National Institute for Health and Care Excellence

Blood transfusion (update)

[B] Technical appendices for safety of tranexamic acid during surgery

NICE guideline NG24

Technical data underpinning evidence review safety of tranexamic acid

November 2025

Draft for Consultation

Copyright

Contents

Appendix A Review protocols

Review protocol for effectiveness review of the safety of tranexamic acid.

ID	Field	Content
0.	PROSPERO registration number	Not applicable
1.	Review title	Safety of tranexamic acid during surgery
2.	Review question	What is the safety of tranexamic acid in the short-term prevention of surgical bleeding?
3.	Objective	Prophylactic tranexamic acid is thought to be associated with reduction in need for blood transfusions in people having surgery. However, there are concerns that it may increase the risk of thrombotic events due to the mechanism of action of the treatment (by inhibiting plasmin, an enzyme that normally would break down fibrin blood clots). Establishing whether this is the case or not using large datasets will assist assessing whether the treatment is safe to use.
4.	Searches	Key papers: Devereaux PJ, Marcucci M, Painter TW, Conen D, Lomivorotov V, Sessler DI, Chan MTV, Borges FK, Martínez-Zapata MJ, Wang CY, Xavier D, Ofori SN, Wang MK, Efremov S, Landoni G, Kleinlugtenbelt YV, Szczeklik W, Schmartz D, Garg AX, Short TG, Wittmann M, Meyhoff CS, Amir M, Torres D, Patel A, Duceppe E, Ruetzler K, Parlow JL, Tandon V, Fleischmann E, Polanczyk CA, Lamy A, Astrakov SV, Rao M, Wu WKK, Bhatt K, de Nadal M, Likhvantsev VV, Paniagua P, Aguado HJ, Whitlock RP, McGillion MH, Prystajecky M, Vincent J, Eikelboom J, Copland I, Balasubramanian K, Turan A, Bangdiwala SI, Stillo D, Gross PL,

		Cafaro T, Alfonsi P, Roshanov PS, Belley-Côté EP, Spence J, Richards T, VanHelder T, McIntyre W, Guyatt G, Yusuf S, Leslie K; POISE-3 Investigators. Tranexamic Acid in Patients Undergoing Noncardiac Surgery. N Engl J Med. 2022 May 26;386(21):1986-1997. Richardson MK, Liu KC, Mayfield CK, Kistler NM, Lieberman JR, Heckmann ND. Tranexamic Acid Is Safe in Patients with a History of Venous Thromboembolism Undergoing Total Joint Arthroplasty. J Bone Joint Surg Am. 2024 Jan 3;106(1):30-38. The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	People having surgery at risk of bleeding that could be reduced or prevented if they receive tranexamic acid

6.	Population	Inclusion: • Adults (age at least 16 years) or children (age less than 16 years) who are not pregnant and are at risk of short-term bleeding. • Pregnant women, trans men and non-binary people (age at least 16 years) at risk of bleeding short-term Exclusion: • Babies (age up to 1 year) who are at risk of short-term bleeding
7.	Intervention	Tranexamic acid (all doses and routes of administration pooled together)
8.	Comparator/Confounding factors	Comparator: • An alternative therapy (with potential vascular activity, this includes other antifibrinolytic therapies) (tranexamic acid and surgery compared to a different treatment and the same surgery) • Placebo (for example: saline, dextrose) (tranexamic acid and surgery compared to placebo and the same surgery) • Usual care (no treatment in addition to surgery) (tranexamic acid and surgery compared to the same surgery) Other comparators: (These comparators will be reported if subgroup analysis is required due to significant heterogeneity in the analysis) • A different dose of tranexamic acid (tranexamic acid at one dose compared to tranexamic acid at another dose) • A different route of administration of tranexamic acid (tranexamic acid delivered by one route of administration compared to tranexamic acid delivered by another route)

		Key confounding factors: (these will be extracted as baseline characteristics for each study) • Age • Sex • Comorbidities
9.	Types of study to be included	• Systematic reviews of comparative studies (including NMAs and IPDs) • Randomised controlled trials (RCTs) • Non-randomised controlled trials/Prospective cohort studies • Retrospective cohort studies or historically controlled studies A hierarchy of evidence approach will be used. If there is insufficient evidence to make a conclusion based on systematic reviews, then RCTs will be considered. If there is insufficient evidence based on RCTs, then prospective cohort studies will be considered etc. Sufficiency will be judged taking into account factors including the number and quality of studies and outcomes reported. Non-randomised studies will only be included if they adjust for key confounding factors. Conference abstracts will not be considered.
10.	Other exclusion criteria	• Studies with a sample size less than 500 in each arm as the baseline rate of thromboembolic events in the surgical population reported in the literature is between 2-13/1000 people. Therefore, restricting this to studies with at least 500 people in each arm means that the chance of there being at least 1 event in each study arm if the study was repeated is reasonable. Therefore, the findings of the study can be taken as less likely to be due to chance than smaller studies.

		• Individual patient data meta-analyses that include at least 500 people in each arm would be eligible for inclusion. • Trials where tranexamic acid is prescribed for long term management of blood loss (for example: for menorrhagia). • Non-English language studies • Non comparative cohort studies • Before and after studies • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	The review is intended to support recommendations for surgical practice in the English and Welsh NHS. This review is taking place as an update of NICE guideline NG24 (Blood transfusion).
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical. The final reported timepoint will be used. It is expected that this timepoint will be within 3 months after the surgery. • All-cause mortality • Thromboembolic (arterial and venous) events after surgery (reported as an aggregate outcome and additionally extracting the specific events) • Pulmonary embolism • Deep vein thrombosis • Myocardial infarction • Ischaemic stroke • Infection • All-cause readmission • Seizures • Reoperation
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will

		be uploaded into EPPI R5 and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One technical analyst will extract relevant data. This will be quality controlled by a senior technical analyst.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non-randomised study, including cohort studies: Cochrane ROBINS-I The quality assessment will be performed by one technical analyst, and this will be quality controlled by a senior technical analyst.

15.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted, and data will be presented as risk ratios or odds ratios for dichotomous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, the following criteria will be used to assess heterogeneity: no serious I^2 = <40%; serious I^2 = 40-60%; very serious I^2 = >60%. Where I^2 is 80% or above, the data will not be pooled. I^2 values of greater than 40% and 60% will be considered as serious and very serious heterogeneity, respectively. Where I^2 is 80% or above the data will not be pooled. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. Publication bias will be investigated using a funnel plot when there are 10 or more studies in an analysis. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/.

		Importance and imprecision of findings will be assessed against minimally important differences (MIDs). MIDs for each outcome are detailed in the methods supplement for this guideline.
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Surgical speciality (general surgery, otolaryngology, gynaecology, orthopaedics, urology, plastic surgery, dentistry, mixed, not stated/unclear) • Anticoagulant or antiplatelet use (yes, no, perioperative anticoagulation, mixed population, not stated/unclear) • Comorbidities that increase risk of thromboembolic events (yes, no, mixed population, not stated/unclear) • Dose (different doses, mixed population, not stated/unclear) • Route of administration (intravenous, topical, oral, intravenous and topical, intravenous and oral, other, not stated/unclear) • Repeated use (single use, repeated use, mixed population, not stated) • Renal function (no relevant impairment, severe renal impairment [as stated or eGFR below 30 mL/min/1.73 m^2], mixed population, not stated/unclear)
17.	Type and method of review	Intervention; Safety review
18.	Language	English
19.	Country	England
20.	Anticipated or actual start date	1/7/2025
21.	Anticipated completion date	9/9/2025
22.	Stage of review at time of this submission	• Preliminary stages – Started • Piloting of study selection process – Started

		• Formal screening of search results against eligibility criteria – Started • Data extraction – Started • Risk of bias (quality) assessment – Started • Data analysis – Started
23.	Named contact	5a. Named contact. National Institute for Health and Care Excellence (NICE) 5b. Named contact e-mail. bloodtransfusion@nice.org.uk 5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
24.	Review team members	Clifford Middleton (Guideline Lead) George Wood (Senior Technical Analyst) Sophia Kemmis-Betty (Health Economics Adviser) Nicola Greenway (Measurement Lead) Magdalena Watras (Pharmacist Clinical Adviser) Danielle Conroy (Project Manager) Philip Alderson (Clinical Advisor)
25.	Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a

		senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
28.	Other registration details	Not applicable
29.	Reference/URL for published protocol	Not applicable
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
31.	Keywords	Adults; Bleeding; Blood transfusion; Children; Deep vein thrombosis; Haemorrhage; Infection; Intervention; Myocardial infarction; Pulmonary embolism; Thromboembolic event; Tranexamic acid; Safety; Stroke; Surgery
32.	Details of existing review of same topic by same authors	Not applicable
33.	Current review status	Completed but not published
34.	Additional information	No additional information
35.	Details of final publication	www.nice.org.uk

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Appendix B Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review. The systemic review searches were run on 21st May 2025, an additional search for randomised controlled trials were run on 7th August 2025.

This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search terms for the blood transfusion population were taken from the transfusion-search-strategies2 from NG24 Blood Trasfusion (November 2015). An additional MeSH heading Blood Loss, Surgical/, was also added to the population searches.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and the review protocol to exclude:

Animal studies

Conference abstracts and posters

Registry entries for ongoing clinical trials or those that contain no results

Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

A date limit of 2020 to 2025 was applied, as this was a unique question looking at the safety of TXA. This date limit was agreed with the Technical Analysts.

Search filters and classifiers

Safety search

Systematic reviews filters:

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. BMC Medical Research Methodology, 12(1), 51.

In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Randomised controlled trials filters:

The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.

The standard NICE modifications were used: the MeSH heading randomized controlled trial/, which is equivalent to randomized controlled trial.pt was exploded to capture newer, narrower terms equivalence trial/ and pragmatic clinical trial. The free-text term randomized.mp was also changed to the (more inclusive) alternative randomi?ed.mp. to capture both UK and US spellings.

Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. BMJ, 330, 1179-1183.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

Saftey searches – systematic review search

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	21 May 2025	Wiley	Issue 5 of 12, May 2025	15
Embase	21 May 2025	Ovid	Embase 1974 to 2025 May 20	766
Epistemonikos	21 May 2025	Epistemonikos	Searched 21 May 2025	84
MEDLINE	21 May 2025	Ovid	1946 to May 20, 2025	474

1 Search strategy history

2 Database name: MEDLINE ALL

Search:
1 NG24.tw. 4
2 exp Specialties, Surgical/ 230271
3 (surg* or operat* or preoperat* or pre-operat* or perioperat* or peri-operat* or intraoperat* or intra-operat* or postoperat* or post-operat*).tw. 3904630
4 exp Perioperative Period/ 110085
5 exp Perioperative Care/ 164967
6 exp Blood Transfusion/ 95956
7 exp Blood Loss, Surgical/ 22257
8 transfus*.ti,ab. 145345
9 (Blood los* or bleed* or bled*).tw. 349001
10 or/2-9 4389049
11 Tranexamic Acid/ 5779
12 (tranexamic or txa or cyklokapron).ti,ab. 8771
13 (ugurol or transamin or kabi 2161 or amchafibrin or amikapron or anvitoff or amstat or anexan or exacyl or frenolyse or rikaparin or tramic or tranex or traxamic or trenaxin or trenolk or unixam).tw. 50
14 or/11-13 9630
15 10 and 14 6370
16 (MEDLINE or pubmed).tw. 428167
17 systematic review.tw. 365193
18 systematic review.pt. 305709
19 meta-analysis.pt. 218038
20 intervention$.ti. 242777
21 or/16-20 863539

22 15 and 21 962
23 (2020* or 2021* or 2022* or 2023* or 2024* or 2025*).ed,dt. 9796673
24 22 and 23 584
25 animals/ 7755111
26 exp Animals, Laboratory/ 1012594
27 exp Animal Experimentation/ 10785
28 exp Models, Animal/ 694837
29 exp Rodentia/ 3754126
30 (rat or rats or mouse or mice or rodent*).ti. 1542991
31 or/25-30 7891250
32 31 not humans/ 5476870
33 24 not 32 583
34 limit 33 to english language 580
35 1 or 34 474

Database name: EMBASE

Search:
1 NG24.tw. 21
2 exp *surgery/ 3227177
3 (surg* or operat* or preoperat* or pre-operat* or perioperat* or peri-operat* or intraoperat* or intra-operat* or postoperat* or post-operat*).tw. 5239616
4 exp perioperative period/ 1347276
5 exp perioperative care/ 183965
6 exp *blood transfusion/ 64193
7 exp *operative blood loss/ 3361
8 transfus*.ti,ab. 242249
9 (Blood los* or bleed* or bled*).tw. 587708
10 or/2-9 7289505
11 tranexamic acid/ 23913
12 (tranexamic or txa or cyklokapron).tw. 13634
13 (ugurol or transamin or kabi 2161 or amchafibrin or amikapron or anvitoff or amstat or anexan or exacyl or frenolyse or rikaparin or tramic or tranex or traxamic or trenaxin or trenolk or unixam).tw. 477
14 or/11-13 25082
15 10 and 14 17729
16 (MEDLINE or pubmed).tw. 525976
17 exp systematic review/ or systematic review.tw. 655874

18 meta-analysis/ 379266
19 intervention$.ti. 336780
20 or/16-19 1223018
21 15 and 20 1780
22 (2020* or 2021* or 2022* or 2023* or 2024* or 2025*).dc. 12100183
23 21 and 22 1030
24 letter.pt. or letter/ 1403296
25 note.pt. 1021844
26 editorial.pt. 849931
27 (letter or comment*).ti. 265493
28 or/24-27 3339354
29 randomized controlled trial/ or random*.ti,ab. 2647665
30 28 not 29 3301265
31 23 not 30 1001
32 animal/ 1734865
33 nonhuman/ 8343518
34 exp Animal Experiment/ 3439983
35 exp Experimental Animal/ 916631
36 animal model/ 1977654
37 exp Rodent/ 4400557
38 (rat or rats or mouse or mice or rodent*).ti. 1738766
39 or/32-38 10972246
40 39 not human/ 7736759
41 31 not 40 998
42 limit 41 to english language 974
43 1 or 42 766

Database name: Cochrane CDSR

Search:
#1 NG24:ti,ab,kw 1
#2 MeSH descriptor: [Specialties, Surgical] explode all trees 3239
#3 (surg* or operat* or preoperat* or pre-operat* or perioperat* or peri-operat* or intraoperat* or intra-operat* or postoperat* or post-operat*):ti,ab,kw 439942
#4 MeSH descriptor: [Perioperative Period] explode all trees 11450
#5 MeSH descriptor: [Perioperative Care] explode all trees 15118
#6 MeSH descriptor: [Blood Transfusion] explode all trees 4745
#7 MeSH descriptor: [Blood Loss, Surgical] explode all trees 3583
#8 transfus*:ti,ab,kw 22318
#9 ((Blood near/2 los*) or bleed* or bled*):ti,ab,kw 49753

#10 {OR #2-#9} 478800 #11 MeSH descriptor: [Tranexamic Acid] explode all trees 1918 #12 (tranexamic or txa or cyklokapron):ti,ab,kw 4652 #13 (ugurol or transamin or kabi 2161 or amchafibrin or amikapron or anvitoff or amstat or anexan or exacyl or frenolyse or rikaparin or tramic or tranex or traxamic or trenaxin or trenolk or unixam):ti,ab,kw 73 #14 {OR #11-#13} 4663 #15 #10 and #14 with Publication Year from 2020 to 2025, with Cochrane Library publication date Between Jan 2020 and May 2025, in Trials 1506 #16 #1 or #15 1507 **15 results in CDSR**

Database name: Epistemonikos

Searches
Title/Abstract ("Tranexamic Acid" OR "Tranexamic Acids" OR txa) AND Title/Abstract ("Blood Transfusion" OR "Blood Transfusions" OR "Blood Loss") AND Publication year: Last 5 years AND Publication type: Systematic review **Total 84**

Saftey searches – randomised control trials search

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	07 August 2025	Wiley	Issue 8 of 12, August 2025	0
Cochrane Central Register of Controlled Trials (CENTRAL)	07 August 2025	Wiley	Issue 7 of 12, July 2025	1518
Embase	07 August 2025	Ovid	Embase 1974 to 2025 May 20	2165
Epistemonikos	07 August 2025	Epistemonikos	Searched 21 May 2025	123

MEDLINE	07 August 2025	Ovid	1946 to May 20, 2025	1091

1 Search strategy history

2 Database name: MEDLINE ALL

Search:
1 NG24.tw. 4
2 exp Specialties, Surgical/ 229552
3 (surg* or operat* or preoperat* or pre-operat* or perioperat* or peri-operat* or intraoperat* or intra-operat* or postoperat* or post-operat*).tw. 3862230
4 exp Perioperative Period/ 109318
5 exp Perioperative Care/ 164373
6 exp Blood Transfusion/ 95673
7 exp Blood Loss, Surgical/ 22121
8 transfus*.ti,ab. 144145
9 (Blood los* or bleed* or bled*).tw. 345359
10 or/2-9 4344056
11 Tranexamic Acid/ 5741
12 (tranexamic or txa or cyklokapron).ti,ab. 8651
13 (ugurol or transamin or kabi 2161 or amchafibrin or amikapron or anvitoff or amstat or anexan or exacyl or frenolyse or rikaparin or tramic or tranex or traxamic or trenaxin or trenolk or unixam).tw. 50
14 or/11-13 9510
15 10 and 14 6292
16 (2020* or 2021* or 2022* or 2023* or 2024* or 2025*).ed,dt. 9490979
17 15 and 16 3126
18 exp Randomized Controlled Trial/ 645402
19 randomi?ed.mp. 1202951
20 placebo.mp. 269709
21 or/18-20 1273177
22 17 and 21 1118
23 animals/ 7713966
24 exp Animals, Laboratory/ 1005995
25 exp Animal Experimentation/ 10738
26 exp Models, Animal/ 689042
27 exp Rodentia/ 3735494
28 (rat or rats or mouse or mice or rodent*).ti. 1536806

29 or/23-28 7848426
30 29 not humans/ 5454877
31 22 not 30 1111
32 limit 31 to english language 1090
33 letter/ 1304881
34 editorial/ 733342
35 news/ 231432
36 exp historical article/ 416813
37 Anecdotes as Topic/ 4748
38 comment/ 1054298
39 (letter or comment*).ti. 216748
40 or/33-39 3031620
41 randomized controlled trial/ or random*.ti,ab. 1789213
42 40 not 41 3003895
43 32 not 42 1087
44 1 or 43 1091

Database name: EMBASE

Search:
1 NG24.tw. 20
2 exp *surgery/ 3198717
3 (surg* or operat* or preoperat* or pre-operat* or perioperat* or peri-operat* or intraoperat* or intra-operat* or postoperat* or post-operat*).tw. 5174640
4 exp perioperative period/ 1330827
5 exp perioperative care/ 181357
6 exp *blood transfusion/ 63871
7 exp *operative blood loss/ 3326
8 transfus*.ti,ab. 240080
9 (Blood los* or bleed* or bled*).tw. 581380
10 or/2-9 7206077
11 tranexamic acid/ 23475
12 (tranexamic or txa or cyklokapron).tw. 13377
13 (ugurol or transamin or kabi 2161 or amchafibrin or amikapron or anvitoff or amstat or anexan or exacyl or frenolyse or rikaparin or tramic or tranex or traxamic or trenaxin or trenolk or unixam).tw. 475
14 or/11-13 24627
15 10 and 14 17393
16 (2020* or 2021* or 2022* or 2023* or 2024* or 2025**).dc,dd**. 11851015
17 15 and 16 8822
18 random:.tw. 2470200

19 placebo:.mp. 636527
20 double-blind:.tw. 324039
21 or/18-20 2776624
22 17 and 21 2479
23 animal/ 1721727
24 nonhuman/ 8251992
25 exp Animal Experiment/ 3401354
26 exp Experimental Animal/ 904770
27 animal model/ 1949479
28 exp Rodent/ 4361165
29 (rat or rats or mouse or mice or rodent*).ti. 1728869
30 or/23-29 10865759
31 30 not human/ 7674108
32 22 not 31 2454
33 conference*.db,pt,su. 6352516
34 32 not 33 2223
35 limit 34 to english language 2167
36 letter.pt. or letter/ 1390369
37 note.pt. 1015556
38 editorial.pt. 843143
39 (letter or comment*).ti. 261208
40 or/36-39 3312646
41 randomized controlled trial/ or random*.ti,ab. 2609928
42 40 not 41 3275077
43 35 not 42 2145
44 1 or 43 2165

1

2 **Database name: Cochrane CDSR & CENTRAL**

Search:
ID Search Hits
#1 NG24:ti,ab,kw 1
#2 MeSH descriptor: [Specialties, Surgical] explode all trees 3239
#3 (surg* or operat* or preoperat* or pre-operat* or perioperat* or peri-operat* or intraoperat* or intra-operat* or postoperat* or post-operat*):ti,ab,kw 439942
#4 MeSH descriptor: [Perioperative Period] explode all trees 11450
#5 MeSH descriptor: [Perioperative Care] explode all trees 15118
#6 MeSH descriptor: [Blood Transfusion] explode all trees 4745
#7 MeSH descriptor: [Blood Loss, Surgical] explode all trees 3583
#8 transfus*:ti,ab,kw 22318
#9 ((Blood near/2 los*) or bleed* or bled*):ti,ab,kw 76480

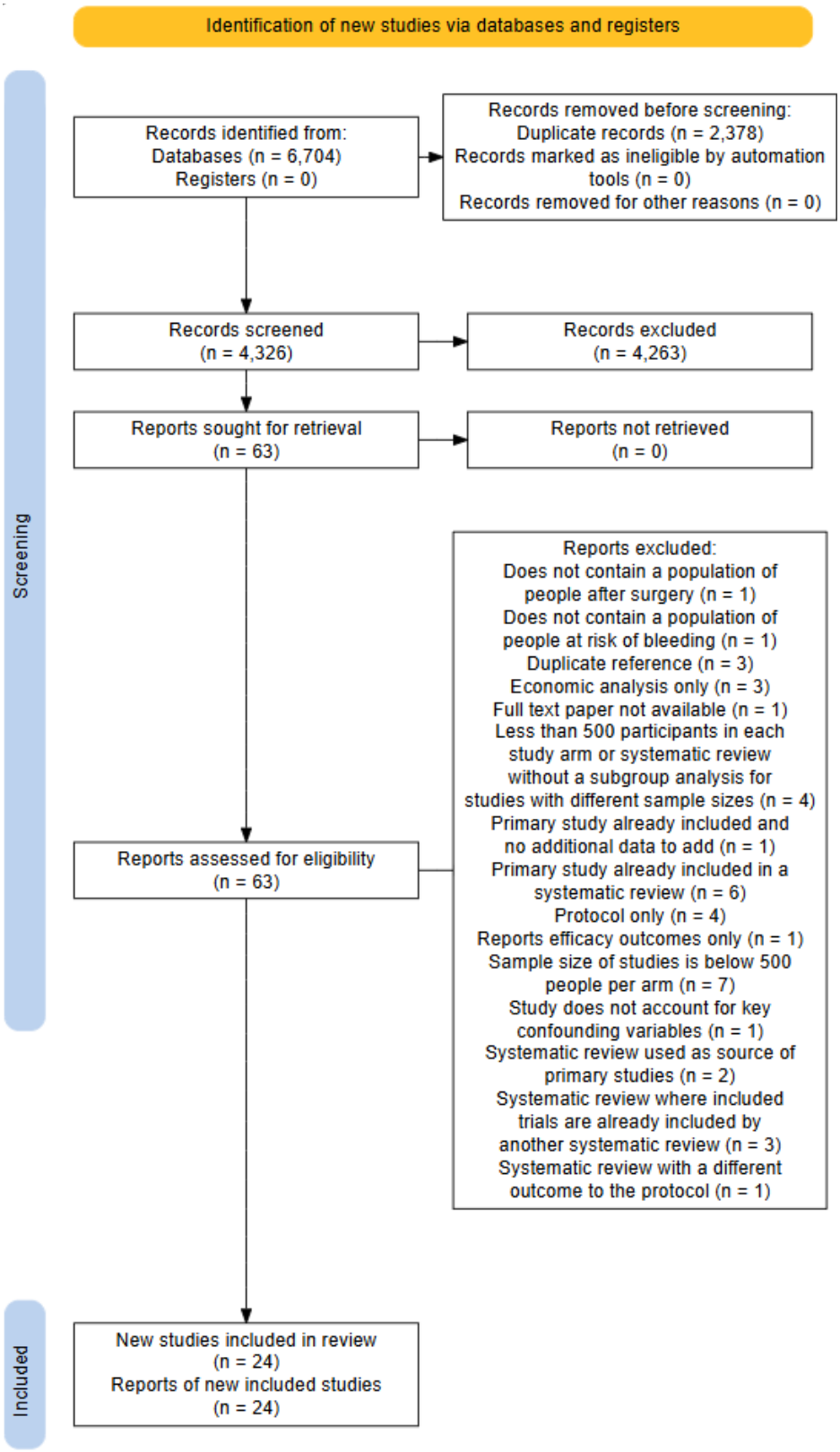
#10 {OR #2-#9} 487320 #11 MeSH descriptor: [Tranexamic Acid] explode all trees 1918 #12 (tranexamic or txa or cyklokapron):ti,ab,kw 4652 #13 (ugurol or transamin or kabi 2161 or amchafibrin or amikapron or anvitoff or amstat or anexan or exacyl or frenolyse or rikaparin or tramic or tranex or traxamic or trenaxin or trenolk or unixam):ti,ab,kw 73 #14 {OR #11-#13} 4663 #15 #10 and #14 with Publication Year from 2020 to 2025, with Cochrane Library publication date Between Jan 2020 and May 2025, in Trials 1617 #16 #1 or #15 1618 #17 "conference":pt 262971 #18 #16 not #17 1518 Results: Cochrane Reviews: 0 **Trials: 1518**

Database name: Epistemonikos

Searches
title:(("Tranexamic Acid" OR "Tranexamic Acids" OR txa)) AND title:(("Blood Transfusion" OR "Blood Transfusions" OR "Blood Loss" OR "Bleed" OR "Bleeding" OR "Bled")) AND title:((surg* OR operat*)) AND Publication year: Last 5 years AND Publication type: Primary study **Total:123**

Appendix C Study selection – effectiveness evidence

Figure 1 Effectiveness evidence study selection



Appendix D Effectiveness evidence tables

D.1 Systematic reviews

D.1.1 Ker, 2024

Bibliographic Reference	Ker, Katharine; Sentilhes, Loic; Shakur-Still, Haleema; Madar, Hugo; Deneux-Tharaux, Catherine; Saade, George; Pacheco, Luis D; Ageron, Francois-Xavier; Mansukhani, Raoul; Balogun, Eni; Brenner, Amy; Prowse, Danielle; Arribas, Monica; Ahmadzia, Homa; Chaudhri, Rizwana; Olayemi, Oladapo; Roberts, Ian; Tranexamic acid for postpartum bleeding: a systematic review and individual patient data meta-analysis of randomised controlled trials.; Lancet (London, England); 2024; vol. 404 (no. 10463); 1657-1667

Study details

Study design	Systematic review with individual patient data (IPD) No comment
Databases searched	International Clinical Trials Registry Platform WHO - searched from inception to August 4th 2024
Dates searched	From inception to August 4th 2024
Sources of funding	Academic or government grant support The Bill and Melinda Gates Foundation
Matching inclusion criteria	Adults (at least 16 years) Women Pregnant women, trans men and non-binary people Women
Other important inclusion criteria	Trials had to have at least 500 women, and a low risk of bias for random sequence generation and allocation concealment
Other important exclusion criteria	None stated
Interventions of interest	Intravenous tranexamic acid No comment Placebo

	Normal saline
Other interventions	No additional information
Comparisons of interest	Tranexamic acid compared to placebo No comment
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery No comment Pulmonary embolism No comment Deep vein thrombosis No comment Myocardial infarction No comment Ischaemic stroke No comment Infection Sepsis Seizure No comment
Consideration of key confounding factors	Age No comment Sex No comment Comorbidities No comment
Subgroups of interest	Surgical speciality

	No comment Dose Thromboembolic events only Route of administration Thromboembolic events only Repeated use Thromboembolic events only
Number of studies included in the review	5

Study arms

Tranexamic acid (N = 27300)

Intravenous tranexamic acid given at 1 gram (or 2 grams for a subset of 5747 women in the WOMAN trial if bleeding continued or restarted within 24 hours) before postpartum haemorrhage diagnosis (or after if in the WOMAN trial) at different times around cord clamping.

Placebo (N = 27093)

Intravenous normal saline in the same procedure as the intervention arm.

Characteristics

Study-level characteristics

Characteristic	Study (N = 54404)
Mean age (SD) (years) Mean (SD)	30.7 (5.9)
Type of birth - Vaginal Sample size	n = 33148 ; % = 61
Type of birth - Caesarean Sample size	n = 21251 ; % = 39
Gestational diabetes Sample size	n = 1427 ; % = 3
Hypertensive disorders of pregnancy Sample size	n = 3437 ; % = 6

Characteristic	Study (N = 54404)
Placental abnormalities Sample size	n = 2663 ; % = 5

Outcomes

Study timepoints

- 3 months (End of follow up. This varied between trials. In the WOMAN trials, it was death, discharge or day 42 if they remained in hospital, for the TRAAP trials it was at 3 months after giving birth, for the TXA-MFMU trial it was at 6 weeks after giving birth.)

Death in 24 hours

Outcome	Tranexamic acid, 3 month, N = 27308	Placebo, 3 month, N = 27096
All-cause mortality Death within 24 hours. Reported in all five trials. No of events	n = 159 ; % = 0.6	n = 206 ; % = 0.8

All-cause mortality - Polarity - Lower values are better

Fatal and non-fatal thromboembolic events

Outcome	Tranexamic acid, 3 month, N = 26571	Placebo, 3 month, N = 26373
Thromboembolic events after surgery Fatal and non-fatal thromboembolic events. Reported in all five trials. No of events	n = 50 ; % = 0.2	n = 52 ; % = 0.2
Thromboembolic events after surgery - Dose - 1 gram Tranexamic acid (n = 16571), Placebo (n = 16388) No of events	n = 20 ; % = 0.1	n = 18 ; % = 0.1
Thromboembolic events after surgery - Dose - mixed (1 gram or 2 grams) Tranexamic acid (n = 10033), Placebo (n = 9985) No of events	n = 30 ; % = 0.3	n = 34 ; % = 0.3

Thromboembolic events after surgery - Polarity - Lower values are better

Pulmonary embolism and deep vein thrombosis

Outcome	Tranexamic acid, 3 month, N = 21502	Placebo, 3 month, N = 21378
Pulmonary embolism Reported in WOMAN, WOMAN-2, TRAAP and TRAAP-2. No of events	n = 17 ; % = 0.1	n = 21 ; % = 0.1
Deep vein thrombosis Reported in WOMAN, WOMAN-2, TRAAP and TRAAP-2. No of events	n = 11 ; % = 0.1	n = 12 ; % = 0.1

Pulmonary embolism - Polarity - Lower values are better

Deep vein thrombosis - Polarity - Lower values are better

Myocardial infarction and stroke

Outcome	Tranexamic acid, 3 month, N = 27025	Placebo, 3 month, N = 26848
Myocardial infarction Reported in all five trials. No of events	n = 4 ; % = 0.02	n = 3 ; % = 0.01
Ischaemic stroke Stroke - downgrade for indirectness as may include haemorrhagic strokes. Reported in all five trials. No of events	n = 10 ; % = 0.04	n = 6 ; % = 0.02

Myocardial infarction - Polarity - Lower values are better

Ischaemic stroke - Polarity - Lower values are better

Sepsis

Outcome	Tranexamic acid, 3 month, N = 25185	Placebo, 3 month, N = 25000
Infection Sepsis No of events	n = 205 ; % = 0.8	n = 202 ; % = 0.08

Infection - Polarity - Lower values are better

Seizures

Outcome	Tranexamic acid, 3 month, N = 26570	Placebo, 3 month, N = 26371
Seizures No of events	n = 46 ; % = 0.2	n = 47 ; % = 0.2

Seizures - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - ROBIS systematic review checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low *(While there are some concerns with the risk in the search, this is likely reflective of the IPD process and for inclusion in this work this will be covered through other approaches. Therefore, this will not affect the rest of the work.)*
Overall study ratings	Applicability as a source of data	Fully applicable *(Except for the stroke outcome where it may include people with haemorrhagic stroke. Also to note that not all people are having surgery so this may limit the applicability of the findings.)*

D.1.2 Taeuber, 2021

Bibliographic Reference	Taeuber I; Weibel S; Herrmann E; Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality A Systematic Review, Meta-analysis, and Meta-regression; JAMA Surg; 2021; vol. 6 (no. 156); e2100884

Study details

Study design	Systematic review With meta-regression
Databases searched	PubMed No comment CENTRAL No comment
Dates searched	1976 to 31/12/2020
Sources of funding	Other author funded by a private organisation Authors received grants and honorarium from private companies. Dr Kranke received support from FreseniusKabi speakers fees, personal fees from TevaRatiopharma and other support from CSL Behring speakers fee. Dr Zacharowski received grants from B. Braun, grants from Fresenius, grants from CSL Behring and grants from Vifor. Dr Beybohm received support from B Braun Belsungen, CSL Behring, Fresenius Kabi and Vifor Pharma. None of these authors were solely involved in any part of the statistical analysis, interpretation, revision of the manuscript.

