Outcomes of Tranexamic Acid Treatment in Patients with Upper Gastrointestinal Bleeding: An Overview of Reviews

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ABSTRACT

Background: *Upper gastrointestinal bleeding (UGIB) is a life-threatening emergency requiring prompt management. Standard treatments include endoscopic intervention, blood transfusions, and pharmacological therapies such as proton pump inhibitors (PPIs) and antifibrinolytics like tranexamic acid (TXA). However, the efficacy of TXA in UGIB remains controversial due to mixed findings. This systematic review analyzed six systematic reviews covering 34,351 patients. The objective is to assess TXA's effectiveness in reducing mortality, rebleeding, and thromboembolic events, as well as secondary outcomes such as transfusion requirements, surgery, hospital stay, and adverse events.* ***Methods:*** *Studies on non-GI bleeding, pediatric populations, and non-peer-reviewed articles were excluded. A comprehensive search across PubMed, Cochrane Library, ScienceDirect, and DOAJ (2014–2024) identified 157 records, with six systematic reviews/meta-analyses (34,351 participants) meeting inclusion criteria. Risk of bias was assessed using AMSTAR 2, with two studies rated as high confidence and four as moderate confidence.* ***Results:*** *Current high-quality evidence does not support routine TXA use for mortality reduction in UGIB. Safety remains uncertain, particularly with prolonged high-dose administration.* ***Conclusion:*** *These findings are consistent with the 2022 Indonesian national consensus, which advises against routine TXA use in UGIB. Future research should focus on optimized dosing strategies, timing of administration, and identification of clinically relevant subgroups to clarify its therapeutic role.*

Keywords*: Internal medicine, tranexamic acid, upper gastrointestinal bleeding, rebleeding, mortality.*

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is a potentially life-threatening and frequently encountered condition in clinical practice.[1] The bleeding originates from a location proximal to the ligament of Treitz, involving the esophagus, stomach, or duodenum. Patients with UGIB may exhibit not only external signs of blood loss but also symptoms such as syncope, fatigue, and shortness of breath due to reduced blood volume.[2] The causes of UGIB are broadly categorized as variceal or non-variceal, with peptic ulcer bleeding being the most common non-variceal cause,[3] accounting for around 75%

of all acute gastrointestinal bleeding cases.[4]

The mortality rate for acute UGIB remains at 5%–10%, a figure largely unchanged since 1945 despite advancements in medications, endoscopic techniques, ICU care, and surgical interventions.[5] A prospective cohort study by Moledina et al. (2017) highlights the significant burden of this condition, reporting that one-third of patients admitted for UGIB died within 60 days of admission, even though rates of rebleeding and readmission were low.[6] The incidence of UGIB has been rising in Indonesia, as evidenced by data from the Gastrointestinal Endoscopy Center at Cipto Mangunkusumo Hospital, which reported a 26.2% increase in endoscopic services from 1,825 patients in 2010 to 2,303 patients in 2013.[7]

The management of acute UGIB poses significant challenges due to its association with increased morbidity, mortality, and healthcare costs, prompting extensive research to improve patient outcomes.[1,8] One critical issue in this area is rebleeding, a phenomenon in which patients initially achieve hemodynamic stability but later experience a recurrence of bleeding. Rebleeding affects 5%–40% of acute UGIB cases and increases the risk of death fourfold, underscoring the need for effective interventions.[9]

Tranexamic acid (TXA), an antifibrinolytic agent, has garnered attention as a potential adjunct in UGIB management.[8,10,11] Tranexamic acid functions by reducing fibrinolysis, slowing the conversion of plasminogen to plasmin, and preventing the breakdown of blood clots, thereby promoting hemostasis. However, this benefit may come at the cost of an increased risk of thromboembolic complications. The use of TXA in acute UGIB remains controversial despite numerous studies over the past decade, as practices vary widely.[9,12] While some clinicians include TXA in initial treatment protocols, others remain cautious due to the lack of consensus on its efficacy and safety.

Despite the growing interest in TXA as a potential adjunct therapy due to its antifibrinolytic properties, there remains a lack of conclusive evidence to support its routine use.[11,13–15] Numerous systematic reviews have been conducted to evaluate the role of TXA in the management of UGIB. However, these reviews have often yielded conflicting results, leaving clinicians without a definitive answer regarding whether TXA should be routinely used in UGIB management and under what specific clinical circumstances it might be beneficial or contraindicated. Before 2022, the national consensus in Indonesia on the management of non-variceal UGIB did not provide specific recommendations regarding the use of tranexamic acid (TXA).[16] This position was reconsidered following the publication of the Haemorrhage ALleviation with Tranexamic Acid – Intestinal System (HALT-IT) trial in 2020, which demonstrated that TXA did not significantly reduce mortality in UGIB patients and was associated with an increased risk of venous thromboembolism (VTE). Consequently, the national consensus was revised in 2022 to recommend against the use of TXA in the management of UGIB.[16]

Regardless of this update, however, variability in clinical practice persists, with some practitioners continuing to use TXA. This variability reflects ongoing debates and differing expert opinions regarding its utility. The publication of new studies and systematic reviews following the HALT-IT trial underscores this lack of consensus. Notably, while many of these systematic reviews have incorporated the HALT-IT findings into their analyses, their conclusions remain inconsistent, and conflicting evidence regarding complications associated with TXA use continues to complicate its evaluation.[10,12,17,18]

Given the abundance of individual systematic reviews and the discrepancies among their findings, an umbrella review—a systematic review of systematic reviews—becomes essential. An umbrella review can address the current gaps in knowledge, reconcile conflicting findings, and establish a clearer understanding of its effectiveness and safety. By synthesizing and analyzing recent evidence, this review aims to provide clarity on the role of TXA in UGIB management and contribute to the development of more informed clinical guidelines. This umbrella review was conducted to address the following structured research question using the PICO framework: (P) patients with upper gastrointestinal bleeding (including variceal

and non-variceal etiologies); (I) administration of tranexamic acid at any dose or duration; (C) placebo, no treatment, or standard care without tranexamic acid; and (O) primary outcomes of mortality, rebleeding, and thromboembolic events, with secondary outcomes including need for surgical intervention, blood transfusion requirements, length of hospital stay, and adverse events.

METHODS

Protocol and Registration

This systematic review of systematic reviews and meta-analyses (umbrella review) was conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was prospectively registered on PROSPERO (CRD42025638060).

