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The Efficacy and Application of Tranexamic Acid in Emergency Medicine: EMAT Clinical Policy- 2024

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EMAT Türkiye Acil Tıp Derneği | EMERGENCY MEDICINE ASSOCIATION OF TURKEY

The Efficacy and Application of Tranexamic Acid in Emergency Medicine: EMAT Clinical Policy- 2024

Prepared and approved by the Emergency Medicine Association of Turkey (EMAT) – Research Committee.

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ABSTRACT

This clinical policy by the Emergency Medicine Association of Turkey (EMAT) provides guidance on the use of tranexamic acid (TXA) in emergency settings. TXA, an antifibrinolytic drug, is used to control bleeding by inhibiting plasminogen. Its applications have expanded from hemophilia and severe menstrual bleeding to include various forms of trauma and surgery-related bleeding. Despite its potential benefits, the use of TXA in emergency settings must be carefully evaluated due to its associated risks, including venous thromboembolism. This policy aims to offer evidence-based recommendations on the indications and contraindications of TXA in different clinical scenarios encountered in emergency departments. The guidelines were developed using the "Grading of Recommendations, Assessment, Development, and Evaluations" (GRADE) approach, incorporating systematic literature reviews, and expert consensus from the EMAT Research Committee. This document focuses on critical clinical questions regarding the efficacy and safety of TXA in situations such as gastrointestinal bleeding, multi-trauma, traumatic brain injury, non-traumatic intracranial hemorrhage, hemoptysis, and epistaxis. By addressing these issues, the policy seeks to assist emergency physicians in making informed decisions about the use of TXA, ultimately aiming to improve patient outcomes.

INTRODUCTION

Tranexamic acid (TXA) is an antifibrinolytic drug known to facilitate thrombosis by inhibiting plasminogen, and it is used to stop or prevent bleeding in many serious cases due to this effect[1]. Initially, TXA was used primarily for hemorrhage prophylaxis or control in hemophilia patients and for managing severe menstrual bleeding. For a long time, it received Food and Drug Administration (FDA) approval only for these two clinical scenarios[2]. Because TXA is inexpensive and its adverse effect profile relatively safe, its indications for use have become widespread over time. These include post-traumatic bleeding, postpartum bleeding, bleeding after surgical procedures (such as tonsillectomy), bleeding after tooth extraction (especially in hemophilia patients), gastrointestinal bleeding, and nasal bleeding. It is also used to stop bleeding in severe bleeding scenarios following excessive fibrinolysis secondary to fibrinolytic treatments.

Although TXA can be lifesaving in certain clinical situations due to its hemostatic effect, it must be used with caution because of

its adverse effect profile. While some studies in the current literature show that TXA reduced mortality, others reported that it did not improve survival[3,4]. Considering that some publications report significant adverse effects, such as an increase in venous thromboembolic events, TXA, like all other treatments, should be used with proper cost-benefit assessments[4]. The conflicting results reported in the literature may be due to methodological differences and errors in the studies, or because the effect of TXA may yield different results in different clinical settings. In this context, instead of using TXA in all bleeding situations, it would be more accurate to determine the clinical situations in which it is effective and apply it only in appropriate scenarios.

This clinical policy was prepared by the Emergency Medicine Association of Turkey-Research Committee (EMAT-Research committee) in 2024. It aims to provide an evidence-based approach and guide physicians on the use of TXA in different clinical scenarios by answering important clinical questions regarding the indications for its use in emergency settings. This clinical policy focuses on the emergency department (ED) uses of the drug, rather than providing a perspective on all indications of TXA.

A summary table of all recommendations included in the guide is presented below (Table 1).

Table 1. Summaries of all recommendations (5 scenarios).

SCENARIO-1		
USE OF TRANEXAMIC ACID IN PATIENTS WITH GASTROINTESTINAL SYSTEM BLEEDING		
Is tranexamic acid an effective and safe treatment option in the emergency management of patients with acute gastrointestinal bleeding?		
LEVEL OF RECOMMENDATION	RECOMMENDATION	LEVEL OF EVIDENCE
Strong Against	Tranexamic acid treatment does not provide benefits in terms of important clinical outcomes such as mortality and rebleeding in patients with acute lower and upper gastrointestinal bleeding. Additionally, considering the increased risk of venous thromboembolism, as a panel, we do not recommend the use of tranexamic acid in patients with acute upper or lower gastrointestinal bleeding.	High

SCENARIO-2		
USE OF TRANEXAMIC ACID IN TRAUMA PATIENTS		
Is tranexamic acid, given in addition to standard treatments, an effective and safe treatment option in patients with multi-trauma who are bleeding or at high risk of bleeding?		
LEVEL OF RECOMMENDATION	RECOMMENDATION	LEVEL OF EVIDENCE
Moderate	We recommend administering intravenous (IV) tranexamic acid in the early period, either pre-hospital or upon arrival at the hospital, as it is beneficial for mortality in multi-trauma patients who are bleeding or at high risk of bleeding. In emergency departments or pre-hospital settings, tranexamic acid should be administered within the first 3 hours after trauma, with an initial 1-gram IV bolus followed by a 1-gram infusion over 8 hours.	Moderate
Moderate	Considering the subgroup analysis results of the CRASH-3 study, which has the largest sample size related to the management of patients with traumatic brain injury (TBI), we recommend the administration of tranexamic acid to patients with moderate TBI (GCS 9-12) and those with mild TBI (GCS 13-15) who have any intracranial hemorrhage, as it may offer a mortality benefit. Specifically, we suggest a 1-gram IV bolus followed by a 1-gram infusion over 8 hours within the first 3 hours after trauma for these patients.	Moderate
Weak	Considering all TBI patients regardless of severity, the routine early administration of tranexamic acid does not appear to have an effect on 28-day mortality and neurological outcomes. However, given the safety profile of tranexamic acid in traumatic patients and the indirect evidence in favor of the drug from the subgroup analysis results of the CRASH-3 study, tranexamic acid administration within the first 3 hours (1-gram IV bolus followed by 1-gram infusion over 8 hours) may be considered in patients with severe TBI (GCS <9	Low
Weak	Due to the lack of evidence on the benefits of tranexamic acid in patients with mild TBI (GCS 13-15) without intracranial hemorrhage, we do not recommend the routine use of tranexamic acid in this patient group.	Very Low

SCENARIO-3		
USE OF TRANEXAMIC ACID IN PATIENTS WITH NON-TRAUMATIC ACUTE INTRACRANIAL HEMORRHAGE?		
Is intravenous tranexamic acid, used in addition to standard care, an effective and safe treatment option in patients with non-traumatic acute intracranial hemorrhage?		
LEVEL OF RECOMMENDATION	RECOMMENDATION	LEVEL OF EVIDENCE
Moderate	In patients with acute non-traumatic intracerebral hemorrhage (ICH), early administration of intravenous (IV) tranexamic acid treatment does not lead to a significant increase in the frequency of side effects. However, it also does not have a positive effect on outcomes such as hematoma expansion, mortality, and neurological sequelae. Therefore, as panel members, we do not recommend the routine use of IV tranexamic acid treatment in patients with acute non-traumatic ICH.	Moderate
Weak	In patients with acute non-traumatic subarachnoid hemorrhage (SAH), early administration of intravenous (IV) tranexamic acid treatment does not lead to a significant increase in the frequency of side effects but it does not appear to have an improving effect on neurological outcomes. Therefore, we do not recommend the routine use of early tranexamic acid in the management of SAH patients.	Low

SCENARIO-4		
USE OF TRANEXAMIC ACID IN PATIENTS WITH HEMOPTYSIS		
Should tranexamic acid be used in addition to standard care in patients with hemoptysis?		
LEVEL OF RECOMMENDATION	RECOMMENDATION	LEVEL OF EVIDENCE
Weak	Tranexamic acid treatment may be considered for patients with non-massive hemoptysis requiring hospitalization or procedures such as bronchoscopy in the emergency department, as no significant adverse effects have been reported.	Very Low
Weak	Studies evaluating the efficacy of nebulized tranexamic acid suggest that the nebulized route appears superior to other methods of delivery. However, due to the small sample sizes of the studies and the IV tranexamic acid doses being well below standard, the panel does not make a recommendation on which treatment route to prefer.	Very Low
Weak	Despite encountering varying doses in studies and daily practice for IV tranexamic acid administration, the panel considers it more reasonable to follow the protocol of 1-gram IV bolus followed by 1-gram IV infusion over 8 hours, as we have more information on the safety profile of this regimen.	Very Low
Weak	There is insufficient evidence regarding the efficacy of tranexamic acid treatment in the management of patients with massive hemoptysis. However, considering the indirect evidence provided by low-level studies in patients with non-massive hemoptysis, the use of tranexamic acid may be considered in cases where interventions such as embolization or bronchoscopy are likely to be delayed.	Very Low

SCENARIO-5		
USE OF TRANEXAMIC ACID IN PATIENTS WITH EPISTAXIS		
Is the application of local tranexamic acid plus compression, as an alternative to standard interventions, an effective and safe treatment option in patients with epistaxis (nosebleeds)?		
LEVEL OF RECOMMENDATION	RECOMMENDATION	LEVEL OF EVIDENCE
Weak	After the application of local tranexamic acid and external nasal compression, although there are conflicting results between anterior nasal packing and placebo applications, no result indicates that tranexamic acid treatment is inferior. Considering the discomfort associated with anterior nasal packing application and studies showing no serious adverse effects, we believe that local application of tranexamic acid could be a potential alternative for emergency physicians in the management of epistaxis in emergency departments.	Low
Weak	Due to conflicting and insufficient evidence regarding the method of delivery for tranexamic acid application and the optimal drug dose, we do not make any specific recommendations and suggest adhering to local protocols.	-

METHODS

This clinical policy has been prepared based on the "Grading of Recommendations, Assessment, Development, and Evaluations" (GRADE) approach and by evaluating the evidence in the literature[5]. The recommendations in the guideline were formulated by considering the level of evidence in the literature. In cases where the evidence was insufficient or conflicting, the relevant clinical questions were answered by voting among the members of the EMAT-Research Committee, advisory committee, based on a majority decision. This clinical policy guideline was first published on the EMAT website (https://tatd.org.tr/arastirma/), announced via social media, and published by the associated EMAT publications. Although the option to update the EMAT clinical policy guidelines earlier in case of a significant development remains open, it has been decided that they will be routinely updated every three years.

Determining the clinical questions

The EMAT identified the clinical policy topics that needed to be prioritized. Selected topics' clinical questions were gathered from doctors nationwide. Announcements were made using the EMAT website (https://tatd.org.tr/arastirma/) and social media tools, and clinical questions were collected using Google Forms. Within the specified timeframe (60 days), the collected clinical questions were ranked by the EMAT-Research Committee, oversight committee members using a 9-point Likert scale based on the priority of the need for answers (1-3: non-critical and unimportant outcomes, 4-6: non-critical but important outcomes, 7-9: critical outcomes). As a result of the voting, it was decided that both non-critical but important outcomes and critical outcomes should be addressed based on evidence.

Systematic literature review and selection of the studies

For each clinical question, a systematic literature review was conducted using the SCOPUS, MEDLINE, and WOS databases with the specified keywords, and the findings were shared in the relevant section of the clinical question.

The articles obtained from the systematic literature review for each clinical question were separately transferred to Rayyan software[6]. Two blinded reviewers independently assessed whether the articles were related to the clinical question by reading the abstracts. Articles on which the two reviewers disagreed were evaluated by a third reviewer, who made the final decision.

Classification of the Evidence

For each critical question, the included articles were critically reviewed by at least two researchers, and the evidence was graded using the GRADEPro software and the GRADE approach (very low, low, moderate, and high levels of evidence). The risk of bias assessment was conducted using the Cochrane Rob-2 and Robins-E tools (Low bias, moderate/some concerns bias, and high bias level). The risk of bias assessment was performed by two blinded reviewers. Articles where the reviewers had conflicting decisions were evaluated by a third reviewer, who made the final decision.

Determining recommendation levels from evidence levels

Based on the evidence tables created using the GRADE approach, recommendations were developed according to appropriate recommendation levels. The levels of recommendations are defined in Table-2 below.

Table 2. The levels of recommendations

LEVEL OF RECOMMENDATION	RECOMMENDATION
Strong	Recommendations supported by moderate to high levels of evidence, indicating that the benefits of the practice significantly outweigh the risks. Recommendations where the majority of panel members agree that the practice is evidently beneficial, even if based on low levels of evidence, especially for critical outcomes.
Moderate	Recommendations supported by conflicting moderate or high levels of evidence on whether the benefits of the practice outweigh its risks. Recommendations supported by low or very low levels of evidence indicating that the benefits outweigh the harms.
Weak	Recommendations supported by conflicting low or very low levels of evidence about whether the benefits of the practice outweigh the harms. Recommendations where panel members disagree on the benefits of the practice.

LEVEL OF RECOMMENDATION	RECOMMENDATION
Strong	Recommendations supported by moderate to high levels of evidence, indicating that the benefits of the practice significantly outweigh the risks. Recommendations where the majority of panel members agree that the practice is evidently beneficial, even if based on low levels of evidence, especially for critical outcomes.
Moderate	Recommendations supported by conflicting moderate or high levels of evidence on whether the benefits of the practice outweigh its risks. Recommendations supported by low or very low levels of evidence indicating that the benefits outweigh the harms.

This clinical policy is a recommendation document aimed at physicians working in emergency departments. The scope of patients includes adults presenting to emergency departments, with pediatric patients excluded from the guide. The EMAT clinical policy reflects the official views of EMAT as they contain evidence-based answers and recommendations from the current literature. However, they are not definitive and final recommendations for physicians. EMAT respects the experiences of physicians and the preferences of patients when making the final decision.

NON-CRITICAL BUT IMPORTANT CLINICAL QUESTIONS

Non-critical but important clinical questions and their evidence-based answers are presented in detail below, along with a discussion of the literature

SCENARIO-1. Is tranexamic acid an effective and safe treatment option in the emergency management of patients with acute gastrointestinal (GI) bleeding?

1. TXA use in GI bleeding	
Level of recommendation and Recommendation	**Level of evidence**
Strong against	
Tranexamic acid does not provide any benefit in terms of critical clinical outcomes such as mortality and rebleeding in patients with acute GI bleeding. Additionally, considering the increased risk of venous thromboembolism, as a panel, we do not recommend the use of tranexamic acid in patients with acute upper or lower GI bleeding	High

Rationale and background for the recommendation

Acute GI bleeding is one of the common causes of significant morbidity and mortality in the ED. While endoscopic methods to identify and stop the bleeding source form the cornerstone of managing patients with GI bleeding, various treatments such as fluid resuscitation, proton pump inhibitors, somatostatin, and erythromycin can also be used in appropriate indications in the early period[7, 8]. In addition to these treatments, another practice that continues to be debated is the use of TXA, an antifibrinolytic. The European Society of Gastrointestinal Endoscopy (ESGE) in its 2021 "*Non-variceal Upper GI Bleeding Guideline*" did not recommend the use of tranexamic acid, while the National Institute for Health and Care Excellence (NICE) in its 2016 "*Guideline for Upper GI Bleeding in Patients Over 16*" and the American College of Gastroenterology (ACG) in its 2021 "*Guideline for Upper GI and Ulcer Bleeding*" do not have a recommendation regarding the use of TXA[7-9]. However, since the efficacy of TXA has been demonstrated in different clinical scenarios, there are differing opinions among physicians about whether it can be used in patients with GI bleeding. This guide aims to provide evidence-based recommendations to emergency physicians for the early management of acute GI bleeding with TXA in patients encountered in the EDs.

Selection of studies

A systematic literature review conducted with the pertinent keywords (Supplementary File-1, at the end of the document) identified a total of 206 studies. Out of the 28 studies related to the research question, only 13 randomized controlled trials (RCTs) were included following an assessment, as there was a sufficient number of RCT designs (Supplementary File-2, at the end of the document).

The bias assessment conducted using the Cochrane Rob-2 tool revealed that 1 article had a low risk of bias, 2 articles had a moderate risk of bias, and 10 articles had a high risk of bias (Figure-1). It was determined that the 3 articles with low and moderate bias risks were not suitable for meta-analysis due to differences in treatment arms or outcomes. While addressing the relevant clinical question, priority was given to the 3 RCTs with low and moderate risk of bias. A summary of the studies is presented in Supplementary File-3 (at the end of the document). GRADE evidence classification tables showing the evidence ratings of the studies are presented in Supplementary File-4 (at the end of the document).

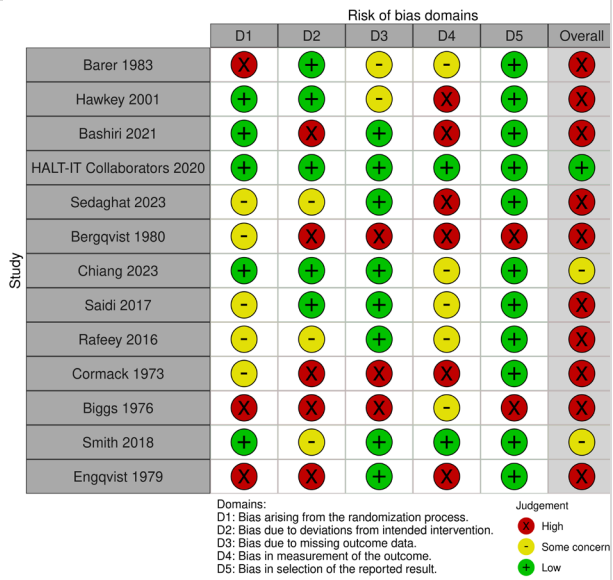

Figure-1: Traffic light charts for GI bleeding articles (Rob-2 Bias Assessment).

Overview of studies and measures of outcome

In the existing studies, the effectiveness of TXA was primarily examined; however, there were variations in the outcome measures and the selection of comparison groups.

The largest study on this topic, and the only one with a low risk of bias, is the HALT-IT study published in 2020. The HALT-IT study, conducted in 15 countries and 164 hospitals, involved adult patients with severe upper or lower acute GI bleeding (those at risk of mortality, hypotensive, tachycardic or with signs of shock, or those requiring transfusion or urgent endoscopy and/or surgical intervention). The study compared intravenous (IV) TXA and placebo, with the primary outcome being 5-day mortality due to bleeding, while 24-hour and 28-day mortality and rebleeding rates were also analyzed. The study, which included a total of 12009 patients, used a modified intention to treat (ITT) analysis, with the analyses conducted on the 11952 patients who received the initial treatment. Bleeding-related death within 5 days of randomization occurred in 222 patients (4%) in the TXA group and in 226 patients (4%) in the placebo group and no statistically significant difference was found (RR 0.99, 95%CI 0.82 to 1.18)[4]. No statistically significant difference was found between the groups in terms of secondary outcomes (bleeding-related death within 24 hours, bleeding-related death within 28 days, rebleeding within 24 hours, rebleeding within 5 days, and rebleeding within 28 days)[4].

The HALT-IT study is one of the rare studies where a broad adverse effect profile was also analyzed. Arterial thromboembolic events (myocardial infarction or stroke) were found to be similar in the TXA group and the placebo group (42 [0.7%] vs. 46 [0.8%], RR 0.92, 95%CI 0.60 to 1.39). Venous thromboembolic events (deep vein thrombosis or pulmonary embolism) were found to be statistically significantly higher in the TXA group compared to the placebo group (48 [0.8%] vs. 26 [0.4%], RR 1.85, 95%CI 1.15 to 2.98). In summary, the HALT-IT study found that TXA did not provide any benefits in preventing mortality and rebleeding and was associated with harmful effects concerning venous thromboembolism. The HALT-IT authors even warned the relevant authorities that the license for TXA in GI bleeding should be reconsidered[4].

Of the 13 RCTs examining the use of TXA in gastrointestinal bleeding, two were found to have a moderate risk of bias. The first study of the two RCTs trials with a moderate risk of bias is the one conducted by Smith and colleagues, which involved 100 patients and was published in 2018. This study was performed on adult patients with lower GI bleeding. In the study, TXA was administered orally and compared with a placebo, evaluating endpoints such as hemoglobin drop, transfusion requirement, length of hospital stay, re-admission, and complications. No statistically significant difference was found between the groups for any of the outcomes (hemoglobin drop, proportions and amounts of transfusion,

length of hospital stay, re-admission, and complications)[10].

In the second study with a moderate risk of bias, dated 2023 and conducted with adult patients over 20 years of age, patients with endoscopically confirmed GI bleeding were included. Early treatment failure within 4 days of the first endoscopy was evaluated as the primary outcome. In this study, which included 60 patients, early treatment failure was reported to be significantly less in the TXA group (6.7% vs. 30%, p=0.042). Both univariate and multivariate analyses found early treatment failure to be less in the TXA group; however, it is noteworthy that the 95% confidence intervals were quite wide in both analyses ((univariate analysis: RR, 0.17, 95%CI, 0.03 to 0.85; p=0.032), (multivariate analysis: RR, 0.10, 95%CI, 0.01 to 0.87; p=0.037)[11].

Among the 13 RCTs investigating the use of TXA in GI bleeding, all 10 studies with a high risk of bias were conducted on patients with upper GI bleeding. In 6 of these, TXA was administered IV to the intervention group, in 2 it was administered orally (PO), and in 2 it was administered via a nasogastric tube. Although TXA was compared with a placebo in most of these studies, in one study it was compared with saline with epinephrine, in another study it was compared with placebo, and cimetidine, and in yet another study it was compared with, lansoprazole, placebo, and TXA + lansoprazole[7-16].

In 8 out of the 10 studies with high-risk bias, the groups were compared in terms of mortality rates. Seven studies found no difference, but one study conducted on 775 patients (Barer et al., 1983) found that mortality was statistically significantly lower in the TXA group compared to the placebo group (6.3% vs. 13.5%, difference in proportions 7.2% (95%CI 1.7 to 12.7)12, 14, 16-21.

In 6 studies, the groups were compared in terms of the need for emergency surgery, and none found a statistically significant difference between the groups[7, 8, 11, 13-15].

In 8 studies, the groups were compared in terms of the need for blood transfusion. Five studies found no statistically significant difference, while 2 studies found a lower need for blood transfusion in the TXA group, and one study found a statistically significant higher need for blood transfusion in the TXA group[7-10, 12, 14-16].

The comparison of groups in terms of rebleeding was conducted in 7 studies with a high risk of bias and in 1 study with a low risk of bias. No statistically significant difference was found in 6 of these 8 studies, while 2 studies found a statistically significant difference in favor of TXA[4, 7-11, 15, 16].

Only 2 studies examined the outcome of continued bleeding, and neither found a statistically significant difference[12, 19].

In 3 studies, the groups were compared in terms of the length of hospital stay; 2 found no difference, while one study found a statistically significant difference in favor of TXA[13-15].

