Outcome measures in clinical trials of tranexamic acid for bleeding

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Declaration

I Amy Brenner, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Background: Acute bleeding is a major public health problem. Tranexamic acid is an antifibrinolytic drug that reduces bleeding by inhibiting blood clot breakdown. Several clinical trials have assessed the effects of tranexamic acid for bleeding. To provide a valid and reliable estimate of the treatment effect, a trial must be well designed with a suitable outcome measure. Due to similarities in pathophysiology and the types of interventions used to treat acute bleeding, clinical trials assessing tranexamic acid often evaluate similar outcomes regardless of the site or cause of bleeding. These trials provide a rich resource for assessing the suitability of different outcome measures. They also deepen our understanding of the natural history of bleeding and the mechanism of action of tranexamic acid. This project aims to inform the choice of outcome measures by exploring the effects of tranexamic acid on bleeding in large clinical trial datasets.

Methods: The effects of tranexamic acid on acute bleeding were assessed by applying a range of methodological approaches to large clinical trial datasets. The tendency for non-differential misclassification of outcomes to cause bias towards the null was exploited as a tool to study the biological effects of tranexamic acid. The impact of misclassification was investigated by varying assumptions about the empirical induction period and locating the least diluted measure of effect. This allowed hypotheses about the biological effects of tranexamic acid to be refined and the selection of outcome measures better able to capture these effects. Descriptive and multivariable analyses of baseline characteristics and the timing and frequency of various outcome events in patients with acute bleeding were used to investigate the natural history of bleeding.

Main findings: An outcome must have the potential to be affected by the trial intervention, be amenable to unbiased measurement, be sufficiently common, and be clinically relevant and important to patients. There is a window of opportunity for a treatment to exert its effects. Inappropriate assumptions about the time from causation to detection (the empirical induction period) can cause non-differential outcome misclassification. Tranexamic acid is most effective when given soon after bleeding onset and appears to work mainly by reducing bleeding on the day of onset. If we intervene too late in the disease process, when the outcome is inevitable or the targeted biological pathways have ceased, there will be no potential for benefit. When the outcome measure includes events that fall outside of the etiologically relevant period or biological pathway, the effect estimate is diulted towards the null.

Impact of work: My work informed the selection of the primary outcome measure in the CRASH-3, HALT-IT and WOMAN-2 trials. By generating new insights into the natural history of acute bleeding and the mechanism of action of tranexamic acid, it also helped the implementation of the trial results, potentially contributing to improvements in patient care, and has influenced research on haemostatic treatments more generally.

Strengths and weaknesses: The large, high-quality trial datasets comprised over 70,000 patients with almost complete follow-up and little missing data, providing reliable effect estimates, and allowing meaningful subgroup and sensitivity analyses and the assessment of different outcome measures. The biological effect of tranexamic acid and impact of dilution from outcome misclassification is consistent with biology and across multiple trials. Some measurement error in the timing of events is inevitable, and some results are imprecise so chance cannot be ruled out as a potential alternative explanation.

Implications for future research: Dilution from outcome misclassification is a common issue in clinical trials, with different implications in superiority trials compared to equivalence or non-inferiority trials. Given the rising cost of research, trials need to be efficient and cost effective. The use of appropriate outcome measures that capture the biological effect of a treatment can reduce non-differential misclassification, increasing statistical power. New

information generated by trials as they are underway can be used to inform adaptive trial design, including the choice of outcome measures.

Conclusions: The concepts presented in this thesis could be applied to clinical trials in other disease areas and might help to inform the choice of outcome measures and generate knowledge on the cause-effect relationship between study interventions and outcome.

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Table of Abbreviations

CI – Confidence interval

CRASH – Clinical Randomisation of an Antifibrinolytic in Severe Haemorrhage

HALT-IT - Haemorrhage ALleviation with Tranexamic acid – Intestinal system

NICE – National Institute for Health and Care Excellence

PAI-1 – Plasminogen Activator Inhibitor 1

PPH – Postpartum haemorrhage

RR – Risk ratio

TBI – Traumatic brain injury

tPA – Tissue Plasminogen Activator

TXA – Tranexamic acid

WHO - World Health Organization

WOMAN – World Maternal Antifibrinolytic

1 Analytic Commentary

1.1 Background

Acute bleeding is a major public health problem, occurring as a complication of injury, childbirth, pregnancy, surgery, gastrointestinal pathologies and other medical conditions. Worldwide, traumatic injury is responsible for over 5 million deaths each year, most from exsanguination or head injury.[1] Severe bleeding after childbirth is the leading cause of maternal mortality, responsible for around 70,000 maternal deaths each year.[2] Women who survive are at increased risk of adverse psychological outcomes including post-traumatic stress disorder and postnatal depression.[3] Because bleeding-related deaths occur soon after bleeding onset, emergency care is essential to reduce mortality.[4]