Eligibility Criteria

The eligibility criteria for this review were designed to ensure a comprehensive and high-quality synthesis. The studies included will evaluate patients with UGIB, encompassing both variceal and non-variceal bleeding. The intervention of interest is the use of TXA, including an analysis of the doses used, with comparators including placebo, no treatment, or standard care without TXA. Outcomes of focus include primary endpoints such as mortality, rebleeding rates, and thromboembolic events (e.g., deep vein thrombosis or pulmonary embolism), as well as secondary endpoints like blood transfusion requirements, need for surgical intervention, length of hospital stay, adverse events, and overall treatment efficacy. Only studies published in peer-reviewed journals, regardless of publication year, were included. Only studies published in English or with an available English translation were included. In addition, studies that do not specifically evaluate TXA or focus solely on non-GI bleeding conditions were excluded. To maintain methodological rigor, only reviews adhering to recognized systematic review methodologies, such as the AMSTAR 2 instrument, will be considered.

Search Strategy and Selection Process

A comprehensive search strategy was employed to identify relevant systematic reviews on the use of tranexamic acid in upper gastrointestinal bleeding. Keywords included combinations of "tranexamic acid," "gastrointestinal bleeding," and "systematic review." The search was restricted to articles published between 2014 and 2024, with a primary focus on studies released after the HALT-IT trial. Databases searched included PubMed, the Cochrane Library, ScienceDirect, and the Directory of Open Access Journals (DOAJ).

Studies were excluded if full texts were not available or if they were published in languages other than English. The database search results were imported into the Mendeley Desktop (version 1.19.8), where duplicate entries were removed. Abstracts and full-text articles were then screened to identify studies meeting the inclusion criteria.

Data extracted from each included review encompassed the number of original studies, sample size and characteristics, the settings in which the studies were conducted, the nature of the included interventions, measured outcomes, and key findings. To assess methodological quality, the risk of bias for each included systematic review was evaluated using the 16-item AMSTAR 2 tool.[19] Reviews were categorized into four confidence levels: high confidence (no critical weaknesses and fewer than three non-critical weaknesses), moderate confidence (one critical weakness and fewer than three non-critical weaknesses), low confidence (more than one critical weakness and fewer than three non-critical weaknesses), and critically low confidence (more than one critical weakness and three or more non-critical weaknesses). This assessment was conducted independently by two of four reviewers, with each item scored as "no," "partial yes," or "yes."

Data Extraction

Data were extracted using a data extraction form developed for the review, based on a template agreed upon by all reviewers. The extracted data included the number of original studies in the review, sample size, and characteristics (e.g., age

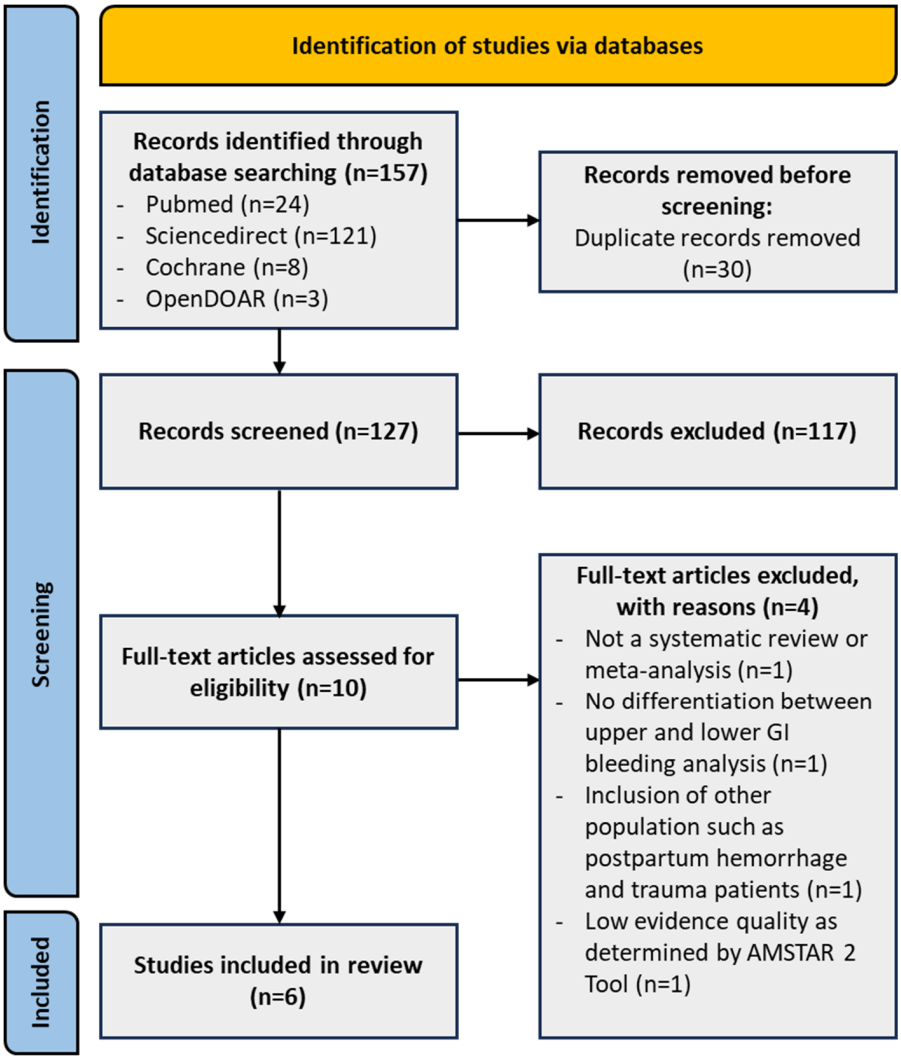


Figure 1. Study Flowchart.

and population type), the nature of the included interventions, measured outcomes (mortality rate, rebleeding rate, thromboembolic events, surgical intervention, blood transfusion requirements, length of hospital stay, adverse events, and overall treatment efficacy), and the results.

In this overview of systematic reviews, clinical outcomes were extracted as reported in the included systematic reviews and meta-analyses. Across the reviews, mortality was generally defined as all-cause mortality during the study follow-up period. Rebleeding typically refers to the recurrence of gastrointestinal bleeding after initial stabilization or endoscopic management, commonly indicated by clinical features such as hematemesis, melena, hemodynamic instability, or a decline in hemoglobin levels requiring further intervention. Transfusion requirement was defined as the need for blood product transfusion or the number of packed red blood cell units administered during hospitalization. Several reviews also evaluated related outcomes, including the need for surgical or endoscopic intervention, intensive care unit admission, and thromboembolic adverse events. As this overview synthesized evidence from multiple systematic reviews, the operational definitions of these outcomes followed those used in the original reviews and their included randomized controlled trials, which were broadly comparable despite minor variations in reporting

Deviations from Registered Protocols

In the original protocol submitted, only systematic reviews were planned for inclusion. However, during our search, we identified some significant meta-analyses that were too relevant to be excluded. To ensure a more comprehensive conclusion and qualitative synthesis, we included all secondary studies (systematic reviews and/or meta-analyses) that aligned with our inclusion criteria. Additionally, during further searching, we identified a single, comprehensive systematic review by Bennet et al. 2014[8], which has served as a foundational reference for numerous past and ongoing discussions regarding TXA use. After a thorough discussion with all reviewers, we determined that including this study was essential to our review. As a result, we extended the timeframe of our study from the last five years to the last decade to accommodate its inclusion.

