National Institute for Health and Care Excellence

Blood transfusion (update)

[B] Evidence review for safety of tranexamic acid during surgery

NICE guideline NG24

Evidence underpinning recommendations 1.1.5 to 1.1.11 and research recommendations

November 2025

Draft for Consultation

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Contents

Safety of tranexamic acid during surgery

1.1 Review question

This evidence review summarises the evidence for:

What is the safety of tranexamic acid for the short-term management of surgical bleeding?

Further technical detail can be found in the separate technical appendices for this review.

1.1.1 Summary of the protocol

Table 1: Summary of the protocol (PICOS)

Population	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 short-term bleeding
Interventions	Tranexamic acid (all doses and routes of administration pooled together)
Comparator	• An additional therapy (with potential vascular activity, this includes other antifibrinolytic therapies) (tranexamic acid and surgery compared to a different treatment and surgery) • Placebo (for example: saline, dextrose) (tranexamic acid and surgery compared to placebo and surgery) • Usual care (no treatment in addition to surgery) (tranexamic acid and surgery compared to surgery) Other comparators: (These comparators will be reported if subgroup analysis if 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)

Outcomes	• 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
Study type	1) Systematic reviews of randomised and non-randomised studies 2) Randomised controlled trials (RCTs) 3) Non-randomised controlled trials/prospective cohort studies 4) 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 and onwards.
Key confounders	• Age • Sex • Comorbidities

Abbreviations: RCTs (randomised controlled trials)

For the full protocol see **appendix A** in the technical appendices document.

1.1.2 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol and in section 1.1.2.2. General methods are described in the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.2.1 Search methods

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 in appendix B 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

1.1.2.2 Methods specific to this review

This review integrates findings from two other systematic reviews. One individual patient data systematic review conducted by Ker, et al 2024 and one systematic review conducted by Taeuber, et al 2021.

The Ker, et al 2024 review was identified as it was an individual patient data systematic review that only included studies with over 500 participants in each treatment arm. While it was recognised that it did not include every potentially relevant study, the richness of the data that would not be achievable within our time constraints was valuable and so this review results were integrated into the analysis without further analysis of the included studies.

The Taeuber, et al 2021 review was identified in the search for the review having fulfilled the criteria of including a subgroup analysis which restricted by sample size. The studies identified by this were then checked for additional outcomes that were relevant to the protocol for the NICE review that were not included in the Taeuber, et al 2021 review. The analyses were then redone

using the methods and processes described in Developing NICE guidelines: the manual and it was presented to the committee for their consideration.

Minimally important differences were decided by the committee a priori by:

- Searching literature for any pre-established minimally important difference values
- Revisiting decisions made by previous guideline committees in this area
- Through committee deliberation

For precision, the committee agreed that a 25% variation in a value would be clinically important. They agreed that this would apply to each outcome. Given this, the differences used for a risk ratio and a hazard ratio were 0.8-1.25.

For determining clinically important differences, the committee used a point estimate of the absolute effect for the intervention studies. They considered two factors when determining the outcome: the baseline rate of the outcome and the impact of the event on the person with the condition. Based on this they agreed that some outcomes required lower thresholds for clinical importance due to their potential impact (for example: mortality), while others may have higher thresholds based on the events being more common at baseline and so a larger absolute effect being required (for example: readmission). The baseline rates for the outcomes were determined from searching literature values. The minimally important differences were:

- All-cause mortality – 1 per 1,000
- Thromboembolic events after surgery – 2% of the baseline control rate
- All other outcomes – 10% of the baseline control rate

1.1.3 Effectiveness evidence

1.1.3.1 Included studies

Study selection

A systematic search was carried out to identify potentially relevant studies as detailed in the methods document. See **appendix B** in the technical

appendices document for the literature search strategy. The study selection process is presented as a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram in **appendix C** in the technical appendices document.

2 systematic reviews were included. The first (Ker, et al 2024) included 5 randomised controlled trial (RCT) studies. The other (Taueber, et al 2021) included 216 studies, but only 7 RCTs included at least 500 participants in each study arm and were included. 1 study only included 500 participants in 1 study arm when 2 arms were combined, this study was included but considered indirect for the analysis).

A further search was conducted to identify randomised controlled trials. This identified an additional 8 RCTs. A further search was not conducted for non-randomised studies. Instead, relevant non-randomised studies were identified by citation searching of included study lists from relevant systematic reviews. This identified 6 non-randomised studies.

In total, 2 systematic reviews, 20 RCTs, 5 of which are included in a systematic review and so are not counted towards the number of studies in the PRISMA diagram and 6 non-randomised studies were included. 1 additional paper was included in the review that included follow-up data for 1 RCT bringing the total included papers to 24. The included studies are summarised in Table 2, 3 and 4. For more details about the 5 RCTs included in the Ker, et al 2024 systematic review, please check the relevant study.