Matching inclusion criteria	Adults (at least 16 years) No comment Children (less than 16 years) No comment
Other important inclusion criteria	Published in English, German, French and Spanish.
Other important exclusion criteria	Studies with only oral or topical tranexamic acid administration.
Interventions of interest	Intravenous tranexamic acid Pooling intravenous tranexamic acid, intravenous and topical tranexamic acid and intravenous and oral tranexamic acid Intravenous and topical tranexamic acid Pooled with intravenous tranexamic acid Intravenous and oral tranexamic acid Pooled with intravenous tranexamic acid Placebo No comment Usual care No treatment
Other interventions	Not applicable
Comparisons of interest	Tranexamic acid compared to placebo No comment Tranexamic acid compared to usual care No comment
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery

	No comment Pulmonary embolism No comment Deep vein thrombosis No comment Ischaemic stroke No comment
Consideration of key confounding factors	Comorbidities No comment
Subgroups of interest	Surgical speciality No comment Comorbidities that increase risk of thromboembolic events No comment
Number of studies included in the review	216

Study arms

Tranexamic acid (N = 33487)

Intravenous tranexamic acid (with or without additional oral or topical tranexamic acid) with anaesthetic medication during surgery

Control (N = 32413)

Placebo or usual care (no treatment)

Characteristics

Study-level characteristics

Characteristic	Study (N = 218)
Tranexamic acid application route - Intravenous Sample size	n = 191 ; % = 87.6
Tranexamic acid application route - Intravenous and Oral Sample size	n = 13 ; % = 6
Tranexamic acid application route - Intravenous and Topical Sample size	n = 6 ; % = 2.8

Characteristic	Study (N = 218)
People at increased risk of developing thromboembolism Sample size = Number of studies Sample size	n = 56 ; % = 26
Surgical speciality - Gastrointestinal Sample size	n = 6 ; % = 2.8
Surgical speciality - Neurological Sample size	n = 18 ; % = 8.3
Surgical speciality - Surgery of the thyroid gland Sample size	n = 1 ; % = 0.46
Surgical speciality - Liver surgery Sample size	n = 5 ; % = 2.3
Surgical speciality - Paediatric Sample size	n = 4 ; % = 1.8
Surgical speciality - Orthopaedic Sample size	n = 115 ; % = 52.8
Surgical speciality - Diabetic haemorrhage Sample size	n = 1 ; % = 0.46
Surgical speciality - Maxillo-facial Sample size	n = 5 ; % = 2.3
Surgical speciality - Gynaecology Sample size	n = 29 ; % = 13.3
Surgical speciality - Trauma Sample size	n = 1 ; % = 0.46
Surgical speciality - Urological Sample size	n = 3 ; % = 1.4
Surgical speciality - Cardiothoracic Sample size	n = 23 ; % = 10.6
Surgical speciality - Otorhinolaryngology Sample size	n = 1 ; % = 0.46

Outcomes

Study timepoints

- after surgery

Main analysis - Thromboembolic events after surgery

Outcome	Tranexamic acid, after surgery, N = 47653	Control, after surgery, N = 45971
Thromboembolic events after surgery Total thromboembolic events No of events	n = 1020 ; % = 2.14	n = 900 ; % = 1.96

Thromboembolic events after surgery - Polarity - Lower values are better

Main analysis - Deep vein thrombosis

Outcome	Tranexamic acid, after surgery, N = 44531	Control, after surgery, N = 42918
Deep vein thrombosis Venous thrombosis No of events	n = 335 ; % = 0.75	n = 263 ; % = 0.61

Deep vein thrombosis - Polarity - Lower values are better

Meta analysis - Pulmonary embolism

Outcome	Tranexamic acid, after surgery, N = 45049	Control, after surgery, N = 43704
Pulmonary embolism No of events	n = 210 ; % = 0.47	n = 195 ; % = 0.45

Pulmonary embolism - Polarity - Lower values are better

Main analysis - All-cause mortality

Outcome	Tranexamic acid, after surgery, N = 39358	Control, after surgery, N = 38515
All-cause mortality Overall mortality No of events	n = 3756 ; % = 9.54	n = 3964 ; % = 10.55

All-cause mortality - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - ROBIS systematic review checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Moderate (*Bias may have been introduced through how the risk of bias process was conducted leading to higher quality outcome ratings and by the study providing less information about the characteristics that may have limited the exploration of results.*)

Section	Question	Answer
Overall study ratings	Applicability as a source of data	Partially applicable *(Applies to only intravenous tranexamic acid,)*

D.2 Randomised controlled trials (RCTs)

D.2.1 CRASH-3 trial collaborators, 2019

Bibliographic Reference CRASH-3 trial collaborators, The; Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial.; Lancet (London, England); 2019; vol. 394 (no. 10210); 1713-1723

Study details

Trial name	CRASH-3 No additional comment
Associated studies	Not applicable No comment
Trial registration number	NCT01402882 No additional comment
Study type	Randomised controlled trial (RCT) No additional comment
Study location	Multicentre Worldwide, 29 countries, 175 hospitals
Study setting	Inpatient: non-elective No additional comment Ambulance Pre-hospital care A&E No additional comment
Study dates	20th July 2012 and 31st January 2019
Sources of funding	Academic or government grant support Funding from the JP Moulton Charitable Trust, NIHR HTA (14/190/01), Joint Global Health Trials, Medical Research

	Council, Department for International Development, Global Challenges Research Fund and the Wellcome Trust (MRM0092111). On author received a grant from the New Brunswick Trauma Program to support the trial in Canada.
Matching inclusion criteria	Adults (age at least 16 years) No additional comment Sample size of at least 500 people in each study arm No additional comment
Other important inclusion criteria	GCS score of 12 or lower or any intracranial bleeding on CT scan, initially 8 hours after injury in 2016 but then shortened to 3 hours after injury to limit recruitment (change made blind to trial data in response to external evidence suggesting that delayed treatment was unlikely to be effective).
Other important exclusion criteria	Major extracranial bleeding
Interventions of interest	Tranexamic acid (intravenous) No additional comment Placebo No additional comment
Comparisons of interest	Tranexamic acid compared to placebo No additional comment
Cointerventions	No additional information.
Subgroup 1: Surgical speciality	Trauma No additional comment
Subgroup 2: Anticoagulant use	Not stated/unclear No additional comment
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Not stated/unclear No additional comment
Subgroup 4: Dose of tranexamic acid	2 grams No comment
Subgroup 5: Route of administration	Intravenous No comment

Subgroup 6: Repeated use of tranexamic acid	Repeated use 1 bolus, 1 infusion
Subgroup 7: Renal function	Not stated/unclear No comment
Outcomes of interest	All-cause mortality No additional comment Thromboembolic events after surgery No additional comment Pulmonary embolism No additional comment Deep vein thrombosis No additional comment Myocardial infarction No additional comment Ischaemic stroke No additional comment Infection Sepsis Seizures
Total number of participants	12737
Duration of follow-up (days)	28
Additional comments	No additional comments

Study arms

Tranexamic acid (N = 6406)

1 gram tranexamic acid infusion over 10 minutes loading dose, followed by a 1 gram tranexamic acid infusion over 8 hours.

Placebo (N = 6331)

Matching placebo.

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 6406)	Placebo (N = 6331)
Female (%) Sample size	n = 906 ; % = 19	n = 893 ; % = 20
Mean age (SD) (years) Mean (SD)	41.7 (19)	41.9 (19)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Anticoagulant use (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities associated with bleeding (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 28 days (Follow up for adverse events 28 days after randomisation)

Mortality

Outcome	Tranexamic acid, 28 day, N = 4613	Placebo, 28 day, N = 4514
All-cause mortality Head injury-related death (downgrade for indirectness) within 3 hours of injury. While it is possible to get data for non-head injury related mortality, it is not possible to combine the two, making it difficult to interpret. No of events	n = 855 ; % = 18.5	n = 892 ; % = 19.8

All-cause mortality - Polarity - Lower values are better

Complications

Outcome	Tranexamic acid, 28 day, N = 6359	Placebo, 28 day, N = 6280
Thromboembolic events after surgery All vascular occlusive events No of events	n = 101 ; % = 1.6	n = 102 ; % = 1.6
Pulmonary embolism No of events	n = 24 ; % = 0.4	n = 32 ; % = 0.5
Deep vein thrombosis No of events	n = 19 ; % = 0.3	n = 16 ; % = 0.3
Ischaemic stroke Stroke No of events	n = 46 ; % = 0.7	n = 42 ; % = 0.7
Myocardial infarction No of events	n = 18 ; % = 0.3	n = 20 ; % = 0.3
Infection Sepsis No of events	n = 411 ; % = 6.5	n = 412 ; % = 6.6
Seizures No of events	n = 206 ; % = 3.2	n = 186 ; % = 3

Thromboembolic events after surgery - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Infection - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Partially applicable *(Population is people after trauma who may or may not go on to have surgery rather than people who are having surgery. The principle is still applicable and so can be included as partially applicable, but is not necessarily the same population. Also, further downgrading for mortality*

Section	Question	Answer
		outcome (due to use of head injury specific mortality only).)

1

D.2.2 Devereaux, 2022

Bibliographic Reference Devereaux, P J; Marcucci, Maura; Painter, Thomas W; Conen, David; Lomivorotov, Vladimir; Sessler, Daniel I; Chan, Matthew T V; Borges, Flavia K; Martinez-Zapata, Maria J; Wang, Chew Yin; Xavier, Denis; Ofori, Sandra N; Wang, Michael K; Efremov, Sergey; Landoni, Giovanni; Kleinlugtenbelt, Ydo V; Szczeklik, Wojciech; Schmartz, Denis; Garg, Amit X; Short, Timothy G; Wittmann, Maria; Meyhoff, Christian S; Amir, Mohammed; Torres, David; Patel, Ameen; Duceppe, Emmanuelle; Ruetzler, Kurt; Parlow, Joel L; Tandon, Vikas; Fleischmann, Edith; Polanczyk, Carisi A; Lamy, Andre; Astrakov, Sergey V; Rao, Mangala; Wu, William K K; Bhatt, Keyur; de Nadal, Miriam; Likhvantsev, Valery V; Paniagua, Pilar; Aguado, Hector J; Whitlock, Richard P; McGillion, Michael H; Prystajecky, Michael; Vincent, Jessica; Eikelboom, John; Copland, Ingrid; Balasubramanian, Kumar; Turan, Alparslan; Bangdiwala, Shrikant I; Stillo, David; Gross, Peter L; Cafaro, Teresa; Alfonsi, Pascal; Roshanov, Pavel S; Belley-Cote, Emilie P; Spence, Jessica; Richards, Toby; VanHelder, Tomas; McIntyre, William; Guyatt, Gordon; Yusuf, Salim; Leslie, Kate; Tranexamic Acid in Patients Undergoing Noncardiac Surgery.; The New England journal of medicine; 2022; vol. 386 (no. 21); 1986-1997

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4 **Study details**

Trial name	POISE-3 No comment
Associated studies	Not applicable No comment
Trial registration number	NCT03505723 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	Multicentre No comment
Study setting	Inpatient: elective and day care No comment

	Inpatient: non-elective No comment
Study dates	June 2018 to July 2021
Sources of funding	Academic or government grant support Canadian Institutes of Health Research, Australian National Health and Medical Research Council, Research Grant Council of Hong Kong, Population Health Research Institute.
Matching inclusion criteria	Adults (age at least 16 years) No comment At short-term risk of bleeding No comment Having surgery No comment
Other important inclusion criteria	45 years of age or older; undergoing inpatient noncardiac surgery; at risk for bleeding and cardiovascular complications according to the criteria previously associated with perioperative bleeding and cardiovascular complications.
Other important exclusion criteria	Undergoing cardiac surgery or intracranial neurosurgery; if the physician planned to administer systemic tranexamic acid during the surgery; creatinine clearance of less than 30 mL per minute; receiving long-term dialysis.
Interventions of interest	Tranexamic acid (intravenous) No comment
Comparisons of interest	Placebo No comment
Cointerventions	Non-cardiac surgery
Subgroup 1: Surgical speciality	Mixed Non-cardiac
Subgroup 2: Anticoagulant or antiplatelet use	Mixed Around 30% of the population took an anticoagulant or antiplatelet in the 24 hours before surgery
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Yes In the inclusion criteria for the surgery

Subgroup 4: Dose	1 gram No comment
Subgroup 5: Route of administration	Intravenous To note, 168 in the intervention arm and 183 in the control arm received topical tranexamic acid, 69 in the intervention arm and 78 in the control arm received additional intravenous tranexamic acid and 23 in the intervention arm and 24 in the control arm received another antifibrinolytic drug.
Subgroup 6: Repeated use	Single use No comment
Subgroup 7: Renal function	No impairment From exclusion criteria
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery Includes troponin level changes rather than specifically myocardial infarctions, so could be considered as a risk of bias condition Pulmonary embolism No comment Deep vein thrombosis No comment Myocardial infarction No comment Ischaemic stroke No comment Infection No comment Seizures No comment

Total number of participants	9535
Duration of follow-up (days)	30
Additional comments	No additional comments

Study arms

Tranexamic acid (N = 4757)

1 gram intravenous tranexamic acid bolus

Placebo (N = 4778)

Matching placebo

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 4757)	Placebo (N = 4778)
Female (%) Sample size	n = 2086 ; % = 44	n = 2097 ; % = 44
Mean age (SD) (years) Mean (SD)	69.5 (9.5)	69.3 (9.4)
Ethnicity (%) - White/Caucasian Sample size	n = 3618 ; % = 76.1	n = 3621 ; % = 75.8
Ethnicity (%) - Asian Sample size	n = 929 ; % = 19.5	n = 950 ; % = 19.9
Ethnicity (%) - Hispanic/Latino Sample size	n = 84 ; % = 1.8	n = 90 ; % = 1.9
Ethnicity (%) - Black/African Sample size	n = 76 ; % = 1.6	n = 71 ; % = 1.5
Ethnicity (%) - Aboriginal Sample size	n = 27 ; % = 0.6	n = 25 ; % = 0.5
Ethnicity (%) - Middle Eastern descent Sample size	n = 15 ; % = 0.3	n = 10 ; % = 0.2
Ethnicity (%) - Pacific Islander Sample size	n = 5 ; % = 0.1	n = 10 ; % = 0.2

Characteristic	Tranexamic acid (N = 4757)	Placebo (N = 4778)
Comorbidities (%) - Congestive heart failure Sample size	n = 674 ; % = 14.2	n = 671 ; % = 14
Comorbidities (%) - History of transient ischaemic attack Sample size	n = 282 ; % = 5.9	n = 247 ; % = 5.2
Comorbidities (%) - Hypertension Sample size	n = 4293 ; % = 90.2	n = 4321 ; % = 90.4
Comorbidities (%) - Diabetes Sample size	n = 1749 ; % = 36.8	n = 1812 ; % = 37.9
Comorbidities (%) - Atrial fibrillation Sample size	n = 478 ; % = 10	n = 445 ; % = 9.3
Comorbidities (%) - Active cancer Sample size	n = 1311 ; % = 27.6	n = 1360 ; % = 28.5
Comorbidities (%) - History of coronary artery disease Sample size	n = 1410 ; % = 29.6	n = 1466 ; % = 30.7
Comorbidities (%) - History of peripheral artery disease Sample size	n = 714 ; % = 15	n = 722 ; % = 15.1
Comorbidities (%) - History of stroke Sample size	n = 400 ; % = 8.4	n = 388 ; % = 8.1
Comorbidities (%) - Undergoing major vascular surgery Sample size	n = 541 ; % = 11.4	n = 544 ; % = 11.4
Renal function (% or mL/min/1.73 m2) (micromol/L) Creatinine Mean (SD)	87 (29)	87 (31)

Outcomes

Study timepoints

- 30 days

Event data (1)

Outcome	Tranexamic acid, 30 day, N = 4757	Placebo, 30 day, N = 4778
All-cause mortality No of events	n = 52 ; % = 1.1	n = 57 ; % = 1.2
Pulmonary embolism Symptomatic pulmonary embolism No of events	n = 24 ; % = 0.5	n = 17 ; % = 0.4
Deep vein thrombosis Any symptomatic or asymptomatic proximal venous thromboembolism No of events	n = 32 ; % = 0.7	n = 28 ; % = 0.6
Myocardial infarction No of events	n = 67 ; % = 1.4	n = 53 ; % = 1.1
Ischaemic stroke Nonhaemorrhagic stroke No of events	n = 24 ; % = 0.5	n = 16 ; % = 0.3
Infection No of events	n = 499 ; % = 10.5	n = 487 ; % = 10.2
Seizures No of events	n = 10 ; % = 0.2	n = 3 ; % = 0.1

All-cause mortality - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Infection - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Hazard ratios (1)

Outcome	Tranexamic acid vs Placebo, 30 day, N2 = 4757, N1 = 4778
All-cause mortality Mean (95% CI)	0.92 (0.63 to 1.33)
Pulmonary embolism Symptomatic pulmonary embolism Mean (95% CI)	1.42 (0.76 to 2.64)
Deep vein thrombosis Any symptomatic or asymptomatic proximal venous thromboembolism	1.15 (0.69 to 1.91)

Outcome	Tranexamic acid vs Placebo, 30 day, N2 = 4757, N1 = 4778
Mean (95% CI)	
Myocardial infarction Mean (95% CI)	1.27 (0.89 to 1.82)
Ischaemic stroke Nonhaemorrhagic stroke Mean (95% CI)	1.51 (0.8 to 2.84)
Infection Mean (95% CI)	1.03 (0.91 to 1.17)
Seizures Mean (95% CI)	3.35 (0.92 to 12.2)

All-cause mortality - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Infection - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Event data (2)

Outcome	Tranexamic acid, 30 day, N = 4581	Placebo, 30 day, N = 4601
Thromboembolic events after surgery Composite cardiovascular events - including myocardial injury after noncardiac surgery, nonhaemorrhagic surgery, peripheral arterial thrombosis and symptomatic proximal venous thromboembolism No of events	n = 649 ; % = 14.2	n = 639 ; % = 13.9
Thromboembolic events after surgery - Type of surgery - Vascular n1 = 684, n2 = 676 No of events	n = 140 ; % = 20.5	n = 126 ; % = 18.6
Thromboembolic events after surgery - Type of surgery - Thoracic n1 = 122, n2 = 141 No of events	n = 23 ; % = 18.9	n = 29 ; % = 20.6

Outcome	Tranexamic acid, 30 day, N = 4581	Placebo, 30 day, N = 4601
Thromboembolic events after surgery - Type of surgery - General n1 = 1726, n2 = 1733 No of events	n = 213 ; % = 12.3	n = 222 ; % = 12.8
Thromboembolic events after surgery - Type of surgery - Spinal n1 = 226, n2 = 199 No of events	n = 40 ; % = 17.7	n = 34 ; % = 17.1
Thromboembolic events after surgery - Type of surgery - Urology n1 = 573, n2 = 602 No of events	n = 58 ; % = 10.1	n = 60 ; % = 10
Thromboembolic events after surgery - Type of surgery - Gynaecology n1 = 156, n2 = 168 No of events	n = 11 ; % = 7.1	n = 13 ; % = 7.7
Thromboembolic events after surgery - Type of surgery - Orthopaedic n1 = 1042, n2 = 1029 No of events	n = 157 ; % = 15.1	n = 154 ; % = 15
Thromboembolic events after surgery - Type of surgery - Plastic n1 = 14, n2 = 22 No of events	n = 3 ; % = 21.4	n = 1 ; % = 4.5
Thromboembolic events after surgery - Type of surgery - Low risk n1 = 38, n2 = 31 No of events	n = 4 ; % = 10.5	n = 0 ; % = 0

Thromboembolic events after surgery - Polarity - Lower values are better

Hazard ratios (2)

Outcome	Tranexamic acid vs Placebo, 30 day, N2 = 4581, N1 = 4601
Thromboembolic events after surgery Composite cardiovascular events - including myocardial injury after noncardiac surgery, nonhaemorrhagic surgery, peripheral arterial thrombosis and symptomatic proximal venous thromboembolism	1.02 (0.92 to 1.14)

Outcome	Tranexamic acid vs Placebo, 30 day, N2 = 4581, N1 = 4601
Mean (95% CI)	
Thromboembolic events after surgery - Type of surgery - Vascular Mean (95% CI)	1.1 (0.87 to 1.4)
Thromboembolic events after surgery - Type of surgery - Thoracic Mean (95% CI)	0.93 (0.54 to 1.61)
Thromboembolic events after surgery - Type of surgery - General Mean (95% CI)	0.96 (0.8 to 1.16)
Thromboembolic events after surgery - Type of surgery - Spinal Mean (95% CI)	1.03 (0.65 to 1.63)
Thromboembolic events after surgery - Type of surgery - Urology Mean (95% CI)	1.03 (0.72 to 1.48)
Thromboembolic events after surgery - Type of surgery - Gynaecology Mean (95% CI)	0.92 (0.41 to 2.09)
Thromboembolic events after surgery - Type of surgery - Orthopaedic Mean (95% CI)	1 (0.8 to 1.25)
Thromboembolic events after surgery - Type of surgery - Plastic Mean (95% CI)	6.81 (0.66 to 70.4)
Thromboembolic events after surgery - Type of surgery - Low risk Mean (95% CI)	NR (NR to NR)

Thromboembolic events after surgery - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - Outcome level

Eventdata(1)-All-causemortality-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Eventdata(2)-Thromboemboliceventsaftersurgery-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness as it includes a blood test change rather than myocardial infarctions themselves which will lead to a very different outcome compared to others in the same group)*

Eventdata(1)-Pulmonaryembolism-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Eventdata(1)-Deepveinthrombosis-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Eventdata(1)-Myocardialinfarction-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Eventdata(1)-Ischaemicstroke-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Eventdata(1)-Infection-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Eventdata(1)-Seizures-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

D.2.3 Guyette, 2020

Bibliographic Reference Guyette, FX; Brown, JB; Zenati, MS; Early-Young, BJ; Adams, PW; Eastridge, BJ; Nirula, R; Vercruysse, GA; O'Keeffe, T; Joseph, B; et, al.; Tranexamic Acid during Prehospital Transport in Patients at Risk for Hemorrhage after Injury: a Double-blind, Placebo-Controlled, Randomized Clinical Trial; JAMA surgery; 2020; vol. 156 (no. 1); 11-20

Study details

Trial name	STAAMP No comment
Associated studies	Not applicable No comment
Trial registration number	NCT02086500 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	United States of America (USA) No comment
Study setting	Inpatient: non-elective Pre-hospital Ambulance

	Pre-hospital A&E Pre-hospital
Study dates	May 1st 2015 to October 31st 2019
Sources of funding	Academic or government grant support Funding from the US Army Medical Research and Material Command.
Matching inclusion criteria	Adults (age at least 16 years) No comment At short-term risk of bleeding No comment
Other important inclusion criteria	Injured people at risk of haemorrhage transported from the scene or transferred from an outside emergency department to a participating site within an estimated 2 hours of the time of injury; experienced at least 1 episode of hypotension or tachycardia
Other important exclusion criteria	Age older than 90 years or younger than 18 years; lack of intravenous or intraosseous access; isolated fall from stranding; document cervical cord injury; known prisoner or pregnancy; traumatic arrest of more than 5 minutes; penetrating brain injury; isolated drowning or hanging; objection to study voiced at scene; wearing a STAAMP study opt-out bracelet
Interventions of interest	Tranexamic acid (intravenous) No comment
Comparisons of interest	Placebo Sterile water
Cointerventions	No additional information
Subgroup 1: Surgical speciality	Trauma No comment
Subgroup 2: Anticoagulant or antiplatelet use	No Less than 12% of people receiving preinjury antiplatelet or anticoagulant medicines
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Not stated/unclear No comment

Subgroup 4: Dose	1-3 grams No comment
Subgroup 5: Route of administration	Intravenous No comment
Subgroup 6: Repeated use	Mixed population No comment
Subgroup 7: Renal function	Not stated/unclear No comment
Outcomes of interest	All-cause mortality No comment Pulmonary embolism No comment Deep vein thrombosis No comment Myocardial infarction No comment Ischaemic stroke No comment Infection No comment Seizures No comment
Total number of participants	927
Duration of follow-up (days)	30
Additional comments	No additional information

Study arms

Tranexamic acid (N = 460)

Tranexamic acid 1 gram in 10mL added to 100mL of 0.9% saline. This could be given alone or followed up by either 1 gram in 10mL added to 100mL of 0.9% saline delivered over 10 minutes. This could be given alone or delivered with the same amount again infused over 8 hours.

Placebo (N = 467)

Matching placebo

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 460)	Placebo (N = 467)
Female (%) Sample size	n = 120 ; % = 26	n = 115 ; % = 25
Mean age (SD) (years) Mean (SD)	41 (17)	42 (18)
Ethnicity (%) - White Sample size	n = 361 ; % = 79.2	n = 353 ; % = 79
Ethnicity (%) - African American Sample size	n = 40 ; % = 8.8	n = 49 ; % = 11
Ethnicity (%) - Asian Sample size	n = 3 ; % = 0.7	n = 2 ; % = 0.4
Ethnicity (%) - Other Sample size	n = 3 ; % = 0.7	n = 2 ; % = 0.4
Ethnicity (%) - Unknown Sample size	n = 49 ; % = 10.7	n = 41 ; % = 9.2
Ethnicity (%) - Hispanic ethnicity Sample size	n = 34 ; % = 7.5	n = 24 ; % = 5.4
Comorbidities (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 30 days

1
2 **Dichotomous outcomes**

Outcome	Tranexamic acid, 30 day, N = 447	Placebo, 30 day, N = 453
All-cause mortality 30 day mortality No of events	n = 36 ; % = 8.6	n = 45 ; % = 9.7
All-cause mortality - No antiplatelet n1 = 343, n2 = 351 No of events	n = 20 ; % = 5.8	n = 13 ; % = 3.7
All-cause mortality - Antiplatelet received n1 = 39, n2 = 44 No of events	n = 7 ; % = 4.9	n = 9 ; % = 44
All-cause mortality - No vitamin K antagonist n1 = 376, n2 = 384 No of events	n = 24 ; % = 6.4	n = 21 ; % = 5.5
All-cause mortality - Vitamin K antagonist received n1 = 11, n2 = 5 No of events	n = 2 ; % = 18.2	n = 1 ; % = 20
Pulmonary embolism No of events	n = 13 ; % = 2.9	n = 7 ; % = 1.5
Deep vein thrombosis No of events	n = 12 ; % = 2.7	n = 7 ; % = 1.5
Myocardial infarction No of events	n = 0 ; % = 0	n = 1 ; % = 1
Ischaemic stroke Stroke - downgrade for indirectness in case of haemorrhagic stroke No of events	n = 1 ; % = 1	n = 4 ; % = 1
Seizures Seizure in the first 24 hours No of events	n = 5 ; % = 1.1	n = 7 ; % = 1.5
Infection Nosocomial infection	n = 88 ; % = 19.7	n = 66 ; % = 14.5

Outcome	Tranexamic acid, 30 day, N = 447	Placebo, 30 day, N = 453
No of events		

All-cause mortality - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Seizures - Polarity - Lower values are better
Infection - Polarity - Lower values are better

Hazard ratio

Outcome	Tranexamic acid vs Placebo, 30 day, N2 = 447, N1 = 453
All-cause mortality 30 day mortality Mean (95% CI)	0.81 (0.59 to 1.11)

All-cause mortality - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - Outcome level

Dichotomousoutcomes-All-causemortality-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Partially applicable *(Number of participants is below 500 in both arms so downgrade once for indirectness)*

Dichotomousoutcomes-Pulmonaryembolism-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Partially applicable *(Number of participants is below 500 in both arms so downgrade once for indirectness)*

Dichotomousoutcomes-Deepveinthrombosis-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Partially applicable *(Number of participants is below 500 in both arms so downgrade once for indirectness)*

Dichotomousoutcomes-Myocardialinfarction-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Partially applicable *(Number of participants is below 500 in both arms so downgrade once for indirectness)*

Dichotomousoutcomes-Ischaemicstroke-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Outcome indirectness as outcome was named 'stroke' rather than 'ischaemic stroke' so may have included people with haemorrhagic strokes, and number of participants is below 500 in both arms so downgrade once for indirectness)*

Dichotomousoutcomes-Seizures-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Partially applicable *(Number of participants is below 500 in both arms so downgrade once for indirectness)*

Dichotomousoutcomes-Infection-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Partially applicable *(Number of participants is below 500 in both arms so downgrade once for indirectness)*

D.2.4 Gwanzura, 2024

Bibliographic Reference Gwanzura, C; Madziyire, MG; Chikwasha, V; Gavi, S; Wright, P; Walker, D; Chirenje, ZM; Efficacy of tranexamic acid for the prevention of post-partum haemorrhage among women undergoing caesarean section in Harare, Zimbabwe: a randomized controlled trial; Advances in global health; 2024; vol. 3 (no. 1); 1-10

1 **Study details**

Trial name	Not applicable No comment
Associated studies	Not applicable No comment
Trial registration number	NCT04733157 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	Zimbabwe No comment
Study setting	Inpatient: elective and day care No comment Inpatient: non-elective No comment
Study dates	Not stated/unclear
Sources of funding	Academic or government grant support Funded by the Fogarty International Center of the National Institute of Health (U.S. NIH Grant/Contract D43TW009343)
Matching inclusion criteria	Adults (age at least 16 years) No comment At short-term risk of bleeding No comment Pregnant women, trans men and non-binary people (age at least 16 years) Women at an estimated gestational age of 37 weeks or more, with a live intrauterine foetus Having surgery looking for an elective or emergency caesarean section
Other important inclusion criteria	No additional comments

Other important exclusion criteria	History of coagulopathies or conditions predisposing them to thromboembolic phenomena; seizure history; autoimmune disease; placental abruption; placenta praevia; abnormally adherent placentae if identified on prenatal ultrasound; eclampsia or HELLP syndrome; known hypersensitivity to TXA; planned general anaesthesia; caesarean delivery for the second twin or second/third triplet(s) after vaginal birth of the first twin; poor understanding of English/Shona languages; those who have received anticoagulants in the week before delivery; investigation for COVID-19 and confirmed COVID-19.
Interventions of interest	Tranexamic acid (intravenous) No comment
Comparisons of interest	Placebo No comment
Cointerventions	Oxytocin 5 international units intravenously after delivery.
Subgroup 1: Surgical speciality	Gynaecology No comment
Subgroup 2: Anticoagulant or antiplatelet use	No Based on exclusion criteria - no anticoagulant in the week before
Subgroup 3: Comorbidities that increase risk of thromboembolic events	No Based on exclusion criteria
Subgroup 4: Dose	1 gram No comment
Subgroup 5: Route of administration	Intravenous No comment
Subgroup 6: Repeated use	Single use No comment
Subgroup 7: Renal function	Not stated/unclear No comment
Outcomes of interest	All-cause mortality Available from the clinical trial record Pulmonary embolism

	Available from the clinical trial record Deep vein thrombosis Available from the clinical trial record Myocardial infarction Available from the clinical trial record Seizures Available from the clinical trial record
Total number of participants	1226
Duration of follow-up (days)	4
Additional comments	Outcome data available from the clinical trial record only

Study arms

Tranexamic acid (intravenous) (N = 613)

Intravenous tranexamic acid (1 gram) administered over 30-60 second at the time of skin incision.

Placebo (N = 613)

Matching placebo.

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (intravenous) (N = 613)	Placebo (N = 613)
Female (%) Sample size	n = 613 ; % = 100	n = 613 ; % = 100
Mean age (SD) - <18 years Sample size	n = 14 ; % = 2.3	n = 16 ; % = 2.6
Mean age (SD) - 18-25 years Sample size	n = 168 ; % = 27.5	n = 195 ; % = 31.8
Mean age (SD) - 26-35 years Sample size	n = 322 ; % = 52.7	n = 321 ; % = 53.4
Mean age (SD) - >35 years Sample size	n = 107 ; % = 17.5	n = 81 ; % = 13.2

Characteristic	Tranexamic acid (intravenous) (N = 613)	Placebo (N = 613)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) Sample size	n = 48 ; % = 7.9	n = 30 ; % = 4.9
Comorbidities (%) - HIV positive Sample size	n = 62 ; % = 10.1	n = 59 ; % = 9.6
Comorbidities (%) - Anaemia Sample size	n = 29 ; % = 4.7	n = 20 ; % = 3.3
Comorbidities (%) - Placenta previa Sample size	n = 2 ; % = 0.3	n = 0 ; % = 0
Comorbidities (%) - Uterine fibroids Sample size	n = 7 ; % = 1.2	n = 5 ; % = 0.8
Comorbidities (%) - Polyhydramnios Sample size	n = 2 ; % = 0.3	n = 1 ; % = 0.2
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 4 days

Dichotomous outcomes

Outcome	Tranexamic acid (intravenous), 4 day, N = 611	Placebo, 4 day, N = 613
All-cause mortality From clinical trial record No of events	n = 0 ; % = 0	n = 0 ; % = 0
Pulmonary embolism	n = 0 ; % = 0	n = 0 ; % = 0

Outcome	Tranexamic acid (intravenous), 4 day, N = 611	Placebo, 4 day, N = 613
From clinical trial record No of events		
Deep vein thrombosis From clinical trial record No of events	n = 0 ; % = 0	n = 0 ; % = 0
Myocardial infarction From clinical trial record No of events	n = 0 ; % = 0	n = 1 ; % = 1
Seizures From clinical trial record No of events	n = 0 ; % = 0	n = 0 ; % = 0

All-cause mortality - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - Outcome level

Dichotomousoutcomes-All-causemortality-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Some concerns due to baseline characteristics being mismatched between the two arms, which appears to be more favourable to the control group)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Pulmonaryembolism-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Some concerns due to baseline characteristics being mismatched between the two arms, which appears to be more favourable to the control group)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Deepveinthrombosis-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Some concerns due to baseline characteristics being mismatched between the two arms, which appears to be more favourable to the control group)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Myocardialinfarction-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Some concerns due to baseline characteristics being mismatched between the two arms, which appears to be more favourable to the control group)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Seizures-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Some concerns due to baseline characteristics being mismatched between the two arms, which appears to be more favourable to the control group)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

D.2.5 Karanicolas, 2024

Bibliographic Reference Karanicolas, Paul J; Lin, Yulia; McCluskey, Stuart A; Tarshis, Jordan; Thorpe, Kevin E; Wei, Alice; Dixon, Elijah; Porter, Geoff; Chaudhury, Prosanto; Nanji, Sulaiman; Ruo, Leyo; Tsang, Melanie E; Skaro, Anton; Eeson, Gareth; Cleary, Sean; Moulton, Carol-Anne; Ball, Chad G; Hallet, Julie; Coburn, Natalie; Serrano, Pablo E; Jayaraman, Shiva; Law, Calvin; Tandan, Ved; Sapisochin, Gonzalo; Nagorney, David; Quan, Douglas; Smoot, Rory; Gallinger, Steven; Metrakos, Peter; Reichman, Trevor W; Jalink, Diederick; Bennett, Sean; Sutherland, Francis; Solano, Edward; Molinari, Michele; Tang, Ephraim S; Warner, Susanne G; Bathe, Oliver F; Barkun, Jeffrey; Kendrick, Michael L; Truty, Mark; Roke, Rachel; Xu, Grace; Lafreniere-Roula, Myriam; Guyatt, Gordon;

Tranexamic Acid in Patients Undergoing Liver Resection: The HeLiX Randomized Clinical Trial.; JAMA; 2024; vol. 332 (no. 13); 1080-1089

Study details

Trial name	HeLiX No comment
Associated studies	Not applicable No comment
Trial registration number	NCT02261415 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	United States of America (USA) No comment Canada No comment
Study setting	Inpatient: elective and day care No comment
Study dates	November 2014 to August 2022
Sources of funding	Academic or government grant support Funding support from Canadian Blood Services, Physicians' Services Incorporated Foundation and the Canadian Institutes of Health Research
Matching inclusion criteria	Adults (age at least 16 years) No comment At short-term risk of bleeding No comment Having surgery No comment
Other important inclusion criteria	Scheduled to undergo liver resection (open or minimally invasive) for a cancer-related indication

Other important exclusion criteria	Severe anaemia (Hb <9 g/dL); arterial or venous thrombosis within the prior 3 months; active treatment with anticoagulants; DIC; creatinine clearance <30mL/min; history of seizure disorder; inability to receive blood products
Interventions of interest	Tranexamic acid (intravenous) No comment
Comparisons of interest	Placebo No comment
Cointerventions	No additional information.
Subgroup 1: Surgical speciality	General surgery Liver surgery
Subgroup 2: Anticoagulant or antiplatelet use	No Exclusion criteria
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Yes All people have a cancer-related indication (from inclusion criteria)
Subgroup 4: Dose	2 grams No comment
Subgroup 5: Route of administration	Intravenous No comment
Subgroup 6: Repeated use	Repeated use No comment
Subgroup 7: Renal function	No impairment Majority of people had low creatinine, so likely no concerns
Outcomes of interest	All-cause mortality No comment Pulmonary embolism No comment Deep vein thrombosis No comment

	Myocardial infarction No comment Ischaemic stroke No comment Infection No comment Reoperation No comment
Total number of participants	1384
Duration of follow-up (days)	90
Additional comments	No additional comments

Study arms

Tranexamic acid (N = 694)

Tranexamic acid 1 gram bolus followed by a 1 gram infusion over 8 hours

Placebo (N = 690)

Matching placebo

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 694)	Placebo (N = 690)
Female (%) Sample size	n = 241 ; % = 38.9	n = 254 ; % = 40.6
Mean age (SD) (years) Mean (SD)	63.1 (11.5)	63.4 (11.4)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Hypertension Sample size	n = 290 ; % = 46.8	n = 308 ; % = 49.2

Characteristic	Tranexamic acid (N = 694)	Placebo (N = 690)
Comorbidities (%) - Hypercholesterolemia Sample size	n = 134 ; % = 21.6	n = 171 ; % = 27.3
Comorbidities (%) - Diabetes Sample size	n = 110 ; % = 17.8	n = 140 ; % = 22.4
Comorbidities (%) - Cirrhosis Sample size	n = 35 ; % = 5.7	n = 26 ; % = 4.2
Comorbidities (%) - Prior liver resection Sample size	n = 34 ; % = 5.5	n = 20 ; % = 3.2
Comorbidities (%) - Prior myocardial infarction Sample size	n = 30 ; % = 4.8	n = 36 ; % = 5.8
Comorbidities (%) - Other thrombosis Sample size	n = 12 ; % = 1.9	n = 11 ; % = 1.8
Comorbidities (%) - Stroke Sample size	n = 6 ; % = 1	n = 15 ; % = 2.4
Comorbidities (%) - Pulmonary embolism Sample size	n = 5 ; % = 0.8	n = 7 ; % = 1.1
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 90 days

Dichotomous outcomes (1)

Outcome	Tranexamic acid, 90 day, N = 680	Placebo, 90 day, N = 674
All-cause mortality Grade V (death) No of events	n = 18 ; % = 2.6	n = 16 ; % = 2.4
Pulmonary embolism No of events	n = 13 ; % = 1.9	n = 7 ; % = 1

Outcome	Tranexamic acid, 90 day, N = 680	Placebo, 90 day, N = 674
Deep vein thrombosis No of events	n = 23 ; % = 3.4	n = 12 ; % = 1.8

All-cause mortality - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better

Dichotomous outcomes (2)

Outcome	Tranexamic acid, 90 day, N = 619	Placebo, 90 day, N = 626
Myocardial infarction Cardiac - Ischaemic (downgrade for indirectness - could include other ischaemic cardiac outcomes) No of events	n = 8 ; % = 1.3	n = 8 ; % = 1.3
Ischaemic stroke Stroke/Transient ischaemic attack - downgrade for indirectness No of events	n = 1 ; % = 0.2	n = 2 ; % = 0.3
Infection Sepsis No of events	n = 24 ; % = 3.9	n = 20 ; % = 3.2
Reoperation No of events	n = 18 ; % = 2.9	n = 17 ; % = 2.7

Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Infection - Polarity - Lower values are better
Reoperation - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - Outcome level

Dichotomousoutcomes(1)-All-causemortality-NoOfEvents-Tranexamic acid-Placebo-t90

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(1)-Pulmonaryembolism-NoOfEvents-Tranexamic acid-Placebo-t90

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(1)-Deepveinthrombosis-NoOfEvents-Tranexamic acid-Placebo-t90

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Myocardialinfarction-NoOfEvents-Tranexamic acid-Placebo-t90

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness as may include other ischaemic cardiovascular events)*

Dichotomousoutcomes(2)-Ischaemicstroke-NoOfEvents-Tranexamic acid-Placebo-t90

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness as may include haemorrhagic strokes and TIAs)*

Dichotomousoutcomes(2)-Infection-NoOfEvents-Tranexamic acid-Placebo-t90

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Reoperation-NoOfEvents-Tranexamic acid-Placebo-t90

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

1

D.2.6 Myles, 2017

Bibliographic Reference	Myles, Paul S.; Smith, Julian A.; Painter, Thomas; Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery; The New England journal of medicine; 2017; vol. 376 (no. 2); 136-148

3

4 **Study details**

Trial name	ATACAS Only uses the Tranexamic acid or placebo half of the trial (also has an aspirin and placebo half - is a 2x2 factorial design)
Associated studies	Myles, Paul S, Smith, Julian A, Kasza, Jessica et al. (2019) Tranexamic acid in coronary artery surgery: One-year results of the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial. The Journal of thoracic and cardiovascular surgery 157(2): 644-652e9 No comment
Trial registration number	ACTRN12605000557639 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	Multicentre Australia, Canada, Hong Kong, Italy, Netherlands, New Zealand, United Kingdom
Study setting	Inpatient: elective and day care No comment
Study dates	March 2006 to October 2015
Sources of funding	Academic or government grant support Grants from the Australian National Health and Medical Research Council (NHMRC ID 334015 and 1009203), the Australian and New Zealand College of Anaesthetists, Monash University; and the National Institute of Health Research. Drs Myles and Cooper were supported on NHMRC Practitioner's Fellowship. Medicine/equipment provided by an organisation for the study Bayer Pharma provided the aspirin and matched placebo tablets used in the aspirin comparison.
Matching inclusion criteria	Adults (age at least 16 years) No comment

	Having surgery Coronary artery surgery Sample size of at least 500 people in each study arm No comment
Other important inclusion criteria	People at increased risk of major complications related to age of coexisting conditions (cardiovascular function, previous cardiovascular surgery, chronic obstructive pulmonary disease, renal impairment, obesity, pulmonary hypertension or peripheral vascular disease).
Other important exclusion criteria	Antiplatelet medication could not be discontinued. Active peptic ulceration. Warfarin or clopidogrel therapy within 7 days of surgery, GIIb/IIIa antagonists within 24 hours of surgery, aspirin within 4 days of surgery, thrombocytopenia or any other known history of bleeding disorder, severe renal impairment, thromboembolic disease (or predisposition towards a thromboembolic state).
Interventions of interest	Tranexamic acid (intravenous) No comment Placebo No comment
Comparisons of interest	Tranexamic acid compared to placebo No comment
Cointerventions	None specific of note. Everyone received anaesthesia for surgery and underwent on-pump or off-pump coronary-artery surgery with or without cardiac-valve replacement or other procedures.
Subgroup 1: Surgical speciality	Cardiothoracic No comment
Subgroup 2: Anticoagulant use	No <10% used either warfarin or heparin within 7 days and 24 hours respectively.
Subgroup 3: Comorbidities that increase risk of thromboembolic events	No <10% had renal impairment, <1% had thrombolysis. Low chance of this.
Subgroup 4: Dose of tranexamic acid	100 mg/kg Average weight 86kg - therefore 8.6 grams. Later in the trial halved to 50 mg/kg.