Umbrella Review Synthesis Methods

The overlap among component studies (such as the original randomized controlled trials) included in the systematic reviews and meta-analyses of this umbrella review was evaluated using the corrected covered area (CCA) method. Since some of the meta-analyses incorporated the same component studies, conducting a meta-analysis of the meta-analyses would have led to multiple counting of certain studies, violating key principles of meta-analysis. To address this, a narrative synthesis was conducted instead. Meta-analyses were categorized based on outcome measures and visualized using forest plots, which summarized key aspects such as effect size, population, sample size, and heterogeneity (e.g., I^2). Effect sizes were reported as originally presented in each systematic review. For systematic reviews that used narrative synthesis, the number of studies reporting statistically significant favorable outcomes such as confidence intervals that did not overlap with zero was determined. These numbers were then expressed as a percentage of the total studies assessed. Findings were then summarized by illustrating the relationship between the proportion of studies showing significant favorable effects and the overall number of studies reporting each outcome.

Given the potential for substantial overlap of primary randomized controlled trials (RCTs) across included meta-analyses, we quantified overlap using the Corrected Covered Area (CCA) method. A high CCA was anticipated because most contemporary systematic reviews incorporated the HALT-IT trial and several earlier RCTs. Despite this overlap, an umbrella review was justified for three reasons. First, systematic reviews published before and after HALT-IT reached divergent conclusions regarding mortality and safety. Second, methodological quality varied across reviews, necessitating appraisal using AMSTAR 2 to determine confidence in pooled estimates. Third, clinical recommendations continue to differ despite the availability of large RCT data. Therefore, this umbrella review was conducted not to re-pool overlapping data, but to critically synthesize how different reviews interpreted shared evidence and how conclusions evolved following HALT-IT.

RESULTS

Study Selection and Characteristics

A total of 157 records were identified through database searches, including PubMed (n=24), ScienceDirect (n=121), Cochrane (n=8), and OpenDOAJ (n=3). After the removal of 30 duplicate records, 127 remained for screening. Following title and abstract screening, 117 records were excluded, leaving 10 full-text articles for eligibility assessment. Of these, four were excluded for the following reasons: not being a systematic review or meta-analysis[15] (n=1), lack of differentiation between upper and lower gastrointestinal bleeding[17] (n=1), inclusion of other populations such as postpartum hemorrhage and trauma patients[12] (n=1), and low methodological quality as determined by the AMSTAR 2 tool[20] (n=1). Six studies met the inclusion criteria and were included in the final review, with most studies published between 2020 and 2021.[8,10,14,18,21,22] **Figure 1** shows the flow diagram of this study.

These reviews analyzed varying numbers of component studies, ranging from six to thirteen, with a total of 57 component studies (including duplicates) and 18 unique studies.

Collectively, the six included reviews covered a total of 34,351 participants. While most studies focused exclusively on upper gastrointestinal (GI) bleeding, Lee et al. (2021) included both upper and lower GI bleeding. Additionally, Lee et al. was the only study that included participants of all ages; however, the reported mean age remained at 55 years, with two of the 13 randomized controlled trials (RCTs) in the review having unclear age data.[14] Notably, two of the six included reviews incorporated the HALT-IT trial, the largest RCT to date on tranexamic acid use in GI bleeding.[10,18]

The characteristics of gastrointestinal bleeding varied across the included systematic reviews. Reporting of bleeding characteristics varied across the included systematic reviews. Several reviews[8,10,14] pooled outcomes across gastrointestinal bleeding populations without consistently distinguishing between variceal and non-variceal etiologies. In contrast, Kamal et al. and Twum et al.[18,21] conducted subgroup analyses according to bleeding type, comparing studies that included non-variceal bleeding with those involving mixed populations of variceal and non-variceal bleeding. Meanwhile, Kan et al. focused on upper gastrointestinal bleeding populations receiving acid suppression therapy, which predominantly reflects non-variceal bleeding.[22] Although the HALT-IT trial did not differentiate between upper and lower GI bleeding in its primary analysis, 89% of the included participants had upper GI bleeding in both the tranexamic acid (n=5,320) and placebo (n=5,361) groups. Given the study's size and relevance, it was included in this review despite the lack of distinction between upper and lower GI bleeding.

Methodological Quality Assessment (AMSTAR-2)

The methodological quality of the included studies was assessed using the AMSTAR 2 tool. The HALT-IT trial was incorporated into two of the six reviews and contributed the majority of participants in those analyses. Earlier RCTs were repeatedly included across pre-2020 meta-analyses, contributing to repeated weighting of small trials in pooled estimates. Two studies[8,21] demonstrated high confidence with no notable weaknesses, and four studies[10,14,18,22] were rated as moderate confidence due to the presence of one critical domain limitation. Common methodological strengths included duplicate study selection and comprehensive search strategies. The most frequent weakness was failure to report funding sources of included trials. No review was rated as low or critically low confidence. **Table 1** presents the overall confidence and key limitations of each study.

The degree of overlap among the component studies was quantified using the Corrected Covered Area (CCA) method, yielding a value of 43.3%, which indicates a very high degree of overlap. Due to this substantial overlap among the included meta-analyses, conducting a meta-analysis of these meta-analyses was deemed inappropriate. Instead, a narrative synthesis approach was used to summarize the findings.

Risk-of-Bias and Study Overlap

The included reviews demonstrated several methodological strengths, such as providing conflict-of-interest statements, conducting study selection in duplicate, and reporting study heterogeneity in meta-analyses. However, a common methodological weakness was the

Table 1. Overall Methodological Quality Assessment Using AMSTAR-2

Studies Included	Overall Confidence	Key Methodological Limitations
Bennet et al. (2014)	High	Minor limitations (conflict of interest reporting partially described)
Twum et al. (2020)	High	Minor limitations (study design selection partially justified)
Kamal et al. (2020)	Moderate	No justification of study design selection; no reporting of funding sources of included studies
Burke et al. (2021)	Moderate	Search strategy not fully comprehensive; funding sources of included studies not reported
Lee et al. (2021)	Moderate	Partial justification of study design selection; no publication bias assessment; funding sources not reported
Kan et al. (2024)	Moderate	No justification of study design selection; no excluded studies list; funding sources not reported

failure to extract data on funding sources, with only Bennet et al. (2014) successfully addressing this aspect.[8] The citation matrix presented in **Table 2** demonstrated substantial duplication of primary trials across reviews.

