PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Tranexamic Acid in Cardiac Surgery: a systematic review and meta-analysis (protocol)
AUTHORS	Alaifan, Thamer; Alenazy, Ahmed; Xiang Wang, Dominic; Fernando, Shannon; Spence, Jessica; Belley-Cote, Emilie; Fox-Robichaud, Alison; Ainswoth, Craig; Karachi, Tim; Kyeremanteng, Kwadwo; Zarychanski, Ryan; Whitlock, Richard; Rochwerg, Bram

VERSION 1 – REVIEW

REVIEWER	Pier Mannuccio Mannucci IRCCS Ca' Granda Maggiore Policlinico Hospital Foundaton Milan Italy
REVIEW RETURNED	15-Feb-2019

GENERAL COMMENTS	I shall be rather brief in my comments, because in general I do not like to see study protocols being published. Yet, you provide good reasons for your strategy to consider them. With these preambles and limitations, I think that it is already well established that the pre- and post-operative administration of tranexamic acid is clinically useful in the frame of cardiac surgery, in terms of lower mortality, morbidity and consumption of blood products. The protocol of this study is designed to provide some additional data and perhaps also answers to some minor questions that as yet are not solved, but not of striking interest. Nevertheless, the protocol is meaningful and the proponents appear to give good guarantees that they will be able to start and perhaps complete the trial. I have quite frankly no important suggestion for protocol improvement to be offered to the authors.

REVIEWER	Paulo Ricardo Saquete Martins-Filho Investigative Pathology Laboratory, Federal University of Sergipe, Brazil
REVIEW RETURNED	25-Feb-2019

GENERAL COMMENTS	The protocol is well written, has important clinical implication, and should be of great interest to the readers. However, minor grammatical and typographical errors should be corrected.

REVIEWER	Lise Estcourt NHSBT, UK
REVIEW RETURNED	18-Jun-2019

GENERAL COMMENTS	This is the protocol for a systematic review of TXA in adult open cardiac surgery A PRISMA-P checklist has not been completed - please complete Abstract: 1. Introduction: Last sentence of introduction doesn't make sense. I assume it is that this review intends to… 2. "Ethics and dissemination: The aim of this systematic review is to summarize the updated evidence on the efficacy and safety of tranexamic acid…" this isn't ethics or dissemination just the aim of the review Background 1. First sentence United States should be in capital letters and cardiac should not. Sentence needs to be rephrased 2. Use bleeding or haemorrhage but don't use both. For example "Tranexamic acid is frequently utilized to enhance hemostasis, particularly when fibrinolysis contributes to hemorrhage. In clinical practice, tranexamic acid has been used to treat menorrhagia, trauma-associated hemorrhage, and to prevent perioperative bleeding associated with orthopedic and cardiac surgery" 3. The authors state that "Tranexamic acid has been associated with …. increased thromboembolic events, graft thrombosis, stroke, and mesenteric ischemia" and use 3 references to support this (references 19-21). 1) The ATACAS trial, however the ATACAS trial only found an increase in seizures. 2) The Hutton review also found no evidence of a difference between TXA and no treatment for thromboembolic events and stroke. 3) The Borger study also found no independent association between CVA and TXA ("Independent predictors of stroke were (in decreasing order of magnitude): age >70 years, left ventricular ejection fraction <40%, previous stroke or transient ischemic attack, normothermic cardiopulmonary bypass, diabetes, and peripheral vascular disease.") I don't know of any reliable evidence that suggests TXA increases the risk of thrombosis as it is a clot stabiliser rather than increasing clot formation. Ker systematic reviews and Henry 2011 review also found no evidence for an increase in thrombosis. 4. There are not just 2 systematic reviews that have looked at either benefits or harms of TXA. There are also these specific cardiac surgery SRs a. Seizures associated with tranexamic acid for cardiac surgery: a meta-analysis of randomized and non-randomized studies Takagi H, Ando T, Umemoto T The Journal of Cardiovascular Surgery. 2017;58((4):):633-641 b. A meta-analysis on efficacy of antifibrinolytic agents during perioperative period in patients undergoing coronary artery bypass grafting treated with antiplatelet agents [Chinese] Ma HP, Keyoumu N, Chen L, Zheng H Chung-Hua Hsin Hsueh Kuan Ping Tsa Chih [Chinese Journal of Cardiology]. 2011;39((8):):759-63. c. Tranexamic acid is associated with less blood transfusion in off-pump coronary artery bypass graft surgery: a systematic review and meta-analysis