As discussed in detail above, the results of studies with low and moderate risk of bias indicate that TXA does not provide significant benefits in patients with both upper and lower GI bleeding and may even increase the risk of venous thromboembolism. Although some studies reported benefits in favor of TXA for certain outcomes, these findings were low level of evidence due to the small sample sizes and high risk of bias in these studies. Even though the three studies with low and moderate risk of bias were not suitable for meta-analysis, the very large sample size in the HALT-IT study (12,009 patients), which has a low risk of bias, alone makes the results of this study highly significant (Supplementary File-4, at the end of the document).

SCENARIO-2. Is tranexamic acid, given in addition to standard care, an effective and safe treatment option in patients with multi-trauma who are bleeding or at high risk of bleeding?

2. Use of tranexamic acid in multitravma patients	
Level of recommendation and Recommendations	**Level of evidence**
Moderate	
In patients with bleeding or at high risk of bleeding due to multi-trauma, we recommend administering IV tranexamic acid in the pre-hospital setting or early after hospital arrival, due to evidence suggesting it is beneficial for mortality. We recommend administering tranexamic acid within the first 3 hours after trauma as a 1-gram IV bolus followed by a 1-gram IV infusion over 8 hours	**Moderate**
Considering the subgroup analysis results of the CRASH-3 study, which has the largest sample size related to the management of patients with traumatic brain injury (TBI), we recommend the administration of tranexamic acid to patients with moderate TBI (GCS 9-12) and those with mild TBI (GCS 13-15) who have any intracranial hemorrhage, as it may offer a mortality benefit. Specifically, we suggest a 1-gram IV bolus followed by a 1-gram infusion over 8 hours within the first 3 hours after trauma for these patients.	**Moderate**
Weak	
Considering all TBI patients regardless of severity, the routine early administration of tranexamic acid does not appear to have an effect on 28-day mortality and neurological outcomes. However, given the safety profile of tranexamic acid in traumatic patients and the indirect evidence in favor of the drug from the subgroup analysis results of the CRASH-3 study, tranexamic acid administration within the first 3 hours (1-gram IV bolus followed by 1-gram infusion over 8 hours) may be considered in patients with severe TBI (GCS <9).	**Low**
Due to the lack of evidence on the benefits of tranexamic acid in patients with mild TBI (GCS 13-15) without intracranial hemorrhage, we do not recommend the routine use of tranexamic acid in this patient group.	Very Low

Rationale and background for the recommendations

Trauma remains one of the leading causes of mortality worldwide, with approximately four million deaths annually attributed to trauma according to the World Health Organization[22]. Consequently, risk stratification in trauma patients and innovations in diagnosis and treatment continue to be hot topics of current research. Notably, the impact of TXA on outcomes in various trauma populations has been investigated in large, multicenter studies that have gained significant attention in recent years. However, due to the nature of these studies, they exhibit methodological differences.

In this guideline, trauma patients are examined in two separate categories: "general trauma" and "head trauma," based on the focus of existing studies. The aim is to provide evidence-based recommendations on the effects of TXA on various outcomes in these patient groups.

Selection of studies

A literature review using keywords related to trauma and TXA identified a total of 62 studies (Supplementary File-1, at the end of the document). After applying exclusion criteria, a total of 18 RCTs were selected for evaluation[23-40] (Supplementary File-2, at the end of the document). Given the sufficient number of RCTs, it was decided that evidence-based responses to the questions in this guideline would rely solely on RCTs.

Following the bias assessment using the Cochrane RoB-2 tool, all 5 studies under the general trauma category were rated as low risk of bias[23-27], while of the 13 studies under the head trauma category, 9 were rated as high risk of bias, two as moderate risk of bias, and 2 as low risk of bias[28-40] (Figure-2). A detailed summary of the studies is presented in Supplementary File-3 (at the end of the document). GRADE evidence classification tables showing the evidence ratings of the studies are presented in Supplementary File-4 (at the end of the document).

In conclusion, the 18 RCTs were discussed separately under the headings of general trauma (5 studies) and head trauma (13 studies).

Figure -2. Traffic Light charts for studies on the use of tranexamic acid in patients with trauma (RoB-2 Bias Assessment).

SCENARIO-2a. Is tranexamic acid, in addition to standard care, an effective and safe treatment option in patients with general major trauma who are bleeding or at high risk of bleeding?

Overview of studies and measures of outcome

Five RCTs from the literature focused directly on general trauma patients, all of which had low risk of bias[23-27]. While these studies did not explicitly exclude head trauma as a criterion, they generally excluded severe head injuries, such as penetrating head trauma, exposed brain tissue, or patients whose most significant area of trauma was the head. The treatment protocols in these studies typically involved comparing TXA to a placebo, with El-Menyar et al.'s study investigating the effect of continuing a hospital infusion dose of 1g TXA following a pre-hospital routine dose of 1g TXA IV bolus[23-27]. All 5 studies reported 28-day mortality, blood product transfusion requirements, and thromboembolic event rates as outcome measures.

The largest study reporting 28-day mortality in the general trauma population is the CRASH-2 trial, published in 2010, which analyzed data from a total of 20,127 patients[23]. The results showed that 14.5% of patients in the TXA group and 16% in the placebo group had all-cause mortality, with a statistically significant difference favoring TXA (RR0.91, 95%CI 0.85 to 0.97; p=0.0035). Importantly, mortality due to bleeding was significantly lower in the TXA group (RR 0.85, 95%CI 0.76 to 0.96; p=0.0077).

When comparing the need for blood product transfusion and the median number of blood product units transfused, the CRASH-2 study found no significant differences between the groups (RR 0.98, 95%CI 0.96 to 1.01; p=0.21 and p=0.59, respectively).

In terms of fatal and non-fatal vascular occlusive adverse events, 1.7% of patients in the TXA group and 2% in the placebo group experienced such events in the CRASH-2 study, with the difference not being statistically significant (RR 0.84, 95%CI 0.68 to 1.02; p=0.084).

Another study, considered to have a low risk of bias, is the PATCH study conducted by the PATCH study group in 2023 with 1300 patients. The primary endpoint was the comparison of the 6-month Glasgow Outcome Scale – Extended (GOSE) score. No difference was found in the primary outcome between the placebo group and treatment group who received a pre-hospital 1-gram IV bolus of TXA and in-hospital 1-gram maintenance dose (RR 1.00, 95%CI, 0.90 to 1.12; p=0.95). When secondary outcomes were examined, a 28-day mortality rate of 17.3% was observed in the TXA group compared to 21.8% in the placebo group, and the difference between the groups was found to be statistically significant (RR 0.79, 95%CI 0.63 to 0.99). When adverse effects were examined, vascular occlusive events were observed in 23.6% of the TXA group and 19.7% of the placebo group, and the difference was not significant (RR 1.20, 95%CI 0.97 to 1.48)[27].

In Guyett's 2021 STAAMP study, conducted with 894 general trauma patients, four treatment arms were compared: three different TXA protocols in the intervention group and a placebo group. Patients underwent separate randomization at three different times: a 1-gram TXA bolus or placebo bolus pre-hospital, a 1-gram bolus or placebo bolus in-hospital, and a 1-gram TXA or placebo infusion over 8 hours in-hospital. Thus, four separate treatment arms were created: the control arm, which received placebo at all three phases; the reduced TXA arm, which received only a pre-hospital bolus of TXA; the standard TXA arm, which received a pre-hospital bolus of TXA and an 8-hour in-hospital infusion of TXA; and the repeat-dose TXA arm (3 grams of TXA), which received TXA treatment at all three phases[25]. When comparing patients who received TXA

regardless of dose with those who did not, no difference was reported in the 30-day mortality outcome between the TXA and placebo groups (8.1% vs 9.9%, respectively; difference, −1.8; 95%CI −5.6% to 1.9%; p=0.17). Similarly, when subgroups receiving 1 gram and 2 grams of TXA were compared with the placebo, no difference in mortality was observed. However, in the 30-day mortality outcome, a significant difference was observed in the group receiving a total of 3 grams of TXA compared to the placebo group (7.3% vs 10.0%, respectively; difference -2.7%; 95%CI -5.0% to -0.4%; p=0.04). No significant difference was observed between the groups in terms of pulmonary embolism, deep vein thrombosis, and blood product requirements (p=0.78, p=0.83, and p=0.97, respectively).

In contemporary practice, the TXA protocol involves a 1-gram bolus followed by a 1-gram infusion over 8 hours. A meta-analysis was performed, evaluating mortality outcomes using the main results of the CRASH-2 and PATCH studies, along with data from the STAAMP study's standard TXA dose treatment arm and control group, and it indicates that early administration of TXA reduces 30-day mortality (RR 0.90, 95%CI 0.84 to 0.95). Due to differences in dosage and administration of TXA, mortality data from the other two studies were included as a subgroup in the meta-analysis to assess their impact on the main outcomes[24, 26]. When the data of these two studies were included, it was found that they did not significantly alter the primary results, confirming that TXA treatment reduces 30-day mortality (RR 0.90, 95%CI 0.84 to 0.95) (Figure 3). Similarly, a meta-analysis using data from the PATCH and CRASH-2 studies shows that TXA treatment did not lead to an increased frequency of vascular occlusive events compared to placebo (Figure-4).

The results of these five RCTs demonstrate that the administration of TXA in the acute phase can significantly contribute to reducing mortality in general trauma patients. Additionally, it can be inferred that TXA is a safe drug in terms of its adverse effect profile. However, as a panel, we particularly want to emphasize that the patient populations in these studies were those with hemorrhagic shock or at risk of hemorrhagic shock. Therefore, we recommend TXA treatment not for all multi-trauma patients but specifically for those where mortality is particularly feared to be due to hemorrhage, with a moderate level of recommendation.

Panel note: The recommendation level is set to moderate due to the relatively small effect size of the benefit (RR 0.90, 95%CI 0.85 to 0.96).

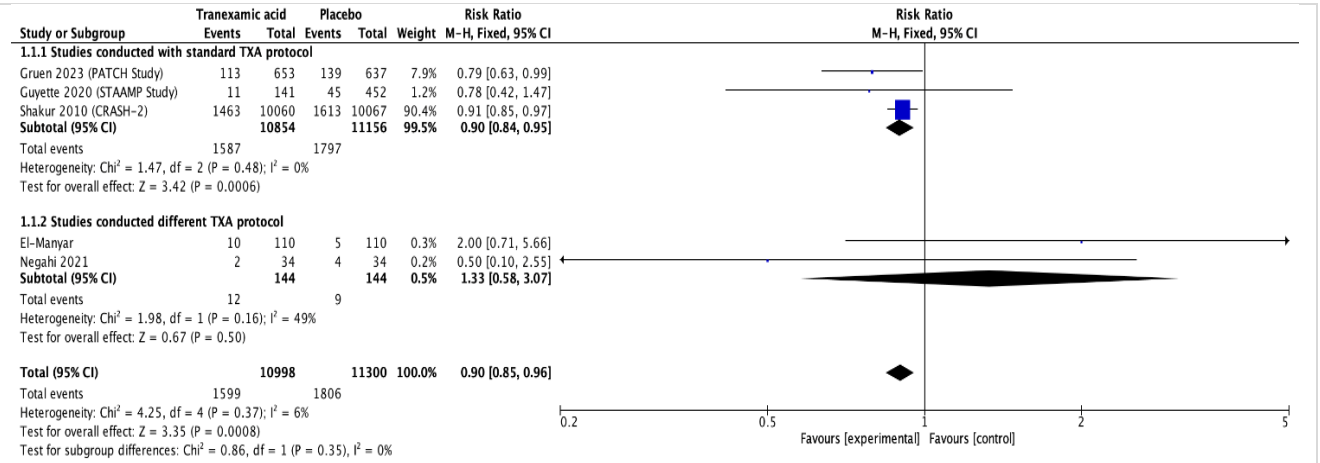

Figure-3. Forest plot illustrating the effectiveness of tranexamic acid treatment on one-month mortality outcomes in general multi-trauma patients with bleeding or high risk of bleeding.
* Standard TXA Protocol: 1-gram TXA bolus followed by a 1-gram TXA infusion over 8 hours.

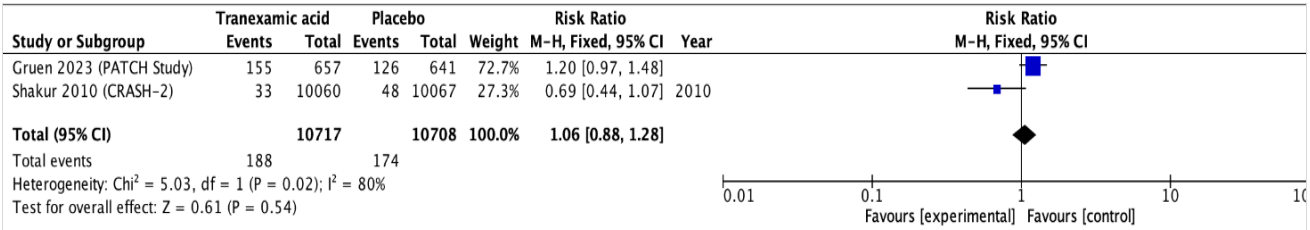

Figure-4. Forest plot illustrating the frequency of vascular occlusive events with tranexamic acid treatment in general multi-trauma patients with bleeding or high risk of bleeding.

SCENARIO-2b. Is tranexamic acid, in addition to standard care, an effective and safe treatment option in patients with traumatic brain injury?

Overview of studies and measures of outcome

In the literature review conducted to address this clinical question, 4 out of 13 RCTs were found to have a low or moderate risk of bias. Therefore, these four studies were given more weight in answering the clinical question. Studies are summarized in Supplementary File-3 (at the end of the document). Except for one, all studies with low or moderate risk of bias were designed with patients suffering from moderate to severe head trauma[28-30]. Only one study had the inclusion criterion of detecting intracranial bleeding after head trauma[31]. Most studies reported 28-day mortality, 6-month favorable neurological outcomes, and thromboembolic complications.

The largest study on this topic is the CRASH-3 trial, published in 2019, which compared a protocol of a 1-gram bolus of TXA followed by a 1-gram infusion over 8 hours with a placebo[29]. In this study, 12.639 patients were randomized, and treatment was started within the first 3 hours for 9.127 of these patients. No significant difference was reported between the groups in terms of the primary outcome of 28-day mortality (TXA 18.5%, placebo 19.8%, RR 0.94, 95%CI 0.86 to 1.02). When the analysis excluded patients with a GCS of 3 and no pupillary response, the difference between the groups increased slightly but did not reach statistical significance (TXA 12.5% vs placebo 14%, RR 0.89, 95%CI 0.80 to 1.00). When this analysis was repeated with only mild to moderate TBI patients (GCS 9 to 15), the authors reported a statistically significant reduction in mortality in favor of TXA (TXA 5.8% vs placebo 7.5%, RR 0.78, 95%CI 0.64 to 0.95).

When evaluating the secondary outcomes of the CRASH-3 study, specifically 28-day functional survival, the mean Disability Rating Scale (DRS) score for the TXA group was calculated as 4.99 (±7.6), compared to 5.03 (±7.6) for the placebo group, with no significant difference found between the groups. Similarly, when comparing all vascular occlusive events, no difference was reported between the groups (RR 0.98, 95%CI 0.74 to 1.28).

Another RCT with a low risk of bias is the study by Yutthakasemsunt et al., conducted in 2013, which randomized a total of 238 head trauma patients and compared the rates of progressive intracranial hemorrhage as the primary outcome[30]. This study reported no significant difference between the groups for the primary outcome (RR 0.65, 95%CI 0.4 to 1.05). Secondary outcomes of this study included unfavorable GOS outcome and mortality, and no significant differences were found between the groups for these outcomes either (RR 0.76, 95%CI 0.46 to 1.27, and RR 0.69, 95%CI 0.35 to 1.39, respectively).

In the 2020 study by Rowell et al., which has a moderate risk of bias, a total of 966 patients with moderate to severe TBI were randomized, and two different TXA treatment protocols were compared with each other and with a placebo[28]. The first treatment protocol involved a 1-gram IV bolus of TXA followed by a 1-gram IV infusion over 8 hours, while the second protocol involved the total dose of 2 grams of TXA given as an IV bolus, and the last protocol was a placebo. The primary outcome was defined as having a Glasgow Outcome Scale Extended (GOSE) score greater than 4 at 6 months, and the two TXA intervention arms were combined for analysis. According to the results, there was no significant difference between the combined TXA group and the placebo group in terms of GOSE>4 at 6 months, 28-day mortality, 6-month Disability Rating Scale (DRS), and intracranial hemorrhage expansion (p=0.16, p=0.26, p=0.29, and p=0.16,

respectively). Although the study compared adverse effects among the three arms, no statistical analysis was performed. Accordingly, thromboembolic adverse effects were observed in 4% of the bolus + maintenance group, 9% of the bolus-only group, and 10% of the placebo group.

The data from the placebo arm of Rowell et al.'s study, along with the mortality and vascular occlusive data from the arm using the 1-gram TXA bolus followed by an 8-hour infusion protocol commonly used in daily practice, were included in a meta-analysis of 28-day mortality and vascular occlusive outcomes, together with the main results of the CRASH-3 and Yutthakasemsunt et al. studies. When evaluating the meta-analysis results, it was found that routine TXA treatment had no effect on 28-day mortality for all TBI patients (RR 0.85, 95%CI 0.62 to 1.17). Regarding the frequency of vascular occlusive events, TXA treatment did not result in an additional increased risk (RR 0.63, 95%CI 0.25 to 1.58) (Figure 5, 6).

Another study with a moderate risk of bias that differs from other studies in terms of patient population and outcomes is the 2019 study by Jokar et al., which randomized a total of 80 patients[31]. This study included only patients with intracranial hemorrhage and analyzed the effect of a 1-gram IV bolus followed by a 1-gram IV maintenance dose of TXA on hemorrhage volume expansion. The results showed significantly less hemorrhage expansion in patients treated with TXA ($p<0.001$).

The other nine RCTs with a high risk of bias have primary outcomes that differ from the aforementioned studies and generally investigate the effects of TXA treatment on the expansion of detected hemorrhagic lesions. Additionally, there is significant heterogeneity in the patient populations. Finally, there is heterogeneity in the reported effectiveness of TXA treatment on primary outcomes; three studies reported significant differences in the investigated primary outcomes, while the remaining studies reported no differences in primary outcomes (Supplementary File-3, at the end of the document).

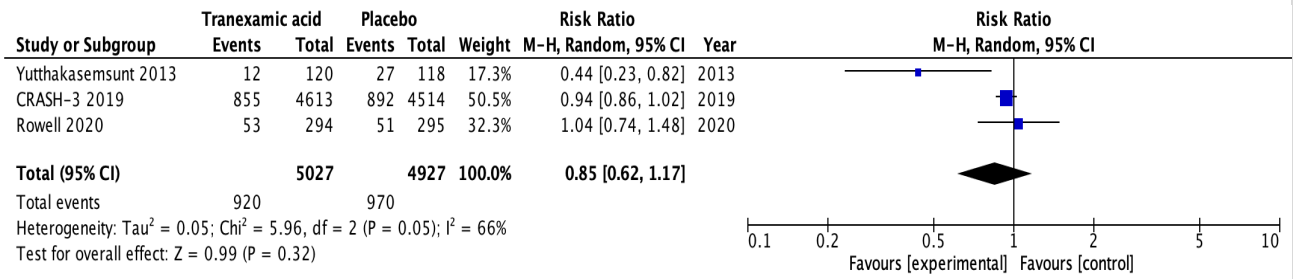

Figure-5. Forest plot illustrating the effectiveness of tranexamic acid treatment on one-month mortality outcomes in TBI patients.

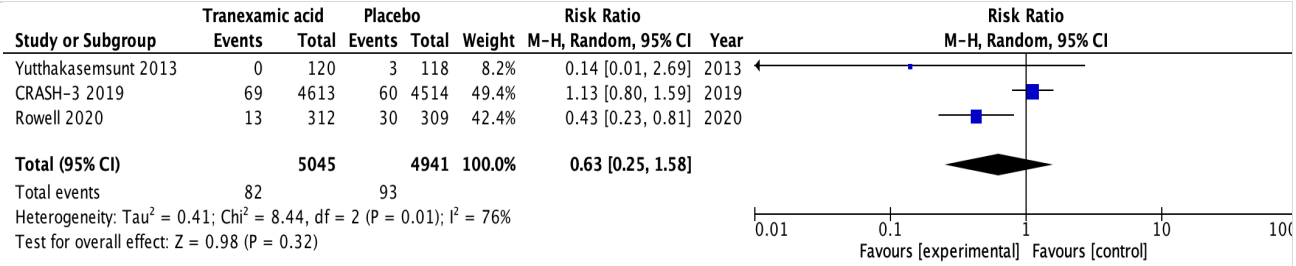

Figure-6. Forest plot illustrating the frequency of vascular occlusive events with tranexamic acid treatment in TBI patients.

SCENARIO-3. Is intravenous tranexamic acid, used in addition to standard care, an effective and safe treatment option in patients with non-traumatic acute intracranial hemorrhage?

3. Use of tranexamic acid in patients with non-traumatic acute intracranial hemorrhage	
Level of recommendation and Recommendations	**Level of evidence**
Moderate	
In patients with acute non-traumatic intracerebral hemorrhage (ICH), early administration of IV tranexamic acid treatment does not lead to a significant increase in the frequency of adverse effects. However, it also does not have a positive effect on outcomes such as hematoma expansion, mortality, and neurological sequelae. Therefore, as panel members, we do not recommend the routine use of IV tranexamic acid treatment in patients with acute ICH.	**Moderate**
Weak	
In patients with acute non-traumatic subarachnoid hemorrhage (SAH), early administration of IV tranexamic acid treatment does not lead to a significant increase in the frequency of adverse effects but it does not appear to have an improving effect on neurological outcomes. Therefore, we do not recommend the routine use of early tranexamic acid in the management of SAH patients.	**Low**

Rationale and background for the recommendations

Although acute intracranial hemorrhages (ICH) are not as frequently encountered as ischemic stroke, they have similar mortality rates and a higher risk of developing permanent disability41. Various studies have investigated the efficacy of antifibrinolytic treatments, particularly early administration of TXA, alongside standard treatments to reduce these adverse effects. However, these studies exhibit differences in their primary outcome measures, main results, and methodologies. In this guideline, intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and post-thrombolytic hemorrhage in ischemic stroke patients are examined under separate headings. The aim is to provide evidence-based recommendations on the use of TXA for emergency physicians managing these patient groups in the early period.