1.1.3.2 Excluded studies

Details of studies excluded at full text, along with the primary reason for exclusion, are given in **appendix I** in the technical appendices document.

1.1.4 Summary of studies included in the effectiveness evidence

Table 2 Summary of systematic reviews included in the effectiveness evidence

Study details	Population	Intervention	Comparator	Outcomes
Ker, Katharine (2024) Not applicable Study type: Systematic review with individual patient data (IPD) Setting: Not applicable Location: Not applicable Funding source: Academic or government grant support Risk of bias: Low	N = 54393 Number of studies = 5 Pregnant women, trans men and non-binary people at short term risk of bleeding Subgroup 1 (speciality): Considered Subgroup 2 (anticoagulant use): Not applicable Subgroup 3 (comorbidities): Not applicable Subgroup 7 (renal impairment): Not applicable	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. Subgroup 4 (dose): 1 gram - 2 grams Subgroup 5 (route): Considered Subgroup 6 (repeated use): Considered	Placebo (n=27093) Intravenous normal saline in the same procedure as the intervention arm.	Thromboembolic events after surgery; All-cause mortality; Pulmonary embolism; Deep vein thrombosis; Myocardial infarction; Ischaemic stroke; Infection; Seizure Follow up: 82 days
Taeuber I (2021) Not applicable	N = 65900 Number of studies = 216	Tranexamic acid (n=33487) Intravenous tranexamic	Control (n=32413) Placebo or usual care (no treatment)	Deep vein thrombosis; Pulmonary embolism; Thromboembolic events

Study details	Population	Intervention	Comparator	Outcomes
Study type: Systematic review Setting: Not applicable Location: Not applicable Funding source: Other author funded by a private organisation Risk of bias: Moderate	Adults (age at least 16 years) and children (age less than 16 years) at short term risk of bleeding Subgroup 1 (speciality): Considered Subgroup 2 (anticoagulant use): Not applicable Subgroup 3 (comorbidities): Considered Subgroup 7 (renal impairment): Not applicable	acid (with or without additional oral or topical tranexamic acid) with anaesthetic medication during surgery Subgroup 4 (dose): Not applicable Subgroup 5 (route): Not applicable Subgroup 6 (repeated use): Not applicable		after surgery; All-cause mortality Follow up: 1 days

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Table 34 Summary of randomised controlled trials included in the effectiveness evidence

Study details	Population	Intervention	Comparator	Outcomes
CRASH-3 trial collaborators, The (2019) CRASH-3 Study type: Randomised controlled trial (RCT) Setting: Ambulance; A&E; Inpatient: non-elective Location: Multicentre Funding source: Academic or government grant support	N = 12737 Adults (age at least 16 years) at short term risk of bleeding Subgroup 1 (speciality): Trauma Subgroup 2 (anticoagulant use): Not stated/unclear Subgroup 3 (comorbidities): Not stated/unclear Subgroup 7 (renal impairment): Not stated/unclear	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. Subgroup 4 (dose): 2 grams Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Repeated use 1 bolus, 1 infusion	Placebo (n=6331) Matching placebo.	Thromboembolic events after surgery; Pulmonary embolism; Deep vein thrombosis; Myocardial infarction; Ischaemic stroke; Infection; All-cause mortality; Seizures Follow up: 28 days
Devereaux, P J (2022) POISE-3 Study type: Randomised controlled trial (RCT) Setting: Inpatient: elective and day care; Inpatient: non-elective Location: Multicentre Funding source:	N = 9535 Adults (age at least 16 years) having surgery at short term risk of bleeding Subgroup 1 (speciality): Mixed Non-cardiac Subgroup 2 (anticoagulant	Tranexamic acid (n=4757) 1 gram intravenous tranexamic acid bolus Subgroup 4 (dose): 1 gram Subgroup 5 (route): Intravenous To note, 168 in the intervention arm and 183	Placebo (n=4778) Matching placebo	All-cause mortality; Thromboembolic events after surgery; Pulmonary embolism; Deep vein thrombosis; Myocardial infarction; Ischaemic stroke; Infection; Seizures Follow up: 30 days

