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Antifibrinolytics (lysine analogues) for the prevention of bleeding in people with haematological disorders

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Editors: Cochrane Central Editorial Service

Corresponding author: Rita Champaneria (rita.solanki@ndcls.ox.ac.uk)
Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK

Rita Champaneria [1] [2]Lise J Estcourt [1] [3] [4]Louise Geneen [1] [2]Susan J Brunskill [1] [2]Carolyn Dorée [1] [2]
Simon J Stanworth [3] [4] [5]Michael JR Desborough [1] [3] [4] [5]

[1] Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK

[2] Nuffield Department of Clinical Laboratory Sciences, University of Oxford, Oxford, UK

[3] Haematology/Transfusion Medicine, NHS Blood and Transplant, Oxford, UK

[4] Radcliffe Department of Medicine, University of Oxford, Oxford, UK

[5] Department of Haematology, Oxford University Hospitals NHS Trust, Oxford, UK

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Abstract

Rationale

People with haematological disorders are frequently at risk of severe or life-threatening bleeding as a result of thrombocytopenia (reduced platelet count). This is despite the routine use of prophylactic platelet transfusions to prevent bleeding once the platelet count falls below a certain threshold. Platelet transfusions are not without risk and adverse events may be life-threatening. A possible adjunct to prophylactic platelet transfusions is the use of antifibrinolytics, specifically the lysine analogues tranexamic acid (TXA) and epsilon aminocaproic acid (EACA). This is an update of a Cochrane review last published in 2016 (with database searches conducted on 7 March 2016).

Objectives

To determine the benefits and harms of antifibrinolytics (lysine analogues) in preventing bleeding in people with haematological disorders.

Search methods

We searched CENTRAL, MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Transfusion Evidence Library, and ongoing trial databases on 21 January 2025. We handsearched the reference lists of all identified randomised controlled trials (RCTs). We contacted the authors of relevant studies, study groups, and experts worldwide known to be active in the field to request information about unpublished material or further information on ongoing studies.

Eligibility criteria

We included RCTs in people with haematological disorders who required prophylactic platelet transfusions to prevent bleeding. We only included RCTs in which the interventions were the lysine analogues TXA or EACA.

Outcomes

We assessed bleeding severity using the World Health Organization (WHO) bleeding scale (ordinal grades 0 to 4, with higher grades indicating more severe bleeding), which has been widely applied in thrombocytopenia studies. The outcomes prioritised for the summary of findings tables were: number of participants with grade 2 bleeding or higher; number of participants with grade 3 bleeding or higher; number of participants with any thromboembolism; all-cause mortality; and adverse events attributable to antifibrinolytic drugs. We provide results only for these outcomes below.

Risk of bias

We used Cochrane's risk of bias 2 (RoB 2) tool. We used this tool to re-assess the previously included trials.

Synthesis methods

For this update, two review authors independently selected trials for inclusion, assessed methodological quality and risk of bias, and extracted data. We used fixed-effect models for the meta-analysis. We analysed dichotomous outcomes using risk ratios (RRs) with 95% confidence intervals (CIs), and the Peto odds ratio (Peto OR) for outcomes with very low event rates (< 3% in both arms). We assessed the certainty of the evidence using the GRADE approach.

Included studies

We included eight RCTs (four newly included studies plus four from the previous versions) with a total of 1041 participants in this review update. Six trials compared TXA to placebo, one trial compared EACA to no EACA, and one trial compared EACA to standard platelet transfusion. We found no trials comparing TXA to EACA. Seven trials recruited adults, while one enroled children.

Synthesis of results

Tranexamic acid (TXA) versus placebo

There may be no difference between TXA and placebo in the risk of experiencing grade 2 bleeding or higher, grade 3 bleeding or higher, thromboembolism, death, and drug-related adverse events, although the certainty of the evidence varied from very low to moderate for these outcomes: grade 2 bleeding or higher: RR 0.89, 95% CI 0.75 to 1.05; I^2 = 7%; 3 studies, 894 participants; moderate-certainty evidence; grade 3 bleeding or higher: RR 1.07, 95% CI 0.51 to 2.22; I^2 = 6%; 3 studies, 894 participants; low-certainty evidence; any thromboembolism: Peto OR 0.85, 95% CI 0.39 to 1.86; I^2 = 0%; 5 studies, 984 participants; low-certainty evidence; all-cause mortality: Peto OR 1.50, 95% CI 0.62 to 3.63; I^2 = 37%; 3 studies, 930 participants; very low-certainty evidence; and number of adverse events attributable to antifibrinolytic drugs: Peto OR 2.24, 95% CI 0.64 to 7.78; I^2 = 0%; 3 studies, 949 participants; very low-certainty evidence.

Epsilon aminocaproic acid (EACA) versus no EACA

The single study addressing this comparison did not report bleeding severity in a form suitable for analysis, and did not report on the number of participants with any thromboembolism or all-cause mortality. The study reported that no patient died of thrombosis. There was insufficient evidence to analyse adverse events attributable to antifibrinolytic drugs.

Authors' conclusions

For people with thrombocytopenia and haematological malignancies, TXA probably makes little to no difference to clinically significant bleeding (i.e. grade 2 or higher), and may make little to no difference to severe or life-threatening bleeding (i.e. grade 3 or higher) or any thromboembolism. The evidence is of very low certainty for all-cause mortality and serious adverse events attributable to antifibrinolytic drugs.

For EACA compared to no EACA, there are insufficient data to assess clinically significant bleeding, life-threatening bleeding, any thromboembolism, all-cause mortality, and serious adverse events.

Those making decisions about administration of prophylactic TXA to people with thrombocytopenia and haematological malignancies should consider that current evidence does not show a benefit or harm for TXA for preventing clinically significant or life-threatening bleeding.

Funding

This Cochrane review had no dedicated funding.

Registration

Protocol (2012): DOI: 10.1002/14651858.CD009733.

Original review (2013): DOI: 10.1002/14651858.CD009733.pub2.

Review update (2016): DOI: 10.1002/14651858.CD009733.pub3.kljkj

Plain language summary

Can antifibrinolytics (medications that help to stabilise the clots that form after bleeding) stop bleeding in people with thrombocytopenia (low platelet count) and blood disorders?

Key messages

- Antifibrinolytics help prevent bleeding by stopping blood clots from breaking down too quickly. Tranexamic acid (TXA) and epsilon aminocaproic acid (EACA) are two antifibrinolytic medications.
- Compared to placebo (an inactive 'dummy' medicine), TXA probably makes little or no difference to the number of people with thrombocytopenia and blood disorders who experience moderate or worse than moderate bleeding. It may make little or no difference to the number who experience severe, life-threatening bleeding, or dangerous blood clots in the blood vessels (thromboembolism).
- We do not know if EACA helps because there was a lack of data.

What are haematological disorders?

Haematological (i.e. blood) disorders are conditions that affect the blood and blood-forming organs (such as bone marrow). They disrupt the blood's normal functions of oxygen transport, clotting, and immunity. Some of these blood disorders are not cancer and may cause problems like anaemia or sickle cell anaemia. Others are cancers of the blood, such as leukaemia, lymphoma, and myeloma.

How are haematological disorders treated?

People with haematological (blood) cancers and other blood disorders are frequently at risk of severe or life-threatening bleeding from having low platelet counts (thrombocytopenia). When the number of platelets in the blood is low, the blood does not clot as it should, so people may bruise or bleed more easily. This may be from bone marrow failure due to an underlying blood disorder, but also from the toxic effect of treatment (chemotherapy) on the bone marrow.

People with low platelets may be given platelet transfusions: that is, receive platelets from donated blood to help prevent bleeding. These transfusions carry risks, ranging from mild reactions such as fevers, to more serious or even life-threatening consequences. These include infections transmitted to the patient from the transfused platelets, despite stringent attempts to prevent this.

What did we want to find out?

Clearly, ways to safely prevent bleeding in people with thrombocytopenia whilst also minimising exposure to transfused platelets would be welcome. One possible way of achieving these goals is the use of antifibrinolytics (also known as lysine analogues): tranexamic acid (TXA) and epsilon aminocaproic acid (EACA).

These medications help to stabilise the clots that form after bleeding, therefore reducing the chances of further bleeding as well as the need for transfusing platelets. There may be risks associated with the use of TXA and EACA: the most important is the increased risk of forming unwanted blood clots (such as deep vein thrombosis (DVT)), which could be potentially life-threatening.

We wanted to find out if TXA and EACA are better than placebo (an inactive 'dummy' medicine) or no medication at reducing the number of people who:

- experienced moderate bleeding or worse;
- experienced severe or life-threatening bleeding;
- experienced any type of thromboembolism (dangerous blood clots);
- died.

We also wanted to find out if TXA or EACA caused any serious unwanted, harmful effects.

What did we do?

We searched for studies that compared TXA or EACA with placebo or no treatment in people with haematological (blood) disorders who have a low platelet count and would usually be treated with platelet transfusions. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and the number of participants involved.

What did we find?

We found eight studies with a total of 1041 participants. Six studies compared TXA to placebo, one compared EACA to no EACA, and one compared EACA to standard platelet transfusion. Seven studies were in adults and one was in children. Five studies were funded by governments, universities, or other non-pharmaceutical organisations; one study received funding from a pharmaceutical company; and the remaining two studies did not provide information about funding.

Main results

In people with haematological disorders who have a low platelet count, tranexamic acid (TXA) compared to placebo:

- probably makes little or no difference to the number who experience moderate or worse than moderate bleeding;
- may make little or no difference to the number who experience severe, life-threatening bleeding, or dangerous blood clots in the blood vessels (thromboembolism).

There was not enough evidence to reach conclusions about the effect of TXA on the risk of death or the risk of serious side effects.

The two studies that looked at epsilon aminocaproic acid (EACA) did not report enough information to allow us to analyse their results.

What are the limitations of the evidence?

In general, we have little to no confidence in the evidence because there were too few studies to be certain about the results of our outcomes. In addition, some of the events we were looking for (e.g. death, dangerous blood clots) happened in very few people, which makes the results uncertain. These limitations mean it is difficult to draw firm conclusions about the effectiveness and safety of antifibrinolytic medications.

How current is this evidence?

The evidence is current to January 2025. This is an update of a review last published in 2016.

Summary of findings

Summary of findings 1

Tranexamic acid (TXA) versus placebo

Tranexamic acid (TXA) compared to placebo for haematological malignancies

Patient or population: haematological malignancies

Setting: hospital

Intervention: tranexamic acid (TXA)

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with TXA				
Number of participants with grade 2 bleeding or higher	401 per 1000	**357 per 1000** (301 to 421)	**RR 0.89** (0.75 to 1.05)	894 (3 RCTs)	⨁⨁⨁◯ **Moderate**[a,b,c]	TXA probably results in little to no difference in grade 2 bleeding or higher.
Number of participants with grade 3 bleeding or higher	29 per 1000	**31 per 1000** (15 to 65)	**RR 1.07** (0.51 to 2.22)	894 (3 RCTs)	⨁⨁◯◯ **Low**[d,e,f]	TXA may result in little to no difference in grade 3 bleeding or higher.
Number of participants with any thromboembolism	28 per 1000	24 per 1000 (11 to 52)	**POR 0.85** (0.39 to 1.86)[h]	984 (5 RCTs)	⨁⨁◯◯ **Low**[f,g]	TXA may result in little to no difference in the number of participants with any thromboembolism.
All-cause mortality	17 per 1000	**26 per 1000** (11 to 60)	**POR 1.50** (0.62 to 3.63)[h]	930 (3 RCTs)	⨁◯◯◯ **Very low**[d,i,j]	The evidence is very uncertain about the effect of TXA on all-cause mortality.
Adverse events attributable to antifibrinolytic drugs	6 per 1000	**14 per 1000** (4 to 47)	**POR 2.24** (0.64 to 7.78)[h]	949 (3 RCTs)	⨁◯◯◯ **Very low**[d,j]	The evidence is very uncertain about the effect of TXA on adverse events attributable to antifibrinolytic drugs.

All reported data are from the 30-day time point.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **POR:** Peto odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Two of the three contributing trials were at low risk of bias across the board and accounted for 97.9% of the weight.

[b]Minimal heterogeneity: I^2 = 7%

[c]Downgraded once for imprecision due to wide confidence intervals crossing the line of no effect, incorporating both benefit and harm.

[d]Only two trials contributed data for this analysis and both were at low risk of bias. The third trial had 0 cases, and therefore did not contribute.

[e]Minimal heterogeneity: I^2 = 6%

[f]Downgraded twice for imprecision due to very wide confidence intervals crossing the line of no effect, incorporating significant benefit and significant harm.

[g]Only two trials contributed data for this analysis and both were at low risk of bias. The other three trials had 0 cases, and therefore did not contribute.

[h]These results use Peto OR due to the low event rate (< 3% in each arm).

[i]Downgraded once for inconsistency, as I^2 = 37% (moderate heterogeneity). Visual inspection of the forest plot shows that contributing trials have opposing directions of effect, although both cross the line of no effect.

[j]Downgraded three times for imprecision due to extremely wide confidence intervals crossing the line of no effect, incorporating significant benefit and significant harm. We also used a random-effects model for this analysis due to moderate heterogeneity.

Summary of findings 2

Epsilon aminocaproic acid (EACA) versus no EACA

Epsilon aminocaproic acid (EACA) compared to no EACA for haematological malignancies

Patient or population: haematological malignancies

Setting: hospital

Intervention: epsilon aminocaproic acid (EACA)

Comparison: no EACA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no EACA	Risk with EACA				
Number of participants with grade 2 bleeding or higher	Not reported					Gallardo 1983 reported 'capillary bleeding' and 'major bleeding', but these data could not be analysed (see Table 1).
Number of participants with grade 3 bleeding or higher	Not reported					
Number of participants with any thromboembolism	Not reported					
All-cause mortality	Not reported					
Mortality – due to thromboembolism	0 per 1000	**0 per 1000** (0 to 0)	**RD 0.00** (-0.19 to 0.19)	18 (1 RCT)	⨁◯◯◯ **Very low**[a,b]	The evidence is very uncertain about the effect of EACA on mortality due to thromboembolism. No other mortality data were available (e.g. all-cause mortality).
Adverse events attributable to antifibrinolytic drugs	Not reported					Gallardo 1983 stated side effects were minimal but provided no further information.

All reported data are from the 30-day time point.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RD:** risk difference; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded for risk of bias due to lack of information regarding one "inevaluable" participant (given the small sample size, this could impact the outcome).
[b]Downgraded for imprecision due to the sample size being significantly below the optimal information size (OIS) for this outcome.

