BMJ Open

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

Katharine Ker, Raoul Mansukhani, Haleema Shakur-Still, Monica Arribas, Danielle Beaumont, Ian Roberts

To cite: Ker K, Mansukhani R, Shakur-Still H, *et al*. Tranexamic acid for gastrointestinal bleeding: can a reduction in the risk of death be discounted? A systematic review and meta-analysis of individual patient data from 64 724 bleeding patients. *BMJ Open* 2023;**13**:e059982. doi:10.1136/bmjopen-2021-059982

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059982).

Received 10 December 2021
Accepted 30 January 2023

Global Health Trials Group, Clinical Trials Unit, LSHTM, London, UK

Correspondence to
Dr Katharine Ker;
katharine.ker@lshtm.ac.uk

ABSTRACT

Objectives HALT-IT was an international, randomised trial which assessed the effects of tranexamic acid (TXA) in 12 009 patients with gastrointestinal (GI) bleeding. The results found no evidence that TXA reduces death. It is widely accepted that results of trials should be interpreted in the context of other relevant evidence. We conducted a systematic review and individual patient data (IPD) meta-analysis to assess if the results of HALT-IT are compatible with evidence for TXA in other bleeding conditions.

Design Systematic review and IPD meta-analysis of randomised trials involving ≥5000 patients assessing TXA for bleeding. We searched our Antifibrinolytics Trials Register on 1 November 2022. Two authors extracted data and assessed risk of bias.

Data synthesis We used a one-stage model to analyse IPD in a regression model stratified by trial. We assessed heterogeneity of the effect of TXA on death within 24 hours and vascular occlusive events (VOEs).

Results We included IPD for 64 724 patients from four trials involving patients with traumatic, obstetric and GI bleeding. Risk of bias was low. There was no evidence for heterogeneity between trials for the effect of TXA on death or for the effect of TXA on VOEs. TXA reduced the odds of death by 16% (OR=0.84, 95% CI: 0.78 to 0.91, p<0.0001; p-heterogeneity=0.40). In patients treated within 3 hours of bleeding onset, TXA reduced the odds of death by 20% (0.80, 0.73 to 0.88, p<0.0001; p-heterogeneity=0.16). TXA did not increase the odds of VOEs (0.94, 0.81 to 1.08, p for effect=0.36; p-heterogeneity=0.27).

Conclusions There is no evidence for statistical heterogeneity between trials assessing the effect of TXA on death or VOEs in different bleeding conditions. When the HALT-IT results are considered in the context of other evidence, a reduction in the risk of death cannot be discounted.

Trial registration number PROSPERO CRD42019128260.Cite Now

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is an individual patient data (IPD) meta-analysis that assesses how the evidence for the effects of tranexamic acid in patients with gastrointestinal bleeding (compares with the evidence from other acute bleeding conditions.
⇒ Allows the results of the HALT-IT trial to be interpreted in the context of other high-quality evidence.
⇒ This analysis includes IPD for 64 724 patients from four high-quality randomised trials with minimal missing data.
⇒ There are important bleeding conditions that are not represented in the analysis such as surgical bleeding.

INTRODUCTION

Tranexamic acid (TXA) reduces bleeding by inhibiting the breakdown of fibrin blood clots. It has been used for many years to reduce heavy menstrual bleeding and bleeding during surgery. More recently, it was shown to improve outcomes in bleeding patients with trauma. The CRASH-2 trial involving 20 211 patients with trauma, showed that TXA reduces the risk of death due to bleeding by one-third when given soon after injury, with no apparent increase in side effects.[1] This finding raised the possibility that TXA could be effective for treating patients with other life-threatening bleeding conditions and several large trials were initiated in response, including the HALT-IT (Haemorrhage Alleviation With Tranexamic Acid - Intestinal System) trial.

The HALT-IT trial was a large international randomised controlled trial assessing the effects of TXA in patients with gastrointestinal (GI) bleeding. An earlier Cochrane Systematic Review included seven small trials of TXA in patients with upper GI bleeding, and suggested that TXA could reduce the risk of death from any cause by 40% (RR: 0.60, 95% CI: 0.42 to 0.87).[2] However, the estimate was imprecise and the methodological quality

of the included trials was poor. There were also questions about the applicability of the evidence to current day patients and the effect on risk of vascular occlusive events (VOEs) was unknown. The HALT-IT trial was initiated with the aim of addressing these uncertainties.

Between 2013 and 2019, 12 009 patients with acute severe GI bleeding were recruited to the HALT-IT trial from 164 hospitals in 15 countries. Patients were randomly assigned to receive TXA (1 g loading dose followed by 3 g maintenance dose over 24 hours) or matching placebo. Outcome data from over 99% patients were included in the final analysis. The results were published in June 2020.[3] There was no difference in the risk of death due to bleeding between TXA treated patients and those given placebo (3.7% vs 3.8%; RR: 0.99; 95% CI: 0.82 to 1.18).

HALT-IT was a high-quality trial that was not subject to the methodological weaknesses of the previous trials of TXA in GI bleeding. Moreover, it involved a heterogeneous group of patients who 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 patients with GI bleeding which are likely to be explained by bias.

It is widely recognised that the results of individual trials should be interpreted in the context of the existing evidence, including an assessment of how similar the results are to those of other trials in the same topic area.[4] Rather than consider the results of the HALT-IT trial in the context of the methodologically flawed previous trials in GI bleeding, it is arguably more useful to consider how the results compare with evidence from the other high-quality trials of TXA that have been conducted in different acute bleeding conditions.

Objectives

To assess if the results of the HALT-IT trial are statistically compatible with the evidence for the effects of TXA in other acute bleeding conditions.

METHODS

Study design

We analysed individual patient data (IPD) from large randomised trials of TXA in patients with acute severe bleeding. The London School of Hygiene & Tropical Medicine's CTU Global Health Trials Group maintains a register of completed and ongoing trials assessing the effects of antifibrinolytic drugs. The register contains records of trials identified through searches of the MEDLINE (Ovid MEDLINE(R) ALL 1946 to 1 November 2022), CENTRAL (searched on 1 November 2022), EMBASE (Ovid EMBASE 1980 to 2022 week 44) and WHO ICTRP (searched on 1 November 2022) electronic databases. Each database was searched using a combination of subject headings and keywords (online supplemental material 1). We searched the register for records of trials assessing the effect of TXA on death and VOEs in patients with acute severe bleeding. An initial search of the register was conducted to 31 May 2021 and subsequently updated on 1 November 2022. 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. Two authors (KK and RM) extracted data from the included trials. Study level data on the inclusion criteria, TXA regimen and risk of bias domains were extracted from the study reports. IPD were obtained for the following variables: age, time of bleeding onset, time trial treatment initiated, systolic blood pressure (SBP), treatment allocation, status at 24 hours (dead/alive) and VOEs during follow-up. We checked IPD against the published trials' results to check for completeness and accuracy. Trials were assessed as being at low, unclear or high risk of bias for random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants, personnel (performance bias); blinding of outcome assessors (detection bias); incomplete outcome data (attrition bias); and selective outcome reporting (reporting bias) according to Cochrane criteria.[5] Only trials judged to be at low risk of bias for random sequence generation, allocation concealment and blinding of outcome assessment were included.

This study was undertaken as part of the work of the Antifibrinolytics Trialists Collaboration. We followed the methods prespecified in the PROSPERO record CRD42019128260, with the exception of limiting this analysis to TXA trials involving 5000 patients or more.

Patient and public involvement

Patient and public representatives were not involved in the design of this IPD analysis.

Outcomes

We assessed the homogeneity of the effect of TXA on death as well as fatal and non-fatal VOEs (myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis). For deaths, we limited the analysis to only those that occurred within 24 hours of bleeding onset. Due to its mechanism of action as an inhibitor of fibrinolysis, we expect TXA to only have an effect on deaths due to bleeding, the large majority of which occur in the first 24 hours. Furthermore, TXA has a short half-life (about 2 hours) and is largely eliminated within 48 hours. Focussing on deaths occurring in the first 24 hours helps us to ensure that we include only those events which are most likely to be affected by the trial treatment, and we avoid the effect of dilution bias that would result from the inclusion of non-bleeding deaths. However, for VOEs we included all events occurring at any point during the follow-up of the trials.