Study details	Population	Intervention	Comparator	Outcomes
Academic or government grant support	use): Mixed Around 30% of the population took an anticoagulant or antiplatelet in the 24 hours before surgery Subgroup 3 (comorbidities): Yes In the inclusion criteria for the surgery Subgroup 7 (renal impairment): No impairment From exclusion criteria	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		
Guyette, FX (2020) STAAMP Study type: Randomised controlled trial (RCT) Setting: Ambulance; A&E; Inpatient: non-elective Location: United States of America (USA) Funding source: Academic or government grant support	N = 927 Adults (age at least 16 years) at short term risk of bleeding Subgroup 1 (speciality): Trauma Subgroup 2 (anticoagulant use): No Less than 12% of people receiving preinjury antiplatelet or anticoagulant medicines Subgroup 3	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 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. Subgroup 4 (dose): 1-3	Placebo (n=467) Matching placebo	All-cause mortality; Pulmonary embolism; Deep vein thrombosis; Seizures; Ischaemic stroke; Myocardial infarction; Infection Follow up: 30 days

Study details	Population	Intervention	Comparator	Outcomes
	(comorbidities): Not stated/unclear Subgroup 7 (renal impairment): Not stated/unclear	grams Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Mixed population		
Gwanzura, C (2024) Not applicable Study type: Randomised controlled trial (RCT) Setting: Inpatient: elective and day care; Inpatient: non-elective Location: Zimbabwe Funding source: Academic or government grant support	N = 1226 Pregnant women, trans men and non-binary people having surgery at short term risk of bleeding Subgroup 1 (speciality): Gynaecology Subgroup 2 (anticoagulant use): No Based on exclusion criteria - no anticoagulant in the week before Subgroup 3 (comorbidities): No Based on exclusion criteria Subgroup 7 (renal impairment): Not stated/unclear	Tranexamic acid (n=613) Intravenous tranexamic acid (1 gram) administered over 30-60 second at the time of skin incision. Subgroup 4 (dose): 1 gram Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Single use	Placebo (n=613) Matching placebo.	All-cause mortality; Pulmonary embolism; Deep vein thrombosis; Myocardial infarction; Seizures Follow up: 4 days
HALT-IT trial, Collaborators (2020) HALT-IT	N = 12009 Adults (age at least 16	Tranexamic acid (n=5994) 1 gram tranexamic acid added to 100 mL of 0.9%	Placebo (n=6015) Matching placebo	All-cause mortality; Thromboembolic events after surgery; Pulmonary

Study details	Population	Intervention	Comparator	Outcomes
Study type: Randomised controlled trial (RCT) Setting: Inpatient: non-elective Location: Multicentre Funding source: Academic or government grant support	years) at short term risk of bleeding Subgroup 1 (speciality): General surgery Gastroenterology rather than surgery Subgroup 2 (anticoagulant use): No <10% were taking anticoagulants Subgroup 3 (comorbidities): Mixed population Around 41% had liver comorbidities, 20% had cardiovascular comorbidities, 7% had malignancy, 72% had any comorbidity. Subgroup 7 (renal impairment): No impairment Probably no based on only 5% having renal comorbidities	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. Subgroup 4 (dose): 4 grams People with active bleeding Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Repeated use		embolism; Deep vein thrombosis; Myocardial infarction; Ischaemic stroke; Infection; Seizures Follow up: 28 days
Karanicolas, Paul J (2024) HeLiX	N = 1384 Adults (age at least 16	Tranexamic acid (n=694) Tranexamic acid 1 gram bolus followed by a 1	Placebo (n=690) Matching placebo	All-cause mortality; Pulmonary embolism; Deep vein thrombosis;

Study details	Population	Intervention	Comparator	Outcomes
Study type: Randomised controlled trial (RCT) Setting: Inpatient: elective and day care Location: Canada Funding source: Academic or government grant support	years) having surgery at short term risk of bleeding Subgroup 1 (speciality): General surgery Liver surgery Subgroup 2 (anticoagulant use): No Exclusion criteria Subgroup 3 (comorbidities): Yes All people have a cancer-related indication (from inclusion criteria) Subgroup 7 (renal impairment): No impairment Majority of people had low creatinine, so likely no concerns	gram infusion over 8 hours Subgroup 4 (dose): 2 grams Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Repeated use		Myocardial infarction; Ischaemic stroke; Infection; Reoperation Follow up: 90 days
Myles, Paul S. (2017) ATACAS Study type: Randomised controlled trial (RCT) Setting: Inpatient: elective and day care Location: Multicentre Funding source:	N = 4662 Adults (age at least 16 years) having surgery at short term risk of bleeding Subgroup 1 (speciality): Cardiothoracic Subgroup 2 (anticoagulant	Tranexamic acid (n=2329) Intravenous tranexamic acid 100mg/kg more than 30 minutes after induction of anaesthesia during coronary artery surgery. During the trial, reports of seizures occurring after administration of	Placebo (n=2333) Intravenous 0.9% saline more than 30 minutes after induction of anaesthesia during coronary artery surgery.	All-cause mortality; Thromboembolic events after surgery; Pulmonary embolism; Deep vein thrombosis; Myocardial infarction; Ischaemic stroke; Infection; Seizures; Reoperation