Selection of studies

A systematic literature review was conducted using the relevant keywords for all non-traumatic intracranial hemorrhages (subarachnoid hemorrhage and intracerebral hemorrhage) resulting in 14 studies (Supplementary File-1, at the end of the document). Due to the sufficient number of RCTs among the articles related to ICH, only the 8 articles designed as RCTs were included for further evaluation (Supplementary File-2, at the end of the document)[42-49]. Bias assessment using the Cochrane Rob-2 tool revealed that 7 articles had low or moderate risk of bias (some concerns), while 1 article had high risk of bias (Figure-7). Due to the sufficient number of RCTs related to SAH, a total of 6 studies were considered for evaluation50-55. In the bias assessment of these 6 studies using the Rob-2 tool, 4 articles were found to have high risk of bias, while 2 studies had low or moderate risk of bias (Figure-8). Summaries of the studies' populations, treatment protocols, primary and secondary endpoints, and main findings are presented in Supplementary File-3 (at the end of the document). GRADE evidence classification tables showing the evidence ratings of the studies are presented in Supplementary File-4 (at the end of the document).

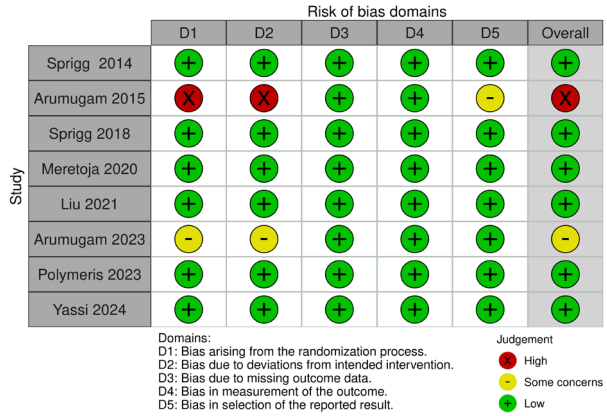

Figure-7. Traffic light charts of articles on the use of TXA in patients with non-traumatic intracerebral hemorrhage (Rob-2 Bias Assessment).

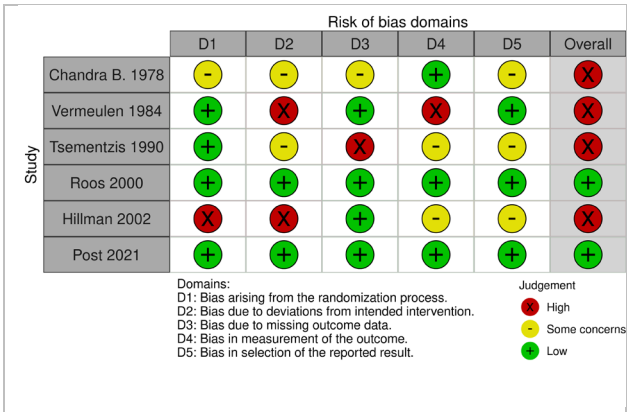

Figure-8. Traffic light charts of articles on the use of TXA in patients with non-traumatic subarachnoid hemorrhage (Rob-2 Bias Assessment).

SCENARIO-3a. Is intravenous tranexamic acid, used in addition to standard care, an effective and safe treatment option in patients with non-traumatic acute intracerebral hemorrhage?

Overview of studies and measures of outcome

In the current studies, the efficacy of the TXA protocol, consisting of a 1-gram IV bolus followed by a 1-gram IV infusion over 8 hours, has been primarily investigated in patients with acute ICH. Only in the 2023 study by Arumugam et al.[46], in addition to the standard 2-gram TXA protocol, a third group was included using a protocol of a 1-gram IV bolus followed by a 2-gram IV infusion over 8 hours. However, in this guideline, only the data from the 2-gram protocol of the relevant study are used. Considering the study populations, all studies, except for the one by Polymeris et al., have defined patients with acute ICH as the primary inclusion population and excluded those using anticoagulation. In contrast, the study by Polymeris et al. targeted patients with acute ICH associated with new generation oral anticoagulants (NOAC)[47]. Therefore, the data from this study have been discussed separately throughout the guideline. There are differences in the endpoints of the current studies. Thus, mortality, neuroclinical outcomes (modified Rankin Scale), hematoma growth, and safety endpoints reported in the studies have been analyzed under separate headings with common studies reporting the relevant outcomes.

a. 90-Day Modified Rankin Scale (mRS): There are 4 studies suitable for meta-analysis that compared the neuroclinical outcomes of TXA versus placebo in patients with acute ICH, reporting mRS scores at day 90[43-45, 49]. According to these studies, TXA treatment in acute ICH patients did not exhibit a significant difference in terms of patients with mRS scores below 3 or those returning to their baseline mRS scores by day 90 (RR 1.03, 95%CI 0.92 to 1.16) (Figure-9A). Among the studies not included in the meta-analysis due to differences in outcome measures or population differences, Arumugam et al.'s TANICH-II study reported mRS values at day 30 and found no statistically significant difference between the TXA and placebo groups[46]. In Sprigg et al.'s 2014 pilot study, day 90 mRS values were reported as mean and standard deviation, showing no difference between the groups (mRS: 3.6±1.9 versus 3.4±2.1; p = 0.82)[42]. Finally, in the TICH-NOAC study involving acute ICH patients associated with NOAC, Polymeris et al. also demonstrated no significant difference in day 90 mRS values between the TXA and placebo groups[47].

b. Hematoma Growth: In most studies, the expansion of the initially identified hematoma on follow-up CT at approximately 24 hours was reported as a significant outcome. Hematoma expansion was defined as a 33% increase in hematoma volume or a net growth of 6 ml on the follow-up CT compared to the initial CT. A meta-analysis of studies reporting the proportion of cases with hematoma expansion between treatment groups indicates that TXA treatment did not result in a significant difference compared to placebo in terms of hematoma expansion; RR 0.91, 95%CI 0.80 to 1.02 (Figure-9B)[42-45, 49]. Among the studies not included in the meta-analysis due to differences in outcome measures or population differences, Arumugam et al.'s 2023

TANICH-II study also showed no statistically significant difference in hematoma growth on follow-up CT between the TXA and placebo groups[46]. Similarly, in the TICH-NOAC study involving acute ICH patients associated with NOAC, Polymeris et al. found no superiority of TXA over placebo in terms of the proportion of patients with hematoma expansion[47].

c. 90-Day Mortality: Among the 8 studies examining the efficacy of TXA treatment in patients with acute ICH, 5 studies clearly reported 90-day mortality data[42-45, 49]. When the pooled mortality data from these 5 studies were analyzed, it was evident that TXA treatment did not reduce mortality in acute ICH patients compared to placebo (RR 1.03, 95%CI 0.89 to 1.19) (Figure-9C). Similarly, in the TICH-NOAC study involving acute ICH patients associated with NOAC, Polymeris et al. demonstrated that TXA treatment did not reduce mortality in this patient group either[47].

d. Thromboembolic Events: The most concerning safety outcome of IV TXA treatment is the increased risk of thromboembolic events. 5 of the current studies clearly reported this adverse effect[42-45, 49]. According to the results of the meta-analysis of these 5 studies, IV TXA did not increase the risk of thromboembolic events compared to placebo (Figure-9D). Similarly, in the TICH-NOAC study where acute ICH patients associated with NOAC were investigated, Polymeris et al. found that TXA treatment did not increase the frequency of thromboembolic events in this patient group either[47].

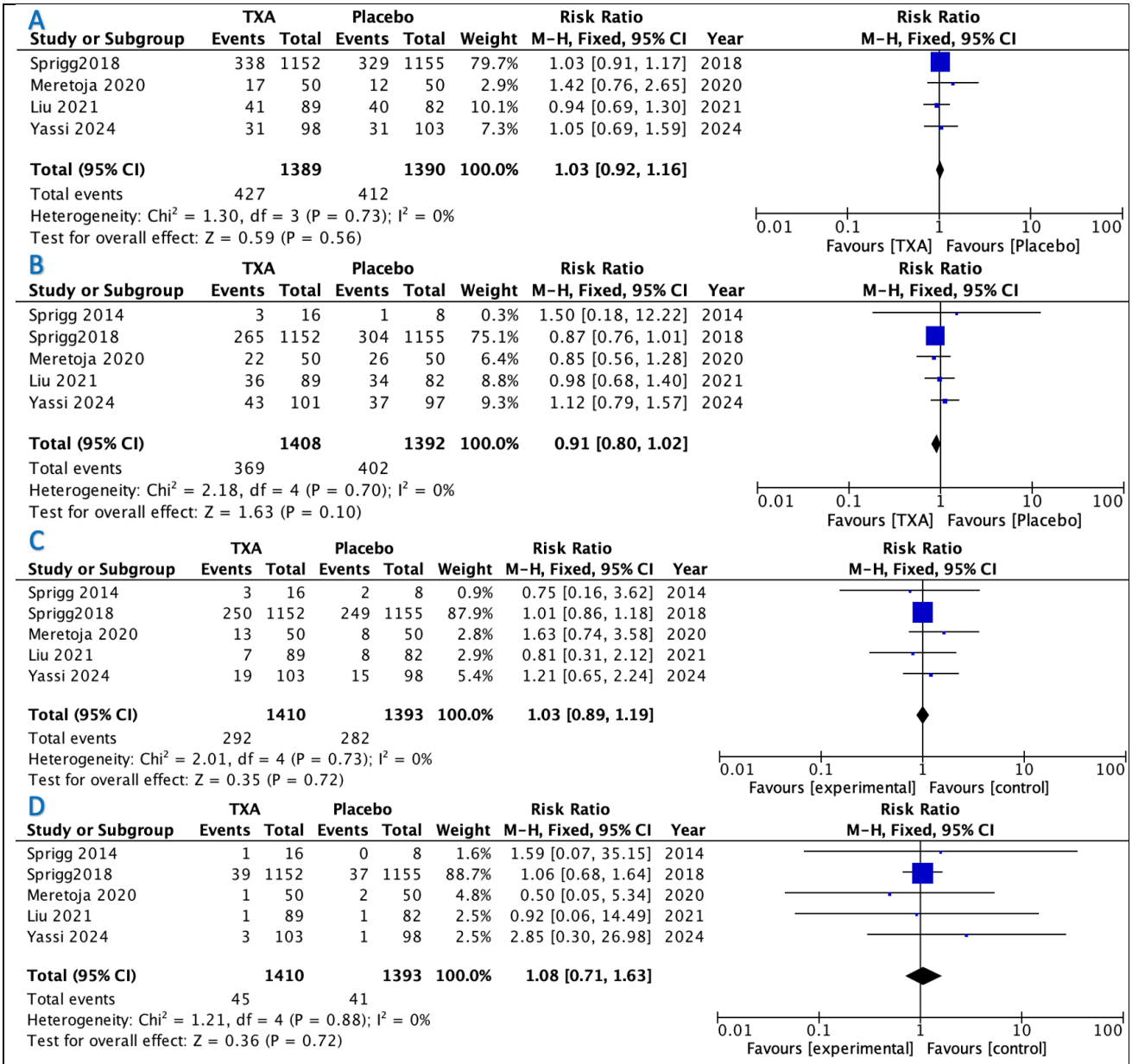

Figure-9: Forest plots demonstrating the efficacy of TXA treatment in non-traumatic intracerebral hemorrhage patients for outcomes including 90-day mRS (Figure-9A), hematoma growth (Figure-9B), 90-day mortality (Figure-9C), and thromboembolic events (Figure-9D).

SCENARIO-3b. Is intravenous tranexamic acid, used in addition to standard care, an effective and safe treatment option in patients with subarachnoid hemorrhage?

Overview of studies and measures of outcome

The majority of the RCTs found in the literature review were conducted in 1990 or earlier and have a high risk of bias. Moreover, the TXA treatment protocols used in these studies, such as 6-gram or 9-gram doses, differ from the 2-gram treatment protocols used today (1-gram bolus followed by 1-gram infusion over 8 hours). In addition to differences in TXA treatment protocols, the diagnostic methods and standard care treatments in studies from approximately 30 years ago differ from those used today, making direct comparisons with current studies challenging. Therefore, a meta-analysis of existing studies was not preferred in this guideline. Instead, a review of the literature focusing on recent studies with a low risk of bias was preferred.

One of the two studies with a low risk of bias is by Post et al. in 2020, and the other is by Roos et al. in 2000[50,51]. In the study by Post et al., the intervention arm, which involved administering 1-gram of TXA as a bolus followed by 1-gram every 8 hours until endovascular treatment (up to a maximum of 24 hours), was compared with placebo in patients diagnosed with aneurysmal subarachnoid hemorrhage. The primary outcome of the study was favorable clinical outcome (mRS score of 0-3 at 6 months). Re-bleeding was determined as the secondary outcome. No significant difference was found in both outcomes. However, a difference was observed in favor of TXA treatment in the outcome of excellent clinical outcome (mRS score of 0-2 at 6 months) (OR 0.74, 95%CI 0.57 to 0.96)[50]. The second study with a low risk of bias by Roos et al. involved patients with aneurysmal subarachnoid hemorrhage and compared the administration of 1-gram IV bolus every 4 hours for the first week (total daily dose of 6 grams) followed by 1.5-grams per oral every 6 hours (total daily dose of 6 grams) during the second and third weeks with placebo in terms of various outcomes. The primary outcome was the Glasgow Outcome Scale (GOS) at the end of 3 months, where no significant difference was found. However, a difference was reported in favor of TXA in terms of re-bleeding (19% vs. 33%, OR 0.58, 95%CI 0.42 to 0.80). No difference was observed in adverse outcomes, including thromboembolic events, in both studies.

However, when considering studies with a high risk of bias, although no differences were observed in outcomes such as mRS or GOS, the risk of re-bleeding was reported to be reduced in favor of TXA. Additionally, these studies indicate that there is no increase in the frequency of adverse effects with TXA treatment.

SCENARIO-4: Is tranexamic acid, used in addition to standard care, an effective and safe treatment option in emergency department management of hemoptysis patients?

4. Use of tranexamic acid in patients with hemoptysis.	
Level of recommendation and Recommendations	**Level of evidence**
Weak	
Tranexamic acid treatment may be considered for patients with non-massive hemoptysis requiring hospitalization or procedures such as bronchoscopy in the emergency department, as no significant adverse effects have been reported.	Very Low
Studies evaluating the efficacy of nebulized tranexamic acid suggest that the nebulized route appears superior to other methods of delivery. However, due to the small sample sizes and the IV tranexamic acid doses being well below standard, the panel does not make a recommendation on which treatment route to prefer.	Very Low
Despite encountering varying doses in studies and daily practice for IV tranexamic acid administration, the panel considers it more reasonable to follow the protocol of 1-gram IV bolus followed by 1-gram IV infusion over 8 hours, as we have more information on the safety profile of this regimen.	Very Low
There is insufficient evidence regarding the efficacy of tranexamic acid treatment in the management of patients with massive hemoptysis. However, considering the indirect evidence provided by low-level studies in patients with non-massive hemoptysis, the use of tranexamic acid may be considered in cases where interventions such as embolization or bronchoscopy are likely to be delayed.	Very Low

Rationale and background for the recommendations

Hemoptysis, often caused by malignancy, infection, or bronchiectasis, is classified as massive or non-massive. In the literature, there are various definitions for massive hemoptysis, ranging from 100 ml/24 hours to 1000 ml/24 hours[56]. Particularly in cases exceeding 300 ml/24 hours, the mortality rate can reach up to 80%[57]. Certain medications are frequently used to stop or reduce bleeding before interventional treatments such as interventional bronchoscopy. TXA, an antifibrinolytic drug, is commonly used for this purpose. However, the role of TXA in the treatment of non-massive hemoptysis remains a topic of debate. Although various studies focus on the efficacy of TXA in the management of patients with hemoptysis, a significant portion of these studies consists of observational studies or RCTs with differing outcome measures and significant methodological variations[58, 59]. Therefore, this guideline aims to provide evidence-based recommendations for the early management of patients with hemoptysis, particularly for emergency department physicians.

Selection of studies

A systematic literature review using all relevant keywords related to hemoptysis (Supplementary File-1, at the end of the document) resulted in 621 studies. Due to the sufficient number of RCTs among the articles related to hemoptysis, only 5 RCTs were selected for further evaluation (Supplementary File-2, at the end of the document). Bias assessment using the Cochrane RoB-2 tool identified 2 studies with moderate risk of bias and 3 studies with high risk of bias (Figure-10). Summaries of the studies, including populations, treatment protocols, primary and secondary outcome measures, and main

results, are presented in (Supplementary File-3, at the end of the document). GRADE evidence classification tables showing the evidence ratings of the studies are presented in Supplementary File-4 (at the end of the document).

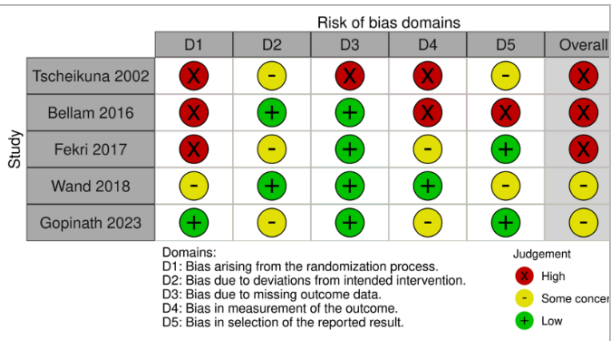

Figure-10. **Traffic light charts of studies on the use of TXA in patients with hemoptysis (RoB-2 Bias Assessment).**

Overview of studies and measures of outcome

Three of the 5 existing studies have a high risk of bias, with significant methodological differences in the methods used to measure outcomes, the preparations used in interventions, and their methods of application. Therefore, a meta-analysis of the existing studies was not preferred in this guideline. Instead, a review of the literature focusing on recent studies with a low risk of bias was preferred.

The 5 RCTs that included patients with non-massive hemoptysis were generally designed with outcomes targeting the cessation of bleeding or the amount of bleeding, but no standard exists in this regard. There were differences in the timeframes for cessation of bleeding, such as 30 minutes and 5 days, as well as varying definitions, including observing the cessation of bleeding via bronchoscopy or external observation, evaluating daily bleeding frequency, or assessing the amount of bleeding using a visual analog scale.

In the study conducted by Tscheikuna et al. in 2002 investigating patients with non-massive hemoptysis, a total of 46 patients were included. The intervention group received oral TXA capsules, 2 capsules three times a day (n=21) and was compared with a placebo control group (n=25). It was stated that patients with massive hemoptysis who might require intervention were excluded from this RCT, and massive hemoptysis was defined as >500 mL/day. It should be noted that this threshold is higher than that used in many other studies. At the end of the study (day 7), 4 patients (19%) in the TXA group and 7 patients (28%) in the placebo group still had hemoptysis, with no statistically significant difference reported (p = 0.514). The sample was divided into three groups based on the amount of hemoptysis and analyzed separately, with results similar to the main analysis. However, it was noted that the sample size was very small for subgroup analysis[60].

In the RCT by Bellam et al. in 2016, which included a total of 66 patients, TXA treatment was applied intravenously. The study included ongoing acute hemoptysis cases. The intervention arm used a loading dose of 1-gram IV TXA diluted with 10 mL of 0.9% normal saline, followed by an 8-hour IV infusion of 1-gram TXA in 500 mL of 0.9% normal saline. The placebo arm used the same protocol without TXA. The study analyzed the frequency and amount of hemoptysis as the outcome. The severity of hemoptysis measured by VAS score was 14.7±15.5 mm in the treatment group and 31.3±22.1 mm in the placebo group, exhibiting a statistically significant difference (p<0.001). However, no differences were found between the two groups in terms of daily number of hemoptysis and volume of hemoptysis assessed on the first and second days.

Although the TXA group was found superior in terms of VAS score, the study was considered as high-risk for bias[61].

In the 2017 study by Fekri et al., TXA (500 mg diluted in 20 mL normal saline) was directly applied to the bleeding site under bronchoscopy in the intervention group, while adrenaline (1 mg diluted in 20 mL normal saline) was applied in the control group. This RCT included a total of 50 patients, and the bleeding cessation time was noted by directly observing clot formation via bronchoscopy. It was reported that TXA (133.9±77.9 seconds) was as effective as adrenaline (136.7±83.5 seconds), (p=0.908). Additionally, no difference was found in the number of applications required to stop the bleeding[62].

In the 2018 RCT by Wand et al., the efficacy of nebulized TXA was investigated. A total of 47 patients admitted to the department of pulmonology were included, with the intervention group receiving 500 mg/5 mL of nebulized TXA three times a day and the control group receiving the same volume and frequency of normal saline. It was reported that on the fifth day, bleeding had stopped in 96% of the TXA group compared to 50% of the placebo group (p<0.0005). Additionally, the volume of hemoptysis was lower in the TXA group on the second and fifth days (p<0.01). Regarding secondary outcomes, there was no difference in 30-day mortality and hemoptysis recurrence. However, TXA was superior in terms of 1-year mortality (4.0% vs 22.7%; p<0.01) and recurrence of hemoptysis (16% vs 18%; p<0.01)[63].

The most recent study is the 2023 RCT conducted by Gopinath et al., which is emergency department-focused and compares different pharmaceutical forms of TXA. This study included a total of 110 patients, with one group receiving 500 mg nebulized TXA (diluted in 5 mL distilled water) three times a day, and the other group receiving 500 mg IV TXA. The outcome was defined as the cessation of bleeding at 30 minutes. It was reported that at the 30-minute evaluation, bleeding had stopped in 72.7% of the nebulized drug group and 50.9% of the IV drug group (p=0.002). The reduction in bleeding volume was significantly higher in the nebulization group compared to the IV group at all observation periods (30 minutes; 6, 12, and 24 hours) (p<0.05)[64].

Adverse effects

In the literature, none of the reviews evaluating the use of TXA in patients with hemoptysis have reported serious thromboembolic adverse effects, such as acute myocardial infarction, stroke, acute renal failure, or death[58, 59, 65]. In the study by Gopinath et al., two patients with COPD in the nebulization group experienced bronchospasm that resolved with standard inhaler beta agonist treatment[64]. In the study by Tscheikuna et al., minor symptoms such as mild headache, slight chest discomfort, and nausea were reported in the TXA group. Additionally, a minor skin rash believed to be an allergic reaction to antituberculosis drugs was reported in one patient in the placebo group. It was also noted that these adverse effects did not lead to discontinuation of the study medications[60]. No adverse effects related to the drug groups were reported in the other three studies included in this guideline[61-63].

SCENARIO-5. Is the application of local tranexamic acid plus compression, as an alternative to standard interventions, an effective and safe treatment option in patients with epistaxis?

5. Use of tranexamic acid in patients with nosebleeds.	
Level of recommendation and Recommendations	**Level of evidence**
Weak	
After the application of local tranexamic acid and external nasal compression, although there are conflicting results between anterior nasal packing and placebo applications, no result indicates that tranexamic acid treatment is inferior. Considering the discomfort associated with anterior nasal packing application and studies showing no serious adverse effects, we believe that local application of tranexamic acid could be a potential alternative for emergency physicians in the management of epistaxis in emergency departments.	Low
Due to conflicting and insufficient evidence regarding the method of delivery for tranexamic acid application and the optimal drug dose, we do not make any specific recommendations and suggest adhering to local protocols.	-

Rationale and background for the recommendations

In the management of patients with nosebleeds in emergency departments, there are various treatment options. While simple external compression is sufficient in most cases, other options include the application of anterior packing that may contain lidocaine or epinephrine, plain packing, or commercially available packing products. Due to the discomfort associated with the routine use of anterior nasal packing for up to three days, short-term local application of TXA has recently become more popular among emergency physicians as an alternative, particularly for nosebleeds that cannot be controlled with simple external compression. Despite the increasing number of studies on the bleeding control effect of TXA in epistaxis patients, there are significant differences in both the results and methodological quality of these studies. Therefore, this guide aims to provide evidence-based summary recommendations for emergency department physicians in the management of epistaxis.

