PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Ker, Katharine; Mansukhani, Raoul; Shakur-Still, Haleema; Arribas, Monica; Beaumont, Danielle; Roberts, Ian

VERSION 1 – REVIEW

REVIEWER	Ibtihal Abdelgadir Sidra Medical and Research Center, Doha , pediatrics
REVIEW RETURNED	17-Jan-2022

GENERAL COMMENTS	Dear authors, This is a well written systematic review, would suggest few points to be considered for review 1. The evidence about TXA on GI bleed had more recent evidence after the 2014 systematic review, please update. 2. Heterogeneity is discussed twice within data analysis, and not clear the way the authors assessed heterogeneity among the involved trials. Please look at the Cochrane handbook of systematic reviews for further information. 3. No mention to the ongoing trials within the results, and appeared within the discussion, and the online supp material, please revise. 4. Which software the authors used for the data synthesis, please share it within the section. 5. The GRADE assessment is now the standard way to assess the evidence in systematic reviews, would suggest adding it to the assessment of results. 6. “We found no strong statistical evidence that the effects of TXA on death or vascular occlusive events varies between different acute severe bleeding conditions. Our pooled estimate suggests that TXA reduces the odds of death within 24 hours by 16%. The estimate increases to 20% when TXA is given within three hours of bleeding onset. There was no evidence for an increased risk in vascular occlusive events associated with TXA.” When we look at the forest blot that is included, the statement above about the effect on death is not correct. There is some evidence to suggest that MI is reported more in participants who received TXA- please revise the statement above to reflect the meta-analysis included. This is also mentioned in discussion, which is not clear, 7. Visual inspection of the forest blot showed difference between the HALT-IT trial and the other included studies, this might be a good point to be discussed among the heterogeneity of the studies included, also including studies with different types and sources of bleeding is one of the limitations of this review. This review is done with a very high standard, however there is inconsistencies between the results shown in the forest blot and the

	one discussed within the text and discussion sections, that needed to be updated and reviewed accordingly.

REVIEWER	Annika Reintam Blaser Tartu Ulikool
REVIEW RETURNED	21-Jan-2022

GENERAL COMMENTS	The authors present an interesting analysis addressing the effect of tranexamic acid in patients with GI bleeding in comparison with using the same drug in other kind of bleeding. I have some questions and comments. Major comments: For a clinician without a strong background of statistics it is difficult to understand what exactly is meant by a conclusion in the abstract "The results of the HALT-IT trial are therefore statistically compatible with a reduction in the risk of death." Please rephrase. Please also report the outcomes and side effects in different trials in a similar way you report baseline characteristics to facilitate the reader obtaining an overview. I understand that the positive effect of TXA if given within 3 hours to patients with GI bleeding cannot be completely excluded. On the other hand, the results of the HALT-IT trial point rather to the other direction. Moreover, it is very likely that a GI bleeding will be commonly detected beyond 3 hours from onset. Clinical manifestation of GI bleeding is likely to occur with some delay and not be immediately obvious. Please discuss this, adding a clinical point of view. I am concerned that the interpretation provided by the authors could be interpreted as evidence supporting the use of TXA in patients with GI bleeding, and I think that such interpretation/conclusion is correct. The HALT-IT trial did not show a difference in mortality, whereas TXA in this trial was suggested to be associated with more venous thromboembolic events and seizures. Indeed, also venous thromboembolic events could possibly be related to the late application of the drug. However, late application could be unavoidable in this kind of bleeding event. I am concerned about the approach in discussion that appears questioning the validity of results of the HALT-IT study with >12000 patients as being underpowered. I think the manuscript should be more balanced in this regard. Currently it seems kind of suggesting that the results of the HALT-IT have changed with this study. Minor: Page 3, line 32: to assess instead of to assesses

REVIEWER	Che-Yi Chou China Medical University Hospital, Division of Nephrology
REVIEW RETURNED	01-Mar-2022

GENERAL COMMENTS	The authors used a one-stage model for the IPD meta-analysis. The heterogeneity of the treatment effects was analyzed using interaction terms between trials with adjustments for confoundings. These methods are acceptable for the aim of the study.