	d. Adler Ma SC, Brindle W, Burton G, Gallacher S, Hong FC, Manelius I, Smith A, Ho W, Alston RP, Bhattacharya K Journal of Cardiothoracic & Vascular Anesthesia. 2011;25((1):):26-35. As well as Henry 2011 that had cardiac sub-groups. Also, Hutton looked at outcomes for TXA separately within their paper Methods 1. Can you please tell me why you are only going to search trial registries for the preceding 2 years as many trials may not yet be published or unpublished and registered more than 2 years ago? 2. Please provide the search strategy for at least 1 database as an appendix 3. Subgroup analyses – there are quite a few subgroup analyses, how will the authors account for multiple analyses? 4. Subgroup analyses - "Patients who received aspirin within 4 days of their procedure vs. no antiplatelets agents (tranexamic acid is more effective in those receiving antiplatelets)". Why is it only aspirin versus no antiplatelet agents as other drugs can be used as single agents? Why 4 days? Aspirin irreversibly inhibits platelets and so its effect will last for 7 days. 5. "Patients receiving dual antiplatelets within 4 days of procedure (tranexamic acid is more effective in those receiving dual antiplatelets)" please state what you are comparing it to. 6. Please define major bleeding as the definitions are so variable between studies that it will be difficult to compare unless that is a pre-defined definition, also what is the time-frame for major bleeding 7. What is the time-frame for thromboembolic events? – not specified Discussion 1. The authors state that TXA has not been shown to reduce mortality. However this is incorrect, tranexamic acid has been shown to reduce mortality, including: CRASH-2 trial in trauma; Ker systematic review in surgery (2012); WOMAN trial in post-partum haemorrhage. 2. Again the authors raise this increased risk of arterial and venous thromboembolic events in TXA studies but the studies they cite do not support this and only support an increased risk of seizures with high doses of TXA as was administered in the ATACAS study. Please remove this statement unless convincing evidence can be provided.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Pier Mannuccio Mannucci

Institution and Country: IRCCS Ca' Granda Maggiore Policlinico Hospital Foundaton

Milan

Italy

Please state any competing interests or state ‘None declared’: none declared

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Please leave your comments for the authors below

I shall be rather brief in my comments, because in general I do not like to see study protocols being published. Yet, you provide good reasons for your strategy to consider them. With these preambles and limitations, I think that it is already well established that the pre- and post-operative administration of tranexamic acid is clinically useful in the frame of cardiac surgery, in terms of lower mortality, morbidity and consumption of blood products. The protocol of this study is designed to provide some additional data and perhaps also answers to some minor questions that as yet are not solved, but not of striking interest. Nevertheless, the protocol is meaningful, and the proponents appear to give good guarantees that they will be able to start and perhaps complete the trial. I have quite frankly no important suggestion for protocol improvement to be offered to the authors.

**Thank you. We are excited to see the results!

Reviewer: 2

Reviewer Name: Paulo Ricardo Saquete Martins-Filho

Institution and Country: Investigative Pathology Laboratory, Federal University of Sergipe, Brazil

Please state any competing interests or state ‘None declared’: None declared

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Please leave your comments for the authors below

The protocol is well written, has important clinical implication, and should be of great interest to the readers. However, minor

grammatical and typographical errors should be corrected.

**Thanks for your comment, we are looking forward for the results, we have again reviewed the paper for grammatical and typographical errors and corrected whenever found.

Reviewer: 3

Reviewer Name: Lise Estcourt

Institution and Country: NHSBT, UK

Please state any competing interests or state 'None declared': None declared
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Please leave your comments for the authors below

This is the protocol for a systematic review of TXA in adult open cardiac surgery

A PRISMA-P checklist has not been completed - please complete

**We have uploaded the PRISMA-P checklist and filled the required fields with page numbers and headings as requested.

Abstract:

1. Introduction: Last sentence of introduction doesn't make sense. I assume it is that this review intends to…

** Thanks. We have revised for clarity and the sentence now reads: "This review intends to summarize the evidence examining the efficacy and safety of tranexamic acid in patients undergoing cardiac surgery."

2. "Ethics and dissemination: The aim of this systematic review is to summarize the updated evidence on the efficacy and safety of tranexamic acid…" this isn't ethics or dissemination just the aim of the review

** We have changed this section to now read: "Formal ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication."

Background

1. First sentence United States should be in capital letters and cardiac should not. Sentence needs to be rephrased

** Revised as suggested, sentence was rephrased and now reads: "Surgical patients in the United States receive 15 million units of red blood cell transfusions annually, cardiac surgical procedures utilize as much as 10% to 15% of this."

