

# BMJ Open Tranexamic acid in cardiac surgery: a systematic review and meta-analysis (protocol)

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**To cite:** Alaifan T, Alenazy A, Xiang Wang D, *et al.* Tranexamic acid in cardiac surgery: a systematic review and meta-analysis (protocol). *BMJ Open* 2019;9:e028585. doi:10.1136/bmjopen-2018-028585

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-028585>).

Received 28 January 2019

Revised 27 August 2019

Accepted 02 September 2019



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## ABSTRACT

**Introduction** Bleeding during cardiac surgery is associated with increased morbidity and mortality. Tranexamic acid is an antifibrinolytic with proven efficacy in major surgeries. Current clinical practice guidelines recommend intraoperative use in cardiac procedures. However, several complications have been reported with tranexamic acid including seizures. This review intends to summarise the evidence examining the efficacy and safety of tranexamic acid in patients undergoing cardiac surgery.

**Methods/design** We will search MEDLINE, Embase, PubMed, ACPJC, CINAHL and the Cochrane trial registry for eligible randomised controlled trials, the search dates for all databases will be from inception until 1 January 2019, investigating the perioperative use of topical and/or intravenous tranexamic acid as a stand-alone antifibrinolytic agent compared with placebo in patients undergoing open cardiac surgery. We categorised outcomes as patient critical or patient important. Selected patient-critical outcomes are: mortality (intensive care unit, hospital and 30-day endpoints), reoperation within 24 hours, postoperative bleeding requiring transfusion of packed red blood cells, myocardial infarction, stroke, pulmonary embolism, bowel infarction, upper or lower limb deep vein thrombosis and seizures. Those outcomes, we perceived as clinical experts to be most patient valued and patients were not involved in outcomes selection process. We will not apply publication date, language, journal or methodological quality restrictions. Two reviewers will independently screen and identify eligible studies using predefined eligibility criteria and then review full reports of all potentially relevant citations. A third reviewer will resolve disagreements if consensus cannot be achieved. We will present the results as relative risk with 95% CIs for dichotomous outcomes and as mean difference or standardised mean difference for continuous outcomes with 95% CIs. We will assess the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation approach.

**Ethics and dissemination** Formal ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication

**Trial registration number** CRD42018105904

## Strengths and limitations of this study

- A comprehensive search strategy of published and unpublished literature.
- Application of grade methodology to assess certainty of the estimates of effect.
- Limitations relate to the anticipated heterogeneity of the included studies including dosing strategy, timing, type of surgery and preoperative antiplatelets therapy.

## BACKGROUND

### Description of the condition

Surgical patients in the USA receive 15 million units of red blood cell transfusions annually, cardiac surgical procedures utilise as much as 10% to 15% of this.<sup>1</sup> Perioperative bleeding is a common complication and is associated with the need for transfusion and reoperation.<sup>2-3</sup> These factors impact negatively on postoperative morbidity, mortality and costs.<sup>4</sup> Coagulopathy, a contributor to excessive bleeding, is linked to the use of cardiopulmonary bypass, which leads to the activation of the intrinsic and extrinsic coagulation pathway, platelet dysfunction and systemic inflammatory response.<sup>5-7</sup> As such, measures to prevent perioperative coagulopathy are recommended.<sup>8</sup> To this end, antifibrinolytic agents are used to prevent the breakdown of blood clots by plasmin.

Tranexamic acid is an antifibrinolytic agent that has been shown to reduce bleeding in major surgeries and trauma patients.<sup>9-10</sup> As a result, current clinical practice guidelines recommend its use in many perioperative settings, including cardiac surgery.<sup>11</sup>

### Description of the intervention

Tranexamic acid acts by reversibly blocking the lysine binding sites of plasminogen, thus

preventing plasmin activation and, as a result, the lysis of polymerised fibrin.<sup>12</sup> Tranexamic acid is frequently utilised to enhance haemostasis, particularly when fibrinolysis contributes to bleeding. In clinical practice, tranexamic acid has been used to treat menorrhagia, trauma-associated bleeding and to prevent perioperative bleeding associated with orthopaedic and cardiac surgery.<sup>13–16</sup> Importantly, the use of tranexamic acid is not without adverse effects. Tranexamic acid has been associated with seizures,<sup>17 18</sup> as well as concerns of possible increased thromboembolic events, including stroke which to date have not been demonstrated in randomised controlled trials.<sup>19 20</sup> Stroke after cardiac surgery might lead to increased mortality and morbidity, in addition to increased intensive care unit (ICU) and hospital lengths of stay.<sup>21 22</sup> Moreover, both the route and quantity for administration of tranexamic acid has varied across cardiac surgery trials.<sup>23 24</sup> Tranexamic acid can be administered orally, topically and intravenously. Topical and intravenous administration are most common in perioperative cardiac surgeries.

