Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients

*Angèle Gayet-Ageron, David Prieto-Merino, Katharine Ker, Haleema Shakur, François-Xavier Ageron, Ian Roberts, for the Antifibrinolytic Trials Collaboration**

Summary

Background Antifibrinolytics reduce death from bleeding in trauma and post-partum haemorrhage. We examined the effect of treatment delay on the effectiveness of antifibrinolytics.

Methods We did an individual patient-level data meta-analysis of randomised trials done with more than 1000 patients that assessed antifibrinolytics in acute severe bleeding. We identified trials done between Jan 1, 1946, and April 7, 2017, from MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, PubMed, Popline, and the WHO International Clinical Trials Registry Platform. The primary measure of treatment benefit was absence of death from bleeding. We examined the effect of treatment delay on treatment effectiveness using logistic regression models. We investigated the effect of measurement error (misclassification) in sensitivity analyses. This study is registered with PROSPERO, number 42016052155.

Findings We obtained data for 40 138 patients from two randomised trials of tranexamic acid in acute severe bleeding (traumatic and post-partum haemorrhage). Overall, there were 3558 deaths, of which 1408 (40%) were from bleeding. Most (884 [63%] of 1408) bleeding deaths occurred within 12 h of onset. Deaths from post-partum haemorrhage peaked 2–3 h after childbirth. Tranexamic acid significantly increased overall survival from bleeding (odds ratio [OR] 1·20, 95% CI 1·08–1·33; p=0·001), with no heterogeneity by site of bleeding (interaction p=0·7243). Treatment delay reduced the treatment benefit (p<0·0001). Immediate treatment improved survival by more than 70% (OR 1·72, 95% CI 1·42–2·10; p<0·0001). Thereafter, the survival benefit decreased by 10% for every 15 min of treatment delay until 3 h, after which there was no benefit. There was no increase in vascular occlusive events with tranexamic acid, with no heterogeneity by site of bleeding (p=0·5956). Treatment delay did not modify the effect of tranexamic acid on vascular occlusive events.

Interpretation Death from bleeding occurs soon after onset and even a short delay in treatment reduces the benefit of tranexamic acid administration. Patients must be treated immediately. Further research is needed to deepen our understanding of the mechanism of action of tranexamic acid.

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*Members of the Antifibrinolytic Trials Collaboration are listed at the end of the Article

Clinical Trials Unit (A Gayet-Ageron MD, K Ker MSc, H Shakur MSc, F-X Ageron MD, Prof I Roberts MD) **and Faculty of Epidemiology and Population Health** (D Prieto-Merino PhD), **London School of Hygiene & Tropical Medicine, London, UK; Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland** (A Gayet-Ageron); **and Department of Emergency Medicine—Northern French Alps Emergency Network, Annecy Genevois Hospital, Annecy, France** (F-X Ageron)

Correspondence to: Prof Ian Roberts, Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK **ian.roberts@lshtm.ac.uk**

Introduction

Acute severe bleeding is a leading cause of death.[1] Traumatic extracranial haemorrhage, often the consequence of road traffic crashes or violence, is responsible for more than two million deaths each year.[2] Traumatic and spontaneous intracranial bleeding are common causes of death and disability.[3] Severe surgical haemorrhage strongly predicts adverse patient outcomes and is associated with an increase in the odds of death by eight times.[4] Thousands of patients are admitted to hospital with gastrointestinal bleeding each year in the UK, with a case fatality of about 10% for upper gastrointestinal bleeding and 3% for lower gastrointestinal bleeding.[5,6] Post-partum haemorrhage accounts for about 100 000 maternal deaths each year worldwide, with the majority occurring in less-developed countries.[7]

Antifibrinolytic drugs (tranexamic acid, aminocaproic acid, aprotinin, and aminomethylbenzoic acid) reduce bleeding by inhibiting the breakdown of fibrin clots.[8,9] Antifibrinolytics reduce surgical bleeding and the need for transfusion by about a third, irrespective of the site of surgery.[10] Administration of tranexamic acid within 3 h of bleeding onset reduces deaths from bleeding in patients with trauma and post-partum haemorrhage.[11–13] We sought to quantify the effect of treatment delay on the effectiveness of antifibrinolytics in acute severe bleeding by analysing individual patient-level data from randomised placebo-controlled trials.