REVIEWER	Yasuhiro Ishiyama Kawasaki Saiwai Hospital
REVIEW RETURNED	16-Jun-2022

GENERAL COMMENTS	This meta-analysis assessed how the results of the HALT-IT trial compared to evidence from other high-quality trials of TXA for the management of severe bleeding. IPD data is used and is a detailed study. In the statistics, is the analysis software not mentioned? Figure.1 would be easier for readers to read if heterogeneity and test for overall effect were added. The results of quality and risk of bias assessment are not described.

REVIEWER	Christina Ramirez UCLA, Biostatistics
REVIEW RETURNED	21-Jun-2022

GENERAL COMMENTS	The manuscript conducts a meta analysis on the use of tranexamic acid in patients with acute bleeding conditions. The manuscript is well-written and uses IPD from large randomized trials with acute severe bleedings. A previous Cochrane review included 7 small trials which were excluded in this analysis as only large trials were included. The authors state that they included trials with > 5000 patients—that should be put on the flow chart. The number of trials that were excluded should also be mentioned. At the time of this review the data for the HALT-IT trial was not available at the website listed in the manuscript, preventing this reviewer from replicating the analysis. The authors state that they “found no heterogeneity between the trials”. How was homogeneity assessed? There is insufficient detail given on the statistical methods to allow one to reproduce the results. More detaila are needed. Supplementary table 4 should provide statistical comparisons.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Ibtihal Abdelgadir, Sidra Medical and Research Center, Doha
Comment: The evidence about TXA on GI bleed had more recent evidence after the 2014 systematic review, please update.
Response: The reviewer is correct that a more recent version was published in 2014, however this section of the Background is referring to the evidence available at the time the HALT-IT trial was initiated and for that reason the 2012 review is referenced.

Comment: Heterogeneity is discussed twice within data analysis, and not clear the way the authors assessed heterogeneity among the involved trials.
Response: We have reordered these paragraphs in the ‘data analysis’ section to improve clarity.

Comment: No mention to the ongoing trials within the results, and appeared within the discussion, and the online supp material, please revise.
Response: We have added further detail about the ongoing trials to the Results section.

Comment: Which software the authors used for the data synthesis, please share it within the section.
Response: We have added a sentence under the 'data analysis' subheading of the 'Methods' to confirm that we used Stata version 16.1 (StataCorp, College Station, Texas 77845 USA) for the analyses.

Comment: The GRADE assessment is now the standard way to assess the evidence in systematic reviews, would suggest adding it to the assessment of results.
Response: We have added an assessment of the quality of the evidence using the GRADE approach as suggested. We have added text to Methods and Results sections in the manuscript and provided further detail in supplementary material 8.

Comment: "We found no strong statistical evidence that the effects of TXA on death or vascular occlusive events varies between different acute severe bleeding conditions. Our pooled estimate suggests that TXA reduces the odds of death within 24 hours by 16%. The estimate increases to 20% when TXA is given within three hours of bleeding onset. There was no evidence for an increased risk in vascular occlusive events associated with TXA." When we look at the forest blot that is included, the statement above about the effect on death is not correct. There is some evidence to suggest that MI is reported more in participants who received TXA- please revise the statement above to reflect the meta-analysis included. This is also mentioned in discussion, which is not clear,
Response: We do not agree. The Forest Plots shown in Figure 1 show that TXA reduces the odds of death compared to placebo. Our statement that the "...pooled estimate suggests that TXA reduces the odds of death within 24 hours by 16%. The estimate increases to 20% when TXA is given within three hours of bleeding onset" is fully consistent with these results. Regarding MI, these results are presented in Table 2. It is not the case that MI is reported more in participants who received TXA as the referee suggests. In fact, there were fewer MIs in the TXA group than in the placebo group (79 [0.2%] vs 106 [0.3%]).

Comment: Visual inspection of the forest blot showed difference between the HALT-IT trial and the other included studies, this might be a good point to be discussed among the heterogeneity of the studies included, also including studies with different types and sources of bleeding is one of the limitations of this review.
Response: We have added a statement in the Discussion section acknowledging the difference between the HALT-IT trial point estimate. The objective of this article was to explore if the results of the HALT-IT trial are compatible with the results of trials involving patients with other bleeding conditions, so we do not agree that including them is limitation of our study, rather it is an inherent aspect of the design. We have acknowledged in the Discussion section that there may be differences between bleeding conditions which may mean that the effect of TXA does in fact vary, despite us not finding any evidence for statistical heterogeneity.