Subgroup 5: Route of administration	Intravenous
Subgroup 6: Repeated use of tranexamic acid	Single use
Subgroup 7: Renal function	No impairment Renal impairment in 7.5% of people. So <15% of people had renal impairment.
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery No comment Pulmonary embolism No comment Deep vein thrombosis No comment Myocardial infarction No comment Ischaemic stroke No comment Infection No comment Seizures Reoperation
Total number of participants	4662
Duration of follow-up (days)	30
Additional comments	No additional comments.

Study arms

Tranexamic acid (intravenous) (N = 2329)

Intravenous tranexamic acid 100mg/kg more than 30 minutes after induction of anaesthesia during coronary artery surgery. During the course of the trial, reports of seizures occurring after administration of tranexamic acid were published and these were considered to be dose related. Given this, the dose was halved to 50mg/kg in January 2012 after 1526 people had been enrolled.

Placebo (N = 2333)

Intravenous 0.9% saline more than 30 minutes after induction of anaesthesia during coronary artery surgery.

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (intravenous) (N = 2329)	Placebo (N = 2333)
Female (%) Sample size	n = 381 ; % = 16.5	n = 390 ; % = 16.8
Mean age (SD) (years) Mean (SD)	66.8 (9.8)	67 (9.6)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Anticoagulant use (%) - Warfarin within 7 days Sample size	n = 27 ; % = 1.2	n = 24 ; % = 1
Anticoagulant use (%) - Heparin within 24 hours Sample size	n = 172 ; % = 7.4	n = 182 ; % = 7.8
Comorbidities associated with bleeding (%) - Renal impairment Sample size	n = 173 ; % = 7.5	n = 170 ; % = 7.3
Comorbidities associated with bleeding (%) - Thrombolysis Sample size	n = 14 ; % = 0.6	n = 22 ; % = 0.9
Renal function (% or mL/min/1.73 m2) Mean (SD)	NR (NR)	NR (NR)

Outcomes

Study timepoints

- 30 days
- 365 days (1 year follow up from Myles 2019)

Dichotomous outcomes (1)

Outcome	Tranexamic acid (intravenous), 30 day, N = 2310	Tranexamic acid (intravenous), 365 day, N = 2237	Placebo, 30 day, N = 2320	Placebo, 365 day, N = 2270
All-cause mortality No of events	n = 26 ; % = 1.1	n = 68 ; % = 3	n = 33 ; % = 1.4	n = 78 ; % = 3.4
Myocardial infarction No of events	n = 269 ; % = 11.6	n = 239 ; % = 10.7	n = 300 ; % = 12.9	n = 274 ; % = 12.2
Thromboembolic events after surgery Aggregate of death, myocardial infarction, stroke, pulmonary embolism and bowel infarction. Downgrade for including mortality (and bowel infarction). No of events	n = 324 ; % = 14	n = NR ; % = NR	n = 362 ; % = 15.6	n = NR ; % = NR
Reoperation Due to any cause No of events	n = 32 ; % = 1.4	n = NR ; % = NR	n = 65 ; % = 2.8	n = NR ; % = NR

All-cause mortality - Polarity - Lower values are better

Myocardial infarction - Polarity - Lower values are better

Thromboembolic events after surgery - Polarity - Lower values are better

Reoperation - Polarity - Lower values are better

Dichotomous outcomes (2)

Outcome	Tranexamic acid (intravenous), 30 day, N = 2309	Tranexamic acid (intravenous), 365 day, N = 2267	Placebo, 30 day, N = 2320	Placebo, 365 day, N = 2289
Pulmonary embolism No of events	n = 15 ; % = 0.6	n = NR ; % = NR	n = 15 ; % = 0.6	n = NR ; % = NR
Ischaemic stroke Stroke No of events	n = 32 ; % = 1.4	n = 45 ; % = 2	n = 35 ; % = 1.5	n = 61 ; % = 2.7

Pulmonary embolism - Polarity - Lower values are better

Ischaemic stroke - Polarity - Lower values are better

Dichotomous outcomes (3)

Outcome	Tranexamic acid (intravenous), 30 day, N = 2311	Tranexamic acid (intravenous), 365 day, N = NA	Placebo, 30 day, N = 2320	Placebo, 365 day, N = NA
Deep vein thrombosis Other thrombotic events (DVT) No of events	n = 12 ; % = 0.5	n = NR ; % = NR	n = 13 ; % = 0.6	n = NR ; % = NR
Infection Sepsis or infection No of events	n = 138 ; % = 6	n = NR ; % = NR	n = 139 ; % = 6	n = NR ; % = NR

Deep vein thrombosis - Polarity - Lower values are better
Infection - Polarity - Lower values are better

Dichotomous outcomes (4)

Outcome	Tranexamic acid (intravenous), 30 day, N = 2304	Tranexamic acid (intravenous), 365 day, N = NA	Placebo, 30 day, N = 2327	Placebo, 365 day, N = NA
Seizures No of events	n = 15 ; % = 0.7	n = NR ; % = NR	n = 2 ; % = 0.1	n = NR ; % = NR

Seizures - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable *(With the exception of the thromboembolic event outcome which includes components that make it partially applicable (mortality as well as thromboembolic events).)*

D.2.7 Myles, 2019

Bibliographic Reference Myles, Paul S; Smith, Julian A; Kasza, Jessica; Silbert, Brendan; Jayarajah, Mohandas; Painter, Thomas; Cooper, D James; Marasco, Silvana; McNeil, John; Bussieres, Jean S; McGuinness, Shay; Byrne, Kelly; Chan, Matthew T V; Landoni, Giovanni; Wallace, Sophie; Forbes, Andrew; Tranexamic acid in coronary artery surgery: One-year results of the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial.; The Journal of

thoracic and cardiovascular surgery; 2019; vol. 157 (no. 2); 644-652e9

Study details

Trial name	ATACAS No comment
Associated studies	Myles, Paul S.; Smith, Julian A.; Painter, Thomas (2017) Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. The New England journal of medicine 376(2): 136-148 For full study extraction see Myles (2017).

D.2.8 Pacheco, 2023

Bibliographic Reference	Pacheco, Luis D; Clifton, Rebecca G; Saade, George R; Weiner, Steven J; Parry, Samuel; Thorp, John M Jr; Longo, Monica; Salazar, Ashley; Dalton, Wendy; Tita, Alan T N; Gyamfi-Bannerman, Cynthia; Chauhan, Suneet P; Metz, Torri D; Rood, Kara; Rouse, Dwight J; Bailit, Jennifer L; Grobman, William A; Simhan, Hyagriv N; Macones, George A; Tranexamic Acid to Prevent Obstetrical Hemorrhage after Cesarean Delivery.; The New England journal of medicine; 2023; vol. 388 (no. 15); 1365-1375

Study details

Trial name	Not applicable No comment
Associated studies	Not applicable No comment
Trial registration number	NCT03364491 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	United States of America (USA) No comment
Study setting	Inpatient: elective and day care No comment
Study dates	March 2018 to July 2021
Sources of funding	Academic or government grant support

	Grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development
Matching inclusion criteria	Adults (age at least 16 years) No comment Pregnant women, trans men and non-binary people (age at least 16 years) No comment Having surgery Scheduled caesarean delivery
Other important inclusion criteria	No comment
Other important exclusion criteria	Transfusion of any blood products before randomisation or a plan to transfuse after randomisation; history of seizures; kidney disease; thromboembolic disease; medical conditions or treatments associated with a high risk of thrombosis; decision not to use blood products; plan to administer prophylactic antifibrinolytic agents preoperatively (apart from oxytocin)
Interventions of interest	Tranexamic acid (intravenous) No comment
Comparisons of interest	Placebo No comment
Cointerventions	No additional information
Subgroup 1: Surgical speciality	Gynaecology No comment
Subgroup 2: Anticoagulant or antiplatelet use	No From exclusion criteria
Subgroup 3: Comorbidities that increase risk of thromboembolic events	No From exclusion criteria
Subgroup 4: Dose	1 gram No comment
Subgroup 5: Route of administration	Intravenous No comment

Subgroup 6: Repeated use	Single use No comment
Subgroup 7: Renal function	Not stated/unclear No comment
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery No comment Myocardial infarction No comment Ischaemic stroke No comment Infection No comment All-cause readmission No comment Seizures No comment Reoperation No comment
Total number of participants	11000
Duration of follow-up (days)	42
Additional comments	No additional comments

Study arms

Tranexamic acid (N = 5529)

1 gram tranexamic acid diluted in 40 mL normal saline given over 10 minutes immediately after cord clamping

Placebo (N = 5471)

Matching placebo

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 5529)	Placebo (N = 5471)
Female (%) Sample size	n = 5529 ; % = 100	n = 5471 ; % = 100
Mean age (SD) (years) Mean (SD)	30.1 (5.8)	30.1 (5.8)
Ethnicity (%) - Non-Hispanic White Sample size	n = 2170 ; % = 39.3	n = 2159 ; % = 39.5
Ethnicity (%) - Non-Hispanic Black Sample size	n = 1334 ; % = 24.1	n = 1310 ; % = 23.9
Ethnicity (%) - Hispanic Sample size	n = 1636 ; % = 29.6	n = 1642 ; % = 30
Ethnicity (%) - Asian Sample size	n = 218 ; % = 3.9	n = 193 ; % = 3.5
Ethnicity (%) - Other, unknown or multiple Sample size	n = 167 ; % = 3	n = 166 ; % = 3
Comorbidities (%) - Pregnancy-related hypertensive disorder Sample size	n = 957 ; % = 17.3	n = 967 ; % = 17.7
Comorbidities (%) - Placental abruption Sample size	n = 43 ; % = 0.8	n = 44 ; % = 0.8
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 42 days

Dichotomous outcomes (1)

Outcome	Tranexamic acid, 42 day, N = 5080	Placebo, 42 day, N = 5009
Infection Postpartum infectious complication by 6 weeks No of events	n = 162 ; % = 3.2	n = 125 ; % = 2.5

Infection - Polarity - Lower values are better

Dichotomous outcomes (2)

Outcome	Tranexamic acid, 42 day, N = 5069	Placebo, 42 day, N = 4996
Thromboembolic events after surgery No of events	n = 12 ; % = 0.2	n = 13 ; % = 0.3
Myocardial infarction No of events	n = 2 ; % = 0.1	n = 0 ; % = 0
Ischaemic stroke No of events	n = 2 ; % = 0.1	n = 0 ; % = 0
Seizures No of events	n = 2 ; % = 1	n = 0 ; % = 0
All-cause readmission No of events	n = 199 ; % = 3.9	n = 162 ; % = 3.2
All-cause mortality No of events	n = 2 ; % = 0.1	n = 2 ; % = 0.1
Reoperation Surgical or radiological interventions in response to bleeding and related complications by 7 days postpartum No of events	n = 233 ; % = 4.2	n = 231 ; % = 4.2

Thromboembolic events after surgery - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Seizures - Polarity - Lower values are better
All-cause readmission - Polarity - Lower values are better
All-cause mortality - Polarity - Lower values are better
Reoperation - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - Outcome level

Dichotomousoutcomes(1)-Infection-NoOfEvents-Tranexamic acid-Placebo-t42

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Thromboemboliceventsaftersurgery-NoOfEvents-Tranexamic acid-Placebo-t42

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Myocardialinfarction-NoOfEvents-Tranexamic acid-Placebo-t42

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Ischaemicstroke-NoOfEvents-Tranexamic acid-Placebo-t42

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Seizures-NoOfEvents-Tranexamic acid-Placebo-t42

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Readmission-NoOfEvents-Tranexamic acid-Placebo-t42

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-All-causemortality-NoOfEvents-Tranexamic acid-Placebo-t42

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Reoperation-NoOfEvents-Tranexamic acid-Placebo-t42

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

D.2.9 Peng, 2020

Bibliographic Reference Peng, H.; Wang, L.; Weng, X.; Zhai, J.; Lin, J.; Jin, J.; Qian, W.; Gao, N.; Effect of tranexamic acid on symptomatic venous thromboembolism in patients undergoing primary total knee arthroplasty; Archives of Medical Science; 2020; vol. 16 (no. 2); 603

Study details

Trial name	Not applicable No comment
Associated studies	Not applicable No comment
Trial registration number	Not applicable No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	China No comment
Study setting	Inpatient: elective and day care No comment
Study dates	January 2013 to May 2015
Sources of funding	Funding unclear or not specified No comment

Matching inclusion criteria	Adults (age at least 16 years) No comment At short-term risk of bleeding No comment Having surgery No comment
Other important inclusion criteria	Primary total knee arthroplasty; standardised venous thromboembolism prophylactic anticoagulant therapy postoperatively; tranexamic acid injection in the perioperative period
Other important exclusion criteria	History of venous thromboembolism, pulmonary embolism and coronary heart disease; coagulopathy; oral NSAIDs discontinued for less than 1 week; allergy to TXA; severe liver and kidney dysfunctions; high risk of thrombosis.
Interventions of interest	Tranexamic acid (intravenous) No comment
Comparisons of interest	Placebo No comment
Cointerventions	No additional information.
Subgroup 1: Surgical speciality	Orthopaedics No comment
Subgroup 2: Anticoagulant or antiplatelet use	Yes Post operative VTE prophylaxis
Subgroup 3: Comorbidities that increase risk of thromboembolic events	No From exclusion criteria
Subgroup 4: Dose	15 mg/kg or 15 mg/kg intravenous + 1 g/50 mL topical No comment
Subgroup 5: Route of administration	Other Either intravenous or intravenous and topical
Subgroup 6: Repeated use	Single use No comment

Subgroup 7: Renal function	No impairment From exclusion criteria
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery Venous thromboembolism - downgrade for indirectness Pulmonary embolism No comment Deep vein thrombosis No comment
Total number of participants	1880
Duration of follow-up (days)	30
Additional comments	Matching placebo

Study arms

Tranexamic acid (N = 720)

Either intravenous tranexamic acid (15 mg/kg) injected 15 minutes before the release of the tourniquet or intravenous tranexamic acid (15 mg/kg) and topical tranexamic acid (1 g/50 mL) before the release of the tourniquet. No information about proportions of each.

Placebo (N = 1160)

Matching placebo

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 720)	Placebo (N = 1160)
Female (%) Sample size	n = 544 ; % = 75.56	n = 976 ; % = 84.14
Mean age (SD) (years) Mean (SD)	66.47 (7.64)	68.4 (8.93)
Ethnicity (%)	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Tranexamic acid (N = 720)	Placebo (N = 1160)
Sample size		
Comorbidities (%) - Hypertension Sample size	n = 396 ; % = 55	n = 560 ; % = 48
Comorbidities (%) - Diabetes Sample size	n = 127 ; % = 18	n = 207 ; % = 18
Comorbidities (%) - Cerebrovascular disease Sample size	n = 71 ; % = 10	n = 193 ; % = 17
Comorbidities (%) - Arrhythmia Sample size	n = 24 ; % = 3	n = 43 ; % = 4
Comorbidities (%) - Hyperlipidaemia Sample size	n = 24 ; % = 3	n = 48 ; % = 4
Comorbidities (%) - History of malignancy Sample size	n = 15 ; % = 2	n = 26 ; % = 2
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 30 days

Dichotomous outcomes

Outcome	Tranexamic acid, 30 day, N = 720	Placebo, 30 day, N = 1160
All-cause mortality No of events	n = 0 ; % = 0	n = 0 ; % = 0
Thromboembolic events after surgery Symptomatic VTE. Downgrade for indirectness as does not include arterial events No of events	n = 24 ; % = 3	n = 39 ; % = 3
Pulmonary embolism PE No of events	n = 6 ; % = 1	n = 2 ; % = 1

Outcome	Tranexamic acid, 30 day, N = 720	Placebo, 30 day, N = 1160
Deep vein thrombosis Near-end DVT No of events	n = 6 ; % = 0.8	n = 6 ; % = 0.5

All-cause mortality - Polarity - Lower values are better
Thromboembolic events after surgery - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - Outcome level

Dichotomousoutcomes-All-causemortality-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Due to concerns about allocation concealment.)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns.)*

Dichotomousoutcomes-Thromboemboliceventsaftersurgery-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Due to concerns about allocation concealment.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Downgrade for outcome indirectness as the outcome does not include arterial events)*

Dichotomousoutcomes-Pulmonaryembolism-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Due to concerns about allocation concealment.)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns.)*

Dichotomousoutcomes-Deepveinthrombosis-NoOfEvents-Tranexamic acid-Placebo-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Due to concerns about allocation concealment.)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns.)*

1

D2.10 Post, 2021

Bibliographic Reference Post R; Germans MR; Tjerkstra MA; Vergouwen MDI; Jellema K; Koot RW; Kruyt ND; Willems PWA; Wolfs JFC; de Beer FC; Kieft H; Nanda D; van der Pol B; Roks G; de Beer F; Halkes PHA; Reichman LJA; Brouwers PJAM; van den Berg-Vos RM; Kwa VIH; van der Ree TC; Bronner I; van de Vlekkert J; Bienfait HP; Boogaarts HD; Klijn CJM; van den Berg R; Coert BA; Horn J; Majoie CBLM; Rinkel GJE; Roos YBWEM; Vandertop WP; Verbaan D; ; Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA): a randomised controlled trial.; Lancet (London, England); 2021; vol. 397 (no. 10269)

3

4 **Study details**

Trial name	ULTRA No comment
Associated studies	Not applicable No comment
Trial registration number	NCT02684812 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	Netherlands No comment
Study setting	Inpatient: non-elective No comment
Study dates	July 24th 2013 to July 29th 2019
Sources of funding	Academic or government grant support Fonds NotOhra (project 102-31) Other author funded by a private organisation Some authors declared funding from pharma companies outside of the current work or academic funding outside of the work.

Matching inclusion criteria	Adults (age at least 16 years) No comment Having surgery No comment Sample size of at least 500 people in each study arm While the study arms had slightly under 500 people in each study arm, this study was included but downgraded for indirectness.
Other important inclusion criteria	Presenting less than 24 hours with signs and symptoms of a subarachnoid haemorrhage, a non-contrast CT confirming this
Other important exclusion criteria	Perimesencephalic bleeding pattern on CT in combination with a GCS of 13-15; without loss of consciousness directly after ictus or focal neurological deficit on admission; traumatic subarachnoid haemorrhage pattern on CT; ongoing treatment for DVT/PE; history of hypercoagulability; pregnancy; severe renal failure (creatinine >150 micromol/L); imminent death within 24 hours.
Interventions of interest	Tranexamic acid (intravenous) No comment Usual care No comment
Comparisons of interest	Tranexamic acid compared to usual care No comment
Cointerventions	Aneurysm treatment (either endovascular or surgical repair).
Subgroup 1: Surgical speciality	Neurosurgery No comment
Subgroup 2: Anticoagulant use	Mixed population Approximately 16% of people used either a platelet inhibitor or anticoagulation
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Not stated/unclear No comment
Subgroup 4: Dose of tranexamic acid	2 grams - 4 grams 2 grams up to 4 grams dependent on the time taken to have the repair

Subgroup 5: Route of administration	Intravenous No comment
Subgroup 6: Repeated use of tranexamic acid	Repeated use No comment
Subgroup 7: Renal function	No impairment Based on exclusion criteria
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery No comment Pulmonary embolism No comment Deep vein thrombosis No comment Ischaemic stroke Use cerebral infarction due to clipping procedure Infection Selection of infectious meningitis due to it being specific to the site being operated on Seizures No comment
Total number of participants	955
Duration of follow-up (days)	183
Additional comments	No additional comments

Study arms

Tranexamic acid (N = 480)

Intravenous bolus of 1 gram tranexamic acid, directly followed by 1 gram continuous intravenous infusion of tranexamic acid every 8 hours. This was

continued until the start of endovascular or surgical treatment of the aneurysm or until a maximum of 24 hours (a maximum of 4 grams in total).

Usual care (N = 475)

Usual care only (no additional treatment).

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 480)	Usual care (N = 475)
Female (%) Sample size	n = 332 ; % = 69	n = 312 ; % = 66
Mean age (SD) (years) Mean (SD)	58.4 (12.6)	58.4 (12.3)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Anticoagulant use (%) - Platelet inhibitor Sample size	n = 61 ; % = 13	n = 61 ; % = 13
Anticoagulant use (%) - Anticoagulation Sample size	n = 15 ; % = 3	n = 19 ; % = 4
Comorbidities associated with bleeding (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 6 months

Dichotomous outcomes (1)

Outcome	Tranexamic acid, 6 month, N = 480	Usual care, 6 month, N = 475
All-cause mortality No of events	n = 128 ; % = 27	n = 114 ; % = 24

Outcome	Tranexamic acid, 6 month, N = 480	Usual care, 6 month, N = 475
Pulmonary embolism No of events	n = 6 ; % = 1	n = 5 ; % = 1
Deep vein thrombosis No of events	n = 0 ; % = 0	n = 2 ; % = 1
Ischaemic stroke Cerebral infarction related to clipping procedure No of events	n = 22 ; % = 26	n = 18 ; % = 21
Seizures No of events	n = 59 ; % = 12	n = 40 ; % = 8

All-cause mortality - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Dichotomous outcomes (2)

Outcome	Tranexamic acid, 6 month, N = 272	Usual care, 6 month, N = 258
Thromboembolic events after surgery No of events	n = 29 ; % = 11	n = 33 ; % = 13
Infection Infectious meningitis No of events	n = 37 ; % = 8	n = 31 ; % = 7

Thromboembolic events after surgery - Polarity - Lower values are better
Infection - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to concerns about the outcome interpretation due to the influence that knowledge of the interventions had on the decision to use different surgical techniques (endovascular approach compared to the surgical approach) and the potential effect this could have on the outcome results. The tranexamic acid outcomes may be more or less favourable dependent on the effects that more people having endovascular repairs may have on*

Section	Question	Answer
		the study given the rarity of the outcomes being measured.)
Overall bias and Directness	Overall Directness	Partially applicable *(Due to the sample size of the study arms being less than 500 people)*

1

D22.11 Roberts I, 2020

Bibliographic Reference HALT-IT trial, Collaborators; Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial.; Lancet (London, England); 2020; vol. 395 (no. 10241); 1927-1936

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4 **Study details**

Trial name	HALT-IT No comment
Associated studies	Not applicable No comment
Trial registration number	NCT01658124 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	Multicentre No comment
Study setting	Inpatient: non-elective No comment
Study dates	July 4th 2013 to June 21st 2019.
Sources of funding	Academic or government grant support UK NIHR HTA programme
Matching inclusion criteria	Adults (age at least 16 years) No comment At short-term risk of bleeding Having significant bleeding where the clinician was substantially uncertain whether to use tranexamic acid

Other important inclusion criteria	The diagnosis of significant bleeding was clinical and significant was defined as a risk of bleeding to death and included patients with hypotension, tachycardia, or signs of shock, or those likely to need transfusion or urgent endoscopy or surgery.
Other important exclusion criteria	Clear indication tranexamic acid should be used or clear contraindication to tranexamic acid.
Interventions of interest	Tranexamic acid (intravenous) No comment
Comparisons of interest	Placebo No comment
Cointerventions	No comment
Subgroup 1: Surgical speciality	General surgery Gastroenterology rather than surgery
Subgroup 2: Anticoagulant or antiplatelet use	No <10% were taking anticoagulants
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Mixed population Around 41% had liver comorbidities, 20% had cardiovascular comorbidities, 7% had malignancy, 72% had any comorbidity.
Subgroup 4: Dose	4 grams People with active bleeding
Subgroup 5: Route of administration	Intravenous No comment
Subgroup 6: Repeated use	Repeated use No comment
Subgroup 7: Renal function	No impairment Probably no based on only 5% having renal comorbidities
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery No comment

	Pulmonary embolism No comment Deep vein thrombosis No comment Myocardial infarction No comment Ischaemic stroke No comment Infection Sepsis Seizures No comment
Total number of participants	12009
Duration of follow-up (days)	28
Additional comments	No additional information

Study arms

Tranexamic acid (intravenous) (N = 5994)

1 gram tranexamic acid added to 100 mL of 0.9% sodium chloride infused by slow intravenous injection over 10 minutes followed by 3 grams tranexamic acid added to 1 L of any isotonic intravenous solution infused at 125 mg/h for 24 hours.

Placebo (N = 6015)

Matching placebo

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (intravenous) (N = 5994)	Placebo (N = 6015)
Female (%) Sample size	n = 2142 ; % = 36	n = 2124 ; % = 35

Characteristic	Tranexamic acid (intravenous) (N = 5994)	Placebo (N = 6015)
Mean age (SD) (years) Mean (SD)	58.1 (17)	58.1 (17)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) Sample size	n = 4308 ; % = 72	n = 4329 ; % = 72
Comorbidities (%) - Cardiovascular Sample size	n = 1108 ; % = 18	n = 1132 ; % = 19
Comorbidities (%) - Respiratory Sample size	n = 337 ; % = 6	n = 324 ; % = 5
Comorbidities (%) - Liver Sample size	n = 2432 ; % = 41	n = 2532 ; % = 42
Comorbidities (%) - Renal Sample size	n = 425 ; % = 5	n = 310 ; % = 5
Comorbidities (%) - Malignancy Sample size	n = 417 ; % = 7	n = 382 ; % = 6
Comorbidities (%) - Other Sample size	n = 999 ; % = 17	n = 968 ; % = 16
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 28 days

Dichotomous outcomes (1)

Outcome	Tranexamic acid (intravenous), 28 day, N = 5956	Placebo, 28 day, N = 5981
All-cause mortality	n = 564 ; % = 9.5	n = 548 ; % = 9.2

Outcome	Tranexamic acid (intravenous), 28 day, N = 5956	Placebo, 28 day, N = 5981
No of events		

All-cause mortality - Polarity - Lower values are better

Dichotomous outcomes (2)

Outcome	Tranexamic acid (intravenous), 28 day, N = 5952	Placebo, 28 day, N = 5977
Thromboembolic events after surgery Any thromboembolic event No of events	n = 86 ; % = 1.4	n = 72 ; % = 1.2
Pulmonary embolism No of events	n = 28 ; % = 0.5	n = 16 ; % = 0.3
Deep vein thrombosis No of events	n = 23 ; % = 0.4	n = 16 ; % = 0.3
Myocardial infarction No of events	n = 24 ; % = 0.4	n = 28 ; % = 0.5
Ischaemic stroke Stroke - however, the inference from the complication list is that this is a thromboembolic event, therefore do not downgrade for not stating ischaemic No of events	n = 19 ; % = 0.3	n = 18 ; % = 0.3
Infection Sepsis No of events	n = 210 ; % = 3.5	n = 216 ; % = 3.6
Seizures No of events	n = 38 ; % = 0.6	n = 22 ; % = 0.4

Thromboembolic events after surgery - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Infection - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - Outcome level

Dichotomousoutcomes(1)-All-causemortality-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Thromboemboliceventsaftersurgery-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Pulmonaryembolism-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Deepveinthrombosis-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Myocardialinfarction-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Ischaemicstroke-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Infection-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes(2)-Seizures-NoOfEvents-Tranexamic acid (intravenous)-Placebo-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

D72.12 Rowell, 2020

Bibliographic Reference

Rowell, Susan E.; Meier, Eric N.; McKnight, Barbara; Kannas, Delores; May, Susanne; Sheehan, Kellie; Bulger, Eileen M.; Idris, Ahamed H.; Christenson, Jim; Morrison, Laurie J.; Frascone, Ralph J.; Bosarge, Patrick L.; Colella, M. Riccardo; Johannigman, Jay A.; Cotton, Bryan A.; Callum, Jeannie; McMullan, Jason T.; Dries, David J.; Tibbs, Brian; Richmond, Neal; Weisfeldt, Myron L.; Tallon, John M.; Garrett, John S.; Zielinski, Martin D.; Aufderheide, Tom P.; Gandhi, Rajesh R.; Schlamp, Rob S.; Robinson, Bryce R.H.; Jui, Jonathan; Klein, Lauren R.; Rizoli, Sandro; Gamber, Mark; Fleming, Michael; Hwang, Jun; Vincent, Laura; Williams, Carolyn; Hendrickson, Audrey; Simonson, Robert; Klotz, Patricia; Sopko, George; Witham, William R.; Ferrara, Michael; Schreiber, Martin A.; Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury.; JAMA; 2020; vol. 324 (no. 10); 961-974

Study details

Trial name	Prehospital TXA for TBI Trial No comment
Associated studies	Not applicable No comment
Trial registration number	NCT01990768 No comment
Study type	Randomised controlled trial (RCT) No comment

Study location	Multicentre United States and Canada United States of America (USA) No comment Canada No comment
Study setting	Inpatient: non-elective No comment Ambulance Pre-hospital A&E No comment
Study dates	May 2015 and March 2017.
Sources of funding	Academic or government grant support Funded by cooperative agreements from the National Heart, Lung and Blood Institute administered by the US Army Medical Research and Material Command. Grants for authors from the National Institutes of Health and US Departments of Defence as well as some universities and charities. Other author funded by a private organisation An author received funding from Octopharma. Another from Haemonetics.
Matching inclusion criteria	Adults (age at least 16 years) No comment Children (age less than 16 years) 15 or older Sample size of at least 500 people in each study arm When combined, the tranexamic acid arm has >500 people in the arm. When not combined <500 people per arm. Downgrade for indirectness and include.

Other important inclusion criteria	Moderate or severe blunt or penetrating traumatic brain injury, Glasgow Coma Scale score of 3-12, at least 1 reactive pupil, systolic blood pressure at least 90 mmHg.
Other important exclusion criteria	Greater than 2 hours after injury
Interventions of interest	Tranexamic acid (intravenous) No comment Placebo No comment
Comparisons of interest	Tranexamic acid compared to placebo No comment
Cointerventions	No additional information
Subgroup 1: Surgical speciality	Trauma No comment
Subgroup 2: Anticoagulant use	Not stated/unclear No comment
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Not stated/unclear No comment
Subgroup 4: Dose of tranexamic acid	2 grams
Subgroup 5: Route of administration	Intravenous
Subgroup 6: Repeated use of tranexamic acid	Mixed population Half had a repeated dose split between two administrations (two 1 gram doses), half a single dose (one 2 gram dose)
Subgroup 7: Renal function	Not stated/unclear
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery

	No comment Pulmonary embolism No comment Deep vein thrombosis No comment Myocardial infarction No comment Ischaemic stroke No comment Infection No comment Seizures
Total number of participants	1063
Duration of follow-up (days)	182
Additional comments	No additional information

Study arms

Tranexamic acid (N = 657)

Out-of-hospital tranexamic acid 1 gram intravenous bolus, in-hospital tranexamic acid 1 gram 8-hour infusion (n=312) or out-of-hospital tranexamic acid 2 gram intravenous bolus and in-hospital placebo 8-hour infusion (n=345). These two arms were combined for the sake of this analysis.