Research in context

Evidence before this study

We sought to identify whether the benefits and harms of antifibrinolytic treatment vary by site of bleeding and time to treatment, by doing an individual patient-level data meta-analysis of relevant randomised trials done with more than 1000 participants. Systematic searches of MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov identified two randomised trials that assessed the effect of time to treatment in subgroup analyses (treatment started less than or more than 3 h since bleeding onset). Both trials had a low risk of bias and both showed that starting tranexamic acid within 3 h of bleeding onset reduced death from bleeding. However, no studies examined whether the effects of treatment varied by site of bleeding or explored the continuous association between treatment delay and the effectiveness and safety of antifibrinolytics.

Added value of this study

This individual patient-level data meta-analysis comprises data on 40 138 bleeding patients from two large trials in traumatic and post-partum bleeding. Most deaths from haemorrhage occur within hours of bleeding onset. We found no evidence that the effectiveness and safety of tranexamic acid varied by site of bleeding but found strong evidence that treatment delay reduces the survival benefit of tranexamic acid administration. Whereas immediate treatment greatly increases the odds of survival, the benefit decreases by about 10% for every 15 min of treatment delay until 3 h, after which there is no benefit.

Implications of all the available evidence

Patients with acute severe bleeding should receive antifibrinolytic treatment as soon as possible after bleeding onset. Trauma patients should be treated at the scene of injury and post-partum haemorrhage should be treated as soon as the diagnosis is made. Clinical audit should record the time from bleeding onset to tranexamic acid treatment, with feedback and best practice benchmarking.

Methods

Search strategy and selection criteria

We did an individual patient-level data meta-analysis of randomised placebo-controlled trials done with more than 1000 patients that assessed the effects of antifibrinolytics (including aprotinin, tranexamic acid, aminocaproic acid, and aminomethylbenzoic acid) in acute severe bleeding. We identified trials done between Jan 1, 1946, and April 7, 2017, from a register of antifibrinolytic trials maintained by the London School of Hygiene & Tropical Medicine Clinical Trials Unit. The register comprises MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, PubMed, Popline, and the WHO International Clinical Trials Registry Platform (appendix). Abstracts were screened for relevant trials and selection criteria were applied. Reasons for exclusion were discussed and discrepancies were solved by consensus. Two reviewers (AG-A and KK) independently extracted data to minimise bias. We analysed individual patient-level data for baseline, outcome, and predictor variables (treatment delay reported in the CRASH-2 trial, dates of randomisation and dates of death in CRASH-2, dates and times of randomisation, and births and deaths in the WOMAN trial) from the selected trials. We prepared a statistical analysis plan before searching for trials. We registered the study protocol in November, 2016 (PROSPERO, number 42016052155). Institutional review board approval was not required.

See Online for appendix

For the **study protocol** see http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016052155

Outcomes

The primary measure of treatment benefit was absence of death from bleeding (ie, survival from bleeding or death from other causes). Death due to bleeding was chosen as the primary outcome because of the mechanism of action of antifibrinolytic drugs. These drugs inhibit the breakdown of fibrin clots and reduce bleeding. All-cause mortality is a composite outcome that combines deaths likely to be affected by antifibrinolytic treatment (eg, deaths from bleeding) with those unlikely to be affected by treatment (eg, sepsis), and this outcome would bias the relative risk towards the null.[14,15] Although some authors believe that tranexamic acid decreases trauma mortality by preventing inflammation, there is little evidence to support this hypothesis and the main effect of tranexamic acid is a reduced risk of exsanguination on the day of injury.[16] Secondary outcomes were vascular occlusive fatal and non-fatal events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis).

We evaluated the quality of the clinical trials selected by assessing sequence generation, allocation concealment, blinding, data completeness, and risk of selective reporting. Two reviewers (AG-A and KK) independently rated the risk of bias according to established criteria.[17]

We estimated treatment delay as the interval between bleeding onset and start of antifibrinolytic treatment. In the CRASH-2 trial, clinicians reported treatment delay. In the WOMAN trial, we estimated treatment delay as the interval between birth and randomisation.

Data analysis

All analyses were done according to the intention-to-treat principle. Data analysis was based on individual patient-level data. For continuous variables, we have reported the mean, SD, and median (IQR). For

categorical variables, we have reported numbers and proportions. We plotted frequency distributions for treatment delay and time to death from bleeding for each trial. We assessed the natural history of death from bleeding by plotting frequency distributions of hours to death from bleeding among untreated women with post-partum haemorrhage. We compared patients who died from exsanguination and were treated within the first hour with those who received later treatment, by use of the χ^2 test (type of injury, sex) or Student's t test (age, systolic blood pressure, heart rate, and volume of blood loss). We have reported deaths and vascular occlusive events by treatment allocation for each trial and overall.