Comment: This review is done with a very high standard, however there is inconsistencies between the results shown in the forest blot and the one discussed within the text and discussion sections, that needed to be updated and reviewed accordingly.
Response: As explained above, we do not agree that there are inconsistencies between the results in the Forest Plots and those in the text.

Reviewer: 2
Dr. Annika Reintam Blaser, Tartu Ulikool
Comment: For a clinician without a strong background of statistics it is difficult to understand what exactly is meant by a conclusion in the abstract "The results of the HALT-IT trial are therefore statistically compatible with a reduction in the risk of death." Please rephrase.

Response: We agree that this statement could be clearer. We have deleted this statement and replaced it with 'When the HALT-IT trial results are considered in the context of other evidence for the effects of TXA, a reduction in the risk of death cannot be discounted'.

Comment: Please also report the outcomes and side effects in different trials in a similar way you report baseline characteristics to facilitate the reader obtaining an overview.
Response: We have added this information as suggested in supplementary material 7.

Comment: I understand that the positive effect of TXA if given within 3 hours to patients with GI bleeding cannot be completely excluded. On the other hand, the results of the HALT-IT trial point rather to the other direction. Moreover, it is very likely that a GI bleeding will be commonly detected beyond 3 hours from onset. Clinical manifestation of GI bleeding is likely to occur with some delay and not be immediately obvious. Please discuss this, adding a clinical point of view.
Response: In response to this and a comment by reviewer 1, we have added text acknowledging the difference in the point estimates of the HALT-IT trial and have considered some of the differences in the clinical presentation of GI bleeding patients which may be important. This has been added to the 'Implications' section of the Discussion.

Comment: I am concerned that the interpretation provided by the authors could be interpreted as evidence supporting the use of TXA in patients with GI bleeding, and I think that such interpretation/conclusion is correct.
Response: Thank you for this insight - such an interpretation is not our intention. We have added a sentence to the 'Implications' section of the 'Discussion' to be clear that we do not recommend that TXA is routinely used for GI bleeding without further research.

Comment: The HALT-IT trial did not show a difference in mortality, whereas TXA in this trial was suggested to be associated with more venous thromboembolic events and seizures. Indeed, also venous thromboembolic events could possibly be related to the late application of the drug. However, late application could be unavoidable in this kind of bleeding event.
Response: We have added text to the Discussion acknowledging the differences in the results of the HALT-IT trial results and differences in the clinical context such as late presentation, that may be important.

Comment: I am concerned about the approach in questioning the validity of results of the HALT-IT study with >12000 patients as being underpowered. I think the manuscript should be more balanced in this regard. Currently it seems kind of suggesting that the results of the HALT-IT have changed with this study.
Response: It is not our intention to suggest that the results of the HALT-IT trial have changed. However, we are offering a different perspective to how they might be interpreted. When considered in isolation under the null hypothesis of no effect, there is no evidence that TXA reduces death in GI bleeding patients. However, there is considerable evidence from other bleeding conditions that it does reduce bleeding death, and it may be more appropriate to use the alternative hypothesis that TXA reduces GI bleeding deaths to a similar extent to that seen in other bleeding conditions. When we do this there is no evidence that the effect of TXA in GI bleeding patients differs from the other evidence and thus a reduction in risk of death cannot be discounted. We have added a paragraph to the Discussion to elaborate on this.

Comment: Page 3, line 32: to assess instead of to assesses
Response: Corrected.

Reviewer: 3
Dr. Che-Yi Chou, China Medical University Hospital

Comment: The authors used a one-stage model for the IPD meta-analysis. The heterogeneity of the treatment effects was analyzed using interaction terms between trials with adjustments for confoundings. These methods are acceptable for the aim of the study.
Response: Thank you for the feedback. No revisions required.

Reviewer: 4
Dr. Yasuhiro Ishiyama, Kawasaki Saiwai Hospital
Comment: In the statistics, is the analysis software not mentioned?
Response: We have added a sentence to the data analysis section to confirm that we used Stata version 16.1 (StataCorp, College Station, Texas 77845 USA).

Comment: Figure.1 would be easier for readers to read if heterogeneity and test for overall effect were added.
Response: These have been added to Figure 1 as suggested.

