

Supplementary Material Table 1. PICO Framework

Population (P)	Intervention (I)	Comparison (C)	Outcome (O)
Patients with non-variceal upper GI bleeding	Tranexamic acid	Placebo	Management of bleeding
Type of Clinical Question	Intervention		
Study Design	Meta-analyses		

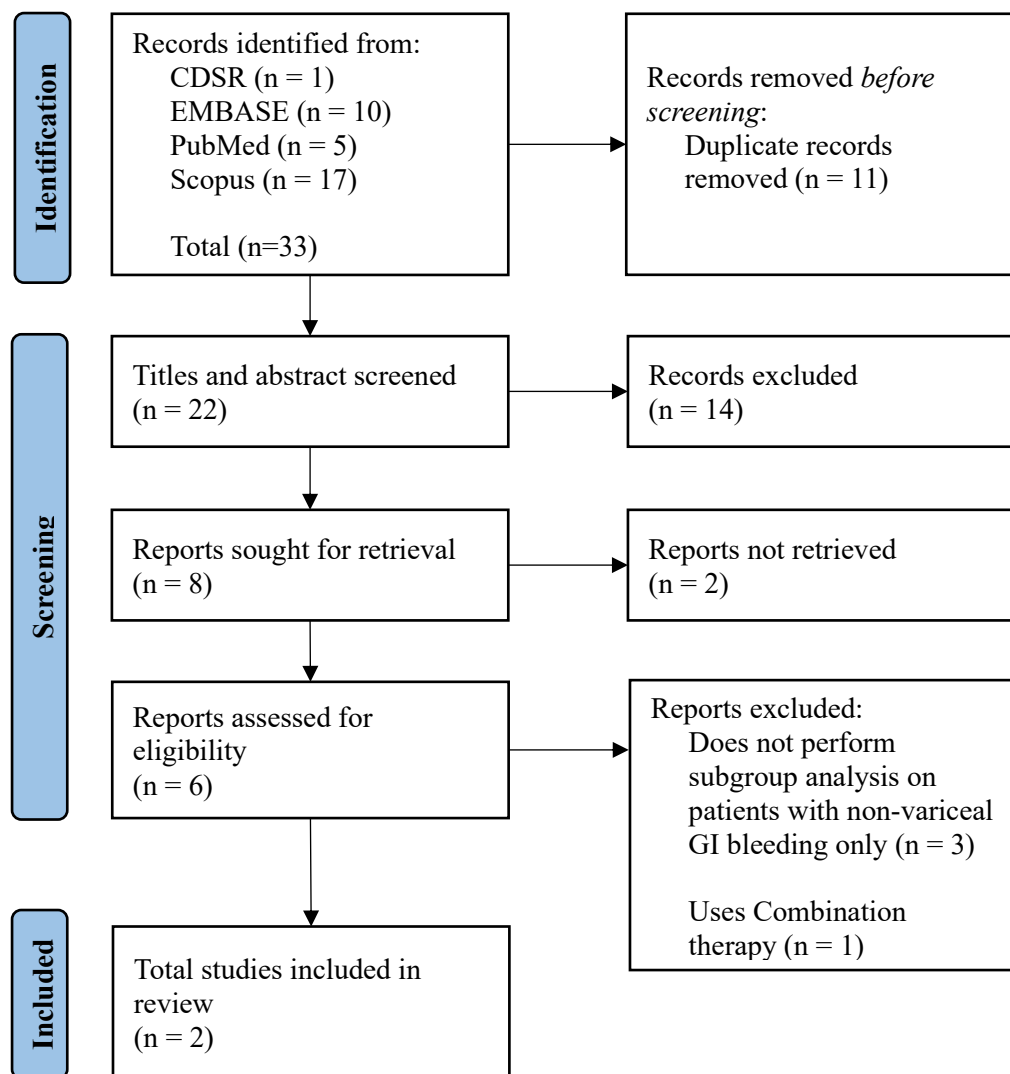
Supplementary Material Table 2. Literature Search Strategy