We examined the effectiveness of antifibrinolytics on binary outcomes using logistic regression. We have reported treatment effects with odds ratios (OR) and 95% CI. We expressed the effect of antifibrinolytics on survival as the OR for absence of death from bleeding (relative treatment benefit). We first assessed the homogeneity of the treatment effects between trials by including an interaction term between the treatment and the trial variable and reporting the p value (model 1, appendix).[18] We anticipated that treatment effect might be affected negatively by treatment delay and explored the effect of treatment delay on treatment effect by including terms for hours of treatment delay and its square (because of the non-linearity of the treatment effect), and interactions between these two variables with treatment group. To check the homogeneity of the effect of treatment delay across trials, we ran a second model with a triple interaction between the terms for treatment delay, the treatment group, and the trial (model 2, appendix). Once homogeneity of the effect of treatment delay across trials was verified, we reported results from a third model including the two interaction terms (model 3, appendix). We quantified the effect of treatment delay on treatment effectiveness by estimating $[100-(\text{OR at time } t-1)/(\text{OR at } t=0-1)\times 100]$, corresponding to the percentage reduction in maximal effectiveness at interval t by use of ORs from model 3. The biological plausibility of model 3 was assessed by reporting relative treatment benefits stratified by 60-min intervals of treatment delay. Because the effect of delay on treatment effectiveness might be confounded by bleeding severity, all models were controlled for systolic blood pressure (5 mm Hg intervals) and age (10-year intervals), which are strong risk factors for death due to bleeding.[19]

Because the time of bleeding onset (ie, time of injury) is often unknown in trauma patients, measurement error is inevitable. We investigated the effect of misclassification of treatment delay in sensitivity analyses using a range of plausible errors.[20] We added a random number of minutes to the treatment delay using a uniform distribution with a constant minimum set at 0 and four sets of maximum value: 15, 30, 45, and 60 min in the CRASH-2 dataset only. The corrections were based on data from an audit of treatment delay in a similar trial in traumatic brain injury (the CRASH-3 trial), in which treatment delay was rarely overestimated but often underestimated (mean underestimation 51 min).[21] In the WOMAN trial, treatment delay might have been overestimated by considering the time of birth as the time of bleeding onset. We therefore subtracted a random number of minutes from the treatment delay using a uniform distribution with a constant minimum set at 0 and one maximum value of 30 min in the WOMAN dataset (post-hoc analysis). For each of the four maximum values in the CRASH-2 dataset and the single maximum value in the WOMAN dataset, we re-estimated the final model 100 times to obtain ranges for the time to treatment interaction (model 3). We ran all analyses in Stata/IC, version 14.2.

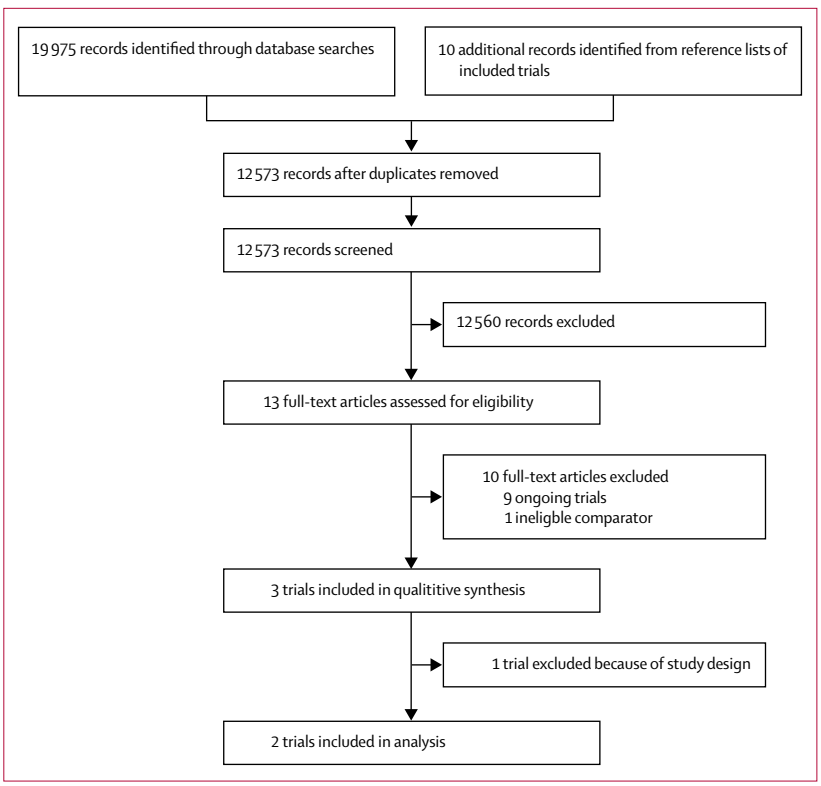

Figure 1: **Study selection**

Role of the funding source

The funders of the CRASH-2 and WOMAN trials had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Studies identified in our search are shown in figure 1. We found three completed[11,12,22] and nine ongoing trials,[21,23–27] (for three ongoing trials no published data were