Comment: The results of quality and risk of bias assessment are not described.
Response: Further detail has been added to the 'Results' section.

Reviewer: 5
Dr. Christina Ramirez, UCLA
Comment: The authors state that they included trials with > 5000 patients—that should be put on the flow chart. The number of trials that were excluded should also be mentioned.
Response: This information is included in the Flowchart provided as supplementary material 3.

Comment: At the time of this review the data for the HALT-IT trial was not available at the website listed in the manuscript, preventing this reviewer from replicating the analysis.
Response: Thank you for pointing this out. We have checked and the HALT-IT trial data are now available from freebird.lshtm.ac.uk.

Comment: The authors state that they "found no heterogeneity between the trials". How was homogeneity assessed?
Response: As described in the 'Data Analysis' subheading within the Methods section, to assess the heterogeneity of the treatment effects between trials we included an interaction term between the treatment and the trial variable. The P-values for heterogeneity of the treatment effects between trials were obtained from a likelihood ratio test of the trial treatment effect interaction term in an adjusted logistic regression model and we considered a P value <0.05 to indicate the presence of statistical heterogeneity.

Comment: There is insufficient detail given on the statistical methods to allow one to reproduce the results. More details are needed.
Response: We have provided further detail on the statistical methods as supplementary material 2.

Comment: Supplementary table 4 should provide statistical comparisons.
Response: It is not usual to conduct significance testing on baseline variables. We are not convinced that doing so would provide useful information, rather it could draw attention to statistical but otherwise unimportant differences. In general, it is recommended that readers look at a table of baseline comparisons and use clinical judgement to decide if any of the differences are substantial enough to have influenced the results. For this reason we have not provided these as suggested.

VERSION 2 – REVIEW

REVIEWER	Ibtihal Abdelgadir Sidra Medical and Research Center, Doha , pediatrics
REVIEW RETURNED	14-Oct-2022

GENERAL COMMENTS	Dear authors, Thank you for submitting this interesting systematic review and meta-analysis for consideration of publication. Please consider the following point for revision. Abstract Objectives: Can be rephrased to be more specific and targeted towards the clinical question asked. The initial part of the partograph is mainly an introduction, please revise. Research/review question is not stated clearly, when look at the conclusion, it indicates that heterogeneity is the focus there. Please revise both abstract and the main text. Search date was done more than 12 months ago, this can be updated before submission, might not identify new trials under consideration, however this is needed for quality assurance. Strengths and limitations 'Allows the results of the HALT-IT trial to be interpreted in the context of high-quality evidence rather than the previous poor-quality trials of TXA in patients with GI bleeding" this statement is not assessed by this review, and even if done, there are ways to evaluate the quality of evidence presented, would suggest to remove. Introduction Evidence used for GI bleed was dated to 2014, few other systematic reviews were published since then, please update the literature as needed. RR reporting is needed in the introduction, summary is sufficient, this can be added to discussion. "HALT-IT was a high-quality trial that was not subject to the methodological weaknesses of the previous trials of TXA in GI bleeding. It was prospectively registered, allocation was adequately randomised and concealed, participants and investigators were blind to allocation status, and there was minimal loss to follow-up. Moreover, it involved a heterogeneous group of patients that are representative of the patients with GI bleeding seen in current day practice. Based on the HALT-IT trial, we can therefore confidently discount the results of the meta-analysis of the previous small trials of TXA in GI bleeding patients which are likely to be explained by bias. " this can be moved to discussion. Quality of included studies to be reviewed within the results and discussion, not introduction. Quality of evidence is assessed by formal methods- please check the Cochrane handbook.. Method "One author (KK) selected trials involving 5000 patients or more, that had been prospectively registered, and were judged to be at low risk of bias for sequence generation, allocation concealment, and blinding of outcome assessment" for quality assurance, and to follow