Selection of studies

A systematic literature review conducted with the relevant keywords (Supplementary File-1, at the end of the document) resulted in 104 studies. Due to the sufficient number of RCTs related to the clinical question, only 11 studies with an RCT design were included for further evaluation (Supplementary File-2, at the end of the document)[66-76]. Using the Cochrane RoB-2 tool for bias assessment, it was determined that 1 article had a low risk, 4 articles had moderate risk, and 6 articles had high risk of bias (Figure-11). Summaries of the studies are presented in Supplementary File-3 (at the end of the document). GRADE evidence classification tables showing the evidence ratings of the studies are presented in Supplementary File-4 (at the end of the document).

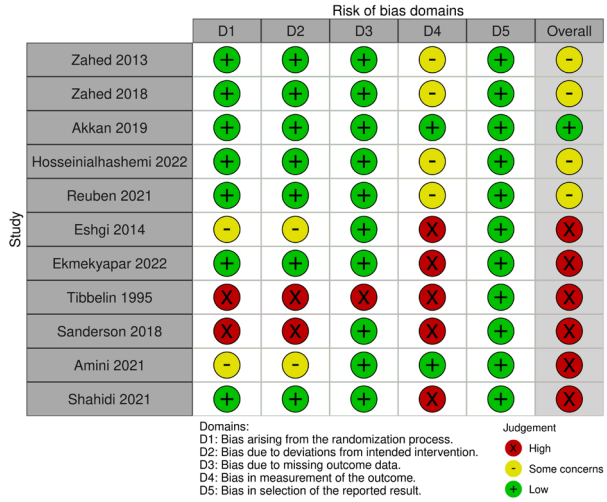

Figure-11. Traffic light charts of articles on the use of TXA in patients with epistaxis (RoB-2 Bias Assessment).

Overview of Studies and Measures of Outcome

In the existing studies, the efficacy of TXA was primarily investigated; however, there were differences in the outcomes and the choice of comparison groups. Similarly, although TXA was applied locally in the studies, different application methods were used, such as simple external pressure after spraying, anterior packing application with TXA-soaked tampons, and TXA-containing gels. Considering the outcomes, the primary endpoint was generally the cessation of bleeding, but there were differences in the time points of this evaluation. Due to these methodological differences among the studies, a meta-analysis was not preferred. Instead, a review of the literature focusing on studies with low and moderate risk of bias was conducted.

The initial studies on this topic were by Zahed et al., who, in their 2013 RCT, included non-traumatic adult patients with ongoing anterior epistaxis, excluding those with bleeding diathesis and INR>1.5. They compared the rates of bleeding cessation within 10 minutes using TXA-soaked cotton tampons versus anterior nasal packing containing epinephrine+lidocaine (2%). In this study, which included a total of 217 patients, the bleeding cessation rate was 71% in the TXA group compared to 31% in the control group, indicating the superiority of TXA in stopping the bleeding (OR 2.28, 95%CI, 1.68 to 3.09; p<0.001)[66].

In another RCT conducted by Zahed et al. in 2018, adult patients using antiplatelet drugs were evaluated for eligibility, but only those whose bleeding did not stop despite 20 minutes of external pressure were included in the study. Patients using anticoagulants, those with INR >1.5, those with trauma, and those with renal disease were excluded, resulting in a total of 124 patients being included. The study compared the rates of bleeding cessation within 10 minutes between topical TXA and anterior nasal packing applications. In the TXA group, 73% of patients achieved bleeding cessation within the first 10 minutes, compared to 44% in the control group, with results statistically significantly favoring TXA (difference 44%, 95%CI %25 to %57)[67].

In a 2017 RCT by Akkan et al., which included adult patients with nosebleeds, three different treatment groups were compared in a total of 135 patients: 1-) nasal compression with TXA, 2-) simple nasal compression with saline, and 3-) nasal tampon using Merocel. The primary outcome was the cessation of bleeding within 15 minutes. The success rate was found to be 91.1% in the TXA group, 93.3% in the Merocel group, and 71.1% in the simple compression group. While there was no statistically significant difference between the TXA and Merocel groups, a statistically significant difference was reported between the placebo group and the other two groups, favoring the TXA and Merocel over the placebo[68].

In a study published by Reuben et al. in 2021, 496 adult patients with nosebleeds that

did not stop with 10 minutes of simple external pressure were included. This study compared the need for anterior nasal packing between the topical application of TXA and a placebo (sterile saline) group. This multicenter study, conducted across 26 centers and the largest study on this topic, found no statistically significant difference between the two groups. The need for nasal packing was 43.7% in the TXA group compared to 41.3% in the placebo group (OR 1.11, 95%CI 0.77 to 1.59)[70].

In a 2022 study by Hosseinialhashemi et al., adult patients with anterior nosebleeds were first evaluated by an ear-nose-throat resident physician. Patients underwent procedures such as nasal compression, ice application, and cold water mouth rinse, and those whose bleeding continued despite these measures were included in the study. The study compared the application of TXA-soaked cotton versus phenylephrine-soaked cotton, focusing on the continuation of bleeding after 15 minutes. Bleeding continued in 50% of patients in the TXA group, while it continued in 64% of patients in the control group. The study reported that bleeding was significantly less in the TXA group (OR 0.56, 95%CI 0.33 to 0.94)[69].

When the overall results of the 6 studies with a high risk of bias were evaluated, 3 studies reported that the local application of TXA was superior to standard treatment[71-76]. In 2 studies, TXA was found to be at least as effective as standard treatment. Only in the study conducted by Eshghi et al. in 2014 TXA was reported to be less effective when compared to a commercial anterior packing product[71].

Because of the local application of TXA, most studies did not report any adverse effects. In the studies that did report adverse effects, no increase in the frequency of adverse events attributable to TXA was observed.

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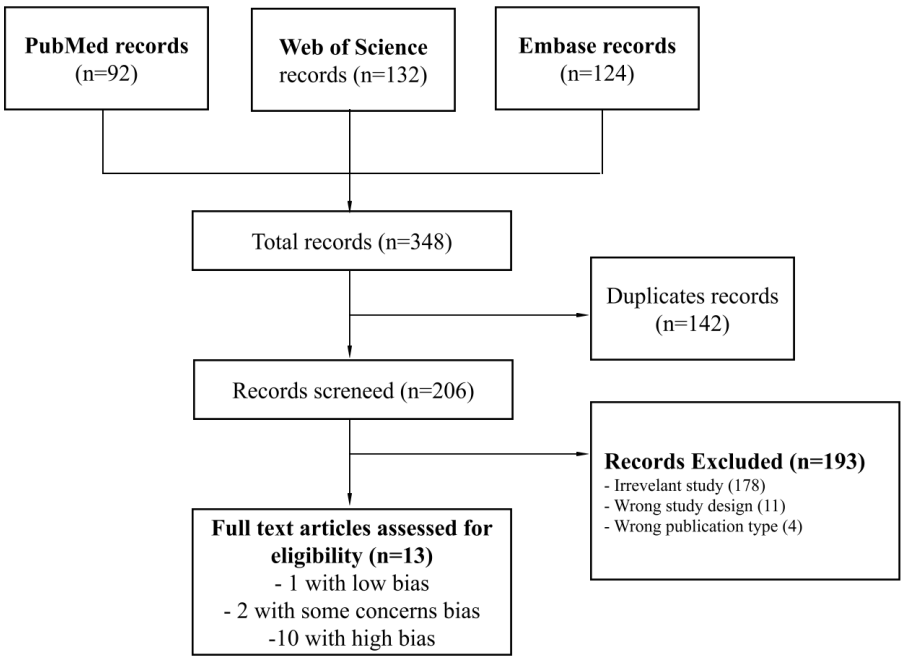
SUPPLEMENTARY FILES

Supplementary File-1. Search Hedges Used in the Systematic Literature Review for the Relevant Clinical Question

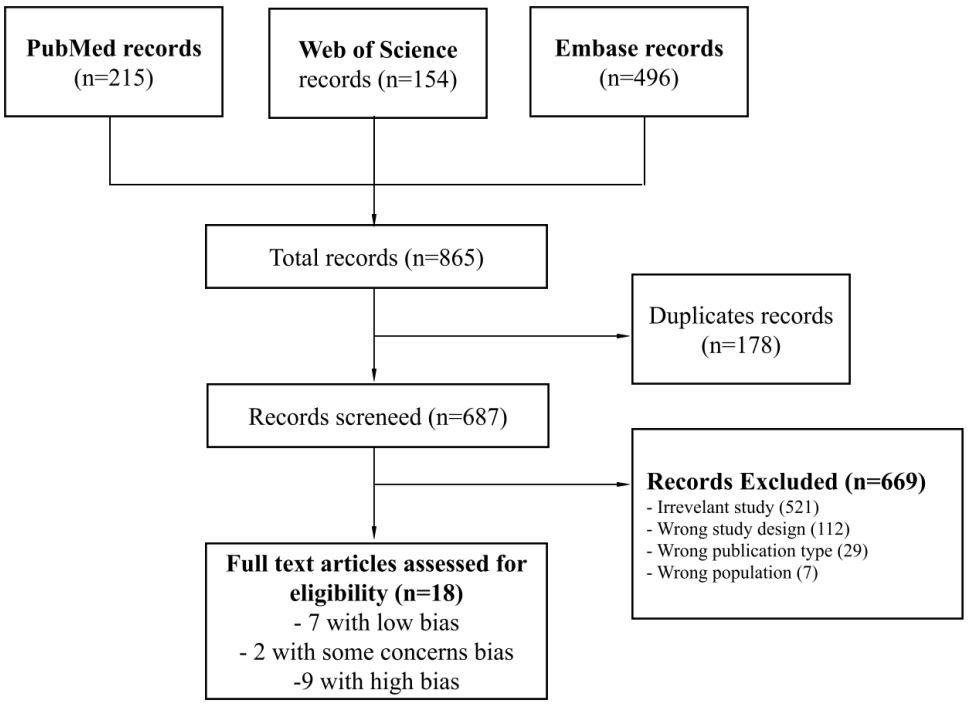
Search Hedges	
Gastrointestinal hemorrhage.	((((((((Hematochezia[Title/Abstract]) OR (Gastrointestinal Hemorrhage[Title/Abstract])) OR (Hematochezias[Title/Abstract])) OR (Hematemesis[Title/Abstract])) OR (Melena[Title/Abstract])) OR (Peptic Ulcer Hemorrhage[Title/Abstract])) OR (Gastrointestinal Bleed*[Title/Abstract])) OR (GI bleed*[Title/Abstract])) OR (GI hemor*[Title/Abstract])) AND (((((((Amchafibrin[Title/Abstract]) OR (Transamin[Title/Abstract])) OR (Exacyl[Title/Abstract])) OR (Cyklokapron[Title/Abstract])) OR (AMCA[Title/Abstract])) OR (Tranexamic Acid[Title/Abstract])) OR (Tranex*[Title/Abstract]))
Multi-trauma.	((((Injury[Title/Abstract]) OR (wounds[Title/Abstract])) OR (trauma[Title/Abstract])) OR (Advanced Trauma Life Support Care[Title/Abstract])) AND (((((((Amchafibrin[Title/Abstract]) OR (Transamin[Title/Abstract])) OR (Exacyl[Title/Abstract])) OR (Cyklokapron[Title/Abstract])) OR (AMCA[Title/Abstract])) OR (Tranexamic Acid[Title/Abstract])) OR (Tranex*[Title/Abstract]))
Intracranial hemorrhage.	(((((((Cerebral Hemorrhage[Title/Abstract]) OR (Intracerebral Hemorrhage[Title/Abstract])) OR (ruptured intracranial aneurysm[Title/Abstract])) OR (intracranial bleeding[Title/Abstract])) OR (Hemorrhagic Stroke[Title/Abstract])) OR (((((((Hemorrhages, Intracranial[Title/Abstract]) OR (posterior Fossa Hemorrhage[Title/Abstract])) OR (Brain Hemorrhage[Title/Abstract])) OR (SAH[Title/Abstract])) OR (Subarachnoid Hemorrhages[Title/Abstract])) OR (Aneurysmal Subarachnoid Hemorrhage[Title/Abstract])) OR ((intracranial haemorrhage[Title/Abstract]))))) AND (((((((Amchafibrin[Title/Abstract]) OR (Transamin[Title/Abstract])) OR (Exacyl[Title/Abstract])) OR (Cyklokapron[Title/Abstract])) OR (AMCA[Title/Abstract])) OR (Tranexamic Acid[Title/Abstract])) OR (Tranex*[Title/Abstract]))
Hemoptysis.	(((((((haemorrhage[Title/Abstract]) OR (haemorr*[Title/Abstract])) OR (Bleeding[Title/Abstract])) OR (hemorrhage[Title/Abstract])) OR (blood[Title/Abstract])) AND ((((((bronchial arteries[Title/Abstract]) OR (lung[Title/Abstract])) OR (lung parenchyma[Title/Abstract])) OR (respiratory tract[Title/Abstract])) OR (Pulmonary[Title/Abstract]))) OR (((hemoptysis[Title/Abstract]) OR (haemoptysis[Title/Abstract])) OR (Hemoptyses[Title/Abstract]))) AND (((((((Amchafibrin[Title/Abstract]) OR (Transamin[Title/Abstract])) OR (Exacyl[Title/Abstract])) OR (Cyklokapron[Title/Abstract])) OR (AMCA[Title/Abstract])) OR (Tranexamic Acid[Title/Abstract])) OR (Tranex*[Title/Abstract]))
Epistaxis.	((nasal haemorrhage[Title/Abstract]) OR ((((nasal haemorr*[Title/Abstract])) OR (nose haemorr*[Title/Abstract])) OR ((((Nasal Bleeding[Title/Abstract]) OR (Nose Bleed[Title/Abstract])) OR (Nosebleed[Title/Abstract])) OR (Epistaxis[Title/Abstract]))))) AND ((((((((Amchafibrin[Title/Abstract]) OR (Transamin[Title/Abstract])) OR (Exacyl[Title/Abstract])) OR (Cyklokapron[Title/Abstract])) OR (AMCA[Title/Abstract])) OR (Tranexamic Acid[Title/Abstract])) OR (Tranex*[Title/Abstract]))

Supplementary File-2. Flowcharts (5 flowcharts) of Studies Identified Through the Systematic Literature Review and Included in the Clinical Policy

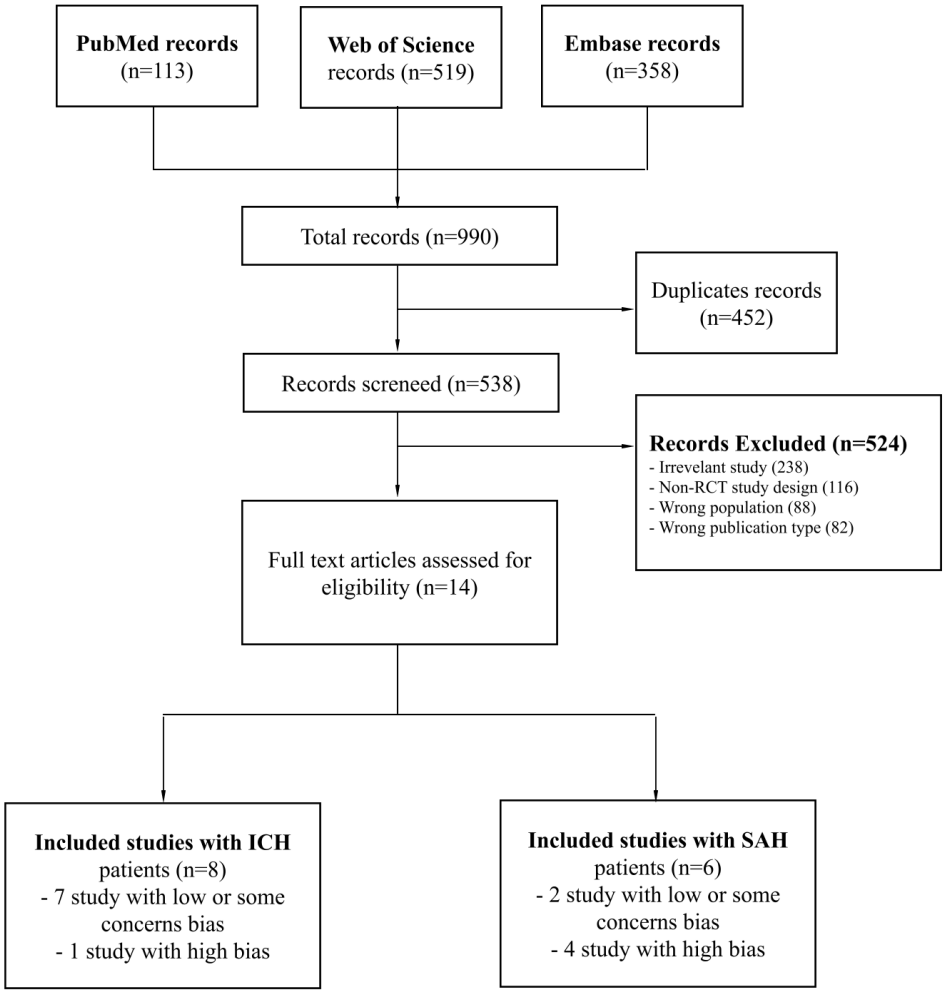
1. Flow Chart of studies on Tranexamic acid for management of patients with acute gastrointestinal bleeding.



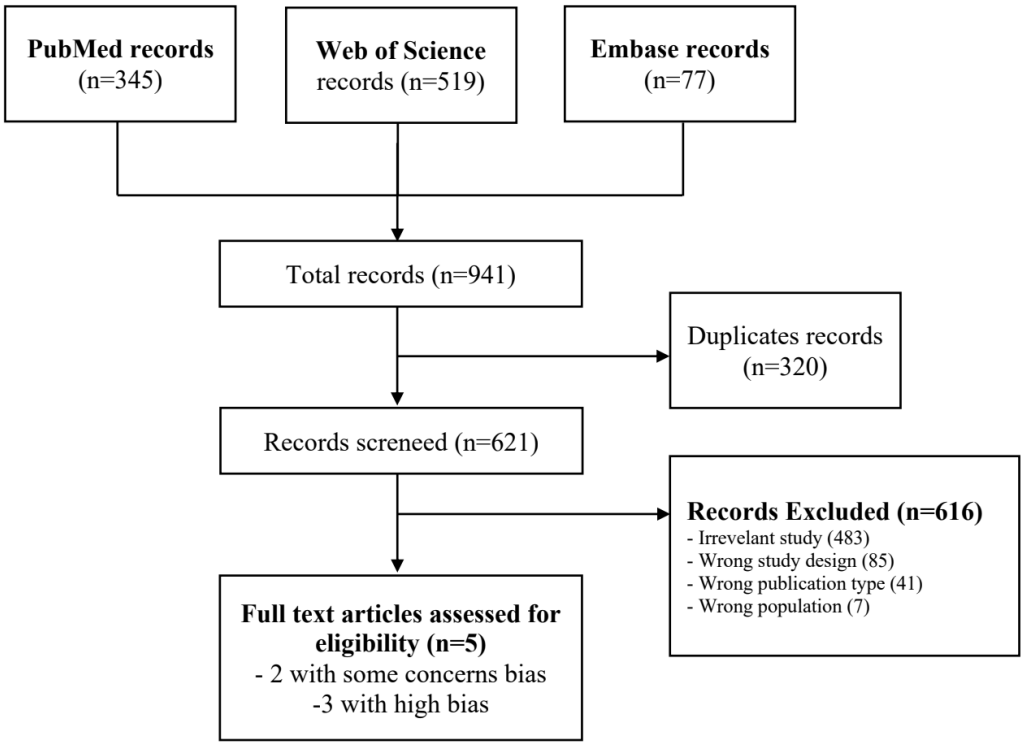
2. Flow Chart of studies on Tranexamic acid for management of patients with trauma.



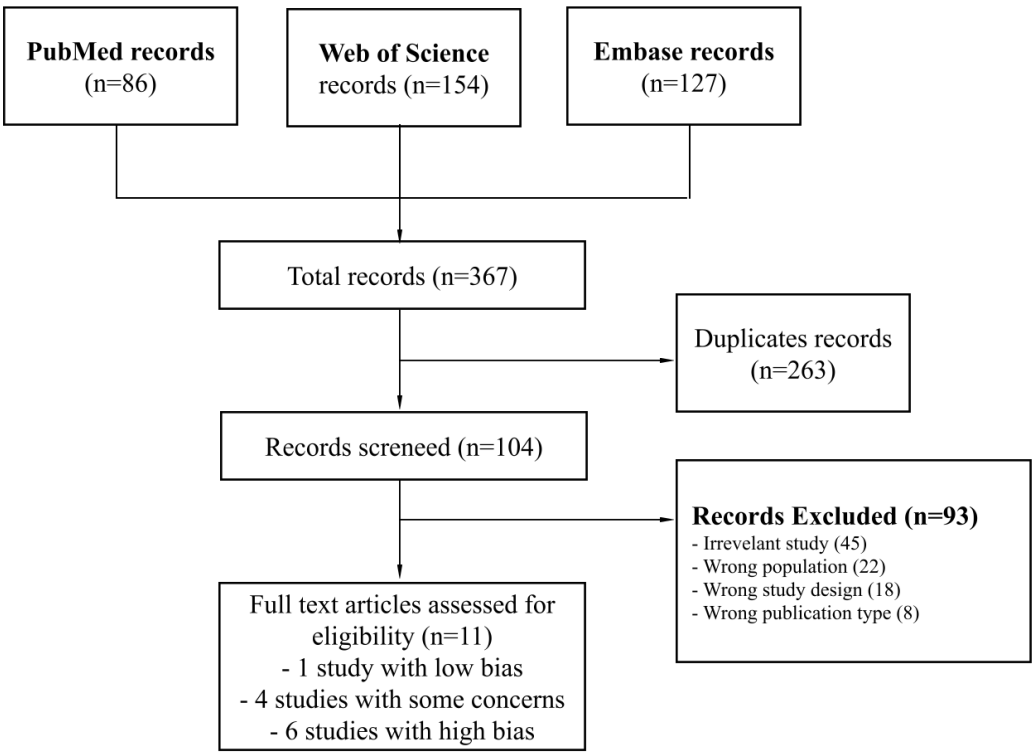
3. Flow Chart of studies on Tranexamic acid for management of patients with non-traumatic intracranial hemorrhage.