available [EUCTR2015-002661-36-GB, NCT01060176, and NCT02936661]; appendix). All completed trials used tranexamic acid. The CRASH-2 trial[11] assessed the effects of tranexamic acid on death and vascular occlusive events in 20 211 bleeding trauma patients. The WOMAN trial[12] assessed the effects of tranexamic acid on death, hysterectomy, and other morbidities in 20 060 women with post-partum haemorrhage. The ATACAS trial[22] assessed the effects of tranexamic acid on death and thrombotic events in 4662 patients undergoing coronary artery surgery. Because all patients in the ATACAS trial were treated 30 min after induction of anaesthesia, we could not explore the effect of treatment delay in this trial. The included trials had low risk of bias for all domains (appendix).

We obtained individual patient-level data for 40 138 participants: 20 127 from the CRASH-2 trial and 20 011 from the WOMAN trial (table 1). The CRASH-2 trial participants were older than WOMAN trial participants. Of the 40 138 participants, 20 094 received tranexamic acid and 20 044 received placebo (table 2). Of the 3558 deaths, 1408 (40%) were due to bleeding, of which 884 (63%) occurred within 12 h of bleeding onset (appendix). In the WOMAN trial, where data on time to death were available, deaths from bleeding peaked at 2–3 h after bleeding onset in untreated women (figure 2). In the WOMAN trial, we excluded 109 (0·5%) patients with a treatment delay of more than 24 h (59 patients in the placebo group and 50 in the tranexamic acid group) on the basis of the WHO definition for primary post-partum haemorrhage.[28] We found no heterogeneity in the treatment effect between trials (model 1: interaction p=0·7243, appendix). Tranexamic acid significantly increased overall survival from bleeding (OR=1·20, 95% CI 1·08–1·33; p=0·001). We found similar results when we excluded from analysis the 2150 deaths from causes other than bleeding (data not shown).

The appendix shows the treatment benefits stratified by 60-min intervals of delay. With the exception of the first hour, effectiveness decreased with increasing treatment delay. Among patients who died from bleeding (appendix), we found that those who received treatment within the first hour were more often women and were younger with a higher proportion of penetrating injuries (for trauma patients). We found no heterogeneity in the interaction between treatment delay and the effect of tranexamic acid between trials (model 2: p=0·1363 for the triple interaction between the trial, tranexamic acid, and treatment delay with linear terms and p=0·3891 for the triple interaction between the trial, tranexamic acid, and treatment delay with squared terms). In model 3, treatment delay appeared to reduce the treatment benefit (p<0·0001 for the trend of increasing benefit with earlier

	CRASH-2 trial	WOMAN trial	Total
Number of patients randomised	20 127	20 011	40 138
Time to treatment (h)			
≤1	7452 (37·0%)	9572 (48·1%)	17 024 (42·5%)
1–3	6033 (30·0%)	5356 (26·9%)	11 389 (28·5%)
>3	6634 (33·0%)	4974 (25·0%)	11 608 (29·0%)
Missing or excluded data	8 (0·0%)	109 (0·5%)	117 (0·3%)
Mean (SD)	2·8 (2·1)	2·5 (3·4)	2·7 (2·9)
Median (IQR)	2·0 (1·0–4·0)	1·1 (0·5–3·0)	1·8 (0·8–4·0)
Age (years)			
≤25	6655 (33·1%)	6541 (32·7%)	13 196 (32·9%)
25–30	3417 (17·0%)	6707 (33·5%)	10 124 (25·2%)
30–35	2413 (12·0%)	4357 (21·8%)	6770 (16·9%)
>35	7640 (38·0%)	2399 (12·0%)	10 039 (25·0%)
Missing data	2 (0·0%)	7 (0·0%)	9 (0·0%)
Mean (SD)	34·6 (14·3)	28·5 (5·7)	31·5 (11·3)
Median (IQR)	30 (24–43)	28 (24–32)	29 (24–35)
Systolic blood pressure (mm Hg)			
≤75	3161 (15·7%)	1666 (8·3%)	4827 (12·0%)
75–90	6885 (34·3%)	5787 (28·9%)	12 672 (31·6%)
>90	10 052 (50·0%)	12 553 (62·8%)	22 605 (56·4%)
Missing data	29 (0·1%)	5 (0·0%)	34 (0·1%)
Mean (SD)	97·0 (27·9)	100·8 (22·7)	98·9 (25·5)
Median (IQR)	91 (80–110)	100 (90–110)	100 (87–110)

