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	**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	**Primary Outcome:** Death due to bleeding within 5 days of randomization. **Secondary Outcomes:** Death due to bleeding within 24	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	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

		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.	at 125 mg/h for 24 hours. **Control:** Placebo (0.9% NaCl)	hours and 28 days; rebleeding within 24 hours, 5 days, and 28 days.	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).	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;	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 current randomized trial was not double blinded.

				the duration of hospitalization; transfusion units of packed red blood cells; mortality; and severe adverse events due to TXA (e.g., seizures, thromboembolic events).	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). 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 compared with 17 of 63 patients given placebo tablets.	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.

					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,	**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 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	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.

		esophageal variceal bleeding, hypersensitivity to TXA, hereditary thromboembolic disorders, use of oral estrogen-containing contraceptives, heart valvular diseases, atrial fibrillation, and those requiring anticoagulant agents) were excluded from the study.			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 surgical intervention.	TXA did not improve the outcomes of patients with acute upper GIH.
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:**	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.

			Placebo (same way)			
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-lactate, while placebo ampoules contained normal saline.	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.
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	**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	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**.**

		known adverse drug reactions to trial drugs.			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 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 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	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.

					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 haemorrhage (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 haemorrhage, 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	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 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 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 having a low risk of bias according to the RoB-2 tool.

				protocol 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.	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).	
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 placebo bolus + IV placebo infusion (8 hours).	**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, nosocomial infections, early seizures,	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 having a low risk of bias using the RoB-2 tool.

				pulmonary embolisms, deep vein thrombosis, and crystalloid resuscitation over 24 hours from admission.		
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:**	**Primary Outcome:** Favorable neurologic function at 6 months (GOS-E>4).	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

			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.	**Secondary Outcomes:** 28-day mortality, 6-month disability rating scale (DRS) score, progression of intracranial hemorrhage, discharge GOS-E score, and discharge DRS score.		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 lower or any ICH on CT scan, and no major extracranial bleeding were included.	**Treatment:** 1g TXA over 10 min then infusion of 1 g over 8 h **Control:** Matching placebo	**Primary Outcome:** Head injury-related mortality in hospital within 28 days of injury. **Secondary Outcomes:** Early head injury-related mortality	Among patients treated within 3 hours of injury, the risk 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]).	In this study, TXA did not result in a significant reduction in mortality among the total population. However, subgroup analysis showed that TXA significantly decreased mortality in patients with mild-to-moderate head trauma but did not affect

				(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.	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).	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	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 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).	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.

				embolism, deep vein thrombosis, and stroke).		
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	**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	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

		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.			TXA group and 3 (6.8%) patients in the placebo group died, but the difference was not significant (p = 0.236).	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	**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.	**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).	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

		had evidence of IPH/contusion on admission brain CT scan were enrolled in the study.	**Control:** Normal saline with the same protocol.		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).	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 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).	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 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	**Treatment:** 1g TXA IV loading dose over 10 minutes and 1g TXA IV	**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	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

		immediate surgical intervention.	infusion over 8 hours. **Control:** Normal saline with same IV protocol.		had a significantly lower volume of ICH 48 hours after the injury (p=0.021).	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 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.	**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 difference (p=0.270).	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.
Mousavinejad 2020	Randomized double-blind placebo-	Patients over 18 years of age who were referred to the hospital within 8	**Treatment:** 1 g TXA in 500 ml of 0.9% normal saline,	**Primary Outcome:** To assess the effect of TXA on	There was no significant difference between the groups in terms of bleeding during surgery,	-

	controlled trial	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.	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.	the reduction of hemorrhage volume during neurosurgery in patients with brain contusion and intraparenchymal hemorrhage admitted to the emergency department.	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 limbs, subarachnoid hemorrhage, hematuria, or	**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 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

		coagulation disorders.				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 **TICH-2**	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,	**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%,	**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	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	There was no increase in VTE (39 [3%] patients in the TXA group vs. 37 [3%] in the placebo group; p=0.98).