Placebo (N = 309)

Out-of-hospital placebo intravenous bolus, in-hospital placebo 8-hour infusion

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 657)	Placebo (N = 309)
Female (%) Sample size	n = 175 ; % = 27	n = 76 ; % = 25

Characteristic	Tranexamic acid (N = 657)	Placebo (N = 309)
Mean age (SD) Mean (SD)	NR (NR)	NR (NR)
Ethnicity (%) - American Indian/Alaska Native Sample size	n = 8 ; % = 1	n = 2 ; % = 1
Ethnicity (%) - Asian Sample size	n = 23 ; % = 4	n = 7 ; % = 3
Ethnicity (%) - Black/African American Sample size	n = 103 ; % = 16	n = 46 ; % = 17
Ethnicity (%) - Native Hawaiian/other Pacific Islander Sample size	n = 2 ; % = 1	n = 1 ; % = 1
Ethnicity (%) - White Sample size	n = 429 ; % = 65	n = 213 ; % = 79
Ethnicity (%) - More than 1 race Sample size	n = 3 ; % = 1	n = 2 ; % = 1
Ethnicity (%) - Hispanic Sample size	n = 83 ; % = 13	n = 40 ; % = 15
Anticoagulant use (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities associated with bleeding (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 28 days (For most outcomes)
- 182 days (6 months follow up (for mortality data only))

Mortality

Outcome	Tranexamic acid, 28 day, N = 603	Tranexamic acid, 182 day, N = 551	Placebo, 28 day, N = 285	Placebo, 182 day, N = 272
All-cause mortality No of events	n = 93 ; % = 15	n = 101 ; % = 18	n = 50 ; % = 18	n = 54 ; % = 20

All-cause mortality - Polarity - Lower values are better

Other outcomes

Outcome	Tranexamic acid, 28 day, N = 657	Tranexamic acid, 182 day, N = 657	Placebo, 28 day, N = 309	Placebo, 182 day, N = 309
Thromboembolic events after surgery Any thromboembolic event No of events	n = 44 ; % = 7	n = NR ; % = NR	n = 30 ; % = 10	n = NR ; % = NR
Pulmonary embolism No of events	n = 9 ; % = 1	n = NR ; % = NR	n = 5 ; % = 2	n = NR ; % = NR
Deep vein thrombosis No of events	n = 13 ; % = 2	n = NR ; % = NR	n = 9 ; % = 3	n = NR ; % = NR
Myocardial infarction No of events	n = 5 ; % = 1	n = NR ; % = NR	n = 1 ; % = 1	n = NR ; % = NR
Ischaemic stroke Thrombotic stroke No of events	n = 16 ; % = 2	n = NR ; % = NR	n = 10 ; % = 3	n = NR ; % = NR
Infection Any infection No of events	n = 105 ; % = 16	n = NR ; % = NR	n = 40 ; % = 13	n = NR ; % = NR
Seizures Seizures or seizure-like activity No of events	n = 22 ; % = 3	n = NA ; % = NA	n = 7 ; % = 2	n = NA ; % = NA

Thromboembolic events after surgery - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Infection - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(For mortality only. Low for all other outcomes.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Due to sample size concerns (being less than 500 participants in each study arm, only reaching >500 when two arms are pooled together). This appears satisfactory but may be a concern.)*

D62.13 Sentilhes, 2018

Bibliographic Reference Sentilhes, L.; Sénat, Marie V.; Le Lous, Maela; Winer, Norbert; Rozenberg, Patrick; Kayem, Gilles; Verspyck, Eric; Fuchs, Florent; Azria, Elie; Gallot, Denis; Korb, Diane; Desbriere, Raoul; Le Ray, Camille; Chauleur, Céline; De Marcillac, Fanny; Perrotin, Franck; Parant, Olivier; Salomon, Laurent; Gauchotte, Emilie; Bretelle, Florence; Sananès, Nicolas; Bohec, Caroline; Mottet, Nicolas; Legendre, Guillaume; Letouzey, Vincent; Haddad, Bassam; Vardon, Delphine; Madar, Hugo; Mattuizzi, Aurélien; Daniel, Valérie; Regueme, Sophie; Roussillon, Caroline; Bénard, Antoine; Georget, Aurore; Darsonval, Astrid; Deneux-Tharaux, Catherine; de Recherche en Obstétrique et Gynécologie, Groupe; Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery; The New England journal of medicine; 2018; vol. 379 (no. 8); 731-742

Study details

Trial name	TRAAP Tranexamic Acid for Preventing Postpartum Haemorrhage Following a Vaginal Delivery Trial
Associated studies	Not applicable No comment
Trial registration number	NCT02302456 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	Multicentre France

	France No comment
Study setting	Inpatient: elective and day care Maternity units
Study dates	January 2015 to December 2016
Sources of funding	Academic or government grant support Supported by the French Ministry of Health under the Clinical Research Hospital Program (PHRCN 1370458 N).
Matching inclusion criteria	Adults (age at least 16 years) No comment Sample size of at least 500 people in each study arm No comment Pregnant women, trans men and non-binary people Pregnant women
Other important inclusion criteria	Singleton pregnancy at 35 weeks 0 days gestation or more and were planning to undergo vaginal delivery.
Other important exclusion criteria	Known or increased risk of venous or arterial thrombosis or bleeding or had a condition potentially impairing initial haemostasis; history of epilepsy or seizure.
Interventions of interest	Tranexamic acid (intravenous) No comment Placebo No comment
Comparisons of interest	Tranexamic acid compared to placebo No comment
Cointerventions	No comment
Subgroup 1: Surgical speciality	Gynaecology No comment
Subgroup 2: Anticoagulant use	No In exclusion criteria
Subgroup 3: Comorbidities that increase	No In exclusion criteria

risk of thromboembolic events	
Subgroup 4: Dose of tranexamic acid	1 gram
Subgroup 5: Route of administration	Intravenous
Subgroup 6: Repeated use of tranexamic acid	Single use
Subgroup 7: Renal function	Not stated/unclear
Outcomes of interest	Thromboembolic events after surgery No comment Pulmonary embolism No comment Deep vein thrombosis No comment Myocardial infarction No comment Ischaemic stroke No comment All-cause readmission No comment Seizures
Total number of participants	4079
Duration of follow-up (days)	84
Additional comments	No additional information

Study arms

Tranexamic acid (N = 2040)

1 gram tranexamic acid intravenous bolus after delivery.

Placebo (N = 2039)

Placebo bolus after delivery.

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 2040)	Placebo (N = 2039)
Female (%) Sample size	n = 2040 ; % = 100	n = 2039 ; % = 100
Mean age (SD) (years) Mean (SD)	30.3 (4.7)	30.2 (5)
Ethnicity (%) - Non-French nationality Sample size	n = 161 ; % = 8.8	n = 162 ; % = 8.9
Anticoagulant use (%) Sample size	n = NA ; % = NA	n = NA ; % = NA
Comorbidities associated with bleeding (%) Sample size	n = NA ; % = NA	n = NA ; % = NA
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 84 day (3 months)

Modified intention-to-treat outcomes

Outcome	Tranexamic acid, 84 day, N = 1844	Placebo, 84 day, N = 1849
Thromboembolic event after surgery Any thromboembolic event No of events	n = 1 ; % = 0.1	n = 4 ; % = 0.2
Deep vein thrombosis No of events	n = 0 ; % = 0	n = 1 ; % = 0.1
Pulmonary embolism	n = 0 ; % = 0	n = 0 ; % = 0

Outcome	Tranexamic acid, 84 day, N = 1844	Placebo, 84 day, N = 1849
No of events		
All-cause readmission Readmission after discharge No of events	n = 18 ; % = 1	n = 16 ; % = 0.9
Seizure No of events	n = 1 ; % = 0.1	n = 0 ; % = 0

Thromboembolic event after surgery - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
All-cause readmission - Polarity - Lower values are better
Seizure - Polarity - Lower values are better

Per-protocol population 2

Outcome	Tranexamic acid, 84 day, N = 1780	Placebo, 84 day, N = 1787
Myocardial infarction No of events	n = 0 ; % = 0	n = 0 ; % = 0
Ischaemic stroke Stroke No of events	n = 0 ; % = 0	n = 0 ; % = 0

Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
People in the modified intention-to-treat population who received the study drug and oxytocin within 10 minutes of delivery.

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

D62.14 Shakur, 2017

Bibliographic Reference Shakur, Haleema; Roberts, Ian; Fawole, Bukola; Chaudhri, Rizwana; El-Sheikh, Mohamed; Akintan, Adesina Lawrence; Qureshi, Zahida; Kidanto, Hussein; Vwalika, Bellington; Abdulkadir, Abdulfetah; Etuk, Saturday J.; Noor, Shehla; Asonganyi, Etienne; Alfirevic, Zarko; Beaumont, Danielle; Ronsmans, Carine; Arulkumaran, Sabaratnam; Grant, Adrian; Afsana, Kaosar; Gülmezoglu, Metin; Hunt, Beverley J.; Olayemi,

Oladapo; Chalmers, Iain; Lumbiganon, Pisake; Piaggio, Gilda; Brady, Tony; Elbourne, Diana; Balogun, Eni; Pepple, Tracey; Prowse, Danielle; Quashi, Nigel; Barneston, Lin; Barrow, Collette; Cook, L; Frimley, Lauren; Gilbert, Daniel; Gilliam, Catherine; Jackson, Robert B.; Kawahara, T; Miah, Hakim; Kostrov, Sergey; Ramos, M; Edwards, Phil; Godec, Thomas; Huque, Sumaya; Okunade, Olujide; Adetayo, Olusade; Kayani, Aasia; Javaid, Kiran; Biryabarema, Chrstine; Tchounzou, Robert; Regmi, Mohan; Dallaku, Kastriot; Sahani, Mateus; Akhter, Sayeba; Meda, Nicolas; Dah, Anthony Kwame; Odekunle, Olufemi; Monehin, Oluwabusola; Ojo, Austin; Akinbinu, Grace; Offiah, Ifeoma; Akpan, Ubong; Udofia, Uduak; Okon, Useneno; Omoronyia, Ezukwa; James, Okpe; Bello, Nike; Adeyemi; Aimakhu, Chris; Akinsanya, Olufemi; Adeleye, Bamidele; Adeyemi, Oluwaseun; Oluwatosin, Kayode; Aboyeji, Abiodun; Adeniran, Abiodun S; Adewale, Adebayo; Olaomo, Noah; Omo-Aghoja, L O; Okpako, Emmanuel; Oyeye, Lucky; Alu, Francis; Ogudu, John; Ladan, Ezekiel; Habib, Ibrahim; Okusanya, Babasola; Onafowokan, Olatunde; Isah, David; Aye, Abalaka; Okogbo, Felix; Aigere, Egbaname; Ogbiti, Mark; Onile, Temitope; Salau, Olaide; Amode, Yinka; Shoretire, Kamil; Owodunni, Adebola; Ologunde, Kehinde; Ayinde, Akintunde; Alao, Moses; Awonuga, Olalekan; Awolaja, Babatunde; Adegbola, Omololu; Habeebu-Adeyemi, Fatimah Murtazha; Okunowo, Adeyemi A; Idris, Hadiza Abdulaziz; Okike, Ola; Madueke, Nneka; Mutihir, Josiah; Joseph, Nankat; Adebudo, Babatunde; Fasanu, Adeniyi; Akintunde, Olugbenga; Abidoye, Olufemi; Opreh, Owigho; Udonwa, Sophia; Dibia, Gladys; Bazuaye, Simeon; Ifemeje, Arafat; Umoiyoho, Aniefiok; Inyang-Etoh, Emmanuel; Yusuf, Sununu; Olayinka, Kayode; Adeyemi, Babalola; Ajenifuja, Olusegun; Ibrahim, Umar; Adamu, Yusuf Baffah; Akinola, Oluwarotimi; Adekola-Oni, Grace; Kua, Paul; Iheagwam, Roseline; Idrisa, Audu; Geidam, Ado; Jogo, Andrea; Agulebe, Joseph; Ikechebelu, Joseph I; Udegbunam, Onyebuchi; Awoleke, Jacob; Adelekan, Oluseyi; Sulayman, Hajaratu; Ameh, Nkeiruka; Onaolapo, Nurudeen; Adelodun, Affiss; Golit, William; Audu, Dachollom; Adeniji, Adetunji; Oyelade, Folasade; Dattijo, Lamaran; Henry, Palmer; Loto, Olabisi M.; Umeora, Odidika; Onwe, Abraham; Nzeribe, Emily; Okorochukwu, Bartthy; Adeniyi, Augustine; Gbejegbe, Emmanuel; Ikpen, Akpojaro; Nwosu, Ikemefuna; Sambo, Abdulrasaq; Ladipo, Olubunmi; Abubakar, Sola; Okike, Ola Nene; Nduka, Enyinnaya Chikwendu; Ezenkwele, E.P.; Onwusulu, Daniel; Irinyenikan, Theresa Azonima; Singh, Swati; Bariweni, Amaitari; Galadanci, Hadiza S; Achara, Peter; Osayande, Osagie; Gana, Mohammed; Jabeen, Kiran; Mobeen, Ayesha; Mufti, Sadaf; Zafar, Maliha; Ahmad, Basharat; Munawar, Maimoona; Gul, Jeharat; Usman, Naseema; Shaheen, Fehmida; Tariq, Mariam; Sadiq, Nadia; Batool, Rabia; Ali, Habiba Sharaf; Jaffer, Manahil; Baloch, Asma; Mukhtiar, Noonari; Ashraf, Tasneem; Asmat, Raheela; Khudaidad, Salma; Taj, Ghazala; Qazi, Roshan; Dars, Saira; Sardar, Faryal; Ashfaq, Sanobar; Majeed, Saeeda; Jabeen, Sadaqat; Karim, Rukhsana; Burki, Farzana; Bukhari, Syeda Rabia; Gul, Fouzia; Jabeen, Musarrat; Sherin, Akhtar; Ain, Qurratul; Rao, Shahid; Shaheen, Uzma; Manzoor, Samina; Masood, Shabween; Rizvi, Shabana; Ali, Anita; Sajid, Abida; Iftikhar, Aisha; Batool,

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Study details

Trial name	WOMAN World Maternal Antifibrinolytic
Associated studies	Not applicable No comment
Trial registration number	NCT00872469 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	Multicentre Worldwide, 21 countries
Study setting	Inpatient: elective and day care Maternity wards
Study dates	March 2010 and April 2016
Sources of funding	Academic or government grant support London School of Hygiene and Tropical Medicine, UK Department of Health, Wellcome Trust and Bill and Melinda Gates Foundation Pharmaceutical/private organisation funding Pfizer

Matching inclusion criteria	Adults (age at least 16 years) No comment Sample size of at least 500 people in each study arm No comment Pregnant women, trans men and non-binary people Pregnant women
Other important inclusion criteria	Clinical diagnosis of post-partum haemorrhage after vaginal birth or caesarean section (500mL after vaginal birth, 1000mL after caesarean section or any blood loss to cause haemodynamic compromise).
Other important exclusion criteria	No additional information.
Interventions of interest	Tranexamic acid (intravenous) No comment Placebo No comment
Comparisons of interest	Tranexamic acid compared to placebo No comment
Cointerventions	All people received usual care (usual care was not described).
Subgroup 1: Surgical speciality	Gynaecology No comment
Subgroup 2: Anticoagulant use	Not stated/unclear No comment
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Not stated/unclear No comment
Subgroup 4: Dose of tranexamic acid	1 gram
Subgroup 5: Route of administration	Intravenous

Subgroup 6: Repeated use of tranexamic acid	Mixed population A second dose could be given if bleeding continued or restarted
Subgroup 7: Renal function	Not stated/unclear
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery No comment Pulmonary embolism No comment Deep vein thrombosis No comment Myocardial infarction No comment Ischaemic stroke No comment Infection Sepsis Seizures
Total number of participants	20060
Duration of follow-up (days)	42
Additional comments	No additional comment

Study arms

Tranexamic acid (N = 10051)

1 gram tranexamic acid by slow intravenous injection (1 mL/min - 100mg/mL)

Placebo (N = 10009)

Matching placebo

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 10051)	Placebo (N = 10009)
Female (%) Sample size	n = 10051 ; % = 100	n = 10009 ; % = 100
Mean age (SD) (years) Sample size	n = NR ; % = NR	n = NR ; % = NR
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Anticoagulant use (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities associated with bleeding (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 42 days

Mortality

Outcome	Tranexamic acid, 42 day, N = 10036	Placebo, 42 day, N = 9985
All-cause mortality Any cause of death No of events	n = 227 ; % = 2.3	n = 256 ; % = 2.6

All-cause mortality - Polarity - Lower values are better

Other outcomes

Outcome	Tranexamic acid, 42 day, N = 10033	Placebo, 42 day, N = 9985
Thromboembolic events after surgery Thromboembolic events - any event No of events	n = 30 ; % = 0.3	n = 34 ; % = 0.3

Outcome	Tranexamic acid, 42 day, N = 10033	Placebo, 42 day, N = 9985
Pulmonary embolism No of events	n = 17 ; % = 0.2	n = 20 ; % = 0.2
Deep vein thrombosis No of events	n = 3 ; % = 0.03	n = 7 ; % = 0.07
Myocardial infarction No of events	n = 2 ; % = 0.02	n = 3 ; % = 0.03
Ischaemic stroke Stroke No of events	n = 8 ; % = 0.08	n = 6 ; % = 0.06
Infection Sepsis No of events	n = 180 ; % = 1.8	n = 185 ; % = 1.9
Seizure No of events	n = 33 ; % = 0.3	n = 43 ; % = 0.4

Thromboembolic events after surgery - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Infection - Polarity - Lower values are better
Seizure - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

D32.15 Shi, 2022

Bibliographic Reference Shi, Jia; Zhou, Chenghui; Pan, Wei; Sun, Hansong; Liu, Sheng; Feng, Wei; Wang, Weijian; Cheng, Zhaoyun; Wang, Yang; Zheng, Zhe; Effect of High- vs Low-Dose Tranexamic Acid Infusion on Need for Red Blood Cell Transfusion and Adverse Events in Patients Undergoing Cardiac Surgery: The OPTIMAL Randomized Clinical Trial.; JAMA; 2022; vol. 328 (no. 4); 336-347

Study details

Trial name	OPTIMAL No comment
Associated studies	Not applicable No comment
Trial registration number	NCT03782350 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	China No comment
Study setting	Inpatient: elective and day care No comment
Study dates	December 2018 to April 2021
Sources of funding	Academic or government grant support Grant funding from the Research Projects on Prevention and Control of Major Chronic Non-infectious Diseases, National Key Research and Development Program
Matching inclusion criteria	Adults (age at least 16 years) No comment At short-term risk of bleeding No comment Having surgery Elective cardiac surgery with cardiopulmonary bypass
Other important inclusion criteria	No additional comments
Other important exclusion criteria	Defective chromatic vision; active intravascular coagulation (DVT, PE, arterial thrombosis or antithrombin III deficiency); history of thrombophilia; previous convulsion or seizure; allergy or contraindication to intravenous tranexamic acid; breastfeeding or pregnancy
Interventions of interest	Tranexamic acid (intravenous) No comment
Comparisons of interest	A different dose of tranexamic acid

	No comment
Cointerventions	No comment
Subgroup 1: Surgical speciality	Cardiothoracic No comment
Subgroup 2: Anticoagulant or antiplatelet use	Mixed Around 20% could be taking anticoagulants or antiplatelets
Subgroup 3: Comorbidities that increase risk of thromboembolic events	No From baseline characteristics <1% of people were taking warfarin, aspirin or clopidogrel in the days before surgery and <6% were taking antiplatelet agents
Subgroup 4: Dose	High dose = 7 grams, Low dose = 1.5 grams High dose = 30 mg/kg bolus, 16 mg/kg/hr during surgery (average weight = 68 kg, so approximately 2 g bolus, 1 g/hr). Low dose = 10 mg/kg bolus. 2 mg/kg/hr during surgery (average weight = 68kg, so approximately 600 mg bolus, 120 mg/hr bolus). Mean total dose - high dose arm = 7.1 (6.9-7.2) grams; low dose arm = 1.4 (1.3-1.4) grams. Dosing duration = 4.8 (4.7-4.9) hours.
Subgroup 5: Route of administration	Intravenous No comment
Subgroup 6: Repeated use	Repeated use No comment
Subgroup 7: Renal function	No impairment <1% of people had chronic kidney dysfunction
Outcomes of interest	All-cause mortality No comment Pulmonary embolism No comment Deep vein thrombosis No comment Myocardial infarction No comment

	Ischaemic stroke 'Stroke' - Downgrade for indirectness as it could include haemorrhagic strokes Seizures No comment Reoperation No comment
Total number of participants	3079
Duration of follow-up (days)	30
Additional comments	No additional comments

Study arms

Tranexamic acid (high dose) (N = 1545)

Intravenous tranexamic acid. High dose = 30 mg/kg bolus, 16 mg/kg/hr during surgery (average weight = 68 kg, so approximately 2 g bolus, 1 g/hr).

Tranexamic acid (low dose) (N = 1534)

Intravenous tranexamic acid. Low dose = 10 mg/kg bolus. 2 mg/kg/hr during surgery (average weight = 68kg, so approximately 600 mg bolus, 120 mg/hr bolus).

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (high dose) (N = 1545)	Tranexamic acid (low dose) (N = 1534)
Female (%) Sample size	n = 573 ; % = 37.6	n = 582 ; % = 38.6
Mean age (SD) (years) Mean (SD)	52.9 (12.3)	52.7 (11.9)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Hypertension Sample size	n = 530 ; % = 35.9	n = 511 ; % = 34.9

Characteristic	Tranexamic acid (high dose) (N = 1545)	Tranexamic acid (low dose) (N = 1534)
Comorbidities (%) - Hyperlipidaemia Sample size	n = 489 ; % = 32.7	n = 517 ; % = 34.7
Comorbidities (%) - Diabetes Sample size	n = 167 ; % = 11	n = 166 ; % = 11
Comorbidities (%) - Previous cardiac surgery Sample size	n = 89 ; % = 5.8	n = 92 ; % = 6.1
Comorbidities (%) - Lacunar infarction Sample size	n = 54 ; % = 3.6	n = 37 ; % = 2.5
Comorbidities (%) - Stroke Sample size	n = 25 ; % = 1.7	n = 32 ; % = 2.2
Comorbidities (%) - Peripheral vascular disease Sample size	n = 16 ; % = 1.1	n = 20 ; % = 1.4
Comorbidities (%) - Endocarditis Sample size	n = 15 ; % = 1	n = 16 ; % = 1.1
Comorbidities (%) - Carotid artery stenosis at least 80% Sample size	n = 12 ; % = 0.8	n = 14 ; % = 1
Comorbidities (%) - Carotid artery surgery Sample size	n = 7 ; % = 0.5	n = 13 ; % = 0.9
Comorbidities (%) - Chronic obstructive pulmonary disease Sample size	n = 3 ; % = 0.2	n = 5 ; % = 0.3
Renal function (% or mL/min/1.73 m2) Chronic kidney dysfunction Sample size	n = 4 ; % = 0.3	n = 7 ; % = 0.5

Outcomes

Study timepoints

- 30 days

Dichotomous outcomes

Outcome	Tranexamic acid (high dose), 30 day, N = 1525	Tranexamic acid (low dose), 30 day, N = 1506
All-cause mortality No of events	n = 9 ; % = 0.6	n = 10 ; % = 0.7
Pulmonary embolism No of events	n = 1 ; % = 0.1	n = 0 ; % = 0
Deep vein thrombosis No of events	n = 15 ; % = 1	n = 12 ; % = 0.8
Myocardial infarction No of events	n = 172 ; % = 11.3	n = 167 ; % = 11.1
Ischaemic stroke Stroke. Downgrade for indirectness as this may include haemorrhagic strokes. No of events	n = 10 ; % = 0.7	n = 8 ; % = 0.5
Seizures No of events	n = 15 ; % = 1	n = 6 ; % = 0.4
Reoperation No of events	n = 16 ; % = 1	n = 21 ; % = 1.4

All-cause mortality - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Seizures - Polarity - Lower values are better
Reoperation - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT - Outcome level

Dichotomousoutcomes-All-causemortality-NoOfEvents-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Pulmonaryembolism-NoOfEvents-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Deepveinthrombosis-NoOfEvents-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Myocardialinfarction-NoOfEvents-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Ischaemicstroke-NoOfEvents-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Partially applicable *(Downgrade as haemorrhagic strokes could be included in the outcome)*

Dichotomousoutcomes-Seizures-NoOfEvents-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Reoperation-NoOfEvents-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

1

D22.16 Sprigg, 2018

Bibliographic Reference Sprigg, Nikola; Flaherty, Katie; Appleton, Jason P.; Salman, Rustam Al-Shahi; Bereczki, Dániel; Beridze, Maia; Christensen, Hanne; Ciccone, Alfonso; Collins, Ronan; Członkowska, Anna; Dineen, Robert A.; Duley, Lelia; Egea-Guerrero, Juan José; England, Timothy J.; Krishnan, Kailash; Laska, Ann Charlotte; Law, Zhe Kang; Öztürk, Şerefnur; Pocock, Stuart J.; Roberts, Ian; Robinson, Thompson G.; Roffe, Christine; Seiffge, David J.; Scutt, Polly; Thanabalan, Jegan; Werring, David J.; Whynes, David K.; Bath, Philip M.W.; Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial; Lancet (London, England); 2018; vol. 391 (no. 10135); 2107-2115

3

4 **Study details**

Trial name	TICH-2 No comment
Associated studies	Not applicable No comment
Trial registration number	ISRCTN93732214 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	Multicentre 12 countries - Denmark, Georgia, Hungary, Ireland, Italy, Malaysia, Poland, Spain, Sweden, Switzerland, Türkiye, and the UK
Study setting	Inpatient: non-elective Acute stroke units
Study dates	March, 1st 2013 and September, 30th 2017.
Sources of funding	Academic or government grant support National Institute of Health Research Health Technology Assessment Programme and Swiss Heart Foundation
Matching inclusion criteria	Adults (age at least 16 years)

	No comment Sample size of at least 500 people in each study arm No comment
Other important inclusion criteria	Within 8 hours of stroke symptom onset (or time last seen well).
Other important exclusion criteria	Intracerebral haemorrhage secondary to anticoagulation, thrombolysis, trauma or a known underlying structural abnormality; contraindication to medication; prestroke dependence (modified Rankin score >4); life expectancy less than 3 months; GCS less than 5.
Interventions of interest	Tranexamic acid (intravenous) No comment Placebo No comment
Comparisons of interest	Tranexamic acid compared to placebo No comment
Cointerventions	No additional information
Subgroup 1: Surgical speciality	Neurosurgery Neurology rather than neurosurgery
Subgroup 2: Anticoagulant use	Mixed population Around 25% had previously used antiplatelet therapy
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Mixed population Around 25% had a previous atherosclerotic cardiovascular disease, around 25% were on previous antiplatelet therapy
Subgroup 4: Dose of tranexamic acid	2 grams
Subgroup 5: Route of administration	Intravenous
Subgroup 6: Repeated use of tranexamic acid	Repeated use 1 gram bolus followed by a 1 hour infusion
Subgroup 7: Renal function	Not stated/unclear

Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery Venous thromboembolism (DVT + PE) Pulmonary embolism No comment Deep vein thrombosis No comment Myocardial infarction ACS or MI Ischaemic stroke Ischaemic stroke or TIA Infection Infections and infestations Seizures
Total number of participants	2325
Duration of follow-up (days)	90
Additional comments	No additional comments

Study arms

Tranexamic acid (N = 1161)

1 gram intravenous tranexamic acid bolus followed by an 8 hour infusion of 1 gram tranexamic acid

Placebo (N = 1164)

Matching placebo

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 1161)	Placebo (N = 1164)
Female (%) Sample size	n = 519 ; % = 45	n = 505 ; % = 43
Mean age (SD) (years) Mean (SD)	69.1 (13.7)	68.7 (13.9)
Ethnicity (%) - White Sample size	n = 986 ; % = 85	n = 992 ; % = 85
Ethnicity (%) - Other Sample size	n = 174 ; % = 15	n = 172 ; % = 15
Anticoagulant use (%) - Previous antiplatelet therapy Sample size	n = 316 ; % = 27	n = 295 ; % = 25
Comorbidities associated with bleeding (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 90 days

Outcomes

Outcome	Tranexamic acid, 90 day, N = 1161	Placebo, 90 day, N = 1164
All-cause mortality Death by day 90 No of events	n = 250 ; % = 22	n = 249 ; % = 21
Thromboembolic events after surgery VTE (combined DVT/PE). Downgrade for indirectness for only including some of the events. No of events	n = 39 ; % = 3.4	n = 37 ; % = 3.2
Pulmonary embolism No of events	n = 20 ; % = 1.7	n = 23 ; % = 2

Outcome	Tranexamic acid, 90 day, N = 1161	Placebo, 90 day, N = 1164
Deep vein thrombosis No of events	n = 19 ; % = 1.6	n = 14 ; % = 1.2
Myocardial infarction ACS or MI No of events	n = 11 ; % = 0.9	n = 6 ; % = 0.5
Ischaemic stroke Ischaemic stroke or TIA No of events	n = 16 ; % = 1.4	n = 11 ; % = 0.9
Infection Infections and infestations No of events	n = 98 ; % = 8.4	n = 116 ; % = 10
Seizure Seizure/convulsions No of events	n = 77 ; % = 6.6	n = 85 ; % = 7.3

All-cause mortality - Polarity - Lower values are better
Thromboembolic events after surgery - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Infection - Polarity - Lower values are better
Seizure - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(For thromboembolic events, excluded events that could have been relevant.)*

D42.17 Williams-Johnson, 2010

Bibliographic Reference Williams-Johnson, J A; McDonald, A H; Strachan, G Gordon; Williams, Eric W.; Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial; Lancet (London, England); 2010; vol. 376 (no. 9734); 23-32

Study details

Trial name	CRASH-2 No comment
Associated studies	Not applicable No comment
Trial registration number	NCT00375258 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	Multicentre Worldwide. 40 countries.
Study setting	Inpatient: non-elective Pre-hospital A&E Pre-hospital
Study dates	May 2005 to February 2010
Sources of funding	Academic or government grant support NIHR HTA programme, BUPA foundation, JP Moulton Charitable Foundation Pharmaceutical/private organisation funding Pfizer
Matching inclusion criteria	Adults (age at least 16 years) No comment Sample size of at least 500 people in each study arm No comment
Other important inclusion criteria	Trauma patients with significant haemorrhage (systolic blood pressure <90mm Hg or heart rate >110 beats per minute or both) or considered at risk of significant haemorrhage who were within 8 hours of injury
Other important exclusion criteria	Clear contraindication to tranexamic acid

Interventions of interest	Tranexamic acid (intravenous) No comment Placebo No comment
Comparisons of interest	Tranexamic acid compared to placebo No comment
Cointerventions	No additional information.
Subgroup 1: Surgical speciality	Trauma No comment
Subgroup 2: Anticoagulant use	Not stated/unclear No comment
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Not stated/unclear No comment
Subgroup 4: Dose of tranexamic acid	2 grams
Subgroup 5: Route of administration	Intravenous
Subgroup 6: Repeated use of tranexamic acid	Repeated use 1 gram bolus followed by 1 gram infusion
Subgroup 7: Renal function	Not stated/unclear
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery No comment Pulmonary embolism No comment Deep vein thrombosis

	No comment Myocardial infarction No comment Ischaemic stroke No comment
Total number of participants	20211
Duration of follow-up (days)	28
Additional comments	No additional information.

Study arms

Tranexamic acid (N = 10096)

Tranexamic acid within 8 hours of injury. Loading dose 1 gram over 10 minutes, then infusion of 1 gram over 8 hours.

Placebo (N = 10115)

Matching placebo

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 10096)	Placebo (N = 10115)
Female (%) Sample size	n = 1654 ; % = 16.4	n = 1617 ; % = 16
Mean age (SD) (years) Mean (SD)	34.6 (14.1)	34.5 (14.4)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Anticoagulant use (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities associated with bleeding (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (% or mL/min/1.73 m2)	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Tranexamic acid (N = 10096)	Placebo (N = 10115)
Sample size		

Outcomes

Study timepoints

- 28 days

Outcome

Outcome	Tranexamic acid, 28 day, N = 10060	Placebo, 28 day, N = 10067
All-cause mortality No of events	n = 1463 ; % = 14.5	n = 1613 ; % = 16
Thromboembolic events after surgery Any vascular occlusive event No of events	n = 168 ; % = 1.7	n = 201 ; % = 2
Pulmonary embolism No of events	n = 72 ; % = 0.7	n = 71 ; % = 0.7
Deep vein thrombosis No of events	n = 40 ; % = 0.4	n = 41 ; % = 0.4
Myocardial infarction No of events	n = 35 ; % = 0.3	n = 55 ; % = 0.5
Ischaemic stroke Stroke No of events	n = 57 ; % = 0.6	n = 66 ; % = 0.7

All-cause mortality - Polarity - Lower values are better
Thromboembolic events after surgery - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable *(No comment)*

D12.18 Zhang, 2024

Bibliographic Reference Zhang P; Jia Y; Lv Y; Fan Y; Geng H; Zhao Y; Song H; Cui H; Chen X; Effects of tranexamic acid preconditioning on the incidence of postpartum haemorrhage in vaginal deliveries with identified risk factors in China: a prospective, randomized, open-label, blinded endpoint trial; Ann Med.; 2024; vol. 56 (no. 1); 2389302-

Study details

Trial name	Zhang 2024 No comment
Associated studies	Not applicable No comment
Trial registration number	ChiCTR2200062464 No comment
Study type	Randomised controlled trial (RCT) No comment
Study location	China No comment
Study setting	Inpatient: elective and day care No comment
Study dates	September 1st 2022 to August 30th 2023
Sources of funding	Academic or government grant support National Key Research and Development Program grant 2021YFC2701500
Matching inclusion criteria	Adults (age at least 16 years) No comment Sample size of at least 500 people in each study arm No comment Pregnant women, trans men and non-binary people No comment
Other important inclusion criteria	Planned vaginal delivery, being at risk for postpartum haemorrhage (multiparity, high-prepregnancy BMI, gestational diabetes mellitus, polyhydramnios, higher or lower maternal age, uterine fibroids, multiple pregnancies, premature rupture of membranes, non-cephalic delivery, previous history of uterine

	surgery, placenta previa marginalise, anaemia, previous history, assisted reproductive technology, induced labour, prolonged second or third stage of labour, use of obstetric apparatus, intrapartum favour, precipitate labour, placenta and foetal membranes retention, placental adhesions, laceration of cervix and vagina, macrosomia, perineal trauma).
Other important exclusion criteria	Contraindications against tranexamic acid, previous history of venous or arterial thrombosis; known cardiovascular, renal or hepatic disease; autoimmune disorder; haematological system disorders with coagulation dysfunction; gestational hypertension, preeclampsia, HELLP syndrome, eclampsia; history of epilepsy.
Interventions of interest	Tranexamic acid (intravenous) No comment Placebo No comment
Comparisons of interest	Tranexamic acid compared to placebo No comment
Cointerventions	Intervention is given immediately after the routine prophylactic oxytocin (10 IU) injection.
Subgroup 1: Surgical speciality	Gynaecology No comment
Subgroup 2: Anticoagulant use	Not stated/unclear No comment
Subgroup 3: Comorbidities that increase risk of thromboembolic events	No Based on exclusion criteria
Subgroup 4: Dose of tranexamic acid	1 gram No comment
Subgroup 5: Route of administration	Intravenous No comment
Subgroup 6: Repeated use of tranexamic acid	Single use No comment
Subgroup 7: Renal function	No impairment Based on exclusion criteria

Outcomes of interest	All-cause mortality Reported in text Thromboembolic events after surgery No comment All-cause readmission No comment Seizures No comment
Total number of participants	2409
Duration of follow-up (days)	90
Additional comments	No additional comments

Study arms

Tranexamic acid (N = 1202)

1 gram tranexamic acid intravascular infusion immediately after the delivery of the infant

Placebo (N = 1207)

Matching placebo immediately after the delivery of the infant

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 1202)	Placebo (N = 1207)
Female (%) Sample size	n = 1202 ; % = 100	n = 1207 ; % = 100
Mean age (SD) (years) Mean (SD)	30.1 (4.47)	30.15 (4.55)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Anticoagulant use (%) Sample size	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Tranexamic acid (N = 1202)	Placebo (N = 1207)
Comorbidities associated with bleeding (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 30 days

Dichotomous outcomes

Outcome	Tranexamic acid, 30 day, N = 924	Placebo, 30 day, N = 953
All-cause mortality No of events	n = 0 ; % = 0	n = 0 ; % = 0
Thromboembolic events after surgery Thromboembolic event No of events	n = 0 ; % = 0	n = 0 ; % = 0
Seizures No of events	n = 0 ; % = 0	n = 0 ; % = 0
All-cause readmission No of events	n = 5 ; % = 0.5	n = 7 ; % = 0.7

All-cause mortality - Polarity - Lower values are better
Thromboembolic events after surgery - Polarity - Lower values are better
Seizures - Polarity - Lower values are better
All-cause readmission - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(No concerns)*
Overall bias and Directness	Overall Directness	Directly applicable *(No concerns)*

D.3 Non-randomised studies

D.3.1 Hsu, 2024

Bibliographic Reference	Hsu YC; Hsu AHS; Wu CT; Tan TL; Wang JW; Kuo FC; Association between IV and topical tranexamic acid use and periprosthetic joint infections in hip and knee arthroplasty: a retrospective study.; BMC musculoskeletal disorders; 2024; vol. 25 (no. 1)

Study details

Trial name	Not applicable No comment
Associated studies	Not applicable No comment
Trial registration number	Not applicable No comment
Study type	Retrospective cohort study No comment
Study location	Taiwan No comment
Study setting	Inpatient: elective and day care No comment
Study dates	January 1st 2009 to December 31st 2020
Sources of funding	Academic or government grant support Supported by Kaohsiung Chang Gung Memorial Hospital, Taiwan
Matching inclusion criteria	Adults (age at least 16 years) No comment At short-term risk of bleeding No comment Having surgery People undergoing primary total hip arthroplasty or total knee arthroplasty
Other important inclusion criteria	No comment

Other important exclusion criteria	People under 18 years old; primary arthroplasty for tumour or fracture aetiologies; previous septic arthritis; follow-up less than 1 year; insufficient patient characteristics data
Key confounding factors accounted for	Age No comment Sex No comment Comorbidities Including heart disease; COPD; diabetes; renal failure; liver disease and rheumatoid arthritis
Other confounding factors accounted for	Surgery type (total knee arthroplasty or total hip arthroplasty); BMI; laterality; preoperative haemoglobin; surgical time; Charlson Comorbidity Index; ASA score >3; general anaesthesia
Interventions of interest	Tranexamic acid (intravenous and topical) Both groups are combined in the propensity score weighting cohort - there is analysis without them but it is not effectively managed for confounding
Comparisons of interest	Usual Care No comment A different route of administration of tranexamic acid No comment
Cointerventions	No comment
Subgroup 1: Surgical speciality	Orthopaedics No comment
Subgroup 2: Anticoagulant or antiplatelet use	Not stated/unclear No comment
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Mixed population No comment
Subgroup 4: Dose	Intravenous: 0.25-1.25 grams. Topical: 1.5 grams. No comment

Subgroup 5: Route of administration	Intravenous and topical No comment
Subgroup 6: Repeated use	Single use No comment
Subgroup 7: Renal function	Mixed population Around 20% had renal failure
Outcomes of interest	Thromboembolic events after surgery DVT/PE - downgrade for indirectness for not including arterial event Infection Periprosthetic joint infection All-cause readmission 90 day readmission
Total number of participants	8042
Duration of follow-up (days)	90
Additional comments	Propensity score weighting. The balance of covariates was assessed using the SMD, with an SMD exceeding 10% indicating a significant imbalance in factors between the two groups. Adjusted regressions were subsequently conducted for outcome analysis.