Background

Description of the condition

People with haematological disorders are frequently at risk of severe or life-threatening bleeding as a result of thrombocytopenia (reduced platelet count). This is commonly a result of the underlying pathology, a side effect of treatment with chemotherapeutic agents, or both. People are administered therapeutic platelet transfusions to treat bleeding and prophylactic platelet transfusions to prevent bleeding once the platelet count falls below a certain threshold (10×10^9/L, or higher if the risk of haemorrhage is raised, e.g. sepsis or the presence of another bleeding diathesis) [1]. However, whilst platelet transfusion reduces the number of patients with clinically significant bleeding events from 50% to 43% [2], this still leaves a significant number of patients with bleeding symptoms.

Platelet transfusions are not without risks. Adverse events may range from mild reactions, such as fever (one in five transfusions), to more serious and even life-threatening events such as bacterial sepsis from transfusion-transmitted infection, or transfusion-related acute lung injury (TRALI) [3]. People may also become refractory to platelet transfusions; the incidence increases with the number of platelet transfusions administered [4]. Once refractory, the ability to treat bleeding with platelet transfusions becomes more difficult, requiring expensive, specially matched platelets that can be difficult to source. Furthermore, the financial cost of platelet transfusions is considerable. Around 292,000 adult doses of platelets are issued in the United Kingdom (UK) each year [3], at an annual cost of approximately GBP 80.4 million [5]; up to two-thirds (67%) of these are given to people with haematological malignancies [6, 7, 8]. Demand for platelets for transfusion sometimes exceeds supply, a shortfall that was particularly apparent in the UK during the COVID-19 pandemic and has continued thereafter [9, 10].

Interventions that can safely prevent bleeding in people with thrombocytopenia, while minimising exposure to allogeneic platelets and reducing financial costs, would be welcomed [11]. One possible adjunct, or even an alternative, to prophylactic platelet transfusions is the use of antifibrinolytics, specifically lysine analogues, such as tranexamic acid (TXA) and epsilon aminocaproic acid (EACA).

This systematic review has been designed to establish the safety and effectiveness of these agents specifically in people with haematological disorders who are at risk of thrombocytopenia and bleeding, due to the disorder itself, its treatment, or both.

Description of the intervention and how it might work

TXA and EACA are synthetic analogues of the amino acid lysine that act by blocking the lysine binding sites on plasminogen. This inhibits the formation of plasmin and therefore prevents fibrinolysis, leading to improved haemostasis [12]. Laboratory studies demonstrate that TXA is approximately 10 times more potent than aminocaproic acid and binds much more strongly to the sites on the plasminogen molecule [13]. It is plausible that if these lysine analogues are effective and safe, the bleeding risk in people with haematological disorders could be reduced, and the requirement for prophylactic platelet transfusions could be minimised.

Although TXA and EACA have been shown to be effective at reducing bleeding in many patient groups [14, 15], there is a concern that these drugs may increase the rate of thromboembolism. While most trials have not shown an increase in thromboembolism risk, a large trial in patients with gastrointestinal haemorrhage found a significant increase in thrombotic risk when participants were given tranexamic acid rather than placebo [16]. This is particularly important in haematology patients, as patients with an underlying malignancy already have a higher rate of thromboembolic disease than the general population. The incidence of venous thromboembolism in people with haematological malignancy is reported as between 3% and 23.5% in different studies [17].

Why it is important to do this review

It is important to reduce the risk of bleeding in people with haematological disorders and thrombocytopenia as effectively and as safely as possible. The following key questions need to be addressed.

- How effective are lysine analogues in preventing bleeding in people with haematological disorders who are thrombocytopenic?
- Does the use of lysine analogues lead to a significant increase in the incidence of thromboembolism?

If lysine analogues are shown to be effective while demonstrating an acceptable safety profile, there would be a strong case for their routine use in people with haematological disorders at significant risk of severe thrombocytopenia.

This is an update of a Cochrane review first published in 2013 and updated in 2016 [18, 19]. Since then, results from two large trials (A-TREAT 2022 [20, 21, 22, 23, 24, 25, 26, 27, 28] and TREATT 2025 [29, 30, 31, 32, 33, 34, 35]) and two smaller ones have been published. Synthesising data from these trials with the existing evidence provides us with more information with which to answer these important research questions.

Objectives

To determine the benefits and harms of antifibrinolytics (lysine analogues) in preventing bleeding in people with haematological disorders.

Methods

Post-protocol changes to the review

We updated the methods section to be compliant with current Cochrane standards. We followed the Methodological Expectations of Cochrane Intervention Reviews (MECIR) guidelines when conducting the review and PRISMA 2020 for the reporting [36, 37].

We have made the following changes to the review since the publication of the protocol [18], the 2016 review update [19], or both.

- We decided to extract only 30-day data, as opposed to other time points, as this is the most clinically useful time point and the one most likely to be reported.
- In this update, we decided not to extract the outcome of laboratory analysis of fibrinolysis. We did not expect any of the included studies to report this outcome as it is a surrogate marker for efficacy, and there are now large trials reporting clinical effectiveness outcomes.
- We decided to present both fixed-effect and random-effects meta-analyses when statistical heterogeneity was moderate or substantial, defined as an I^2 value of 30% or greater. We used fixed-effect models to illustrate how study weighting reflects the precision of individual study estimates. We compared fixed-effect and random-effects results to assess the impact of heterogeneity on pooled estimates. We considered marked differences in results between the two models to be potentially indicative of small-study effects or publication bias.
- For dichotomous outcomes with zero events in one or both arms, we used risk differences (RDs). For outcomes with very low event rates (< 3% in both arms), we used the Peto odds ratio (POR) for meta-analysis.
- We modified our approach to assessing bleeding outcomes by explicitly adopting the World Health Organization's widely used bleeding scale, which runs from grade 0 to grade 4: grade 0 = no bleeding; grade 1 = mild bleeding (not requiring intervention); grade 2 = moderate bleeding (clinically significant bleeding but no major intervention required); grade 3 = severe bleeding (requiring transfusion or invasive intervention); grade 4 = life-threatening or fatal bleeding.
- We reduced the outcomes reported in the summary of findings tables to five key outcomes: the number of participants with grade 2 bleeding or higher; the number with grade 3 bleeding or higher; the number with 'any thromboembolism'; all-cause mortality; and adverse events attributable to antifibrinolytic drugs. We selected grade 2 bleeding or higher as the primary bleeding outcome because it represents the minimum threshold for clinically significant bleeding, in contrast to ‘any bleeding’, which includes clinically irrelevant events. Grade 3 bleeding or higher reflects bleeding severe enough to require clinical intervention, such as blood transfusion, and, although relatively uncommon, represents an important outcome. Most trials of tranexamic acid have not demonstrated an increased risk of thrombosis; however, one large trial in gastrointestinal haemorrhage reported an increased thrombotic risk in that patient group [16]. We therefore included thromboembolic events as a key safety outcome. All-cause mortality and serious adverse events attributable to antifibrinolytic agents are also important safety outcomes.
- Upon closer inspection, we established that Gallardo 1983 [38] compared EACA to no EACA, rather than EACA to placebo, as suggested in the 2016 review.

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), irrespective of language or publication status.

Types of participants

We included participants of any age with a haematological disorder (malignant or non-malignant) who were severely thrombocytopenic due to bone marrow failure (secondary to the disease or to its treatment) and required platelet transfusions. We excluded people with immune thrombocytopenic purpura (ITP) because they are not usually treated with platelet transfusions.

Types of interventions

We only reviewed antifibrinolytic agents that act by competitively inhibiting the conversion of plasminogen to plasmin (lysine analogues): namely, tranexamic acid (TXA) and epsilon aminocaproic acid (EACA). Aprotinin is a serine protease and has a different mechanism of action. We included the following comparisons:

- TXA versus placebo;

- EACA versus no EACA;
- EACA versus placebo;
- TXA versus EACA;
- EACA versus platelet transfusion.

We included any dose of the medication, administered either orally or intravenously.

Outcome measures

We included eligible trials even if they did not report any of the outcomes of this review.

Critical outcomes

- Bleeding, assessed up to 30 days after initiation of study treatment
  - WHO grade 2 bleeding or higher (clinically significant bleeding)
  - WHO grade 3 bleeding or higher (severe to life-threatening bleeding)
- Thromboembolism (any, arterial, and venous) up to 30 days after initiation of study treatment

Important outcomes

- 'Any' bleeding (WHO grade 1 bleeding or higher)
- Mortality (all-cause)
- Mortality (secondary to bleeding)
- Mortality (secondary to thromboembolism)
- Number of platelet transfusions or platelet components per participant
- Number of red cell transfusions or red cell components per participant
- Adverse events attributable to antifibrinolytic agents
- Adverse events attributable to transfusion (e.g. transfusion reactions, antibody development)
- Disseminated intravascular coagulation (DIC)
- Quality of life (QoL)

These outcomes were extracted up to 30 days after initiation of study treatment.

Search methods for identification of studies

We formulated search strategies in collaboration with the Cochrane Haematological Malignancies Group.

In order to reduce publication and retrieval bias, we did not restrict our search by language, date, or publication status.

Electronic searches

The Systematic Review Initiative Information Specialist (CD) formulated search strategies in collaboration with the Cochrane Haematological Malignancies Group. We searched the following electronic databases (see Supplementary material 1 for details):

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Issue 12 on 21 January 2025;
- MEDLINE (Ovid, from 1946 to 21 January 2025);
- Embase (Ovid, from 1974 to 21 January 2025);
- CINAHL (EBSCOhost, from 1937 to 21 January 2025);
- PubMed (NLM, e-publications only on 21 January 2025);
- LILACS (Bireme, from 1982 to 21 January 2025);
- Transfusion Evidence Library (Evidentia, from 1950 to 21 January 2025);
- Web of Science, Conference Proceedings Citation Index – Science (CPCI-S, Clarivate, from 1990 to 21 January 2025).

We combined searches in MEDLINE, Embase, and CINAHL with adaptations of the Cochrane RCT search filters, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* [39].

Databases of ongoing trials

We also searched the following ongoing trial databases (all years) on 21 January 2025 (see Supplementary material 1 for details):

- ClinicalTrials.gov;
- WHO International Clinical Trials Registry Platform (ICTRP);
- CENTRAL (in the Cochrane Library, Issue 12);
- HKU Clinical Trials Registry (HKUCTR).

Searching other resources

We augmented database searching with the following methods.

- Handsearching of reference lists
    - We checked references of all identified trials, relevant review articles, and current treatment guidelines for further literature.
    - We limited these searches to the 'first generation' reference lists.
- Personal contacts
    - We contacted authors of relevant studies, study groups, and experts worldwide who are known to be active in the field for unpublished material or further information on ongoing studies.
- Searching for post-publication amendments
    - We searched MEDLINE, Embase, and the Retraction Watch Database (via EndNote 2025: https://support.clarivate.com/Endnote/s/article/EndNote-20-Retraction-Alerts) for post-publication amendments (including errata, retractions, corrigenda, and expressions of concern) to all included studies and their related secondary published papers.

Data collection and analysis

Selection of studies

For this update, two review authors (MD, RC) independently screened the titles and abstracts of all potentially relevant papers. We excluded clearly irrelevant trials at this stage. We obtained the full texts of all potentially relevant trials. Working independently, two review authors (MD, RC) assessed these for eligibility against the criteria outlined above. We resolved all disagreements through discussion without the need for a third review author. We sought further information from trial authors if the article contained insufficient data to make a decision about eligibility. We designed a trial eligibility form to help in the assessment of relevance, using the criteria outlined above. We recorded the reasons why potentially relevant full-text studies failed to meet the eligibility criteria.

Data extraction and management

For this update, two review authors (MD, RC) conducted data extraction according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* [40]. Two review authors re-checked all study data extracted for previous versions of this review by returning to the original publications (RC, LG). We resolved any disagreements about data extraction by consensus. We were not blinded to the names of authors, institutions, journals, or the outcomes of the trials. Two review authors (LJE, SS) were investigators in the TREATT 2025 trial but were not involved in data extraction or risk of bias assessment in this update. We piloted the data extraction forms in the previous versions of this review [41; 19]. We used a standardised data extraction form to record the following items.

- General information: review author's name, date of data extraction, trial ID, first author of trial, author's contact address (if available), citation of paper, objectives of the trial.
- Trial details: trial design, location, setting, sample size, power calculation, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow-up, stratification, stopping rules described, results, conclusion, and funding.
- Risk of bias assessment: randomisation process, protocol deviations, missing outcome data, measurement of the outcome, and selection of the reported result.
- Characteristics of participants: age, gender, ethnicity, total number recruited, total number randomised, total number analysed, types of haematological disease, lost to follow-up numbers, dropouts (percentage in each arm) with reasons, protocol violations, current treatment, previous treatments.
- Interventions: experimental and control interventions, type of antifibrinolytic given, timing of intervention, adherence to interventions, additional interventions given, especially in relation to platelet and red cell transfusions, and any differences between interventions.
- Outcomes measured: number, site, and severity of bleeding episodes; thromboembolism (venous and arterial); mortality (all-cause; due to bleeding; due to thromboembolism); number of platelet transfusions; number of red cell transfusions; adverse effects attributable to antifibrinolytic agents; adverse effects attributable to transfusions (e.g. transfusion reactions, development of platelet antibodies); disseminated intravascular coagulation (DIC); quality of life.

We retrieved the data from both full-text and abstract reports of studies. Where these sources did not provide sufficient information, we contacted authors and study groups for additional details.

Risk of bias assessment in included studies

Working independently, two review authors (RC, LG) assessed all included studies using Cochrane's RoB 2 tool [42]. We disregarded previously published risk of bias assessments using the RoB 1 tool, and used the updated RoB 2 tool to re-assess studies.

The RoB 2 tool covers all types of bias that are currently understood to potentially affect the results of randomised trials. These are:

- bias due to the randomisation process;
- bias due to deviations from the intended interventions;
- bias due to missing outcome data;
- bias in the measurement of the outcome;
- bias in the selection of the reported result.

Thus, we assessed the design, conduct, and analysis of the included trials using a series of signalling questions and an algorithm that maps the five possible answers to the signalling questions (i.e. yes, probably yes, no, probably no, and no information) to a proposed judgement. This results in an assessment for each domain of low risk of bias, high risk of bias, or some concerns. Due to the age of some studies, they were often deemed as having some concerns, likely due to historical reporting standards, and the lack of explicit information regarding their methods. In future updates, where there are sufficient data, we will explore the impact of bias through sensitivity analyses.

Where review authors differed in their assessment of bias, we resolved disagreements by consensus. If we were unable to resolve disagreements by consensus, we would have consulted an additional review author (SJB).

Measures of treatment effect

We followed recommendations in the *Cochrane Handbook* when selecting our effect measures [43].

For dichotomous outcomes, we extracted the numbers of participants in the treatment and control groups and calculated risk ratios (RRs) with 95% confidence intervals (CIs) to summarise treatment effects. When trials reported zero events in one or both arms, we calculated risk differences (RDs). When both groups had low event rates (< 3%), we analysed the data using Peto's odds ratio (POR) method.