Data analysis

Data on all randomised patients were included regardless of whether or not they received the trial treatment (ie, on an intention-to-treat basis).

We used a one-stage model to conduct the IPD meta-analysis. The one-stage approach analyses IPD in a single meta-analysis based on a regression model stratified by trial. This approach allows for the investigation of within and between trial variances and estimation of the effect of TXA in a single analytical model.

To assess the heterogeneity of treatment effects, we included data from all patients irrespective of the time interval between bleeding onset and randomisation. However, previous analyses of IPD data show an apparent time to treatment effect on risk of death, with TXA most effective when given early (ie, within 3 hours) of bleeding onset, with no effect when given beyond this period.[6] Therefore, for deaths, we also assessed the heterogeneity of treatment effects for the subset of patients treated within 3 hours of bleeding onset. To assess the heterogeneity of the treatment effects between trials, we included an interaction term between the treatment and the trial variable. The analyses were controlled for SBP, age and time to treatment. 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. We considered a p value <0.05 to indicate the presence of statistical heterogeneity. We used a logistic regression model to calculate adjusted ORs and 95% CIs. Further details of the statistical methods are given in online supplemental material 2. We used Stata vV.16.1 for all analyses (StataCorp, College Station, Texas, USA).

Quality of the evidence

We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to assess the certainty of evidence for each outcome. We considered the impact of the risk of bias of individual trials, precision of pooled effect estimate, heterogeneity between trials, indirectness of the evidence and impact of reporting biases on the pooled effect estimate. The evidence for each outcome was rated as high, moderate, low or very low.

RESULTS

Description of trials

Through the initial search, we identified four completed trials published between 2010 and 2020 that assessed the effects of TXA for the treatment of acute severe haemorrhage involving 5000 or more patients; the CRASH-2,[1 7] WOMAN,[8] CRASH-3[9] and HALT-IT[3] trials (online supplemental material 3). All IPD for these trials are freely available alongside their data dictionaries from the FreeBIRD data repository (freebird.lshtm.ac.uk).[10–13] The subsequent update of the search in November 2022, identified one further trial, the POISE-3 (PeriOperative ISchemic Evaluation-3) trial[14] published in May 2022, however due to the time required to obtain and process IPD from trials, it was not feasible to include the IPD in this analysis. We also identified a further seven potentially eligible ongoing trials of TXA involving patients with surgical bleeding,[15 16] obstetric bleeding,[17–19] mild traumatic brain injury[20] and haemorrhagic stroke.[21] Details of the included and ongoing trials are presented in online supplemental material 4.

Each of the four included trials for which IPD were available, assessed the effects of intravenous TXA in different acute haemorrhagic conditions. The CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) trial assessed the effects of TXA in 20 211 adult patients with trauma with, or at risk of, significant bleeding who were recruited in 274 hospitals in 40 countries. Patients were randomly assigned to receive TXA (1 g loading dose then infusion of 1 g over 8 hours) or placebo as soon as possible after, and within 8 hours of, injury. Patients were followed up until death, discharge or until 28 days after injury, whichever occurred first. The outcomes included death, VOEs, blood transfusion and disability. IPD were available for 20 127 of all randomised patients.

The WOMAN (World Maternal Antifibrinolytic) trial involved 20 060 women with postpartum haemorrhage who were recruited in 193 hospitals in 21 countries. Women were randomly assigned to receive 1 g TXA or placebo. If bleeding continued after 30 min or stopped and restarted within 24 hours of the first dose, a second dose of 1 g TXA or placebo could be given. Women were followed up until death, discharge or until 42 days after birth, whichever occurred first. The outcomes included death, hysterectomy, surgical intervention, VOEs, blood transfusion and quality of life. IPD were available for 20 021 of all randomised women.

The CRASH-3 (Clinical Randomisation of an Antifibrinolytic in Significant Head Injury) trial involved 12 737 adults with traumatic brain injury who were recruited in 175 hospitals in 29 countries. Patients were randomly assigned to receive TXA (1 g loading dose hours) or placebo. Patients were followed up until death, discharge or until 28 days after injury, whichever occurred first. The outcomes included death, VOEs, neurosurgery, complications and disability. IPD were available for 12 639 of all randomised patients.

The HALT-IT (Haemorrhage Alleviation With Tranexamic Acid - Intestinal System) trial involved 12 009 adults with upper or lower GI bleeding who were recruited in 164 hospitals in 15 countries. Patients were randomised to receive TXA (1 g loading dose then infusion of 3 g over 24 hours) or placebo as soon as possible after bleeding onset. Patients were followed up until death, discharge or until 28 days after bleeding onset, whichever occurred first. The outcomes included death, VOEs, surgery or radiological intervention, blood transfusion, complications and functional status. IPD were available for 11 937 of all randomised patients.

Table 1 Baseline characteristics of patients contributing data to the IPD meta-analysis

	CRASH-2	WOMAN	CRASH-3	HALT-IT	All
Randomised (N)	20211	20060	12737	12009	65017
Contributing IPD (N)	20127	20021	12639	11937	64724
Time to treatment (%)					
≤3	13485 (67)	14928 (75)	9127 (72)	1926 (16)	39466 (61)
3–8	6613 (33)	3637 (18)	3474 (28)	3136 (26)	16860 (26)
>8	21 (0.1)	1446 (7)	38 (0.3)	6874 (58)	8379 (13)
Missing	8 (0)	10 (0)	0 (0)	1 (0)	19 (0)
Mean (SD)	2.8 (2.4)	3.4 (23.4)	2.9 (2.8)	21.9 (36.8)	6.5 (21.8)
Median (IQR)	2 (1-4)	1.1 (.5–3.1)	2.4 (1.6–3.5)	11 (5–24)	2.4 (1–5)
Age					
<20	2142 (11)	1021 (5)	956 (8)	110 (1)	4229 (7)
20–39	11666 (58)	18312 (91)	5266 (42)	1455 (12)	36699 (57)
40–59	4869 (24)	681 (3)	3399 (27)	4664 (39)	13613 (21)
60–79	1315 (7)	0 (0)	2279 (18)	4184 (35)	7778 (12)
≥80	134 (1)	0 (0)	739 (6)	1524 (13)	2397 (4)
Missing	1 (0)	7 (0)	0 (0)	0 (0)	8 (0)
Mean (SD)	34.6 (14.3)	28.3 (5.7)	43.1 (19.8)	58 (17)	38.6 (17.7)
Median (IQR)	30 (24–43)	28 (24–32)	40 (25–58)	58 (46–70)	33 (25–50)
SBP					
<75	3042 (15)	1606 (8)	59 (0)	327 (3)	5034 (8)
75–90	7004 (35)	5853 (29)	478 (4)	2426 (20)	15761 (24)
>90	10052 (50)	12557 (63)	12062 (95)	9149 (77)	43820 (68)
Missing	29 (0)	5 (0)	40 (0)	35 (0)	109 (0)
Mean (SD)	97.0 (27.9)	100.8 (22.7)	130.6 (26.3)	111.1 (23.6)	107.4 (28.2)
Median (IQR)	91 (80–110)	100 (90–110)	129 (110–145)	110 (95–125)	100 (90–121)

IPD, individual patient data; SBP, systolic blood pressure.

Together 65017 patients were included in the four trials; of these, we included individual patient-level data for 64724 (>99%) participants (table 1). Of the 64724 patients for who IPD were available, 32411 were randomly allocated to receive TXA and 32313 to receive placebo, and 39466 (61%) patients were treated within 3 hours of bleeding onset. All of the trials collected data on death and VOEs.