Study arms

Tranexamic acid (all types) (N = 3364)

Either intravenous tranexamic acid (50 mg/mL) administered as a single dose of 10mg/kg 10 minutes before skin incision or topical tranexamic acid 1.5-3 grams into the joint capsule or infused into the drainage tube

Usual care (N = 4378)

No tranexamic acid

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (all types) (N = 3364)	Usual care (N = 4378)
Female (%) Sample size	n = 2617 ; % = 78	n = 3189 ; % = 73

Characteristic	Tranexamic acid (all types) (N = 3364)	Usual care (N = 4378)
Mean age (SD) (years) Mean (SD)	67.7 (10.6)	68.1 (10)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Heart disease Sample size	n = 165 ; % = 4.5	n = 203 ; % = 4.6
Comorbidities (%) - COPD Sample size	n = 100 ; % = 2.7	n = 92 ; % = 2.1
Comorbidities (%) - Diabetes Sample size	n = 760 ; % = 20.7	n = 978 ; % = 22.3
Comorbidities (%) - Liver disease Sample size	n = 57 ; % = 1.6	n = 107 ; % = 2.4
Comorbidities (%) - Rheumatoid arthritis Sample size	n = 97 ; % = 2.6	n = 169 ; % = 3.9
Renal function (% or mL/min/1.73 m2) Renal failure Sample size	n = 430 ; % = 11.8	n = 1199 ; % = 27.4

Baseline characteristics before propensity score matching (after matching is not provided)

Outcomes

Study timepoints

- 90 days

Dichotomous outcomes

Outcome	Tranexamic acid (all types) vs Usual care, 90 day, N2 = 3664, N1 = 3637
Thromboembolic events after surgery Odds ratio/95% CI	1.21 (0.37 to 3.93)
Infection Odds ratio/95% CI	0.53 (0.36 to 0.8)

Outcome	Tranexamic acid (all types) vs Usual care, 90 day, N2 = 3664, N1 = 3637
All-cause readmission Odds ratio/95% CI	1.15 (0.35 to 3.72)

Thromboembolic events after surgery - Polarity - Lower values are better
Infection - Polarity - Lower values are better
All-cause readmission - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - ROBINS-I: a tool for non-randomised studies of interventions

Dichotomousoutcomes-Thromboemboliceventsaftersurgery-OddsRatioNineFivePercentCI-Tranexamic acid (all types)-Usual care-t90

Section	Question	Answer
Overall bias	Risk of bias judgement	Low *(No major concerns)*
Overall bias	Directness	Partially Applicable *(Outcome indirectness as it does not include arterial thrombotic events)*

Dichotomousoutcomes-Infection-OddsRatioNineFivePercentCI-Tranexamic acid (all types)-Usual care-t90

Section	Question	Answer
Overall bias	Risk of bias judgement	Low *(No major concerns)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-All-causereadmission-OddsRatioNineFivePercentCI-Tranexamic acid (all types)-Usual care-t90

Section	Question	Answer
Overall bias	Risk of bias judgement	Low *(No major concerns)*
Overall bias	Directness	Directly applicable *(No concerns)*

D.3.2 Hulde, 2023

Bibliographic Reference Hulde N; Zittermann A; Deutsch MA; von Dossow V; Gummert JE; Koster A; Moderate Dose of Tranexamic Acid and Complications after Valvular Heart Surgery.; The Thoracic and cardiovascular surgeon; 2023; vol. 71 (no. 3)

Study details

Trial name	Not applicable

	No comment
Associated studies	Not applicable No comment
Trial registration number	Not applicable No comment
Study type	Retrospective cohort study No comment
Study location	Germany No comment
Study setting	Inpatient: elective and day care No comment
Study dates	July 2009 and September 2018
Sources of funding	No funding No comment
Matching inclusion criteria	Adults (age at least 16 years) No comment At short-term risk of bleeding No comment Having surgery Valvular heart surgery
Other important inclusion criteria	No comment
Other important exclusion criteria	No comment
Key confounding factors accounted for	Age No comment Sex No comment Comorbidities

	Including diabetes mellitus; hypertension; stroke; myocardial infarction; chronic obstructive pulmonary disease; peripheral artery disease; three-vessel disease; carotid stenosis >50%; previous cardiac surgery
Other confounding factors accounted for	Body mass index; left ventricular ejection fracture; eGFR; carotid stenosis >50%; Euroscore II; Aspirin use; Type of surgery (valve surgery, combined valve plus CABG surgery)
Interventions of interest	Tranexamic acid (intravenous) No comment
Comparisons of interest	Usual Care No comment
Cointerventions	No comment
Subgroup 1: Surgical speciality	Cardiothoracic Valvular heart surgery
Subgroup 2: Anticoagulant or antiplatelet use	Perioperative anticoagulation Heparinisation during bypass
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Mixed population Around 73% of people had hypertension.
Subgroup 4: Dose	Median dose 1.9 grams (1.6-3.1 grams) No comment
Subgroup 5: Route of administration	Intravenous No comment
Subgroup 6: Repeated use	Repeated use No comment
Subgroup 7: Renal function	Not stated/unclear eGFR mean is around 73.2 mL/min/1.73 m2 so some people could have severe renal impairment. Overall unclear.
Outcomes of interest	All-cause mortality No comment Ischaemic stroke

	Downgrade for indirectness as includes haemorrhagic stroke Seizures No comment
Total number of participants	13293
Duration of follow-up (days)	30
Additional comments	No additional information

Study arms

Tranexamic acid (all doses) (N = 10200)

Tranexamic acid doses above and below 25 mg/kg body weight intravenously for valvular heart surgery. 1 gram bolus was given after heparinization, followed by a continuous infusion of 0.2 grams/hour until termination of bypass. In the priming volume of the bypass system, 0.5 grams of tranexamic acid was added. Median dose 1.9 grams (1.6-3.1 grams).

Usual care (N = 3053)

No tranexamic acid

Tranexamic acid (high dose) (N = 1078)

Tranexamic acid dose above and equal to 25 mg/kg body weight intravenously

Tranexamic acid (low dose) (N = 1975)

Tranexamic acid dose below 25 mg/kg body weight intravenously

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (all doses) (N = 10200)	Usual care (N = 3053)	Tranexamic acid (high dose) (N = 1078)	Tranexamic acid (low dose) (N = 1975)
Female (%) Sample size	n = 1260 ; % = 41	n = 1294 ; % = 42	n = NR ; % = NR	n = NR ; % = NR
Mean age (SD) (years) Mean (SD)	68.1 (11.8)	68.1 (11.9)	NR (NR)	NR (NR)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

Characteristic	Tranexamic acid (all doses) (N = 10200)	Usual care (N = 3053)	Tranexamic acid (high dose) (N = 1078)	Tranexamic acid (low dose) (N = 1975)
Comorbidities (%) - Diabetes mellitus Sample size	n = 619 ; % = 20.3	n = 563 ; % = 18.4	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Hypertension Sample size	n = 2289 ; % = 75	n = 2196 ; % = 71.9	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Stroke Sample size	n = 115 ; % = 3.8	n = 84 ; % = 2.8	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Myocardial infarction Sample size	n = 204 ; % = 6.7	n = 183 ; % = 6	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Chronic obstructive pulmonary disease Sample size	n = 287 ; % = 9.4	n = 235 ; % = 7.7	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Peripheral artery disease Sample size	n = 142 ; % = 4.7	n = 124 ; % = 4.1	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Three-vessel disease Sample size	n = 355 ; % = 11.6	n = 318 ; % = 10.4	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Previous cardiac surgery Sample size	n = 189 ; % = 6.2	n = 139 ; % = 4.6	n = NR ; % = NR	n = NR ; % = NR
Renal function (% or mL/min/1.73 m2) (ml/min/1.73 m2) Mean (SD)	72.3 (22.6)	73.2 (23)	NR (NR)	NR (NR)

Baseline characteristics for propensity score matched pairs. Number of people in the tranexamic acid (all doses) group is 3053.

Outcomes

Study timepoints

- 30 days

Dichotomous outcomes

Outcome	Tranexamic acid (all doses), 30 day, N = 3053	Usual care, 30 day, N = 3053	Tranexamic acid (high dose), 30 day, N = 1078	Tranexamic acid (low dose), 30 day, N = 1975
All-cause mortality Thirty day mortality No of events	n = 66 ; % = 2.2	n = 63 ; % = 2.1	n = NR ; % = NR	n = NR ; % = NR
Ischaemic stroke Downgrade for indirectness as this includes haemorrhagic strokes No of events	n = 71 ; % = 2.3	n = 69 ; % = 2.3	n = NR ; % = NR	n = NR ; % = NR
Seizures No of events	n = 72 ; % = 2.4	n = 32 ; % = 1	n = NR ; % = NR	n = NR ; % = NR
Seizures - Severe renal impairment n1 = 107, n2 = 107 No of events	n = 7 ; % = 6.1	n = 6 ; % = 5.4	n = NR ; % = NR	n = NR ; % = NR
Seizures - No renal impairment n1 = 2874, n2 = 2914 No of events	n = 65 ; % = 2.2	n = 26 ; % = 0.9	n = NR ; % = NR	n = NR ; % = NR

All-cause mortality - Polarity - Lower values are better

Ischaemic stroke - Polarity - Lower values are better

Seizures - Polarity - Lower values are better

Risk ratios

Outcome	Tranexamic acid (all doses) vs Usual care, 30 day, N2 = 3053, N1 = 3053	Tranexamic acid (high dose) vs Tranexamic acid (low dose), 30 day, N2 = 1078, N1 = 1975
All-cause mortality 30 day mortality Relative risk/95% CI	1.05 (0.74 to 1.49)	NR (NR to NR)
Ischaemic stroke Downgrade for	1.03 (0.74 to 1.44)	NR (NR to NR)

Outcome	Tranexamic acid (all doses) vs Usual care, 30 day, N2 = 3053, N1 = 3053	Tranexamic acid (high dose) vs Tranexamic acid (low dose), 30 day, N2 = 1078, N1 = 1975
indirectness as this includes haemorrhagic strokes Relative risk/95% CI		
Seizures Relative risk/95% CI	2.28 (1.5 to 3.47)	2.32 (1.45 to 3.72)

All-cause mortality - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - ROBINS-I: a tool for non-randomised studies of interventions

Dichotomousoutcomes-All-causemortality-NoOfEvents-Tranexamic acid (all doses)-Usual care-Tranexamic acid (high dose)-Tranexamic acid (low dose-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Low *(No concerns)*
Overall bias	Directness	Directly applicable *(No concerns)*

Riskratios-Ischaemicstroke-RelativeRiskNineFivePercentCI-Tranexamic acid (all doses)-Usual care-Tranexamic acid (high dose)-Tranexamic acid (low dose-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Low *(No concerns)*
Overall bias	Directness	Partially Applicable *(Downgrade for indirectness as may have included haemorrhagic strokes)*

Riskratios-Seizures-RelativeRiskNineFivePercentCI-Tranexamic acid (all doses)-Usual care-Tranexamic acid (high dose)-Tranexamic acid (low dose-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Low *(No concerns)*
Overall bias	Directness	Directly applicable *(No concerns)*

D.3.3 Maeda, 2018

Bibliographic Reference	Maeda T; Michihata N; Sasabuchi Y; Matsui H; Ohnishi Y; Miyata S; Yasunaga H; Safety of Tranexamic Acid During Pediatric Trauma: A Nationwide Database Study.; Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies; 2018; vol. 19 (no. 12)

Study details

Trial name	Not applicable No comment
Associated studies	Not applicable No comment
Trial registration number	Not applicable No comment
Study type	Retrospective cohort study No comment
Study location	Japan No comment
Study setting	Inpatient: non-elective No comment A&E No comment
Study dates	July 2010 and March 2014
Sources of funding	Academic or government grant support Grants from the Ministry of Health, Labour and Welfare, Japan and the Research Grant on Regulatory Science of Pharmaceuticals and Medical Devices from the Japan Agency for Medical Research and Development. Individual authors received grants from this ministry and the Ministry of Education, Culture, Sports, Science and Technology, Japan.
Matching inclusion criteria	Children (age less than 16 years) Less than or equal to 12 years old At short-term risk of bleeding After trauma

Other important inclusion criteria	Confirmed diagnosis of six categories of trauma recorded as main diagnoses who received blood transfusion. The six sites of trauma were: head and neck injury, thoracic injury, torso injury (abdomen, lower back, lumbar spine, pelvis and external genitals), injury to extremities (shoulder, arm, wrist, hip, thigh, foot, knee and ankle), multiple injury and injury to unspecified part of trunk, limb or body region.
Other important exclusion criteria	Not clear if excluding babies. However, the interquartile range is between 4 and 9, so most likely it does.
Key confounding factors accounted for	Age No comment Sex Gender
Other confounding factors accounted for	Body weight; body height; trauma site; hospital volume; academic hospital; PICU admission; ambulance transfer; number of beds Does not clearly exclude comorbidities. However, this may be due to the population demographic and the context of the study and so may already be accounted for by people not having comorbidities entering the study. Therefore, this study has been included but this will be reflected in the risk of bias.
Interventions of interest	Tranexamic acid (intravenous) No dose provided
Comparisons of interest	Usual Care No tranexamic acid treatment
Cointerventions	Everyone received blood transfusions
Subgroup 1: Surgical speciality	Paediatric Paediatric trauma
Subgroup 2: Anticoagulant or antiplatelet use	Not stated/unclear No comment
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Not stated/unclear No comment
Subgroup 4: Dose	Not stated/unclear

	No comment
Subgroup 5: Route of administration	Not stated/unclear No comment
Subgroup 6: Repeated use	Not stated/unclear No comment
Subgroup 7: Renal function	Not stated/unclear No comment
Outcomes of interest	All-cause mortality No comment Thromboembolic events after surgery No comment Seizures No comment
Total number of participants	61779
Duration of follow-up (days)	1
Additional comments	Nationwide survey. Propensity score matching using a logistic regression model for tranexamic acid use as a function of age, gender, body weight, height, trauma sites, hospital type, PICU admission, ambulance transfer and hospital volume matching within a calliper (less than or equal to 0.2 of the pooled SD of the estimated logits) using the nearest-neighbour method without replacement). They estimated the balance in baseline variables using SDs with differences greater than 10% being imbalanced.

Study arms

Tranexamic acid (N = 1914)

After matching

Usual care (N = 1914)

After matching

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 1914)	Usual care (N = 1914)
Female (%)	n = 662 ; % = 35	n = 664 ; % = 35

Characteristic	Tranexamic acid (N = 1914)	Usual care (N = 1914)
Sample size		
Mean age (SD) (years) Median (IQR)	7 (4 to 9)	7 (4 to 9)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) Sample size	n = NR ; % = NR	n = NR ; % = NR
Renal function (% or mL/min/1.73 m2) Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- 1 day (Survey so no follow up time, 1 day used as a proxy)

Dichotomous outcomes

Outcome	Tranexamic acid, 1 day, N = 1914	Usual care, 1 day, N = 1914
All-cause mortality In-hospital mortality No of events	n = 13 ; % = 0.68	n = 18 ; % = 0.94
Thromboembolic events after surgery Thromboembolism No of events	n = 1 ; % = 0.05	n = 2 ; % = 0.1
Seizure No of events	n = 7 ; % = 0.37	n = 0 ; % = 0

All-cause mortality - Polarity - Lower values are better
Thromboembolic events after surgery - Polarity - Lower values are better
Seizure - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - ROBINS-I: a tool for non-randomised studies of interventions

Dichotomousoutcomes-All-causemortality-NoOfEvents-Tranexamic acid-Usual care-t1

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(Due to concerns about confounding, classification of interventions and missing data)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Thromboemboliceventsaftersurgery-NoOfEvents-Tranexamic acid-Usual care-t1

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(Due to concerns about confounding, classification of interventions and missing data)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Seizure-NoOfEvents-Tranexamic acid-Usual care-t1

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(Due to concerns about confounding, classification of interventions and missing data)*
Overall bias	Directness	Directly applicable *(No concerns)*

D.3.4 Thapaliya, 2024

Bibliographic Reference Thapaliya A; Mittal MM; Ratcliff TL; Mounasamy V; Wukich DK; Sambandam SN; Usage of Tranexamic Acid for Total Hip Arthroplasty: A Matched Cohort Analysis of 144,344 Patients.; Journal of clinical medicine; 2024; vol. 13 (no. 16)

Study details

Trial name	Not applicable No comment
Associated studies	Not applicable No comment
Trial registration number	Not applicable No comment
Study type	Retrospective cohort study No comment
Study location	Multicentre

	USA, Canada and Western Europe
Study setting	Inpatient: elective and day care No comment
Study dates	1st January 2003 and 1st January 2024, data was sourced on the 18th of April 2024
Sources of funding	No funding No comment
Matching inclusion criteria	Adults (age at least 16 years) 18 years old and above At short-term risk of bleeding No comment Having surgery Total hip arthroplasty
Other important inclusion criteria	Split into two groups: people who received tranexamic acid 24 hours prior to total hip arthroplasty and people who did not. Data was sourced from the TriNetX Research network.
Other important exclusion criteria	No additional exclusion criteria.
Key confounding factors accounted for	Age No comment Sex No comment Comorbidities Diabetes mellitus
Other confounding factors accounted for	Smoking status; overweight/obesity status
Interventions of interest	Tranexamic acid (intravenous and topical) No dose, no information about route but implied that it could have been either from introduction

Comparisons of interest	Usual Care No tranexamic acid
Cointerventions	Total hip arthroplasty
Subgroup 1: Surgical speciality	Orthopaedics No comment
Subgroup 2: Anticoagulant or antiplatelet use	Not stated/unclear No comment
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Not stated/unclear No comment
Subgroup 4: Dose	Not stated/unclear No comment
Subgroup 5: Route of administration	Not stated/unclear Likely intravenous and/or topical
Subgroup 6: Repeated use	Not stated/unclear No comment
Subgroup 7: Renal function	Not stated/unclear No comment
Outcomes of interest	Pulmonary embolism No comment Deep vein thrombosis No comment Myocardial infarction No comment Infection Periprosthetic joint infection
Total number of participants	180149
Duration of follow-up (days)	90

Additional comments	Matching using a greedy nearest neighbour matching algorithm. Standard mean differences were analysed to ensure balance between the cohorts after matching.

Study arms

Tranexamic acid (N = 72172)

No information about route, dose or repeated use (107912 before matching)

Usual care (N = 72172)

No additional information (72237 before matching)

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (N = 72172)	Usual care (N = 72172)
Female (%) Sample size	n = 37761 ; % = 52	n = 37733 ; % = 52
Mean age (SD) (years) Mean (SD)	63.4 (11.6)	63.4 (11.6)
Ethnicity (%) - Hispanic or Latino Sample size	n = 1897 ; % = 3	n = 2743 ; % = 4
Ethnicity (%) - Asian Sample size	n = 744 ; % = 1	n = 535 ; % = 1
Ethnicity (%) - Black or African American Sample size	n = 6226 ; % = 9	n = 7365 ; % = 10
Ethnicity (%) - White Sample size	n = 58896 ; % = 82	n = 57712 ; % = 80
Ethnicity (%) - Other Race Sample size	n = 1166 ; % = 2	n = 1247 ; % = 2
Comorbidities (%) - Diabetes mellitus Sample size	n = 9081 ; % = 13	n = 9260 ; % = 13

Outcomes

Study timepoints

- 90 days

Dichotomous outcomes

Outcome	Tranexamic acid, 90 day, N = 72172	Usual care, 90 day, N = 72172
Pulmonary embolism No of events	n = 373 ; % = 0.5	n = 412 ; % = 0.6
Deep vein thrombosis Deep vein thrombosis (lower extremity) No of events	n = 605 ; % = 0.8	n = 707 ; % = 1
Myocardial infarction No of events	n = 271 ; % = 0.4	n = 267 ; % = 0.4
Infection Periprosthetic joint infection No of events	n = 409 ; % = 0.6	n = 506 ; % = 0.7

Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Infection - Polarity - Lower values are better

Risk ratios

Outcome	Tranexamic acid vs Usual care, 90 day, N2 = 72172, N1 = 72172
Pulmonary embolism Relative risk/95% CI	0.91 (0.79 to 1.04)
Deep vein thrombosis Deep vein thrombosis (lower extremity) Relative risk/95% CI	0.86 (0.76 to 0.95)
Myocardial infarction Relative risk/95% CI	1.02 (0.86 to 1.2)
Infection Periprosthetic joint infection Relative risk/95% CI	0.81 (0.71 to 0.92)

Pulmonary embolism - Polarity - Lower values are better
Deep vein thrombosis - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Infection - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - ROBINS-I: a tool for non-randomised studies of interventions

Dichotomousoutcomes-Pulmonaryembolism-NoOfEvents-Tranexamic acid-Usual care-t90

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate *(Due to limited information about the intervention)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Deepveinthrombosis-NoOfEvents-Tranexamic acid-Usual care-t90

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate *(Due to limited information about the intervention)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Myocardialinfarction-NoOfEvents-Tranexamic acid-Usual care-t90

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate *(Due to limited information about the intervention)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Infection-NoOfEvents-Tranexamic acid-Usual care-t90

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate *(Due to limited information about the intervention)*
Overall bias	Directness	Directly applicable *(No concerns)*

D.3.5 Wang, 2022

Bibliographic Reference	Wang E; Yuan X; Wang Y; Chen W; Zhou X; Hu S; Yuan S; Tranexamic Acid Administered During Off-Pump Coronary Artery Bypass Graft Surgeries Achieves Good Safety Effects and Haemostasis.; Frontiers in cardiovascular medicine; 2022; vol. 9

Study details

Trial name	Wang 2022A Referred to as Wang 2022A for the purposes of this review.

Associated studies	Not applicable No comment
Trial registration number	Not applicable No comment
Study type	Retrospective cohort study No comment
Study location	China No comment
Study setting	Inpatient: elective and day care No comment
Study dates	January 1st 2009 to December 31st 2019
Sources of funding	Academic or government grant support Funded by the National Clinical Research Center of Cardiovascular Diseases, Funwai Hospital, the Chinese Academy of Medical Sciences and the National Natural Science Foundation of China
Matching inclusion criteria	Adults (age at least 16 years) No comment At short-term risk of bleeding No comment Having surgery Off-pump coronary artery bypass
Other important inclusion criteria	No additional criteria
Other important exclusion criteria	No additional criteria
Key confounding factors accounted for	Age No comment Sex No comment

	Comorbidities Left ventricular dysfunction; insulin-dependent diabetes; hyperlipidaemia; hypertension; chronic kidney disease; peripheral vascular disease; cerebrovascular accident; previous cardiac surgery; acute coronary syndrome; left main stem disease; three-vessel disease
Other confounding factors accounted for	Pre-operative intra-aortic balloon pump; time between coronary angiographic and operation <3 days; risk factors for bleeding; use of aspirin, clopidogrel or ticagrelor within 5 days before surgery; low-molecular weight heparin within 24 hours preoperatively; angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers; use of nitrates, beta-blockers, calcium-channel blockers and statins; the surgeons' experience (at least 100 CABGs/year); operation year (years from 2009-2014, 2015-2019); emergency surgery; heparin neutralisation ratio; left internal mammary artery (use during surgery?) and duration of surgery (min).
Interventions of interest	Tranexamic acid (intravenous) 1 gram dose 30 minutes before skin incision at 2 grams/hour and continued at 200-800 mg/hour during the entire operation.
Comparisons of interest	Usual Care No comment
Cointerventions	No comment
Subgroup 1: Surgical speciality	Cardiothoracic No comment
Subgroup 2: Anticoagulant or antiplatelet use	Mixed Majority of people were on some sort of anticoagulant or antiplatelet (24% on LWMH, 0.7% on ticagrelor, 17% on clopidogrel, 14% on aspirin).
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Yes Majority of people had a comorbidity that increased the risk of thromboembolic events
Subgroup 4: Dose	High dose: median 66.67 (57.69-75.76) mg/kg. Low dose: median 39.68 (34.72-43.87) mg/kg. No comment
Subgroup 5: Route of administration	Intravenous No comment
Subgroup 6: Repeated use	Repeated use No comment

Subgroup 7: Renal function	No impairment Around 7% of people had CKD
Outcomes of interest	All-cause mortality No comment Pulmonary embolism No comment Myocardial infarction No comment Ischaemic stroke Stroke - downgrade for indirectness as it may include haemorrhagic strokes Seizures No comment
Total number of participants	18380
Duration of follow-up (days)	30
Additional comments	Propensity score matching using a calliper width of 0.01 and the nearest-neighbour matching method without replacement. Matches were selected in accordance with the clinical and statistical significant ($p < 0.05$). Matching was based on a standardized difference of <0.1.

Study arms

Tranexamic acid (intravenous) (N = 6184)

1 gram dose 30 minutes before skin incision at 2 grams/hour and continued at 200-800 mg/hour during the entire operation. 10969 people before matching.

Usual care (N = 6184)

No tranexamic acid. 7411 people before matching.

High dose tranexamic acid (N = 3813)

At least 50 mg/kg. Median dose 66.67 (57.69-75.76) mg/kg.

Low dose tranexamic acid (N = 3813)

Less than 50 mg/kg. Median dose 39.68 (34.72-43.87) mg/kg.

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (intravenous) (N = 6184)	Usual care (N = 6184)	High dose tranexamic acid (N = 3813)	Low dose tranexamic acid (N = 3813)
Female (%) Sample size	n = 1379 ; % = 22	n = 1390 ; % = 22	n = 808 ; % = 21	n = 837 ; % = 22
Mean age (SD) (years) Mean (SD)	61.55 (8.74)	61.61 (8.87)	61.77 (8.52)	61.74 (8.65)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Insulin dependent diabetes Sample size	n = 681 ; % = 11	n = 696 ; % = 11.3	n = 494 ; % = 13	n = 489 ; % = 12.8
Comorbidities (%) - Hyperlipidaemia Sample size	n = 4135 ; % = 66.9	n = 4148 ; % = 67.1	n = 2808 ; % = 73.6	n = 2830 ; % = 74.2
Comorbidities (%) - Hypertension Sample size	n = 3893 ; % = 63	n = 3880 ; % = 62.7	n = 2453 ; % = 64.3	n = 2450 ; % = 64.3
Comorbidities (%) - Chronic kidney disease Sample size	n = 407 ; % = 6.6	n = 382 ; % = 6.2	n = 271 ; % = 7.1	n = 248 ; % = 6.5
Comorbidities (%) - COPD Sample size	n = 87 ; % = 1.4	n = 102 ; % = 1.6	n = 60 ; % = 1.6	n = 39 ; % = 1
Comorbidities (%) - Peripheral vascular disease Sample size	n = 606 ; % = 9.8	n = 626 ; % = 10.1	n = 434 ; % = 11.4	n = 440 ; % = 11.5
Comorbidities (%) - Cerebrovascular accident Sample size	n = 813 ; % = 13.1	n = 823 ; % = 13.3	n = 560 ; % = 14.7	n = 524 ; % = 13.7

Characteristic	Tranexamic acid (intravenous) (N = 6184)	Usual care (N = 6184)	High dose tranexamic acid (N = 3813)	Low dose tranexamic acid (N = 3813)
Comorbidities (%) - Previous cardiac surgery Sample size	n = 178 ; % = 2.9	n = 168 ; % = 2.7	n = 126 ; % = 3.3	n = 119 ; % = 3.1
Comorbidities (%) - Preoperative atrial fibrillation Sample size	n = 97 ; % = 1.6	n = 97 ; % = 1.6	n = 70 ; % = 1.8	n = 57 ; % = 1.5
Comorbidities (%) - Acute coronary syndrome Sample size	n = 1397 ; % = 22.6	n = 1408 ; % = 22.8	n = 807 ; % = 21.2	n = 791 ; % = 20.7
Comorbidities (%) - Left main stem disease Sample size	n = 961 ; % = 15.5	n = 959 ; % = 15.5	n = 467 ; % = 12.2	n = 458 ; % = 12
Comorbidities (%) - Three-vessel disease Sample size	n = 4592 ; % = 74.3	n = 4575 ; % = 74	n = 2974 ; % = 78	n = 2997 ; % = 78.6
Renal function (% or mL/min/1.73 m2) Mean (SD)	91.84 (21.88)	91.51 (21.97)	90.98 (21.69)	90.73 (21.38)

Outcomes

Study timepoints

- 30 days

Dichotomous outcomes

Outcome	Tranexamic acid (intravenous), 30 day, N = 6184	Usual care, 30 day, N = 6184	High dose tranexamic acid, 30 day, N = 3813	Low dose tranexamic acid, 30 day, N = 3813
All-cause mortality Death from any cause within 30 days No of events	n = 19 ; % = 0.3	n = 14 ; % = 0.2	n = 11 ; % = 0.3	n = 11 ; % = 0.3

Outcome	Tranexamic acid (intravenous), 30 day, N = 6184	Usual care, 30 day, N = 6184	High dose tranexamic acid, 30 day, N = 3813	Low dose tranexamic acid, 30 day, N = 3813
Pulmonary embolism No of events	n = 7 ; % = 0.1	n = 6 ; % = 0.1	n = 8 ; % = 0.2	n = 4 ; % = 0.1
Myocardial infarction No of events	n = 177 ; % = 2.9	n = 143 ; % = 2.3	n = 145 ; % = 3.8	n = 137 ; % = 3.6
Ischaemic stroke Stroke - downgrade for indirectness as may include haemorrhagic stroke No of events	n = 47 ; % = 0.8	n = 34 ; % = 0.5	n = 30 ; % = 0.8	n = 27 ; % = 0.7
Seizures No of events	n = 6 ; % = 0.1	n = 8 ; % = 0.1	n = 3 ; % = 0.1	n = 3 ; % = 0.1

All-cause mortality - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Adjusted odds ratios

Outcome	Tranexamic acid (intravenous) vs Usual care, 30 day, N2 = 6184, N1 = 6184	High dose tranexamic acid vs Low dose tranexamic acid, 30 day, N2 = 3813, N1 = 3813
All-cause mortality Death from any cause within 30 days Odds ratio/95% CI	0.75 (0.26 to 2.16)	1 (0.43 to 2.31)
Pulmonary embolism Odds ratio/95% CI	1.17 (0.39 to 3.47)	2 (0.6 to 6.64)
Myocardial infarction Odds ratio/95% CI	1.24 (0.99 to 1.54)	1.06 (0.84 to 1.34)
Ischaemic stroke Stroke. Downgrade for indirectness as the value	1.38 (0.89 to 2.15)	1.11 (0.66 to 1.87)

Outcome	Tranexamic acid (intravenous) vs Usual care, 30 day, N2 = 6184, N1 = 6184	High dose tranexamic acid vs Low dose tranexamic acid, 30 day, N2 = 3813, N1 = 3813
may include haemorrhagic strokes. Odds ratio/95% CI		
Seizures Odds ratio/95% CI	0.75 (0.26 to 2.16)	1 (0.2 to 5)

All-cause mortality - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - ROBINS-I: a tool for non-randomised studies of interventions

Dichotomousoutcomes-All-causemortality-NoOfEvents-Tranexamic acid (intravenous)-Usual care-High dose tranexamic acid-Low dose tranexamic acid-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Low *(No concerns)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Pulmonaryembolism-NoOfEvents-Tranexamic acid (intravenous)-Usual care-High dose tranexamic acid-Low dose tranexamic acid-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Low *(No concerns)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Myocardialinfarction-NoOfEvents-Tranexamic acid (intravenous)-Usual care-High dose tranexamic acid-Low dose tranexamic acid-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Low *(No concerns)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Ischaemicstroke-NoOfEvents-Tranexamic acid (intravenous)-Usual care-High dose tranexamic acid-Low dose tranexamic acid-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Low *(No concerns)*
Overall bias	Directness	Partially Applicable *(Downgraded for outcome indirectness as may include haemorrhagic strokes)*

Dichotomousoutcomes-Seizures-NoOfEvents-Tranexamic acid (intravenous)-Usual care-High dose tranexamic acid-Low dose tranexamic acid-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Low *(No concerns)*
Overall bias	Directness	Directly applicable *(No concerns)*

D.3.6 Wang, 2022

Bibliographic Reference	Wang, E; Yuan, X; Wang, Y; Chen, W; Zhou, X; Hu, S; Yuan, S; Blood conservation outcomes and safety of tranexamic acid in coronary artery bypass graft surgery; International journal of cardiology; 2022; vol. 348; 50-56

Study details

Trial name	Wang 2022B Referred to as Wang 2022B for the purposes of this review.
Associated studies	Not applicable No comment
Trial registration number	Not applicable No comment
Study type	Retrospective cohort study No comment
Study location	China No comment
Study setting	Inpatient: elective and day care No comment Inpatient: non-elective No comment
Study dates	January 1st 2009 to December 31st 2019

Sources of funding	Academic or government grant support Funding from the National Clinical Research Center of Cardiovascular Disease, Fuwai Hospital, Chinese Academy of Medical Sciences and National Nature Science Foundation of China.
Matching inclusion criteria	Adults (age at least 16 years) No comment At short-term risk of bleeding No comment Having surgery Coronary artery bypass surgeries
Other important inclusion criteria	No comment
Other important exclusion criteria	Age below 18 years; enrolled in randomised control trials; missing values
Key confounding factors accounted for	Age No comment Sex No comment Comorbidities Including left ventricular dysfunction, insulin dependent diabetes, hyperlipidaemia, hypertension, chronic kidney disease, peripheral vascular disease, cerebrovascular accident, previous cardiac surgery, acute coronary syndrome, left main stem disease and three-vessel disease
Other confounding factors accounted for	Preoperative IABP time between CAG and operation less than 3 days; number of risk factors for bleeding; aspirin within 5 days; clopidogrel within 5 days; ticagrelor within 5 days; low molecular weight heparin within 24 hours; nitrates; beta-blockers; calcium channel blockers; ACE inhibitors or ARBs; statin; surgeons with at least 100 CABGs/year; operation year; emergent surgery; open-chamber; on-pump; LIMA; duration of surgery; heparin neutralisation ratio.
Interventions of interest	Tranexamic acid (intravenous) No comment

Comparisons of interest	Usual Care No tranexamic acid A different dose of tranexamic acid No comment
Cointerventions	No comment
Subgroup 1: Surgical speciality	Cardiothoracic No comment
Subgroup 2: Anticoagulant or antiplatelet use	Mixed Around 50% received an anticoagulant or an antiplatelet before surgery
Subgroup 3: Comorbidities that increase risk of thromboembolic events	Yes Likely all people have a comorbidity that increase the risk of thromboembolic events by the nature of having a CABG and the list of comorbidities being stated
Subgroup 4: Dose	High dose subgroup = >50 mg/kg, Low dose subgroup = <50 mg/kg 8645 received high-dose, 8645 received low dose. High median (IQR): 67.57 mg/kg (59.52-76.92 mg/kg). Low median (IQR): 40 mg/kg (34-43 mg/kg).
Subgroup 5: Route of administration	Intravenous No comment
Subgroup 6: Repeated use	Not stated/unclear No comment
Subgroup 7: Renal function	No impairment Based on number of people with CKD being less than 10% and eGFR averaging at 90 mL/min/1.73m2
Outcomes of interest	All-cause mortality No comment Pulmonary embolism No comment Myocardial infarction No comment

	Ischaemic stroke No comment Seizures No comment
Total number of participants	21038
Duration of follow-up (days)	30
Additional comments	Propensity score matching to a calliper width of 0.01, nearest neighbour matching without replacement to the thirty-four covariates. A sensitivity analysis was performed using a binary logistic regression where the 34 covariates and tranexamic acid or tranexamic acid dose were used as covariates and the binary outcome events were used as dependent variables with the "enter" method to calculate the adjusted odds ratios.