		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.	infused over 8 hours. **Control:** The comparator was a matching placebo (normal saline 0.9%), administered with an identical regimen.	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).	(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).	
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; contraindications for antifibrinolytic therapy; very large intracerebral hemorrhage (>70 mL); brainstem hemorrhage;	**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 administration 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 Categorical shift in mRS 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	There were two (4%) thromboembolic complications in the placebo group and one (2%) in the TXA group. (p=0.57)

		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 contraindication 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 therapy is contraindicated or that could affect participation in the study, as judged by the investigator.		**Safety:** Major thromboembolic events (myocardial infarction, ischemic stroke, or pulmonary embolism) Death due to any cause, both by 90 days.	by 90 days (OR 2-38 [0.66-8.67], p=0.19).	
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).	**Treatment:** IV TXA, 1 g in 100 mL 0.9% NaCl infused over 10 minutes,	**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	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	Due to the neutral results reported from the STOP-AUST trial, the study was terminated in March 2020, with a final

		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 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.	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.	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 embolism). Safety outcomes were collected through day 90.	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).	enrollment of 171 patients.
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:**	**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	**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	No serious adverse event was observed in the study.

		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.	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.		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).	
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,	**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	-

		vascular malformation, or other secondary causes.			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 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.	**Treatment:** 1 g loading dose in 100 mL normal saline infused over 10 minutes, followed by another 1 g in 250 mL normal saline 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.	**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 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.	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 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.	Due to lack of funding, the TICH-NOAC study was terminated early before reaching the target enrollment of 218 patients.
Post 2021	Randomized open label placebo-controlled trial	**Inclusion Criteria:** Adults aged 18 years or older with SAH.	**Treatment:** IV bolus of 1 g TXA, directly followed by 1 g	**Primary Outcome:** At 6 months after randomization, clinical outcome classified as	In the TXA group, 287 patients (60%) and in the control group, 300 patients (64%) had a	All serious adverse events, including thromboembolic events, did not differ

		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 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.	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 the aneurysm or until a maximum of 24 hours (i.e., a maximum of 4 g TXA in total). **Control:** Only standard care.	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.	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 (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.	between the two groups.

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 excluded if a diagnosis other than a ruptured aneurysm was confirmed by CT or angiography, or if death was deemed imminent.	**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.	-
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,	**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.	**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.

		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.	**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.			
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 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	**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. **Control:** Standard care plus saline. **Standard Care:** Conventional treatment included bed rest with intensive nursing care for three weeks, dexamethasone	**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 between the groups in terms of rebleeding.	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 comparing with today's studies. There is no mention of blindness in the study.

			if cerebral edema developed, and saline injection. All treatments were continued until 21 days after the last hemorrhage.			
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	**Treatment:** Patients received TXA, 9 g a day in six doses, until the	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.	-

		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.	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.		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. **Exclusion Criteria:** Patients more than 72 hours after hemorrhage; presence of DVT; coagulation disorders; renal insufficiency; pregnancy; previous anti-fibrinolytic treatment;	**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 TXA orally per day in 4 doses for the third and fourth weeks. **Control:**	**Primary Outcome:** Comparing five point GCS at three months. **Secondary Outcome:** Intracranial complications; rebleeding, infarction, hydrocephalous, local oedema from a hematoma, or epilepsy.	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 100 patients (42%) in the TXA group. In the TXA group, 21 patients (9%) had rebleeding, compared	-

		negative angiography in terms of aneurysm.	No details provided.		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.	**Treatment:** TXA (500 mg diluted in up to 20 mL of saline) **Control:** Adrenaline (1 mg	**Primary Outcome:** Bleeding control determined by direct observation of clot formation	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

		Exclusion Criteria: Declined to participate, successful bleeding control with cold saline, cardiovascular disease, bleeding tendency, or anticoagulant and antiplatelet drug consumption.	diluted in up to 20 mL of saline) If necessary, all repeated up to 3 times.	through the bronchoscope.		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,	**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%; $p<0.001$).	-

		visible 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; pregnancy; recent use of anticoagulant drugs; or those who were prisoners.	**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.

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 chitosan-impregnated tampon, trade-named 'ChitoHem', from ChitoTech Company Inc.	**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 EpiCell tampon group ($P=0.013$). However, no significant difference was observed between the TXA group and the	No serious adverse events were observed in the study.

					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 carboxypolymethylene. 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	**Treatment:** Topically applied IV TXA on a 15 cm cotton pledget **Control:** Usual care consisting of ANP	**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	No serious adverse event was observed in the study.

		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.	with tetracycline ointment soaked cotton for 3 days.		difference with a percentage difference of 44% (95% CI 26% to 57%).	
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 or venous thrombosis, those taking anticoagulants, antiplatelet drugs, and even aspirin, besides patients with leukemia, lymphoma, and polycythemia vera, and pregnant women.	**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 the TXA group patients and 33.3% of the control group patients.	TXA administration was associated with fewer side effects than tampon application (nausea, vomiting).

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