Database	Time of Search	Search Strategy	Records Found
CDSR	28/06/2023 14.14	((("upper GI") OR ("upper-GI") OR ("upper") NEXT ("GI") OR ("gastrointestinal")) AND ("bleed*") OR ("hemorrhage")) NOT ("varice*")) AND ("tranexamic acid") Filter on meta-analysis and publication date for the last 10 years	1
EMBASE	28/06/2023 14.18	((upper AND gi) OR (upper gi) OR (upper AND (gi OR gastrointestin*))) AND (bleed* OR hemorrhag*) NOT varice* AND tranexamic acid AND [meta analysis]/lim AND ([english]/lim OR [indonesian]/lim) Filter on publication date for the last 10 years	10
PubMed	28/06/2023 14.20	((("upper GI") OR (upper-GI) OR ((upper) AND ((GI) OR (gastrointestin*))) AND ((bleed*) OR (hemorrhag*)) NOT (varice*)) AND (tranexamic acid) Filter on meta-analysis and publication date for the last 10 years	5
Scopus	28/06/2023 14.25	TITLE-ABS-KEY (((("upper GI") OR ("upper-GI") OR ("upper") AND ((GI) OR ("gastrointestin*")) AND ("bleed*") OR ("hemorrhag*")) AND NOT ("varice*")) AND TITLE ("tranexamic acid")) Filter on reviews and publication date for the last 10 years	17

Supplementary Material Table 3. Inclusion and Exclusion Criteria

Element	Inclusion Criteria	Exclusion Criteria
Study design/characteristic	• Meta-analysis of RCTs • Meta-analysis of systematic reviews of RCTs	• Not written in English or Bahasa Indonesia
Population	• Patients with upper GI bleeding	• Patients <18 years old of age • Analyses patients with variceal upper GI bleeding
Intervention	• Tranexamic acid	• Combination therapy
Comparator	• Placebo	• No placebo used in the control group
Outcome	• Mortality • Uncontrolled bleeding • Rebleeding • Need for transfusion • Thromboembolic event	

RCT: randomized controlled trial; GI: gastrointestinal.



Supplementary Material Figure 1. Study Selection Flowchart

Supplementary Material Table 4. Study Characteristics of Selected Articles

No.	Author (year)	Population characteristics		Study Characteristics						Main Result
		Size	Age (year)	Study design	Location	Inclusion criteria	Intervention (I)	Comparator (C)	Outcome parameters (O)	
1	Kamal, et al (2020) ⁹	Total: 14100 patients from 12 RCTs	Patients under 18 years of age are excluded	Meta-analysis of RCTs	Albania, Australia, Egypt, Georgia, Ireland, Malaysia, Nepal, Nigeria, Pakistan, Papua New Guinea, Romania, Saudi Arabia, Spain, Sudan, and UK	RCTs that compared tranexamic acid with placebo in UGIB. Studies that only included patients under 18 years of age, non-randomized trials and review articles are excluded	Tranexamic acid, oral or IV, 2 – 4.5 g daily	Placebo	Non-variceal UGIB subgroup: Mortality	Subgroup analysis including only those patients with non-variceal bleeding showed no difference in mortality; (RR 0.84; 95% CI; 0.63–1.11, I ² = 2%)
2	Twum-Barimah, et al (2019) ¹⁰	Non-Variceal UGIB Subgroup: 829 patients from 5 RCTs	Include all age group, but analysis for the pediatric patients is separated	Meta-analysis of RCTs	Australia, Iran, Russia, Sweden, UK.	RCTs that compared tranexamic acid use in UGIB, either variceal or nonvariceal bleeding irrespective of the severity, to placebo across all age groups.	Tranexamic acid, oral or IV, 2.25 – 6 g daily	Placebo	Non-variceal UGIB subgroup: Mortality	Beneficial effect of tranexamic acid on mortality was seen in studies that investigated only patients with nonvariceal bleeding (RR 0.45; 95% CI 0.23-0.88, P = 0.02; I ² = 0%)

Supplementary Material Table 5. Critical Appraisal of Included Systematic Review based on OCEBM