### How does the intervention work?

Fibrinolysis is the mechanism of clot breakdown and involves a cascade of interactions between zymogens and enzymes that act in concert with clot formation to maintain blood flow.<sup>25</sup> During extracorporeal circulation, such as cardiopulmonary bypass used in cardiac surgery, multiplex changes in haemostasis arise that include accelerated thrombin generation, platelet dysfunction and enhanced fibrinolysis.<sup>26</sup> Tranexamic acid inhibits fibrinolysis, a putative mechanism of bleeding after cardiopulmonary bypass, by forming a reversible complex with plasminogen.<sup>27</sup>

### Why it is important to do this review?

Currently, no definitive and up to date meta-analysis summarises the efficacy and potential for harm of tranexamic acid in cardiac surgery. Several meta-analyses have been conducted, but they did not include recent large randomised controlled trials (RCTs)<sup>20</sup> or comprehensively looked at both efficacy and harm. Furthermore, one of these reviews grouped tranexamic acid with aprotinin and aminocaproic acid<sup>28</sup> while the most recent meta-analysis studied the effect in patients undergoing coronary artery bypass grafting (CABG) without the use of cardiopulmonary bypass.<sup>29</sup>

### Objectives

We plan to conduct a systematic review and meta-analysis of RCTs to investigate the use of tranexamic acid in adult patients who underwent cardiac surgery.

## METHODS/DESIGN

### Types of studies

We will only include RCTs which studied tranexamic acid in adults who underwent open cardiac surgery.

We will impose no language or methodological quality restrictions.

### Types of participants

The population of interest is adult patients (18 years of age or older) who underwent open cardiac surgery including but not limited to CABG (on-pump or off-pump and midline sternotomy or thoracotomy), valve surgery or ascending aorta and arch surgery including combined surgeries. We will exclude studies investigating transcatheter valvular procedures.

### Types of interventions and comparators

The intervention of interest is administration of tranexamic acid in the perioperative period (defined as between 24 hours preoperatively and up to 24 hours postoperatively). We will include studies that examined the intravenous and topical mode of delivery of tranexamic acid and will include all dosing strategies. We will exclude studies that did not use tranexamic acid as a stand-alone agent (ie, in combination with another antifibrinolytic). The comparator or control group must include only patients who did not receive antifibrinolytic agents (either usual care or placebo).

### Types of outcome measures

We will focus on outcomes we perceive as clinical experts to be most patient-important in order to assess the efficacy and safety of tranexamic acid. We categorised outcomes from a patient-perspective as either critical or important. The selected critical outcomes are: mortality (ICU, hospital and 30-day endpoints), reoperation within 24 hours, postoperative bleeding requiring transfusion of packed red blood cells, myocardial infarction (MI), stroke, venous thromboembolism (VTE) within 3 months (that includes pulmonary embolism, upper or lower limb deep vein thrombosis), bowel infarction and seizures. The important outcomes are: bleeding (defined as chest tube output in millilitre within 24 hours postoperatively), transfusion of other blood products (fresh frozen plasma and platelets), ICU length of stay and hospital length of stay. For thromboembolic complications: MI, stroke, VTE and bowel infarction we will capture harm to the longest duration of follow-up available in the included studies up to 3 months following surgery. The time frame for all other outcomes is during ICU stay unless otherwise mentioned.