	the PRISMA standards, two authors were needed to assess the studies for inclusion, and risk of bias assessment. Results Description of trail is not easy to follow, please revise. While discussing this on the narrative section of the review, please state it with reference to individual study data, including essential information. Joining the results in data synthesis will be more suitable in another section of the review. Table 1, What does mean (SD), Median(IQR) indicate here it was presented three times but not clear which data is assessed, please revise the table. Risk of bias assessment is not fully discussed within the main manuscript; this is usually recommended. Results This section needs extensive revision. Comparisons, outcomes and effect of intervention to be reported following the PRISMA standards. Heterogeneity is part of the outcome assessment, not main outcome. Table 5&7 in the supplementary file- revise the displayed results and indicate clearly the label of the data shown, e.g. numbers and percentages… Discussion The effect of intervention is to be discussed first, with clear comparison and outcomes. Please revise. The effect on mortality and vascular events were assessed by the GRADE assessment and was shown that there is moderate quality evidence for the shown results. This should be reported as shown in the assessment. Outcomes results discussion is recommended to be done separately, each individual outcome separate from others, Most of the discussion is targeted towards finding from HALT-IT trial. This could be modified to include other included studies within reasonable contribution to discussion. Author's opinion against other small trials with lower quality methodology is not assessed on this systematic review, so cannot be part of the discussion and conclusion. I would suggest adding the meta-analysis figures done as part of the data synthesis to the review, if not feasible to be done on the main manuscript, can be shared on the supplementary files.

REVIEWER	Annika Reintam Blaser Tartu Ulikool
REVIEW RETURNED	29-Sep-2022

GENERAL COMMENTS	I thank the authors for their response and think that the manuscript has improved. To me as a clinician, the discussion around the hypothesis that the HALT-IT trial was underpowered to show the beneficial effect of TXA on mortality, is still not entirely clear. The effect of TXA on mortality in the HALT-IT was rather showing the opposite direction, so despite a chance, there was actually no signal in this study that the effect would become significant with adding patients. Moreover, if the

	mortality within 24h is considered, then such patients were commonly not included (mean time to randomization >20h) in the HALT-IT. And this (late manifestation and late admission to the hospital) will probably hold also for any future trials on GI bleeding. I fully agree with your added statement “Without such additional insight, TXA should not be recommended as a treatment for GI bleeding” . Please consider adding it (also) in conclusions. I think that it is important for the reader to clearly understand that the conclusion of the HALT-IT is still valid after this study: Tranexamic acid should not be used for the treatment of gastrointestinal bleeding outside the context of a randomised trial. I did not see Figure 1 included in submission?

REVIEWER	Yasuhiro Ishiyama, Kawasaki Saiwai Hospital
REVIEW RETURNED	05-Oct-2022

GENERAL COMMENTS	It seems to be a good paper that has been revised to take into account the reviewers' suggestions.

REVIEWER	Christina Ramirez UCLA, Biostatistics
REVIEW RETURNED	13-Oct-2022

GENERAL COMMENTS	In the supplementary materials, there is a formatting issue with the models. The model is cut and pasted twice for both Model 1 and Model 2.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2 comments: Dr. Annika Reintam Blaser, Tartu Ulikool

I thank the authors for their response and think that the manuscript has improved.

To me as a clinician, the discussion around the hypothesis that the HALT-IT trial was underpowered to show the beneficial effect of TXA on mortality, is still not entirely clear. The effect of TXA on mortality in the HALT-IT was rather showing the opposite direction, so despite a chance, there was actually no signal in this study that the effect would become significant with adding patients. Moreover, if the mortality within 24h is considered, then such patients were commonly not included (mean time to randomization >20h) in the HALT-IT. And this (late manifestation and late admission to the hospital) will probably hold also for any future trials on GI bleeding.

Response: We do not agree that the HALT-IT trial results show an opposite effect on mortality. It is true that there were more deaths in the TXA-treated group, but the effect estimate was compatible with both an increase and decrease in risk (death within 24 hr: TXA 102/5956 (1.7%) placebo 97/5981 (1.6%) aRR=1.05; 95% CI 0.78 to 1.39). This result may reflect a true absence of effect or a lack of statistical power to detect an effect. We accept that when considered in isolation the observation that the HALT-IT paper may have been underpowered is not obvious. However, when considering the data in the context of other evidence (as we have done), the possibility that HALT-IT was underpowered becomes apparent and this is the message of our paper.

We agree that there are differences between GI bleeding patients and those with life-threatening bleeding due to other causes which may mean that the effect of TXA could differ. We have reflected on this in the Discussion and have added a further comment to clarify that a

trial adequately powered to detect a more realistic event cannot be assumed to observe a beneficial treatment effect in GI bleeding patients.