2. Use bleeding or haemorrhage but don't use both. For example "Tranexamic acid is frequently utilized to enhance hemostasis, particularly when fibrinolysis contributes to hemorrhage. In clinical practice, tranexamic acid has been used to treat menorrhagia, trauma-associated hemorrhage, and to prevent perioperative bleeding associated with orthopedic and cardiac surgery"

** Thank you for this suggestion. The manuscript has been revised as suggested, and we have used bleeding instead of hemorrhage in all instances.

3. The authors state that "Tranexamic acid has been associated with …. increased thromboembolic events, graft thrombosis, stroke, and mesenteric ischemia" and use 3 references to support this (references 19-21). 1) The ATACAS trial, however the ATACAS trial only found an increase in seizures. 2) The Hutton review also found no evidence of a difference between TXA and no treatment for thromboembolic events and stroke. 3) The Borger study also found no independent association between CVA and TXA ("Independent predictors of stroke were (in decreasing order of magnitude): age >70 years, left ventricular ejection fraction <40%, previous stroke or transient ischemic attack, normothermic cardiopulmonary bypass, diabetes, and peripheral vascular disease.") I don't know of any reliable evidence that suggests TXA increases the risk of thrombosis as it is a clot

stabiliser rather than increasing clot formation. Ker systematic reviews and Henry 2011 review also found no evidence for an increase in thrombosis.

** Thank you for this great comment. Firstly, there was an editing error in our referencing, which may have confused the numbering. The Koster et al trial demonstrated an increased risk of convulsive seizures and not thrombosis; we have revised this in the background and changed the referencing to support the statement: “Tranexamic acid has been associated with seizures [17,18]”.

With regards to reference of Borger 2001, we have now revised the statement to be more specific as well as corrected the referencing issue, the sentence now reads: “Stroke after cardiac surgery might lead to increased mortality and morbidity, in addition to increased intensive care unit (ICU) and hospital lengths of stay (LOS) [21-22].”

In regards to thrombosis, the reviewer is absolutely correct, to date no high quality evidence suggests that tranexamic acid increases clot formation outside observational studies and case reports. As part of our review, we intend to look at the risk of thromboembolic complication and examine if there is an association with TxA. In response to the reviewer’s comment, we have revised the manuscript to be more specific, it now reads: “….as well as concerns of possible increased thromboembolic events including stroke which to-date have not been demonstrated in randomized controlled trials [19-20] “

4. There are not just 2 systematic reviews that have looked at either benefits or harms of TXA. There are also these specific cardiac surgery SRs

a. Seizures associated with tranexamic acid for cardiac surgery: a meta-analysis of randomized and non-randomized studies Takagi H, Ando T, Umemoto T The Journal of Cardiovascular Surgery. 2017;58((4):):633-641

b. A meta-analysis on efficacy of antifibrinolytic agents during perioperative period in patients undergoing coronary artery bypass grafting treated with antiplatelet agents [Chinese] Ma HP, Keyoumu N, Chen L, Zheng H Chung-Hua Hsin Hsueh Kuan Ping Tsa Chih [Chinese Journal of Cardiology]. 2011;39((8):):759-63.

c. Tranexamic acid is associated with less blood transfusion in off-pump coronary artery bypass graft surgery: a systematic review and meta-analysis

d. Adler Ma SC, Brindle W, Burton G, Gallacher S, Hong FC, Manelius I, Smith A, Ho W, Alston RP, Bhattacharya K Journal of Cardiothoracic & Vascular Anesthesia. 2011;25((1):):26-35.

As well as Henry 2011 that had cardiac sub-groups. Also, Hutton looked at outcomes for TXA separately within their paper

**In response to the reviewer’s comment, we have added these references to the introduction. However, of all of these previous reviews, none have examined both efficacy and harm, while including the most recent randomized controlled trials (such as ATACS 2017, Takagi 2017 and Dia 2018). As such we think there is benefit in continuing with this comprehensive review.