Until 2010, there were no proven life-saving drug treatments for acute bleeding. The mainstay of patient care included interventions to support coagulation and maintain vital organ perfusion such as blood product transfusion to replace lost blood, intravenous fluids to restore circulatory volume, and surgery to control the bleeding. Because most trials of such interventions are small or of low methodological quality, or both, uncertainties remain regarding the optimal approach to haemostatic resuscitation, including which combination and quantity of blood products and replacement fluids to give.[5–7] However, in the past decade clinical trials of tranexamic acid have made some progress towards improving survival after acute bleeding.

Randomised trials provide evidence on the safety and effectiveness of new interventions. To provide high quality evidence that can inform clinical practice and improve patient care, a trial must be well designed and rigorously conducted. When the sample size is large enough, random error is minimised and the random allocation of participants to treatment groups eliminates confounding. Allocation concealment and blinding of trial participants and staff are common methods to reduce bias due to knowledge of group allocation, such as recall and observer bias. Various methods can be used to reduce measurement error, protocol non-adherence and loss to follow-up. Yet even when all these biases are minimised, a trial's outcome measure may fail to capture the biological effect of a treatment.

Choosing a suitable outcome measure is a critical aspect of trial design. The primary outcome should be 'capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial'.[8] In any trial, the primary objective is to provide a valid and reliable estimate of the effect of an intervention(s). An individualized approach is needed to achieve this, tailoring the primary outcome to fit the cause-effect relationship under study. The use of a standardised set of outcomes (a core outcome set) facilitates study comparisons and evidence synthesis,[9] but this unified approach should not take priority over the primary objective. Ideally, the outcome measure will accurately capture a sufficiently common, important, and etiologically relevant event that has the potential to be affected by the intervention. As such, the disease's natural history and pathophysiology, the trial intervention's mode of action, and the study population's characteristics are key considerations.

Because severe bleeding often has similar pathophysiological consequences regardless of the site of bleeding, most interventions are aimed at correcting haemorrhagic shock and coagulopathy. These interventions are not site-specific and are often included in generic major haemorrhage protocols.

Due to similarities in pathophysiology and the types of interventions used to treat acute bleeding, clinical trials assessing the risks and benefits of haemostatic treatments such as tranexamic acid often evaluate similar patient outcomes regardless of the cause or site of bleeding.[5,10–12] Yet until recently there had been little research on outcome measures in trials of haemostatic treatments.

Tranexamic acid is an antifibrinolytic drug that reduces bleeding by inhibiting the breakdown of fibrin blood clots. Based on evidence from randomised trials it is included in the World Health Organization List of Essential Medicines and treatment guidelines for traumatic injury and postpartum haemorrhage. However, for decades the drug was not used in acute severe bleeding as its inventors, Utako and Shosuke Okamoto, had intended.[13] Instead, tranexamic acid was first used in dentistry and surgery. In 2001, a systematic review of antifibrinolytic drugs for perioperative blood transfusion found 18 trials of tranexamic acid comprising 1,342 participants.[14] The review suggested that when given just before surgical incision tranexamic acid reduces blood transfusion by over a third. Subsequent systematic reviews and clinical trials have provided strong evidence that tranexamic acid reduces surgical bleeding and other important bleeding-related outcomes.[15,16]