I fully agree with your added statement "Without such additional insight, TXA should not be recommended as a treatment for GI bleeding". Please consider adding it (also) in conclusions. I think that it is important for the reader to clearly understand that the conclusion of the HALT-IT is still valid after this study: Tranexamic acid should not be used for the treatment of gastrointestinal bleeding outside the context of a randomised trial.

Response: We have added this statement to the conclusions as suggested.

I did not see Figure 1 included in submission?

Response: Figure 1 was included as part of the resubmission – we refer to the editors to confirm if the Figure was available to the reviewers.

Reviewer 4: Dr. Yasuhiro Ishiyama, Kawasaki Saiwai Hospital

It seems to be a good paper that has been revised to take into account the reviewers' suggestions.

Response: Thank you.

Reviewer 5: Dr. Christina Ramirez, UCLA

In the supplementary materials, there is a formatting issue with the models. The model is cut and pasted twice for both Model 1 and Model 2.

Response: We thank the reviewer for pointing out this error which we have now corrected.

Reviewer1: Dr. Ibtihal Abdelgadir, Sidra Medical and Research Center, Doha

Abstract
Objectives: Can be rephrased to be more specific and targeted towards the clinical question asked. The initial part of the partograph is mainly an introduction, please revise.

Response: We disagree. The question under study is to assess the compatibility (i.e. heterogeneity) of the results of the HALT-IT trial with the evidence from other high-quality trials. The first sentence provides context to our question and we have opted not to make any revisions in light of this comment.

Research/review question is not stated clearly, when look at the conclusion, it indicates that heterogeneity is the focus there. Please revise both abstract and the main text.

Response: The reviewer is correct – the exploration of heterogeneity is the key objective. This is clearly stated within the Introduction section of the Abstract and 'Objectives' of the main text. No revisions have been made.

Search date was done more than 12 months ago, this can be updated before submission, might not identify new trials under consideration, however this is needed for quality assurance.

Response: We agree and have updated the searches as suggested. The main text and supplementary material 3 and 4 have been updated accordingly. We identified one further eligible trial (POISE-3) published in May 2022, however due to the time required to obtain, and process individual patient data, the IPD are not currently available for us to include in this present analysis. We also identified one further ongoing trial which we have referenced in the main text and included in supplementary table 4.

Strengths and limitations

'Allows the results of the HALT-IT trial to be interpreted in the context of high-quality evidence rather than the previous poor-quality trials of TXA in patients with GI bleeding" this statement is not assessed by this review, and even if done, there are ways to evaluate the quality of evidence presented, would suggest to remove.

Response: We have removed "... rather than the previous poor-quality trials of TXA in patients with GI bleeding" as suggested from this section.

Introduction
Evidence used for GI bleed was dated to 2014, few other systematic reviews were published since then, please update the literature as needed.

Response: This statement refers to the evidence available when the HALT-IT trial was conceived, thus the 2014 date is appropriate. Furthermore, there has been no update of the Cochrane systematic review since, and the 2014 remains the latest version.

RR reporting is needed in the introduction, summary is sufficient, this can be added to discussion. "HALT-IT was a high-quality trial that was not subject to the methodological weaknesses of the previous trials of TXA in GI bleeding. It was prospectively registered, allocation was adequately randomised and concealed, participants and investigators were blind to allocation status, and there was minimal loss to follow-up. Moreover, it involved a heterogeneous group of patients that are representative of the patients with GI bleeding seen in current day practice. Based on the HALT-IT trial, we can therefore confidently discount the results of the meta-analysis of the previous small trials of TXA in GI bleeding patients which are likely to be explained by bias. " this can be moved to discussion.

Response: We have opted not to move this paragraph as suggested. This paragraph introduces the reader to the HALT-IT trial and we feel should remain to provide context to our review.

Quality of included studies to be reviewed within the results and discussion, not introduction.

Response: It was not our intention for this text in the Introduction to be viewed as part of the review process. We have removed detail from this section to avoid confusion.

Quality of evidence is assessed by formal methods- please check the Cochrane handbook..
Response: We used Cochrane's risk of bias tool to assess the included trials. We had omitted the reference to this and thank the reviewer for pointing this out. We have added the reference to the revised version.