There were differences between the characteristics of patients included in the HALT-IT trial and those included in the other three trials (online supplemental material 5). On average, patients in the HALT-IT trial were almost 24 years older and were treated 9 hours later, than patients in the other three trials. Average SBP was also slightly higher in HALT-IT trial patients, although there was little difference in SBP among the subset of patients treated within 3 hours.

The included trials were judged to be at low risk of bias for all domains (online supplemental material 6). The randomisation sequence was computer-generated and allocation was adequately concealed in all trials. Participants, caregivers and outcome assessors were blind to allocation status in all trials and there were minimal missing data (<1%). There were no issues concerning the completeness or integrity of IPD from any trial.

Heterogeneity of the effect of TXA between trials

Outcome data for patients contributing IPD from the included trials are presented in online supplemental material 7.

We found no heterogeneity between trials for the effect of TXA on death within 24 hours (figure 1). Overall, there were 2792 (4%) deaths within 24 hours. The combined estimate from the analysis, including all patients irrespective of time since bleeding onset, suggests that TXA reduces the odds of death by 16% compared with placebo (0.84, 0.78 to 0.91; p<0.0001). The p value for heterogeneity between trials was 0.40. The certainty of evidence was judged to be moderate for this outcome (online supplemental material 8).

Among patients treated 3 hours or sooner after bleeding onset there were 2085 (5%) deaths within 24 hours. In these patients, TXA reduces the odds of death by 20% compared with placebo (0.80, 0.73 to 0.88; p<0.0001).

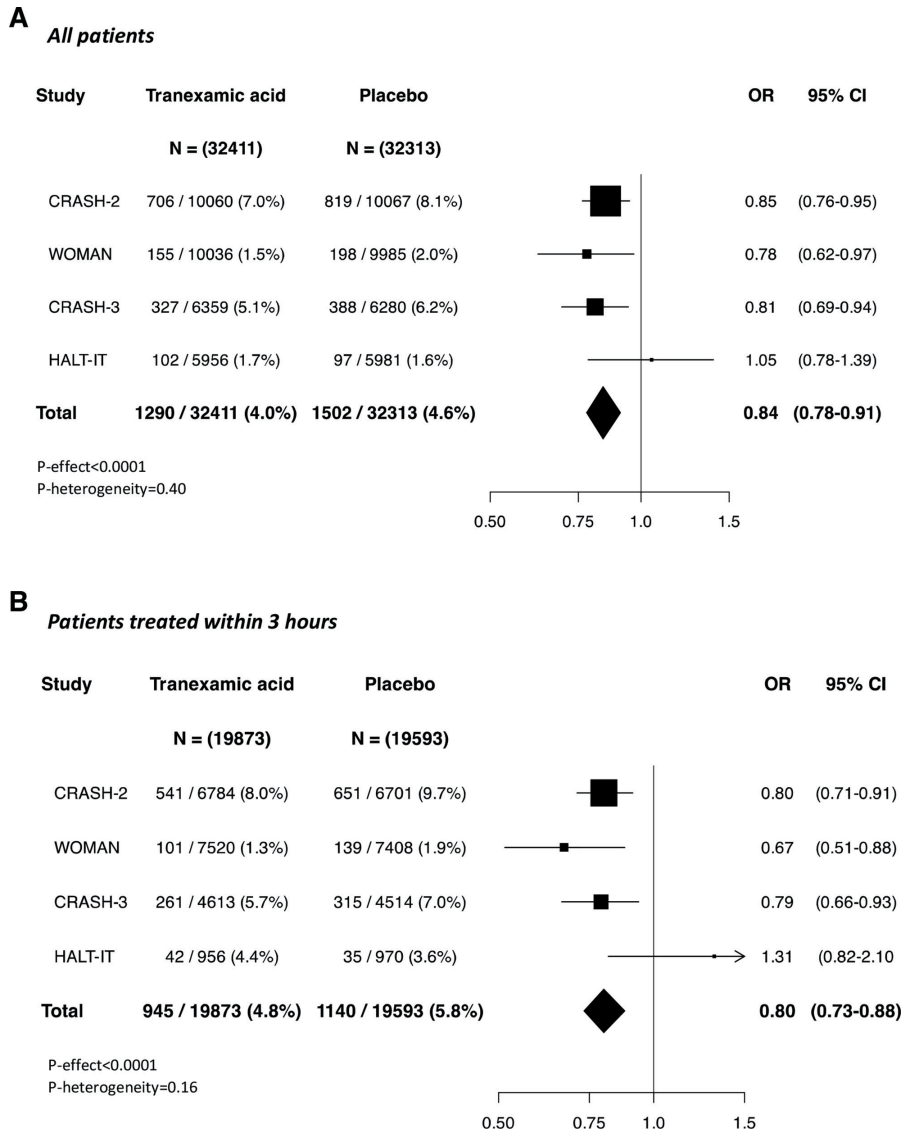

Figure 1 Results of IPD meta-analyses of the effect of TXA on death within 24 hours in (A) all patients and (B) patients treated within 3 hours of bleeding onset. The effect estimates are adjusted for age, systolic blood pressure and time to treatment. IPD, individual patient data; TXA, tranexamic acid.

The p value for heterogeneity was 0.16. The certainty of evidence was judged to be moderate for this outcome (online supplemental material 8).

Overall, 795 (1%) patients suffered a fatal or non-fatal vascular occlusive event.

We found no heterogeneity between trials for the effects of TXA on VOEs (p value for heterogeneity=0.27). The combined estimate suggests that TXA does not increase the odds of a vascular occlusive event compared with placebo (0.94, 0.81 to 1.08; p=0.37).

Table 2 and online supplemental material 9 shows the results for the effect of TXA on VOEs by type. We found no heterogeneity between trials for effect of TXA on VOEs when considered separately. The combined

Table 2 Effect of TXA on VOEs

VOEs	TXA n (%)	Placebo n (%)	OR (95% CI)	P value for effect	P value for heterogeneity
Any VOE	386 (1.2)	409 (1.3)	0.94 (0.81 to 1.08)	0.36	0.27
Myocardial infarction	79 (0.2)	106 (0.3)	0.73 (0.54 to 0.98)	0.04	0.87
Stroke	131 (0.4)	132 (0.4)	0.99 (0.78 to 1.26)	0.93	0.76
Deep vein thrombosis	85 (0.3)	76 (0.2)	1.12 (0.82 to 1.52)	0.49	0.18
Pulmonary embolism	141 (0.4)	139 (0.4)	1.01 (0.80 to 1.28)	0.91	0.18

TXA, tranexamic acid; VOEs, vascular occlusive events.

estimates suggest that there is no increase in odds of myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism in patients treated with TXA. The certainty of evidence was judged to be low for all VOEs outcomes (online supplemental material 8).

DISCUSSION

We found no strong statistical evidence that the effects of TXA on death or VOEs 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 3 hours of bleeding onset. The quality of evidence was judged to be moderate for the mortality outcomes. There was no evidence for an increased risk in VOEs associated with TXA, however these estimates are imprecise; being compatible with both an increase and decrease in risk, and the quality of the evidence was judged to be low for these outcomes.

Strengths and limitations

We limited our analysis to large randomised controlled trials at low risk of bias (ie, prospectively registered, adequately concealed and blinded outcome assessment), and we obtained individual patient-level data from four out of five trials meeting our inclusion criteria, which constitutes about 90% of the existing data. All four trials were judged to be at low risk of bias for all domains and together provided data on 64 724 patients with minimal (<1%) missing data. We can therefore be confident that they provide reliable estimates of the effects of TXA and that our results are unlikely to be explained by bias. Each trial assessed the effects of TXA in a different bleeding condition, enabling our analysis to explore heterogeneity across several acute bleeding scenarios. However, there are important bleeding conditions that are not represented in our analysis such as surgical bleeding. The recently completed POISE-3 trial[14] assessed the effects of TXA in surgery patients as are several of the potentially eligible ongoing trials we identified. Repeating our analyses when IPD from these trials are available would provide further insight into the effects of TXA across acute severe bleeding conditions.