Results of Meta-Analyses

A summary of the results from multiple meta-analyses assessing the efficacy and safety of TXA compared to placebo or no treatment in patients with UGIB was presented in **Table 3**. The table evaluates several key clinical outcomes, including mortality, rebleeding rates, need for surgical intervention, blood transfusion requirements, and thromboembolism events. Each study reported relative risk (RR) or odds ratio (OR) along with confidence intervals (95% CI), heterogeneity (I^2), and p-values to assess statistical significance.

Results of Forest Plot Synthesis

The forest plots summarizing pooled estimates from the six included reviews are presented in **Table 3**. For mortality, earlier reviews showed relative risk estimates favoring tranexamic acid, whereas more recent analyses demonstrated attenuation of effect, with confidence intervals crossing unity. A similar pattern was observed for rebleeding, where several analyses suggested benefit, but statistical significance was inconsistent, and precision varied. Estimates for surgical intervention generally favored tranexamic acid, although most confidence intervals overlapped 1.0. In contrast, transfusion requirements showed effect estimates clustered around unity across all reviews, indicating no clear benefit. For thromboembolic events, point estimates were imprecise with wide confidence intervals consistently crossing 1.0, precluding definitive conclusions regarding safety. The forest plots reflect heterogeneity in magnitude and certainty of effect, with signals of benefit in earlier analyses that are not consistently sustained in more contemporary evidence.

Results of Narrative Synthesis

TXA was associated with a reduction in mortality across several studies, with relative risks (RR) ranging from 0.59 to 0.95. Three studies[8,14,21] demonstrated significant reductions in mortality, with RR estimates around 0.60, indicating a 40% reduction in mortality risk compared to placebo. Notably, these studies had low heterogeneity (I^2 = 0%), implying consistency in the findings. However, Kamal et al. (2020)[18] and Burke et al. (2021)[10] found no significant mortality benefit (RR 0.87 and 0.95, respectively). Kamal et al.[18] further conducted sensitivity analyses and identified publication bias, leading to an adjusted effect size of RR 0.97 (95% CI 0.83–1.13), showing no mortality

Table 2. Citation matrix of included reviews and component RCTs

Primary RCT	Bennett et al, 2014	Twum et al, 2020	Kamal et al, 2020	Burke et al, 2021	Lee et al, 2021	Kan et al, 2024
Chiang et al, 2023	–	–	–	–	–	✓
Sedaghat et al, 2023	–	–	–	–	–	✓
Bashiri et al, 2021	–	–	–	–	–	✓
HALT-IT 2020	–	–	✓	✓	–	–
Karadas et al,2020	–	–	✓	–	✓	–
Smith et al, 2018	–	–		–	✓	–
Tavakoli et al, 2018	–	✓	✓	–	✓	–
Saidi et al, 2017	–	✓	✓	–	✓	✓
Bagnenko et al, 2011	✓	✓	✓	✓	✓	
Hawkey et al, 2001	✓	✓	✓	✓	✓	✓
Von Holstein et al, 1987	✓	✓	✓	✓	✓	✓
Von Holstein et al, 1987 (2)	–	–	–	–	✓	–
Barer et al, 1983	✓	✓	✓	–	✓	–
Hollanders et al, 1982	–	–	–	–	✓	–
Bergqvist et al, 1980	✓	✓	✓	✓	✓	–
Engqvist et al, 1979		✓	✓	✓	✓	–
Biggs et al, 1976	✓	✓	✓	✓	–	–
Cormack et al, 1973	✓	✓	✓	✓	✓	–

benefit after correction. Additionally, Kan et al. (2024)[22] found a non-significant trend favoring TXA (RR 0.74, 95% CI 0.34–1.60), although the small sample size limited statistical power.

All studies reported reduced rebleeding rates, although with variable significance. Two studies[8,14] reported a trend toward reduced rebleeding (RR 0.72 and RR 0.84), but this was not statistically significant. Similar findings were reported by Twum et al. (2020)[21] and Kamal et al. (2020)[18], where pooled risk reductions were observed (RR 0.79–0.90), but without statistical significance. In contrast, Burke et al. (2021)[10] and Kan et al. (2024)[22] demonstrated significant reductions in rebleeding rates, with RRs of 0.64 (95% CI 0.47–0.86) and 0.63 (95% CI 0.41–0.96), respectively.

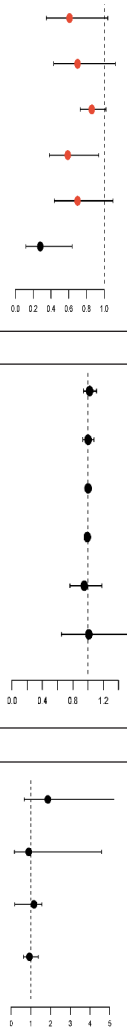
The need for additional intervention, such as surgery and blood transfusion, was evaluated across multiple studies. Bennet et al. (2014)[8] and Twum et al. (2020)[21] found non-significant trends favoring TXA (RRs 0.61 and 0.70, respectively) in reducing surgical intervention needs. However, Burke et al. (2021) demonstrated a statistically significant reduction in surgery rates (RR 0.59, 95% CI 0.38–0.94, p = 0.03). Similarly, Kan et al. (2024)[22] found a substantial reduction in the need for salvage therapy (RR 0.28, 95% CI 0.12–0.64), indicating that TXA, particularly when combined with acid suppression, significantly reduced the likelihood of requiring additional interventions. Conversely, Kamal et al. (2020)[18] found no significant difference (RR 0.86, 95% CI 0.73–1.02), and Lee et al. (2021)[14]reported a non-significant reduction (RR 0.70, 95% CI 0.44–1.10). TXA did not significantly reduce blood transfusion needs. Five studies[8,10,18,21,22] all reported RR values were near 1.00, indicating no difference between the TXA and placebo groups. Kan et al. (2024)[22] also assessed the amount of blood transfused and found a significant reduction in the number of blood units required among patients receiving TXA (mean difference: −1.08, 95% CI −1.44 to −0.71), suggesting that TXA may not reduce the transfusion rates but could lower overall transfusion volume.