Method
"One author (KK) selected trials involving 5000 patients or more, that had been prospectively registered, and were judged to be at low risk of bias for sequence generation, allocation concealment, and blinding of outcome assessment" for quality assurance, and to follow the PRISMA standards, two authors were needed to assess the studies for inclusion, and risk of bias assessment.

Response: The reviewer is correct that it is encouraged that two review authors assess for inclusion and risk of bias, however, a second reviewer was not available at the time required for this review, although data were extracted by two authors. We note that PRISMA does not stipulate that two authors are involved, rather that the number of reviewers involved is reported, as we have done.

Results
Description of trail is not easy to follow, please revise. While discussing this on the narrative section of the review, please state it with reference to individual study data, including essential information. Joining the results in data synthesis will be more suitable in another section of the review.

Response: We have substantially revised this section and added further detail to improve clarity.

Table 1, What does mean (SD), Median(IQR) indicate here it was presented three times but not clear which data is assessed, please revise the table.

Response: Thank you for pointing this out. Yes, we agree that this was unclear. We have re-formatted the table to make it clearer that these refer to the data item listed above in the table (now bolded).

Risk of bias assessment is not fully discussed within the main manuscript; this is usually recommended.

Response: The results of the risk of bias assessment are summarised in page 8 and in supplementary material 6. Since all include trials were rated as low risk for all domains, we are unclear what further discussion should be added to the main text. We have not made any revisions in light of this comment.

Results
This section needs extensive revision. Comparisons, outcomes and effect of intervention to be reported following the PRISMA standards. Heterogeneity is part of the outcome assessment, not main outcome.

Response: We appreciate that reviews of trials are often focussed on quantifying the effect of an intervention, and the pooled estimate is therefore given prominence when reporting the results. Our review is somewhat different, in that our focus is on assessing the heterogeneity of the effects of TXA between trials. For this reason, we think that it is appropriate to report the results of the assessment of heterogeneity first. This approach does not go against the PRISMA statement which does not stipulate the order in which the results of a meta-analysis should be reported. We have therefore opted not to make any revisions in light of this comment.

Table 5&7 in the supplementary file- revise the displayed results and indicate clearly the label of the data shown, e.g. numbers and percentages…

Response: We have re-formatted and added additional detail to these tables as suggested.

Discussion
The effect of intervention is to be discussed first, with clear comparison and outcomes. Please revise. The effect on mortality and vascular events were assessed by the GRADE assessment and was shown that there is moderate quality evidence for the shown results. This should be reported as shown in the assessment.

Response: As explained above, our main objective was to assess the compatibility of the results of the HALT-IT trial with those from other trials, therefore we judge that it is appropriate to discuss the results of the assessment of heterogeneity first. However, we have added the results of the GRADE assessment as suggested.

Outcomes results discussion is recommended to be done separately, each individual outcome separate from others,

Response: We are not clear what revisions the reviewer is suggesting here. We have described the outcomes separately in the Discussion and followed the PRISMA recommendations. We look to the editors to provide further guidance (if required) about this point.

Most of the discussion is targeted towards finding from HALT-IT trial. This could be modified to include other included studies within reasonable contribution to discussion.

Response: The focus on the HALT-IT trial is intentional and in keeping with our objective. We have opted not to make any revisions in light of this comment.

Author's opinion against other small trials with lower quality methodology is not assessed on this systematic review, so cannot be part of the discussion and conclusion.

Response: First, our statement regarding the poor quality of the previous, small trials is not our opinion, rather it is based on the observations of the authors of the Cochrane review which we have referenced. Second, we disagree that such information cannot be considered in our Discussion, indeed it is good practice to reflect on evidence from other research articles. We have opted not to make any revisions in light of this comment.

I would suggest adding the meta-analysis figures done as part of the data synthesis to the review, if not feasible to be done on the main manuscript, can be shared on the supplementary files.

Response: The Forest Plots for the death within 24 hours meta-analyses are provided in Figure 1 and we have added the Forest Plots for the vascular occlusive events meta-analyses in supplementary material 8 as suggested by the reviewer.

VERSION 3 – REVIEW

REVIEWER	Ibtihal Abdelgadir Sidra Medical and Research Center, Doha , pediatrics
REVIEW RETURNED	07-Dec-2022

GENERAL COMMENTS	Dear Authors, Thank you for submitting this revised review. No further comments or suggestions added. Kind regards