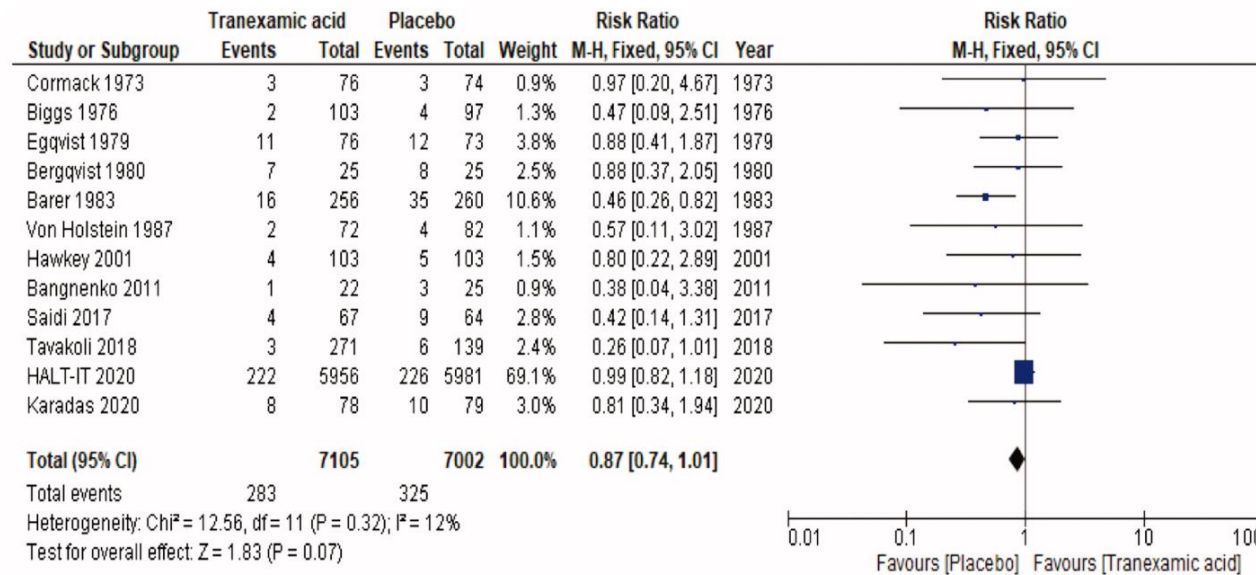
Appraisal Component	Kamal, et al (2020)⁹	Twum-Barimah, et al (2019)¹⁰	Comments
Level of evidence*	Level 1	Level 1	Both are systematic review of RCTs
VALIDITY			
Were the research question and PICO defined clearly	Yes	Yes	Kamal, et al (2020): PICO stated in methods. P: Adult patients with UGIB. I: Tranexamic acid. O: Placebo. O: Efficacy and adverse events Twum-Barimah, et al (2019): PICO stated in methods. P: Patients with UGIB. I: Tranexamic acid. O: Placebo. O: Efficacy and adverse events
Is it unlikely that important, relevant studies were missed?	Yes	Yes	Kamal, et el (2020): Included Pubmed & MEDLINE, Embase, Web of Science Core Collection and CENTRAL up to June 25, 2020 using specific keywords clearly stated and MeSH words, without restrictions of publishing time and language. Twum-Barimah, et al (2019): Included PubMed, Embase, CINAHL and CENTRAL up to December 10, 2019 using specific

			keywords clearly stated and MeSH words, without restrictions of publishing time and language. Hand searching was done for gray literature.
Were the criteria used to select articles for inclusion appropriate?	Yes	Yes	Kamal, et al (2020): Clearly stated inclusion criteria and appropriate for PICO: only RCTs that compared tranexamic acid with placebo in UGIB. We excluded studies that only included patients under 18 years of age, non-randomised trials and review articles. Twum-Barimah, et al (2019): Randomised controlled trials (RCTs) that compared tranexamic acid use in upper gastrointestinal bleeding to other treatment modalities for upper gastrointestinal bleeding across all age groups were eligible for inclusion. Participants of the primary studies were patients with either variceal or nonvariceal bleeding irrespective of the severity of bleeding.
Were the included studies sufficiently valid for the type of question asked?	Yes	Yes	Both studies: Quality of studies included were assessed using the Cochrane tool for bias risk assessment by two investigators. Non-randomized, non-blinded, incomplete outcome data, and selective outcome reporting.