Implications

We found no statistical evidence that the effect of TXA on death or VOEs varies between bleeding conditions, thus the results of the HALT-IT trial appear to be statistically compatible with the evidence from trials in other acute bleeding conditions. Assuming that there is no true biological or statistical heterogeneity, the pooled estimate from a meta-analysis of data from high-quality randomised trials is the most reliable guide to the approximate effect estimate in patients with GI bleeding. Under this assumption, we cannot discount the possibility that early treatment with TXA reduces the risk of death due to GI bleeding by 20%. This reduction is considerably smaller than that estimated by the meta-analysis of previous trials and is smaller than the difference the HALT-IT trial was powered to detect.

However, absence of evidence does not equate to evidence of absence and we cannot say with certainty that the effects of TXA do not differ between bleeding conditions, only that we found no evidence for it in our analysis. HALT-IT was the only included trial not to observe a statistically significant reduction in the risk of death, indeed there were more deaths among patients receiving TXA than those receiving placebo. There are differences in the clinical presentation of patients with GI bleeding which may be important. Compared with patients with other bleeding, those with GI bleeding tend to be much older with comorbidities and present for treatment much later, often beyond the 3-hour time period during which TXA is most effective. Furthermore, we cannot exclude the possibility that there is variation in the physiology of bleeding which may mean that the effects of TXA vary between patients with different bleeding conditions, and specifically that the effects are different in patients with GI bleeding. Indeed, recent research shows that patient with variceal bleeding due to liver disease have a mixed fibrinolytic profile, with some having increased fibrinolysis but others having profound hypofibrinolysis.[22] Further research into the fibrinolytic responses of patients with acute severe bleeding is required to better understand the risk–benefit profile of TXA in patients with GI bleeding. Without such additional insight, TXA should not be recommended as a treatment for GI bleeding.

The HALT-IT trial is the largest trial in patients with GI bleeding conducted to date, yet it was insufficiently powered to detect the modest effect of TXA on death observed by this meta-analysis. Despite the methodological shortcomings of the previous trials in patients with GI bleeding, the large relative reduction in all-cause mortality observed by the meta-analysis of these trials is difficult to ignore and may ultimately have contributed to the underpowering of the HALT-IT trial. When setting the target difference for a sample size calculation, investigators are encouraged to consider evidence from previous trials alongside expert opinion to specify the magnitude of difference in outcome between treatment groups that would be both clinically important and realistic to detect.[23] For the CRASH-2, WOMAN and CRASH-3 trials, there were no previous trials of TXA in their respective bleeding conditions, thus the target differences for these trials were based solely on expert clinical opinion of plausible treatment effects. However, for the HALT-IT trial there was evidence from the systematic review of previous trials to also consider. This could have contributed to the underpowering of the HALT-IT trial by influencing clinical opinion about the potential magnitude of the treatment effect, which had been grossly exaggerated by the previous trials. Even more fundamentally, this flawed evidence almost prevented the HALT-IT trial from taking place at all, with many, including the funders and reviewers of the protocol, questioning whether the trial

was needed in light of the existing evidence. Based on this response it seems unlikely that prospective funders would have looked favourably on a proposal for a larger trial, powered to detect a more modest, but realistic effect. However, given the potentially important clinical and physiological differences outlined above, it cannot be assumed that an adequately powered trial would observe a beneficial treatment effect.

In 2015, we published an article arguing that systematic reviews of small unreliable trials, increase waste by promoting underpowered trials.[24] The experience of the HALT-IT trial seems to support this view. We encourage investigators to employ caution when using results of systematic reviews based on small studies to inform the design of new trials.

CONCLUSIONS

In the HALT-IT trial, there was no significant reduction in bleeding deaths with TXA. When the null hypothesis is that TXA has no effect on deaths, the trial results are consistent with it. When we know little about the effects of a drug, a null hypothesis of no effect seems reasonable. However, there is strong evidence that TXA reduces bleeding deaths after trauma and postpartum haemorrhage. In the light of this, it may be reasonable to use the alternative hypothesis that TXA cuts GI bleeding deaths to a similar extent to that seen in trauma and postpartum haemorrhage. When we do this, we find no evidence that the effect of TXA on GI bleeding deaths is different from that in these other bleeding scenarios. Our conclusion after considering the two different perspectives is that while there is no evidence that TXA reduces GI bleeding deaths, we cannot rule out the possibility that it does. However, based on current evidence TXA should not be recommended as a treatment for GI bleeding.

Acknowledgements We are extremely grateful to the many trial collaborators based throughout the world who contributed to the CRASH-2, WOMAN, CRASH-3 and HALT-IT trials. This article was prepared on behalf of the Antifibrinolytics Trialists Collaboration (ATC) which aims to increase knowledge about the effects of antifibrinolytics. We are grateful to all members of the ATC who contribute to its overall objectives.

Contributors KK: designed the methods; conducted the bibliographic searches; identified eligible trials; extracted data; assessed risk of bias; interpreted the results; and wrote the final manuscript. Member of the HALT-IT trial Protocol Committee. KK is the study guarantor. RM: designed the methods; conducted the statistical analyses; contributed to the preparation of the final manuscript. HALT-IT trial statistician. HS-S: conceived the study; coordinated the generation of the trial data; contributed to the preparation of the final manuscript. Project Director of the HALT-IT trial. MA: coordinated the generation of the trial data; contributed to the preparation of the final manuscript. Trial Manager of the HALT-IT trial. DB: coordinated the generation of the trial data; contributed to the preparation of the final manuscript. Senior Trial Manager of the HALT-IT trial. IR: conceived the study; designed the methods; interpreted the results; contributed to the preparation of the final manuscript. Chief Investigator of the HALT-IT trial.

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 and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval We judge that separate institutional review board approval for this analysis is not required. This study involves the analysis of existing trial data. Each trial providing individual patient data received local ethical approval. All patients contributing data to this analysis provided consent for their participation in the original trials. This original consent included approval for the use of their anonymised data in future research studies. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. The trial data included in this analysis are available for download from the FreeBIRD data repository (freebird.lshtm.ac.uk).

ORCID iD

Katharine Ker http://orcid.org/0000-0002-1514-5005

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Supplementary material

1. Ovid MEDLINE search strategy

1. exp Antifibrinolytic Agents/
2. (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.
3. exp Aprotinin/
4. (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren).ab,ti.
5. exp Tranexamic Acid/
6. (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.
7. exp Aminocaproic Acids/ or exp 6-Aminocaproic Acid/
8. (((aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan).ab,ti.
9. exp 4-Aminobenzoic Acid/tu [Therapeutic Use]
10. (PAMBA or para-aminomethylbenzoic or p-aminomethylbenzoic or amino?methylbenzoic acid or Gumbix or Styptopur or H-4-AMB-OH or CAS:56-91-7 or H-4AMBZ-OH or NH2-CH2-PH4-COOH or TIMTEC-BB SBB006704 or "RARECHEM AL BW 0005" or Amino-p-toluicacid).ti,ab.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 10
12. randomi?ed.ab,ti.
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. placebo.ab.
16. clinical trials as topic.sh.
17. randomly.ab.
18. trial.ti.
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. (animals not (humans and animals)).sh.
21. 19 not 20
22. 11 and 21

2. Statistical methods for calculating the combined effect estimate of tranexamic acid across the included trials

We assume the relationship between the odds of death within 24 hours of bleeding onset and treatment arm and other variables is described by the formula:

$$\text{logit death} = \beta_0 + \beta_1 \text{treat} + \beta_2 \text{trial} + \beta_3 \text{age} + \beta_4 \text{SBP} + \beta_5 \text{time}$$
(Model 1)

Where :
treat is 0 or 1 depending on whether the patient was randomised to receive placebo or TXA
SBP is systolic blood pressure
Age is patient age at randomisation
time is time between bleeding onset and randomisation

We used the same method for calculating the effect of tranexamic acid across trials on myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism.

