinephrine FFP	Intubation ICU admission Mortality LOS in ED, ICU, Hospital Side effects of TXA Time to improvement Time to administer TXA therapy	None of the patients were intubated following TXA therapy (two patient intubated prior to TXA therapy) Three had ICU admission No mortality reported	Median symptom to door and TXA time were 246 min and 269 min Median door to TXA is 41 min The mean Time to improvement was 100 (26) min	TXA can be used in TXA induced angioedema treatment plans in emergency department (favourable)

Contd...

Table 1: Contd...

First author, year and study design	Other treatment taken	Outcomes measured	Outcomes – intubation, ICU admission and mortality	Other outcomes	Conclusion (favourable or not)
				85% of patients experienced partial or complete resolution of symptoms following TXA Mean ED LOS is 3.5 (1.9) h 6. Median hospital LOS and ICU stay were 1.5 (0.8–2.8) and 1.9 (1.5–6.2) days Mean duration of MV is 2.5 (1.4) days One patient had a recurrent attack within 28 days needing ED visit	
Lindauer, 2024[8] Retrospective multicenter cohort study	Rx group: Steroids Epinephrine IV Epinephrine IM H1 blocker H2-blocker FFP C1 esterase inhibitor Control group: Steroids Epinephrine IV Epinephrine IM H1 blocker H2-blocker FFP C1 esterase inhibitor	Intubation ICU admission Mortality Length of stay in hospital Side effects of TXA Time to initiation of TXA therapy ED revisit within 7 days Thrombotic events within 7 days of hospital stay	Nine were intubated in the intervention group. (7 received Rx before intubation and 2 after intubation) Control group had 12 intubated patients 33 (Rx group) versus 30 (Control group) had ICU admissions There was one mortality each in Rx and Control group	The median LOS was longer in Rx group compared to Control group (40.2 vs. 21 h) Median (IQR) time to initiate TXA was 1.3 (2.3) h Return to ED within 7 days were 2 (Rx group) and 10 (Control group) Rx group presented with severe symptoms than control group (stage 3 angioedema - 42.5% Rx, 26.5% Control group, Stage 1 angioedema - 34.3% Rx, 64.6% Control group)	Patients on TXA therapy had higher rates of ICU admission, longer LOS, and greater need for intubation (unfavourable – The outcome may be due to severity of the symptoms in the TXA group)
Martinez Manzano, 2021[6] Retrospective Case series	H1/H2 blockers Corticosteroid IM epinephrine	Intubation ICU admission. Mortality Length of stay in hospital Side effects of TXA Time to initiation of TXA therapy	None of the patients were intubated following TXA therapy.(2 patient were intubated prior to TXA and treated in ICU) Two had ICU admission No mortality reported	Median LOS was 1.2 days Median time to initiate TXA was 3.1 h Four patients had prior episode of angioedema	Use of TXA in ACEi induced angioedema seems appropriate and feasible (favourable)

Rx group: Treatment group, NA: Not available, IM: Intramuscular, SC: Subcutaneous, ACE: Angiotensin-converting enzyme, FFP: Fresh frozen plasma, ICU: Intensive care unit, TXA: Tranexamic acid, ACEI: Angiotensin-converting enzyme inhibitors, LOS: Length of stay, ED: Emergency department, IV: Intravenous

potent vasoactive peptide responsible for vasodilation and increased vascular permeability, which contribute to angioedema. By attenuating this pathway, TXA may help reduce bradykinin-mediated vascular leakage and edema.[17]

Tranexamic acid efficacy, safety, and potential confounders

TXA was administered primarily through the intravenous route (93.2% of cases), with doses ranging from 100 mg to 4 g; though oral administration was reported in few. Key outcomes assessed included hospital length of stay, ICU admissions, intubation, and mortality. Across studies, no TXA-related adverse events and a low mortality rate (0.75%) were reported, suggesting a potential safety profile. However, clinical outcomes are likely influenced by several variables, including TXA dose, route, timing, patient characteristics (e.g., age, race, and severity), concurrent therapies, and study setting. Frequent use of concurrent therapies, such as corticosteroids, antihistamines, epinephrine, icatibant, FFP, and C1-INH, introduces significant confounding. In some studies, TXA was preferentially used in patients with more severe symptoms, further complicating comparisons. These factors limit the ability to attribute outcomes solely to TXA and highlight the need for cautious interpretation and further controlled trials.