Study details	Population	Intervention	Comparator	Outcomes
Academic or government grant support; Medicine/equipment provided by an organisation for the study	use): No <10% used either warfarin or heparin within 7 days and 24 hours respectively. Subgroup 3 (comorbidities): No <10% had renal impairment, <1% had thrombolysis. Low chance of this. Subgroup 7 (renal impairment): No impairment Renal impairment in 7.5% of people. So <15% of people had renal impairment.	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. Subgroup 4 (dose): 100 mg/kg Average weight 86kg - therefore 8.6 grams. Later in the trial halved to 50 mg/kg. Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Single use		Follow up: 30 days
Pacheco, Luis D (2023) Not applicable Study type: Randomised controlled trial (RCT) Setting: Inpatient: elective and day care Location: United States of America (USA)	N = 11000 Pregnant women, trans men and non-binary people having surgery at short term risk of bleeding Subgroup 1 (speciality): Gynaecology	Tranexamic acid (n=5529) 1 gram tranexamic acid diluted in 40 mL normal saline given over 10 minutes immediately after cord clamping Subgroup 4 (dose): 1 gram	Placebo (n=5471) Matching placebo	All-cause mortality; Thromboembolic events after surgery; Myocardial infarction; Ischaemic stroke; Infection; Seizures; Reoperation; All-cause readmission Follow up: 42 days

Study details	Population	Intervention	Comparator	Outcomes
Funding source: Academic or government grant support	Subgroup 2 (anticoagulant use): No From exclusion criteria Subgroup 3 (comorbidities): No From exclusion criteria Subgroup 7 (renal impairment): Not stated/unclear	Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Single use		
Peng, H. (2020) Not applicable Study type: Randomised controlled trial (RCT) Setting: Inpatient: elective and day care Location: China Funding source: Funding unclear or not specified	N = 1880 Adults (age at least 16 years) having surgery at short term risk of bleeding Subgroup 1 (speciality): Orthopaedics Subgroup 2 (anticoagulant use): Yes Post operative VTE prophylaxis Subgroup 3 (comorbidities): No From exclusion criteria Subgroup 7 (renal impairment): No impairment From exclusion criteria	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. Subgroup 4 (dose): 15 mg/kg or 15 mg/kg intravenous + 1 g/50 mL topical Subgroup 5 (route): Other Either intravenous or	Placebo (n=1160) Matching placebo	Thromboembolic events after surgery; All-cause mortality; Pulmonary embolism; Deep vein thrombosis Follow up: 30 days

Study details	Population	Intervention	Comparator	Outcomes
		intravenous and topical Subgroup 6 (repeated use): Single use		
Post R (2021) ULTRA Study type: Randomised controlled trial (RCT) Setting: Inpatient: non-elective Location: Netherlands Funding source: Academic or government grant support; Other author funded by a private organisation	N = 955 Adults (age at least 16 years) having surgery at short term risk of bleeding Subgroup 1 (speciality): Neurosurgery Subgroup 2 (anticoagulant use): Mixed population Approximately 16% of people used either a platelet inhibitor or anticoagulation Subgroup 3 (comorbidities): Not stated/unclear Subgroup 7 (renal impairment): No impairment Based on exclusion criteria	Usual care (n=475) Usual care only (no additional treatment). Subgroup 4 (dose): 2 grams - 4 grams 2 grams up to 4 grams dependent on the time taken to have the repair Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Repeated use	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).	All-cause mortality; Thromboembolic events after surgery; Pulmonary embolism; Deep vein thrombosis; Ischaemic stroke; Seizures; Infection Follow up: 183 days
Rowell, Susan E. (2020) Prehospital TXA for TBI Trial	N = 1063 Adults (age at least 16 years) and children (age	Tranexamic acid (n=657) Out-of-hospital tranexamic acid 1 gram intravenous bolus, in-	Placebo (n=309) Out-of-hospital placebo intravenous bolus, in-	All-cause mortality; Thromboembolic events after surgery; Pulmonary embolism; Deep vein

Study details	Population	Intervention	Comparator	Outcomes
Study type: Randomised controlled trial (RCT) Setting: Ambulance; A&E; Inpatient: non-elective Location: Multicentre Funding source: Academic or government grant support; Other author funded by a private organisation	less than 16 years) at short term risk of bleeding Subgroup 1 (speciality): Trauma Subgroup 2 (anticoagulant use): Not stated/unclear Subgroup 3 (comorbidities): Not stated/unclear Subgroup 7 (renal impairment): Not stated/unclear	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. Subgroup 4 (dose): 2 grams Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Mixed population Half had a repeated dose split between two administrations (two 1 gram doses), half a single dose (one 2 gram dose)	hospital placebo 8-hour infusion	thrombosis; Myocardial infarction; Ischaemic stroke; Infection; Seizures Follow up: 182 days
Shi, Jia (2022) OPTIMAL	N = 3079	Tranexamic acid (low dose) (n=1534)	Tranexamic acid (high dose) (n=1545)	All-cause mortality; Pulmonary embolism;