Method for checking if tranexamic acid effectiveness varies across trials.

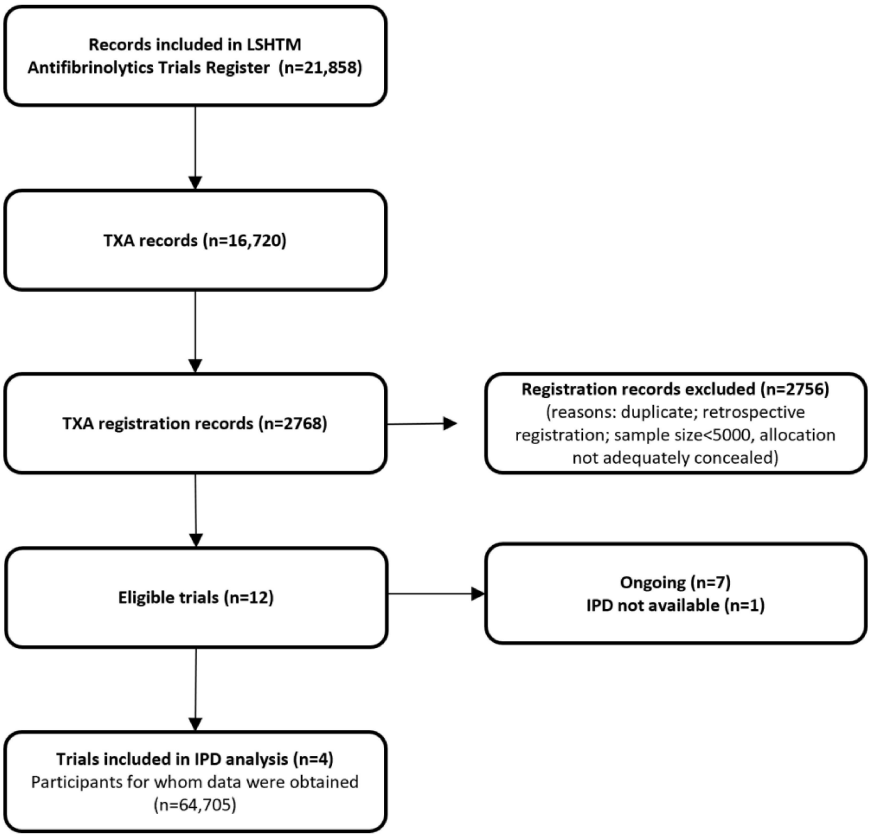
To test for the heterogeneity of tranexamic acid effectiveness across the four trials we added an interaction term to our model (see model 2).

$$\text{logit death} = \beta_0 + \beta_1 \text{treat} + \beta_2 \text{trial} + \beta_3 \text{treat} * \text{trial} + \beta_4 \text{age} + \beta_5 \text{SBP} + \beta_6 \text{time}$$
(Model 2)

We then used a likelihood ratio test to test the hypothesis that model 2 wasn't a better fit to our data compared to model 1.

We used the same method to test for the heterogeneity of tranexamic acid across trials for myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism.

3. Flow diagram of the identification and selection of trials



4. Characteristics of included and ongoing trials

Trial	Participants	Intervention	Outcomes
Eligible completed trials contributing IPD for analysis			
CRASH-2 (ISRCTN86750102; NCT00375258) Status: Complete	N=20,211 Adult (>16 years) trauma patients with, or at risk of, significant bleeding.	A loading dose of 1 g tranexamic acid or placebo will be administered as soon possible, followed by a maintenance dose of 1 g TXA or placebo over eight hours.	*Primary:* Death. *Secondary:* Vascular occlusive events, blood transfusion requirements, disability.
WOMAN (ISRCTN76912190; NCT00872469; PACTR201007000192283) Status: Complete	N=20,060 Women with clinically diagnosed postpartum haemorrhage following vaginal delivery of a baby or caesarean section. The clinical diagnosis of PPH may be based on any of the following: estimated blood loss after vaginal delivery of a baby> 500 mL OR >1000 mL from caesarean section OR blood loss sufficient to compromise the haemodynamic status of the woman.	1g tranexamic acid by intravenous injection or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. If after 30 minutes bleeding continues, or if it stops and restarts within 24 hours after the first doe given.	*Primary:* Death or hysterectomy. *Secondary:* Death, surgical intervention, blood transfusion, health status, thromboembolic events, other relevant medical events, length of stay at hospital/time spent at an intensive care unit, mechanical ventilation, status of breastfed baby/ies.
CRASH-3 (ISRCTN15088122; NCT01402882; EudraCT2011-003669-14; PACTR20121000441277) Status: Complete	N= 12,737 Adults with TBI who were within 3 h of injury, had a Glasgow Coma Scale score of 12 or lower or any intracranial bleeding on CT scan, and no major extracranial bleeding.	Loading dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. Maintenance dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) given after the loading dose is finished.	*Primary:* head injury-related death in hospital within 28 days of injury in patients treated within 3 h of injury *Secondary:* early head injury-related death (within 24 h after injury), all-cause and cause-specific mortality, disability, vascular occlusive events, seizures, complications, neurosurgery, days in intensive care unit, and adverse events within 28 days of randomisation.

HALT-IT (ISRCTN11225767; NCT01658124) Status: Complete	N=12,009 Adults with acute significant upper or lower gastrointestinal bleeding. The diagnosis of significant bleeding was clinical but 'significant' implied a risk of bleeding to death and included patients with hypotension, tachycardia, or signs of shock, or those likely to need transfusion or urgent endoscopy or surgery.	Loading dose of tranexamic acid (1g by intravenous injection) or placebo (sodium chloride 0.9%) will be given as soon as possible after randomisation, followed by an intravenous infusion of 3g of tranexamic acid or placebo (sodium chloride 0.9%) over 24 hours.	*Primary:* death due to bleeding within 5 days of randomisation. *Secondary:* death due to bleeding within 24 hours and within 28 days of randomisation, all-cause and cause-specific mortality at 28 days, rebleeding within 24 hours, within 5 days and within 28 days of randomisation, surgery or radiological intervention, blood product transfusion, thromboembolic events, seizures, other complications (including other significant cardiac event, sepsis, pneumonia, respiratory failure, renal failure, liver failure), days in intensive care unit, and functional status.
Other eligible completed trials not contributing IPD to this analysis			
POISE-3 (NCT03505723) Status: Complete	N=9535 Patients undergoing non-cardiac surgery who are at risk of a perioperative cardiovascular event.	Patients will receive a 1g loading dose of intravenous tranexamic acid within 20 minutes before skin incision and a 1g loading dose of intravenous tranexamic acid at the end of surgery (wound closure) or matching placebo.	*Primary:* A composite of life-threatening bleeding, major bleeding, and critical organ bleeding, a composite of myocardial injury after noncardiac surgery, non-hemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism. *Secondary:* A net risk-benefit outcome as a composite of vascular death, and non-fatal life-threatening, major or critical organ bleeding, myocardial injury after noncardiac surgery, stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism, International Society on Thrombosis and Haemostasis (ISTH) major bleeding, bleeding independently associated with mortality after noncardiac surgery, myocardial injury after noncardiac surgery, myocardial infarction.
Potentially eligible ongoing trials			
WOMAN-2	N=10,000 (planned)	A single dose of 1 g of tranexamic acid or placebo (sodium chloride 0.9%) by intravenous injection	*Primary*: postpartum haemorrhage *Secondary:* postpartum blood loss, haemoglobin, haemodynamic instability,