Table 1: **Baseline characteristics of patients in participating trials**

	CRASH-2 trial		WOMAN trial		Total	
	Tranexamic acid (n=10 060)	Placebo (n=10 067)	Tranexamic acid (n=10 034)	Placebo (n=9977)	Tranexamic acid (n=20 094)	Placebo (n=20 044)
Any cause of death	1463 (14·5%)	1613 (16·0%)	227 (2·3%)	255 (2·6%)	1690 (8·4%)	1868 (9·3%)
Death due to bleeding	489 (4·9%)	574 (5·7%)	155 (1·5%)	190 (1·9%)	644 (3·2%)	764 (3·8%)
Non-bleeding death	974 (9·7%)	1039 (10·3%)	72 (0·7%)	65 (0·7%)	1046 (5·2%)	1104 (5·5%)
Vascular occlusive events	168 (1·7%)	201 (2·0%)	31 (0·3%)	34 (0·3%)	199 (1·0%)	235 (1·2%)
Vascular death	33 (0·3%)	48 (0·5%)	10 (0·1%)	11 (0·1%)	43 (0·2%)	59 (0·3%)
Myocardial infarction*	35 (0·4%)	55 (0·5%)	2 (0·0%)	3 (0·0%)	37 (0·2%)	58 (0·3%)
Stroke*	57 (0·6%)	66 (0·7%)	8 (0·1%)	6 (0·1%)	65 (0·3%)	72 (0·4%)
Pulmonary embolism*	72 (0·7%)	71 (0·7%)	17 (0·2%)	20 (0·2%)	89 (0·4%)	91 (0·5%)
Deep vein thrombosis*	40 (0·4%)	41 (0·4%)	3 (0·0%)	7 (0·1%)	43 (0·2%)	48 (0·2%)

*Includes both fatal and non-fatal events.

Table 2: **Deaths and vascular occlusive events by treatment allocation**

treatment, figure 3) after adjustment for age and systolic blood pressure. When given immediately, tranexamic acid significantly improved survival (OR=1·72, 95% CI 1·42–2·10; p<0·0001) but the benefit decreased with increasing delay in a non-linear association (p=0·0109 for the interaction between treatment group and treatment delay squared). We estimated the time at which the lower bound of the 95% CI crossed the null value to be 135 min, with no apparent treatment benefit observed at 180 min. From model 3, we estimated that the treatment benefit decreased by 10% for every 15 min of treatment delay (figure 4). We found the same results after exclusion of deaths from other causes (data not shown).

After applying a random correction of up to 60 min to treatment delay for patients in the CRASH-2 trial and a random subtraction of up to 30 min to treatment delay in the WOMAN trial (post-hoc analysis), the relative treatment benefit from immediate tranexamic acid treatment varied between 70% (OR 1·70, 95% CI 1·38–2·11) and 82% (1·82, 1·47–2·25), with an average of 77% (1·77, 95% CI 1·43–2·18; appendix). The timepoint at which tranexamic acid had no effect increased from 180 min to 200 min.

The risk of vascular occlusive events was higher in patients with traumatic bleeding than in those with post-partum haemorrhage. There was no increase in fatal vascular occlusive events with tranexamic acid (OR 0·73, 95% CI 0·49–1·09; p=0·1204), with no heterogeneity between trials (p=0·5956; appendix). There were fewer cases of myocardial infarction (mostly reported in CRASH-2) with tranexamic acid (OR=0·64, 95% CI 0·43–0·97; p=0·0371) but there was no significant reduction in other vascular occlusive events. Treatment delay did not modify the effect of tranexamic acid on vascular occlusive events even after correction for misclassification. Adjustment for age or systolic blood pressure did not influence the results.