For continuous outcomes, we extracted means and standard deviations (SDs). When studies measured outcomes using the same scale, we calculated mean differences (MDs) with 95% CIs. We planned to use standardised mean differences (SMDs) for outcomes measured using different scales. When studies reported standard errors of the mean (SEMs), we converted them to SDs and used these values in all analyses for this review.

We anticipated trials would report some of their outcome data as median and interquartile ranges (IQRs) due to a skew in particular distributions. Where trials reported data as median and IQR, we presented these results as reported in a table of non-analysable data (Table 1). We attempted to contact authors of data provided as median and IQRs to obtain mean and SD.

We had planned to calculate the number needed to treat for an additional beneficial/harmful outcome (NNTB/NNTH) with 95% CIs. As there was little to no difference in all outcomes, we did not perform these calculations.

Unit of analysis issues

We did not prespecify in the protocol how we would deal with any unit of analysis issues. We encountered no unit of analysis issues in most included trials, as the unit of randomisation and analysis was the participant.

We included one cross-over randomised trial (Fricke 1991 [44]). If the data from the trial had been interpretable, we would have treated the trial in accordance with recommendations in the *Cochrane Handbook* [45].

Dealing with missing data

We followed recommendations in the *Cochrane Handbook* for dealing with missing study data [46]. In view of the time that has elapsed since the publication of four of the eight included studies, we made no attempt to contact individual study authors or institutions regarding missing data for trials included in the previous iteration of this review.

We did attempt to contact the authors of the four newly included trials (i.e. by reaching out up to two times by email) in order to obtain information that was missing or unclear in the published report. We received responses from research teams for A-TREAT 2022 and TREATT 2025. Both teams provided the data requested. The authors of the other two trials did not respond (McCormick 2020 [47, 48, 49]; PROBLEMA 2022 [50, 51]). We also contacted the authors of two currently ongoing trials for information regarding the status of the trials (NCT03801122 [52, 53]; Tay 2016 [54, 55, 56]). Authors of both trials replied and provided the necessary information.

Reporting bias assessment

We did not perform a formal assessment of reporting biases because none of the meta-analyses included at least 10 trials. In future updates of this review, we will explore potential publication bias (small trial bias) by generating a funnel plot and conducting statistical testing using a linear regression test. A P value of less than 0.1 would be considered significant for this test [46].

Synthesis methods

If trials were sufficiently homogenous in their trial design, we carried out a meta-analysis according to the recommendations in the *Cochrane Handbook* [43]. For statistical analysis, we entered data into Review Manager (RevMan) software [57]. We used the Wald-type method for calculating confidence intervals, and restricted maximum likelihood (REML) for estimating heterogeneity when using the random-effects model because heterogeneity was moderate to high ($I^2 > 30\%$), following the methods described in the *Cochrane Handbook* [43].

We used the I^2 statistic to measure heterogeneity amongst the trials in each analysis. We regarded heterogeneity as high if I^2 was greater than 30% [43].

One review author (RC) entered outcome data into the software, while a second review author (MD or LG) confirmed that these data were accurate. As stated in the original protocol, we used the fixed-effect model for analyses, and also used the random-effects model for outcomes with moderate or high heterogeneity ($I^2 > 30\%$) in order to avoid overweighting smaller studies. Where I^2 exceeded 30%, we planned to assess and report both fixed-effect and random-effects results to explore the impact of model choice. However, this was not required because we analysed the only outcome with substantial heterogeneity using the Peto method, which applies a fixed-effect model only.

Investigation of heterogeneity and subgroup analysis

We intended to conduct three subgroup analyses because the effect of antifibrinolytic treatment on our outcomes of interest may be impacted by any of the following variables.

- Age group: children (< 16 years) versus adults (16 years and older).
- Underlying haematological diagnoses: acute leukaemias, high-grade and low-grade lymphoproliferative disease, myeloma, myelodysplasia, myeloproliferative neoplasms, and aplastic anaemia.
- Type of treatment (e.g. chemotherapy, autologous and allogeneic transplantation, immunosuppression).

We had insufficient data to conduct any of these subgroup analyses. However, in future updates of the review, we will explore these subgroup analyses if we have appropriate data.

Sensitivity analysis

We did not perform a formal sensitivity analysis due to a lack of comparable data. Had we had sufficient data, we would have conducted sensitivity analyses for our critical outcomes in all comparisons to assess the robustness of our findings by including only those trials:

- at low risk of bias for the randomisation process (RoB 2 domain 1);
- with a low loss to follow-up (25% of participants or less).

In future updates of this review, we will explore these sensitivity analyses if we have appropriate and sufficient data.

Certainty of the evidence assessment

RC and LG used the GRADE approach to assess the certainty of the evidence, as outlined in the *Cochrane Handbook* [58]. We used GRADEpro software to conduct the assessment [59].

We provided the rationale for downgrading the certainty of the evidence in the footnotes of the summary of findings tables. We resolved any disagreements about GRADE assessments through discussion, and did not need to involve a third review author (LJE).

We presented the following outcomes in a summary of findings tables for each comparison:

- number of participants with WHO grade 2 bleeding or higher (clinically significant bleeding);
- number of participants with WHO grade 3 bleeding or higher (severe to life-threatening bleeding);
- number of participants with any thromboembolism;
- all-cause mortality;
- adverse events due to antifibrinolytic agents.

Equity considerations

We did not investigate equity-related characteristics in this review due to a lack of comparable data for factors such as race, gender, age, and location. In future review updates, we hope to be able to perform an equity-related

assessment with a larger sample of participants.

Consumer involvement

We did not involve consumers in this review. However, in any future update of this review, we would work with consumers to ensure that the outcomes included are relevant to them and that the interpretation of the results and implications of the findings are presented in an appropriate clinical context.

Results

Description of studies

For details of the included, excluded, and ongoing studies, see Supplementary material 2, Supplementary material 3, and Supplementary material 4, respectively. Table 2 provides an overview of the included studies' characteristics.

Results of the search

Details of the results of the searches for the 2013 and 2016 versions of this review are available in the publication by Wardrop and colleagues [41], and Estcourt and colleagues [19], respectively. The 2016 version of the review included four trials assessing a total of 86 participants [19].

We report here the results of the update search only (see Figure 1). Additionally, on 27 November 2025, in compliance with the latest Cochrane guidance [39], we searched for post-publication amendments to all our included studies (both primary and secondary references) and found one erratum for a secondary publication of the A-TREAT 2022 study (see Ilich 2023).

In January 2025, an update search was run, identifying 2313 records. Following removal of duplicates and previously screened records, two review authors (MD, RC) independently screened 105 records (79 references plus 26 ongoing trials) by title and abstract. We excluded 75 records as they did not meet the eligibility criteria. The same two authors undertook full-text screening of the 30 remaining articles. Of these, we excluded four articles, consisting of three full-text articles and one ongoing trial registration.

We deemed six trials (26 articles) as eligible for inclusion in this update (A-TREAT 2022; McCormick 2020; NCT03801122; PROBLEMA 2022; TREATT 2025; Tay 2016). Of these, three studies were classified as ongoing in the previous update and are now included in the review (A-TREAT 2022; PROBLEMA 2022; TREATT 2025); McCormick 2020 is a newly identified included trial; and two are newly identified ongoing trials (NCT03801122; Tay 2016).

Included studies

There are a total of eight trials included in this review update, comprising four trials included in the previous review (Avvisati 1989 [60]; Fricke 1991; Gallardo 1983; Shpilberg 1995 [61, 62]), and four newly-included trials (A-TREAT 2022; McCormick 2020; PROBLEMA 2022; TREATT 2025). Of note, both McCormick 2020 and PROBLEMA 2022 were prematurely terminated, with slow recruitment cited as the reason. Select results for McCormick 2020 have been reported in a conference abstract, but more comprehensively using a trial registration website (https://clinicaltrials.gov/study/NCT03806556). We are awaiting full publication of the results of this trial. Similarly, results from PROBLEMA 2022 have also only been disseminated using a trial registration website (https://clinicaltrials.gov/study/NCT02074436), and have not yet been published as a manuscript.

Design

The eight trials were published between 1983 and 2025. All were published in English. The results for two trials were published only on www.clinicaltrials.gov (McCormick 2020; PROBLEMA 2022). Results for Gallardo 1983 were reported in a conference abstract. The remaining five trials disseminated their results in full-text publications (A-TREAT 2022; Avvisati 1989; Fricke 1991; Shpilberg 1995; TREATT 2025). All but one were parallel RCTs; Fricke 1991 was a cross-over trial. Five were multi-centre trials (A-TREAT 2022; Avvisati 1989; PROBLEMA 2022; Shpilberg 1995; TREATT 2025) and two were single-centre (Gallardo 1983; McCormick 2020). Fricke 1991 did not provide details about recruiting centres.

Setting

The trials were conducted across several countries. The recruiting countries were Italy and the Netherlands (Avvisati 1989), Israel (Shpilberg 1995), the USA (A-TREAT 2022; Fricke 1991; Gallardo 1983; McCormick 2020; PROBLEMA 2022), and the UK and Australia (TREATT 2025).

Sample sizes

The trials included 1041 participants. Seven trials reported the number of participants randomised, while PROBLEMA 2022 did not report this information (though 29 participants were analysed). The number of participants randomised across the remaining seven trials ranged from eight to 616.

The sample size in five trials was less than 50 participants per trial (Avvisati 1989 (N = 12); Fricke 1991 (N = 8); Gallardo 1983 (N = 18); McCormick 2020 (N = 11); Shpilberg 1995 (N = 38)). The sample sizes in A-TREAT 2022 and TREATT 2025 were considerably larger at 337 and 616, respectively.

Participants

Seven trials enroled adults (18 years and older) (A-TREAT 2022; Avvisati 1989; Fricke 1991; Gallardo 1983; PROBLEMA 2022; Shpilberg 1995; TREATT 2025), while McCormick 2020 focused on children (two to 21 years). The population characteristics and primary diagnoses varied between the studies; see Supplementary material 2 and Table 2 for further details.

Interventions

Six trials compared tranexamic acid (TXA) to placebo (A-TREAT 2022; Avvisati 1989; Fricke 1991; McCormick 2020; Shpilberg 1995; TREATT 2025), one trial compared epsilon aminocaproic acid (EACA) to no EACA (Gallardo 1983), while the eighth trial compared EACA to standard platelet transfusion (PROBLEMA 2022). We did not identify any RCTs that directly compared TXA to EACA.

Co-interventions

The included trials reported platelet transfusions as co-interventions, with four trials specifying a platelet transfusion threshold (Gallardo 1983; McCormick 2020; PROBLEMA 2022; TREATT 2025). The Gallardo 1983 trial gave participants platelet transfusions if their platelet count was lower than 20 x 10^9/L, defining this threshold as the "days at risk of bleeding". McCormick 2020 used a platelet transfusion threshold of 30,000/µL or lower. Like Gallardo 1983, PROBLEMA 2022 also used a threshold of 20 x 10^9/L, administering additional platelet transfusions in case of grade 3 or grade 4 bleeding. TREATT 2025 administered prophylactic platelet transfusions at threshold counts of 10×10^9 platelets per L or more, in accordance with national guidance. Participants in the A-TREAT 2022 trial were given a platelet transfusion when their platelet count fell below 10,000 or at the clinician's discretion. Two trials administered platelet transfusions solely at the clinician's discretion (Avvisati 1989; Fricke 1991). Shpilberg 1995 did not specify a threshold.

Outcomes

The number of trials reporting the critical and important outcomes are presented in Table 3. No trial reported data for all outcomes of interest. TREATT 2025 reported on all outcomes except disseminated intravascular coagulation (DIC). Indeed, none of the included trials reported outcome data for DIC.

We extracted only 30-day outcome data, as we deemed this to be the most clinically meaningful time point and the one most likely to be reported.

Excluded studies

This review update lists 34 excluded studies, comprised of articles excluded in previous versions of the review [19, 41], as well as four articles excluded from this updated search following full-text eligibility screening (Byreddy 2022 [63, 64, 65] (three articles); IRCT20230104057046N2 [66]). The reasons for exclusion are as follows.

- Nine trials examined ineligible participant groups (Amar 2003 [67]; Byams 2007 [68]; Celebi 2006 [69]; McConnell 2011 [70]; McConnell 2012 [71]; Mevio 1983 [72]; Movafegh 2011 [73]; NCT01980355 [74]; Yang 2001 [75]).
- Three trials examined an ineligible intervention (Bedirhan 2001 [76]; Jeserschek 2003 [77]; Katzel 1998 [78]).
- One trial (reported in three articles) examined an ineligible comparator (Byreddy 2022).
- One trial examined an ineligible route of administration (IRCT20230104057046N2).
- Fourteen studies were not RCTs (Antun 2013 [79]; Bartholomew 1989 [80]; Ben-Bassat 1990 [81]; Cattan 1963 [82]; Chakrabarti 1998 [83]; Dean 1997 [84]; Fossa 1978 [85]; Gardner 1980 [86]; Garewal 1985 [87]; Kalmadi 2006 [88]; Rathi 2015 [89]; Sanz 2010 [90]; Schwartz 1986 [91]; Wassenaar 2008 [92]).
- Six articles were reviews rather than primary studies (Bates 2011 [93]; Breen 2012 [94]; Brown 2002 [95]; Levy 2005 [96]; Marti-Carvajal 2011 [97]; Rickles 2007 [98]).

See Supplementary material 3 for further details.

Ongoing studies

In this update, we identified two ongoing trials: the PATH trial (Tay 2016) and T-TRAP trial (NCT03801122).

The PATH trial is multi-centre, comparing TXA to prophylactic platelet transfusion in adults undergoing autologous haematopoietic stem cell transplantation for haematological malignancies. It was initially a pilot study which demonstrated feasibility by successfully recruiting 100 participants. These participants were then rolled over into the phase III study, which is currently ongoing. Trial completion is due in February 2027 with an estimated 662 participants to be enroled (Tay 2016).

T-TRAP is a three-arm trial comparing two doses of TXA to no TXA. The trial registration page reports the trial was completed in July 2022, but there has not yet been a full-text publication. The primary contact for this trial reported

that plans to disseminate the results in a publication are underway but not yet complete. The trial completed in July 2022, recruiting 18 participants (NCT03801122).

See Supplementary material 4 for further details.