The safety profile of TXA remains an area of concern, particularly regarding thromboembolic events. It should be noted that the risk of thromboembolism with TXA

Table 3. Summary of meta-analyses results reported for TXA outcomes compared with placebo or no treatment

	Model	Number of studies	n	Value (95% CI)	Forest plot	P value*	I^2 (%)
Mortality (n = 33,779)							
Bennet et al, 2014	RR, Random	8	1,701	0.60 [0.42, 0.87]		0.90	0
Twum et al, 2020	RR, Random	10	2,031	0.59 [0.43, 0.82]		0.81	0
Kamal et al, 2020	RR, Fixed	12	14,107	0.87 [0.74, 1.01]		0.32	12
Burke et al, 2021	RR, Random	8	13,122	0.95 [0.80, 1.13]		0.92	0
Lee et al, 2021	RR, Random	11	2,109	0.60 [0.45, 0.80]		0.92	0
Kan et al, 2024	RR, Random	6	709	0.74 [0.34, 1.60]		0.40	2
					0.0 0.5 1.0 1.5		
Rebleeding rates (n=20,676)							
Bennet et al, 2014	RR, Random	7	1,651	0.72 [0.50, 1.03]		0.07	48.59
Twum et al, 2020	RR, Random	8	1,750	0.79 [0.61, 1.02]		0.24	23
Kamal et al, 2020	RR, Fixed	9	13,695	0.90 [0.79, 1.02]		0.31	15
Burke et al, 2021	RR, Random	6	1,063	0.64 [0.47, 0.86]		0.42	0
Lee et al, 2021	RR, Random	8	1,821	0.84 [0.61, 1.15]		0.32	14
Kan et al, 2024	RR, Random	6	696	0.63 [0.41, 0.96]		0.21	31
					0.0 0.2 0.4 0.6 0.8 1.0		

Need of surgical intervention (n=32,777)							
Bennet et al, 2014	RR, Random	7	1,551	0.61 [0.35, 1.04]		0.01	62.9
Twum et al, 2020	RR, Random	9	1,863	0.70 [0.43, 1.13]		0.01	60
Kamal et al, 2020	RR, Fixed	11	13,944	0.86 [0.73, 1.02]		0.04	48
Burke et al, 2021	RR, Random	7	12,972	0.59 [0.38, 0.94]		0.04	56
Lee et al, 2021	RR, Random	10	2,025	0.70 [0.44, 1.10]		0.03	53
Kan et al, 2024	RR, Random	3	422	0.28 [0.12, 0.64]		0.59	0
Blood transfusion requirements (n=27,463)							
Bennet et al., 2014	RR, Random	5	931	1.02 [0.94, 1.11]		0.69	0
Twum et al., 2020	RR, Random	8	1,763	1.00 [0.93, 1.08]		0.46	0
Kamal et al., 2020	RR, Fixed	9	9,961	1.00 [0.99, 1.01]		0.78	0
Burke et al., 2021	RR, Random	6	12,868	0.99 [0.97, 1.02]		0.78	0
Lee et al., 2021	OR, Fixed	7	1,422	0.95 [0.76, 1.18]		0.17	34
Kan et al, 2024	RR, Random	4	518	1.01 [0.65, 1.55]		0.94	0
Thromboembolism events (n=27,752)							
Bennet et al., 2014	RR, Random	4	1,095	1.86[0.66,5.24]		0.49	0
Twum et al., 2020	RR, Random	6	1,041	0.89 [0.17, 4.59]		0.11	55
Kamal et al., 2020	RR, Fixed	8	13,127	1.16 [0.187, 1.56]		0.17	38
Burke et al., 2021	RR, Random	3	12,489	0.93 [0.62, 1.39]		0.41	0



*P values refer to the statistical significance of the pooled overall effect estimate. Heterogeneity was assessed using the I² statistic and Cochran's Chi-square test.

was not significantly increased in all four studies reporting the numbers[8,10,18,21], with RR values ranging from 0.89 to 1.86, with wide confidence intervals crossing the null value, suggesting uncertainty in risk estimation. Bennet et al. (2014)[8] reported an increased risk (RR 1.86, 95% CI 0.66–5.24), but this was not statistically significant. Similarly, Twum et al. (2020)[21] and Burke et al. (2021)[10] found no significant difference in thromboembolism risk (RRs 0.89 and 0.93, respectively). Kamal et al. (2020)[18], however, observed an increased risk of venous thromboembolism (RR 1.94, 95% CI 1.23–3.05), particularly in patients receiving high-dose TXA (RR 2.21, 95% CI 1.32–3.69). This shows that the risk may be dose-dependent, emphasizing the need for caution with higher doses of TXA. Heterogeneity was moderate to high (I^2 up to 55%), reflecting the variability in reported adverse events.

Results According to the Risk of Bias

Two of the studies included[8,21] were marked as high-confidence, and the rest[10,14,18,22] as moderate-confidence. Regarding mortality outcomes, high-confidence studies[8,21] found a significant reduction in mortality with TXA (RR 0.60, 95% CI 0.45–0.80; $I^2 = 0\%$), indicating a 40% lower risk of death compared to placebo. However, it should be highlighted that one of the high-confidence studies[8] initially showed a mortality benefit (RR 0.60, $p = 0.007$), but when high-risk trials were excluded in sensitivity

analyses, statistical significance was lost (RR 0.73, 95% CI 0.45–1.19), suggesting potential bias in the primary pooled estimate. In contrast, three of the moderate-confidence studies[10,18,22] found no mortality benefit (RR 0.87–0.95), with Kamal et al. detecting publication bias in their funnel plot analysis. Regarding rebleeding outcomes, high-confidence studies[8,21] reported a trend toward reduced rebleeding, but this did not reach statistical significance (RR 0.72–0.79). Some moderate-confidence studies[10,22] found statistically significant reductions in rebleeding rates, whereas other moderate-confidence studies[14,18] reported no significant effect on rebleeding (RR 0.84–0.90), with concerns about data heterogeneity. In terms of surgical intervention needs, high-confidence studies[8,21] showed inconsistent results, with non-significant reductions in surgery rates (RR 0.61–0.70). Regarding blood transfusion requirements, all studies, regardless of confidence level, found no significant reduction in transfusion rates (RR ~1.00, I^2 = 0%). However, Kan et al. (2024)[22], a moderate-confidence study found that TXA reduced the total transfusion volume but not the number of transfusions required. For thromboembolism risk, high-confidence studies[8,21] found no significant increase in thromboembolic events (RR 0.89–1.86, I^2 = 0%). However, moderate-confidence studies[10,18] detected an increased risk of venous thromboembolism in the high-dose TXA groups (RR 2.21, 95% CI 1.32–3.69).

Summary of findings

The key findings from six meta-analyses, examining TXA's impact on mortality, rebleeding rates, surgical intervention, blood transfusion needs, and thromboembolism risk, are presented in **Table 4.** The table highlights the effect estimates (relative risk or odds ratio), statistical significance (p-values), and heterogeneity (I^2) across studies.