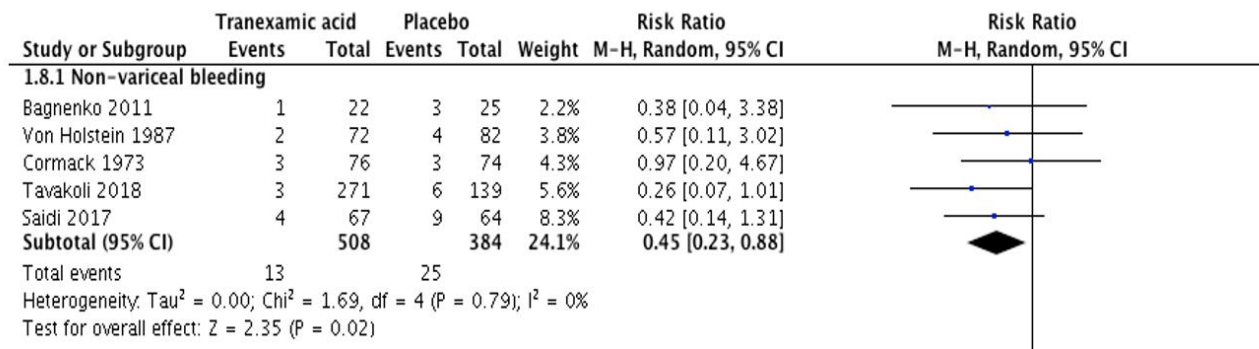
Were the results similar from study to study?	Yes	Yes	Kamal, et el (2020): Heterogeneity between studies were low for outcomes of mortality in UGIB patients (I^2 =12%) and non-variceal UGIB patients only subgroup analysis (I^2 = 2%). Twum-Barimah, et al (2019): Heterogeneity between studies were low for outcomes of mortality in UGIB patients (I^2 =0%) and non-variceal UGIB patients only subgroup analysis (I^2 = 0%).
IMPORTANCE			
What is the result?	Kamal, et el (2020): Supplementary Material Figure 2 showcases the forest plot of the meta-analysis by Kamal, et al. which shows the analysis for 14,107 UGIB patients from 12 RCTs which revealed tranexamic acid use does not had a clinically beneficial impact on patients’ outcome with the (RR 0.84; 95% CI: 0.63–1.11; I^2 = 2%). The study also provides subgroup analysis for non-variceal UGIB patients which revealed tranexamic acid use does not had a clinically beneficial impact on patients’ outcome with the (RR 0.84; 95% CI: 0.63–1.11; I^2 = 2%). However, the table was not accessible. Twum-Barimah, et al (2019): Supplementary Material Figure 3 showcases the forest plot of the meta-analysis by Twum-Barimah, et al. which shows the subgroup analysis for 829 non-variceal UGIB patients from 5 RCTs which revealed tranexamic acid use had a clinically beneficial impact on reducing mortality in non-variceal UGIB patients (RR 0.45; 95% CI: 0.23-0.88, p = 0.02; I^2 = 0%)		
APPLICABILITY			

Were the study patients similar to your own?	Yes	Yes	Both studies included patients with general UGIB, but provided subgroup analysis for non-variceal UGIB patients. Both studies also included data from various sites, mostly from USA and Europe. However, some RCTs included in the studies does not have separate analysis on non-variceal UGIB patient only.
Is the treatment feasible in my setting?	Yes	Yes	Both studies use tranexamic acid as the treatment, which is readily available in Indonesia.
Will this evidence make a clinically important impact on your conclusions about what to offer or tell your patient?	No	No	Kamal, et al (2020): The meta-analysis revealed there is no difference in mortality in non-variceal UGIB patients with tranexamic acid use compared to placebo. Twum-Barimah, et al (2019): The meta-analysis revealed tranexamic acid reduced non-variceal UGIB patients' risk of mortality compared to placebo. However, the result of all RCTs included in this meta-analysis reveals no significant difference in risk of mortality in non-variceal UGIB patients with tranexamic acid use compared to placebo.

**based on OCEBM 2011 guidelines for level of evidence*



Supplementary Material Figure 2: Forest plot of RCTs of tranexamic acid versus placebo in UGIB patients (Kamal, et al: 2020).⁹



Supplementary Material Figure 3: Forest plot of RCTs of tranexamic acid versus placebo in only non-variceal UGIB patients Subgroup (Twum-Barimah, et al: 2019).¹⁰

Supplementary Material Table 6. PICO Criteria Relevance of Included Study

No.	Author	Similarity in population	Similarity in intervention	Similarity in comparator	Similarity in outcome
1.	Kamal, et al (2020)	+/-	+	+	+
2.	Twum-Barimah, et al (2019)	+/-	+	+	+

+ : *high similarity*

+/- : *uncertain similarity*