Risk of bias in included studies

One study had significant methodological problems with its design (Fricke 1991). We did not include this study in our analyses. In short, study authors defined the overall success of TXA as either five failures of placebo and none of the drug, or seven failures of placebo and one of the drug. They defined the overall failure of TXA as two failed courses of the drug, and failure of a course as a participant receiving a platelet transfusion for bleeding during a four-week study period. Participants received a variable number of courses of drug/placebo. The three participants who completed the study received between three (two TXA, one placebo) and nine courses (five TXA, four placebo) of treatment. The five participants who did not complete the study received between zero and 20 courses (10 TXA, 10 placebo) of treatment. Of the three participants who completed the study, two did not have any successful courses of treatment. The third participant had three of five successful courses with TXA and one of four successful courses with placebo. However, the authors classified this as a failure of TXA (two failed courses with TXA). Interim analyses were conducted after each treatment course, and the study completion criteria were asymmetric, biasing conclusions against TXA: only two TXA failures were required to classify TXA as ineffective, whereas classification of TXA as effective required at least five placebo failures and no TXA failures.

Bleeding outcomes

Figure 2 presents our judgements about each risk of bias item for the seven studies that contributed data for this outcome. We judged four trials to be at high risk of bias, two at low risk of bias, and one to raise some concerns overall.

We judged five trials to raise some concerns regarding the randomisation process. In three trials, limited reporting – likely reflecting publication in the 1980s and 1990s – prevented full assessment. We judged two trials to be at low risk of bias (A-TREAT 2022; TREATT 2025).

Four of seven trials were at low risk of bias for deviations from the intended intervention, and one was at unclear risk (PROBLEMA 2022). We judged two trials, both published in the 1980s, to be at high risk of bias because of insufficient information on blinding and participant cross-over (Avvisati 1989; Gallardo 1983).

We judged five trials to be at low risk of bias due to missing outcome data. We judged both EACA trials to be at high risk of bias because outcome data were missing for a proportion of participants (Gallardo 1983; PROBLEMA 2022).

We judged four trials to be at high risk of bias in the measurement of the outcome because of limited detail on how bleeding outcomes were assessed and by whom, and insufficient information to determine whether outcome assessors were blinded (Avvisati 1989; Gallardo 1983; PROBLEMA 2022; Shpilberg 1995).

Most trials raised some concerns regarding selection of the reported result. We judged PROBLEMA 2022 to be at high risk of bias: although it had a protocol, statistical analysis plan, and trial registration, no full-text publication was available for comparison, and outcome data were reported only at six months despite authors stating that 30-day data would also be provided.

Thromboembolism

Figure 3 presents our judgements about each risk of bias item for the five studies that contributed data for this outcome. We judged that A-TREAT 2022 and TREATT 2025 were at overall low risk, two trials raised some concerns, and one trial was at overall high risk.

The two bigger trials, A-TREAT 2022 and TREATT 2025, provided clear details about the randomisation process and were therefore at low risk. The remaining three trials did not report as much information about how randomisation was done, omitting important details.

We judged all but Avvisati 1989 to be at low risk of bias for deviations from the intended intervention. Avvisati 1989 was at high risk for this domain due to a lack of information regarding who in the clinical team was blinded.

All trials were at low risk of bias for missing outcome data (domain 3) and measurement of the outcome (domain 4).

A-TREAT 2022 and TREATT 2025 were again the only two trials at low risk of bias for selection of the reported results. The remaining three trials raised some concerns. Avvisati 1989 and Shpilberg 1995 did not have a trial registration, statistical analysis plan, or protocol, which could be attributed to historical reporting standards. While McCormick 2020 did have a protocol and statistical analysis plan attached to the trial registration, this trial was prematurely terminated (due to the COVID-19 pandemic). The data they reported appear to be the interim analyses that trialists stated they would conduct when recruitment reached 10 participants. There is no full-text publication associated with this trial, so it is not possible to determine if what was stated in the protocol was actually done.

Mortality (all-cause and due to bleeding or thromboembolism)

Figure 4 presents our judgements about each risk of bias item for the seven studies that contributed data for this outcome. We judged two trials to have an overall low risk of bias, one raised some concerns, and four were at overall high risk.

We judged two trials that provided adequate details about the randomisation process to have a low risk of bias. Five trials raised some concerns for bias, linked to a lack of clarity as to how randomisation was performed, how allocation was concealed, as well as unclear baseline differences.

Domain 2 (deviation from intended intervention) was better reported, with four trials at low risk, one raising some concerns, and two at high risk (Avvisati 1989; Gallardo 1983). Avvisati 1989 was not clear if the 'attending physician' and 'investigator' were one and the same person. Lack of information about blinding was also an issue for Gallardo 1983. In addition, trialists stated that one participant was 'not evaluable' but they provided no further information about this participant.

All trials were at low risk of bias for missing outcome data (domain 3) except Gallardo 1983, which had one participant not included in the analyses. Trialists provided no information about which group this participant was assigned to or why they were inevaluable. With only nine people per group, this loss to follow-up could easily impact outcomes.

Six of seven trials reported domain 4 (measurement of outcome) well and were deemed to be at low risk of bias. We judged Shpilberg 1995 to be at high risk of bias for measurement of the outcome, as the authors did not explicitly report whether any deaths occurred. While they reported "no thromboembolic events" and "no fatal bleeding", indicating no deaths attributable to these causes, they did not report all-cause mortality and, therefore, deaths from other causes cannot be excluded. The statement that "TA was well tolerated and no side effects were observed" does not resolve this uncertainty, as it may apply only to the intervention group.

Finally, we deemed two trials to be at low risk of bias for selection of reported results, four to raise some concerns, and one at high risk. The lack of a full-text publication and provision of data from six months rather than the prespecified 30 days contributed to PROBLEMA 2022 being classed as high risk.

Adverse events (attributable to antifibrinolytic drugs or transfusion)

Figure 5 presents our judgements about each risk of bias item for the six studies that contributed data for this outcome. We deemed two trials to be at overall low risk of bias, one raised some concerns, and three were at overall high risk.

The two most recent trials provided adequate information about the randomisation process (domain 1), allocation concealment, and baseline differences. The other four trials raised some concerns, mainly due to lack of detail about randomisation and how allocation was concealed. There was also evidence of baseline imbalances.

There was better reporting of domain 2 (deviation from intended interventions), we judged all TXA trials to be at low risk, one EACA trial to be at high risk, and the other raised some concerns. We considered PROBLEMA 2022 to have some concerns, it was an open-label trial due to the nature of the interventions (oral versus transfusion), but it was unclear if any of the participants crossed over to the other treatment arm. We deemed Gallardo 1983 to be at high risk as there was no information regarding blinding.

Five of the six trials adequately addressed missing outcome data (domain 3), and we thus judged them to be at low risk of bias. We deemed Gallardo 1983 to be at high risk in this domain, as the authors provided no information for one participant whose data were not analysed.

For measurement of the outcome, we rated three trials as low risk and three as high risk (Gallardo 1983; PROBLEMA 2022; Shpilberg 1995). Gallardo 1983 referred to 'side effects' as being 'minimal', with no further information as to how the outcome was measured. PROBLEMA 2022 prespecified outcome assessment and causality criteria in the protocol, combining objective measures (e.g. blood tests) with subjective clinical assessment. According to the study report, trialists assessed outcomes twice weekly, which may introduce recall bias, although medical records were reportedly used during the in-patient period. Shpilberg 1995 provided no information about how data were collected and when, though participants were inspected daily for bleeding events, so likely assessed at the same time. There was also no information on what "side effects" investigators were checking for.

For selection of the reported results, we judged two trials to have a low risk of bias, three raised some concerns (Gallardo 1983; McCormick 2020; Shpilberg 1995), and one was high risk (PROBLEMA 2022). Gallardo 1983 and Shpilberg 1995 were not supported by a protocol, statistical analysis plan, or trial registration. McCormick 2020 did provide these supporting materials, but reported what appears to be interim analyses of the participants available before the trial was prematurely terminated. There is as yet no full publication; therefore, only descriptive statistics are available. We deemed PROBLEMA 2022 to be at high risk despite providing a trial registration, protocol, and statistical analysis plan, because the authors reported outcome data at six months rather than the prespecified 30 days. Similar to McCormick 2020, PROBLEMA 2022 also does not have a full-text publication, therefore only providing descriptive statistics (mean, SD, median, range).

Transfusions (platelets or red blood cells)

Figure 6 presents our judgements about each risk of bias item for the six studies that contributed data for this outcome. We rated A-TREAT 2022 and TREATT 2025 as having an overall low risk of bias, McCormick 2020 and Shpilberg 1995 as raising some concerns, and Avvisati 1989 and Gallardo 1983 as overall high risk.

We judged only two trials to have a low risk of bias for the randomisation process, and four as raising some concerns. A common thread amongst these four trials was inadequate reporting of the randomisation process and allocation concealment. There were also important baseline differences. For example, McCormick 2020 reported

skewed data on participant age: there was a wider range for the TXA group (three to 18 years) but a lower median age compared to the placebo group. Also, most participants in the TXA group had lymphoid leukaemia, while no one in the placebo group had this type of leukaemia. We are unclear of the impact of this disparity on our outcomes, but with such small sample sizes, just one person could make a large difference. Shpilberg 1995 reported data for two populations: those receiving induction chemotherapy and those receiving consolidation chemotherapy. It is unclear whether the consolidation chemotherapy group was independent of the induction chemotherapy group, and so we did not consider participants in that group in this review. It is also unclear whether the consolidation group was a subset of the induction group, or if participants were re-randomised, or continued in their previously assigned group.

For deviations from the intended interventions, we deemed four trials to have a low risk of bias and two as high risk. Avvisati 1989 and Gallardo 1983 were insufficiently clear about how blinding was done and who was blinded.

Five of six trials were at low risk of bias for missing outcome data (domain 3). We deemed Gallardo 1983 as high risk in this domain due to a lack of information on one participant who was not included in their analyses. Authors failed to report which treatment arm this participant belonged to and why they were labelled as 'inevaluable'.

We found the same five trials to be at low risk in domain 4 (measurement of the outcome) and Gallardo 1983 to be at high risk. Trialists reported platelet transfusions as rates per total number of days at risk of bleeding, and the groups differed in the number of days at risk, limiting comparability between groups. Although a platelet transfusion threshold was prespecified and applied consistently, the outcome measurement was biased.

We judged A-TREAT 2022 and TREATT 2025 to have a low risk of bias for selection of the reported result, whilst the remaining four trials raised some concerns. Avvisati 1989, Gallardo 1983, and Shpilberg 1995 did not have a protocol, statistical analysis plan, or trial registration. Furthermore, Gallardo 1983 was only available as a conference abstract. We judged McCormick 2020 to raise some concerns, despite having a protocol, statistical analysis plan, and trial registration: this trial does not yet have a full-text publication but has instead posted an interim analysis of 10 participants on the trial registration.

Disseminated intravascular coagulation (DIC)

None of the included studies reported the incidence of DIC.

Quality of life (QoL)

Figure 7 presents our judgements about each risk of bias item for the one study that contributed data for this outcome (TREATT 2025). We assessed it as low risk overall, with well-described randomisation and allocation concealment methods, and blinding throughout the study, including outcome assessors. Trialists assessed QoL using standard, well-validated questionnaires. Initially, data for approximately one-third of the study participants appeared to be missing. However, personal communication with the trialists clarified that one participating country (Australia, 193 participants randomised) did not assess this outcome. We thus assessed the trial as at low risk, as nearly all those randomised and eligible to assess QoL were analysed.

See Supplementary material 5 for full details of the risk of bias of the included studies.

Synthesis of results

See Summary of findings table 1, Summary of findings table 2, Table 1, and Supplementary material 6 for further information.

As noted in Synthesis methods, where I^2 exceeded 30%, we planned to assess and report results from both fixed-effect and random-effects analyses to explore the impact of model choice. However, only one outcome (Comparison 1, all-cause mortality) met this criterion (I^2 = 37%). We used Peto OR due to the low event rate (< 3% per arm), and so could not assess the random-effects model as the Peto method applies a fixed-effect model only.

Comparison 1. Tranexamic acid (TXA) versus placebo

Six trials evaluated this comparison (A-TREAT 2022; Avvisati 1989; Fricke 1991; McCormick 2020; Shpilberg 1995; TREATT 2025). Further information is available in Summary of findings table 1 and Table 1.

We excluded Fricke 1991 (eight participants; used a cross-over design) from the outcome analysis because the study's data were uninterpretable due to major methodological flaws in the study design (see Table 2 for details of the study design). In addition to the high risk of attrition, reporting, and 'other' bias (see Risk of bias in included studies and the risk of bias table in Supplementary material 2), the number of study cycles varied, depending on the results of previous cycles of treatment. All these factors meant that it was impossible to fully understand the data in this trial, and we therefore omitted Fricke 1991 from the synthesis.

A full summary of all analyses related to this comparison can be found in Supplementary material 6.

Critical outcomes

Bleeding: clinically significant bleeding (WHO grade 2 or higher)

A-TREAT 2022, McCormick 2020, and TREATT 2025 reported bleeding outcome data, in the form of 'any bleeding', 'grade 2+ bleeding', and 'grade 3+ bleeding', and were sufficiently homogeneous to pool their data in a

meta-analysis. TXA probably has little to no effect on grade 2 bleeding or higher compared to placebo (RR 0.89, 95% CI 0.75 to 1.05; I^2 = 7%; 3 studies, 894 participants; moderate-certainty evidence; Figure 8; Analysis 1.2; Summary of findings table 1).

Bleeding: severe to life-threatening bleeding (WHO grade 3 or higher)

TXA may have little to no effect on grade 3 bleeding or higher compared to placebo (RR 1.07, 95% CI 0.51 to 2.22; I^2 = 6%; 3 studies, 894 participants; low-certainty evidence; Figure 9; Analysis 1.3; Summary of findings table 1).

Avvisati 1989 and Shpilberg 1995 also reported bleeding data, but the data were not in a form suitable for analysis. Avvisati 1989 reported a cumulative bleeding score, while Shpilberg 1995 reported the mean number of bleeding events. We present these data in Table 1.

Thromboembolism (any, arterial, and venous)

Five trials reported data for this outcome (A-TREAT 2022; Avvisati 1989; McCormick 2020; Shpilberg 1995; TREATT 2025). There were no reported thromboembolic events in Avvisati 1989, McCormick 2020, and Shpilberg 1995.

A-TREAT 2022 only reported data for 'any thromboembolism' whilst McCormick 2020 and TREATT 2025 reported the number of any, arterial, and venous thromboembolic events. Authors of TREATT 2025 directly provided us with the 30-day data. Avvisati 1989 and Shpilberg 1995 did not differentiate between arterial and venous thromboembolisms. Both trials reported that no thromboembolic events occurred. For these two trials, we assumed that there were zero events for any, arterial, and venous thromboembolism.

Any thromboembolism

TXA may have little to no effect on the number of participants experiencing any thromboembolism (Peto OR 0.85, 95% CI 0.39 to 1.86; I^2 = 0%; 5 studies, 984 participants; low-certainty evidence; Figure 10; Analysis 1.4; Summary of findings table 1).