The section now reads: “Currently, no definitive and up-to-date meta-analysis summarizes 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 randomized controlled trials (RCTs) or comprehensively examined both efficacy and harm. Furthermore, one of these reviews grouped tranexamic acid with aprotinin and aminocaproic acid [28] while the most recent meta-analysis studied the effect in patients undergoing CABG without the use of cardiopulmonary bypass [29]. “

Methods

1. Can you please tell me why you are only going to search trial registries for the preceding 2 years as many trials may not yet be published or unpublished and registered more than 2 years ago?

** Revised as suggested, we clarified the search strategy in the methods section under searching other resources. We intend to search unpublished and ongoing trials with no time restrictions. However, we will search conference abstracts published only in the last 2 years.

2. Please provide the search strategy for at least 1 database as an appendix

** We have uploaded the EMBASE search strategy as an appendix as requested.

3. Subgroup analyses – there are quite a few subgroup analyses, how will the authors account for multiple analyses?

** We have not planned specific statistical adjustments for multiple subgroup analyses. We will use criteria as outlined in the User's Guide for the Medical Literature (1) to assess for credible subgroup effects. This includes limiting potential for spurious findings by ensuring subgroups are delineated a priori with hypothesis regarding direction of effect.

(1) Guyatt G, Rennie D, Meade M, Cook D. Users' Guides to the Medical Literature : A Manual for Evidence-Based Clinical Practice, 3rd ed. New York, USA : McGraw-Hill Professional Publishing, 2015.

4. Subgroup analyses - "Patients who received aspirin within 4 days of their procedure vs. no antiplatelets agents (tranexamic acid is more effective in those receiving antiplatelets)". Why is it only aspirin versus no antiplatelet agents as other drugs can be used as single agents? Why 4 days? Aspirin irreversibly inhibits platelets and so its effect will last for 7 days.

**This subgroup is problematic for a number of reasons (including those raised by the reviewer), and as such, upon reflection, we have decided to remove as one of our subgroups of interest. This will also help in limiting the number of analyses planned as per comment #3 above.

5. "Patients receiving dual antiplatelets within 4 days of procedure (tranexamic acid is more effective in those receiving dual antiplatelets)" please state what you are comparing it to.

** Subgroup removed as above.

6. Please define major bleeding as the definitions are so variable between studies that it will be difficult to compare unless that is a pre-defined definition, also what is the time-frame for major bleeding

**Thank you. We are capturing bleeding based on 2 parameters. 1) Number of patients with post-operative bleeding requiring transfusion of packed red blood cells during ICU admission and 2) chest tube output in milliliters in the first 24-hour time frame postoperatively.

The section on outcome measures has been revised as suggested, it now reads "The important outcomes are: bleeding (defined as chest tube output in milliliter within 24 hours post-operatively), transfusion of other blood products (fresh frozen plasma and platelets), ICU length of stay, and hospital length of stay. The time frame for all outcomes is during ICU stay unless otherwise mentioned."

7. What is the time-frame for thromboembolic events? – not specified

** The time frame for all outcomes is during ICU stay unless otherwise mentioned. This has been added to the outcome section of the manuscript as per comment #6 above.

. Discussion

1. The authors state that TXA has not been shown to reduce mortality. However this is incorrect, tranexamic acid has been shown to reduce mortality, including: CRASH-2 trial in trauma; Ker systematic review in surgery (2012); WOMAN trial in post-partum haemorrhage.

**Thanks, we have made this important revision to state that TXA has not been shown to reduce mortality in cardiac surgery patients. The section now reads “Despite its demonstrated benefits in the prevention of bleeding, tranexamic acid has not been shown to reduce mortality in cardiac surgery.”

2. Again the authors raise this increased risk of arterial and venous thromboembolic events in TXA studies but the studies they cite do not support this and only support an increased risk of seizures with high doses of TXA as was administered in the ATACAS study. Please remove this statement unless convincing evidence can be provided.

**The statement has been deleted from the discussion.

We are grateful for the opportunity to improve the presentation of our work and hope that we have addressed the suggestions and concerns raised through the peer-review and editorial review process.

VERSION 2 – REVIEW

REVIEWER	Lise Estcourt NHS Blood and Transplant, UK
REVIEW RETURNED	12-Aug-2019

GENERAL COMMENTS	The authors have responded well to my previous comments. My only concern now is that as the authors want to capture harms as well as benefits in cardiac surgery the very short time-frame for capturing harms (ICU stay) may not adequately capture harms from a thromboembolic perspective. Stroke may be detected within this short time-frame but VTE may not. Hospitalisation can increase risk of VTE for 3 months afterwards and therefore other potential risk factors could also lead to an increased risk for this period of time.