4. Flow Chart of studies on Tranexamic acid for management of patients with hemoptysis.



5. Flow Chart of studies on Tranexamic acid for management of patients with anterior epistaxis.



Supplementary File-3. Tables (5 tables) Containing Summaries of Studies Related to the Clinical Question.

Table 1. Summaries of Studies Investigating the Efficacy of Tranexamic Acid in Patients with Gastrointestinal Bleeding

Study	Design	Participants	Interventions	Outcomes	Main Results	Comments
Studies with low or uncertain risk of bias (moderate risk)						
Smith 2018	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** All patients aged ≥18 years requiring admission with lower GI hemorrhage. **Exclusion Criteria**: Age <18 years, inability to give informed consent, history, or strong family history of thromboembolic disease, known gastrointestinal malignancy, warfarin or other anticoagulant treatment, drug-eluting stent insertion within the last 12 months or bare metal stent insertion within 12 weeks, pregnancy or breastfeeding, and known allergy to TXA or its excipients. Patients with known upper GIH were excluded, and where doubt existed, either nasogastric tube insertion or gastroscopy was performed to exclude those with an upper GIH.	**Treatment:** TXA 1000 mg every 6 hours PO. Intervention was continued for 4 days PO. **Control:** Placebo (undefined).	**Primary Outcome:** Blood loss, as determined by the reduction in hemoglobin levels. **Secondary Outcomes:** Transfusion rates, transfusion volume, intervention rates for bleeding, length of hospital stay, readmission, and complication rates (venous thromboembolic events, cerebrovascular accidents, transient ischemic attacks, or acute coronary syndrome).	One hundred patients were randomly assigned to receive either a placebo or TXA (50 vs. 50). There was no difference between the groups with respect to the hemoglobin drop (11 g/L for TXA vs. 13 g/L for placebo; p=0.945). There was no difference in transfusion rates (for TXA vs. 16/47 for placebo; p=0.661), mean transfusion volume (1.27 vs. 1.93 units; p=0.355), intervention rates (7/49 vs. 13/47; p=0.134), length of hospital stay (4.67 vs. 4.74 days; p=0.934), readmission, or complication rates. No complications occurred as a direct result of TXA use.	One patient in the control arm had a thromboembolic event within 30 days of admission (acute coronary syndrome); however, there were no adverse events or complications related directly to TXA. No unplanned analyses were performed.

HALT-IT 2020	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Patients were enrolled if they were above the minimum age considered an adult in their country (either 16 years or older or 18 years or older) and if the responsible clinician was substantially uncertain whether to use TXA. The diagnosis of significant bleeding (upper or lower GIH) was clinical, and significant bleeding was defined as a risk of bleeding to death. This included patients with hypotension, tachycardia, signs of shock, or those likely to need transfusion, urgent endoscopy, or surgery.	**Treatment:** A loading dose of 1 g TXA was added to 100 mL of 0.9% NaCl and infused over 10 minutes, followed by 3 g TXA added to 1 L of any isotonic IV solution and infused at 125 mg/h for 24 hours. **Control:** Placebo (0.9% NaCl)	**Primary Outcome:** Death due to bleeding within 5 days of randomization. **Secondary Outcomes:** Death due to bleeding within 24 hours and 28 days; rebleeding within 24 hours, 5 days, and 28 days.	Randomly allocated 12,009 patients to receive TXA (5,994, 49.9%) or matching placebo (6,015, 50.1%), of whom 11,952 (99.5%) received the first dose of the allocated treatment. There was no statistically significant difference between the groups in terms of the primary outcome: death due to bleeding within 5 days of randomization occurred in 222 (4%) of 5,956 patients in the TXA group and in 226 (4%) of 5,981 patients in the placebo group (Risk Ratio 0.99, 95% CI 0.82 to 1.18). There was no statistically significant difference between the groups in terms of secondary outcomes (death due to bleeding within 24 hours, death due to bleeding within 28 days, rebleeding within 24 hours, rebleeding within 5 days, rebleeding within 28 days).	Modified ITT analysis was performed instead of ITT analysis. The HALT-IT trial is an international, randomized, double-blind (participants and trial staff), placebo-controlled trial conducted in 164 hospitals in 15 countries. Arterial thromboembolic events (myocardial infarction or stroke) were similar in the TXA group and placebo group (42 (0.7%) of 5,952 vs. 46 (0.8%) of 5,977; Risk Ratio 0.92; 95% CI 0.60 to 1.39). Venous thromboembolic events (deep vein thrombosis or pulmonary embolism) were higher in the TXA group than in the placebo group (48 (0.8%) of 5,952 vs. 26 (0.4%) of 5,977; Risk Ratio 1.85; 95% CI 1.15 to 2.98).

Chiang 2023	Randomized controlled trial, non-blinded	**Inclusion Criteria:** The study enrolled patients aged ≥20 years who had peptic ulcer bleeding with major stigmata of recent hemorrhage detected by esophagogastroduodenoscopy. **Exclusion Criteria**: The study excluded patients with poor renal function (serum creatinine >2.9 mg/dL), tumor ulcer bleeding, allergies to TXA, acute thromboembolic events within 1 week, or those who were unable to temporarily halt antiplatelet or anticoagulation treatment.	**Treatment:** 1.25 g of TXA powder was applied to the peptic ulcer sites of patients in the TXA group before the endoscopic procedure was completed. **Control:** Standard endoscopic therapy.	**Primary Outcome:** Early treatment failure of the index ulcer within 4 days after the initial endoscopic treatment. **Secondary Outcomes:** Index ulcer rebleeding within 28 days, index ulcer rebleeding requiring transarterial embolization or emergent surgery; the duration of hospitalization; transfusion units of packed red blood cells; mortality; and severe adverse events due to TXA (e.g., seizures, thromboembolic events).	Sixty patients were included in the study. Thirty patients in each group were randomly assigned to the TXA group or the standard group. For the primary outcome, the early treatment failure rate was lower in the TXA group than in the standard group (6.7% vs. 30%, respectively; p=0.042). The periods of freedom from treatment failure for both 4 days and 28 days were significantly longer in the TXA group than in the standard group (p=0.023). The univariate analysis indicated that TXA was associated with a lower rate of early treatment failure (relative risk, 0.17; 95% CI, 0.03 to 0.85; p=0.032). The multivariate analysis indicated that the TXA spray was the only independent factor that prevented early treatment failure (Relative Risk 0.10; 95% CI, 0.01 to 0.87; p=0.037).	The current randomized trial was not double blinded.

					There were no statistically significant differences in the other secondary outcomes: emergent surgery, duration of hospitalization, transfusion units of packed red blood cells, mortality, and severe adverse events.	
Studies with high risk of bias						
Cormack 1973	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** All patients admitted with upper gastrointestinal tract bleeding, except those with conditions known to be fatal, were included in the trial until 150 patients had been studied. Diagnosis was based on frank hematemesis and/or melaena.	**Treatment:** 15 g TXA tablets PO eight-hourly for seven days **Control:** Placebo (undefined)	Mortality, need for surgery, and continuing or rebleeding necessitating further blood-transfusion.	Of the 150 patients, 76 were found to have received TXA and 74 had received placebo tablets. In each group, 3 patients, all older than sixty, died. Including these patients based on continued bleeding, rebleeding, and the need for further transfusion or surgery, treatment was judged to have failed in 15 patients receiving TXA and 20 patients receiving placebo. The difference was not significant. However, excluding patients with bleeding due to hiatus hernia or esophageal varices, treatment was deemed to have failed in 7 of 62 patients given TXA	One patient had continuous nausea and vomiting while receiving TXA, but these symptoms continued after the drug was stopped. Treatment was discontinued in another patient who complained of epigastric pain. No patient developed symptoms or signs of thromboembolism.

					compared with 17 of 63 patients given placebo tablets. This difference ($p<0.05$) is significant and suggests that TXA favorably influenced bleeding caused by peptic ulceration or erosion.	
Rafeey 2016	Randomized placebo-controlled trial	**Inclusion Criteria:** The study included children under 18 years of age with a diagnosis of bleeding gastric or duodenal ulcer on endoscopy. **Exclusion Criteria:** contraindication for endoscopy, hospitalization for another illness, coagulopathy, altered post-surgical anatomy of the stomach or duodenum, presence of intrahepatic portosystemic shunt, treatment with other endoscopic or surgical modalities within 14 days prior to the intended application of TXA, hemodynamic instability, and hemoglobin drop of more than 2 g/dL in 2 hours.	**Treatment:** 10 mL of saline with 5 mL (1 vial containing 500 mg) of TXA was directly applied to the surface of the ulcer. **Control:** The same amount of saline with 1/10000 epinephrine was injected submucosally into the four quadrants of the ulcer margins.	**Primary Outcome:** Evidence of clinically rebleeding confirmed by repeated upper gastrointestinal endoscopy or surgery within the first 2 days after the index endoscopy. **Secondary Outcomes:** Surgical intervention, mortality, hospital stay, blood transfusion, repeated endoscopy during hospital stay.	Sixty-three patients (30 girls, 33 boys) were recruited. The patients were randomly divided into case and control groups. Rebleeding occurred in 15 (11.4%) and 21 (9.8%) patients in the case and control groups, respectively ($p=0.50$). The frequency of blood transfusion episodes and the duration of hospital stay were not statistically different between the groups ($p=0.06$ and $p=0.07$, respectively).	There is no mention of blindness in the study.
Sedaghat 2023	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** All patients aged over 18 years with an unstable hemodynamic state, defined as a systolic blood pressure under 90 mmHg and a heart rate over 110 beats per minute, and who fulfilled informed consent were included in the study (upper GIH). **Exclusion Criteria:** Patients under the age of 18 years, pregnant or breastfeeding patients, and those with contraindications for the use of TXA (history of thromboembolic disorder, esophageal variceal bleeding, hypersensitivity to TXA,	**Treatment:** TXA 1g IV in 10 min and then IV infusion (1 g/8 h) **Control:** Placebo (undefined)	Rebleeding, need for blood transfusion, hospital stay, adverse effects, and mortality	Eighty-six patients were enrolled (43 in each group). Rebleeding occurred in 11 (25.6%) patients in the TXA group and in 20 (46.5%) patients in the control group, which was statistically significant ($p=0.043$). Blood transfusion was required in	One patient treated with TXA experienced an adverse effect associated with the medication, which was a skin reaction to TXA. Compared to placebo TXA was not associated with significant adverse effects.

		hereditary thromboembolic disorders, use of oral estrogen-containing contraceptives, heart valvular diseases, atrial fibrillation, and those requiring anticoagulant agents) were excluded from the study.			only 3 (7%) patients in the TXA group compared with 14 (32.6%) patients in the control group (p=0.003). Six (14%) patients experienced a hospital stay of longer than five days in the TXA group, compared with 15 (34.9%) patients in the control group, which was statistically significant (p=0.024). There were no significant differences in the mortality rate between the groups (p>0.05).	
Bashiri 2021	Randomized double-blind controlled trial	**Inclusion Criteria:** The study was conducted in patients with a diagnosis of upper GIH. To establish this diagnosis, all patients underwent endoscopy within the first 24 hours of admission. **Exclusion Criteria:** Patients younger than 18 years, those with contraindications to receiving TXA, kidney disorders, pregnant or lactating women, esophageal or gastric varices, coagulation disorders, and severe liver disease were excluded. Patients with diagnoses other than upper gastrointestinal bleeding during endoscopy were also excluded.	**Treatment:** TXA was injected 1g and then IV infusion (1 g/8 h) **Control:** Conventional treatments for upper GI bleeding including fluid therapy and pantoprazole infusion	Hospital length of stay, the need for endoscopy and blood transfusion, and rebleeding	A total of 70 patients with acute upper GIH were randomly divided into 2 groups (35 in the TXA group and 35 in the control group). No statistically significant differences were observed regarding admission duration, rebleeding, or the need for endoscopy between the two groups. The need for blood transfusion was significantly higher in the TXA group compared to the control group (60% vs 22.9%, p<0.001). None of the patients required	TXA did not improve the outcomes of patients with acute upper GIH.

					surgical intervention.	
Barer 1983	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Fifty patients with massive upper GIH were included in the study. Massive bleeding was defined as hematemesis and/or melena, with the patient showing circulatory involvement on arrival or in anamnesis. **Exclusion criteria** were not mentioned.	**Treatment:** An oral solution including TXA was administered through the gastric tube every four hours for two days. When active treatment was given an oral dose of 2g was administered on each occasion. **Control:** Placebo (same way)	Mortality, hemoglobin, and hematocrit levels, need of surgery, blood transfusion	A total of 50 patients entered the trial (25 in the TXA group and 25 in the placebo group). The mortality rate in the TXA group was 12.3%, compared to 22.7% in the placebo group (no p value was provided). Hemoglobin levels were 89.7 g/L in the TXA group and 93.5 g/L in the placebo group. The mean number of blood transfusion units was 6.0 in the placebo group and 8.1 in the TXA group.	The study results revealed no effect on transfusion requirements or operation frequency but showed a slightly reduced mortality and delayed death. Neither p values nor effect sizes were provided in the study. The statistical analysis of the study was very inadequate.
Biggs 1976	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Patients included in the trial presented consecutively to the accident and emergency center. Hemorrhage was observed by a medical officer or confirmed by gastric aspiration and examination of the feces for melaena. Only patients who required hospitalization were included in the trial. **Exclusion Criteria:** Patients who were pregnant, had chronic renal impairment, had undergone previous vascular surgery, or had a history of a thromboembolic episode within the preceding 12 months were excluded.	**Treatment:** Ampoules and tablets containing 500 mg of TXA were administered as follows: two ampoules IV and two tablets orally every eight hours for 48 hours, followed by two tablets orally every eight hours for an additional 72 hours. **Control:** Placebo tablets contained cellulose-	Transfusion requirements, morbidity, surgical intervention, and mortality.	Two hundred patients entered the trial (103 in the TXA group and 97 in the placebo group). The total transfusion requirements were not significantly different between the two groups. The difference in operation rate was significant ($p<0.001$). The difference in mortality between the two groups was not significant.	There were no major adverse effects of therapy. Minor adverse effects encountered were similar in both groups.

			lactate, while placebo ampoules contained normal saline.			
Hawkey 2001	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** All identifiable patients admitted to the two hospitals because of suspected upper GIH over a 16-month period were considered for trial entry. **Exclusion Criteria:** Bleeding so severe as to require immediate surgical intervention, conditions making active treatment inappropriate (for example, terminal malignancy), pregnancy, lactation, active thromboembolism or intravascular coagulopathy, creatinine level above 250 µmol/L, use of phenytoin, and known adverse drug reactions to trial drugs.	**Treatment:** TXA 2 g PO, followed by 1 g PO four times daily **Control-1:** Placebo **Control-2:** Lansoprazole (treated for up to four days with lansoprazole 60 mg PO, followed by 30 mg PO four times daily) **Control-3:** TXA+ Lansoprazole	**Endoscopic Endpoint:** Blood in the stomach (using the five-point endoscopic assessment). **Clinical Endpoints:** Amount of blood transfused, incidence of rebleeding, need for surgical intervention, or death.	Of 414 patients with suspected upper gastrointestinal bleeding (103 TXA, 103 placebo, 102 lansoprazole, and 106 TXA + lansoprazole), 379 underwent endoscopy. Upper gastrointestinal bleeding was confirmed in 316 patients. Trial treatments were evaluable on a per-protocol basis in 228 patients, but an intention-to-treat analysis was performed for all 414 patients. Sixteen patients required surgery within 30 days, and sixteen died on index admission. There were no differences in clinical outcomes (blood transfusion, death, and need for surgery). The amount of blood in the stomach at endoscopy was significantly reduced by both lansoprazole (OR 0.22, 95% CI 0.07 to 0.63) and TXA (OR	There were no significant differences in the number or pattern of adverse events, severe adverse events, or adverse events leading to withdrawal among the four treatment groups (there is no table presenting adverse events). The statistical analysis quality of the study was poor, and effect sizes were not presented.

					0.27, 95% CI 0.09 to 0.81), although there was no evidence of synergy.	
Saidi 2017	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** All patients with an initial clinical diagnosis of upper GIH were primarily recruited. **Exclusion Criteria:** Endoscopic examination was performed on all recruited patients within 24 hours of presentation, and any patient without a demonstrable benign gastric or duodenal lesion was excluded from the study. Patients were not eligible for inclusion if they were pregnant or lactating, had a gastrointestinal malignancy, a history of thromboembolism, myocardial infarction, ischemic cerebrovascular accident, end-stage renal disease, an allergy to TXA, ongoing anticoagulation therapy, congenital or acquired coagulopathy, or were reluctant to enroll in the study.	**Treatment:** TXA was administered at a dose of 1 gram diluted in 250 ml of saline solution via nasogastric tube within the first 30 minutes of patients' arrival at the emergency department. **Control:** Placebo (250 ml saline)	**Primary Outcome:** Amount of blood needed for transfusion. **Secondary Outcomes**: Rebleeding, need for surgical intervention, postoperative 30-day mortality rates, and occurrence of deep vein thrombosis.	One hundred thirty-one patients were analyzed (67 TXA, 64 placebo). There were 13 (9.92%) cases of death (30-day mortality) in the study population: 4 in the TXA group (5.97%) and 9 in the placebo group (14.06%). Upper GIH-related mortality was reduced in TXA-treated patients, but the difference did not reach the level of significance (p=0.150). During the study, no emergency surgery for upper GIH was performed. Transfusion requirements were significantly higher in patients not receiving TXA. Patients in the TXA group received an average of 1.77±1.08 units, while the average amount of packed RBCs received by the placebo group was 2.9±1.61 units. This difference was statistically	Thromboembolic complications (arterial or venous thrombosis) were seen in neither group within 30 days. No other side effects were observed during treatment with intra-gastric TXA.

					significant (p<0.001). The number of rebleeding episodes was 4 (6%) in the TXA group, compared to 12 (18.8%) in the placebo group (p=0.033). There was also a significant difference between the two groups in the number of emergency endoscopies: 6 (9%) in the TXA group vs. 14 (21.9%) in the placebo group (p=0.040).	

GIH: Gastrointestinal Hemorrhage, TXA: Tranexamic Acid, PO: Peroral, IV: Intravenous, ITT: Intention to treat, CI: Confidence Interval, OR: Odds Ratio, RBC: Red Blood Cell

Table 2. Summaries of Studies Investigating the Efficacy of Tranexamic Acid in Patients with Trauma

Study	Design	Participants	Interventions	Outcomes	Main Results	Comments
Studies with low or uncertain risk of bias (moderate risk)						
CRASH-2 2010	Randomized double-blind placebo-controlled trial	Adult trauma patients with significant hemorrhage (systolic blood pressure <90 mm Hg or heart rate >110 beats per min, or both), or who were considered to be at risk of significant hemorrhage, and who were within 8 h of injury.	**Treatment:** Loading dose of 1 g of TXA infused over 10 min, followed by an IV infusion of 1 g over 8 h **Control:** Placebo (0.9% saline) with the same protocol.	**Primary Outcome:** Effects of early administration of a short course of TXA on death in hospital within 4 weeks of injury. **Secondary Outcomes:** Vascular occlusive events, surgical intervention, and units of blood products transfused.	In the TXA group, 1463 patients (14.5%) and in the placebo group, 1613 patients (16%) had all-cause mortality. TXA significantly reduced all-cause mortality (p=0.0035). The relative risk (RR) of death with TXA was 0.91 (95% CI=0.85 to 0.97). Mortality due to bleeding occurred in 489 patients (4.9%) in the TXA group and 574 patients (5.7%) in the placebo group, with the difference being significant (p=0.0077). The RR of death due to bleeding with TXA was 0.85 (95% CI=0.76 to 0.96).	The CRASH-2 study is an international, multicenter, double-blind, placebo-controlled trial. The study is well-designed, conducted, and reported, resulting in a low risk of bias according to RoB-2. The study concluded that TXA has a significant impact on all-cause mortality and mortality due to bleeding in adult trauma patients with significant hemorrhage or at risk of significant hemorrhage.
El-Menyar 2021	Randomized double-blind placebo-controlled trial	Adult patients with trauma who are at risk of bleeding (CRASH-2 criteria).	**Treatment:** 1g IV TXA in hospital over 8 hours. **Control:** Normal saline with the same protocol. Both groups received 1g TXA prehospital.	**Primary Outcome:** 24-hour (early) and 28-day (late) mortality. **Secondary Outcomes:** In-hospital thromboembolic complications, multiorgan failure, blood transfusions, massive transfusion protocol	The second TXA dose had no effect on 28-day mortality compared with placebo (OR 0.476 ([95% CI 0.157-1.442], p=0.18). Additionally, the second TXA dose had no effect on 24-hour mortality compared	The study concluded that TXA did not have an effect on mortality in actively bleeding patients. However, the LOS and bleeding volume were significantly lower in the TXA group. The study was classified as

				activation, and hospital length of stay. The outcomes of the study are stated as the effect of TXA on mortality, hospital LOS, and use of blood products.	with placebo (OR 1.000 [95% CI 0.062-16.192], p=0.47). The number of deaths in the TXA and placebo groups was 2 (5.9%) and 4 (11.8%), respectively (p=0.33). The median (IQR) bleeding volume for the TXA group was significantly lower than that of the control group [1000 cc (1200) vs. 1500 cc (1050), p=0.03]. The median length of hospital stay among the TXA group was lower than that of the placebo group (6 days vs. 10 days, p=0.004).	having a low risk of bias according to the RoB-2 tool.
Guyette 2020	Randomized double-blind placebo-controlled trial	Patients with prehospital hypotension (systolic blood pressure below 90 mmHg) or tachycardia (heart rate over 110 beats per minute) before arrival at the hospital within the initial 2 hours.	**Treatment:** **a.** 1g TXA IV bolus + IV placebo bolus + IV placebo infusion (8 hours), **b.** 1g TXA IV bolus + IV placebo bolus + 1g TXA IV infusion (8 hours), **c.** 1g TXA IV bolus + 1g TXA IV bolus + 1 g TXA IV infusion (8 hours). **Control:** Normal saline as placebo; IV placebo bolus + IV	**Primary Outcome:** To assess the effectiveness of TXA administered before hospitalization in injured patients at risk for hemorrhage on 30-day mortality. **Secondary Outcomes:** 24-hour in-hospital mortality, blood component resuscitation volumes at 6 hours and 24 hours, incidence of multiorgan failure, acute respiratory distress syndrome,	8.1% of the TXA group and 9.9% of the placebo group had 30-day mortality, and the difference was not significant (p=0.17). In patients with severe shock (systolic blood pressure below 70 mmHg), the TXA group had a significantly lower rate of 30-day mortality.	This multicenter, double-blinded, randomized controlled trial concluded that 1 g of prehospital TXA administration did not improve 30-day mortality. However, in the severe hypotensive subgroup of patients, TXA resulted in lower 30-day mortality. It is also worth noting that the study was well-designed, conducted, analyzed, and reported, and was evaluated as

			placebo bolus + IV placebo infusion (8 hours).	nosocomial infections, early seizures, pulmonary embolisms, deep vein thrombosis, and crystalloid resuscitation over 24 hours from admission.		having a low risk of bias using the RoB-2 tool.
PATCH 2023	Randomized double-blind placebo-controlled trial	Adult patients (≥18 years of age) with suspected severe traumatic injuries who were treated at the scene by paramedics or physicians and transported by road or air ambulance to participating trauma centers.	**Treatment:** Prehospital 1g IV TXA and in-hospital 1g IV TXA with 8-hours infusion. **Control:** Matching placebo (normal saline) with the same protocol.	**Primary Outcome:** Survival with a favorable functional outcome at 6 months after injury, assessed using the Glasgow Outcome Scale-Extended (GOS-E). **Secondary Outcomes:** All-cause mortality within 28 days and within 6 months after injury.	Survival with a favorable functional outcome at 6 months occurred in 307 of 572 patients (53.7%) in the TXA group and 299 of 559 patients (53.5%) in the placebo group (risk ratio, 1.00; 95% CI, 0.90 to 1.12; p=0.95). At 28 days after injury, 113 of 653 patients (17.3%) in the TXA group and 139 of 637 patients (21.8%) in the placebo group had mortality (risk ratio, 0.79; 95% CI, 0.63 to 0.99). By 6 months, 123 of 648 patients (19.0%) in the TXA group and 144 of 629 patients (22.9%) in the placebo group had mortality (risk ratio, 0.83; 95% CI, 0.67 to 1.03).	This international multicenter double-blind randomized controlled trial concluded that among adults with major trauma and suspected trauma-induced coagulopathy who were being treated in advanced trauma systems, prehospital administration of TXA followed by an infusion over 8 hours did not result in a greater number of patients surviving with a favorable functional outcome at 6 months compared to placebo. The study is very well designed, conducted, and reported, with a RoB-2 assessment indicating a low risk of bias.
Studies with high risk of bias						
NONE	-	-	-	-	-	-
Characteristics of the trials about isolated head trauma with low or some concerns risk of bias						