### Search methods for identification of studies

We will search the following electronic databases: MEDLINE, Embase, PubMed, ACPJC, CINAHL and the Cochrane trial registry from inception for eligible articles with no language restriction. Keyword search terms include tranexamic acid, antifibrinolytic, coronary artery bypass grafting, cardiac surgery, cardiac valve surgery, ascending aorta and arch surgery, lysine analogue, bleeding, re-sternotomy and CABG; detailed search strategy (see online supplementary file). Search dates for all databases will be from inception until 1 January

2019. Although we plan to update the search just prior to submission to ensure it is as up to date as possible

### Searching other resources

Two reviewers will independently search for eligible articles. In addition, we will search for unpublished and ongoing trials on the WHO International Clinical Trials Registry, metaRegister of Controlled Trials, ClinicalTrials.gov, Conference Proceedings Citation Index-Science. We will also search conference abstracts from the following societies published in the last 2 years: American Heart Association, American College of Cardiology, European Society of Cardiology, American Society of Thoracic Surgeons, Canadian Cardiovascular Society, European Association for Cardio-Thoracic Surgery, American Society of Anesthesiology, Society of Critical Care Medicine, Canadian Critical Care Society and European Society of Intensive Care Medicine.

### Data collection and analysis

After identifying potentially relevant articles through the search process described above, reviewers working in pairs will independently screen all citations and references using specific predefined eligibility criteria. We will screen in two stages: first reviewing titles and abstracts, and second reviewing the full-text. Disagreements in screening will be resolved by discussion and consensus with the help of a third reviewer if needed.

### Data extraction and management

Data extraction will be done independently and in duplicate using predesigned data abstraction forms. Abstracted data will include the study title, first author, relevant demographic data, intervention and control, results for outcomes of interest and information on the methodological quality for each study. A third reviewer will resolve discrepancies in data extraction between reviewers.

### Assessment of risk of bias in included studies

Two reviewers will independently assess the risk of bias of included studies using the Cochrane Collaboration tool for assessing risk of bias in RCTs.<sup>30</sup> We will assess risk of bias individually for each outcome. A third reviewer will be available to resolve any disagreements. For each study, we will include a description for all domains assessed, along with comments if necessary and a final judgement. The risk of bias of a trial will be categorised as follows: (1) low risk of bias, where bias is not present or if present, unlikely to affect outcomes, (2) high risk of bias, where outcomes are likely to be significantly affected by bias, (3) unclear risk of bias, where the reported information is inadequate to properly assess bias.

Included trials will be assessed for adequate sequence generation, allocation sequence concealment, blinding, selective outcome reporting and other bias. Sequence generation will be considered adequate if the study explicitly described an appropriate randomisation procedure to generate an unpredictable sequence of allocation, including computerised randomisation, use

of random number tables and coin tossing. Concealment of allocation will be considered adequate if specific methods to protect allocation were documented and implemented. Performance bias will be considered low if a study reported participant, caregiver and/or researcher blinding. Blinding of outcome assessment will be considered adequate if outcome assessors and adjudicators were blinded. Within-study selective reporting of outcomes will be examined by reviewing the a priori study protocol, if available. If the study protocol is not available, we will compare the outcomes listed in the 'Methods/design' section with those reported in the manuscript.

### Measures of treatment effect

When pooling of outcome data is appropriate, RevMan 5.3 software will be used to conduct meta-analyses. We will use the method of DerSimonian and Laird to pool effect sizes for each outcome under a random effects model; study weights will be measured using the inverse variance method. We will present the results as relative risk (RR) with 95% CIs for dichotomous outcomes and as mean difference or standardised mean difference with 95% CIs for continuous outcomes.

We plan to perform random effects analysis for all outcomes of interest. If significant unexplained heterogeneity exists, or if there is an insufficient number of RCTs for meta-analysis, we will describe data qualitatively. The number needed to treat (NNT) with 95% CIs will be derived from pooled risk ratios and its 95% CIs utilising assumed control risk (ACR) for each outcome similar to the approach recommended by the Cochrane collaboration;  $NNT=1/(ACR \times (1 - RR))$ .<sup>31</sup>

### Dealing with missing data

If we encounter missing data, we will attempt to contact the study authors for additional information. If we cannot obtain additional data, we will analyse the available data and report the potential impact of missing data in the discussion.

### Assessment of heterogeneity

We will assess for heterogeneity between studies using the  $X^2$  test for homogeneity, where  $p < 0.10$  indicates substantial heterogeneity, and the  $I^2$  statistic. We consider  $I^2 > 50\%$  to be significant heterogeneity, which will be further investigated with subgroup analyses to assess clinical and methodological sources of heterogeneity in intervention effect.