DISCUSSION

Upper gastrointestinal bleeding (UGIB) is one of the most common potentially life-

Table 4. Summary of evidence for the outcomes of TXA in UGIB

Outcome	Effect Estimate (RR or OR, 95% CI)	Significance (p-value)	Heterogeneity (I^2, %)	Summary of Findings
Mortality (n = 33,779)	0.60–0.95	Mixed (p = 0.007–0.92)	Low (I^2 = 0–12%)	High-confidence studies showed significant mortality reduction (RR ~0.60), whereas moderate-confidence studies found no benefit (RR ~0.87–0.95). Sensitivity analyses suggest publication bias.
Rebleeding (n = 20,676)	0.63–0.90	Mixed (p = 0.003–0.31)	Low to moderate (I^2 = 0–48.6%)	Two moderate-confidence studies found significant reductions in rebleeding (RR ~0.63–0.64), while two moderate- and one high- confidence studies found non-significant trends (RR ~0.72–0.90).
Need for Surgery (n = 32,777)	0.28–0.86	Mixed (p = 0.03–0.59)	Moderate to high (I^2 = 48–63%)	Two moderate-confidence studies found significant reductions (RR 0.59–0.28), while two moderate-confidence and two high-confidence studies showed no significant effect.
Blood Transfusion Rate (n = 27,463)	0.99–1.02	Non-significant (p = 0.55–0.94)	Low (I^2 = 0%)	No study found TXA to reduce transfusion rates. However, one moderate-confidence study found that TXA reduced the overall transfusion volume.
Thromboembolism Events (n = 27,752)	0.89–2.21	Mixed (p = 0.11–0.73)	Moderate (I^2 = 0–55%)	High-confidence studies found no significant increased risk, but one moderate-confidence study showed an increased risk in high-dose TXA (RR 2.21).

Strong negative	Weak negative	Non-significant	Weak positive	Strong positive

threatening conditions found in the emergency unit. Recent management of UGIB includes medications, blood transfusions, surgery, and endoscopy. The medications often given are PPIs, antifibrinolytic agents, and prophylactic antibiotics.[23] However, the use of antifibrinolytic agents in UGIB, such as TXA, remains debated due to its effectiveness and efficacy being controversial, as studies have reported mixed results regarding its clinical benefits and potential risks. Recent high-quality evidence from the HALT-IT trial involving over 12,000 patients demonstrated that tranexamic acid did not significantly reduce mortality in acute gastrointestinal bleeding and was associated with a higher incidence of venous thromboembolic events.[24] In this context, the present overview aimed to synthesize and critically appraise the available systematic reviews to provide a comprehensive assessment of the current evidence regarding the efficacy and safety of tranexamic acid in gastrointestinal bleeding.

Tranexamic acid (TXA) plays a key role in bleeding management and is commonly used in trauma care, orthopedic surgery, and postpartum hemorrhage.[15] TXA is an antifibrinolytic agent that prevents plasminogen from binding to fibrin. In patients with unstable bleeding, fibrinolysis activity may be overactivated, leading to significantly increased bleeding. Most adverse reactions to TXA are mild to moderate, and severe reactions are very rarely reported.[25]

In this review, three studies found that TXA reduced mortality, with the relative risk (RR) ranging from 0.60 to 0.95, indicating up to a 40% reduction in mortality risk compared to placebo, with low heterogeneity ($I^2 = 0\%$). The early arrival of patients to the emergency room is likely influencing the mortality benefit of TXA, considering that TXA has a short half-life. However, a large study such as the HALT-IT trial reported that TXA did not reduce death from gastrointestinal bleeding. This study, conducted in 164 hospitals across 15 countries with 12,009 participants, suggested that the result was likely influenced by difficulties in determining the onset of bleeding and the time of patient presentation.[24] This was contrasted by another large study, albeit for trauma patients, the CRASH-2 trial, which showed that TXA significantly reduced mortality, primarily in trauma patients with bleeding, if administered within 3 hours of injury.[26]

The heterogeneity in dosing strategies across trials represents a critical factor in interpreting both efficacy and safety outcomes. Earlier, smaller studies suggesting mortality or rebleeding benefits predominantly employed lower-dose regimens administered over shorter durations. In contrast, the HALT-IT trial used a high-dose 24-hour infusion protocol and did not demonstrate a mortality benefit, while identifying an increased incidence of venous thromboembolic events.[24] Although a causal dose–response relationship cannot be definitively established from available data, the divergence in dosing strategies raises the possibility that thromboembolic risk may be influenced by cumulative exposure and prolonged infusion.

Timing of administration may also be clinically relevant. Evidence from trauma populations has suggested benefit when TXA is administered early; however, in UGIB, bleeding onset is frequently uncertain, and delayed presentation is common. Within the included reviews, no adequately powered subgroup analysis confirmed that early administration (<3 hours) improves mortality in UGIB. Therefore, extrapolation of timing-dependent benefit from non-UGIB settings is not supported by direct evidence in this population.

The HALT-IT trial represents the most methodologically robust and largest randomized evaluation of tranexamic acid in gastrointestinal bleeding to date. In this multicenter trial, tranexamic acid did not reduce mortality from gastrointestinal bleeding and was associated with an increased risk of venous thromboembolic events, particularly with the high-dose 24-hour infusion regimen used. When HALT-IT was incorporated into subsequent meta-analyses, the previously reported mortality benefit observed in earlier reviews was attenuated or no longer statistically significant. This pattern suggests that the mortality reductions reported in pre-HALT-IT meta-analyses were largely driven by smaller, earlier trials with limited sample sizes and potential methodological constraints. Therefore, when prioritizing the highest-quality

contemporary evidence, current data do not support the routine use of tranexamic acid for mortality reduction in upper gastrointestinal bleeding.

Rebleeding is a major complication in UGIB that can significantly impact patient outcomes. It is more pronounced in unstable patients and can result in increased mortality. In this review, most studies reported that TXA reduced rebleeding rates, although the statistical significance varied. Burke et al. (2021)[10] and Kan et al. (2024)[22] demonstrated significant reductions in rebleeding rates. Four other studies showed reduced bleeding rates, but without statistical significance.[8,14,18,21] The risk of rebleeding increases in patients with severe anemia, those over 60 years of age, and those with higher NSAID consumption.[27] Despite the mixed results, the overall trend showed that TXA may have a favorable effect on reducing rebleeding, particularly when administered promptly.

The need for surgical intervention is another critical aspect of UGIB management. In this review, we found conflicting evidence regarding the need for surgery in TXA therapy. Bennet et al. (2014)[8] and Twum et al. (2020)[21] found that TXA did not significantly reduce the need for surgery (RRs 0.61 and 0.70, respectively). However, Burke et al. (2021)[10] and Kan et al. (2024)[22] demonstrated a statistically significant reduction in the surgical rates. Burke's study showed a decreased need for surgery in a cohort of patients with upper GI bleeding. Kan et al. also reported a reduction in the need for salvage therapy in the TXA with acid suppression group compared with the acid suppression group alone.