Arterial thromboembolism

We analysed four studies with 658 participants (Peto OR 0.99, 95% CI 0.06 to 15.86; I^2 not applicable; 4 studies, 658 participants; Analysis 1.5). There was no clear evidence of an effect.

Venous thromboembolism

We analysed four studies with 658 participants (Peto OR 1.24, 95% CI 0.33 to 4.62; I^2 not applicable; 4 studies, 658 participants; Analysis 1.6). There was no clear evidence of an effect.

Important outcomes

'Any' bleeding (WHO grade 1 or higher)

We analysed three studies with 894 participants (RR 0.90, 95% CI 0.82 to 0.99; I^2 = 0%; 3 studies, 894 participants; Analysis 1.1). There was no clear evidence of an effect.

Mortality (all-cause)

Three trials reported this outcome (A-TREAT 2022; McCormick 2020; TREATT 2025), and were sufficiently homogeneous to pool their data in a meta-analysis. TXA may make little to no difference to all-cause mortality compared to placebo, but the evidence is very uncertain (Peto OR 1.50, 95% CI 0.62 to 3.63; I^2 = 37%; 3 studies, 930 participants; very low-certainty evidence; Figure 11; Analysis 1.7; Summary of findings table 1). We were unable to apply the random-effects model as planned (I^2 > 30%) due to the use of the Peto OR.

Mortality (secondary to bleeding)

Four trials reported this outcome (A-TREAT 2022; McCormick 2020; Shpilberg 1995; TREATT 2025). There were no deaths due to bleeding across all four studies (RD 0.00, 95% CI −0.01 to 0.01; I^2 = 0%; 4 studies, 976 participants; Analysis 1.8).

Mortality (secondary to thromboembolism)

Three trials reported this outcome (A-TREAT 2022; McCormick 2020; TREATT 2025). There were no deaths due to thromboembolism across the three studies.

Avvisati 1989 and Shpilberg 1995 reported that 'no thromboembolic events occurred' in their respective trials. We assumed that this also meant no deaths from thromboembolism occurred. Therefore, these two trials also contributed data for this outcome (RD 0.00, 95% CI −0.01 to 0.01; I^2 = 0%; 5 studies, 984 participants; Analysis 1.9).

Number of platelet transfusions or number of platelet components per participant

Five trials provided data for this outcome (A-TREAT 2022; Avvisati 1989; McCormick 2020; Shpilberg 1995; TREATT 2025). McCormick 2020 reported the number of platelet transfusions as median and interquartile range. We were unsuccessful in obtaining the data as means and standard deviations, despite several attempts to contact the authors. We report the study data in Table 1.

We were able to pool data from three studies (A-TREAT 2022; TREATT 2025; Shpilberg 1995), using only the induction chemotherapy group data from Shpilberg 1995 in the analysis. There appears to be no difference in the number of platelet transfusions between the TXA and placebo groups (MD −0.18, 95% CI −0.78 to 0.43; I^2 = 0%; 3 studies, 961 participants; Analysis 1.10).

Avvisati 1989 and Shpilberg 1995 both reported the number of platelet components. Avvisati 1989 reported this outcome as the total number of platelet transfusions used in each study arm; Shpilberg 1995, as the number of platelet components per participant. The Avvisati 1989 data were not in a format that we could analyse, and we instead present these data as reported in Table 1.

Number of red cell transfusions or number of red cell components per participant

Five trials reported data for this outcome (A-TREAT 2022; Avvisati 1989; McCormick 2020; Shpilberg 1995; TREATT 2025). McCormick 2020 reported the number of red cell transfusion data as median and interquartile range. As with the previous outcome, we were unsuccessful in obtaining the data as means and standard deviations, despite several attempts to contact the authors. We report the study data in Table 1. We were able to pool data from three studies (A-TREAT 2022; TREATT 2025; Shpilberg 1995), using only the induction chemotherapy group data from Shpilberg 1995 in the analysis. There appears to be no difference in the number of red cell transfusions between the TXA and placebo groups (MD −0.22, 95% CI −0.65 to 0.21; I^2 = 0%; 3 studies, 961 participants; Analysis 1.11).

Avvisati 1989 and Shpilberg 1995 both reported the number of red cell components. Avvisati 1989 reported this outcome as the total number of red cell components used in each study arm; Shpilberg 1995, as the number of red cell components per participant. The Avvisati 1989 data were not in a format that we could analyse, and we instead present these data as reported in Table 1.

Adverse events attributable to antifibrinolytic agents

Four trials reported this outcome (A-TREAT 2022; McCormick 2020; Shpilberg 1995; TREATT 2025). We are awaiting clarification of these data from McCormick 2020. Therefore, this trial has not contributed to any analyses for this outcome. Shpilberg 1995 reported that no side effects were observed.

Homogeneity in the studies allowed us to pool data from A-TREAT 2022, Shpilberg 1995, and TREATT 2025. There may be little to no difference in the number of adverse events related to antifibrinolytic drugs between the TXA and placebo groups, but the evidence is very uncertain (Peto OR 2.24, 95% CI 0.64 to 7.78; I^2 = 0%; 3 studies, 949 participants; very low-certainty evidence; Figure 12; Analysis 1.12; Summary of findings table 1).

Adverse events attributable to transfusion (e.g. transfusion reactions, antibody development)

One trial reported unambiguous data for this outcome (TREATT 2025). McCormick 2020 did not distinguish between adverse events due to the treatment drug and those due to transfusion. Therefore, we did not use data from McCormick 2020 in the analysis of this outcome. Shpilberg 1995 stated that "no side effects were observed." We assumed this meant that there were no adverse events due to transfusion.

There appears to be no difference between TXA and placebo in the number of adverse events related to transfusions (Peto OR 0.51, 95% CI 0.10 to 2.52; I^2 not applicable; 2 studies, 635 participants; Analysis 1.13).

Disseminated intravascular coagulation (DIC)

None of the included studies reported this outcome.

Quality of life (QoL)

One trial reported this outcome as the mean and adjusted change in total score (TREATT 2025). TREATT 2025 reported changes from baseline to study day 30 in total scores measured by the Functional Assessment of Cancer Therapy–General (FACT-G) and Functional Assessment of Cancer Therapy–Thyroid (FACT-Th). These data are displayed in Analysis 1.14. There was no statistically significant difference in any of the presented change data.

Comparison 2: epsilon aminocaproic acid (EACA) versus no EACA

One trial evaluated this comparison (Gallardo 1983). See Summary of findings table 2.

Critical outcomes

Bleeding

Gallardo 1983 did not report severity of bleeding data in a form suitable for analysis. Authors reported bleeding as the proportion of days at risk of bleeding (defined as a platelet count of less than 20 x 10^9/L). We report the data for "capillary bleeding" and "major bleeding" in Table 1.

Important outcomes

Mortality (secondary to thromboembolism)

The trial reported that no participants died of thrombosis (RD 0.00, 95% CI −0.19 to 0.19; I^2 not applicable; 1 study, 18 participants; very low-certainty evidence; Analysis 2.1). The evidence is very uncertain about the effect of TXA

on mortality due to thromboembolism. As there were no data for all-cause mortality, we presented mortality secondary to thromboembolism in Summary of findings table 2.

Number of platelet transfusions or platelet components

Gallardo 1983 did not report the number of platelet transfusions or platelet components per participant. They reported platelet transfusions per days at risk (see Table 1 of data unsuitable for analysis).

Adverse events attributable to antifibrinolytic agents

Gallardo 1983 described no specific adverse events, but stated that "side effects were minimal" (see Table 1).

Unreported outcomes

Gallardo 1983 did not report the following outcomes: WHO grade 2 bleeding or higher; WHO grade 3 bleeding or higher; 'any' bleeding (WHO grade 1 bleeding or higher); thromboembolism (any, arterial, venous), mortality (all-cause, secondary to bleeding), number of red blood cell transfusions or number of red cell components, adverse events of transfusion, DIC, and QoL.

Other comparisons: epsilon aminocaproic acid (EACA) versus standard prophylactic platelet transfusion

One trial evaluated this comparison (PROBLEMA 2022). The results of this trial have not been disseminated in a full-text publication. Instead, results from the 6-month follow-up (not 30 days) have been posted on the trial registration website. We report these data in Table 1.

Equity assessment

We did not carry out a formal health equity assessment. Tranexamic acid is an inexpensive and widely available drug and could therefore be used across a range of healthcare settings, including low-resource settings. Any lack of demonstrated benefit may have implications for efficient use of healthcare resources across diverse settings.

Reporting biases

It was not possible to assess reporting bias, due to the lack of trials.

Discussion

Summary of main results

This review aimed to evaluate the effectiveness and safety of antifibrinolytic drugs (lysine analogues) in preventing bleeding in people with haematological disorders. The previous version of this review included four trials with 86 participants [19]. In this update, we identified four new published trials, including two large trials at low risk of bias (A-TREAT 2022; TREATT 2025). Thus, this update includes eight RCTs with a total of 1041 participants. Six trials compared tranexamic acid (TXA) with placebo (A-TREAT 2022; Avvisati 1989; Fricke 1991; McCormick 2020; Shpilberg 1995; TREATT 2025), one trial compared epsilon aminocaproic acid (EACA) with no EACA (Gallardo 1983), and one trial compared EACA with platelet transfusion (PROBLEMA 2022). No trials compared TXA to EACA. All but one trial was in adults; McCormick 2020 involved children (two to 21 years).

Tranexamic acid (TXA) versus placebo

The certainty of the evidence varied from very low (for mortality and adverse events) to moderate (for grade 2 bleeding or higher). Compared to placebo, TXA probably makes little to no difference to the number of participants with grade 2 bleeding or higher.

There may be little to no difference between TXA and placebo in the risk of experiencing grade 3 bleeding or higher, or any thromboembolism.

The evidence is very uncertain about the effect of TXA on all-cause mortality and adverse events attributable to antifibrinolytic drugs.

Epsilon aminocaproic acid (EACA) versus no EACA

Grade 2 bleeding or higher, Grade 3 bleeding or higher, and all-cause mortality were not reported for this comparison. The evidence is very uncertain about the effect of EACA on mortality due to thromboembolism.

No thromboembolic events were reported and there was insufficient evidence to analyse adverse events attributable to antifibrinolytic agents.

EACA versus standard prophylactic platelet transfusion

Grade 2 bleeding or higher, Grade 3 bleeding or higher, and any thromboembolism data were not reported for this comparison. All-cause mortality and adverse events attributable to antifibrinolytic drugs were reported. These data were measured at six months, and therefore could not contribute to any analyses.

Limitations of the evidence included in the review

Study design

All the trials in this review were randomised controlled trials. We judged two large recent trials to be of high quality and at an overall low risk of bias (A-TREAT 2022; TREATT 2025). Two trials have not been published in full and have not undergone peer review (McCormick 2020; PROBLEMA 2022). Other trials included in the analyses were run more than thirty years ago and practice has changed since then (Avvisati 1989; Fricke 1991; Gallardo 1983; Shpilberg 1995). The smaller trials were at higher risk of bias and had substantial methodological problems. One trial used a cross-over design, and we were unable to extract data for synthesis due to limitations in the design of the study (Fricke 1991).

Population

The results of this review are largely based on two randomised trials conducted in high-resource settings (A-TREAT 2022; TREATT 2025). It is possible that these results may not reflect resource-poor settings where some treatments, such as platelet transfusions, may not be readily accessible. The trials included a range of haematological malignancies. There were insufficient data to conduct subgroup analysis by underlying diagnosis or treatment. It is possible that there may be subgroups of people who may benefit more (or less) from antifibrinolytic therapy, but this could not be ascertained from the data in this review. Most of the data pertained to adults.

Interventions and comparators

Most of the data in this review was for TXA compared to placebo. There are gaps in the evidence for EACA compared to placebo, and for TXA or EACA compared to platelet transfusion. There were also no trials comparing TXA to EACA.

Tranexamic acid was given orally or intravenously in the trials and at different doses. The two larger trials gave a clear rationale for this pragmatic approach: namely, that patients are often unable to take medications by mouth when undergoing chemotherapy (A-TREAT 2022; TREATT 2025). This approach matches clinical practice.

In interpreting the results of this review, it should be noted that four of the completed studies were conducted at least 30 years ago (Avvisati 1989; Fricke 1991; Gallardo 1983; Shpilberg 1995), during which time chemotherapy protocols, predicted overall survival rates, and supportive care, including transfusion, have changed substantially.

Outcomes and follow-up

Some studies did not present data in a form suitable for meta-analysis; we presented these results narratively.

The reporting of 'any' bleeding was difficult to interpret in many studies. The WHO scoring system for bleeding was not in place at the time when some of these studies were conducted, and insufficient data were available to reliably apply WHO grading retrospectively across all studies.

The two EACA trials reported far fewer outcomes of interest compared to the trials involving TXA. There was a complete lack of thromboembolism data from the EACA trials, while reporting of bleeding and mortality data was patchy. The evidence base was too limited to assess the effects of EACA for treatment.

No studies reported disseminated intravascular coagulation (DIC) as an outcome.

We analysed outcome data collected within 30 days of treatment initiation, as this timeframe captures the period of highest bleeding risk.

Limitations of the review processes

There were no clear biases identified in the review process. We conducted a comprehensive search of data sources (including multiple databases and clinical trial registries) to ensure that we captured all relevant trials. We imposed no language restrictions in the searches. We carefully assessed the relevance of each trial identified, and performed all screening and data extractions in duplicate. We prespecified all outcomes and subgroups prior to analysis.

To ensure consistency in applying the eligibility criteria between previous versions of the review and this update, we re-assessed all previously included and excluded studies and applied the current outcome definitions uniformly. This process involved verifying all previously extracted outcome data, extracting additional information where available, and conducting more detailed risk of bias assessments, with all studies re-assessed using Cochrane's ROB 2 tool.

We considered whether the exclusion of Fricke 1991 from the narrative synthesis might introduce a risk of publication bias. Given the study's methodological limitations and high risk of bias across several domains (see Risk of bias in included studies), we judged that exclusion of this study from the narrative synthesis was appropriate.

Two review authors (SS, LJE) were primary investigators of an included trial (TREATT 2025). Neither were involved in the risk of bias assessments or data extraction.

Agreements and disagreements with other studies or reviews

While the previous version of this review was unable to draw firm conclusions because of limited evidence [19], the expanded evidence base in this update allows more robust assessment of outcomes for TXA. The findings suggest that, compared to placebo, TXA probably makes little to no difference to the number of participants with grade 2 bleeding or higher, and may make little to no difference to the number with grade 3 bleeding or higher, or any thromboembolism. Consistent with the 2016 version of the review, evidence for EACA remains limited, and there are no head-to-head comparisons of TXA with EACA.