Study details	Population	Intervention	Comparator	Outcomes
Study type: Randomised controlled trial (RCT) Setting: Inpatient: elective and day care Location: China Funding source: Academic or government grant support	Adults (age at least 16 years) having surgery at short term risk of bleeding Subgroup 1 (speciality): Cardiothoracic Subgroup 2 (anticoagulant use): Mixed Around 20% could be taking anticoagulants or antiplatelets Subgroup 3 (comorbidities): 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 7 (renal impairment): No impairment <1% of people had chronic kidney dysfunction	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). 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): Intravenous	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).	Deep vein thrombosis; Myocardial infarction; Ischaemic stroke; Seizures; Reoperation Follow up: 30 days

Study details	Population	Intervention	Comparator	Outcomes
		Subgroup 6 (repeated use): Repeated use		
Sprigg, Nikola (2018) TICH-2 Study type: Randomised controlled trial (RCT) Setting: Inpatient: non-elective Location: Multicentre Funding source: Academic or government grant support	N = 2325 Adults (age at least 16 years) at short term risk of bleeding Subgroup 1 (speciality): Neurosurgery Neurology rather than neurosurgery Subgroup 2 (anticoagulant use): Mixed population Around 25% had previously used antiplatelet therapy Subgroup 3 (comorbidities): Mixed population Around 25% had a previous atherosclerotic cardiovascular disease, around 25% were on previous antiplatelet therapy Subgroup 7 (renal impairment): Not stated/unclear	Tranexamic acid (n=1161) 1 gram intravenous tranexamic acid bolus followed by an 8 hour infusion of 1 gram tranexamic acid Subgroup 4 (dose): 2 grams Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Repeated use 1 gram bolus followed by a 1 hour infusion	Placebo (n=1164) Matching placebo	All-cause mortality; Thromboembolic events after surgery; Pulmonary embolism; Deep vein thrombosis; Myocardial infarction; Ischaemic stroke; Infection; Seizures Follow up: 90 days

Study details	Population	Intervention	Comparator	Outcomes
Williams-Johnson, J A (2010) CRASH-2 Study type: Randomised controlled trial (RCT) Setting: A&E; Inpatient: non-elective Location: Multicentre Funding source: Academic or government grant support; Pharmaceutical/private organisation funding	N = 20211 Adults (age at least 16 years) at short term risk of bleeding Subgroup 1 (speciality): Trauma Subgroup 2 (anticoagulant use): Not stated/unclear Subgroup 3 (comorbidities): Not stated/unclear Subgroup 7 (renal impairment): Not stated/unclear	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. Subgroup 4 (dose): 2 grams Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Repeated use 1 gram bolus followed by 1 gram infusion	Placebo (n=10115) Matching placebo	All-cause mortality; Thromboembolic events after surgery; Pulmonary embolism; Deep vein thrombosis; Myocardial infarction; Ischaemic stroke Follow up: 28 days
Zhang P (2024) Zhang 2024 Study type: Randomised controlled trial (RCT) Setting: Inpatient: elective and day care Location: China Funding source: Academic or government grant support	N = 2409 Pregnant women, trans men and non-binary people at short term risk of bleeding Subgroup 1 (speciality): Gynaecology Subgroup 2 (anticoagulant use): Not stated/unclear	Tranexamic acid (n=1202) 1 gram tranexamic acid intravascular infusion immediately after the delivery of the infant Subgroup 4 (dose): 1 gram Subgroup 5 (route): Intravenous	Placebo (n=1207) Matching placebo immediately after the delivery of the infant	Thromboembolic events after surgery; Seizures; All-cause readmission; All-cause mortality Follow up: 90 days

Study details	Population	Intervention	Comparator	Outcomes
	Subgroup 3 (comorbidities): No Based on exclusion criteria Subgroup 7 (renal impairment): No impairment Based on exclusion criteria	Subgroup 6 (repeated use): Single use		

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Table 56 Summary of non-randomised studies included in the effectiveness evidence