(ISRCTN62396133; NCT03475342) Status: Recruiting	Women with moderate or severe anaemia (Hb level < 100 g/L or packed cell volume (PCV) < 30%), who have given birth vaginally and for who the responsible clinician is substantially uncertain whether to use TXA. Planned trial end date: August 2023	will be given immediately after the umbilical cord is cut or clamped, and no more than 15 min later.	shock index, quality of life (maternal), expected side effects of trial medication, exercise tolerance, interventions to control primary postpartum haemorrhage (medical and surgical, receipt of blood product transfusion, vascular occlusive events, symptoms of anaemia, organ disfunction, sepsis, in hospital death, length of hospital stay, admission to and time spent in higher level facility, status of baby/ies, thromboembolic events in breastfed babies, adverse events.
ChiCTR1900025695 Status: Recruiting	N=6000 (planned) Adults undergoing primary unilateral arthroplasty; and with at least one risk factor for thrombosis (previous history of DVT, PE, myocardial infarction, stroke, transient ischemic attack, post-coronary stenting, post-coronary artery bypass grafting, and hypercoagulable state). Planned trial end date: April 2020	Intravenous tranexamic acid versus no tranexamic acid. No further details described.	*Primary:* VTE within 3 months after operation; blood transfusion rate; *Secondary:* Haemoglobin level, total bleeding volume, length of hospitalisation, hospitalisation costs.
NCT03364491 Status: Recruitment completed	N=11,000 (planned) Women undergoing scheduled or unscheduled caesarean section. Planned trial end date: August 2021	A single dose of 1g tranexamic acid administered intravenously immediately following umbilical cord clamping (or as soon as possible afterwards) or matching placebo.	*Primary:* Maternal death or transfusion of packed red blood cells *Secondary:* Estimated blood loss, surgical or radiological interventions to control bleeding and related complications (laparotomy, evacuation of hematoma, hysterectomy, uterine packing, intrauterine balloon tamponade, interventional radiology), transfusion related acute lung injury, transfusion of other blood products, acute kidney injury, thromboembolic events (venous or arterial), ischemic stroke, or myocardial infarction, new-onset seizure activity, postpartum infectious complications, admission to the intensive care unit for more than 24 hours, maternal death, use of

			uterotonics other than oxytocin, change in haemoglobin, TXA side effects, open label use of TXA or other antifibrinolytic, length of stay, hospital re-admission, any transfusion-associated reactions.
CRASH-4 (EudraCT2020-003391-40; NCT04521881) Status: Recruiting	N=10,000 (planned) Patients aged ≥70 years with symptomatic mild (GCS ≥13) traumatic brain injury. Planned trial end date: March 2025	A single dose of 500mg tranexamic acid given by intramuscular injection or matching placebo.	*Primary:* Discharge from the emergency department within 24 hours of arrival. *Secondary:* Intracranial bleeding on CT scan; death (intracranial bleeding-related, other causes); disability (Barthel scale); global assessment of ability to selfcare functioning; vascular occlusive events (pulmonary embolism, myocardial infarction, deep vein thrombosis, stroke); seizures; pneumonia; injection site reaction; other adverse events, patient management (neurosurgery, days in ICU, days in hospital); re-admission to hospital within 28 days; dementia diagnosis at 1 year.
TICH-3 (EudraCT2021-001050-62; ISRCTN97695350)	N=5,500 (planned) Adult patients with intracerebral haemorrhage confirmed on brain imaging within 4.5 hours of symptom onset. Planned trial end date: February 2028	2g tranexamic acid given as 100 ml infusion over 10 min or matching placebo.	*Primary:* Early death (≤7 days) *Secondary:* Disability measured by modified Rankin Scale (mRS) at day 180, venous thromboembolism/ischaemic events/seizures measured by review of medical notes at day 7; quality of life measured by EQ-5D visual analogue score (VAS) at day 180; cognition measured by AD-8 at day 180; health economics (use of antihypertensive medication, Do Not Resuscitate orders, admission to intensive care, neurosurgical intervention, hospital length of stay and discharge disposition) measured by review of medical notes at day 180.
TRACTION (NCT04803747) Status: Recruiting	N=8,320 (planned) A multicentre, randomized, registry-based cluster-crossover trial. Participating centres will be centrally and randomly allocated to receive either TXA or matching placebo at 1 month intervals for a total of 8 months. Patients aged ≥18 years undergoing surgery	1g tranexamic acid bolus (2g for patients over 100 kg) administered within 10 minutes of the first surgical incision, followed by 1g given at 2-4 hours of surgery or prior to skin closure, at the discretion of the anaesthesiologist, or matching placebo.	*Primary:* number of patients requiring transfused RBC; number of patients with VTE events. *Secondary:* number of RBC units transfused; in-hospital diagnosis of myocardial infarction, stroke, deep vein thrombosis or pulmonary embolus; length of hospital stay; ICU admission;

	known to be associated with a baseline RBC transfusion rate of ≥ 5%, will be included. Planned trial end date: April 2023		3-month survival; number of days at home to day 30; proportion of eligible patients who receive the policy intervention.
I'M WOMAN (ISRCTN12590098; NCT05562609) Status: Not yet recruiting	N=30,000 (planned) A multicentre, placebo-controlled, randomised trial to assess the effects of intramuscular (IM) and intravenous (IV) TXA in women at increased risk of PPH Planned trial end date: September 2025	1g IM tranexamic acid and IV placebo; or 1g IV tranexamic acid and IM placebo; or matching placebo. The trial treatment will be given just prior to skin incision (after draping) in caesarean births and at crowning in vaginal births.	*Primary:* A clinical diagnosis of primary PPH. *Secondary:* Surgical and postpartum blood loss, interventions for bleeding (drugs for PPH treatment, blood transfusion, non-surgical and surgical interventions), prespecified maternal adverse events (nausea, retching, vomiting, dizziness, skin reaction or pain at injection sites, thromboembolic events, seizure, sepsis, organ dysfunction), days in ICU/HDU, length of hospital stay, death by cause, neonatal outcomes (breastfeeding, congenital abnormality, death by cause, thromboembolic event, seizure, intracranial or pulmonary bleeding, bruising), other adverse events.

5. Baseline characteristics of HALT-IT and three previous trials, overall and for the subset of patients treated within 3 hours of bleeding onset

	≤3 hours		Total	
Baseline variable	**3 previous trials**	**HALT-IT**	**3 previous trials**	**HALT-IT**
Contributing IPD	37,540	1,926	52,787	11,937
Time to treatment (hrs)				
Mean (SD)	1.4 (0.9)	2 (0.8)	3.1 (14.6)	21.9 (36.8)
Median (IQR)	1.0 (0.7-2.8)	2 (1-3)	2 (1-4)	11 (5-24)
Missing (%)	0 (0)	0 (0)	18 (<0.1)	1 (<0.01)
Age (years)				
<20 (%)	2918 (8)	25 (1)	4119 (8)	110 (1)
20-39 (%)	25,617 (68)	231 (12)	35,244 (67)	1455 (12)
40-59 (%)	6146 (16)	866 (45)	8949 (17)	4664 (39)
60-79 (%)	2351 (6)	616 (32)	3594 (7)	4184 (35)
≥80 (%)	503 (1)	188 (10)	873 (2)	1524 (13)
Missing (%)	5 (<0.1)	0 (0)	8 (<0.1)	0 (0)
Mean (SD)	33.7 (14.1)	55.8 (16.3)	34.2 (14.7)	58 (17.0)
Median (IQR)	30 (24-38)	55 (45-66)	30 (24-40)	58 (46-70)
SBP				
≤75 (%)	3364 (9)	106 (6)	4707 (9)	327 (3)
75-90 (%)	9447 (25)	606 (31)	13,335 (25)	2426 (20)
>90 (%)	24,688 (66)	1206 (63)	34,671 (66)	9149 (77)
Missing (%)	41 (0.1)	8 (0.4)	74 (0.1)	35 (0.3)
Mean (SD)	106.1 (28.8)	104.6 (23.9)	106.5 (29)	111.1 (23.6)
Median (IQR)	100 (90-120)	100 (90-118)	100 (90-120)	110 (95-125)