Several non-randomised studies have used TXA or EACA in people with haematological disorders (Bartholomew 1989; Ben-Bassat 1990; Chakrabarti 1998; Dean 1997; Gardner 1980; Garewal 1985; Kalmadi 2006; Schwartz 1986; Wassenaar 2008; 63; 99). However, most of these studies were small or did not have a comparator arm, making it difficult to draw any valid conclusions on the effectiveness and safety of antifibrinolytics.

Authors' conclusions

Implications for practice

For people with thrombocytopenia and haematological malignancies, tranexamic acid (TXA) probably makes little to no difference to clinically significant bleeding (i.e. World Health Organization (WHO) bleeding scale grade 2 or higher), and may make little to no difference to severe or life-threatening bleeding (WHO grade 3 and 4 bleeding), or the occurrence of any thromboembolism, compared to placebo. The evidence was of very low certainty for the effects of TXA versus placebo on all-cause mortality and serious adverse events attributable to antifibrinolytic drugs.

For epsilon aminocaproic acid (EACA) compared to no EACA, there were insufficient data to assess any of the review's key outcomes (i.e. number of participants with WHO grade 2 bleeding or higher, grade 3 bleeding or higher, any thromboembolism, all-cause mortality, and serious adverse events attributable to antifibrinolytic drugs).

Those making decisions about administration of prophylactic TXA to people with thrombocytopenia and haematological malignancies should consider that current evidence does not show a benefit or harm for TXA for preventing clinically significant, severe, or life-threatening bleeding.

Implications for research

As there is no evidence of harm from using antifibrinolytic drugs for people with thrombocytopenia and haematological malignancies, there is a good rationale for continuing research. Areas for future research where evidence gaps remain include the following:

- the use of tranexamic acid in specific patient subgroups defined by underlying haematological diagnoses or treatment modalities. Given the similarities in trial design between the two largest trials (A-TREAT 2022; TREATT 2025), analysis of individual patient data from these trials may provide sufficient data to assess this question;
- risks and benefits of TXA for children with thrombocytopenia and haematological malignancies;
- EACA compared to placebo for both adults and children with thrombocytopenia and haematological malignancies;
- TXA or EACA compared to platelet transfusion for both adults and children with thrombocytopenia and haematological malignancies.

Supplementary materials

[For display in the published PDF only] Supplementary materials are available with the online version of this article: 10.1002/14651858.CD009733.pub4.

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Supplementary material 1

CD009733-SUP-01-searchStrategy.html

Search strategies

Supplementary material 2

CD009733-SUP-02-characteristicsOfIncludedStudies.html

Characteristics of included studies

Supplementary material 3

CD009733-SUP-03-characteristicsOfExcludedStudies.html

Characteristics of excluded studies

Supplementary material 4

CD009733-SUP-04-characteristicsOfOngoingStudies.html

Characteristics of ongoing studies

Supplementary material 5

CD009733-SUP-05-riskOfBias2.html

Risk of bias

Supplementary material 6

CD009733-SUP-06-analyses.html

Analyses

Supplementary material 7

CD009733-SUP-07-dataPackage.zip

Data package

Additional information

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Sally Hopewell and Mike F Murphy were authors on the previous version of this review.

Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Toby Lasserson, Cochrane Acting Editor-in-Chief;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Gail Quinn, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported the editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Faith Armitage, Cochrane Central Production Service;
- Peer-reviewers (provided comments and recommended an editorial decision): Lindsay Robertson, Cochrane (methods review); Jo Platt, Central Editorial Information Specialist (search review).

Contributions of authors

Rita Champaneria screened and selected trials, extracted data, assessed risk of bias, evaluated the evidence using the GRADE framework, analysed results, and prepared this update of the review.

Lise Estcourt was a content expert (blood components, including red blood cells, platelets, plasma, cryoprecipitate, and alternatives). She contributed to the development of the protocol as well as the previous versions of the review.

Louise Geneen checked previously extracted data, assessed risk of bias, evaluated the evidence using the GRADE framework, and commented on the review.

Susan Brunskill was the methodological expert. She contributed to the preparation of this and previous updates of the review and to protocol development.

Carolyn Dorée was the information specialist. She developed and implemented the search strategies, contributed to the preparation of this and previous updates of the review, and contributed to protocol development.

Simon Stanworth was a content expert (clinical indications for blood transfusion components) and contributed to protocol development.

Michael Desborough was a content expert (platelet disorders and transfusions). He screened and selected trials, extracted data, assessed risk of bias, and prepared this and previous updates of the review.

Declarations of interest

Rita Champaneria (RC): none declared.

Lise Estcourt (LJE): chief investigator of one of the completed studies (TREATT) included in the review. This major research trial was funded by NHS Blood and Transplant. LJE also holds the position of Medical Director for Transfusion, NHS Blood and Transplant. LJE was not involved in assessment of bias, data extraction, or GRADING of outcomes related to thE TREATT trial.

Louise Geneen (LJG): none declared.

Susan Brunskill (SB): none declared.

Carolyn Dorée (CD): none declared.

Simon Stanworth (SS): chief investigator of one of the completed studies (TREATT) included in the review. This major research trial was funded by NHS Blood and Transplant. SS is a Consultant Haematologist at NHS Blood and Transplant and also Oxford University Hospitals NHS Foundation Trust. NHS Blood and Transplant manufacture blood components, and a key aim of this review is to explore the effects of the intervention on platelet needs. SS was not involved in assessment of bias, data extraction, or GRADING of outcomes related to the TREATT trial.

Michael Desborough (MD): medical doctor (Consultant Haematologist) at Oxford University Hospitals NHS Foundation Trust.

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Internal sources

- NHS Blood and Transplant, UK
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External sources

- Cochrane Haematology, Germany
  Editorial support

Registration and protocol

A protocol was published by Wardrop and colleagues in 2012 [18].

Data, code and other materials

As part of the published Cochrane review, the following is made available for download by users of the Cochrane Library (see Supplementary material 7):

- full search strategies for each database;
- full citations of each unique report for all studies (included, ongoing, or awaiting classification, or excluded at the full-text screening) in the final review;
- analysis data, including overall estimates and settings, subgroup estimates, and individual data rows.

Appropriate permissions have been obtained for such use. Analyses and data management were conducted within Cochrane's authoring tool, RevMan, using the inbuilt computation methods.

Risk of bias assessment (ROB 2) consensus data can be downloaded from the Oxford University Repository.

History

Protocol first published: Issue 3, 2012
Review first published: Issue 7, 2013

Date	Event	Description
11 February 2026	New citation required and conclusions have changed	Searches were re-run. We identified six trials eligible for inclusion. Of these, three trials listed as ongoing in the 2016 update have all now completed and disseminated their results (A-TREAT 2022; PROBLEMA 2022; TREATT 2025). Three are new to this update search (McCormick 2020; NCT03801122; Tay 2016). McCormick 2020 has completed and reported results and is included in this review update. NCT03801122 and Tay 2016 are ongoing.
11 February 2026	New search has been performed	Changes from the protocol/ 2016 update: • We decided to remove the laboratory fibrinolysis outcome from this update. We do not expect this to be presented in any of the included papers and its inclusion would disrupt the flow of the review. • We decided to only extract 30-day data, as opposed to other time points, as this is the most clinically useful time point for this review and is most likely to be reported. • We reduced the number of outcomes reported in the summary of findings tables to the five outcomes we regarded as the most clinically important.

Date	Event	Description

		• We decided to include another eligible comparison: EACA versus platelet transfusion.
		• We re-named a comparison. The trial by Gallardo and colleagues was initially described as 'EACA versus placebo'. Upon closer inspection of the trial information, we realised that it compared EACA to no EACA. This is how we will report the Gallardo trial going forward.
		• We re-assessed all included studies (old and new) using Cochrane's ROB 2 tool.
		• Two new review authors joined the review team (R Champaneria and L Geneen). Two review authors who contributed to the 2016 update have been removed as authors, and are instead listed in the Acknowledgements (S Hopewell, MF Murphy).
		• For this update, we searched the databases from January 2015 onwards (the search for the previous review was in March 2016). We omitted several of the original databases searched for this review, for the following reasons:
		  ◦ Database of Abstracts of Reviews of Effects (DARE) – no longer included in The Cochrane Library and not updated beyond 15 March 2015;
		  ◦ IndMed – this database is no longer available online;
		  ◦ KoreaMed & PakMediNet – these databases have been searched during four previous update searches for this review, but neither produced any relevant citations not found elsewhere;
		  ◦ ISRCTN & EU Clinical Trials Registers – recent versions of both these trial registers are included within WHO ICTRP.

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Tables

Table 1

Non-analysable data for all outcomes

Study	Antifibrinolytic drug (intervention)	No antifibrinolytic drug (control/ placebo)	Time point	Notes *MD/RR (95% CI) where available**
Comparison 1: TXA vs placebo				
Bleeding: non-standard definitions/reporting				
Avvisati 1989 *Study outcome ROB: high*	Cumulative haemorrhagic score: 3, N = 6	Cumulative haemorrhagic score: 42, N = 6	14 days	Haemorrhagic score 0–3 per day (bleeding: 1, no bleed: 0 over 3 sites).
Shpilberg 1995 – induction chemo group *ROB: high*	Mean 6.2, SD 2.9, N = 16	Mean 4.5, SD 3.6, N = 22	NR	Bleeding events (per person) MD 1.70 (-0.37, 3.77)
Shpilberg 1995 – consolidation chemo group *ROB: high*	Mean 1.1, SD 1.4, N = 10	Mean 2.6, SD 2.2, N = 8	NR	Bleeding events (per person) MD -1.50 (-3.25, 0.25)
Shpilberg 1995 – induction chemo group *ROB: high*	Mean 8.3, SD 4.8, N = 16	Mean 5.6, SD 4.8, N = 22	NR	Cumulative haemorrhagic score 0–3 per day, 0: no bleeding, 3: major bleeding MD 2.70 (-0.39, 5.79)
Shpilberg 1995 – consolidation chemo group *ROB: high*	Mean 1.3, SD 1.8, N = 10	Mean 5.1, SD 3.6, N = 8	NR	Cumulative haemorrhagic score 0–3 per day, 0: no bleeding, 3: major bleeding MD -3.80 (-6.53, -1.07)^^ P < 0.05
Thromboembolism				
Shpilberg 1995 – consolidation chemo group *ROB: some concerns*	0/10	0/8	NR	Unclear if these participants are a subset of the induction chemo group
Mortality due to bleeding				
Shpilberg 1995 – consolidation chemo group *ROB: high*	0/10	0/8	NR	Unclear if these participants are a subset of the induction chemo group
Platelet transfusions per person				
Avvisati 1989 *ROB: high*	Total units: 69, N = 6	Total units: 222, N = 6	14 days	P = 0.045
McCormick 2020 *ROB: some concerns*	Median 1.5, range 0 to 2, N = 6	Median 4, range 1 to 9, N = 5	"30 days from discontinuation of study drug"	
Shpilberg 1995 – consolidation chemo group *ROB: some concerns*	Mean 3.7, SD 4.1, N = 10	Mean 9.3, SD 3.3, N = 8	NR	MD -5.60 (-9.02, -2.18)^^ P < 0.05 Unclear if these participants are a subset of the induction chemo group
RBC transfusions per person				

Avvisati 1989 *ROB: high*	Total units: 28, N = 6	Total units: 56, N = 6	14 days	P = 0.016
McCormick 2020 *ROB: some concerns*	Median 0.5, range 0 to 3, N = 6	Median 1, range 0 to 2, N = 5	"30 days from discontinuation of study drug"	
Shpilberg 1995 – consolidation chemo group *ROB: Some concerns*	Mean 4.1, SD 2.8, N = 10	Mean 4.1, SD 3.4, N = 8	NR	MD 0.00 (-2.93, 2.93) Unclear if these participants are a subset of the induction chemo group
Adverse events: "side effects"				
Shpilberg 1995 – consolidation chemo group *ROB: high*	"no side effects were observed"		NR	Unclear if these participants are a subset of the induction chemo group
Comparison 2: EACA vs no EACA				
Bleeding: "capillary bleeding" – skin, mucous membranes, conjunctivae, nose, or guaiac-positive bleeding in GI or GU tract				
Gallardo 1983 *ROB: high*	31% of days at risk of bleeding (of 158 days at risk), N = 9 (assumed)	50% of days at risk of bleeding (of 80 days at risk), N = 9 (assumed)	NR	Abstract only. Limited info regarding days at risk and bleeding. 1 patient excluded, unclear which group
Bleeding: "major bleeding" – nose bleeding requiring posterior packing, gross GI or GU tract, and CNS				
Gallardo 1983 *ROB: high*	15% N = 9 (assumed)	19% N = 9 (assumed)	NR	Abstract only. Limited info. 1 patient excluded, unclear which group
Platelet transfusions per person				
Gallardo 1983 *ROB: high*	1 every 13.3 days "at risk of bleeding" N = 9 (assumed)	1 every 10.5 days "at risk of bleeding" N = 9 (assumed)	NR	Abstract only. Limited info. 1 patient excluded, unclear which group
Adverse events: "side effects"				
Gallardo 1983 *ROB: high*	"minimal"		NR	Abstract only. Limited info. 1 patient excluded, unclear which group
Other comparisons: EACA vs prophylactic platelet transfusion				
Bleeding: any major bleeding (WHO 3 to 4)				
PROBLEMA 2022 *ROB: high*	"Study was terminated early due to difficulties with enrolment. No outcome measures were assessed." PROBLEMA 2022 reported data for WHO 3 and WHO 4. However, the data appear to be in error as all in the EACA group had WHO 4 and all in the prophylactic platelet tx group had WHO 3, which is clinically very unlikely.			
All-cause mortality				
PROBLEMA 2022 *ROB: high*	5/15	5/14	6-month data only	RR 0.93 (0.34, 2.54)
Adverse events due to antifibrinolytic				
PROBLEMA 2022 *ROB: high*	9/15	8/14	6-month data only	RR 1.05 (0.57, 1.94)
Adverse events due to transfusion				
PROBLEMA 2022 *ROB: high*	1/15	0/14	6-month data only	RR 2.81 (0.12, 63.83)

*MD/RR (95% CI) calculated by review authors; reported P values are as reported by study authors only.

^^ statistically significant difference between antifibrinolytic (intervention) and control: favours intervention

Risk of bias (ROB) refers to the overall ROB for this study and outcome. For more detail, see Figure 2; Figure 3; Figure 4; Figure 5; Figure 6; Figure 7.