Study details	Population	Intervention	Comparator	Outcomes
Hsu YC (2024) Not applicable Study type: Retrospective cohort study Setting: Inpatient: elective and day care Location: Taiwan Funding source: Academic or government grant support	N = 8042 Adults (age at least 16 years) having surgery at short term risk of bleeding Subgroup 1 (speciality): Orthopaedics Subgroup 2 (anticoagulant use): Not stated/unclear Subgroup 3 (comorbidities): Mixed population Subgroup 7 (renal impairment): Mixed population Around 20% had renal failure	Usual care (n=4378) No tranexamic acid Subgroup 4 (dose): Intravenous: 0.25-1.25 grams. Topical: 1.5 grams. Subgroup 5 (route): Intravenous and topical Subgroup 6 (repeated use): Single use	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	Infection; All-cause readmission; Thromboembolic events after surgery Follow up: 90 days
Hulde N (2023) Not applicable Study type: Retrospective cohort study Setting: Inpatient: elective and day care Location: Germany	N = 13293 Adults (age at least 16 years) having surgery at short term risk of bleeding Subgroup 1 (speciality): Cardiothoracic	Usual care (n=3053) No tranexamic acid Subgroup 4 (dose): Median dose 1.9 grams (1.6-3.1 grams) Subgroup 5 (route): Intravenous	Tranexamic acid (low dose) (n=1975) Tranexamic acid dose below 25 mg/kg body weight intravenously Tranexamic acid (high dose) (n=1078)	All-cause mortality; Ischaemic stroke; Seizures Follow up: 30 days

Study details	Population	Intervention	Comparator	Outcomes
Funding source: No funding	Valvular heart surgery Subgroup 2 (anticoagulant use): Perioperative anticoagulation Heparinisation during bypass Subgroup 3 (comorbidities): Mixed population Around 73% of people had hypertension. Subgroup 7 (renal impairment): Not stated/unclear eGFR mean is around 73.2 mL/min/1.73 m2 so some people could have severe renal impairment. Overall unclear.	Subgroup 6 (repeated use): Repeated use	Tranexamic acid dose above and equal to 25 mg/kg body weight intravenously 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).	
Maeda T (2018) Not applicable Study type: Retrospective cohort study Setting: Inpatient: non-elective; A&E Location: Japan	N = 61779 Children at short term risk of bleeding Subgroup 1 (speciality): Paediatric Paediatric trauma	Usual care (n=1914) After matching Subgroup 4 (dose): Not stated/unclear Subgroup 5 (route): Not stated/unclear	Tranexamic acid (n=1914) After matching	All-cause mortality; Thromboembolic events after surgery; Seizures Follow up: 1 days

Study details	Population	Intervention	Comparator	Outcomes
Funding source: Academic or government grant support	Subgroup 2 (anticoagulant use): Not stated/unclear Subgroup 3 (comorbidities): Not stated/unclear Subgroup 7 (renal impairment): Not stated/unclear	Subgroup 6 (repeated use): Not stated/unclear		
Thapaliya A (2024) Not applicable Study type: Retrospective cohort study Setting: Inpatient: elective and day care Location: Multicentre Funding source: No funding	N = 180149 Adults (age at least 16 years) having surgery at short term risk of bleeding Subgroup 1 (speciality): Orthopaedics Subgroup 2 (anticoagulant use): Not stated/unclear Subgroup 3 (comorbidities): Not stated/unclear Subgroup 7 (renal impairment): Not stated/unclear	Usual care (n=72172) No additional information (72237 before matching) Subgroup 4 (dose): Not stated/unclear Subgroup 5 (route): Not stated/unclear Likely intravenous and/or topical Subgroup 6 (repeated use): Not stated/unclear	Tranexamic acid (n=72172) No information about route, dose or repeated use (107912 before matching)	Pulmonary embolism; Deep vein thrombosis; Myocardial infarction; Infection Follow up: 90 days
Wang E (2022) Wang 2022A Study type: Retrospective cohort study	N = 18380 Adults (age at least 16 years) having surgery at short term risk of bleeding	Usual care (n=6184) No tranexamic acid. 7411 people before matching. Subgroup 4 (dose): High	Tranexamic acid (n=6184) 1 gram dose 30 minutes before skin incision at 2 grams/hour and continued at 200-800 mg/hour during	All-cause mortality; Pulmonary embolism; Myocardial infarction; Ischaemic stroke; Seizures

Study details	Population	Intervention	Comparator	Outcomes
Setting: Inpatient: elective and day care Location: China Funding source: Academic or government grant support	Subgroup 1 (speciality): Cardiothoracic Subgroup 2 (anticoagulant 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): Yes Majority of people had a comorbidity that increased the risk of thromboembolic events Subgroup 7 (renal impairment): No impairment Around 7% of people had CKD	dose: median 66.67 (57.69-75.76) mg/kg. Low dose: median 39.68 (34.72-43.87) mg/kg. Subgroup 5 (route): Intravenous Subgroup 6 (repeated use): Repeated use	the entire operation. 10969 people before matching. Low dose tranexamic acid (n=3813) Less than 50 mg/kg. Median dose 39.68 (34.72-43.87) mg/kg. High dose tranexamic acid (n=3813) At least 50 mg/kg. Median dose 66.67 (57.69-75.76) mg/kg.	Follow up: 30 days
Wang, E (2022) Wang 2022B Study type: Retrospective cohort study Setting: Inpatient: elective	N = 21038 Adults (age at least 16 years) having surgery at short term risk of bleeding	Tranexamic acid (low dose) (n=8645) Intravenous tranexamic acid (less than 50 mg/kg) Subgroup 4 (dose): High	Tranexamic acid (high dose) (n=8645) Intravenous tranexamic acid (greater than and equal to 50 mg/kg)	All-cause mortality; Myocardial infarction; Ischaemic stroke; Pulmonary embolism; Seizures