Rowell 2020	Randomized double-blind placebo-controlled trial	Out-of-hospital TBI patients with GCS≤12 and SBP≥90mmHg, aged≥15.	**Treatment:** Out-of-hospital 1g TXA IV bolus and in-hospital 1g TXA IV infusion in 8 hours. **Control 1:** Out-of-hospital 2g TXA IV bolus and in-hospital placebo IV infusion in 8 hours. **Control 2:** Out-of-hospital placebo IV bolus and in-hospital placebo IV infusion in 8 hours.	**Primary Outcome:** Favorable neurologic function at 6 months (GOS-E>4). **Secondary Outcomes:** 28-day mortality, 6-month disability rating scale (DRS) score, progression of intracranial hemorrhage, discharge GOS-E score, and discharge DRS score.	Sixty-five percent of the patients in the TXA group and sixty-two percent of the patients in the placebo group had favorable neurologic function at 6 months (p=0.084).	This is a multicenter, double-blind, randomized controlled trial. TXA showed no significant difference between the intervention groups in terms of favorable neurologic function. The study was evaluated as having some concerns in the RoB-2 assessment.
Jokar 2017	Randomized single-blinded, placebo-controlled trial	TBI patients aged 15 years and older, within 2 hours of injury onset, and with acute ICH (volume of less than 30 ml) based on CT scan findings, were included.	**Treatment:** A bolus of 1g TXA in 100 ml 0.9% NaCl over 10 minutes, followed by a continuous infusion of 1g TXA in 500 ml 0.9% NaCl over 8 hours. **Control:** 0.9% normal saline administered in the same manner.	**Primary Outcome:** Investigate the effect of TXA on the extent of ICH growth within 48 hours.	Brain CT scans taken 48 hours after TBI showed a significant increase in hemorrhage volume in both groups (p<0.001). However, the increase in ICH volume in the TXA group was significantly less than that in the control group (p=0.04). The mean total hemorrhage expansion was 1.7 ± 9.7 ml in the TXA group and 4.3 ± 12.9 ml in the placebo group (p<0.001).	The study found that TXA had a significant positive effect on hemorrhage expansion in patients with acute intracranial hemorrhage. It is worth noting that the authors did not elaborate on the randomization process, so the study was evaluated as having some concerns regarding the risk of bias in the RoB-2 tool.
CRASH-3 2019	Randomized double-blind placebo-controlled trial	Adult patients with TBI who were within 3 hours of injury, had a GCS score of 12 or	**Treatment:** 1g TXA over 10 min then infusion of 1 g over 8 h	**Primary Outcome:** Head injury-related mortality	Among patients treated within 3 hours of injury, the risk	In this study, TXA did not result in a significant reduction in mortality among

		lower or any ICH on CT scan, and no major extracranial bleeding were included.	**Control:** Matching placebo	in hospital within 28 days of injury. **Secondary Outcomes:** Early head injury-related mortality (within 24 hours after injury), all-cause and cause-specific mortality, disability, vascular occlusive events (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism), seizures, complications, neurosurgery, days in the intensive care unit, and adverse events within 28 days of randomization.	of head injury-related death was 18.5% in the TXA group versus 19.8% in the placebo group (855 vs. 892 events; RR 0.94 [95% CI 0.86–1.02]). Subgroup analysis revealed that the risk of head injury-related death was reduced with TXA in patients with mild-to-moderate head injury (RR 0.78 [95% CI 0.64–0.95]), but not in patients with severe head injury (RR 0.99 [95% CI 0.91–1.07]; p value for heterogeneity 0.030).	the total population. However, subgroup analysis showed that TXA significantly decreased mortality in patients with mild-to-moderate head trauma but did not affect mortality in patients with severe head trauma. The large cohort and multiple centers involved in the study enhance the generalizability of the results. Additionally, the study received a low risk rating from the RoB-2 evaluation due to its transparent and rigorous methodology and detailed reporting.
Yutthakasemsunt 2013	Randomized double-blind placebo-controlled trial	Trauma patients older than 16 years with moderate to severe TBI (post-resuscitation GCS score of 4 to 12), who had a brain CT scan performed within eight hours of injury and for whom there was no immediate indication for surgery, were eligible for inclusion.	**Treatment:** Loading dose of 1.0 gram TXA administered over 30 minutes, followed by a maintenance dose of 1.0 gram TXA infused over eight hours. **Control:** Matching placebo (sterile water) with the same protocol.	**Primary Outcome:** Presence of progressive ICH. **Secondary Outcomes:** Mortality, functional status assessed using the GOS at hospital discharge, blood transfusion, neurosurgical operations, and any in-hospital thromboembolic events (myocardial infarction, pulmonary embolism, deep vein thrombosis, and stroke).	Progressive intracranial hemorrhage was present in 21 (18%) of patients allocated to TXA and in 32 (27%) of patients allocated to placebo. The difference was not statistically significant [RR=0.65 (95% CI 0.40 to 1.05)]. The relative risk of death from all causes in patients allocated to TXA compared	This study concluded that TXA did not have a positive effect on progressive intracranial hemorrhage in patients with TBI. TXA also did not result in a reduced risk for an unfavorable clinical outcome. It is worth noting that this study was well-designed, conducted, analyzed, and reported, and was evaluated as having a low risk of bias in the RoB-2 tool.

					with placebo was 0.69 (95% CI 0.35 to 1.39), and the relative risk for an unfavorable outcome on the GOS was 0.76 (95% CI 0.46 to 1.27).	
Characteristics of the trials about isolated head trauma with high risk of bias						
Chakroun-Walha 2018	Randomized open labeled placebo-controlled study	Trauma patients who are 18 years or older, admitted to the emergency department with TBI, and who have ICH on the first or second brain CT scan.	**Treatment:** 1 g TXA in 100 mL of normal saline administered over 10 minutes, followed by a maintenance dose of 1 g TXA in 500 mL of normal saline infused over 8 hours. **Control:** Standard care without TXA	**Primary Outcome:** Three primary outcome measures were defined: need for transfusion, need for surgery, and 28-day mortality.	Ninety-six patients in the TXA group and eighty-four patients in the standard care group were included. In the TXA group, 23 patients (24%) required neurosurgery, compared to 16 patients (19%) in the standard care group (p=0.4). Within 28 days, 19 patients (22.6%) in the TXA group and 27 patients (28.1%) in the standard care group died (p=0.4). No significant difference was observed between the groups regarding 1-day PRBC, 3-day PRBC, 7-day PRBC, 1-day FFP, 3-day FFP, 1-day platelet, 3-day platelet, 7-day platelet transfusions.	Randomization of the study was based on patient registration numbers, and an appropriate method was not used. Additionally, although the study design could have been double-blind, it was conducted as an open-label study, introducing a risk of bias for both patients and practitioners. There is no information on whether the study followed an ITT or per-PP approach. Furthermore, the sample size was not calculated. After randomization, there was an unequal distribution between the groups, with a significantly higher number of abdominal trauma patients assigned to the TXA group. Due to these deficiencies, the study was considered to have a high risk of bias according to the RoB-2 tool.

Mojalal 2020	Randomized double-blind placebo-controlled trial	Trauma patients older than 18 years, with detection of intracranial hemorrhage on brain CT scan—including subdural hematoma, epidural hematoma, intracerebral hemorrhage, and intraventricular hemorrhage—but without subarachnoid hemorrhage, were included in the study. Patients had to be within 8 hours of trauma incidence, with no history of anticoagulant use or blood coagulation system impairments such as hemophilia or idiopathic thrombocytopenic purpura.	**Treatment:** 1g (10cc) TXA in 100cc normal saline **Control:** 10cc distilled water in 100cc normal saline	**Primary Outcome:** The effect of TXA on cerebral hemorrhage volume.	Mean hemorrhage volumes in the intervention groups after 24 hours showed no significant difference (p=0.098). However, delta hemorrhage volumes were not compared. In the 7-day period, 8 (14.2%) patients in the TXA group and 3 (6.8%) patients in the placebo group died, but the difference was not significant (p = 0.236).	The study found that TXA had no significant effect on 7-day mortality. However, the authors used PP analysis, and a disproportionate number of patients in the placebo group were lost to follow-up. Additionally, the baseline characteristics of the intervention groups differed drastically, raising concerns about the randomization process and analysis. The study was assessed as having a high risk of bias according to the RoB-2 tool.
Atia 2021	Randomized placebo-controlled trial	Trauma patients with isolated TBI who are older than 18 years and presented to the emergency department within the first 3 hours of injury onset.	**Treatment:** 1 g TXA infused over 10 minutes, followed by an IV infusion of 1 g over eight hours. **Control:** 0.9% normal saline administered in the same manner.	**Primary Outcome:** To evaluate the effect of TXA on changes in the volume of ICH in patients with TBI.	The expansion of hemorrhagic mass volume was 1.5 ml (±4.4) in the TXA group and 5.1 ml (±11.3) in the control group, with a significant difference (p=0.038). Additionally, 34 (68%) patients in the TXA group and 21 (42%) patients in the control group showed reduced hemorrhagic mass volume on the second CT scan, and this difference was also significant (p=0.016).	The study found that the TXA group had significantly less hemorrhagic mass volume and growth, as well as a higher rate of reduced hemorrhagic mass volume. Additionally, the TXA group had a significantly lower LOS, although mortality rates and the rate of unfavorable outcomes did not differ between groups. However, the study had major methodological shortcomings and was evaluated as having a high risk of bias using the RoB-2 tool.

Fakharian 2019	Randomized double-blind placebo-controlled trial	Trauma patients older than 13 years, with isolated blunt head trauma or those with multiple trauma for whom head injury was the first priority, who arrived at the hospital within less than 3 hours of the injury, and who had evidence of IPH/contusion on admission brain CT scan were enrolled in the study.	**Treatment:** 1 g TXA in 100 ml normal saline infused over 10 minutes, followed by a maintenance dose of 1 g in 1000 ml normal saline infused over 8 hours. **Control:** Normal saline with the same protocol.	**Primary Outcome:** To investigate the effect of TXA on the size of the intracranial hemorrhage 24 and 72 hours after the injury.	Twenty-nine (72.5%) of the TXA group and 22 (55%) of the placebo group had an increase in the size of the hemorrhage 24 hours after the trauma, and the difference was not significant (p=0.10). Thirty (75%) of the TXA group and 26 (65%) of the placebo group had an increase in the size of the hemorrhage 72 hours after the trauma, and the difference was not significant (p=0.32).	The study concluded that TXA had no significant effect on hemorrhage size 24 and 72 hours after the trauma. However, there are some critical shortcomings, such as the miscalculation of proportions in the results section of the primary outcome data. Furthermore, the primary outcome measure could be more specific as a continuous variable to compare rather than a dichotomous one. Therefore, the study was evaluated as having a high risk of bias according to the RoB-2 tool.
Safari 2021	Randomized double-blind placebo-controlled trial	Patients with ICH (16 to 65 years of age) following TBI, who did not require surgical intervention.	**Treatment:** 1 g TXA within the first 3 hours of admission, followed by 1 gram every 6 hours for 48 hours. **Control:** Normal saline on admission, and at hours 6, 24, and 48.	**Primary Outcome:** Comparison of hematoma expansion on 24 and 48-hour control CT scans. **Secondary Outcomes:** Comparison of midline shift at 24 and 48 hours. Comparison of GCS at 24 hours and discharge.	Hematoma volume at 24 hours in the TXA group was 6.0 ml (±9.3), and in the control group, it was 12.3 ml (±11.8) (p=0.01). Hematoma volume at 48 hours in the TXA group was 6.2 ml (±7.4), and in the control group, it was 12.1 ml (±14.2) (p=0.01). Midline shift at 24 hours in the TXA group was 0.6 mm (±1), and in the control group, it was 0.8 mm (±3.1) (p=0.62). Midline shift at 48 hours in	The study has multiple limitations. The treatment protocols differ, with the TXA group receiving 9 injections while the control group received 4 injections, which may have negatively affected the blinding. Additionally, the methods section provides very little information about the study, and no flow chart is included. For these reasons, the study was assessed as having a high risk of bias according to the

					the TXA group was 0.6 mm (±1.8), and in the control group, it was 0.9 mm (±2.3) (p=0.40). GCS at 24 hours in the TXA group was 12.3 (±1.8), and in the control group, it was 11.1 (±2.6) (p=0.53). GCS at 48 hours in the TXA group was 14.1 (±1.6), and in the control group, it was 13.9 (±1.9) (p=0.49).	RoB-2 evaluation.
Fathey 2021	Randomized double-blind placebo-controlled trial	Adult patients with TBI and a GCS of 4 to 12, for whom there was no indication for immediate surgical intervention.	**Treatment:** 1g TXA IV loading dose over 10 minutes and 1g TXA IV infusion over 8 hours. **Control:** Normal saline with same IV protocol.	**Primary Outcome:** The effect of TXA on the volume of ICH in patients with TBI.	There was no significant difference between the groups in terms of ICH volume after the first 24 hours (p=0.117). However, the TXA group had a significantly lower volume of ICH 48 hours after the injury (p=0.021).	The study found that TXA might lead to a lower increase in ICH 48 hours after the injury in TBI patients. However, it was evaluated as having "some concerns" using the RoB-2 tool.
Fakharian 2018	Randomized double-blind placebo-controlled trial	Patients with isolated TBI or multiple trauma where TBI was the primary issue, who arrived at the hospital within 8 hours of the injury, aged 15 years and older, with non-penetrating injuries and any type of traumatic intracranial bleeding (including subdural hemorrhage, subarachnoid hemorrhage, contusion, intraventricular hemorrhage, and epidural	**Treatment:** 1g TXA in 100 mL of normal saline in 10 minutes and then with a maintenance dose of 1 g per 1000 mL of normal saline for 8 hours. **Control:** Normal saline with the same protocol.	**Primary Outcome:** The effect of TXA on the growth of the hemorrhagic lesion.	The incidence of hemorrhagic lesion growth was 20.5% in the TXA group and 22.7% in the placebo group, with no significant difference (p=0.870). The mean (SD) hemorrhagic lesion growth was 9.4 (15.3) in the TXA group and 10.2 (10.1) in the placebo group, also without significant	The study found no significant difference in terms of hemorrhagic lesion incidence or hemorrhagic growth volume between the intervention groups. The study was assessed as having a high risk of bias according to the RoB-2 evaluation.

		hematoma) on admission CT scans, no need for brain surgery within the first 8 hours, no coagulation disorders, serum creatinine levels <2 mg/dL, and who were not pregnant, were enrolled in the study.			difference (p=0.270).	
Mousavinejad 2020	Randomized double-blind placebo-controlled trial	Patients over 18 years of age who were referred to the hospital within 8 hours after trauma, diagnosed with brain contusion with intraparenchymal hemorrhage by brain CT scan, and had no significant extradural hemorrhage (e.g., abdominal bleeding), no fracture or deformity in membranes, no hematuria, and no coagulation disorders.	**Treatment:** 1 g TXA in 500 ml of 0.9% normal saline, administered as an IV infusion over 10 minutes, followed by an additional 1 g TXA in 500 ml of 0.9% normal saline, administered as an IV infusion over 8 hours. **Control:** Normal saline administered with the same protocol.	**Primary Outcome:** To assess the effect of TXA on the reduction of hemorrhage volume during neurosurgery in patients with brain contusion and intraparenchymal hemorrhage admitted to the emergency department.	There was no significant difference between the groups in terms of bleeding during surgery, bleeding after surgery, hemoglobin drop during surgery, hemoglobin drop after surgery, and mortality rate (p=0.83, p=0.62, p=0.89, p=0.97, and p=0.87, respectively).	-
Ebrahimi 2019	Randomized double-blind placebo-controlled trial	Patients over 18 years of age, presenting to the emergency department within the first 8 hours of trauma, with confirmed isolated subdural or epidural intracranial hemorrhage via CT scan, who require surgery based on clinical condition and neurosurgeon opinion, and who do not have significant extracranial hemorrhage (e.g., intra-abdominal hemorrhage), fractures or deformities in the	**Treatment:** 1 g TXA with 500 ml of 0.09% normal saline and IV infusion within 10 min. Plus 1g TXA with 500 ml of 0.09% normal saline and IV infusion within 8 hours. **Control:** Normal saline with the same protocol.	**Primary Outcome:** To assess the effect of TXA on intraoperative bleeding in patients with traumatic subdural and epidural hemorrhage.	Results cannot be reported as a proper analysis for the outcome was not performed.	The study has critical errors. First, although the authors stated that they randomized 20 patients each to the intervention and control groups for two different patient groups, a discrepancy is evident when examining Table 1. The study has critical errors. First, although the authors claimed to have randomized 20 patients each to the intervention and control groups for two

		limbs, subarachnoid hemorrhage, hematuria, or coagulation disorders.				different patient types, a discrepancy is evident in Table 1. For patients with subdural hematoma, 18 were randomized to the intervention group and 22 to the control group. For patients with epidural hematoma, 24 were randomized to the intervention group and 16 to the control group. This inconsistency is not addressed in the text or flowchart but becomes evident when the numbers in the table are summed. Additionally, the outcome data were not analyzed appropriately. Instead of conducting separate analyses for subdural and epidural hematoma patients, four groups were compared in a single analysis, resulting in an inappropriate and meaningless comparison. Due to these issues, the study was classified as having a high risk of bias according to the RoB-2 tool.

TXA: Tranexamic Acid, ICH: Intracranial Hemorrhage, IPH: Intraparencymal Hemorrhage, LOS: Length of Stay, OR: Odds Ratio, RR: Relative Risk, IV: Intravenous, IQR: Interquartile Range, SD: Standart Deviation, CI: Confidence Interval, GOS: Glagow Outcome Scale, GOS-E: Glasgow Outcome Scale Extended, DRS: Disability Rating Scale, TBI: Traumatic Brain Injury, CT: Computed Tomography, GCS: Glagow Coma Scale, PRBC: Packed Red Blodd Cells, FFP: Fresh Frozen Plasma, PP: Per protocol, ITT: Intention to Treat, RoB-2: Risk of Bias tool

Table 3. Summaries of Studies Investigating the Efficacy of Tranexamic Acid in Patients with non-traumatic Intracerebral Hemorrhage

Study	Design	Participants	Interventions	Outcomes	Main Results	Comments
Studies with low or some concerns risk of bias						
Sprigg 2014	Randomized double-blind placebo-controlled trial Phase-2	**Inclusion Criteria:** Adult patients with acute (within 24 hours of onset) spontaneous intracerebral hemorrhage (ICH) were identified and enrolled. **Exclusion Criteria:** Secondary ICH (due to anticoagulation or known vascular malformations) Previous venous thromboembolic disease (VTE) Recent ischemic events (within the past 12 months), including ischemic stroke (IS), myocardial infarction, or peripheral artery disease (PAD) Renal impairment (estimated GFR<50 mL/min) Pregnancy or breastfeeding	**Treatment:** 1 g TXA loading dose infused over 10 minutes, followed by 1 g infused over 8 hours. **Control:** Matching placebo (0.9% normal saline) administered with the same regimen as TXA.	**Primary Outcome:** Trial feasibility (proxy for trial acceptability: number of patients screened who are eligible for enrollment and who gave informed consent). **Secondary Outcomes:** Tolerability (adverse events occurring during or after administration of TA) and safety (clinical information on ischemic events [IS, transient ischemic attack, acute coronary syndrome, PAD] and VTE were also recorded). Change in hematoma volume from baseline to 24 h and hematoma location).	Sixteen patients received TXA, and eight patients received placebo. There were no significant differences in functional outcomes between the groups (mRS 3.6 (1.9) in TXA vs. 3.4 (2.1) in placebo; p=0.82). There was no difference in the incidence of any serious adverse events (six patients [37.5%] vs. two patients [25%]; p=1). Hematoma volume increase was greater in the control group (9.7%) compared to the TXA group (5.4%).	This study was conducted prior to the TICH-2 study to assess tolerability and feasibility outcomes.