Blood transfusion requirements are often used as an indirect marker of bleeding severity and treatment efficacy. TXA is now regarded as part of the Patient Blood Management (PBM) program within transfusion medicine, designed to reduce blood loss and consequently minimize exposure to allogeneic blood in patients undergoing elective surgery.[28] The majority of studies included in this review did not find a significant reduction in transfusion rates with TXA use, as RR values were consistently around 1.00. However, Kan et al. reported a reduction in the total volume of blood transfused, suggesting that TXA may reduce the overall bleeding burden without necessarily decreasing the number of transfusion events.[22] TXA is also considered part of the transfusion protocols for massive transfusion when used within 3 hours of injury.[29] This nuance highlights the importance of considering both transfusion rates and volumes when evaluating bleeding management strategies.

One of the most concerning potential adverse effects of TXA use is the risk of thromboembolic events. Although HALT-IT reported a higher incidence of venous thromboembolic events in the TXA group[24] pooled analyses demonstrated wide confidence intervals, and the overall certainty of evidence regarding thromboembolic risk remains limited. It should also be noted that most of the affected population consisted of patients with liver disease, resulting in a greater risk of death, as they accounted for nearly three-quarters of the fatalities. The HALT-IT trial also noted that prolonged use and higher doses of TXA in the study might have contributed to the occurrence of thromboembolic events.

Methodological quality and bias play an essential role in interpreting the results of these studies. While some high-confidence studies demonstrated robust methodologies with minimal bias, others had potential limitations, such as publication bias or high heterogeneity. Sensitivity analyses from some studies revealed that removing high-risk trials diminished the observed mortality benefit, emphasizing the importance of critically appraising study quality when concluding.

It should be noted that this umbrella review identified a very high degree of overlap among included systematic reviews (CCA 43.3%), indicating that pooled estimates across meta-analyses are not statistically independent, as many relied on the same set of underlying RCTs. Consequently, apparent consistency in effect estimates, particularly in earlier reviews suggesting mortality benefit, may reflect repeated aggregation of identical small trials rather than independent confirmation of effect. Furthermore, the inclusion of the HALT-IT trial fundamentally altered the evidence landscape. Reviews conducted before

2020 were dominated by small, single-center trials with limited methodological rigor and potential publication bias. When HALT-IT was incorporated into later meta-analyses, the pooled mortality benefit mostly attenuated. The apparent benefit seen in early meta-analyses should be interpreted cautiously, as it likely reflects small-study effects rather than reproducible mortality reduction.

Given the conflicting evidence, the role of TXA in managing UGIB remains uncertain. TXA may benefit certain patient populations, particularly when administered early, but its efficacy and safety likely depend on factors such as dosage, timing, and underlying patient characteristics. Additionally, the potential for thromboembolic complications warrants careful consideration, especially when using higher doses or in patients with predisposing factors. A clinically important consideration that was not consistently addressed in the included reviews is the distinction between variceal and non-variceal upper gastrointestinal bleeding. Although most component studies focused on UGIB,[8,10,14,18,21,22] stratified analyses according to bleeding etiology were rarely reported, and pooled subgroup estimates were not available. Given that the HALT-IT trial contributed substantially to the overall evidence base and included 89% patients with upper gastrointestinal bleeding,[9] its neutral mortality findings likely apply broadly across mixed UGIB populations rather than a specific etiologic subgroup. However, because detailed stratified mortality and safety analyses by confirmed variceal versus non-variceal source were not consistently provided, the present overview cannot determine whether treatment effects differ between these groups. Importantly, thromboembolic events were reported at an aggregate level in the major trials and reviews, without robust subgroup breakdowns. Therefore, current evidence is insufficient to conclude that TXA is safer in non-variceal bleeding or that risk differs meaningfully between etiologies. In the absence of adequately powered subgroup analyses, stratified clinical recommendations cannot be made, and routine use in either variceal or non-variceal UGIB is not supported by the highest-quality available evidence. Further research is needed to address current knowledge gaps, including well-designed randomized controlled trials that specifically evaluate optimal dosing strategies, timing of administration, and patient selection criteria. Moreover, future studies should focus on stratifying results based on baseline thromboembolic risk and comorbidities to better identify which patients are most likely to benefit from TXA therapy.

LIMITATIONS

This overview of reviews has several limitations that should be considered when interpreting the findings. First, as this study synthesizes previously published systematic reviews and meta-analyses, the analysis is inherently retrospective and dependent on the methodology and reporting quality of the included reviews and their primary studies. Although most of the included systematic reviews primarily analyzed randomized controlled trials, variations in study design, patient populations, tranexamic acid dosing regimens, and clinical management strategies may introduce heterogeneity across the pooled evidence. In addition, differences in the operational definitions of outcomes such as rebleeding, transfusion requirements, and need for further intervention across the original trials may affect the comparability of results. Finally, potential confounding factors related to differences in bleeding etiology, severity of hemorrhage, and concomitant treatments could not be fully controlled at the overview level, as the analysis relied on aggregated data reported in the included systematic reviews.

CONCLUSION

Current high-quality evidence, largely influenced by the HALT-IT trial, does not demonstrate a mortality benefit of tranexamic acid in upper gastrointestinal bleeding. Although earlier smaller trials suggested potential reductions in mortality and rebleeding, these signals were not consistently confirmed in large-scale contemporary data. Evidence regarding rebleeding and need for intervention remains mixed, and concerns persist regarding possible dose-related thromboembolic risk, particularly with prolonged high-dose regimens. Therefore, routine use of tranexamic acid in

upper gastrointestinal bleeding is not supported by the strongest available evidence, and this conclusion is consistent with the 2022 Indonesian consensus, which advises against its routine administration. Its use, if considered, should be individualized and carefully weighed against potential risks. Future research should focus on clarifying optimal timing, dosing strategies, and identifying specific patient subgroups, such as variceal versus non-variceal bleeding, in whom benefit may be more likely. Further evaluation of safety outcomes, particularly thromboembolic complications, is essential to better define its role in clinical practice.

AVAILABILITY OF DATA

All data used in this review were sourced from previously published systematic reviews. The extracted data and database search strategies can be provided upon reasonable request. To obtain access, please contact the corresponding author via email.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest related to this study. No financial, professional, or personal affiliations influenced the conduct, interpretation, or reporting of the findings presented in this review.