Several off-label therapies used for ACEI-induced angioedema are derived from hereditary angioedema treatments, including icatibant, ecallantide, FFP, and C1-INH. While icatibant and ecallantide show mixed efficacy and are limited by high cost and availability, FFP

Table 2: Grade evidence profile and summary of findings table for the effect of tranexamic acid on avoiding intubation and intensive care admission

Outcome	Number of studies	Certainty assessment						Number of patients - Tranexamic acid	Effect; Absolute (95% CI)	Certainty
		Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Avoiding intubation	4 (Beauchêne *et al*., 2018,[9] Hasara *et al*., 2021,[7] Lindauer *et al*., 2024,[8] Martinez Manzano *et al*., 2021[6])	Nonrandomized studies	Serious (some studies have confounding issues, missing data, etc.)	Serious (I^2=50.17%)	Not serious (studies are directly relevant to the population and outcomes of interest)	Not serious (narrow CI)	None	118/125 (94.4%)	0.98 (0.91–1.00)	⊕⊕◯◯ low
Avoiding intensive care admission	4 (Beauchêne *et al*., 2018,[9] Hasara *et al*., 2021,[7] Lindauer *et al*., 2024,[8] Martinez Manzano *et al*., 2021[6])	Nonrandomized studies	Serious (some studies have confounding issues, missing data, etc.)	Serious (I^2=73.15%)	Not serious (studies are directly relevant to the population and outcomes of interest)	Serious (wider CI)	None	91/133 (68.4%)	0.76 (0.58–0.90)	⊕◯◯◯ very low

CI: Confidence interval

offers a more accessible and cost-effective option despite safety concerns. C1-INH has shown promise in case reports, but a lack of clinical trials and limited emergency access restrict its use. Importantly, no direct studies compare these agents with TXA, limiting evidence.

Clinical/methodological/statistical heterogeneity

Clinical heterogeneity across studies was evident, reflecting differences in patient demographics, ACE inhibitor types, TXA dose, route, timing, and concurrent treatments. Methodological variability, including differences in study design, sample size, and outcome definitions, further contributed to inconsistency. Frequent use of cointerventions – such as corticosteroids, H1/H2 blockers, epinephrine, FFP, and C1-INH – introduced additional confounding. These factors likely underlie the moderate-to-high statistical heterogeneity observed and support cautious interpretation of pooled results.

Meta-analysis findings

The efficacy of TXA in preventing intubation and ICU admission in ACE inhibitor-induced angioedema was analyzed across four studies. The pooled proportion of patients not requiring intubation was 0.98 (95% CI: 0.91–1.00), with moderate heterogeneity ($I^2 = 50.2\%$, $P = 0.11$). For ICU admission, 76% did not require ICU care (95% CI: 0.58–0.90), though substantial heterogeneity was present ($I^2 = 73.15\%$, $P < 0.00$), reflecting differences in study populations and methods.

Implications for clinical practice

TXA may be a potentially effective and accessible treatment for ACEI-induced angioedema, with reported doses ranging from 100 mg to 4 g given (most common 1 g) via intravenously or orally. Preliminary findings suggest that TXA may possibly reduce the need for intubation and ICU admissions in patients. Although TXA is widely available, low-cost, and showed no reported adverse effects in the included studies, the supporting evidence is limited and of very low quality due to retrospective design, bias, and inconsistency. Although TXA may be a potential early treatment option,[18-22] robust RCTs are needed to confirm its efficacy and safety.