Study arms

Tranexamic acid (all doses) (N = 10519)

All doses of intravenous tranexamic acid (both less than and greater than and equal to 50 mg/kg).

No tranexamic acid (N = 10519)

No tranexamic acid

Tranexamic acid (high dose) (N = 8645)

Intravenous tranexamic acid (greater than and equal to 50 mg/kg)

Tranexamic acid (low dose) (N = 8645)

Intravenous tranexamic acid (less than 50 mg/kg)

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid (all doses) (N = 10519)	No tranexamic acid (N = 10519)	Tranexamic acid (high dose) (N = 8645)	Tranexamic acid (low dose) (N = 8645)
Female (%) Sample size	n = 2387 ; % = 23	n = 2321 ; % = 22	n = 1813 ; % = 21	n = 1784 ; % = 21
Mean age (SD) (years) Mean (SD)	61.26 (8.88)	61.24 (8.78)	61.05 (8.67)	61.07 (8.68)

Characteristic	Tranexamic acid (all doses) (N = 10519)	No tranexamic acid (N = 10519)	Tranexamic acid (high dose) (N = 8645)	Tranexamic acid (low dose) (N = 8645)
Ethnicity (%) Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR
Comorbidities (%) - Insulin dependent diabetes Sample size	n = 924 ; % = 8.8	n = 924 ; % = 8.8	n = 964 ; % = 11.2	n = 947 ; % = 11
Comorbidities (%) - Hyperlipidaemia Sample size	n = 6366 ; % = 60.5	n = 6368 ; % = 60.5	n = 5876 ; % = 68	n = 5888 ; % = 68.1
Comorbidities (%) - Hypertension Sample size	n = 6454 ; % = 61.4	n = 6397 ; % = 60.8	n = 5420 ; % = 62.7	n = 5426 ; % = 62.8
Comorbidities (%) - Chronic kidney disease Sample size	n = 740 ; % = 7	n = 731 ; % = 6.9	n = 578 ; % = 6.7	n = 593 ; % = 6.9
Comorbidities (%) - COPD Sample size	n = 128 ; % = 1.2	n = 158 ; % = 1.5	n = 132 ; % = 1.5	n = 114 ; % = 1.3
Comorbidities (%) - Peripheral vascular disease Sample size	n = 960 ; % = 9.1	n = 898 ; % = 8.5	n = 888 ; % = 10.3	n = 902 ; % = 10.4
Comorbidities (%) - Cerebrovascular accident Sample size	n = 1257 ; % = 11.9	n = 1256 ; % = 11.9	n = 1099 ; % = 12.7	n = 1109 ; % = 12.8
Comorbidities (%) - Previous cardiac surgery Sample size	n = 331 ; % = 3.1	n = 293 ; % = 2.8	n = 276 ; % = 3.2	n = 268 ; % = 3.1
Comorbidities (%) - Preoperative atrial fibrillation Sample size	n = 317 ; % = 3	n = 282 ; % = 2.7	n = 295 ; % = 3.4	n = 305 ; % = 3.5

Characteristic	Tranexamic acid (all doses) (N = 10519)	No tranexamic acid (N = 10519)	Tranexamic acid (high dose) (N = 8645)	Tranexamic acid (low dose) (N = 8645)
Comorbidities (%) - Acute coronary syndrome Sample size	n = 2494 ; % = 23.7	n = 2496 ; % = 23.7	n = 1815 ; % = 21	n = 1847 ; % = 21.4
Comorbidities (%) - Left main stem disease Sample size	n = 1699 ; % = 16.2	n = 1691 ; % = 16.1	n = 908 ; % = 10.5	n = 917 ; % = 10.6
Comorbidities (%) - Three-vessel disease Sample size	n = 7689 ; % = 73.1	n = 7741 ; % = 73.6	n = 6543 ; % = 75.7	n = 6544 ; % = 75.7
Comorbidities (%) - Preoperative IABP Sample size	n = 127 ; % = 1.2	n = 109 ; % = 1	n = 108 ; % = 1.2	n = 102 ; % = 1.2
Comorbidities (%) - Left ventricular dysfunction (ejection fraction <40%) Sample size	n = 306 ; % = 2.9	n = 329 ; % = 3.1	n = 303 ; % = 3.5	n = 311 ; % = 3.6
Renal function (% or mL/min/1.73 m2) (ml/min/1.73 m2) Mean (SD)	91.28 (22.08)	90.84 (22.33)	91.31 (21.73)	90.37 (21.72)

Reporting baseline characteristics after propensity score matching. People in the high dose and low dose subgroups were subgrouped from the overall dataset and then propensity matched from that (rather than subgrouped from the already propensity matched dataset).

Outcomes

Study timepoints

- 30 days

Dichotomous outcomes

Outcome	Tranexamic acid (all doses), 30 day, N = 10519	No tranexamic acid, 30 day, N = 10519	Tranexamic acid (high dose), 30 day, N = 8645	Tranexamic acid (low dose), 30 day, N = 8645
All-cause mortality No of events	n = 86 ; % = 0.8	n = 70 ; % = 0.7	n = 50 ; % = 0.6	n = 59 ; % = 0.7
Pulmonary embolism No of events	n = 13 ; % = 0.1	n = 9 ; % = 0.1	n = 8 ; % = 0.1	n = 10 ; % = 0.1
Myocardial infarction No of events	n = 472 ; % = 4.5	n = 342 ; % = 3.3	n = 487 ; % = 5.6	n = 452 ; % = 5.2
Ischaemic stroke 'Stroke'. Downgrade for indirectness as may include haemorrhagic strokes. No of events	n = 113 ; % = 0.1	n = 78 ; % = 0.7	n = 95 ; % = 1.1	n = 86 ; % = 1
Seizures No of events	n = 18 ; % = 0.2	n = 17 ; % = 0.2	n = 14 ; % = 0.2	n = 8 ; % = 0.1

All-cause mortality - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Adjusted odds ratios

Outcome	Tranexamic acid (all doses) vs No tranexamic acid, 30 day, N2 = 10519, N1 = 10519	Tranexamic acid (high dose) vs Tranexamic acid (low dose), 30 day, N2 = 8645, N1 = 8645
All-cause mortality Odds ratio/95% CI	1.07 (0.79 to 1.45)	1.05 (0.74 to 1.48)
Pulmonary embolism Odds ratio/95% CI	1.1 (0.53 to 2.3)	0.92 (0.42 to 2.03)
Myocardial infarction Odds ratio/95% CI	1.37 (1.21 to 1.56)	1.11 (0.99 to 1.24)

Outcome	Tranexamic acid (all doses) vs No tranexamic acid, 30 day, N2 = 10519, N1 = 10519	Tranexamic acid (high dose) vs Tranexamic acid (low dose), 30 day, N2 = 8645, N1 = 8645
Ischaemic stroke 'Stroke'. Downgrade for indirectness as may include haemorrhagic strokes. Odds ratio/95% CI	1.28 (1 to 1.65)	1.18 (0.9 to 1.53)
Seizures Odds ratio/95% CI	0.65 (0.37 to 1.13)	1.23 (0.62 to 2.44)

All-cause mortality - Polarity - Lower values are better
Pulmonary embolism - Polarity - Lower values are better
Myocardial infarction - Polarity - Lower values are better
Ischaemic stroke - Polarity - Lower values are better
Seizures - Polarity - Lower values are better

Critical appraisal - Critical Appraisal - ROBINS-I: a tool for non-randomised studies of interventions

Dichotomousoutcomes-All-causemortality-NoOfEvents-Tranexamic acid (all doses)-No tranexamic acid-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate *(Concerns about limited data reporting about the intervention so difficult to determine about the dose and repeated use of tranexamic acid from the information provided)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Pulmonaryembolism-NoOfEvents-Tranexamic acid (all doses)-No tranexamic acid-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate *(Concerns about limited data reporting about the intervention so difficult to determine about the dose and repeated use of tranexamic acid from the information provided)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Myocardialinfarction-NoOfEvents-Tranexamic acid (all doses)-No tranexamic acid-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate *(Concerns about limited data reporting about the intervention so difficult to determine about the dose and repeated use of tranexamic acid from the information provided)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Ischaemicstroke-NoOfEvents-Tranexamic acid (all doses)-No tranexamic acid-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate *(Concerns about limited data reporting about the intervention so difficult to determine about the dose and repeated use of tranexamic acid from the information provided)*
Overall bias	Directness	Directly applicable *(No concerns)*

Dichotomousoutcomes-Seizures-NoOfEvents-Tranexamic acid (all doses)-No tranexamic acid-Tranexamic acid (high dose)-Tranexamic acid (low dose)-t30

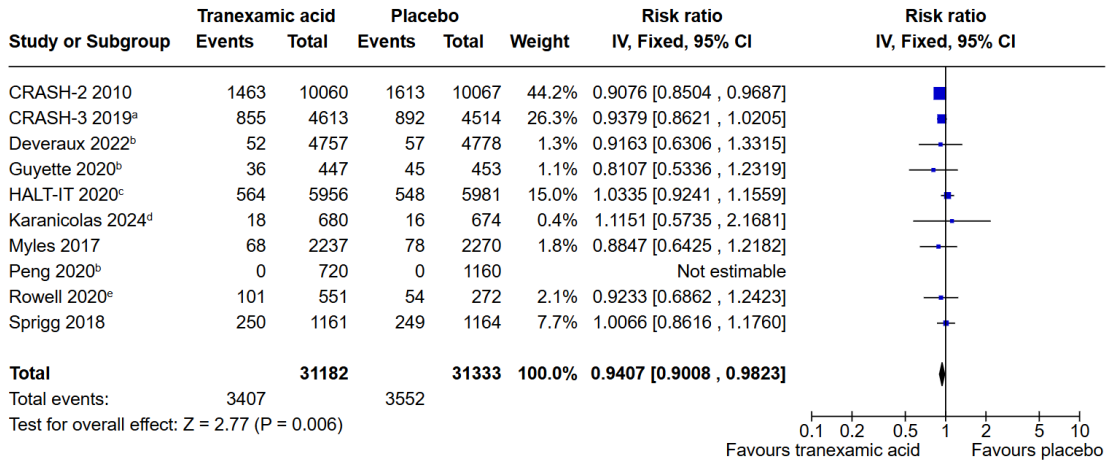
Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate *(Concerns about limited data reporting about the intervention so difficult to determine about the dose and repeated use of tranexamic acid from the information provided)*
Overall bias	Directness	Directly applicable *(No concerns)*

Appendix E Forest plots

E.1 Adults and children at short term risk of blood loss

E.1.1 Tranexamic acid compared to placebo

Figure 2 All-cause mortality (risk ratio) at end of trial



Footnotes

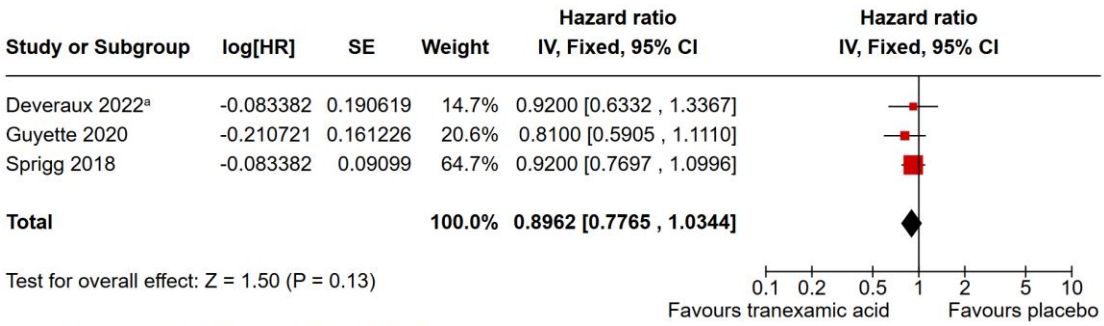
[a]Within 3 hours of injury
[b]30 days
[c]28 days
[d]90 days
[e]6 months

Abbreviations: CI: confidence intervals; IV: Inverse variance

While there were zero events in both arms of one study, this was thought to likely be unimportant to the overall meta-analysis (likely a reflection of the study not being sufficiently powered to capture the events rather than a true reflection of the safety event) and so a risk ratio was used rather than a risk difference to maintain the benefits of the risk ratio in the analysis.

Both hazard ratio and risk ratio results are presented for all-cause mortality. When presented to the committee, they were highlighted to instances where studies reported both measures to avoid double counting.

Figure 3 All-cause mortality (hazard ratio) at end of trial

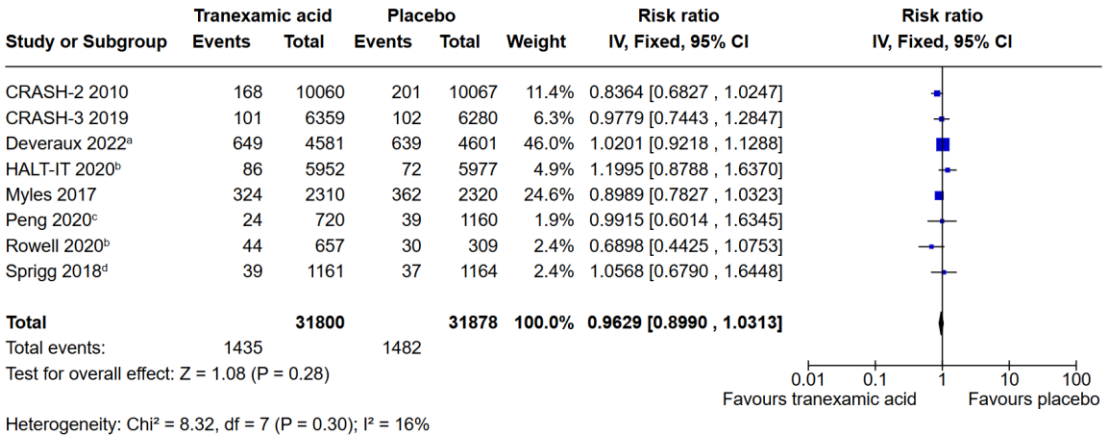


Footnotes

[a]30 days

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 4 Thromboembolic events after surgery at end of trial

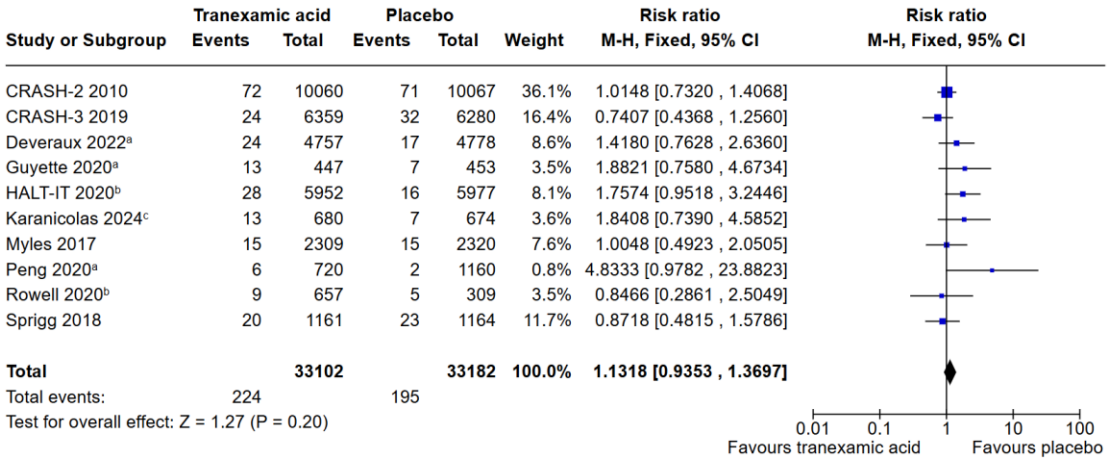


Footnotes

[a]30 days
[b]28 days
[c]30 days, "symptomatic venous thromboembolic event"
[d]Combined deep vein thrombosis and pulmonary embolism data only

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 5 Pulmonary embolism at end of trial

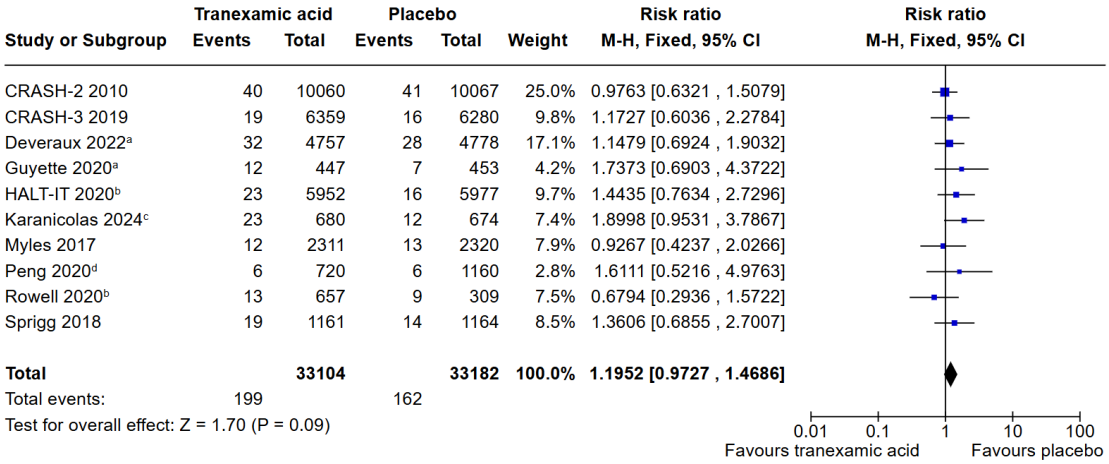


Footnotes

[a]30 days
[b]28 days
[c]90 days

Abbreviations: CI: confidence intervals; M-H: Mantel-Haenszel

Figure 6 Deep vein thrombosis at end of trial

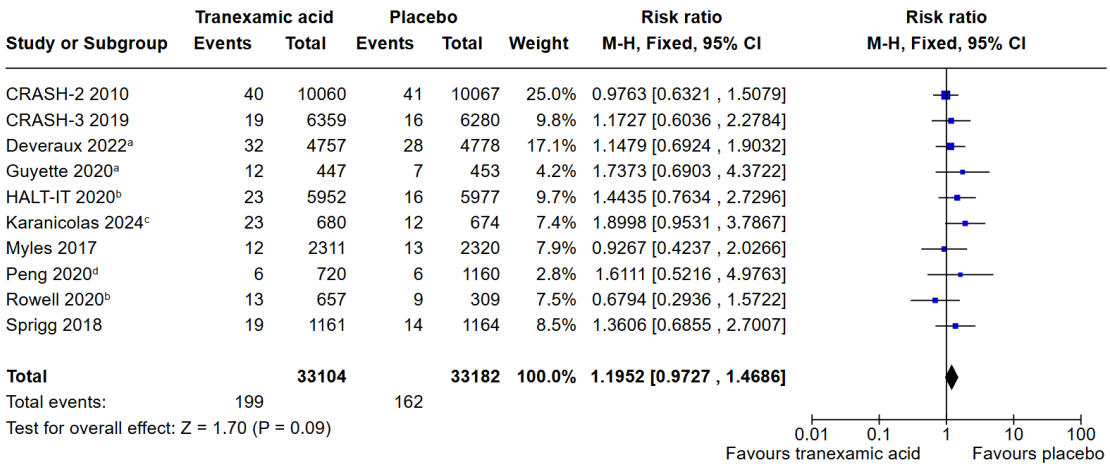


Footnotes

[a]30 days
[b]28 days
[c]90 days
[d]30 days, "near-end"

Abbreviations: CI: confidence intervals; M-H: Mantel-Haenszel

Figure 7 Deep vein thrombosis at end of trial

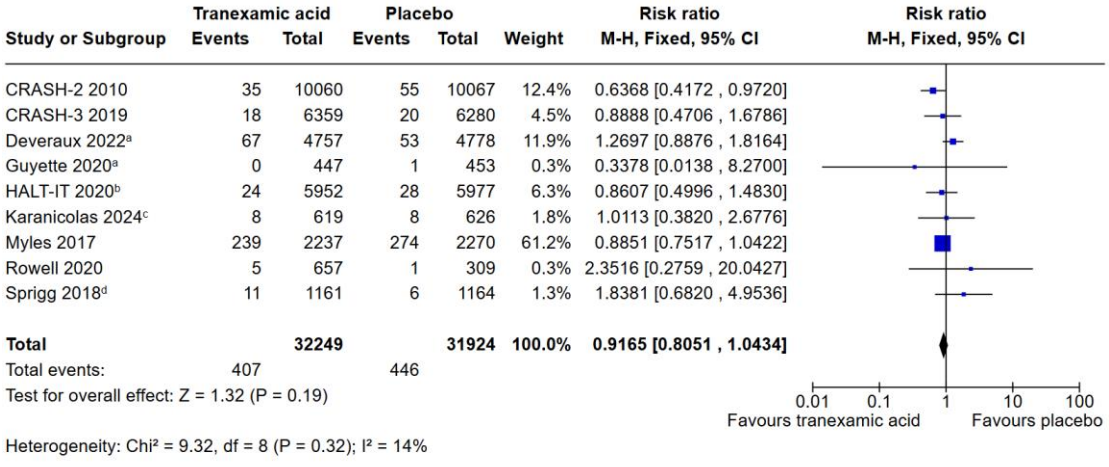


Footnotes

[a]30 days
[b]28 days
[c]90 days
[d]30 days, "near-end"

Abbreviations: CI: confidence intervals; M-H: Mantel-Haenszel

Figure 8 Myocardial infarction at end of trial

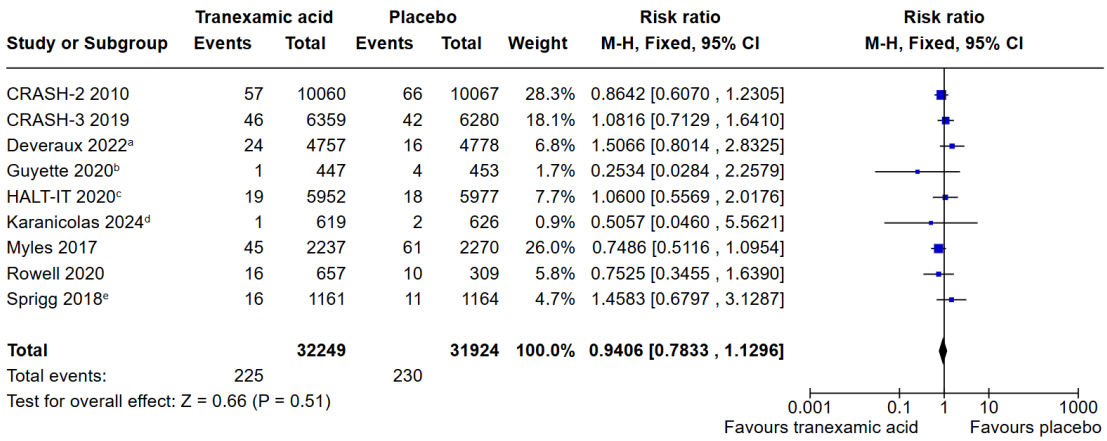


Footnotes

[a]30 days
[b]28 days
[c]90 days, "cardiac - ischaemic"
[d]Includes all ACS

Abbreviations: CI: confidence intervals; M-H: Mantel-Haenszel

Figure 9 Ischaemic stroke at end of trial

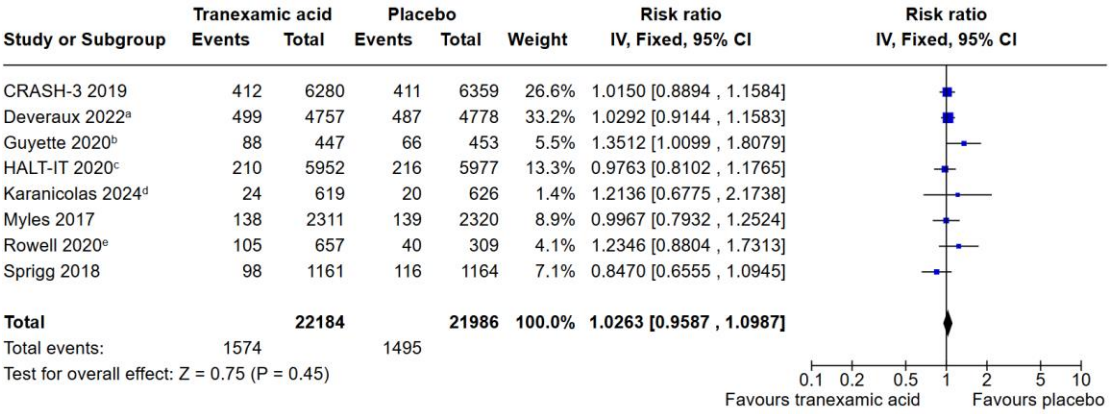


Footnotes

[a]30 days
[b]30 days, "stroke"
[c]28 days
[d]90 days, "Stroke/transient ischaemic attack"
[e]Includes TIAs

Abbreviations: CI: confidence intervals; M-H: Mantel-Haenszel

Figure 10 Infection at end of trial

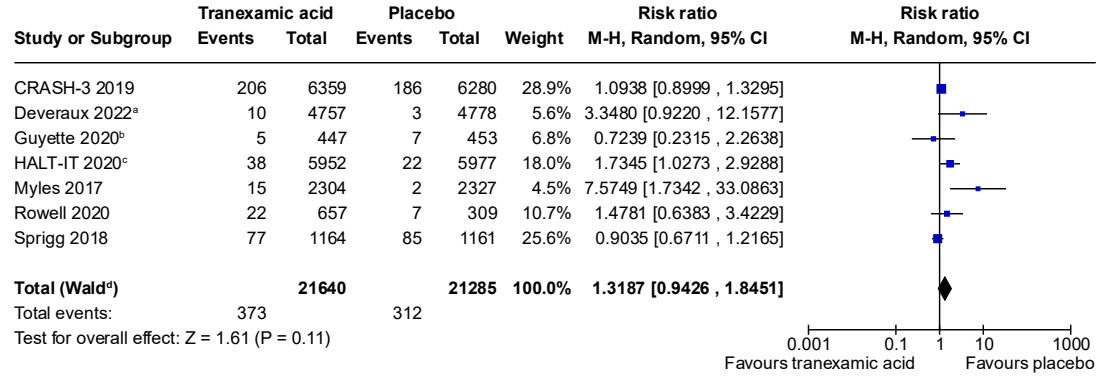


Footnotes

[a]30 days
[b]Nosocomial infection
[c]28 days, sepsis
[d]90 days, "sepsis"
[e]28 days

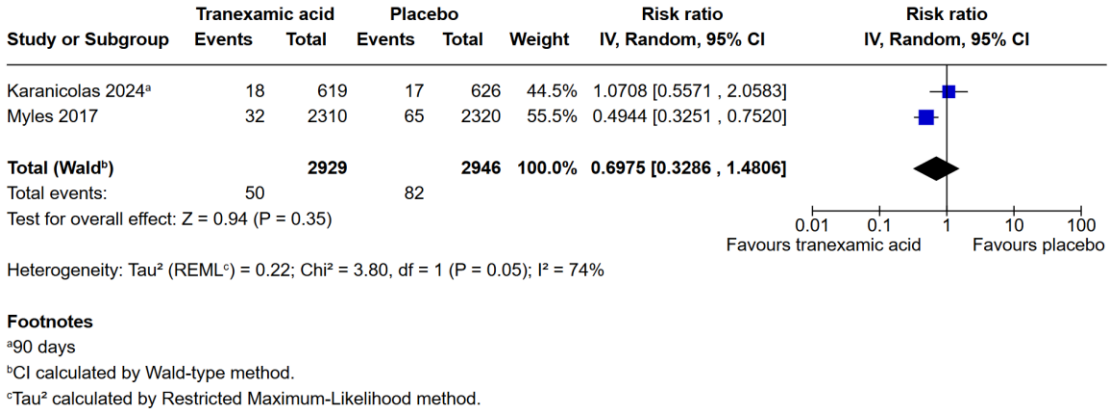
Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 11 Seizures at end of trial



Abbreviations: CI: confidence intervals; M-H: Mantel-Haenszel

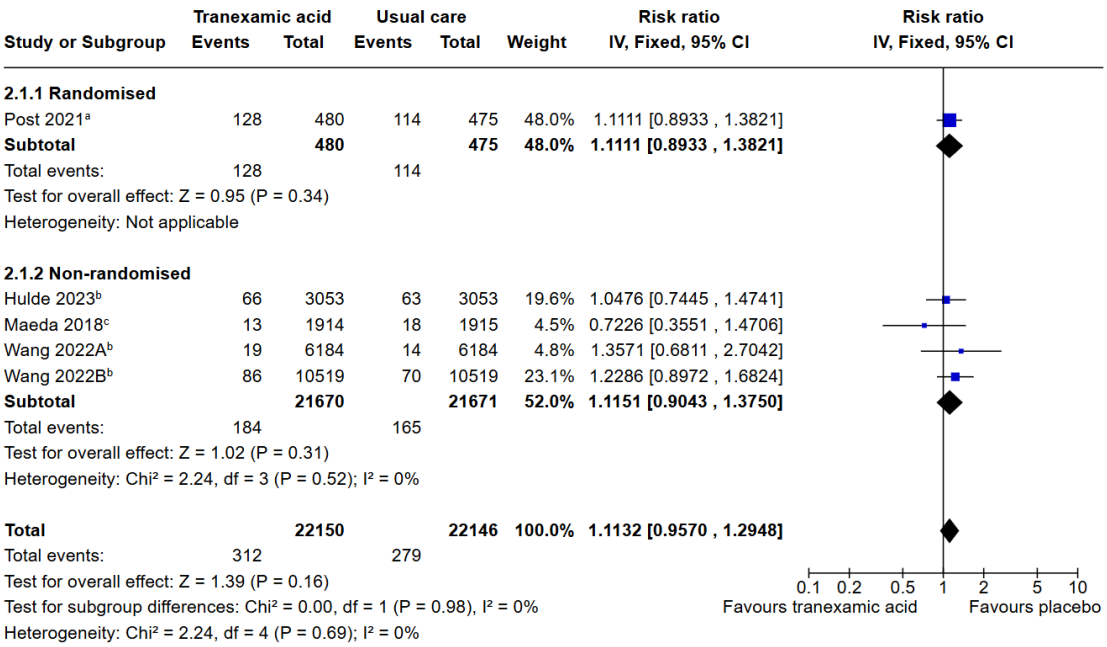
Figure 12 Reoperation at end of trial



Abbreviations: CI: confidence intervals; IV: Inverse variance

E.1.2 Tranexamic acid compared to usual care

Figure 13 All-cause mortality at end of trial



Footnotes

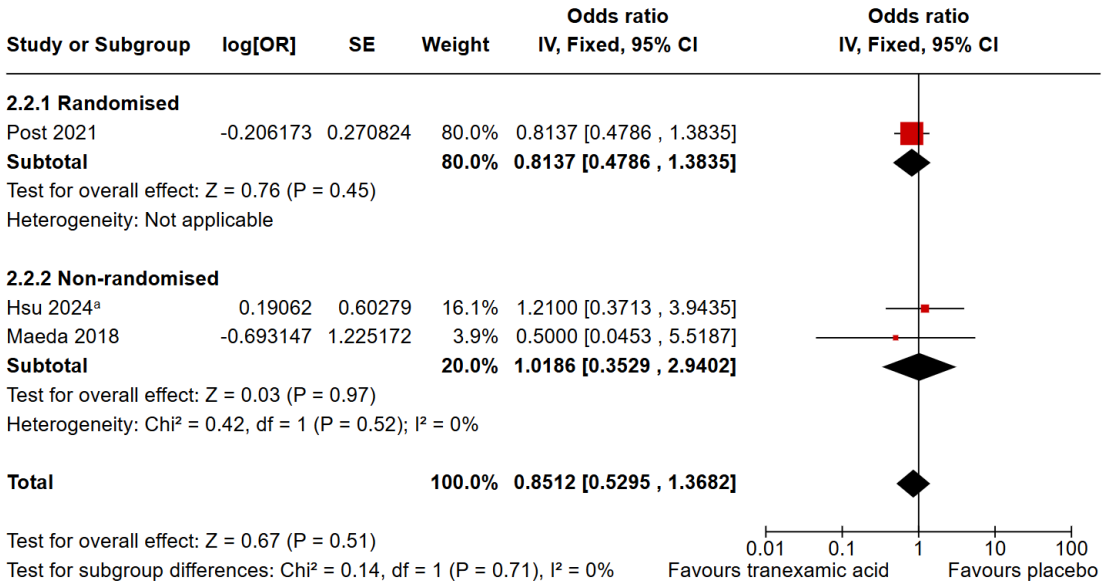
[a]At 6 months

[b]30 days

[c]After surgery

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 14 Thromboembolic events after surgery at end of trial