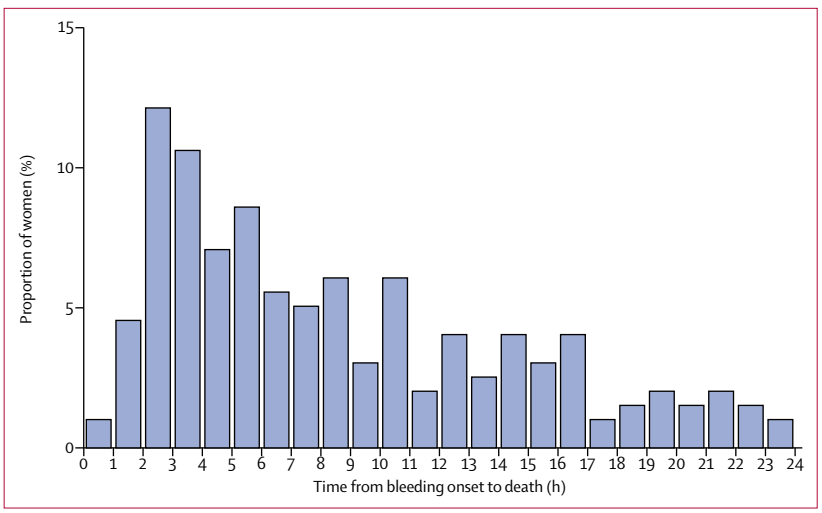

Figure 2: **Hours from onset of bleeding to death from bleeding among untreated women with post-partum haemorrhage**

Discussion

The principal findings of our individual patient-level data meta-analysis are that most deaths from bleeding occur on the day of onset and many occur within the first few hours. Deaths from post-partum haemorrhage peak at 2–3 h after childbirth. Tranexamic acid improves survival but treatment delay reduces the benefit. Every 15 min of treatment delay appears to decrease the benefit by about 10%, with no benefit after 3 h. We found no increase in vascular occlusive events with tranexamic acid.

Our study has various strengths and limitations. First, to reduce selection bias we excluded trials with fewer than 1000 patients. Small trials are underpowered to assess effects on death and there is an increased risk of selective reporting.[29] Second, time of death was only available for post-partum haemorrhage. However, the distribution of deaths by days since bleeding onset was similar in traumatic and post-partum bleeding, and studies show that deaths from traumatic bleeding also peak in the first few hours after injury.[30] Third, we assessed the effect of treatment delay on treatment effectiveness by use of logistic regression models with second-order polynomials to take into account the non-linearity of treatment effect. Because an on–off step function in treatment effectiveness is biologically implausible and highly unlikely, we used treatment delay as a continuous variable. To explore the interaction between treatment effect and time, we used all observations of patients treated within 24 h from bleeding onset and not only within 3 h. Although we found no statistical heterogeneity in the interaction between treatment delay and the effect of tranexamic acid between trials, whether the physiology of bleeding varies by cause is open to question. Treatment delay might be under-estimated in trauma, since many injuries are unwitnessed, and it might have been over-estimated in post-partum haemorrhage because time of birth was taken as the time of onset. Because of these uncertainties, we did sensitivity analyses with a range of plausible errors. Results of these analyses support the conclusion that prompt treatment is essential. Fourth, deaths due to bleeding and deaths from vascular occlusive events could have been misclassified.[11,12] Some deaths attributed to bleeding might have been due to thrombotic disseminated intravascular coagulation, especially those occurring several hours after onset. Although results adjusted for age and systolic blood pressure were similar, we cannot exclude the possibility that other unmeasured factors might have influenced the results. The large sample size—more than 40 000 patients with acute severe bleeding—provided a precise assessment of the effect of treatment delay with statistically significant results. All analyses were done on an intention-to-treat basis and missing data were negligible.

Our findings indicate that even a short treatment delay reduces the survival benefit from tranexamic acid. With the exception of the first hour, we found a clear trend of decreasing effectiveness with increasing treatment delay.