Study details	Population	Intervention	Comparator	Outcomes
and day care; Inpatient: non-elective Location: China Funding source: Academic or government grant support	Subgroup 1 (speciality): Cardiothoracic Subgroup 2 (anticoagulant use): Mixed Around 50% received an anticoagulant or an antiplatelet before surgery Subgroup 3 (comorbidities): 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 7 (renal impairment): No impairment Based on number of people with CKD being less than 10% and eGFR averaging at 90 mL/min/1.73m2	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): Intravenous Subgroup 6 (repeated use): Not stated/unclear	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	Follow up: 30 days

See **appendix D** in the technical appendices document for full evidence tables.

1.1.5 Summary of effectiveness evidence

The high and moderate certainty evidence shows low event rates of all complications with point estimates for thromboembolic events ranging from 14 events fewer per 10,000 people to 28 events more per 10,000 people.

- The highest certainty estimates for thromboembolic events after surgery was moderate certainty showed a reduction of 14 events per 10,000 people when compared to placebo.

- Estimates for myocardial infarction and ischaemic stroke showed a reduction of 14 events per 10,000 people and probably little to no change with 2 events per 10,000 people respectively when compared to placebo.

- An estimate for pulmonary embolism showed that tranexamic acid probably increases the risk by 9 events per 10,000 people when compared to placebo.

All high and moderate certainty sources of evidence showed an important reduction in all-cause mortality events ranging from 21 to 41 fewer events per 10,000 people when compared to placebo.

High certainty evidence showed no or very little difference in rates of infection at 30 more events per 10,000 people. However, evidence for when tranexamic acid was compared to usual care indicated that it probably increases the risk of infection with rates of 159 more events per 10,000.

High certainty evidence indicated a clinically important harm in seizures at 26 more events per 10,000 people from tranexamic acid at higher doses when compared to tranexamic acid at lower doses.

Informative statements were adapted from GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) Guidance 26. See **appendix F** in the technical appendices document for a GRADE summary table containing full details for all outcomes.

1.1.6 Economic evidence

See review A: “Is tranexamic acid clinically and cost-effective in reducing the number of blood transfusions required and length of hospital stay in people with anticipated minor blood loss from surgery compared to placebo or no additional treatment?” for information about the economic evidence for people taking tranexamic acid to prevent short term bleeding during surgery.

1.1.7 Committee discussion and interpretation of the evidence

1.1.7.1 What are the key issues and priorities relating to this question?

Bleeding during and after surgery can vary in significance. For the majority of adults, losing less than 1 unit of blood (500 ml) will likely lead to no important functional effect. However, bleeding a small amount in areas with the lack of room for expansion or where blood can have a toxic effect (for example: brain, eye, neck), can have important effects (for example: stroke, visual loss, airway compromise). Additionally, if their initial haemoglobin was low or if they are more susceptible to adverse effects from blood loss (for example: due to comorbidities) then a small amount of blood loss can be very important and can mean that they require a blood transfusion.

Blood transfusion can be a costly procedure, as blood donation levels are generally lower than the supply available in the UK. It is also associated with potential risks such as transfusion reactions, serious allergic reactions and rarely infection. Therefore, where possible, finding alternatives to blood transfusion so that it can be provided to those who require it the most when they need it is preferable.

In 2015, the blood transfusion guideline recommended to “Offer tranexamic acid to adults undergoing surgery who are expected to have at least moderate blood loss (greater than 500 ml).” It recommended to ‘consider’ tranexamic acid for children with at least moderate blood loss (greater than 10% blood volume). Implementation has been complicated due to multiple factors, including:

- lack of knowledge about the benefits of tranexamic acid
- difficulty assessing amount of expected blood loss ahead of time
- uncertainty about who is responsible for considering administration of the medicine
- concerns over risks from tranexamic acid outweighing benefits.