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REFERENCES

1. Kamboj AK, Hoversten P, Leggett CL. Upper gastrointestinal bleeding: Etiologies and management. Mayo Clin Proc. 2019;94(4):697–703.
2. Wilkins T, Wheeler B, Carpenter M. Upper Gastrointestinal bleeding in adults: Evaluation and management. Am Fam Physician. 2020;101(5):294–300.
3. Orpen-Palmer J, Stanley AJ. Update on the management of upper gastrointestinal bleeding. BMJ Med. 2022;1(1):e000202.
4. Merza N, Masoud AT. Trends of upper gastrointestinal bleeding mortality in the United States before and during the COVID-19 era: Estimates from the centers for disease control WONDER database. Gastroenterol Res. 2023;16(3):165–70.
5. Aljarad Z, Mobayed BB. The mortality rate among patients with acute upper GI bleeding (with/without EGD) at Aleppo University Hospital: A retrospective study. Ann Med Surg. 2021;71:102958.
6. Moledina SM, Komba E. Risk factors for mortality among patients admitted with upper gastrointestinal bleeding at a tertiary hospital: a prospective cohort study. BMC Gastroenterol. 2017;17(1):165.
7. Sayuti M, Aulia I. Epidemiology and etiology of bleeding gastrointestinal tract at Cut Meutia General Hospital, North Aceh, 2019-2021. J Med Nusant. 2023;1(3):69–74.
8. Bennett C, Klingenberg SL, Langholz E, et al. Tranexamic acid for upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2014;2014(11): CD006640.
9. Brenner A, Afolabi A, Ahmad SM, et al. Tranexamic acid for acute gastrointestinal bleeding (the HALT-IT trial): statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial. Trials. 2019;20(1):467.
10. Burke E, Harkins P, Ahmed I. Is there a role for tranexamic acid in upper GI bleeding? A systematic review and meta-analysis. Surg Res Pract. 2021;2021:8876991.
11. Cai J, Ribkoff J, Olson S, et al. The many roles of tranexamic acid: An overview of the clinical indications for TXA in medical and surgical patients. Eur J Haematol. 2019;104(2):79.
12. Ker K, Mansukhani R, Shakur-Still H, et al. Tranexamic acid for gastrointestinal bleeding: can a reduction in the risk of death be discounted? A systematic review and meta-analysis of individual patient data from 64 724 bleeding patients. BMJ Open. 2023;13(2):e059982.
13. Dionne JC, Oczkowski SJW, Hunt BJ, et al. Tranexamic acid in gastrointestinal bleeding: A systematic review and meta-analysis. Crit Care Med. 2022;50(3):E313–9.
14. Lee PL, Yang KS, Tsai HW, et al. Tranexamic acid for gastrointestinal bleeding: A systematic review with meta-analysis of randomized clinical trials. Am J Emerg Med. 2021;45:269–79.
15. Scherdin Y, Halldestam I, Redeen S. Incidence and mortality related to gastrointestinal bleeding, and the effect of tranexamic acid on gastrointestinal bleeding. Gastroenterol Res. 2021;14(3):165–72.
16. Indonesian Society of Gastroenterology. National consensus on management of non-variceal upper gastrointestinal tract bleeding in Indonesia. Acta Med Indones. 2022;46(2):163–71.
17. O'Donnell O, Gallagher C, Davey MG, et al. A

systematic review and meta-analysis assessing the use of tranexamic acid (TXA) in acute gastrointestinal bleeding. Ir J Med Sci. 193(2).
18. Kamal F, Khan MA, Lee-Smith W, et al. Efficacy and safety of tranexamic acid in acute upper gastrointestinal bleeding: meta-analysis of randomised controlled trials. Scand J Gastroenterol. 2020;55(12):1390–7.
19. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:4008.
20. Nutbeam T. In adult patients presenting as emergencies with upper gastrointestinal bleeding, does tranexamic acid decrease mortality? African J Emerg Med. 2015;5(2):85–92.
21. Twum-Barimah E, Abdelgadir IS, Gordon M, et al. Tranexamic acid for upper gastrointestinal bleeding: A systematic review and meta-analysis of randomized controlled trials. Gastroenterology. 2020;158(6):S-583.
22. Kan SW, Tan YP, Tay MZ, et al. Tranexamic acid with acid suppression versus acid suppression alone as therapy for upper gastrointestinal bleeding: A meta-analysis of randomized controlled trials. J Gastroenterol Hepatol. 2024;1–6.
23. Lau LHS, Sung JJY. Treatment of upper gastrointestinal bleeding in 2020: New techniques and outcomes. Dig Endosc. 2021;33(1):83–94.
24. Colomina MJ, Contreras L, Guilabert P, et al. Clinical use of tranexamic acid: evidence and controversies. Brazilian J Anesthesiol (English Ed. 2022;72(6):795–812.
25. Roberts I, Shakur-Still H, Afolabi A, et al. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. Lancet. 2020;395(10241):1927–36.
26. Roberts I, Prieto-merino D, Manno D. Mechanism of action of tranexamic acid in bleeding trauma patients : an exploratory analysis of data from the CRASH-2 trial. 2014;1–5.
27. Rațiu I, Lupușoru R, Popescu A, et al. Acute gastrointestinal bleeding: A comparison between variceal and nonvariceal gastrointestinal bleeding. Medicine (Baltimore). 2022;(October).
28. Franchini M, Mannucci PM. The never-ending success story of tranexamic acid in acquired bleeding. Haematologica. 2020;105(5):1201–5.
29. Meneses E, Boneva D, McKenney M, et al. Massive transfusion protocol in the adult trauma population. Am J Emerg Med. 2020;38(12):2661–6.

SUPPLEMENTARY TABLE.

Question	Bennet 2014	Twum 2020	Kamal 2020	Burke 2021	Lee 2021	Kan 2024
Did the research questions and inclusion criteria for the review include the components of PICO?	YES	YES	YES	YES	YES	YES
Did the report of the review contain an explicit statement that the review methods were established before the conduct of the review, and did the report justify any significant deviations from the protocol?	YES	YES	YES	YES	YES	YES
Did the review authors explain their selection of the study designs for inclusion in the review?	YES	PARTIAL YES	NO	YES	PARTIAL YES	NO
Did the review authors use a comprehensive literature search strategy?	YES	YES	YES	NO	YES	YES
Did the review authors perform study selection in duplicate?	YES	YES	YES	YES	YES	YES
Did the review authors perform data extraction in duplicate?	YES	YES	YES	YES	YES	YES
Did the review authors provide a list of excluded studies and justify the exclusions?	YES	YES	NO	YES	YES	NO
Did the review authors describe the included studies in adequate detail?	YES	YES	YES	YES	YES	YES
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	YES	YES	YES	YES	YES	YES
Did the review authors report on the sources of funding for the studies included in the review?	YES	YES	NO	NO	NO	NO
If a meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results?	YES	YES	YES	YES	YES	YES
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	YES	YES	YES	YES	YES	YES
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	YES	YES	YES	YES	YES	YES
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	YES	YES	YES	YES	YES	YES
If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	YES	YES	YES	YES	NO	YES
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	PARTIAL YES	YES	PARTIAL YES	YES	YES	YES