Sprigg 2018	Randomized double-blind placebo-controlled trial Phase-3	**Inclusion Criteria:** Adults with acute ICH were eligible for inclusion if they were admitted to a participating hospital within 8 hours of stroke symptom onset (or time last seen well). **Exclusion criteria:** ICH secondary to anticoagulation , thrombolysis, trauma, or a known underlying structural abnormality; patients for whom TXA was thought to be contraindicated ; prestroke dependence with an mRS score >4; life expectancy less than 3 months; and GCS score less than 5.	**Treatment:** IV 1 g TXA as a loading dose in 100 mL normal saline 0.9% infused over 10 minutes, followed by another 1 g in 250 mL normal saline 0.9%, infused over 8 hours. **Control:** The comparator was a matching placebo (normal saline 0.9%), administered with an identical regimen.	**Primary Outcome:** Functional status at day 90, as assessed with the mRS. **Secondary Outcomes:** Neurological impairment at day 7 or discharge (whichever came first), assessed with the NIHSS; health-related quality of life measured with EuroQoL-5 dimensions (EQ-5D) health utility status and visual analogue scale; activities of daily living according to the Barthel index; cognition assessed via a modified Telephone Interview for Cognitive Status (TICS-M) and verbal fluency; mood assessed with the Zung Depression Scale (ZDS); costs (length of hospital stay and discharge destination); and radiological efficacy (change in hematoma volume from baseline to 24 h and hematoma location).	A total of 1161 participants were randomly assigned to receive TXA, and 1164 to receive placebo. There was no difference in the distribution (shift) in the mRS at day 90, with an adjusted odds ratio (aOR) of 0.88 (95% CI 0.76-1.03, p=0.11). Fewer participants had hematoma expansion at day 2 in the TXA group (265 [25%] of 1054 participants) than in the placebo group (304 [29%] of 1058 participants; aOR 0.80, 95% CI 0.66 to 0.98, p=0.030). The mean increase in hematoma volume from baseline to 24 hours was also less in the TXA group (3.72 mL, SD 15.9) than in the placebo group (4.90 mL, SD 16.0; adjusted mean difference -1.37, 95% CI -2.71 to -0.04, p=0.0432).	There was no increase in VTE (39 [3%] patients in the TXA group vs. 37 [3%] in the placebo group; p=0.98).
Meretoja 2020 STOP-AUST	Randomized double-blind placebo-controlled trial Phase 2	**Inclusion Criteria:** Patients were eligible if they were aged 18 years or older, had a non-traumatic ICH with a spot sign, and were treatable within 4-5 hours of symptom onset and within 1 hour of CT angiography. **Exclusion Criteria:** GCS score of less than 8; contraindicatio	**Treatment:** IV TXA 1 g in 100 mL 0.9% NaCl over 10 minutes, followed by 1 g in 500 mL 0.9% NaCl infusion over 8 hours. **Control:** 0.9% NaCl with the same administratio n schedule.	**Primary Outcome:** The presence of ICH growth by 24 hours (±3) after the start of study drug administration, defined as at least a 33% or 6 mL increase from baseline, adjusted for baseline ICH volume. **Secondary Outcomes:** mRS 0-4 or return to prestroke score at 90 days mRS 0-3 or return to prestroke score at 90 days	The primary efficacy outcome was not different between the two groups, 26 (52%) of 50 patients in the placebo group and 22 (44%) of 50 of the TXA group had growth of ICH from baseline to 24 h (OR 0.72 [95% CI 0.32-1.59], p=0.41). Eight (16%) of 50 patients in the placebo group and 13 (26%) of 50 in the TXA group died from any cause by 90 days (OR 2-38 [0.66-8.67], p=0.19).	There were two (4%) thromboembolic complications in the placebo group and one (2%) in the TXA group. (p=0.57)

		ns for antifibrinolytic therapy; very large intracerebral hemorrhage (>70 mL); brainstem hemorrhage; ICH known or suspected by the study investigator to be secondary to trauma, aneurysm, vascular malformation, hemorrhagic transformation of ischemic stroke, cerebral venous thrombosis, thrombolytic therapy, tumor, or infection; contrast already administered in 24 hours before initial CT or contraindicatio n to contrast agents; thromboembolic events in the past 12 months; planned surgery for the ICH within 24 hours; hereditary or acquired hemorrhagic diathesis or coagulation factor deficiency; use of anticoagulation agents; pregnancy; concurrent use of hemostatic agents; participation in another investigational study in the past 30 days; known terminal illness; or any condition in which the study		Categorical shift in mRS at 90 days **Safety:** Major thromboembolic events (myocardial infarction, ischemic stroke, or pulmonary embolism) Death due to any cause, both by 90 days.		

		therapy is contraindicated or that could affect participation in the study, as judged by the investigator.				
Liu 2021 TRAIGE	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Acute primary spontaneous ICH within 6 hours of symptom onset (or time last seen well). **Exclusion Criteria:** ICH secondary to tumor, trauma, aneurysm, vascular malformation, hemorrhagic conversion of ischemic stroke, venous sinus thrombosis or central nervous system infection, anticoagulant therapy, infratentorial ICH, GCS score<8, an ICH volume>70 mL, parenchymal hemorrhage expanding to fill one side of the lateral ventricle or more than half of both lateral ventricles, clinical history or current evidence suggestive of venous or	**Treatment:** IV TXA, 1 g in 100 mL 0.9% NaCl infused over 10 minutes, followed by 1 g in 250 mL 0.9% NaCl infused over 8 hours. **Control:** 0.9% NaCl, administered with the same regimen. All randomized patients received therapy within 8 hours of onset.	**Primary Outcome:** Presence of hematoma expansion by 24 hours (±2) after the start of drug administration, defined as an absolute increase of more than 6 mL or a relative growth of more than 33% from baseline. **Secondary Outcomes:** Absolute ICH growth volume and absolute intraventricular hemorrhage (IVH) growth volume at 24 hours (±2), poor clinical outcome (defined as death or major disability, mRS 4-6), other thromboembolic events (including venous thrombosis and other peripheral arterial embolisms), and death due to any cause, all assessed by 90±7 days. **Safety Outcome:** Major thromboembolic events (acute myocardial ischemia, acute cerebral ischemia and acute pulmonary	Thirty-six (40.4%) of eighty-nine patients in the TXA group and thirty-four (41.5%) of eighty-two patients in the placebo group had hematoma expansion at 24 hours (OR 0.96, 95% CI 0.52 to 1.77, p=0.89). The mean ICH volume change from baseline to 24 hours was 7.1 ± 16.0 mL, with 6.6 ± 16.5 mL in the TXA group and 7.6 ± 15.6 mL in the placebo group (p=0.70). Two patients had major thromboembolic events (acute cerebral infarction), one in each group (p=0.96).	Due to the neutral results reported from the STOP-AUST trial, the study was terminated in March 2020, with a final enrollment of 171 patients.

		arterial thrombotic events within the previous 6 months, pregnancy, within 30 days postpartum or lactating, planned surgery for the ICH within 24 hours of onset, contraindication of TXA, and prestroke dependency with a mRS score>2.		embolism). Safety outcomes were collected through day 90.		
Arumugam 2023 TANICH II	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Patients aged 18 years or older (of any gender) diagnosed with hypertensive ICH that occurred within 8 hours of onset. The lesion must be located in the supratentorial area and unsuitable for surgical intervention. **Exclusion Criteria:** ICH due to causes other than hypertension; use of anticoagulants or antiplatelets; known blood disorders; hepatic or renal impairment; infection; history of venous thrombosis or embolic disease; recent ischemic event (within 12 months); pregnancy; or breastfeeding.	**Treatment-1:** 2 g TXA (1 g of TXA as a slow bolus over 10 min followed by 1 g of TXA infusion over 8 hours. **Treatment-2:** 3 g TXA (1 g of TXA as a slow bolus over 10 min followed by 2 g of TXA infusion over 8 hours) groups. **Control:** 10 mL of normal saline as a slow bolus over 10 min followed by 100 mL of normal saline infusion over 8 hours.	**Primary Outcome:** Hematoma enlargement on CT scan 24 hours after treatment. **Secondary Outcomes:** Differences in SBP and WBC at presentation versus 24 hours; safety of TXA; and the patient's GOS and mRS scores at 30 days post-discharge.	In the placebo group, the change in hematoma volume was 1.8 mL (range: -1.06 to 4.6 mL). In the TXA 2g group, the change in hematoma volume was 0.3 mL (range: -1.27 to 1.93 mL), and in the TXA 3g group, the change in hematoma volume was -0.2 mL (range: -1.39 to 1.02 mL). There was no statistically significant difference in the mean changes in hematoma volume among the three study groups (p=0.315).	No serious adverse event was observed in the study.

Yassi 2024 STOP-MSU	Randomized double-blind placebo-controlled trial Phase-2	**Inclusion Criteria:** Presented with acute spontaneous ICH confirmed by non-contrast CT, were aged 18 years or older, and were eligible to be treated with the investigational product within 2 hours of stroke onset. **Exclusion Criteria:** Baseline GCS score of less than 8; brainstem hemorrhage; intracerebral hematoma volume exceeding 70 mL as measured by the ABC/2 method; use of heparin, low-molecular weight heparin, GPIIb/IIIa antagonists, or oral anticoagulants within the previous 72 hours; and bleeding known or suspected to be secondary to trauma, aneurysm, vascular malformation, or other secondary causes.	**Treatment:** TXA 1 g over 10 min followed by 1 g over 8 hours. **Control:** Normal saline over 10 min followed by normal saline over 8 hours.	**Primary Outcome:** Presence or absence of intracerebral hematoma growth by 24 hours (with a target range of 18 to 30 hours), defined as either at least a 33% relative increase or at least a 6 mL absolute increase from baseline on CT. **Secondary Outcomes:** mRS score of less than 3 or equal to the pre-stroke baseline at 90 days, mRS score of less than 4 or equal to the pre-stroke baseline at 90 days, the ordinal mRS distribution at 90 days, and the utility-weighted mRS at 90 days. **Secondary Safety Outcomes:** Mortality within 7 days and 90 days, and the occurrence of major thromboembolic events within 90 days, defined as ischemic stroke, myocardial infarction, or pulmonary embolism.	Ninety-eight (49%) participants were assigned to the placebo group, and 103 (51%) were assigned to the TXA group. Hematoma growth occurred in 37 (38%) of 97 assessable participants in the placebo group and 43 (43%) of 101 assessable participants in the TXA group (aOR 1.31 [95% CI 0.72 to 2.40], standardized risk difference 0.06 [95%CI 0.07 to 0.19]; p=0.37). No significant differences were observed in secondary functional outcomes at 90 days. One (1%) participant in the placebo group experienced a major thromboembolic event at 90 days, compared to three (3%) participants in the TXA group.	-
Polymeris 2023 TICH-NOAC	Randomized double-blind placebo-controlled trial **Phase-2**	**Inclusion Criteria:** Adults with acute nontraumatic NOAC-related ICH within 12 hours of symptom onset (or, in patients with unknown symptom	**Treatment:** 1 g loading dose in 100 mL normal saline infused over 10 minutes, followed by another 1 g in 250 mL normal saline	**Primary Outcome:** The presence of hematoma expansion on follow-up imaging at 24 (±3) hours, defined as an intracerebral hematoma volume increase of at least	A total of 67 patients were enrolled, with 32 assigned to TXA and 31 to placebo. Overall, 26 participants (41%) experienced hematoma expansion (HE). The primary outcome did not differ between the treatment arms, with 12 of 32 participants in the	Due to lack of funding, the TICH-NOAC study was terminated early before reaching the target enrollment of 218 patients.

		onset, if the time since last known to be well divided by 2 was less than 12 hours) and who were taking any NOAC (last intake within 48 hours). **Exclusion Criteria:** Severe preexisting disability (mRS score greater than 4), GCS score less than 5, prior treatment with vitamin K antagonists, ICH known or suspected to be secondary to trauma, vascular malformation, tumor, or other underlying structural abnormality, pregnancy, planned neurosurgical hematoma evacuation within 24 hours, and pulmonary embolism or deep vein thrombosis within the preceding 2 weeks.	infused over 8 hours. **Control:** Placebo with an identical administration regimen. Concurrent use of other hemostatic agents (e.g., idarucizumab, andexanet alfa, and 4fPCC) was not an exclusion criterion.	33% or 6 mL from baseline. **Secondary Outcomes:** Symptomatic hematoma expansion, defined as hematoma expansion with neurological deterioration (worsening of NIHSS score by at least 4 points or GCS score by at least 2 points) or death within 7 days; absolute hematoma volume change by 24 (±3) hours; ordinal mRS score, mRS score of 0 to 4, and mRS score of 0 to 3 at 90 days; in-hospital death; death within 90 days; major thromboembolic events (ischemic stroke, myocardial infarction, or deep vein thrombosis/pulmonary embolism defined as clinical syndromes with supporting paraclinical evidence) within 90 days; and neurosurgical intervention up to day 2.	TXA group (38%) and 14 of 31 in the placebo group (45%) showing HE OR adjusted for baseline hematoma volume, 0.63 [95% CI, 0.22-1.82]; p=0.40; unadjusted OR, 0.73 [0.27-1.99]; p=0.54). No difference in major thromboembolic events was observed in participants allocated to TXA and concomitant treatment with 4fPCC.	
Post 2021	Randomized open label placebo-controlled trial	**Inclusion Criteria:** Adults aged 18 years or older with SAH. **Exclusion criteria**: Perimesencephalic bleeding combined with a GCS score of 13-15 without loss of consciousness directly after the ictus or focal neurological deficit on	**Treatment:** IV bolus of 1 g TXA, directly followed by 1 g continuous IV infusion of TXA every 8 hours in addition to standard care. Treatment was continued until the start of endovascular or surgical treatment of	**Primary Outcome:** At 6 months after randomization, clinical outcome classified as good (mRS 0-3) and poor (mRS 4-6). **Secondary Outcomes:** Excellent clinical outcome (mRS 0-2) at 6 months, and all-cause mortality at 30 days and after 6 months.	In the TXA group, 287 patients (60%) and in the control group, 300 patients (64%) had a good clinical outcome (mRS 0-3; OR 0.87, 95% CI 0.67-1.13). The excellent clinical outcome (mRS 0-2) was significantly lower in the TXA group compared to the control group (OR 0.74, 95% CI 0.57-0.96). Rebleeding was reported in 49 patients (10%) in the TXA group, versus 66 patients (14%) in the control group	All serious adverse events, including thromboembolic events, did not differ between the two groups.

		admission; traumatic subarachnoid hemorrhage; ongoing treatment for deep vein thrombosis or pulmonary embolism; a history of a hypercoagulability disorder; pregnancy; severe renal failure (serum creatinine >150 µmol/L); or imminent death within 24 hours.	the aneurysm or until a maximum of 24 hours (i.e., a maximum of 4 g TXA in total). **Control:** Only standard care.		(OR 0.71, 95% CI 0.48–1.04). There was no difference in all-cause mortality at 30 days and 6 months between the two groups. A total of 229 patients were randomized to receive TXA, and 233 received placebo. In the TXA group, 114 out of 229 patients (50%) had a poor outcome, compared to 105 out of 223 patients (45%) in the placebo group (RR 1.10, 95% CI 0.91–1.34). TXA significantly reduced rebleeding (44 patients [19%] in TXA vs. 77 patients [33%] in placebo; OR 0.58, 95% CI 0.42–0.80) but did not affect delayed cerebral ischemia or other events.	
Roos 2000	**Randomized Controlled Trial**	**Inclusion Criteria:** Patients with aneurysmal SAH diagnosed via brain CT were included. **Exclusion Criteria:** Being under 18 years old, pregnancy, a lapse of more than 96 hours after SAH onset, planned surgery to clip the aneurysm, and planned endovascular coiling of the aneurysm within 48 hours of admission. Other exclusions were the use of antifibrinolytic drugs, the presence of DVT, a history of blood coagulation disorders or renal failure. Additionally, patients were	**Treatment:** An IV bolus of 6 g per day (1 g every 4 hours) during the first week, followed by 6 g per day orally (1.5 g every 6 hours) in the second and third weeks. **Control:** The placebo regimen was not detailed. All patients also received standard medical treatment with nimodipine, 360 mg per day orally (60 mg every 4 hours) for 3 weeks.	**Primary Outcome:** Overall condition of each patient after 3 months measured on the five-point GOS. **Secondary Outcomes:** The occurrence of specific events, such as progressive clinical deterioration from onset, rebleeding, delayed cerebral ischemia, hydrocephalus, postoperative ischemia, the causes of poor outcome.	A total of 229 patients were randomized to receive TXA, and 233 patients received placebo. For the primary outcome, 114 patients out of 229 (50%) in the TXA group had a poor outcome, compared to 105 patients out of 223 (45%) in the placebo group (RR 1.10, 95% CI 0.91 to 1.34). For secondary outcomes, treatment with TXA significantly reduced rebleeding, with 44 patients (19%) in the TXA group and 77 patients (33%) in the placebo group (OR 0.58, 95% CI 0.42 to 0.80). However, TXA had no effect on delayed cerebral ischemia or other events.	-

		excluded if a diagnosis other than a ruptured aneurysm was confirmed by CT or angiography, or if death was deemed imminent.				
Studies with high risk of bias						
Arumugam 2015	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Adult (>18 years old) patients with atraumatic hypertensive intracerebral hemorrhage and a supratentorial lesion within 8 hours of onset, inappropriate for surgical intervention, were included. **Exclusion Criteria:** Patients on anticoagulation therapy, with brainstem bleed, intraventricular bleed, SAH suggestive of a ruptured aneurysm, malignant HT, blood disorders, infection, hepatic or renal failure, previous thrombosis or embolic disease, recent ischemic event, and pregnant or breast-feeding women.	**Treatment:** TXA 1 g diluted in 100 mL of 0.9% saline administered over 10 minutes, followed by a maintenance dose of 1 g/h for 8 hours. **Control:** Placebo, with no information provided on administration. **Standard Care:** Blood pressure was controlled with 200 mg labetalol hydrochloride injection, targeting a SBP of 140-160 mmHg.	**Primary Outcome:** 24 hours later, hematoma enlargement on CT	The size of hematoma growth was 0.21 (IQR 1.07) in the TXA group and 3.07 (IQR 2.60) in the control group. Statistical analysis information on this outcome was not provided.	No serious adverse events were observed in the study.
Chandra B. 1978	Randomized placebo-controlled trial	**Inclusion Criteria:** Patients with SAH resulting from a ruptured intracranial aneurysm who were admitted were included. The criteria were: Acute onset of headache	**Treatment:** Standard care plus TXA. The dose of TXA was 6 g per day (each ampule contained 250 mg of TXA), administered as 1 g every 4 hours IV.	**Primary Outcome:** Three weeks later, rebleeding or death.	In the placebo group, 4 of 19 patients experienced rebleeding, and 5 patients died. In the treatment group, 1 of 20 patients experienced rebleeding, and 1 patient died. Although no statistical information was provided, it appears there was a statistically significant difference	No serious adverse event was observed in the study. The study dates to 1978, so the standard of care is more advanced today. This potential confounder should be considered when

		Evidence of meningeal irritation Blood-stained cerebrospinal fluid not due to trauma Angiographic demonstration of an intracranial aneurysm Fresh subarachnoid hemorrhage not older than 7 days	**Control:** Standard care plus saline. **Standard Care:** Conventional treatment included bed rest with intensive nursing care for three weeks, dexamethasone if cerebral edema developed, and saline injection. All treatments were continued until 21 days after the last hemorrhage.		between the groups in terms of rebleeding.	comparing with today's studies. There is no mention of blindness in the study.
Hillman 2002	Randomized open label controlled trial	**Inclusion Criteria:** Only patients with CT-verified aneurysmal SAH within 48 hours prior to the first hospital admission were included. **Exclusion Criteria:** Pregnancy, age younger than 15 years, and a history of thromboembolic disease.	**Treatment:** 1 g of TXA was given IV immediately before the patients were transported to the regional neurosurgical center. This initial dose was followed by a second dose of 1 g after 2 hours, and therapy continued with doses of 1 g every 6 hours until the aneurysm was occluded, up to 72 hours of treatment post-SAH. **Control:** No information provided.	**Primary Outcome:** Rebleeding after 8 hours randomization	Six patients of the 254 suffered rebleeds in TXA group, as compared 27 patients of the 251 patients rebleed only hours in control group ($p<0.001$).	No serious side effects were reported.

Tsementzis 1990	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** The trial involved patients with a diagnosis of SAH confirmed by lumbar puncture (xanthochromic CSF) or CT brain scan. **Exclusion Criteria:** Patients more than 72 hours after hemorrhage; patients in coma with fixed, dilated pupils for whom death seemed imminent; patients with known blood dyscrasias, including signs of disseminating intravascular coagulation; patients with a history or findings of renal failure or acute myocardial infarction; pregnant women; patients with deep vein thrombosis; patients taking antihypertensive medication; and patients taking medicines known to affect the fibrinolytic and/or coagulation system.	**Treatment:** Patients received TXA, 9 g a day in six doses, until the time of successful surgery or four weeks from ictus, whichever came first. TXA was given every 4 hours in half-hour infusions of 1.5 g in 50 ml of saline for one week, followed by 3 tablets (0.5 g each) every 4 hours for the remaining 3 weeks. **Control:** This group received the placebo treatment in an otherwise identical manner.	Outcome was assessed at discharge from the hospital and at one, three, and six-month intervals after discharge using the GOS.	Fifty patients received TXA and the remaining 50 received placebo treatment. No difference in 6-month GCS scores. Recurrent hemorrhage occurred from demonstrable aneurysms in 12 patients in the TXA group and 12 in the control group. 19 subjects (38%) were death in TXA group and in 14 subjects (28%) were death in placebo ($p>0.05$). There was no major difference between the treated and placebo groups in the incidence of DVT and pulmonary embolus.	-
Vermeulen 1984	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Patients with the diagnosis of aneurysmal SAH confirmed by lumbar puncture or CT brain scan.	**Treatment:** 6 g TXA IV per day in 6 doses for the first week, 4 g TXA IV per day in 4 doses for the second week, and then 6 g	**Primary Outcome:** Comparing five point GCS at three months. **Secondary Outcome:** Intracranial complications;	There was no difference in the five-point GCS at three months between groups. In the control group, a total of 105 patients (44%) survived without neurologic deficit, compared with	-

		Exclusion Criteria: Patients more than 72 hours after hemorrhage; presence of DVT; coagulation disorders; renal insufficiency; pregnancy; previous anti-fibrinolytic treatment; negative angiography in terms of aneurysm.	TXA orally per day in 4 doses for the third and fourth weeks. **Control:** No details provided.	rebleeding, infarction, hydrocephalous, local oedema from a hematoma, or epilepsy.	100 patients (42%) in the TXA group. In the TXA group, 21 patients (9%) had rebleeding, compared to 56 patients (24%) in the placebo group ($p<0.001$). In terms of VTE, 20 patients in the TXA group had events, compared to 18 patients in the placebo group ($p>0.05$).	

mRS: Modified Rankin Scale, ICH: Intracranial Hemorrhage, TXA: Tranexamic Acid, VTE: Venous Thromboembolic Events, IS: Ischemic Stroke, GFR: Glomerular Filtration Rate, PAD: Peripheral Arterial Disease, IV: Intravenous, NIHSS: National Institutes of Health Stroke Scale, EuroQoL-5D: EuroQoL-5 dimensions, TICS-M: Telephone Interview for Cognitive Status, GCS: Glasgow Coma Scale, CI: Confidence Interval, SD: Standard Deviation, aOR: Adjusted Odds Ratio, ZDS: Zung Depression Scale, CT: Computed Tomography, OR: Odds Ratio, IVH: Intraventricular Hemorrhage, SBP: Systolic Blood Pressure, WBC: White Blood Cell, GOS: Glasgow Outcome Scale, NOAC: Non-vitamin K antagonist Oral Anticoagulants, HE: Hematoma Expansion, 4fPCC: Four-factor Prothrombin Complex Concentrate, SAH: Subarachnoid Hemorrhage, DVT: Deep Venous Thrombosis, IQR: Interquartile Range, CSF: Cerebrospinal Fluid

Table 4. Summaries of Studies Investigating the Efficacy of Tranexamic Acid in Patients with Hemoptysis.