CI: confidence interval; **CNS**: central nervous system; **GI**: gastrointestinal; **GU**: genitourinary; **MD**: mean difference; **N**: number of participants reported; **NR**: not reported; **RR**: risk ratio; **SD**: standard deviation; **tx**: transfusion

Table 2

Overview of study characteristics

Trial	No. of participants randomised	No. of participants receiving antifibrinolytics	No. of participants platelet refractory/ allo-immunisation	Diagnosis of patients	Treatment of underlying disease	Antifibrinolytic dose, route, frequency	Treatment started	Treatment stopped	When were platelet transfusions given
Tranexamic acid studies									
A-TREAT 2022	337	168	Patients were not refractory to platelets at the time of enrolment.	9 AA 21 ALL 151 AML 2 CLL 8 CML 12 Hodgkin lymphoma 29 Non-Hodgkin 37 MDS lymphoma 25 Myeloma 17 Myelofibrosis 19 Other	Acute chemo- or immunotherapy without transplant, Allogeneic HSCT, Acute autologous HSCT	1.3 g orally every 8 hours or 1.0 g IV every 8 hours	Study treatment was initiated as soon as possible following activation.	The study drug was discontinued once the platelet count was > 30,000/μL for 46 hours without transfusion or until 30 days after treatment activation, whichever came first.	Prophylactic: patients were treated with a prophylactic platelet transfusion once their platelet count fell below 10,000 or at clinician discretion.
Avvisati 1989	12	6	NR	APML	Chemotherapy	2 g, IV in 500 mL 5% glucose every 8 hours	1st day of antileukaemic treatment	After 6 days	Prophylactic: physicians decided whether to give extra platelet concentrates.
Fricke 1991	8 Only 3 completed study	8	At least 3	7 AA 1 MDS	NR	20 mg/kg orally every 8 hours	After 4-day trial period to assess drug tolerance	Successive 4/52 courses or until WHO grade 2 bleeding	Therapeutic: "we allowed each patient's personal physician to determine the need for platelet transfusion. In every case, the decision to transfuse was based on some form of bleeding, such as severe petechiae, blood blisters, and gum or nose bleeding."
McCormick	11	6	NR	4 LL 2 ML 2 Lymphom	Chemotherapy or Autologous/ Allogeneic HSCT	10 mg/kg IV, diluted in normal saline to a total volume of 15 mL, every 8 ho	From randomisation	Platelet count as < 30,000/μL until discharge or spontaneous platelet recovery (maximum 30 days)	Information about prophylactic or therapeutic transfusion not reported. Threshold information also not reported.

2020				a 3 Solid tumour		urs (or three times a day)			
Shpilberg 1995	38*	NR*	NR	AML	Chemotherapy	1 g orally, every 6 hours	Platelets < 20 or rapidly falling and < 50	Platelet count > 20 for 2 consecutive counts	Therapeutic: information about when additional platelets would be transfused was not reported.
TREATT 2025	616	310	TXA: 1/310, Placebo: 6/306	264 AML 20 ALL 2 APML 12 CML 7 CLL 29 Hodgkin lymphoma 132 Non-Hodgkin lymphoma 71 Myeloma 40 MDS 38 Other	Chemotherapy, Autograft HSCT, Allograft HSCT	1 g IV or 1.5 g orally every 8 hours	Trial treatment was started as soon as possible, and no later than 72 hours after the first recorded platelet count of 30×10^9 platelets per L or less.	Trial treatment continued until the participant had a spontaneous increase in platelet count from 30×10^9 platelets/L or less to more than 50×10^9 platelets/L, 3 consecutive days with platelet counts of more than 30×10^9 platelets/L and no platelet transfusions, or it was 30 days since trial treatment commenced.	Prophylactic: prophylactic platelet transfusions were maintained as standard of care
EACA studies									
Gallardo 1983	19	9	NR	15 AML 4 ALL (1 patient not evaluable)	Chemotherapy	Loading dose 100 mg/kg 12 to 24 g/day thereafter (route of administration and frequency not reported)	Platelet count < 20 x 10^9/L	Platelet count ≥ 20 x 10^9/L	Prophylactic: it is not clear at what threshold additional platelets were transfused
PROBLEMA 2022	NR	15	NR	NR	Chemotherapy or HSCT	1000 mg orally twice a day if platelets < 20 x 10^9/L	Given if platelets < 20 x 10^9/L	NR	Prophylactic: additional platelets transfused if grade ≥ 2 bleeding

*In Shpilberg 1995, it is unclear how many independent participants were included: 38 participants were randomised in the induction chemotherapy group (TXA or placebo), and then 18 participants undergoing consolidation chemotherapy were assessed. There is some suggestion that those assessed during consolidation chemotherapy may be a subset of those assessed during induction chemotherapy, and it is also not mentioned whether these participants were re-randomised, continued as previously randomised, or were independent (new) participants. We have therefore only included the induction chemotherapy patients and data in our analyses.

AA: aplastic anaemia; **ALL**: acute lymphoblastic leukaemia; **AML**: acute myeloid leukaemia; **APML**: acute promyelocytic leukaemia; **CLL**: chronic lymphocytic leukaemia; **CML**: chronic myeloid leukaemia; **EACA**: epsilon aminocaproic acid; **HSCT**: haematopoietic stem cell transplantation; **IV**: intravenous; **LL**: lymphoid leukaemia; **MDS**: myelodysplastic syndrome; **ML**: myeloid leukaemia; **NR**: not reported; **RCT**: randomised controlled trial; **TXA**: tranexamic acid; **WHO**: World Health Organization

Table 3

Overview of outcomes reported by studies

	Bleeding					Thromboembolism			Mortality			Transfusions		Adverse events			
	WHO1 or 1+ or "any"	WHO2 or 2+	WHO3 or 3+	WHO 4	Other	Any	Arterial (ATE)	Venous (VTE)	All-cause	Due to bleeding	Due to thromboembolism	Platelet tx per person	RBCs tx per person	Attributable to antifibrinolytic agent	Attributable to transfusion	DIC	HRQoL
Intervention: TXA																	
A-TREAT 2022		Y	Y	Y		Y			Y	Y	Y	Y	Y	Y			
Avvisati 1989					Y (NA)	Y	Y	Y			Y	Y (NA)	Y (NA)				
Fricke 1991					Y (NA)							Y (NA)	Y (NA)	Y (NA)			
McCormick 2020	Y	Y	Y	Y		Y	Y	Y	Y	Y	Y	Y (NA)	Y (NA)	Y			
Shpilberg 1995					Y (NA)	Y	Y	Y		Y	Y	Y	Y	Y	Y		
TREATT 2025	Y	Y	Y	Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y
Intervention: EACA																	
Gallardo 1983					Y (NA)						Y	Y (NA)		Y (NA)	Y (NA)		
PROBLEMA 2022			Y (NA)	Y (NA)					Y (NA)					Y (NA)	Y (NA)		

Y: Yes, analysable data were reported for this outcome; **Y (NA)**: Yes, data were reported, but were unsuitable for analysis (e.g. reported as median and range, or after 30-day time point)

ATE: arterial thromboembolism; **DIC**: disseminated intravascular coagulation; **HRQoL**: health-related quality of life; **RBC**: red blood cell; **tx**: transfusions; **VTE**: venous thromboembolism; **WHO**: World Health Organization

WHO bleeding grades

- WHO1: WHO grade 1 bleeding, clinically non-significant (WHO 1+ includes all grades 1 to 4, i.e. "any" bleeding)
- WHO2: WHO grade 2 bleeding, clinically significant (WHO 2+ includes all grades from 2 to 4, i.e. any clinically significant bleeding)
- WHO3: WHO grade 3 bleeding, bleeding that requires red cell transfusion (WHO 3+ includes grades 3 and 4)
- WHO4: WHO grade 4 bleeding, life-threatening or fatal bleeding

We extracted no data from Fricke 1991 due to major methodological problems in the study design.

Gallardo 1983 reported the outcome of adverse events due to antifibrinolytic drugs. Authors described no specific adverse events; they only stated that side effects were minimal.

Shpilberg 1995 reported 'no side effects were observed'. We have inferred that this meant adverse events due to antifibrinolytic drugs as well as transfusion were both zero.

Mortality due to thrombosis was not reported by Avvisati 1989 or Shpilberg 1995. We have inferred that if 'no thromboembolic events occurred' in these trials, then no deaths from thrombosis could have occurred either.

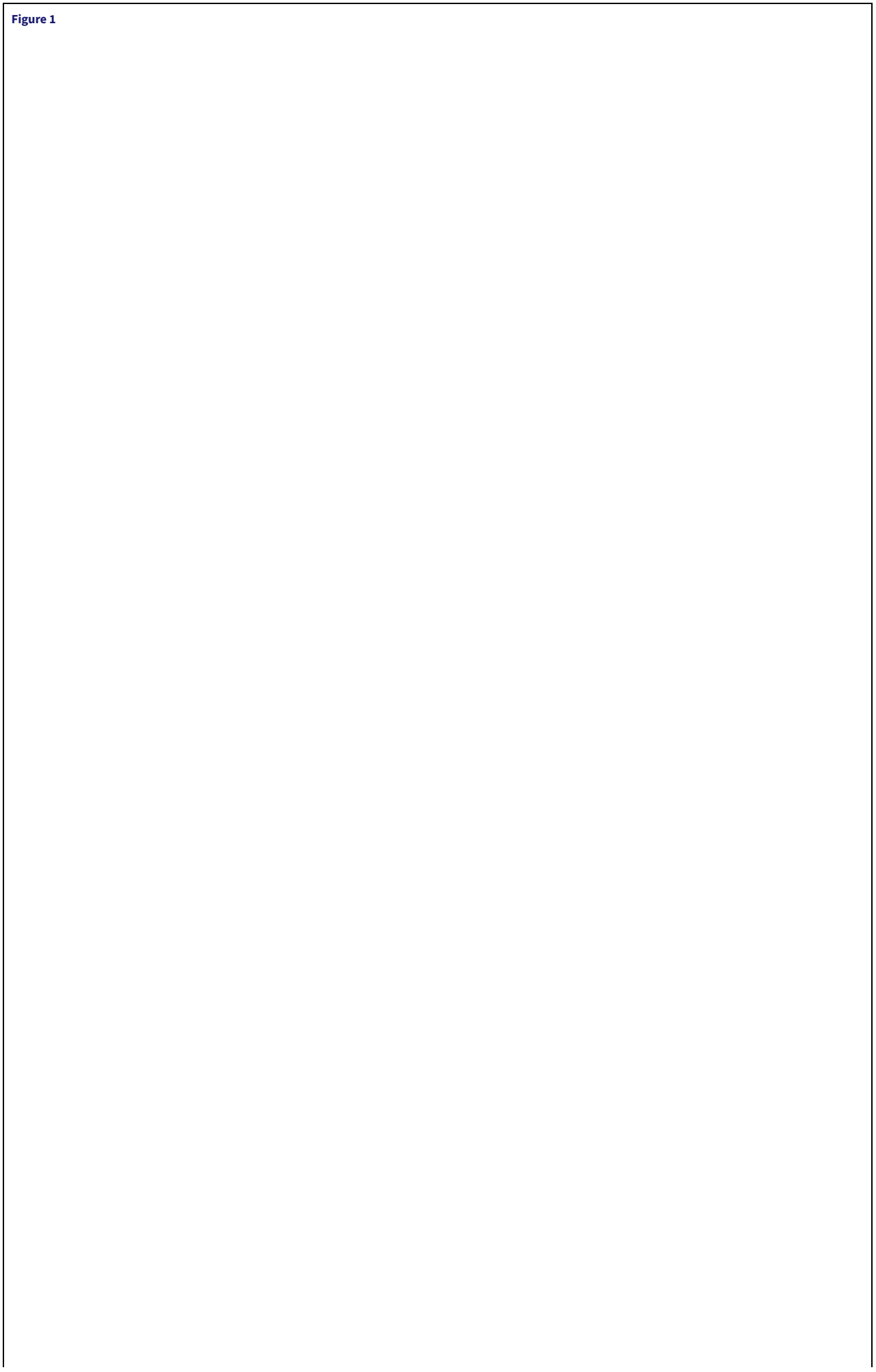
Avvisati 1989 and Shpilberg 1995 both report that 'no thromboembolic events occurred' in their trials. From this statement, we inferred that arterial and venous thromboembolic events must also be zero.

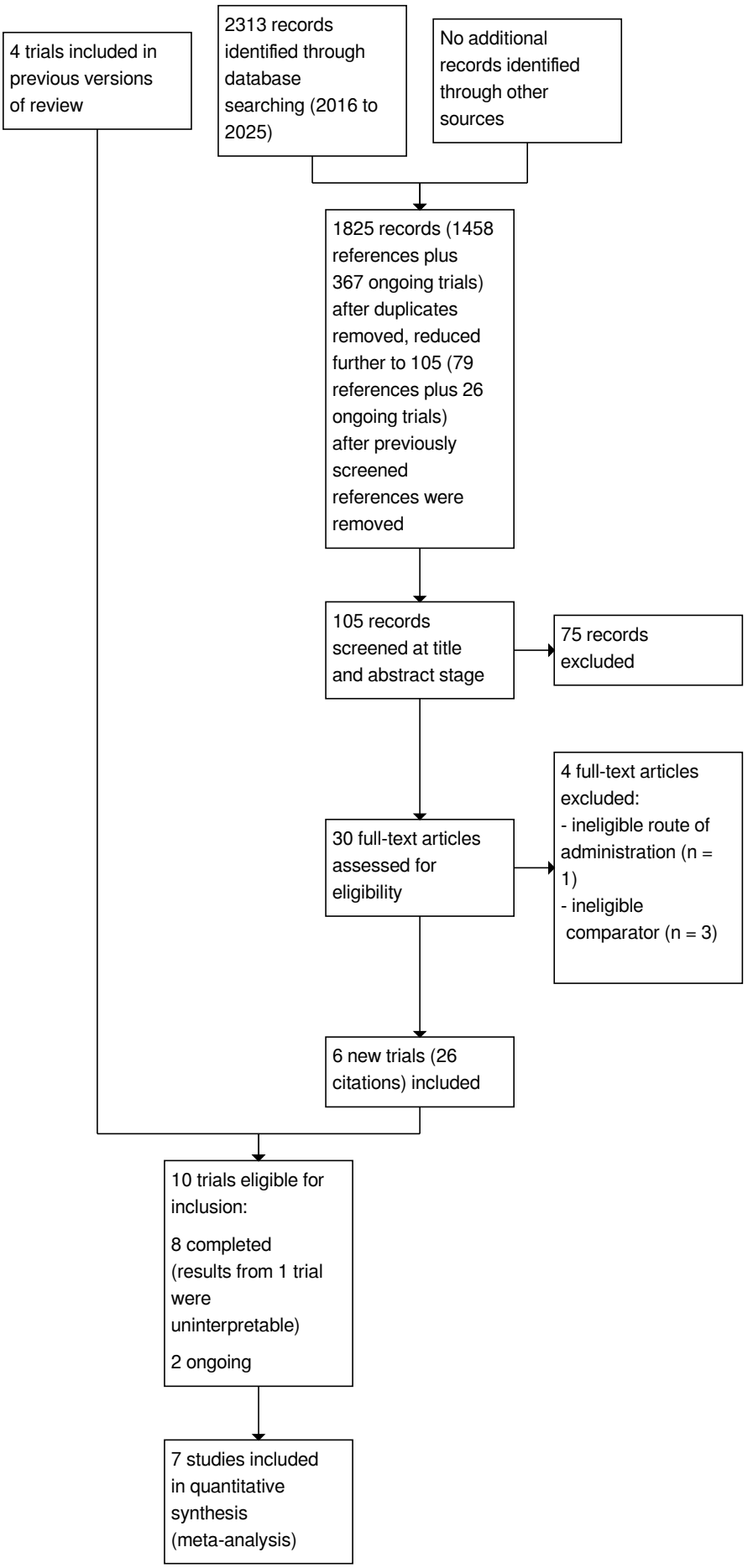
No trial reported disseminated intravascular coagulation (DIC).