The committee agreed that the most important outcomes were: all-cause mortality, thromboembolic (arterial and venous) events after surgery, pulmonary embolism, deep vein thrombosis, myocardial infarction, ischaemic stroke, infection, all-cause readmission, seizures and reoperation. All-cause mortality was agreed by committee members with lived experience to be the most important outcome to them. The committee agreed that they wanted to capture a range of thromboembolic events, including proximal and distal, arterial and venous events affecting small and large vessels. They emphasised that there was importance in considering symptomatic events first but also that asymptomatic thromboses and emboli could still be relevant and could provide useful information – they highlighted that this dichotomy would be reflected in the practices of different studies and across different countries. They highlighted that readmission and reoperation were good measures of overall health state and wellness after the procedure. Infection is more likely after surgery and could indicate haematoma formation. Seizures are a concern after tranexamic acid administration as tranexamic acid metabolites can cross the blood brain barrier and cause seizures. This is more likely for people with significant renal impairment.

1.1.7.2 Certainty of evidence and the balance of effects

The evidence ranged from high to very low certainty:

- when compared to placebo, the majority was of moderate certainty
- when compared to usual care, the majority was of very low certainty
- when different doses of tranexamic acid were compared, the majority was of low certainty.

The effects were all small, but due to the nature of the review, small effects were often clinically important (as the minimally important difference was related to the control group event rate).

When compared to placebo (when a range of values are shown, this indicates different values found when studies providing hazard ratios are used to

determine the values compared to when studies providing data used to inform risk ratios are used), this showed:

- clinically important desirable effects on all-cause mortality (21-41 fewer events per 10,000 people) and reoperations (108 fewer events per 10,000 people)
- clinically important undesirable effects on deep vein thrombosis (9-11 more events per 10,000 people) and seizures (15-26 more events per 10,000 people)
- no clinically important difference in infection (30 more events per 10,000 people)
- inconsistent results on thromboembolic events after surgery (14 fewer to 28 more per 10,000 people), pulmonary embolism (17 fewer to 9 more per 10,000 people), myocardial infarction (14 fewer to 30 more per 10,000 people), ischaemic stroke (2 fewer to 17 more per 10,000 people).

The results compared to usual care were inconsistent with those comparing to placebo. This included a mixture of randomised and non-randomised studies which may have affected the interpretation and applicability of the results.

The results comparing different doses of tranexamic acid to each other showed the there was a higher risk of seizures at higher doses compared to lower doses (18 more events per 10,000 people) based on high certainty data.

The evidence for pregnant women, trans men and non-binary people indicated differences when compared to placebo:

- clinically important desirable effects on all-cause mortality (14 fewer events per 10,000 people), thromboembolic events after surgery (2 fewer events per 10,000 people), pulmonary embolism (2 fewer events per 10,000 people), deep vein thrombosis (1 fewer event per 10,000

people), myocardial infarction (1 fewer event per 10,000 people) and ischaemic stroke (2 fewer events per 10,000 people)

- clinically important undesirable effects on infection (12 more events per 10,000 people) and all-cause readmission (46 more events per 10,000 people)

- no clinically important difference on seizures (0 fewer events per 10,000 people) and reoperation (3 fewer events per 10,000 people).

The committee agreed that the lower event rates may be due to them representing a healthier population that may otherwise be unlikely to have adverse events. This would correspond with the lower control group event rates.

There were no undesirable effects identified in the clinical evidence for review [A]. When considering the results from review [A] and [B] in conjunction, the committee agreed that there is a very small increased risk of thromboembolic events (including deep vein thrombosis and myocardial infarction) and seizures (particularly when higher doses of tranexamic acid are administered).

These are not seen with pregnant women, trans men and non-binary people, where evidence was more limited, but showed very small important increases in the risk of all-cause readmission and infections, and decreases in the risk of all-cause mortality.

Weighing up the benefits and the harms, the committee agreed that tranexamic acid is safe for most people having surgery. While there are potential risks, these are outweighed by the benefits in most cases. While there is uncertainty in the benefits for people with minor blood loss, the committee agreed that these are likely a reflection of the limitations of meta analysing very different studies together. They agreed that people with mean blood loss closer to 0 ml and closer to 500 ml can have very different clinical outcomes which makes it harder to compare the two.

1.1.7.3 Resources and cost-effectiveness

See review [A] for more information.

1.1.7.4 Equity

See review [A] for more information.

1.1.7.5 Acceptability and values

See review [A] for more information.

1.1.7.6 Feasibility

See review [A] for more information.

1.1.7.7 Strength of the recommendations

See review [A] for more information.

1.1.8 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.5 to 1.1.11 and the research recommendation on the effectiveness of tranexamic acid for children and the effectiveness of tranexamic acid for specific vascular surgeries. Other evidence supporting these recommendations can be found in the evidence review on the effectiveness of tranexamic acid for anticipated minor blood loss (A).

1.1.9 References

1.1.9.1 Effectiveness evidence

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