Study	Design	Participants	Interventions	Outcomes	Main Results	Comments
Studies with "some concerns" risk of bias						
Ori Wand 2018	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Adult patients (aged ≥18 years) admitted with hemoptysis during the previous 24 hours. **Exclusion Criteria:** Massive hemoptysis, respiratory or hemodynamic instability, pregnancy, renal failure, hepatic failure, coagulopathy, known hypersensitivity to TXA, or treatment with TXA prior to screening.	**Treatment:** Nebulized TXA 500 mg/5 mL three times daily. **Control:** Normal saline 0.9% 5 mL three times daily.	**Primary Outcome:** The difference of resolution of hemoptysis during the first 5 days from admission and the daily volume of expectorated blood.	Resolution of bleeding was 96% in the TXA group compared to 50% in the placebo group ($p<0.0005$). TXA treatment was also associated with significantly reduced amounts of expectorated blood ($p<0.010$).	A higher LOS was detected in the TXA group. No serious adverse events were observed.
Gopinath 2023	Randomized open label controlled trial	**Inclusion Criteria:** Adults (≥18 years old) who presented to triage with reports of active hemoptysis were included. **Exclusion Criteria:** Massive, life-threatening hemoptysis on presentation to the emergency department, hemodynamic instability, the need for mechanical ventilation or immediate interventional procedures, hypersensitivity to TXA, or prior treatment with TXA.	**Treatment:** Nebulized TXA (500 mg mixed with 5 mL distilled water) three times daily. **Control:** IV TXA (500 mg) three times daily.	**Primary Outcome:** The cessation of bleeding at 30 minutes following TXA administration.	Cessation of bleeding was 72.7% in the nebulization arm and 50.9% in the IV arm ($p=0.0019$).	The reduction in the amount of expectorated blood was significantly greater in the nebulization arm compared to the IV arm.
Studies with "high" risk of bias						

Fekri 2017	Randomized double-blind controlled trial	**Inclusion Criteria:** Patients who already had hemoptysis or those who started bleeding after biopsy and could not be controlled with cold saline lavage during bronchoscopy. **Exclusion Criteria:** Declined to participate, successful bleeding control with cold saline, cardiovascular disease, bleeding tendency, or anticoagulant and antiplatelet drug consumption.	**Treatment:** TXA (500 mg diluted in up to 20 mL of saline) **Control:** Adrenaline (1 mg diluted in up to 20 mL of saline) If necessary, all repeated up to 3 times.	**Primary Outcome:** Bleeding control determined by direct observation of clot formation through the bronchoscope.	The mean time of bleeding control was 133.9±77.91 seconds in the TXA group and 136.66±83.5 seconds in the adrenaline group (p=0.908).	For both groups, the drug from the other arm was used as rescue medication, and the rate of this usage was not statistically significant between the two groups.
Bellam 2016	Randomized single-blind placebo-controlled trial	**Inclusion Criteria:** Adult patients with acute onset of ongoing hemoptysis. **Exclusion Criteria:** Massive hemoptysis, pregnancy, drug allergy, renal failure, use of oral contraceptive agents or antifibrinolytic agents, and those requiring intubation.	**Treatment:** IV TXA in a loading dose of 1 g over 10 min diluted in 10 ml of 0.9% normal saline, followed by 1 g TXA over 8 h diluted in 500 ml of 0.9% normal saline. **Placebo:** Same protocol without TXA.	**Primary Outcome:** Frequency and quantity of haemoptysis (VAS; 0–100 mm)	Frequency, quantity and VAS score of haemoptysis severity were 2.23±2.11/day, 34.19±67.0 ml and 14.72±15.7 ml respectively in the treatment group and 2.29±2.0/day, 90.4±79.0 ml and 31.33±22.12 respectively in the placebo group; statistically significant difference exists in only VAS (p=0.001).	No adverse event was noted in the treatment group.
Tscheikuna 2002	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Patients with hemoptysis either as outpatients or inpatients on the ward. **Exclusion Criteria:** Massive hemoptysis.	**Treatment:** TXA 250 mg capsules, two capsules three times a day, one-week treatment pack. **Placebo:** Capsules, one-week treatment pack.	**Primary Outcome:** Cessation of hemoptysis	In the TXA group, 4 patients (19.04%) and in the placebo group, 7 patients (28%) had hemoptysis on the 7th day, with no statistically significant difference (p=0.514).	In the TXA group, 3 patients experienced minor adverse reactions, while there was one allergic reaction in the placebo group.

TXA: Tranexamic Acid, LOS: Length of Stay, IV: Intravenous, VAS: Visual Analog Scale

Table 5. Summaries of Studies Investigating the Efficacy of Tranexamic Acid in Patients with Epistaxis.

Study	Design	Participants	Interventions	Outcomes	Main Results	Comments
Studies with low or some concerns risk of bias						
Zahed 2013	Randomized controlled trial	**Inclusion Criteria:** Adult patients experiencing ongoing epistaxis were enrolled. **Exclusion Criteria:** Major trauma, posterior epistaxis, known history of bleeding disorder, INR>1.5, shock, and visible bleeding vessel.	**Treatment:** A cotton pledget soaked in TXA (500 mg/5 mL) was inserted into the nostril on the bleeding side. **Control:** Usual shrinkage with a cotton pledget soaked in epinephrine + lidocaine (2%) for 10 minutes, followed by packing with several cotton pledgets covered with tetracycline.	**Primary Outcome:** Bleeding cessation within 10 minutes.	In the study, 107 patients were treated with TXA while 110 patients comprised the control group. Bleeding was arrested in 71% of the TXA group, compared with 31.2% in the anterior nasal packing group (OR, 2.28; 95% CI, 1.68 to 3.09; p<0.001).	No serious adverse event was observed in the study.
Zahed 2018	Randomized controlled trial	**Inclusion Criteria:** Adult patients presenting with acute ongoing anterior epistaxis and currently using antiplatelet drugs (aspirin, clopidogrel, or both) were screened for eligibility. Patients with persistent bleeding requiring additional treatment after 20 minutes of external compression were included. **Exclusion Criteria:** Patients with traumatic epistaxis, current use of anticoagulant drugs, inherited bleeding disorders, INR>1.5, shock, visible	**Treatment:** Topical application of TXA at a concentration of 500 mg/5 mL. **Control:** Anterior nasal packing (ANP).	**Primary Outcome:** Bleeding cessation within 15 minutes.	Treatment (TXA) n=62, Control (ANP) n=62. Bleeding was stopped in 73% of patients in the TXA group, compared with 29% in the ANP group, indicating a significant difference of 44% (95% confidence interval, 26% to 57%; p<0.001).	-

		bleeding vessel, or a history of renal disease.				
Akkan 2019	Randomized controlled trial	**Inclusion Criteria:** Adult patients with active, spontaneous anterior epistaxis were included. **Exclusion Criteria:** Patients using current anticoagulation therapy, those with hemodynamic instability or altered mental status, traumatic epistaxis, resolved epistaxis on admission, or a known bleeding disorder.	**Treatment:** Nasal compression with TXA **Control 1:** Simple nasal external compression **Control 2:** Nasal packing (using Merocel)	**Primary Outcome:** Bleeding cessation within 15 minutes.	Saline (n=45), TXA (n=45), and nasal packing (n=45) were evaluated. The success rate was 91.1% in the TXA group, 93.3% in the nasal packing group, and 71.1% in the saline solution group. Statistically significant differences were observed among the groups. Pairwise comparisons revealed no statistically significant difference between the TXA and nasal packing groups. However, there was a statistically significant difference between the saline solution group and each of the other two groups.	Despite the study being designed as double-blind, neither the physicians nor the patients in the TXA and saline solution groups were blinded to the nasal packing due to its nature. Therefore, the study cannot be considered fully blinded. Notably, this was the only study that provided blinding of the outcome assessor.
Hosseinialhashemi 2022	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Adult patients with spontaneous atraumatic anterior epistaxis were assessed by an ENT resident physician. If bleeding was not controlled by initial measures, including squeezing the nose, applying an ice pack, and continuously irrigating the mouth with cold water for at least 10 minutes, they were included. **Exclusion Criteria:** Patients with unstable hemodynamic status; known nasopharyngeal malignancy;	**Treatment:** A cotton pledget soaked in 5mL of TXA solution **Control:** A cotton pledget soaked in 10 mL (0.05 g) of phenylephrine hydrochloride.	**Primary Outcome:** Bleeding cessation within 15 minutes.	In the TXA group (n=120), the rate of bleeding continuing after 15 minutes was 50%, compared to 64% in the control group (n=120). The need for nasal packing was significantly lower in the TXA group (OR 0.56, 95% CI 0.33 to 0.94).	The primary outcome of this study was the need for nasal packing 15 minutes after the initial application. However, this outcome was mistakenly interpreted as bleeding cessation within 15 minutes.

		pregnancy; recent use of anticoagulant drugs; or those who were prisoners.				
Reuben 2021	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Adult patients presenting with nosebleeds initially underwent simple external pressure applied to the nose for less than 10 minutes before being included in the study. If bleeding did not stop, vasoconstrictor medication was applied topically to the nostrils. After this routine practice, eligible patients were randomly assigned to either the intervention or placebo groups.	**Treatment:** The intervention was TXA 4ml for topical (intranasal) use, prepared as a clear, colorless 100mg/mL solution. **Control:** Sterile water, which was indistinguishable from the TXA.	**Primary Outcome:** Use of anterior nasal packing at any time.	In the study, 254 patients received TXA, while 242 patients received a placebo. Among those receiving TXA, 111 participants (43.7%) required anterior nasal packing in the emergency department, compared to 100 participants (41.3%) in the placebo group. There was no statistically significant difference in the rate of anterior nasal packing between the two groups (odds ratio 1.11, 95% confidence interval 0.77 to 1.59).	The study was conducted across 26 centers. Out of all participants, 12 reported a total of 14 adverse reactions. Specifically, nine participants (3.5%) in the TXA group reported at least one adverse reaction, compared to three participants (1.2%) in the placebo group. However, the difference in adverse reactions between the two groups was not statistically significant.
Studies with high risk of bias						
Eshghi 2014	Randomized controlled trial	**Inclusion Criteria:** Children with coagulopathies and epistaxis that could not be controlled with simple localized pressure or ice. **Exclusion Criteria:** Patients with other acquired bleeding disorders or those receiving additional coagulation factors.	**TXA Group:** The commercially available TXA from Rasht Company. **EpiCell Tampon Group:** The commercially available ORC tampon, trade-named 'EpiCell', from ChitoTech Company Inc. **ChitoHem Tampon Group:** The commercially available	**Primary Outcome:** Bleeding cessation within 10 minutes.	In the study, 31 patients were included and assigned to all three groups. The rates of bleeding cessation were 20.7% in the TXA group, 41.4% in the EpiCell tampon group, and 80% in the ChitoHem tampon group. Statistically significant differences were found between the ChitoHem tampon group and the TXA group ($P<0.001$), as well as between the ChitoHem tampon group and the	No serious adverse events were observed in the study.

			chitosan-impregnated tampon, trade-named 'ChitoHem', from ChitoTech Company Inc.		EpiCell tampon group (P=0.013). However, no significant difference was observed between the TXA group and the EpiCell tampon group (p=0.125).	
Ekmekyapar 2022	Randomized double-blind controlled trial	**Inclusion Criteria:** Adult patients with non-traumatic epistaxis. **Exclusion Criteria:** Patients whose bleeding had stopped upon admission, those with bleeding disorders, use of blood thinners, history of hypertension, drug abuse, or recent nasal surgery.	The study involved three agents absorbed onto cotton strips used as nasal packing tampons: **Treatment:** TXA (Transamine 50 mg/ml) **Control-1:** Epinephrine (Adrenaline 1 mg 1:1000 1 ml) **Control-2:** Lidocaine (Lidocaine HCl 1% 10 mg/ml)	**Primary Outcome:** Time to cessation of bleeding (min)	In the study, 36 patients were treated with TXA, 36 with epinephrine, and 36 with lidocaine. The mean times to cessation of bleeding were 9.9±3.2 min for the lidocaine group, 10.3±4.5 min for the epinephrine group, and 8.9±3.4 min for the TXA group. There were no statistically significant differences between the groups (lidocaine vs. epinephrine: p=0.870; lidocaine vs. TXA: p=0.502; epinephrine vs. TXA: p=0.242).	No drug-related side effects were observed.
Tibbelin 1995	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Adult patients with ongoing nosebleed. **Exclusion Criteria:** Patients with known impaired hemostasis, skull and/or nose fractures, or perforation.	**Treatment:** TXA Gel (15 ml) **Control:** Placebo gel (glycine)	**Primary Outcome:** Bleeding cessation in 30 min.	In the study, 30 patients were assigned to the TXA group and 36 to the placebo group. The rate of patients whose bleeding stopped within 30 minutes was 60% in the TXA group and 76% in the placebo group. No statistically significant difference was found between the groups (p=0.16).	Unlike the other studies, this study favored a per-protocol analysis. The presence of glycine in the placebo group might have influenced the results. Additionally, both gels contained methargan, propagin, and carboxypoly methylene. No serious adverse events were observed during the study.

Sanderson 2018	Randomized controlled trial	**Inclusion Criteria:** Patients (adult or children) with new acute or recurrent epistaxis currently taking ASA, clopidogrel, or both were accessed for eligibility. Of these, patients with epistaxis not controlled with 20 min of external pressure were included. **Exclusion Criteria:** Patients with traumatic epistaxis, current anticoagulant use, inherited bleeding or platelet disorders, INR>1.5, shock, visible bleeding vessel, a history of renal disease.	**Treatment:** Topically applied IV TXA on a 15 cm cotton pledget **Control:** Usual care consisting of ANP with tetracycline ointment soaked cotton for 3 days.	**Primary Outcome:** Bleeding cessation within 10 minutes.	In the study, 62 patients were assigned to the TXA group and 62 to the ANP group. Bleeding cessation occurred in 73% of the TXA group and 29% of the ANP group, showing a statistically significant difference with a percentage difference of 44% (95% CI 26% to 57%).	No serious adverse event was observed in the study.
Amini 2021	Randomized double-blind placebo-controlled trial	**Inclusion Criteria:** Adult patients with an episode of epistaxis and were under treatment with antiplatelet drug. **Exclusion Criteria:** Patients with multiple trauma, hereditary hemorrhagic or platelet disorders, hemophilia, renal dysfunction, or obvious bleeding from other parts of the body.	**Treatment:** A wad of cotton steeped in the injectable form of TXA (500mg/5ml) **Control:** A wad of cotton steeped in phenylephrine (1:100,000) + lidocaine (2%)	**Primary Outcome:** Time to cessation of bleeding (min)	In the study, 50 patients were assigned to the TXA group and 50 to the PANP group. The mean time to stop bleeding was 6.70±2.35 minutes in the TXA group compared to 11.50±3.64 minutes in the PANP group, with a statistically significant difference (p=0.002).	No side effects were reported in the study.
Shahidi 2021	Randomized single-blind controlled trial	**Inclusion Criteria:** Patients with anterior epistaxis or those with the previous epistaxis were enrolled. Only the patients who had bleeding from one nasal passage. **Exclusion Criteria:** Patients with trauma, posterior epistaxis, and a history of bleeding disorders, seizures, arterial	**Treatment:** A 15-cm-long gas was soaked with TXA (500 mg/5ml) and placed in the bleeding nasal passage **Control:** A tampon lubricated with tetracycline, which was left in the nasal passage for three days.	**Primary Outcome:** Bleeding cessation time (min) Bleeding cessation in 10 min, 20 min and 30 min were also compared.	In the study, 60 patients were assigned to the TXA group and 60 to the control group. The mean bleeding cessation time was 9.33±1.47 minutes in the TXA group compared to 18.59±2.33 minutes in the control group, with a statistically significant difference (p=0.011). Bleeding cessation within 10 minutes occurred in 80% of	TXA administration was associated with fewer side effects than tampon application (nausea, vomiting).

		or venous thrombosis, those taking anticoagulants, antiplatelet drugs, and even aspirin, besides patients with leukemia, lymphoma, and polycythemia vera, and pregnant women.			the TXA group patients and 33.3% of the control group patients.	

TXA: Tranexamic Acid, ANP: Anterior Nasal Packing, PANP: Phenylephrine Lidocaine Anterior Nasal Packing, INR: International Normalized Ratio, ENT: Ear Nose Throat, OR: Odds Ratio, CI: Confidence Interval

Supplementary File-4. GRADE evidence Level Classification Tables.

Question: Effectiveness of Tranexamic acid for management of patients with acute gastrointestinal bleeding.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tranexamic acid	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality at one month												
8	randomized trials	not serious[a]	not serious	not serious	not serious	none			not pooled	see comment	⊕⊕⊕⊕ High	IMPORTANT
Re-bleeding in early period												
9	randomized trials	not serious[a]	not serious	not serious	not serious	none			not pooled	see comment	⊕⊕⊕⊕ High	IMPORTANT
Venous Thromboembolism												
13	randomized trials	not serious[a]	not serious	not serious	not serious	none			not pooled	see comment	⊕⊕⊕⊕ High	IMPORTANT

CI: confidence interval

Explanations

a. Although the majority of existing studies have a high risk of bias, the evidence obtained from the HALT-IT study, which has a low risk of bias, was considered to be reliable because of its large sample size.

Question: Effectiveness of Tranexamic acid for management of patients with trauma.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tranexamic acid	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality within one-month for multi trauma patients with risk or absolute significant hemorrhage.												
5	randomized trials	not serious	not serious	not serious	serious	none	1599/10998 (14.5%)	1806/11300 (16.0%)	**RR 0.90** (0.85 to 0.96)	**16 fewer per 1.000** (from 24 fewer to 6 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT
Vascular occlusive events for isolated head trauma with all traumatic brain injury.												
2	randomized trials	not serious	not serious	not serious	not serious	none	188/10717 (1.8%)	174/10708 (1.6%)	**RR 1.06** (0.88 to 1.28)	**1 more per 1.000** (from 2 fewer to 5 more)	⊕⊕⊕⊕ High	IMPORTANT
Mortality within one-month for isolated head trauma with all traumatic brain injury.												
3	randomized trials	not serious	not serious	serious[a]	serious[b]	none	920/5027 (18.3%)	970/4927 (19.7%)	**RR 0.85** (0.62 to 1.17)	**30 fewer per 1.000** (from 75 fewer to 33 more)	⊕⊕◯◯ Low	IMPORTANT
Vascular occlusive events for isolated head trauma with all traumatic brain injury.												
3	randomized trials	not serious	serious[c]	not serious	serious[b]	none	82/5045 (1.6%)	93/4941 (1.9%)	**RR 0.63** (0.25 to 1.58)	**7 fewer per 1.000** (from 14 fewer to 11 more)	⊕⊕◯◯ Low	IMPORTANT
Mortality within one-month for isolated head trauma with low-modarate traumatic brain injury (GCS>8).												
1	randomized trials	not serious	not serious	not serious	serious[d]	none	166/2846 (5.8%)	207/2769 (7.5%)	**RR 0.78** (0.64 to 0.95)	**16 fewer per 1.000** (from 27 fewer to 4 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Benefit effect has only been shown in patients with mild to moderate TBI.
b. The confidence interval is wide when pooled data is considered.
c. I2 value is 76%
d. Wide confidence interval

Question: Effectiveness of tranexamic acid for management of patients with non-traumatic intracerebral hemorrhage.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[TXA]	[Placebo]	Relative (95% CI)	Absolute (95% CI)		
90th day mRS score<3												
4	randomized trials	not serious	not serious	not serious	serious[a]	none	427/1389 (30.7%)	412/1390 (29.6%)	**RR 1.03** (0.92 to 1.16)	**9 more per 1.000** (from 24 fewer to 47 more)	⊕⊕⊕◯ Moderate	IMPORTANT
Hematoma growth												
5	randomized trials	not serious	not serious	not serious	serious[a]	none	369/1408 (26.2%)	402/1392 (28.9%)	**RR 0.91** (0.80 to 1.02)	**26 fewer per 1.000** (from 58 fewer to 6 more)	⊕⊕⊕◯ Moderate	IMPORTANT
90th day mortality												
5	randomized trials	not serious	not serious	not serious	serious[a]	none	292/1410 (20.7%)	282/1393 (20.2%)	**RR 1.03** (0.89 to 1.19)	**6 more per 1.000** (from 22 fewer to 38 more)	⊕⊕⊕◯ Moderate	IMPORTANT
Thromboembolic events												
5	randomized trials	not serious	not serious	not serious	serious[a]	none	45/1410 (3.2%)	41/1393 (2.9%)	**RR 1.08** (0.71 to 1.63)	**2 more per 1.000** (from 9 fewer to 19 more)	⊕⊕⊕◯ Moderate	IMPORTANT

CI: confidence interval; **RR:** risk ratio. **Explanations**: a. Power lower than 0.80

Question: Effectiveness of tranexamic acid for management of patients with non-traumatic subarachnoid hemorrhage.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
Good neurological outcome (mRS or GOS)												
6	randomized trials	serious	not serious	serious	serious	none			not pooled	see comment	⊕◯◯◯ Very low	IMPORTANT
Re-bleeding												
6	randomized trials	serious	serious	not serious	serious	none			not pooled	see comment	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval

Question: Effectiveness of tranexamic acid for management of patients with hemoptysis.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
Cessation of hemoptysis												
4	randomized trials	very serious	not serious	very serious[a]	serious	none			not pooled	see comment	⊕◯◯◯ Very low	

CI: confidence interval

Explanations

a. Difference in comparisons and intervention protocols.

Question: Effectiveness of tranexamic acid for management of patients with anterior epistaxis.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tranexamic acid	Conventional (Placebo or ANP)	Relative (95% CI)	Absolute (95% CI)		
Cessation of haemorrhage in early period												
11	randomized trials	not serious	serious[a]	serious[b]	not serious	none			not pooled	see comment	⊕⊕◯◯ Low	IMPORTANT
Advers/Side Effects												
9	randomized trials	not serious	not serious	serious[b]	not serious	none			not pooled	see comment	⊕⊕⊕◯ Moderate	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. There are different results between large sample studies and others.
b. Differences in comparisons and interventions.