6. Assessment of risk of bias of included trials contributing IPD

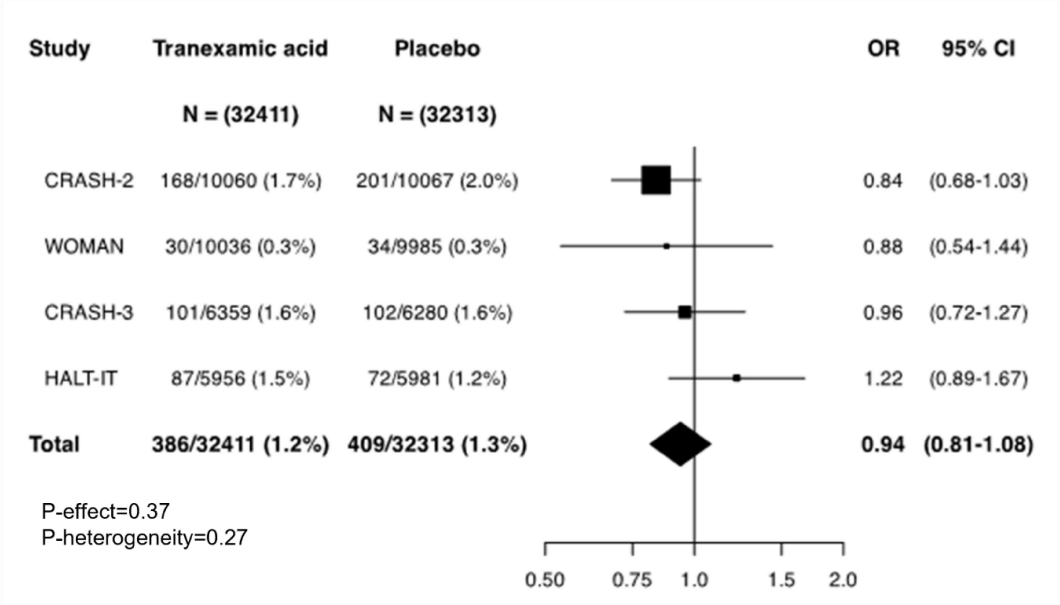
Risk of bias domain	CRASH-2	WOMAN	CRASH-3	WOMAN	HALT-IT
Generation of random sequence	**LOW RISK** Computer-generated	**LOW RISK** Computer-generated	**LOW RISK** Computer-generated	**LOW RISK** Computer-generated	**LOW RISK** Computer-generated
Concealment of allocation	**LOW RISK** Central allocation	**LOW RISK** Central allocation	**LOW RISK** Central allocation	**LOW RISK** Central allocation	**LOW RISK** Central allocation
Blinding	**LOW RISK** Patients, caregivers, and those assessing outcomes were blinded	**LOW RISK** Patients, caregivers, and those assessing outcomes were blinded	**LOW RISK** Patients, caregivers, and those assessing outcomes were blinded	**LOW RISK** Patients, caregivers, and those assessing outcomes were blinded	**LOW RISK** Patients, caregivers, and those assessing outcomes were blinded
Missing outcome data	**LOW RISK** Follow-up >99%	**LOW RISK** Follow-up >99%	**LOW RISK** Follow-up >99%	**LOW RISK** Follow-up >99%	**LOW RISK** Follow-up >99%
Selective outcome reporting	**LOW RISK** Prospectively registered. Complete IPD obtained	**LOW RISK** Prospectively registered. Complete IPD obtained	**LOW RISK** Prospectively registered. Complete IPD obtained	**LOW RISK** Prospectively registered. Complete IPD obtained	**LOW RISK** Prospectively registered. Complete IPD obtained

7. Outcome data for patients contributing data to the IPD meta-analysis

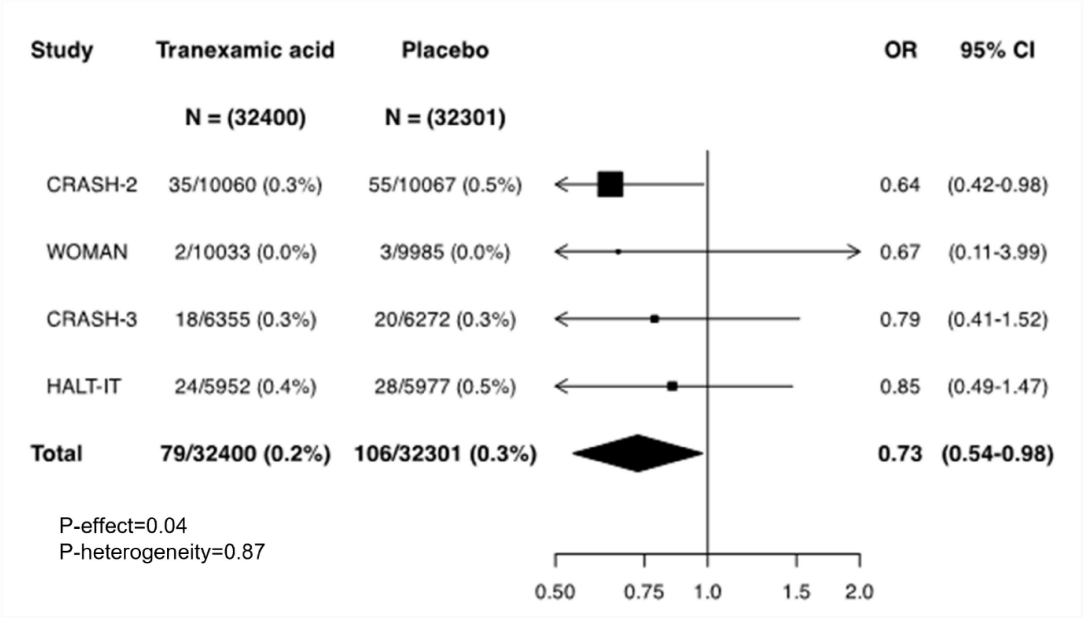
	CRASH-2	WOMAN	CRASH-3	HALT-IT	ALL
Randomised (N)	20,211	20,060	12,737	12,009	65,017
Contributing IPD (N)	20,127	20,021	12,639	11,937	64,724
Death within 24 hrs n (%)					
All patients	1525 (7.6)	353 (1.8)	715 (5.7)	199 (1.7)	2792 (4.3)
Patient treated within 3 hrs	1192 (8.8)	240 (1.6)	576 (6.3)	77 (4.0)	2085 (5.3)
Vascular occlusive events n (%)					
Any event	369 (1.83)	64 (0.32)	203 (1.61)	159 (1.33)	795 (1.23)
Myocardial infarction	90 (0.45)	5 (0.02)	38 (0.30%)	52 (0.44)	185 (0.29)
Stroke	123 (0.61)	14 (0.07)	88 (0.70)	38 (0.32)	263 (0.41)
Deep vein thrombosis	81 (0.40)	10 (0.05)	35 (0.28)	35 (0.29)	161 (0.25)
Pulmonary embolism	143 (0.71)	37 (0.18)	56 (0.44)	44 (0.37)	280 (0.43)

8. Results of IPD meta-analyses of the effect of TXA on vascular occlusive events. The effect estimates are adjusted for age, systolic blood pressure and time to treatment.