### Assessment of reporting biases

We will look for potential publication bias using a funnel plot if more than 10 trials are included for an outcome. For continuous outcomes, the Egger test<sup>30</sup> will be used to detect funnel plot asymmetry. For dichotomous outcomes, we will use the arcsine test. All analyses will be performed using RevMan or Stata.

### Subgroup analysis and investigation of heterogeneity

Potential and expected clinical sources of heterogeneity include different patient demographics, dosing strategies, route of administration and type of cardiac surgery. To explore significant heterogeneity, if a sufficient number of trials are available, we will conduct the following prespecified subgroup analyses (hypothesised direction of effect in parentheses):

- ▶ Off-pump versus on-pump cardiac surgery (tranexamic acid is more effective in on-pump surgery).
- ▶ Type of surgery (tranexamic acid is more effective in valvular heart surgery or aortic arch/ascending aorta surgery as compared with CABG).
- ▶ Combined procedures versus single procedure (tranexamic acid is more effective in combined procedures).
- ▶ Urgent versus elective surgery (tranexamic acid is more effective in urgent surgeries).
- ▶ Single dose versus multiple doses and/or continuous infusion (multiple doses or continuous infusion is more effective).
- ▶ High versus low risk for bias studies (tranexamic acid is more effective in high risk of bias studies).

We will use the  $\chi^2$  test for each subgroup hypothesis ( $p < 0.10$  for significance). We will conduct meta-regression to assess the effect of tranexamic dose as a continuous independent variable on the outcomes using Stata hypothesising that higher dose is more effective. If subgroups effects are credible, we will present the outcomes separately for each subgroup.

### Sensitivity analysis

A priori sensitivity analysis will be performed, excluding studies only reported as abstracts. Post hoc sensitivity analysis will be performed if required.

### Assessing the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess the quality of evidence for each outcome.<sup>32</sup> The GRADE system classifies the quality of the aggregate body of evidence as high, moderate, low or very low. The evidence will be evaluated using the following criteria: (1) study design and rigour of its execution (ie, individual study risk of bias), (2) the extent to which the evidence could be applied to patients of interest (ie, directness), (3) the consistency of results, (4) the analysis of the results (ie, precision) and (5) the likelihood of publication bias. The following three factors will increase the quality of evidence if present: (1) a strong or very strong association between an intervention and the observation of interest, (2) a highly statistically significant relationship between dose and effect and (3) a plausible confounding variable that could explain a reduced effect or could explain an effect if one was not anticipated. We will summarise the overall quality of evidence for the intervention taking into consideration both desirable and adverse outcomes. We

will include an evidence profile in the results showing the GRADE assessments and pooled analysis per outcome.

### Patient and public involvement

We categorised outcomes as we perceived it as clinical experts to be more patient valued into patient critical and patient important outcomes. but there were no patients involved in the process of selection.

### DISCUSSION

Bleeding is one of the major complications of cardiac surgeries.<sup>5</sup> The inhibition of fibrinolysis inhibition using lysine analogues is a common approach used to reduce the intraoperative and postoperative bleeding associated with cardiac surgery.<sup>33</sup> Tranexamic acid is the most common lysine analogue used in clinical use. Despite its demonstrated benefits in the prevention of bleeding tranexamic acid has not been shown to reduce mortality in cardiac surgery. Despite trial level data, the balance between bleeding prevention and the hypothetical side effects of tranexamic acid remains uncertain.

Our systematic review and meta-analysis are intended to summarise the evidence examining the efficacy and safety of tranexamic acid in patients undergoing cardiac surgery. We will examine the effect of the type of surgery, patient population and dosing strategies. Strengths of this protocol include a comprehensive search strategy of published and unpublished literature and application of GRADE methodology to assess certainty of the estimates of effect. Limitations relate to the anticipated heterogeneity of the included studies.

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**Acknowledgements** We would like to express our gratitude to Sandy Culley for guidance in designing and carrying out our search strategy.

**Contributors** TA, AA, BR, CA, EB-C conceived the idea for this systematic review. All authors (TA, AA, DXW, SMF, JS, EB-C, AF-R, TK, KK, RZ, RW and BR) developed the methodology for the systematic review. The manuscript was drafted by TA, AA, DXW and BR and revised by all authors. TA, AA and DXW will screen potential studies, perform duplicate independent data abstraction, risk of bias assessment

and GRADE assessment with help from other authors. BR will conduct the data synthesis. BR is the guarantor of the review.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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