Only one trial measured quality of life (TREATT 2025). We reported these results in Analysis 1.14.

Figures

Figure 1





PRISMA study flow diagram for 2025 update searches

Figure 2

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
TXA vs placebo									
A-TREATT 2022	TXA (IV or oral)	Placebo (IV or oral)	Bleeding outcomes	+	+	+	+	+	+
Avvisati 1989	TXA (IV)	Placebo (IV)	Bleeding outcomes	!	-	+	-	!	-
McCormick 2020	TXA (IV)	Placebo (IV)	Bleeding outcomes	!	+	+	+	!	!
Shpilberg 1995	TXA (oral)	Placebo (oral)	Bleeding outcomes	!	+	+	-	!	-
TREATT 2025	TXA (IV or oral)	Placebo (IV or oral)	Bleeding outcomes	+	+	+	+	+	+
EACA vs no EACA/transfusion									
Gallardo 1983	EACA (NR)	no EACA	Bleeding outcomes	!	-	-	-	!	-
PROBLEMA 2022	EACA (oral)	prophylactic plt tx	Bleeding outcomes	!	!	-	-	-	-

Summary of review authors' risk of bias assessments for bleeding outcomes.

D1: randomisation process
D2: deviations from the intended interventions
D3: missing outcome data
D4: measurement of the outcome
D5: selection of the reported result

Figure 3

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
TXA vs placebo									
A-TREATT 2022	TXA (IV or oral)	Placebo (IV or oral)	Thromboembolism	+	+	+	+	+	+
Avvisati 1989	TXA (IV)	Placebo (IV)	Thromboembolism	!	-	+	+	!	-
McCormick 2020	TXA (IV)	Placebo (IV)	Thromboembolism	!	+	+	+	!	!
Shpilberg 1995	TXA (oral)	Placebo (oral)	Thromboembolism	!	+	+	+	!	!
TREATT 2025	TXA (IV or oral)	Placebo (IV or oral)	Thromboembolism	+	+	+	+	+	+

Summary of review authors' risk of bias assessments for thromboembolism outcomes.

D1: randomisation process
D2: deviations from the intended interventions
D3: missing outcome data
D4: measurement of the outcome
D5: selection of the reported result

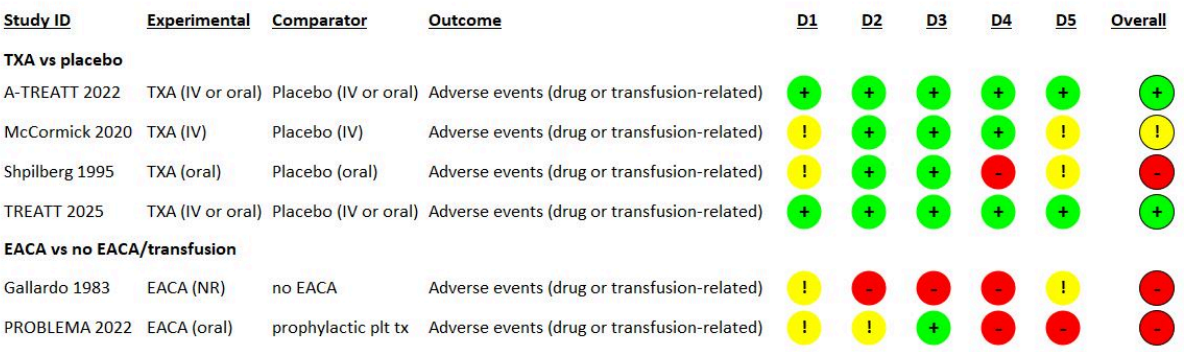
Figure 4

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
TXA vs placebo									
A-TREATT 2022	TXA (IV or oral)	Placebo (IV or oral)	Mortality	+	+	+	+	+	+
Avvisati 1989	TXA (IV)	Placebo (IV)	Mortality	!	-	+	+	!	-
McCormick 2020	TXA (IV)	Placebo (IV)	Mortality	!	+	+	+	!	!
Shpilberg 1995	TXA (oral)	Placebo (oral)	Mortality	!	+	+	-	!	-
TREATT 2025	TXA (IV or oral)	Placebo (IV or oral)	Mortality	+	+	+	+	+	+
EACA vs no EACA/transfusion									
Gallardo 1983	EACA (NR)	no EACA	Mortality	!	-	-	+	!	-
PROBLEMA 2022	EACA (oral)	prophylactic plt tx	Mortality	!	!	+	+	-	-

Summary of review authors' risk of bias assessments for mortality outcomes.

D1: randomisation process
D2: deviations from the intended interventions
D3: missing outcome data
D4: measurement of the outcome
D5: selection of the reported result

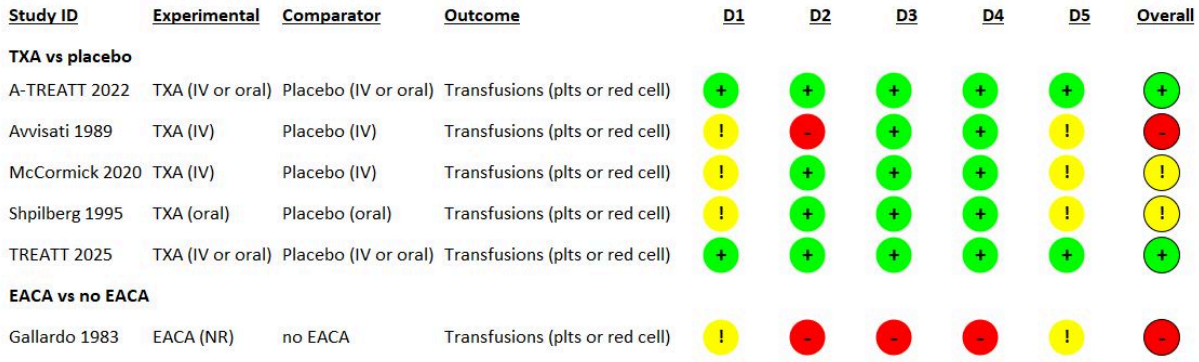
Figure 5



Summary of review authors' risk of bias assessments for adverse event outcomes.

D1: randomisation process
D2: deviations from the intended interventions
D3: missing outcome data
D4: measurement of the outcome
D5: selection of the reported result

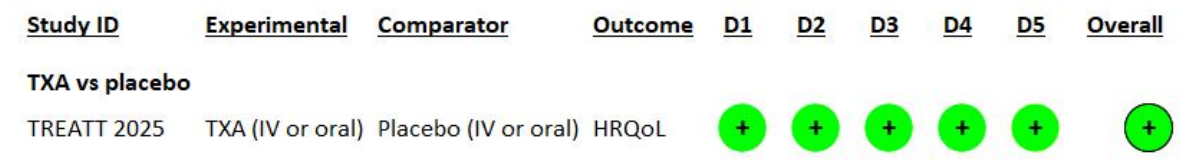
Figure 6



Summary of review authors' risk of bias assessments for tranfsusion outcomes.

D1: randomisation process
D2: deviations from the intended interventions
D3: missing outcome data
D4: measurement of the outcome
D5: selection of the reported result

Figure 7



Summary of review authors' risk of bias assessments for quality of life outcome.

D1: randomisation process
D2: deviations from the intended interventions
D3: missing outcome data
D4: measurement of the outcome
D5: selection of the reported result

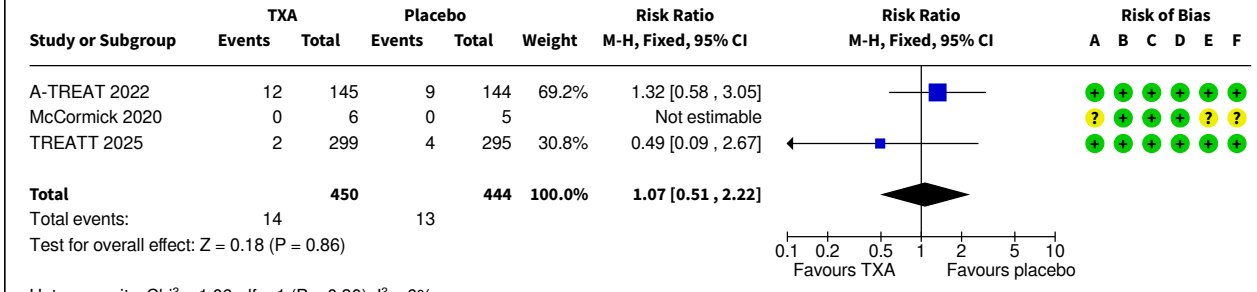
Figure 8

Heterogeneity: Chi² = 2.15, df = 2 (P = 0.34); I² = 7%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Forest plot for TXA versus placebo: WHO grade 2 bleeding or higher (clinically significant bleeding)

Figure 9

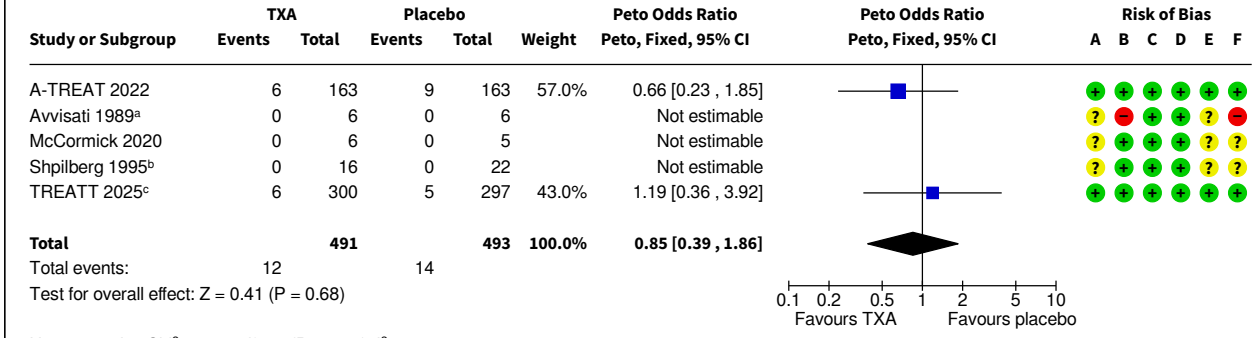


Heterogeneity: Chi² = 1.06, df = 1 (P = 0.30); I² = 6%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Forest plot for TXA versus placebo: WHO grade 3 bleeding or higher (severe or life-threatening bleeding)

Figure 10



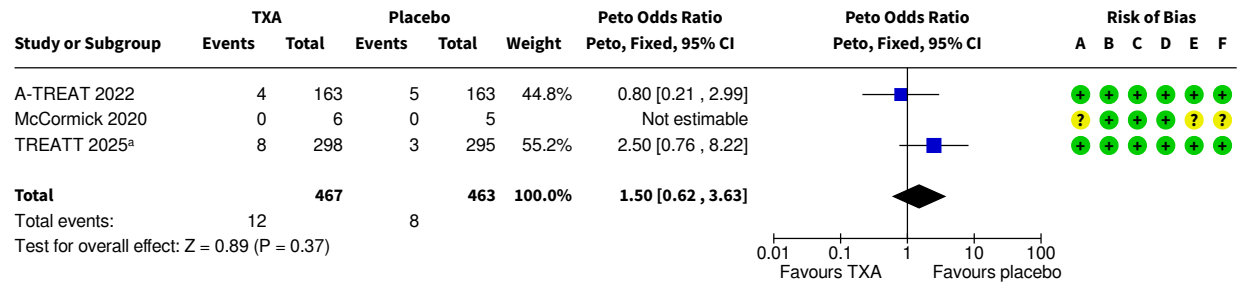
Heterogeneity: Chi² = 0.54, df = 1 (P = 0.46); I² = 0%

Footnotes
[a]Follow-up for this outcome was 14 days
[b]Only data from the induction group contributed to this analysis
[c]Data provided by triallists is for 'Symptomatic thrombotic events up to 30 days'

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Forest plot for TXA versus placebo: number of participants with 'any' thromboembolism

Figure 11



Heterogeneity: Chi² = 1.58, df = 1 (P = 0.21); I² = 37%

Footnotes

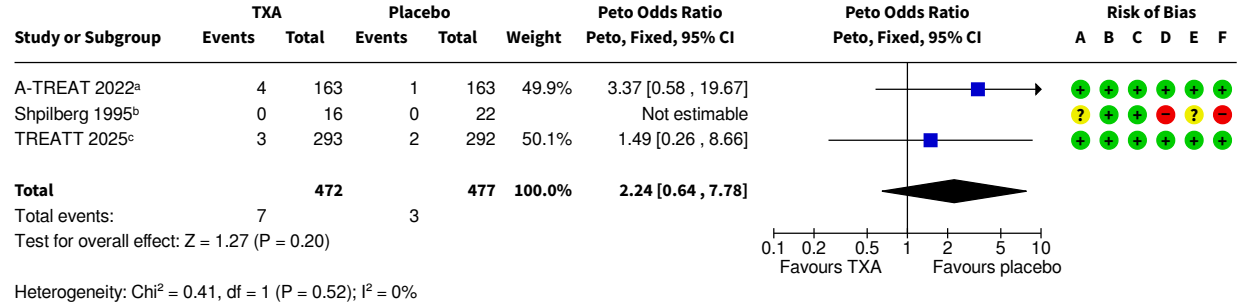
[a]Data provided by triallists

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Forest plot for TXA versus placebo: all-cause mortality

Figure 12



Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%

Footnotes

[a]Data provided by triallists
[b]Only data from the induction group contributed to this analysis
[c]No. of people discontinued due to unacceptable adverse reaction to treatment; no SUSARs (suspected unexpected serious adverse reaction) reported

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Forest plot for TXA versus placebo: adverse events attributable to antifibrinolytic agents