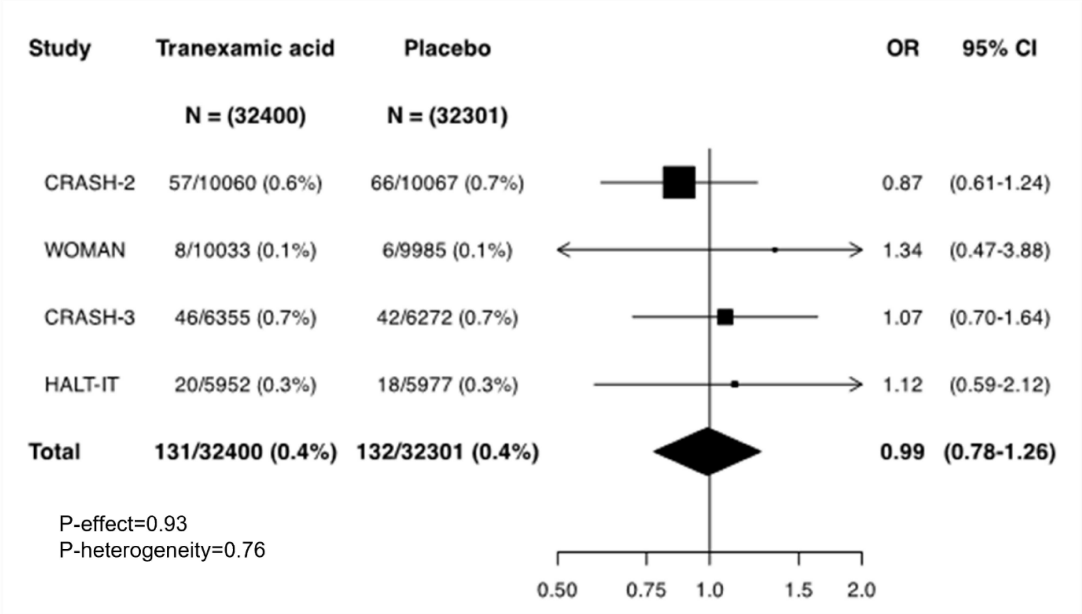
Any vascular occlusive event



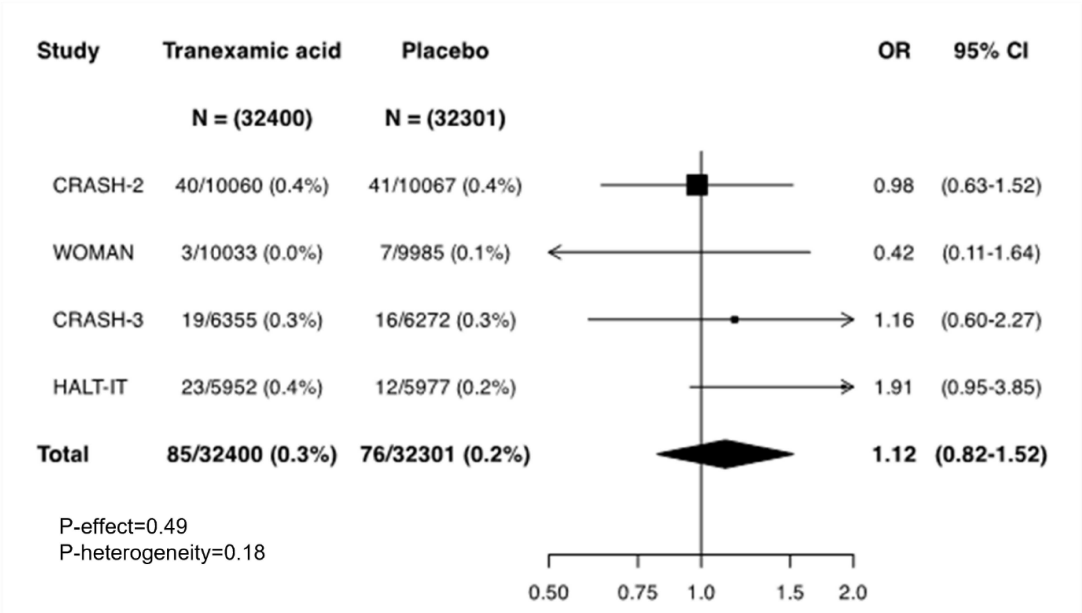
Myocardial infarction



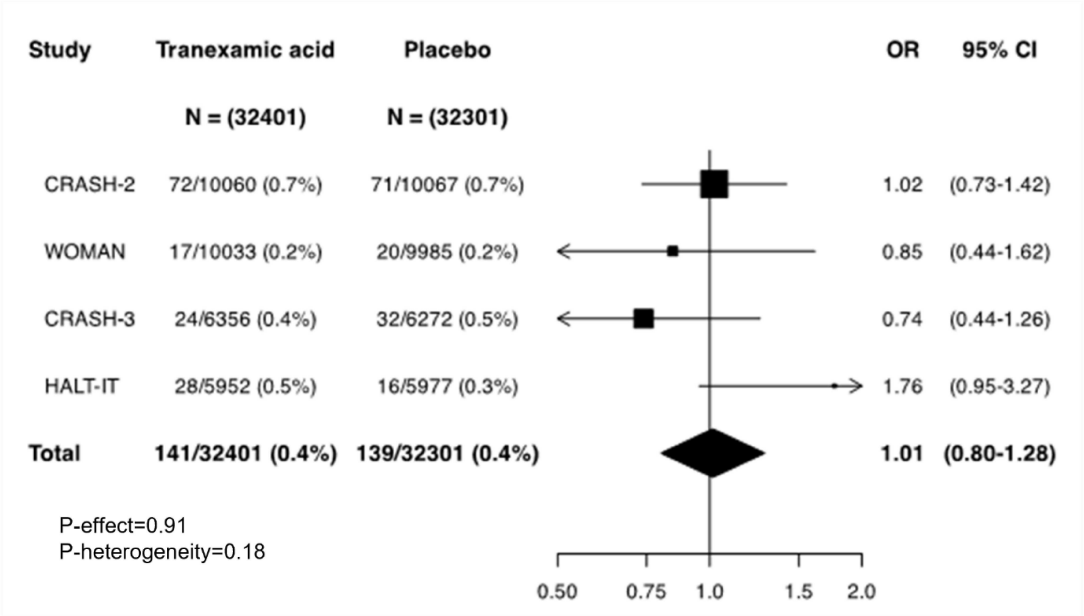
Stroke



Deep vein thrombosis



Pulmonary embolism



9. Certainty of the evidence for each outcome as assessed using the GRADE approach

	Quality assessment							n/N		Effect	
Outcome	**# trials**	**Design**	**Risk of bias**	**Inconsistency**	**Imprecision**	**Indirectness**	**Reporting bias**	**TXA**	**Placebo**	**Odds ratio (95% CI)**	**Quality**
Deaths within 24 hrs (all patients)	4	RCT	Not serious	Not serious	Not serious	Serious[1]	None	1290/32411	1502/32313	0.84 (0.78 to 0.91)	Moderate ⊕⊕O⊕
Deaths within 24 hrs (patients treated within 3 hrs)	4	RCT	Not serious	Not serious	Not serious	Serious[1]	None	945/19873	1140/19593	0.80 (0.73 to 0.88)	Moderate ⊕⊕O⊕
Fatal or non-fatal vascular occlusive event	4	RCT	Not serious	Not serious	Serious[2]	Serious[1]	None	386/32414	409/32313	0.94 (0.81 to 1.08)	Low ⊕OO⊕
Myocardial infarction	4	RCT	Not serious	Not serious	Serious[2]	Serious[1]	None	79/32414	106/32313	0.73 (0.54 to 0.98)	Low ⊕OO⊕
Stroke	4	RCT	Not serious	Not serious	Serious[2]	Serious[1]	None	131/32414	132/32313	0.99 (0.78 to 1.26)	Low ⊕OO⊕
DVT	4	RCT	Not serious	Not serious	Serious[2]	Serious[1]	None	85/32414	76/32313	1.12 (0.82 to 1.52)	Low ⊕OO⊕
Pulmonary embolism	4	RCT	Not serious	Not serious	Serious[2]	Serious[1]	None	141/32414	139/32313	1.01 (0.80 to 1.28)	Low ⊕OO⊕

[1]Downgraded one level for indirectness: absence of trials assessing effects in other important bleeding conditions e.g. surgical bleeding

[2]Downgraded one level for imprecision: The CIs for the pooled effect estimate are consistent with both an appreciable benefit and appreciable harm.