Recommendations for future research

This review underscores the lack of high-quality evidence on TXA for ACEI-induced angioedema, with only a few retrospective studies and no RCTs to date. Future research should focus on well-powered RCTs and prospective multicenter studies to better assess TXA's efficacy and safety. These studies should focus on optimal dosing, treatment duration, administration route, dose frequency, and standardized outcomes such as symptom resolution time, hospital/ICU stay duration, intubation rates, and recurrence. Evaluating adverse effects across diverse populations is also vital

to inform clinical guidelines and decision-making. Apart from TXA, no direct comparative studies have been conducted between different agents for ACEI-induced angioedema. Future research is needed to facilitate more comprehensive comparisons of efficacy and adverse effects, ultimately aiding in the selection of the most appropriate treatment.[11]

Limitation and strength

This systematic review is among the first to assess TXA for ACEI-induced angioedema, based on a comprehensive search across multiple databases. However, the overall evidence quality is low, with all studies being retrospective, primarily observational, and case series, with no RCTs. Most were single-arm studies, lacking a comparison group, except one which limits the robustness of findings. The small sample size (133 patients) reduces generalizability, and moderate-to-substantial heterogeneity reflects variability in patient profiles, TXA dosing, timing, and co-treatments. The absence of standardized TXA protocols and frequent use of concurrent therapies confound interpretation. Long-term efficacy, recurrence, and safety data remain limited. The literature search was last updated in February 2025, so studies published after that may not have been captured. Limited data precluded subgroup analysis. Publication bias could not be assessed due to the limited (<10) studies.

Conclusion

TXA may be a potential treatment option for angioedema induced by ACEIs. Our review indicates a possible association between TXA use and reduced rates of intubation and ICU admission in these patients. However, this finding is based on retrospective data, and the lack of RCTs limits the strength of the evidence. Confounding from concurrent therapies and variability in TXA use warrant cautious interpretation. Given these significant gaps, more robust prospective and RCTs are needed to draw firmer conclusions about the efficacy and safety of TXA in ACEI-induced angioedema and to guide clinical decision-making.

Author contributions' statement

SM, KIC: Conceptualization (lead), Resources (lead), Writing-original draft (lead), Writing, Reviewing and Editing (lead), Visualization (lead). SP, GR, AR: Conceptualization (equal), Writing Reviewing, and Editing (equal). YK, EG, and AK: Writing Review and Editing (Supporting).

Conflicts of interest

None Declared.

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Supplementary Table 1: Proportional meta-analysis on "Nonrequirement of intubation posttranexamic acid treatment

Method: Freeman-Tukey proportional transformation (inverse double arcsine square root), Random effect model (REML method)				
Author, year	**Total**	**Events**	**Weight % (random)**	**Proportion (95% CI)**
Beauchêne *et al.*, 2018	31	31	28.73	1 (0.95–1)
Hasara *et al.*, 2021	14	14	18.86	1 (0.88–1)
Lindauer *et al.*, 2024	71	64	38.28	0.90 (0.82–0.96)
Manzano *et al.*, 2021	9	9	14.13	1 (0.82–1)
Total	125	118	100	0.98 (0.91–1)

Test of heterogeneity τ^2=0.04, I^2 (inconsistency)=50.17%, H^2=2.01, Test of homogeneity Cochrane $Q=\chi^2$=6.03 (df=3), $P>Q$=0.1102, Test of theta=0: Z=17.55, $P>Z$=0.0000, Invftukey pooled proportion (theta)=0.98 (0.91–1). CI: Confidence interval, REML: Random-effects model with restricted maximum likelihood

Supplementary Table 2: Proportional meta-analysis on "Nonrequirement of intensive care unit admission posttranexamic acid treatment

Method: Freeman-Tukey proportional transformation (inverse double arcsine square root), Random effect model (REML method)				
Author, year	**Total**	**Events**	**Weight % (random)**	**Proportion (95% CI)**
Beauchêne *et al.*, 2018	33	29	27.45%	0.88 (0.74–0.97)
Hasara *et al.*, 2021	16	13	22.12%	0.81 (0.58–0.97)
Lindauer *et al.*, 2024	73	40	31.46%	0.55 (0.43–0.66)
Manzano *et al.*, 2021	11	9	18.96%	0.82 (0.53–1.00)
Total	133	91	100%	0.76 (0.55–0.90)

Test of heterogeneity τ^2=0.10, I^2 (inconsistency)=73.15%, H^2=3.72, Test of homogeneity Cochrane Q=χ^2=14.41 (df=3), $P>Q$=0.0024, Test of theta=0: Z=9.98, $P>Z$=0.0000, Invftukey pooled proportion (theta)=0.76 (0.58–0.90). CI: Confidence interval, REML: Random-effects model with restricted maximum likelihood