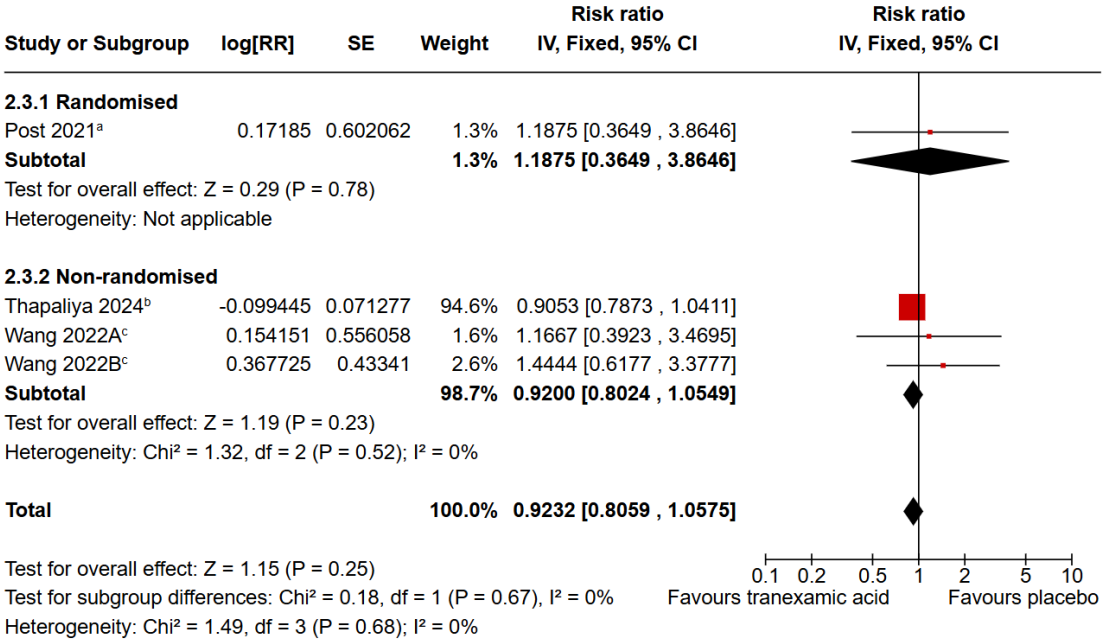


Footnotes

[a]90 days

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 15 Pulmonary embolism at end of trial



Footnotes

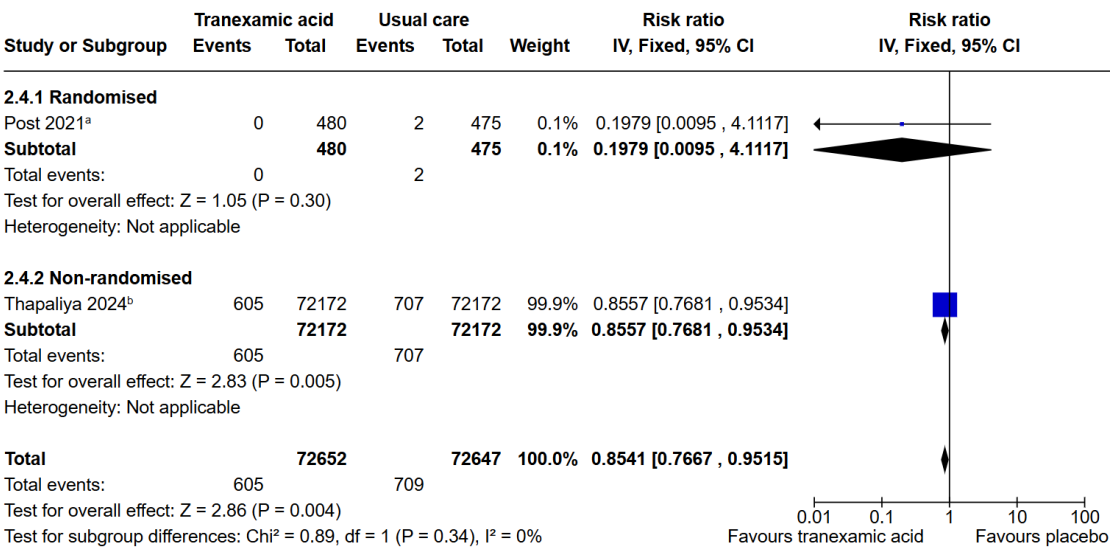
[a]After surgery

[b]90 days

[c]30 days

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 16 Deep vein thrombosis at end of trial



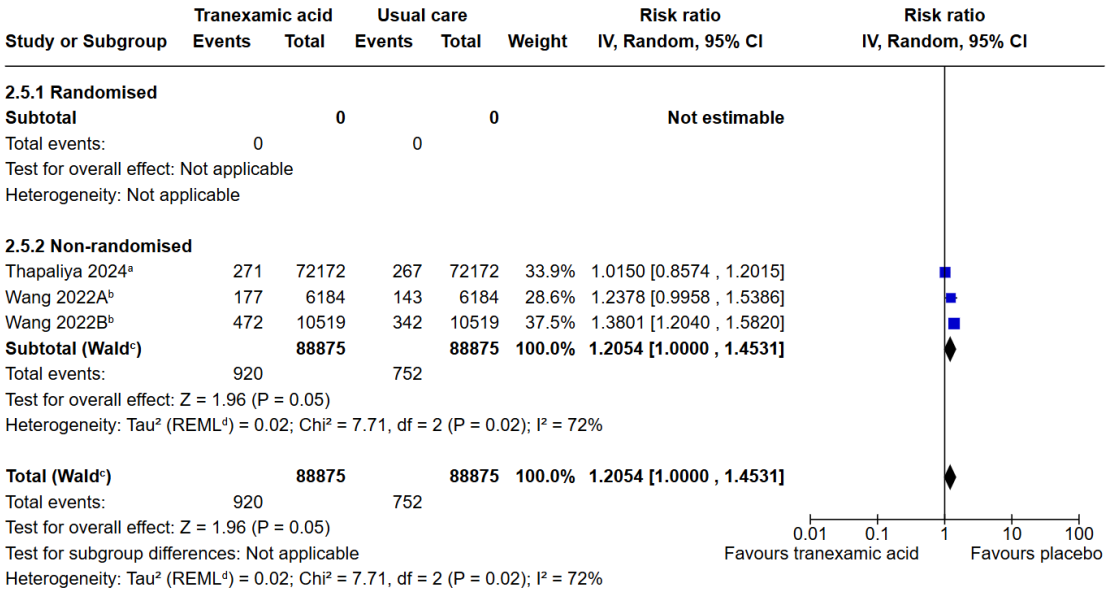
Footnotes

[a]After surgery

[b]90 days

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 17 Myocardial infarction at end of trial



Footnotes

[a]90 days

[b]30 days

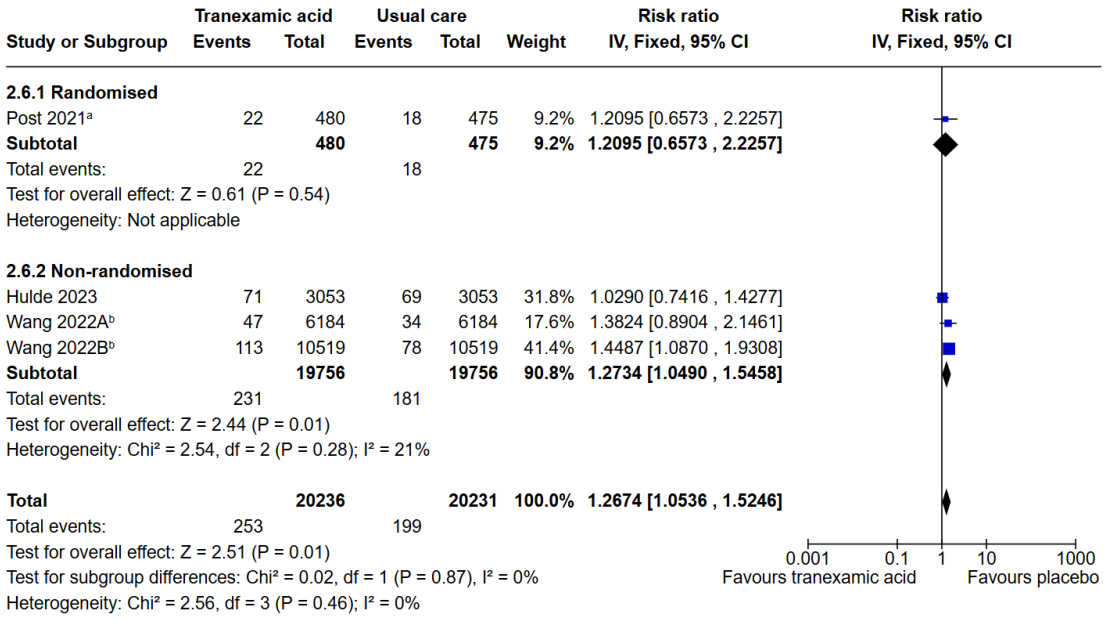
[c]CI calculated by Wald-type method.

[d]Tau² calculated by Restricted Maximum-Likelihood method.

Abbreviations: CI: confidence intervals; IV: Inverse variance

A risk ratio was used to capture the benefits of the studies included in the non-randomised analysis. The study included in the randomised analysis was included in the GRADE analysis using a risk difference instead. Analyses including a single study are not routinely presented in this appendix and so this forest plot is not shown in this report.

Figure 18 Ischaemic stroke at end of trial



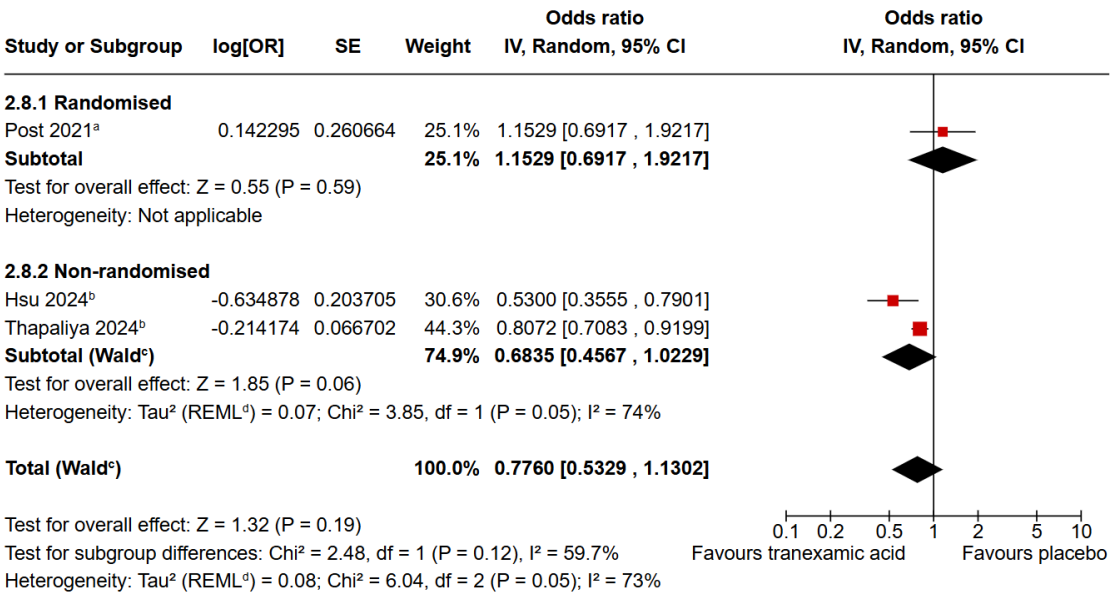
Footnotes

[a]Cerebral infarction related to clipping procedure after surgery

[b]30 days, "stroke"

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 19 Infection at end of trial



Footnotes

[a]After surgery

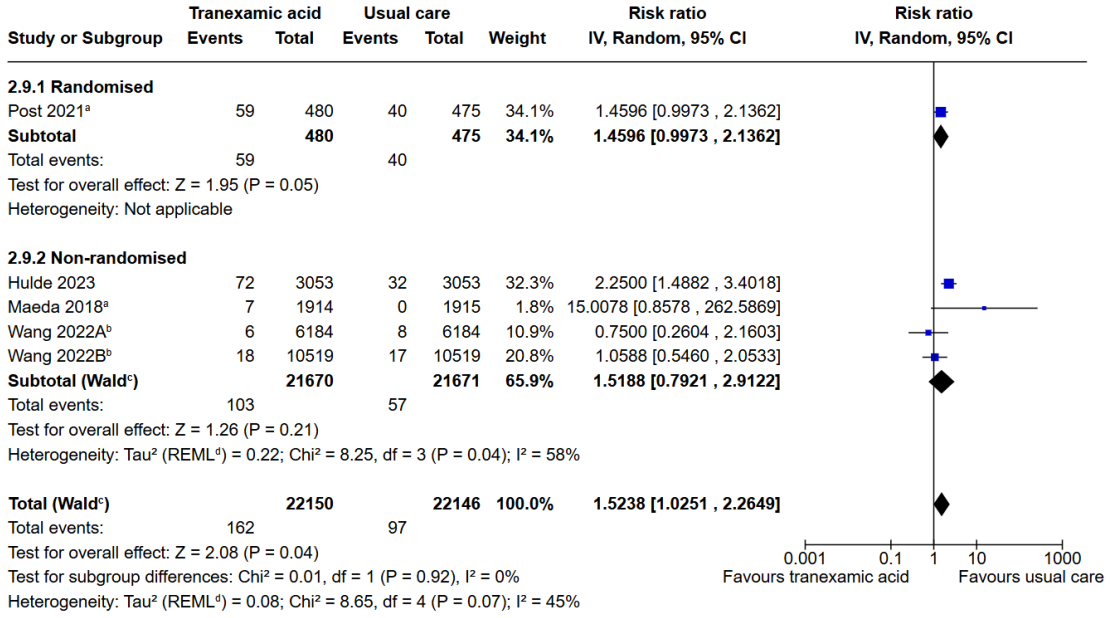
[b]90 days

[c]CI calculated by Wald-type method.

[d]Tau² calculated by Restricted Maximum-Likelihood method.

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 20 Seizures at end of trial



Footnotes

[a]After surgery

[b]30 days

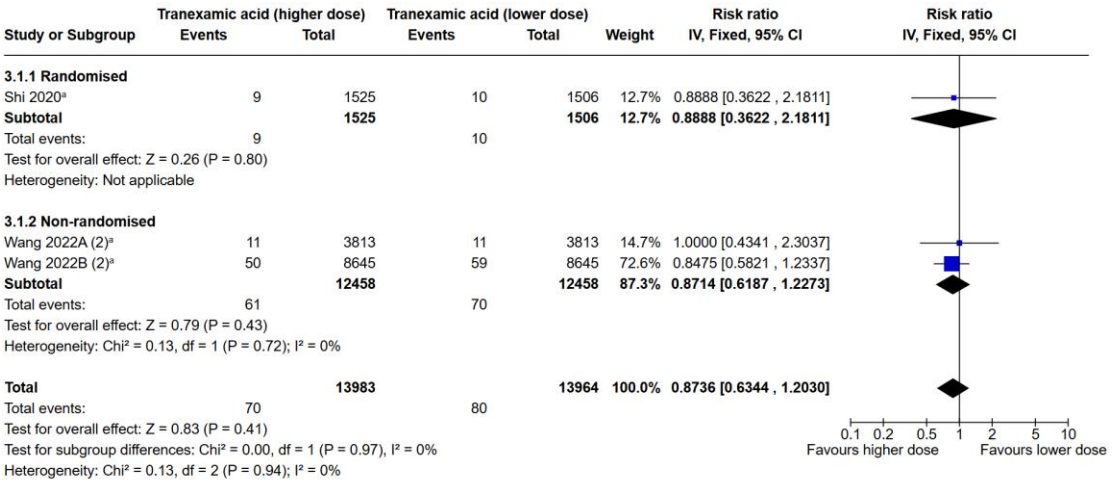
[c]CI calculated by Wald-type method.

[d]Tau² calculated by Restricted Maximum-Likelihood method.

Abbreviations: CI: confidence intervals; IV: Inverse variance

E.1.3 Tranexamic acid (higher dose) compared to tranexamic acid (lower dose)

Figure 21 All-cause mortality at end of trial

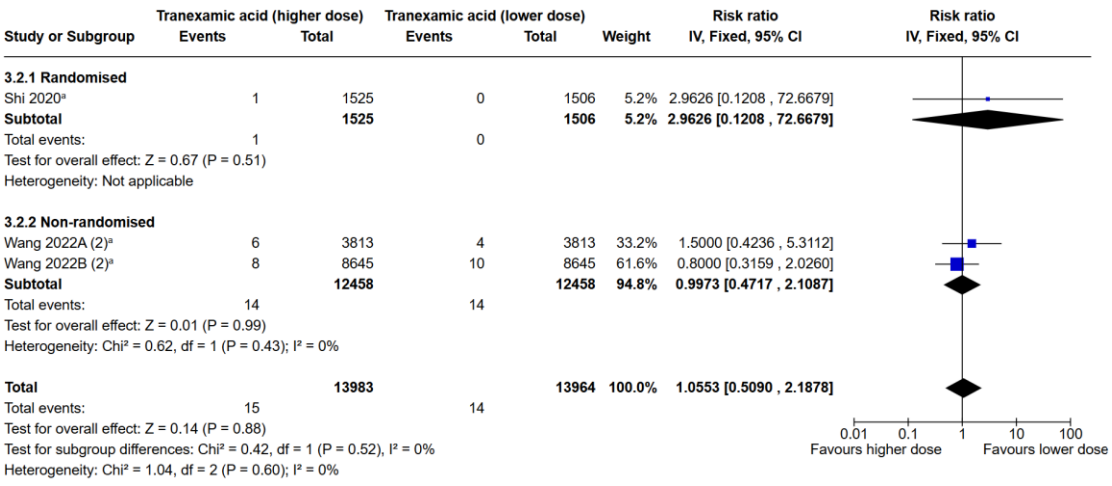


Footnotes

[a]30 days

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 22 Pulmonary embolism at end of trial

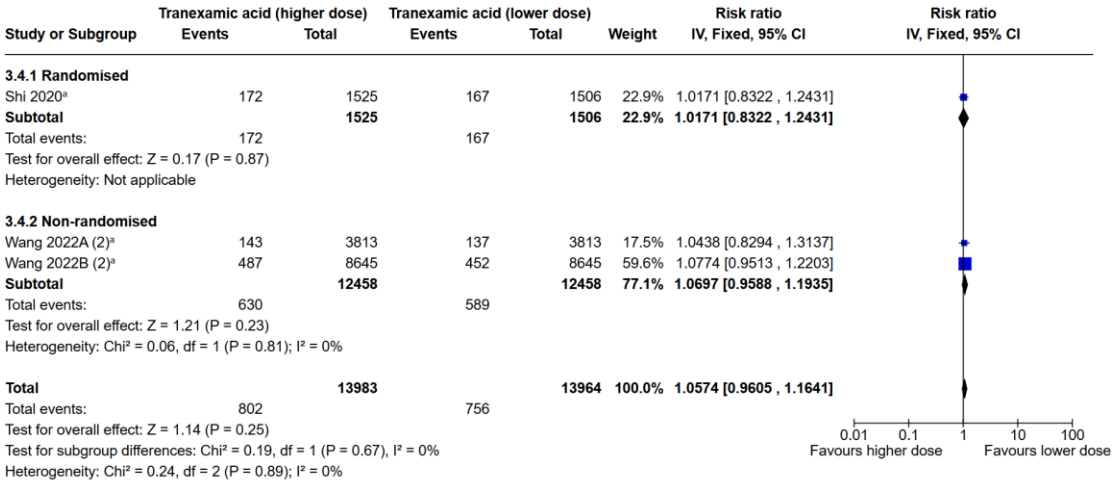


Footnotes

[a]30 days

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 23 Myocardial infarction at end of trial

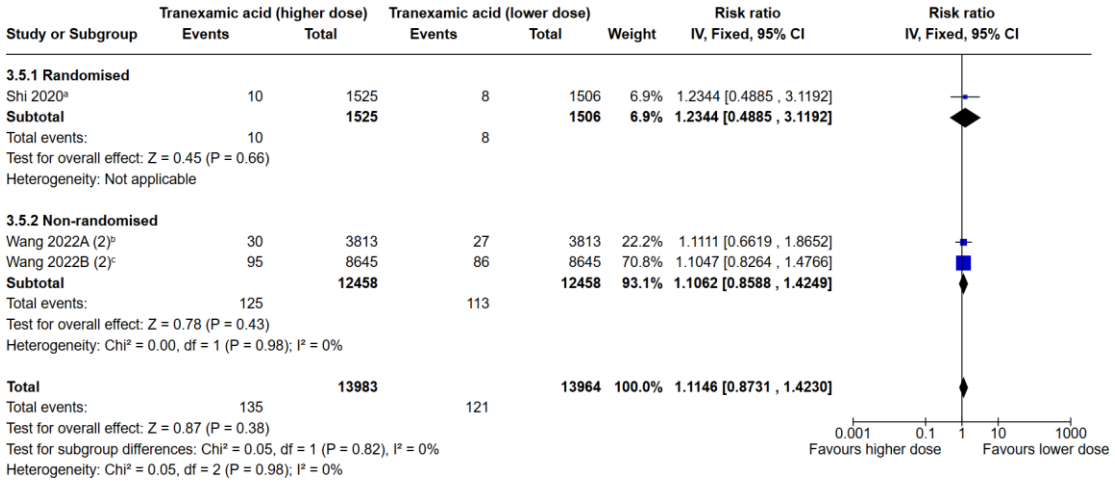


Footnotes

[a]30 days

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 24 Ischaemic stroke at end of trial

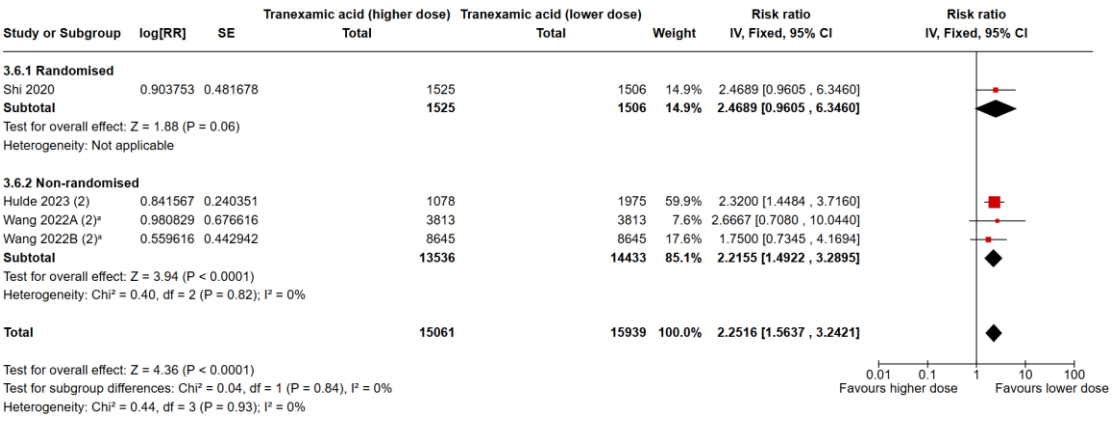


Footnotes

[a]30 days
[b]30 days, "stroke"
[c]30 days, 'stroke'

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 25 Seizures at end of trial

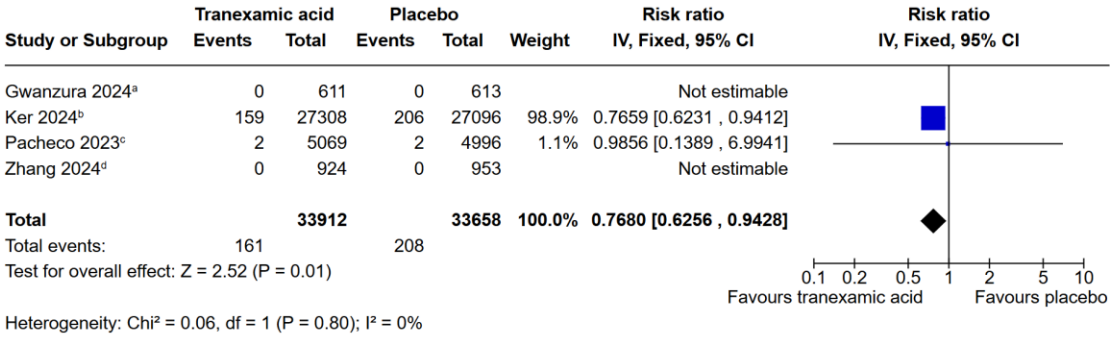


Abbreviations: CI: confidence intervals; IV: Inverse variance

E.2 Women, trans men and non-binary people at short term risk of blood loss

E.2.1 Tranexamic acid compared to placebo

Figure 26 All-cause mortality at end of trial

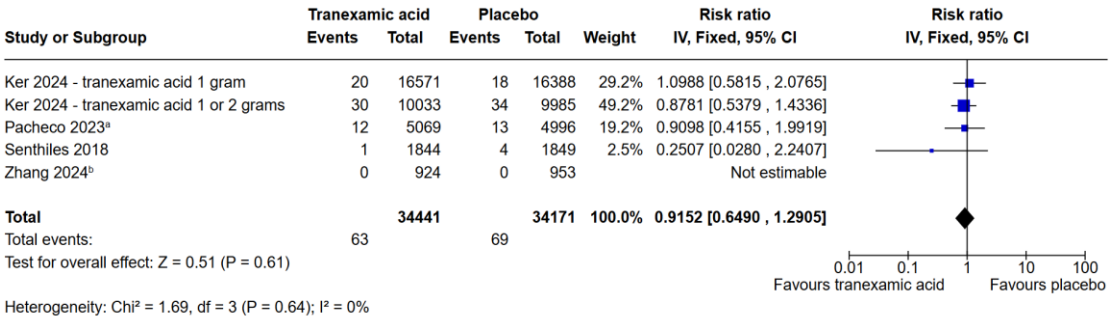


Abbreviations: CI: confidence intervals; IV: Inverse variance

While there were zero events in both arms of two studies, this was thought to likely be unimportant to the overall meta-analysis (likely a reflection of the study not being sufficiently powered to capture the events rather than a true

reflection of the safety event) and so a risk ratio was used rather than a risk difference to maintain the benefits of the risk ratio in the analysis.

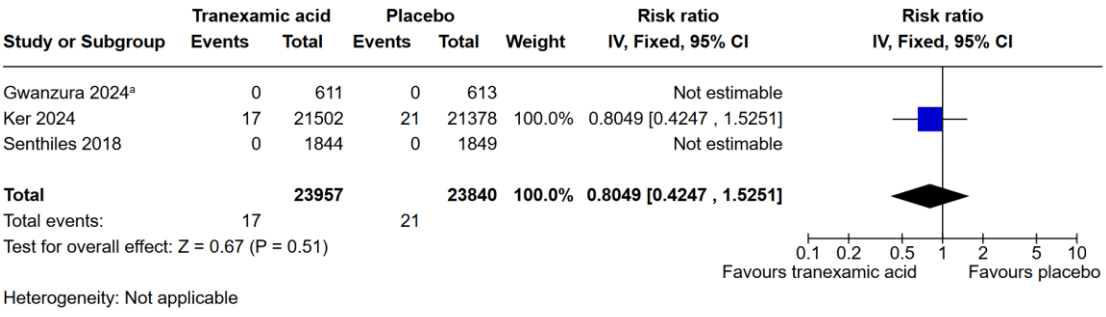
Figure 27 Thromboembolic events after surgery at end of trial



Abbreviations: CI: confidence intervals; IV: Inverse variance

While there were zero events in both arms of one study, this was thought to likely be unimportant to the overall meta-analysis (likely a reflection of the study not being sufficiently powered to capture the events rather than a true reflection of the safety event) and so a risk ratio was used rather than a risk difference to maintain the benefits of the risk ratio in the analysis.

Figure 28 Pulmonary embolism at end of trial

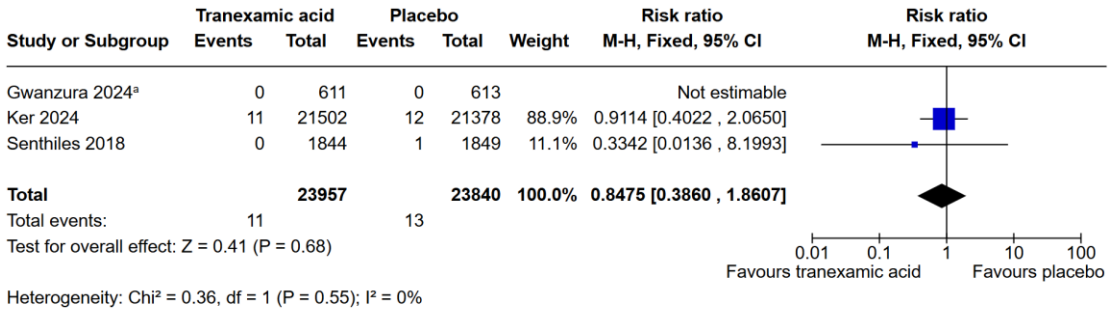


Abbreviations: CI: confidence intervals; IV: Inverse variance

While there were zero events in both arms of one study, this was thought to likely be unimportant to the overall meta-analysis (likely a reflection of the

study not being sufficiently powered to capture the events rather than a true reflection of the safety event) and so a risk ratio was used rather than a risk difference to maintain the benefits of the risk ratio in the analysis.

Figure 29 Deep vein thrombosis at end of trial



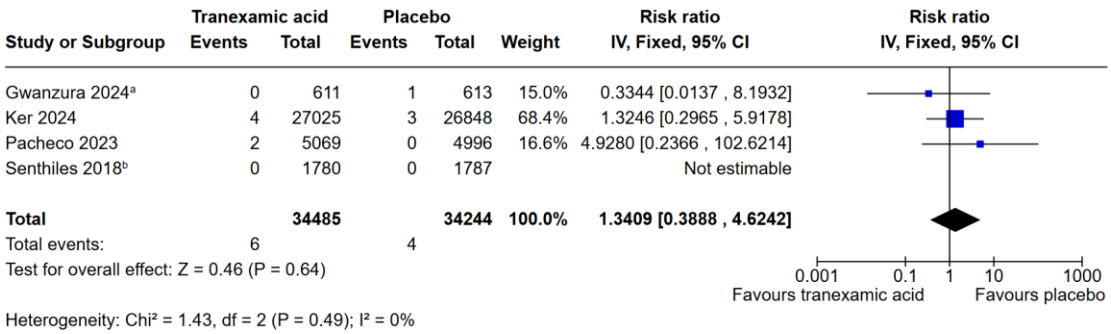
Footnotes

[a]4 days

Abbreviations: CI: confidence intervals; IV: Inverse variance

While there were zero events in both arms of one study, this was thought to likely be unimportant to the overall meta-analysis (likely a reflection of the study not being sufficiently powered to capture the events rather than a true reflection of the safety event) and so a risk ratio was used rather than a risk difference to maintain the benefits of the risk ratio in the analysis.

Figure 30 Myocardial infarction at end of trial



Footnotes

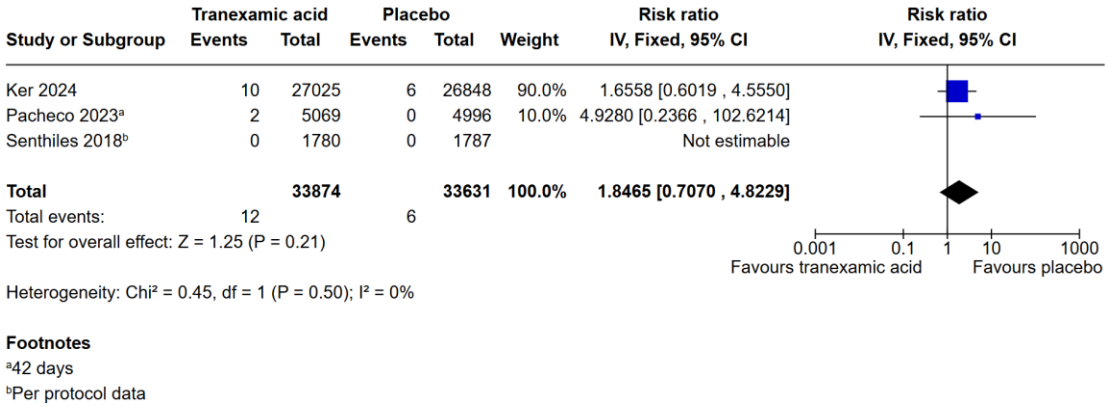
[a]4 days

[b]Per protocol data

Abbreviations: CI: confidence intervals; IV: Inverse variance

While there were zero events in both arms of one study, this was thought to likely be unimportant to the overall meta-analysis (likely a reflection of the study not being sufficiently powered to capture the events rather than a true reflection of the safety event) and so a risk ratio was used rather than a risk difference to maintain the benefits of the risk ratio in the analysis.

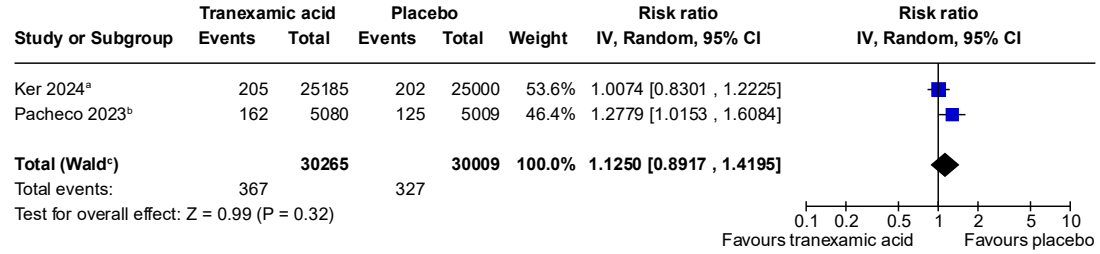
Figure 31 Ischaemic stroke at end of trial



Abbreviations: CI: confidence intervals; IV: Inverse variance

While there were zero events in both arms of one study, this was thought to likely be unimportant to the overall meta-analysis (likely a reflection of the study not being sufficiently powered to capture the events rather than a true reflection of the safety event) and so a risk ratio was used rather than a risk difference to maintain the benefits of the risk ratio in the analysis.

Figure 32 Infection at end of trial



Heterogeneity: Tau² (REML[d]) = 0.02; Chi² = 2.40, df = 1 (P = 0.12); I² = 58%

Footnotes

[a]Sepsis

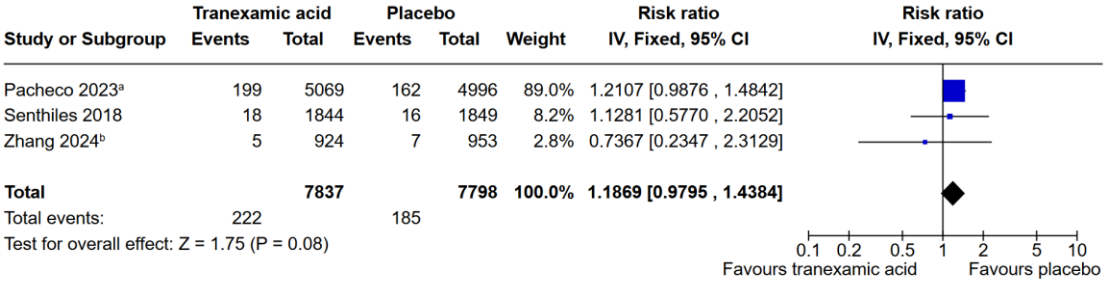
[b]42 days

[c]CI calculated by Wald-type method.

[d]Tau² calculated by Restricted Maximum-Likelihood method.

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 33 All-cause readmission at end of trial



Heterogeneity: Chi² = 0.73, df = 2 (P = 0.70); I² = 0%

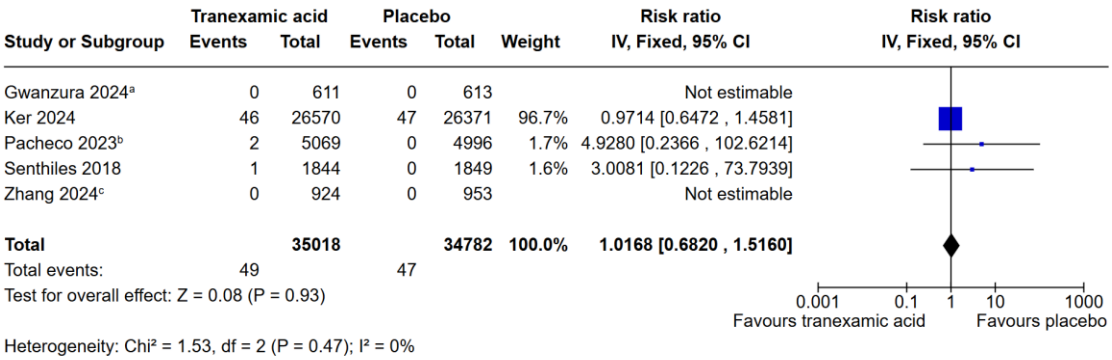
Footnotes

[a]42 days

[b]30 days

Abbreviations: CI: confidence intervals; IV: Inverse variance

Figure 34 Seizures at end of trial



Footnotes

[a]4 days

[b]42 days

[c]30 days

Abbreviations: CI: confidence intervals; IV: Inverse variance

While there were zero events in both arms of two studies, this was thought to likely be unimportant to the overall meta-analysis (likely a reflection of the study not being sufficiently powered to capture the events rather than a true reflection of the safety event) and so a risk ratio was used rather than a risk difference to maintain the benefits of the risk ratio in the analysis.