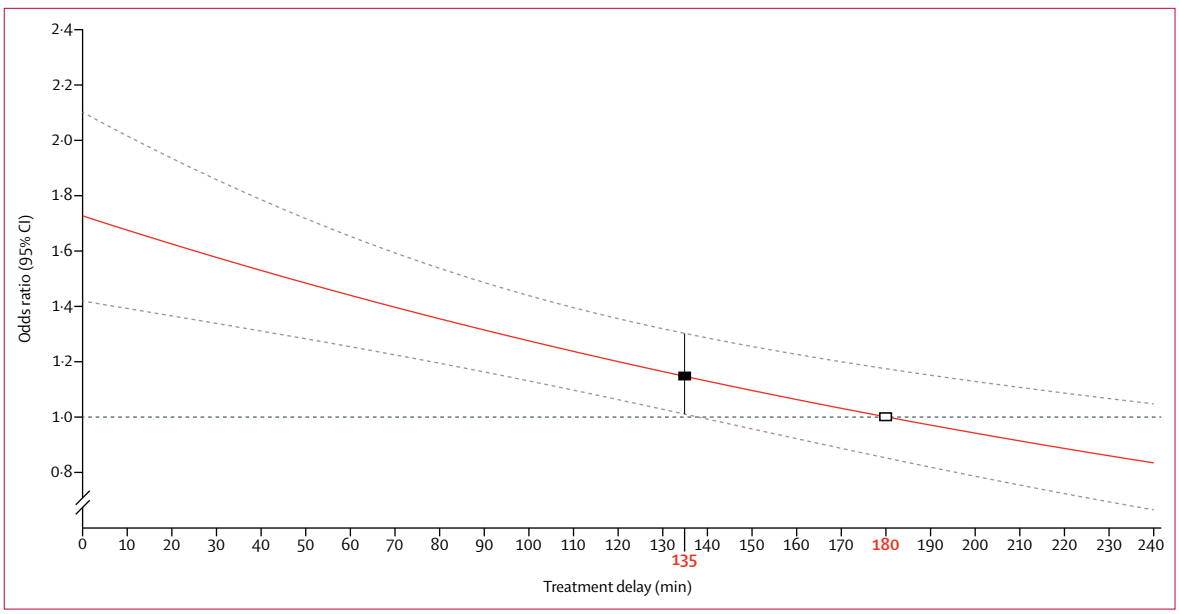

Figure 3: **Effect of treatment delay on treatment benefit (model 3)**
The red line shows the best fitted model for the association between the protective effect of tranexamic acid (odds ratio for not dying from bleeding) and duration of treatment delay in minutes (p_{slope}<0·0001). The grey lines are the lower and upper bounds of the 95% CI for this model. Estimates are derived from a logistic regression model of not dying from bleeding explained by the interaction of getting tranexamic acid and treatment delay (linear and squared terms) and adjusted for trial, age (5-year intervals), and systolic blood pressure (10-mm Hg intervals). The white square shows the timepoint at which the model estimates a null effect of tranexamic acid (a treatment delay of 180 min). The black square shows the timepoint at which the lower 95% CI model estimates a null effect of tranexamic acid (a treatment delay of 135 min).

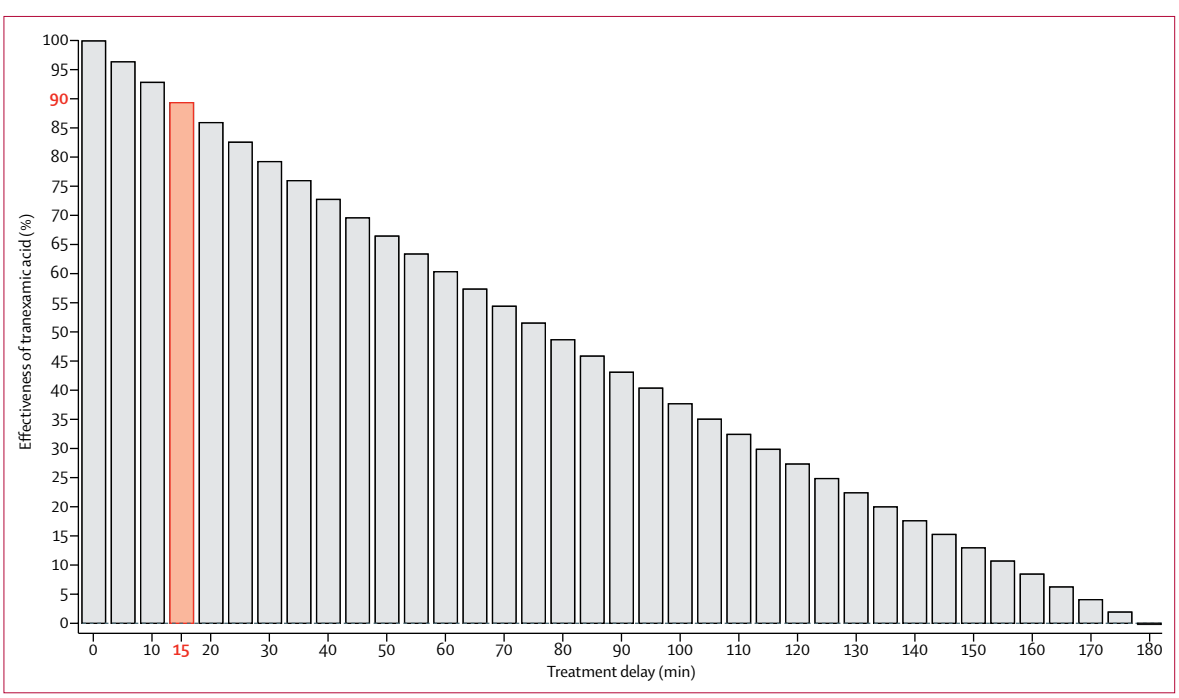

Figure 4: **Reduction in effectiveness of tranexamic acid with increasing treatment delay**
The bars represent the estimated treatment effectiveness (y-axis, estimated by [(OR at time $t-1$)/(OR at $t=0-1$) × 100] in %) at 5-min intervals of treatment delay. The bar highlighted in red shows the estimated treatment effectiveness (90%) with a treatment delay of 15 min.