Appendix F GRADE summary

F.1 Adults and children at short term risk of blood loss

F.1.1 Tranexamic acid compared to placebo

Table 1 Effectiveness evidence summary: tranexamic acid compared to placebo

Outcome	Number of studies	Sample size	GRADE components	GRADE	Effect measure	Effect size	Control group rate	Absolute effect	Reasons	Minimally important difference

All-cause mortality at end of trial, study types: randomised trials, scale: risk ratio, units: not applicable	10	62515	Risk of bias: Serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Not serious Other considerations: None	Moderate	Risk Ratio	0.9407 (0.90084 , 0.98232)	1134 per 10,000 people	41 fewer event per 10,000 people, 95 fewer to 13 more Clinically important benefit	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROB 2	MID (clinical importance) = 10 events per 10,000 people

All-cause mortality at end of trial, study types: randomised trials, scale: hazard ratio, units: not applicable	3	10435	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Serious Other considerations: None	Moderate	Hazard Ratio	0.89618 (0.77645, 1.03438)	671 per 10,000 people	21 fewer event per 10,000 people, 122 fewer to 79 more Clinically important benefit	Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 10 events per 10,000 people

Thromboembolic events after surgery at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	8	63678	Risk of bias: Not serious Indirectness: Serious Inconsistency: Not serious Imprecision: Not serious Other considerations: None	Moderate	Risk Ratio	0.96287 (0.89895, 1.03134)	465 per 10,000 people	14 fewer events per 10,000 people, 47 fewer to 20 more Clinically important benefit	Indirectness: Downgraded once. Serious indirectness due to >50% of overall weighting partially direct or indirect. Outcome indirectness as thromboembolic events after surgery aggregate is not consistently including same events.	MID (clinical importance) = 10 events per 10,000 people

Thromboembolic events after surgery at end of trial, study types: randomised trials, scale: hazard ratio, units: not applicable	1 (Deveraux 2022)	9182	Risk of bias: Not serious Indirectness: Serious Inconsistency: Serious - single study Imprecision: Not serious Other considerations: None	Low	Hazard Ratio	1.02 (0.91631, 1.135420)	1389 per 10,000 people	28 more events per 10,000 people, 134 fewer to 189 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Indirectness: Downgraded once. Serious indirectness due to >50% of overall weighting partially direct or indirect. Outcome indirectness as thromboembolic events after surgery aggregate is not consistently including same events.	MID (clinical importance) = 28 events per 10,000 people

Pulmonary embolism at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	10	66284	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Serious Other considerations: None	Moderate	Risk Ratio	1.13181 (0.93527 , 1.36966)	59 per 10,000 people	9 more events per 10,000 people, 3 fewer to 21 more Clinically important harm	Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 6 events per 10,000 people

Pulmonary embolism at end of trial, study types: randomised trials, scale: hazard ratio, units: not applicable	1 (Deverau x 2022)	9535	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations: None	Very low	Hazard Ratio	1.42 (0.76189 , 2.64657)	67 per 10,000 people	17 fewer events per 10,000 people, 47 fewer to 14 more Clinically important benefit	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 7 events per 10,000 people

Deep vein thrombosis at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	10	66286	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Serious Other considerations: None	Moderate	Risk Ratio	1.19518 (0.97267, 1.46859)	49 per 10,000 people	11 more event per 10,000 people, 0 fewer to 23 more Clinically important harm	Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 5 events per 10,000 people

Deep vein thrombosis at end of trial, study types: randomised trials, scale: hazard ratio, units: not applicable	1 (Deveraux 2022)	9535	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations: None	Very low	Hazard Ratio	1.15 (0.6912, 1.91333)	59 per 10,000 people	9 more events per 10,000 people, 23 fewer to 41 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 6 events per 10,000 people

Myocardial infarction at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	9	64173	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Not serious Other considerations: None	High	Risk Ratio	0.91655 (0.80514 , 1.04337)	140 per 10,000 people	14 fewer events per 10,000 people, 31 fewer to 4 fewer Clinically important benefit	No downgrading required	MID (clinical importance) = 14 events per 10,000 people

Myocardial infarction at end of trial, study types: randomised trials, scale: hazard ratio, units: not applicable	1 (Deveraux 2022)	9535	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Serious Other considerations: None	Low	Hazard Ratio	1.27 (0.8881, 1.81612)	111 per 10,000 people	30 more events per 10,000 people, 15 fewer to 75 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 12 events per 10,000 people

Ischaemic stroke at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	9	64173	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Serious Other considerations: None	Moderate	Risk Ratio	0.94064 (0.78328 , 1.12961)	72 per 10,000 people	2 fewer events per 10,000 people, 15 fewer to 11 more No clinically important difference	Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 8 events per 10,000 people

Ischaemic stroke at end of trial, study types: randomised trials, scale: hazard ratio, units: not applicable	1 (Deverau x 2022)	9535	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Serious Other considerations: None	Low	Hazard Ratio	1.51 (0.801420, 2.84506)	33 per 10,000 people	17 more events per 10,000 people, 9 fewer to 43 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 4 events per 10,000 people

Infection at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	8	44170	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Not serious Other considerations: None	High	Risk Ratio	1.02631 (0.95872 , 1.09866)	680 per 10,000 people	30 more events per 10,000 people, 21 fewer to 80 more No clinically important difference	No downgrading required	MID (clinical importance) = 68 events per 10,000 people

Infection at end of trial, study types: randomised trials, scale: hazard ratio, units: not applicable	1 (Deverau x 2022)	9535	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Not serious Other considerations: None	Moderate	Hazard Ratio	1.03 (0.908380, 1.16791)	1019 per 10,000 people	30 more events per 10,000 people, 104 fewer to 164 more No clinically important difference	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default	MID (clinical importance) = 102 events per 10,000 people

Seizures at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	7	42925	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Very serious Imprecision: Serious Other considerations: None	Very low	Risk Ratio	1.31874 (0.94256 , 1.84507)	147 per 10,000 people	26 more events per 10,000 people, 2 fewer to 50 more Clinically important harm	Inconsistency: Downgraded twice. Very serious heterogeneity (serious I2 = >60%) unexplained by subgroup analysis. Random effects analysis used Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 15 events per 10,000 people

Seizures at end of trial, study types: randomised trials, scale: hazard ratio, units: not applicable	1 (Deverau x 2022)	9535	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Serious Other considerations: None	Low	Hazard Ratio	3.35 (0.91994 , 12.19917)	6 per 10,000 people	15 more events per 10,000 people, 0 fewer to 30 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 1 events per 10,000 people

Reoperation at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	2	5875	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Very serious Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	0.69748 (0.328580, 1.48058)	278 per 10,000 people	108 fewer events per 10,000 people, 184 fewer to 31 fewer Clinically important benefit	Inconsistency: Downgraded twice. Very serious heterogeneity (serious I2 = >60%) unexplained by subgroup analysis. Random effects analysis used Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 28 events per 10,000 people

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F.1.2 Tranexamic acid compared to usual care

3 **Table 2 Effectiveness evidence summary: tranexamic acid compared to usual care**

Outcome	Number of studies	Sample size	GRADE components	GRADE	Effect measure	Effect size	Control group rate	Absolute effect	Reasons	Minimally important difference

All-cause mortality at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Post 2021)	955	Risk of bias: Serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Serious Other considerations: None	Very low	Risk Ratio	1.11111 (0.89328, 1.38206)	2400 per 10,000 people	267 more events per 10,000 people, 471 fewer to 1004 more Clinically important harm	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROB 2 Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Serious imprecision because 95%	MID (clinical importance) = 10 events per 10,000 people

									CI crosses 1 MID (RR 0.8-1.25)	

All-cause mortality at end of trial (non-randomised), study types: non-randomised studies, scale: not applicable, units: not applicable	4	43341	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Serious Other considerations: None	Moderate	Risk Ratio	1.11508 (0.904280, 1.375020)	76 per 10,000 people	9 more events per 10,000 people, 8 fewer to 26 more No clinically important difference	Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 10 events per 10,000 people

Thromboembolic events after surgery at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Post 2021)	530	Risk of bias: Very serious Indirectness: Serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations: None	Very low	Odds Ratio	0.81369 (0.47856, 1.38352)	1279 per 10,000 people	213 fewer events per 10,000 people, 809 fewer to 383 more Clinically important benefit	Risk of bias: Downgraded twice. Very serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at high risk of bias as per ROB 2 Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Indirectness: Downgraded once. Serious indirectness	MID (clinical importance) = 26 events per 10,000 people

									due to >50% of overall weighting partially direct or indirect. Outcome indirectness as thromboembolic events after surgery aggregate is not consistently including same events. Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	

Thromboembolic events after surgery at end of trial (non-randomised), study types: non-randomised studies, scale: not applicable, units: not applicable	2	11130	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Very serious Other considerations: None	Low	Odds Ratio	1.01855 (0.35285, 2.94017)	36 per 10,000 people	5 more events per 10,000 people, 18 fewer to 28 more Clinically important harm	Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 1 events per 10,000 people

Pulmonary embolism at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Post 2021)	955	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	1.1875 (0.36489, 3.864640)	105 per 10,000 people	20 more events per 10,000 people, 117 fewer to 156 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 11 events per 10,000 people

Pulmonary embolism at end of trial (non-randomised), study types: non-randomised studies, scale: not applicable, units: not applicable	3	177750	Risk of bias: Serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Not serious Other considerations: None	Moderate	Risk Ratio	0.920040 (0.80244, 1.05487)	48 per 10,000 peopl e	4 fewer events per 10,000 people, 10 fewer to 2 fewer No clinically important differenc e	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROBINS-I	MID (clinical importance) = 5 events per 10,000 people

Deep vein thrombosis at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Post 2021)	955	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	0.19792 (0.00953, 4.111680)	42 per 10,000 people	42 fewer events per 10,000 people, 100 fewer to 16 more Clinically important benefit	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 5 events per 10,000 people

Deep vein thrombosis at end of trial (non-randomised), study types: non-randomised studies, scale: not applicable, units: not applicable	1 (Thapaliya 2024)	144344	Risk of bias: Serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Serious Other considerations: None	Very low	Risk Ratio	0.85573 (0.76808, 0.95338)	98 per 10,000 people	14 fewer events per 10,000 people, 24 fewer to 4 fewer Clinically important benefit	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROBINS-I Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Serious imprecision because 95%	MID (clinical importance) = 10 events per 10,000 people

									CI crosses 1 MID (RR 0.8-1.25)	

Myocardial infarction at end of trial (non-randomised), study types: randomised trials, scale: not applicable, units: not applicable	3	177750	Risk of bias: Serious Indirectness: Not serious Inconsistency: Very serious Imprecision: Serious Other considerations: None	Very low	Risk Ratio	1.205420 (0.99996, 1.45311)	85 per 10,000 people	19 more events per 10,000 people, 10 more to 28 more Clinically important harm	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROBINS-I Inconsistency: Downgraded twice. Very serious heterogeneity (serious I2 = >60%) unexplained by subgroup analysis. Random effects analysis used Serious imprecision because 95%	MID (clinical importance) = 9 events per 10,000 people

									CI crosses 1 MID (RR 0.8-1.25)	

Ischaemic stroke at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Post 2021)	955	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	1.20949 (0.65727, 2.225680)	379 per 10,000 people	79 more events per 10,000 people, 185 fewer to 344 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 38 events per 10,000 people

Ischaemic stroke at end of trial (non-randomised), study types: non-randomised studies, scale: not applicable, units: not applicable	3	39512	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Serious Other considerations: None	Moderate	Risk Ratio	1.27343 (1.04903, 1.54584)	92 per 10,000 people	25 more events per 10,000 people, 5 more to 46 more Clinically important harm	Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 10 events per 10,000 people

All-cause readmission at end of trial (non-randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Hsu 2024)	7301	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations: None	Very low	Odds Ratio	1.15 (0.352740, 3.74917)	19 per 10,000 people	3 fewer events per 10,000 people, 18 fewer to 23 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 2 events per 10,000 people

Infection at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Post 2021)	530	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Serious Other considerations: None	Low	Odds Ratio	0.77605 (0.53286, 1.13022)	1202 per 10,000 people	159 more events per 10,000 people, 485 fewer to 803 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 121 events per 10,000 people

Infection at end of trial (non-randomised), study types: non-randomised studies, scale: not applicable, units: not applicable	2	151645	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Very serious Other considerations: None	Low	Odds Ratio	1.15292 (0.6917, 1.921660)	76 per 10,000 people	21 fewer event per 10,000 people, 29 fewer to 13 fewer Clinically important benefit	Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 8 events per 10,000 people

Seizures at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Post 2021)	955	Risk of bias: Serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Serious Other considerations: None	Very low	Risk Ratio	1.459640 (0.99733, 2.13624)	842 per 10,000 people	387 more events per 10,000 people, 49 fewer to 823 more Clinically important harm	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROB 2 Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Serious imprecision because 95%	MID (clinical importance) = 85 events per 10,000 people

									CI crosses 1 MID (RR 0.8-1.25)	

Seizures at end of trial (non-randomised), study types: non-randomised studies, scale: not applicable, units: not applicable	4	43341	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	1.51881 (0.7921, 2.91223)	26 per 10,000 people	21 more event per 10,000 people, 10 more to 33 more Clinically important harm	Inconsistency: Downgraded once. Serious heterogeneity (I2 = 40 to 60%) unexplained by subgroup analysis. Random effects analysis used Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 3 events per 10,000 people

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2 F.1.3 **Tranexamic acid (higher dose) compared to tranexamic acid (lower dose)**

3 **Table 3 Effectiveness evidence summary: tranexamic acid (higher dose) compared to tranexamic acid (lower dose)**

Outcome	Number of studies	Sample size	GRADE components	GRADE	Effect measure	Effect size	Control group rate	Absolute effect	Reasons	Minimally important difference

All-cause mortality at end of trial (randomised), study types: randomised trials, scale: risk ratio, units: not applicable	1 (Shi 2020)	3031	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	0.88879 (0.36218, 2.18109)	66 per 10,000 people	7 fewer events per 10,000 people, 64 fewer to 49 more No clinically important difference	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 10 events per 10,000 people

All-cause mortality at end of trial (non-randomised), study types: non-randomised studies, scale: risk ratio, units: not applicable	2	24916	Risk of bias: Serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Serious Other considerations: None	Low	Risk Ratio	0.87141 (0.61871, 1.22733)	56 per 10,000 people	7 fewer events per 10,000 people, 25 fewer to 11 more No clinically important difference	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROBINS-I Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 10 events per 10,000 people

Pulmonary embolism at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Shi 2020)	3031	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations : None	Very low	Risk Ratio	2.96265 (0.12079, 72.66788)	0 per 10,000 people	7 more events per 10,000 people, 6 fewer to 19 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 0 events per 10,000 people

Pulmonary embolism at end of trial (non-randomised), study types: non-randomised studies, scale: not applicable, units: not applicable	2	24916	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Very serious Other considerations: None	Low	Risk Ratio	0.99731 (0.47169, 2.10868)	11 per 10,000 people	0 fewer events per 10,000 people, 8 fewer to 8 more No clinically important difference	Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 2 events per 10,000 people

Deep vein thrombosis at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Shi 2020)	3031	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	1.23443 (0.57976, 2.62833)	80 per 10,000 people	19 more events per 10,000 people, 49 fewer to 86 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 8 events per 10,000 people

Myocardial infarction at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Shi 2020)	3031	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Not serious Other considerations: None	Moderate	Risk Ratio	1.01711 (0.83218, 1.24313)	1109 per 10,000 people	19 more events per 10,000 people, 229 fewer to 266 more No clinically important difference	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default	MID (clinical importance) = 111 events per 10,000 people

Myocardial infarction at end of trial (non-randomised), study types: non-randomised studies, scale: not applicable, units: not applicable	2	24916	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Not serious Other considerations: None	High	Risk Ratio	1.06972 (0.95879, 1.19348)	473 per 10,000 people	33 more events per 10,000 people, 23 fewer to 89 more No clinically important difference	No downgrading required	MID (clinical importance) = 48 events per 10,000 people

Ischaemic stroke at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Shi 2020)	3031	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	1.23443 (0.48853, 3.11917)	53 per 10,000 people	12 more events per 10,000 people, 43 fewer to 67 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 6 events per 10,000 people

Ischaemic stroke at end of trial (non-randomised), study types: non-randomised studies, scale: not applicable, units: not applicable	2	24916	Risk of bias: Serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Serious Other considerations: None	Low	Risk Ratio	1.10619 (0.85877, 1.42489)	91 per 10,000 people	10 more events per 10,000 people, 15 fewer to 34 more Clinically important harm	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROBINS-I Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 10 events per 10,000 people

Seizures at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Shi 2020)	3031	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Serious Other considerations: None	Low	Risk Ratio	2.46885 (0.96048, 6.346)	40 per 10,000 people	59 more events per 10,000 people, 1 fewer to 118 more Clinically important harm	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 4 events per 10,000 people

Seizures at end of trial (non-randomised), study types: randomised trials, scale: not applicable, units: not applicable	3	27969	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Not serious Other considerations: None	High	Risk Ratio	2.21555 (1.49222, 3.28949)	35 per 10,000 people	18 more events per 10,000 people, 2 fewer to 34 more Clinically important harm	No downgrading required	MID (clinical importance) = 4 events per 10,000 people

Reoperation at end of trial (randomised), study types: randomised trials, scale: not applicable, units: not applicable	1 (Shi 2020)	3031	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	0.75241 (0.394180, 1.436220)	139 per 10,000 people	35 fewer events per 10,000 people, 113 fewer to 44 more Clinically important benefit	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 14 events per 10,000 people

F.2 Women, trans men and non-binary people at short term risk of blood loss

F.2.1 Tranexamic acid compared to placebo

Table 4 Effectiveness evidence summary: tranexamic acid compared to placebo

Outcome	Number of studies	Sample size	GRADE components	GRADE	Effect measure	Effect size	Control group rate	Absolute effect	Reasons	Minimally important difference

All-cause mortality at end of trial, study types: randomised trials, scale: risk ratio, units: not applicable	4	67570	Risk of bias: Serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Serious Other considerations: None	Low	Risk Ratio	0.76797 (0.62557, 0.94278)	62 per 10,000 people	14 fewer events per 10,000 people, 25 fewer to 3 fewer Clinically important benefit	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROB 2 and ROBIS Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 10 events per 10,000 people

Thromboembolic events after surgery at end of trial, study types: randomised trials, scale: risk ratio, units: not applicable	5	68612	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Very serious Other considerations: None	Low	Risk Ratio	0.91518 (0.64903, 1.29048)	20 per 10,000 people	2 fewer events per 10,000 people, 8 fewer to 5 fewer Clinically important benefit	Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 1 events per 10,000 people

Pulmonary embolism at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	3	47797	Risk of bias: Serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	0.804860 (0.42475 , 1.52512)	9 per 10,000 people	2 fewer events per 10,000 people, 7 fewer to 3 fewer Clinically important benefit	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROB 2 and ROBIS Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 1 events per 10,000 people

Deep vein thrombosis at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	3	47797	Risk of bias: Serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	0.847500 (0.38601, 1.86068)	5 per 10,000 people	1 fewer event per 10,000 people, 5 fewer to 3 fewer Clinically important benefit	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROB 2 and ROBIS Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 1 events per 10,000 people

Myocardial infarction at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	4	68729	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Very serious Other considerations: None	Low	Risk Ratio	1.34093 (0.38885, 4.62416)	1 per 10,000 people	1 fewer event per 10,000 people, 1 fewer to 2 fewer Clinically important benefit	Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 1 events per 10,000 people

Ischaemic stroke at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	3	67505	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Very serious Other considerations: None	Low	Risk Ratio	1.84654 (0.70699 , 4.82285)	2 per 10,000 people	2 fewer events per 10,000 people, 1 fewer to 4 fewer Clinically important benefit	Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 1 events per 10,000 people

Infection at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	2	60274	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious Imprecision: Serious Other considerations: None	Low	Risk Ratio	1.1250 (0.8917, 1.4195)	109 per 10,000 people	12 more events per 10,000 people, 5 fewer to 29 more Clinically important harm	Inconsistency: Downgraded once. Serious heterogeneity (I2 = 40 to 60%) unexplained by subgroup analysis. Random effects analysis used Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 11 events per 10,000 people

All-cause readmission at end of trial, study types: randomised trials, scale: not applicable, units: not applicable	3	15635	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Serious Other considerations: None	Moderate	Risk Ratio	1.18695 (0.97947 , 1.43837)	237 per 10,000 people	46 more events per 10,000 people, 5 fewer to 97 more Clinically important harm	Serious imprecision because 95% CI crosses 1 MID (RR 0.8-1.25)	MID (clinical importance) = 24 events per 10,000 people

Seizures at end of trial, study types: randomised trials, scale: risk ratio, units: not applicable	5	69800	Risk of bias: Serious Indirectness: Not serious Inconsistency: Not serious Imprecision: Very serious Other considerations: None	Very low	Risk Ratio	1.01683 (0.682, 1.51604)	14 per 10,000 people	0 fewer events per 10,000 people, 5 fewer to 6 more No clinically important difference	Risk of bias: Downgraded once. Serious risk of bias in the evidence contributing to the outcomes. More than 50% of the weight of the evidence came from studies at moderate or high risk of bias as per ROB 2 and ROBIS Very serious imprecision because 95% CI crosses 2 MIDs (RR 0.8-1.25)	MID (clinical importance) = 2 events per 10,000 people

Reoperation at end of study, study types: randomised trials, scale: not applicable, units: not applicable	1 (Pachecho 2023)	10065	Risk of bias: Not serious Indirectness: Not serious Inconsistency: Serious - single study Imprecision: Not serious Other considerations: None	Moderate	Risk Ratio	0.99413 (0.83225, 1.1875)	462 per 10,000 people	3 fewer events per 10,000 people, 88 fewer to 82 more No clinically important difference	Inconsistency: Single study-downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default	MID (clinical importance) = 47 events per 10,000 people

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Appendix G Excluded studies

Effectiveness

Table 5 Studies excluded from the effectiveness review

Study	Reason for exclusion
Ageron, Francois-Xavier, Gayet-Ageron, Angele, Ker, Katharine et al. (2020) Effect of tranexamic acid by baseline risk of death in acute bleeding patients: a meta-analysis of individual patient-level data from 28 333 patients. British journal of anaesthesia 124(6): 676-683	- Systematic review where included trials are already included by another systematic review *CRASH-2 and WOMAN - other systematic review includes these trials and additional outcomes have been extracted already from these trials so no additional information to be gained from including this review*
Ageron, Francois-Xavier; Shakur-Still, Haleema; Roberts, Ian (2022) Effects of tranexamic acid treatment in severely and non-severely injured trauma patients. Transfusion 62suppl1: 151-s157	- Systematic review where included trials are already included by another systematic review *CRASH-2 and CRASH-3 - already reported in another systematic review and additional outcomes have been extracted so no additional data to be gained from this review*
Akosman, Izzet, Lovecchio, Francis, Fourman, Mitchell et al. (2023) Is High-Dose Tranexamic Safe in Spine Surgery? A Systematic Review and Meta-Analysis. Global spine journal 13(7): 2085-2095	- Sample size of studies is below 500 people per arm
Bazeer, N., Miners, A., Roberts, I. et al. (2022) Economic evaluation of tranexamic acid for the treatment of acute gastrointestinal bleeding: a cost-effectiveness analysis using data from the HALT-IT randomised controlled trial. BMJ Open 12(7): e060505	- Economic analysis only
Calderon Martinez, Ernesto, Briceno Silva, Gabriela D, Sanchez Cruz, Camila et al. (2025) Tranexamic acid as treatment for acute gastrointestinal bleeding: A comprehensive systematic review and meta-analysis. Indian journal of gastroenterology : official journal of the Indian Society of Gastroenterology 44(3): 311-329	- Systematic review used as source of primary studies *Relevant studies already included. People with active gastrointestinal bleeding so in a lot of cases studies were not relevant.*
Chowdhury, Debkumar (2023) To Assess the Outcomes Associated With the Use of Tranexamic Acid in the Open Fixation of Pelvic and	- Sample size of studies is below 500 people per arm

Study	Reason for exclusion
Acetabular Fractures. Cureus 15(4): e38232	
Couture P, Lebon JS, Laliberté É et al. (2017) Low-Dose Versus High-Dose Tranexamic Acid Reduces the Risk of Nonischemic Seizures After Cardiac Surgery With Cardiopulmonary Bypass. Journal of cardiothoracic and vascular anesthesia 31(5): 1611-1617	- Study does not account for key confounding variables
Dang, Xiangji, Liu, Mei, Yang, Qiang et al. (2024) Tranexamic acid may benefit patients with preexisting thromboembolic risk undergoing total joint arthroplasty: a systematic review and meta-analysis. EFORT open reviews 9(6): 467-478	- Sample size of studies is below 500 people per arm *Majority of studies were below 500 participants in each arm with no subgroup analysis to investigate the difference in removing these studies. Also limited population for people undergoing total joint arthroplasty only.*
Djoudjou, T, Alamri, O, Aljuwayr, A et al. (2025) Intravenous tranexamic acid in gastrointestinal bleeding: A systematic review and meta-analysis of randomized controlled trials. The American journal of emergency medicine 97: 175-182	- Sample size of studies is below 500 people per arm *Includes the HALT-IT RCT which has over 500 people per arm. However, this is the only study that does, and it does not have a subgroup analysis for different sample sizes.*
Durand-Zaleski, I, Deneux-Tharaux, C, Seco, A et al. (2021) An economic evaluation of tranexamic acid to prevent postpartum haemorrhage in women with vaginal delivery: the randomised controlled TRAAP trial. BJOG : an international journal of obstetrics and gynaecology 128(1): 114-120	- Economic analysis only
Falbe-Hansen J; Jacobsen B; Lorenzen E (1974) Local application of an antifibrinolytic in tonsillectomy. A double-blind study. The Journal of laryngology and otology 88(6): 565-568	- Reports efficacy outcomes only *Study only reports efficacy outcomes (discussing bleeding) rather than safety outcomes specified in the protocol*
Houston, Brett L, Uminski, Kelsey, Mutter, Thomas et al. (2020) Efficacy and Safety of Tranexamic Acid in Major Non-Cardiac Surgeries at High Risk for Transfusion: A Systematic Review and Meta-Analysis. Transfusion medicine reviews 34(1): 51-62	- Sample size of studies is below 500 people per arm *Subgroup analysis reported based on sample size, but only for efficacy outcomes.*
Huang, Honghao, Xin, Mei, Wu, Xiqiang et al. (2022) The efficacy of tranexamic acid treatment with different time and doses for traumatic brain injury: a systematic review and	- Sample size of studies is below 500 people per arm *Systematic review without a subgroup for sample size, citations checked. No additional studies to add.*

Study	Reason for exclusion
meta-analysis. Thrombosis journal 20(1): 79	
Ker, Katharine, Mansukhani, Raoul, Shakur-Still, Haleema et al. (2023) Tranexamic acid for gastrointestinal bleeding: can a reduction in the risk of death be discounted? A systematic review and meta-analysis of individual patient data from 64 724 bleeding patients. BMJ open 13(2): e059982	- Systematic review where included trials are already included by another systematic review *CRASH-2, WOMAN, CRASH-3 and HALT-IT (which was not included). Additional outcomes had been extracted so nothing additional to gain. HALT-IT shall be added and extracted.*
Ker, Katharine, Shakur-Still, Haleema, Sentilhes, Loic et al. (2023) Tranexamic acid for the prevention of postpartum bleeding: Protocol for a systematic review and individual patient data meta-analysis. Gates open research 7: 3	- Protocol only
Lin, Yu-Cheng, Wang, Tsu-Hsien, Kang, Yi-No et al. (2025) Effect of tranexamic acid on children with traumatic bleeding: A systematic review and meta-analysis. The American journal of emergency medicine 97: 65-71	- Less than 500 participants in each study arm or systematic review without a subgroup analysis for studies with different sample sizes *Mixture of studies with over 500 participants in each arm and less than 500 participants with no subgroup analysis based on sample size. Citations checked and relevant studies included.*
Marcucci, Maura, Painter, Thomas W, Conen, David et al. (2022) Rationale and design of the PeriOperative ISchemic Evaluation-3 (POISE-3): a randomized controlled trial evaluating tranexamic acid and a strategy to minimize hypotension in noncardiac surgery. Trials 23(1): 101	- Protocol only
Murao, Shuhei, Nakata, Hidekazu, Roberts, Ian et al. (2021) Effect of tranexamic acid on thrombotic events and seizures in bleeding patients: a systematic review and meta-analysis. Critical care (London, England) 25(1): 380	- Does not contain a population of people after surgery *Contains people after surgery, trauma, post-partum haemorrhage, spontaneous intracranial haemorrhage and gastrointestinal haemorrhage - given indirectness is not ideal candidate for inclusion*
Post, Rene, Germans, Menno R, Coert, Bert A et al. (2020) Update of the ULtra-early TRranexamic Acid after Subarachnoid Hemorrhage (ULTRA) trial: statistical analysis plan. Trials 21(1): 199	- Protocol only
Prejbeanu, Radu, Mioc, Mihail Lazar, Tsiridis, Eleftherios et al. (2025) The Influence of Tranexamic Acid (TXA) on Postoperative Infection Rates Following Total Hip Arthroplasty	- Systematic review used as source of primary studies *Review includes a study with less than 500 participants in each study arm without a subgroup analysis based on sample size. Other studies are*

Study	Reason for exclusion
(THA)-A Systematic Review. Journal of clinical medicine 14(9)	*non-randomised studies with more than 500 participants in each study arm.*
Rangwala, H.S., Rangwala, B.S., Alotaibi, M. et al. (2025) Clinical Outcomes with High- versus Low-Dose Tranexamic Acid Infusion in Patients Undergoing Cardiac Surgery: A Systematic Review and Meta-Analysis. Thoracic and Cardiovascular Surgeon	- Less than 500 participants in each study arm or systematic review without a subgroup analysis for studies with different sample sizes *Includes some studies with more than 500 participants and some with less with no subgroup analysis. Citations checked and added to review if relevant.*
P.S. Rashmi, T.R. Sudha, Prabhudev Prema PRAV (2010) Role of Tranexamic acid in reducing blood loss during and after cesarean section a randomized case control prospective study. Journal of medical research and practice: 40-3	- Full text paper not available
Roberts, Ian, Shakur-Still, Haleema, Aeron-Thomas, Amy et al. (2021) Tranexamic acid to reduce head injury death in people with traumatic brain injury: the CRASH-3 international RCT. Health technology assessment (Winchester, England) 25(26): 1-76	- Primary study already included in a systematic review *No additional data to add.*
Roberts, Ian, Shakur-Still, Haleema, Afolabi, Adefemi et al. (2021) A high-dose 24-hour tranexamic acid infusion for the treatment of significant gastrointestinal bleeding: HALT-IT RCT. Health technology assessment (Winchester, England) 25(58): 1-86	- Primary study already included and no additional data to add *No additional data to add.*
Rohwer, Christa, Rohwer, Anke, Cluver, Catherine et al. (2024) Tranexamic acid for preventing postpartum haemorrhage after caesarean section. The Cochrane database of systematic reviews 11: cd016278	- Less than 500 participants in each study arm or systematic review without a subgroup analysis for studies with different sample sizes *Checked for relevant citations which were included in the review.*
Sentilhes, Loic, Benard, Antoine, Madar, Hugo et al. (2023) Tranexamic acid for reduction of blood loss after Caesarean delivery: a cost-effectiveness analysis of the TRAAP2 trial. British journal of anaesthesia 131(5): 893-900	- Economic analysis only
Sentilhes, Loic, Senat, Marie V, Le Lous, Maela et al. (2021) Tranexamic Acid for the Prevention of Blood Loss after Cesarean	- Primary study already included in a systematic review *Included in an individual patient data systematic review which included all relevant outcomes and more individual person data.*

Study	Reason for exclusion
Delivery. The New England journal of medicine 384(17): 1623-1634	
Sentilhes, L., Sénat, Marie V., Le Lous, Maela et al. (2018) Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. The New England journal of medicine 379(8): 731-742	- Primary study already included in a systematic review *Included in an individual patient data systematic review which included all relevant outcomes and more individual person data.*
Shakur, Haleema, Roberts, Ian, Fawole, Bukola et al. (2017) Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet (London, England) 389(10084): 2105-2116	- Primary study already included in a systematic review *Included in an individual patient data systematic review which included all relevant outcomes and more individual person data.*
Shi, Jia, Zhou, Chenghui, Liu, Sheng et al. (2020) Outcome impact of different tranexamic acid regimens in cardiac surgery with cardiopulmonary bypass (OPTIMAL): Rationale, design, and study protocol of a multicenter randomized controlled trial. American heart journal 222: 147-156	- Protocol only
Sprigg, Nikola, Flaherty, Katie, Appleton, Jason P et al. (2019) Tranexamic acid to improve functional status in adults with spontaneous intracerebral haemorrhage: the TICH-2 RCT. Health technology assessment (Winchester, England) 23(35): 1-48	- Primary study already included in a systematic review *No additional data to add.*
Tran, A., Fernando, S.M., Rochwerg, B. et al. (2024) Prognostic factors associated with venous thromboembolism following traumatic injury: A systematic review and meta-analysis. Journal of Trauma and Acute Care Surgery 97(3): 471	- Does not contain a population of people at risk of bleeding *Systematic review investigating prognostic factors associated with VTE after traumatic injury rather than about tranexamic acid use specifically.*
Tsan, S E H, Viknaswaran, N L, Cheong, C C et al. (2023) Prophylactic intravenous tranexamic acid and thromboembolism in non-cardiac surgery: a systematic review, meta-analysis and trial sequential analysis. Anaesthesia 78(9): 1153-1161	- Sample size of studies is below 500 people per arm *Lots of studies with less than 500 people in each arm with no subgroup analysis to separate the studies where there are more participants from those with less.*
Vishal, A.K., Aggarwal, M.K., Sharma, S.K. et al. (2023) SAFETY AND EFFICACY OF PROPHYLACTIC TRANEXANIC	- Less than 500 participants in each study arm or systematic review without a subgroup analysis for studies with different sample sizes

Study	Reason for exclusion
ACID IN REDUCING BLOOD LOSS DURING AND AFTER CAESAREAN DELIVERY: A COMPARATIVE STUDY. International Journal of Academic Medicine and Pharmacy 5(3): 407	*Slightly less than 500 participants in each study arm and all relevant outcomes report 0 events in both arms so does not have a sufficient number of participants to be powered to investigate the outcomes. Given this, it is considered to not be relevant to include as indirect evidence as it will not add anything useful to the evidence that is already included.*
WOMAN-2 Trial, Collaborators (2024) The effect of tranexamic acid on postpartum bleeding in women with moderate and severe anaemia (WOMAN-2): an international, randomised, double-blind, placebo-controlled trial. Lancet (London, England) 404(10463): 1645-1656	- Primary study already included in a systematic review *Included in an individual patient data systematic review which included all relevant outcomes and more individual person data.*
Zufferey, Paul Jacques, Lanoiselee, Julien, Graouch, Billal et al. (2021) Exposure-Response Relationship of Tranexamic Acid in Cardiac Surgery. Anesthesiology 134(2): 165-178	- Systematic review with a different outcome to the protocol *Focussing on efficacy outcome and seizure risk and looking at dose exposure as the major comparison. Not relevant to the protocol for this review.*

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