The apparently lower treatment effect within the first hour might be due to random variability or limitations in timing the onset of bleeding (appendix). Alternatively, a larger proportion of patients treated within an hour of bleeding onset might have unsurvivable haemorrhage.[30] Trauma patients treated within an hour of injury were more likely

to have penetrating injuries than those treated later (appendix). With regard to the decrease in treatment effectiveness with increasing delay, several hypotheses can be proposed. First, we should expect some time lag between administration of tranexamic acid and its effect on mortality. It is unlikely that deaths occurring very soon after tranexamic acid administration could have been prevented by tranexamic acid. However, their inclusion in the trial will bias (dilute) the treatment effect towards the null. Given the temporal distribution of deaths from bleeding shown in figure 2, the extent of this null bias would increase with increasing treatment delay. Second, the ability to form a clot depends on fibrinogen concentrations. In patients with trauma and post-partum haemorrhage, low serum fibrinogen is predictive of life threatening bleeding.[31,32] Fibrinogen falls rapidly in severe bleeding because of its consumption during clot formation. However, fibrinolysis and fibrinogenolysis would increase the consumption of fibrinogen. Early tranexamic acid treatment should protect fibrinogen stores and maintain the ability to form a stable fibrin clot. Indeed, we should consider tranexamic acid as an intervention to prevent rather than treat coagulopathy. Further research into the mechanism of action of tranexamic acid in acute severe bleeding should improve our understanding of the observed time to treatment interaction.

These findings have various implications for clinical care. Bleeding patients should receive antifibrinolytics as soon as possible for three reasons. First, most deaths from haemorrhage occur within hours of bleeding onset. By reducing bleeding, tranexamic acid has the potential to prevent the hypoxia and acidosis that accompanies severe bleeding, but it must be given before tissue damage is irreversible. Second, the benefit of tranexamic acid treatment appears to decrease with increasing treatment delay. Third, we found no evidence of adverse effects associated with tranexamic acid treatment, so it can be given safely as soon as bleeding is suspected. Given the importance of early treatment, time from bleeding onset to treatment should be audited with feedback provided to health-care professionals. National or regional quality improvement initiatives, with best practice benchmarking of time to treatment, might improve survival.

We found nine ongoing trials of antifibrinolytics in acute severe bleeding. Two of these will provide additional data on the effect of treatment delay in severe extracranial bleeding. Because the data from these two trials will increase the number of participants by only 5%, it is unlikely that they will have a material effect on our conclusions. Nonetheless, ongoing trials should deepen our understanding of the safety and effectiveness of antifibrinolytics in traumatic and spontaneous intracranial bleeding, which are major causes of death and disability worldwide. Our review protocol also proposed an analysis of the extent to which the balance of benefits and harms of antifibrinolytic treatment vary with baseline risk. These results will be reported in a future publication.

Contributors

IR proposed the meta-analysis. AG-A, KK, and IR reviewed the scientific literature and wrote the study protocol. AG-A, DP-M, and IR were responsible for the statistical analysis plan, data analysis, data interpretation, and drafting. AG-A, DP-M, KK, HS, F-XA, and IR contributed to the interpretation of the results, critical revision of the manuscript, and approved the final version. AG-A, DP-M, KK, HS, F-XA, and IR agreed to be accountable for all aspects of the work.

Anti-fibrinolytic Trials Collaborators

Aasia Kayani, Amber Geer, Bernard Ndungu, Bukola Fawole, Catherine Gilliam, Cecelia Adetayo, Collette Barrow, Danielle Beaumont, Danielle Prowse, David I'Anson, Eni Balogun, Hakim Miah, Haleema Shakur, Ian Roberts, Imogen Brooks, Julio Onandia, Katharine Ker, Kiran Javaid, Laura Suncuan, Lauren Frimley, Mia Reid, Monica Arribas, Myriam Benyahia, Olujide Okunade, Phil Edwards, Rizwana Chaudhri, Sergey Kostrov, Sneha Kansagra, and Tracey Pepple.

Declaration of interests

We declare no competing interests.

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