Motivated by the evidence from surgical trials, in 2004 an international team of researchers began a programme of research to evaluate the role of tranexamic acid in severe bleeding. A systematic review of antifibrinolytics for traumatic injury found just two studies with less than 100 participants.[17] Given the need for a large high quality trial, the CRASH-2 trial was launched. This randomised, double-blind, placebo-controlled trial assessed the effects of tranexamic acid in 20,211 bleeding trauma victims.[18] The primary outcome was death at 28 days. Tranexamic acid significantly reduced all-cause mortality (RR 0.91, 95% CI 0.85-0.97) and death due to bleeding (RR 0.85, 95% CI 0.76-0.96), with no increase in vascular occlusive events. Although patients were eligible if they were within 8 hours of their injury, it was apparent that most of the treatment benefit occurred in patients treated early.[19] The reduction in death due to bleeding was greatest when tranexamic acid was given within 3 hours of injury (RR 0.72, 95% CI 0.63-0.83), most bleeding deaths happened early, and the drug appeared to work by reducing bleeding on the day of injury.[20]

While the CRASH-2 trial was underway, the investigators conjectured that tranexamic acid could also be used to treat severe bleeding after childbirth, or postpartum haemorrhage (PPH), and the WOMAN trial was launched in 2009. The WOMAN trial assessed the effects of tranexamic acid in 20,060 women with a clinical diagnosis of PPH. Because PPH is a life-threatening emergency, doctors will rightly do everything they think might help save the mother's life first, then randomise them into the trial last. Randomisation happens once everything else is done, including the decision to operate. The primary outcome was death from all causes or hysterectomy within 42 days, but during the trial the investigators noticed that the decision to conduct an emergency peripartum hysterectomy was often made around the time of randomisation, so it was unlikely to be affected by tranexamic acid. Informed by this observation and the CRASH-2 results, the researchers prespecified death due to bleeding as a key secondary outcome with a subgroup analysis by time to treatment.[21] Tranexamic acid reduced death due to bleeding (RR = 0.81, 95% CI 0.65-1.00), particularly when given within 3 hours of childbirth (RR 0.69, 95% CI 0.52-0.91), with evidence that late treatment was ineffective. There was no effect on the composite outcome of death or hysterectomy (RR 0.97, 95% CI 0.87-1.09), and no increase in thromboembolic events or complications. Most maternal deaths due to bleeding occurred within 24 hours of childbirth.

Although the CRASH-2 trial included polytrauma patients with extra- and intracranial injuries, patients with isolated traumatic brain injury (TBI) were excluded because of safety concerns. The CRASH-3 trial was launched to assess the effects of tranexamic acid in trauma victims with an isolated TBI, a missing subgroup of the CRASH-2 trial. The time window for eligibility was originally within 8 hours of injury, but as accumulating evidence highlighted the time critical nature of tranexamic acid, we amended the protocol to limit recruitment to patients within 3 hours of injury.[22] For the same reason, the primary outcome was head injury death among patients randomised within 3 hours of injury.[23] We also prespecified a sensitivity analysis excluding the most severely brain damaged patients, who had little potential to benefit from tranexamic acid. The trial randomly allocated 12,737 patients to receive tranexamic acid or placebo, 9,202 of whom were randomised within 3 hours of injury. There were fewer head injury deaths in the tranexamic acid group (RR = 0.94, 95% CI 0.86-1.02). As predicted, the treatment effect became stronger when the most severely brain damaged patients were excluded (RR = 0·89, 95% CI 0·80–1·00).[24] Deaths in patients with isolated head injury tended to occur slightly later in the clinical course than deaths in polytrauma patients.[25] A meta-analysis of data from the CRASH-2 and CRASH-3 trials and two other high quality trials of tranexamic acid in polytrauma victims found a significant reduction in all-cause mortality with early tranexamic acid (pooled RR = 0.87, 95% CI 0.82-0.93).[26–28]

Meanwhile, the HALT-IT trial assessed the effects of tranexamic acid in 12,009 patients with gastrointestinal bleeding. We originally prespecified all-cause mortality as the primary outcome because we believed that most deaths would be due to bleeding. However, as the trial was underway, we observed that over half of all deaths were due to non-bleeding causes such as cancer and sepsis. Based on the findings from previous trials, we did not expect tranexamic acid to reduce these deaths, nor did we expect it to reduce deaths from rebleeding episodes several days after randomisation.[4] The primary outcome was changed to death due to bleeding within 5 days of randomisation.[29] However, there was no evidence that tranexamic acid reduced death from gastrointestinal bleeding, with an increase in venous thromboembolic events (deep vein thrombosis or pulmonary embolism; RR = 1.85; 95% CI 1.15-2.98).[30]

These trials of tranexamic acid represent some of the largest datasets on acute bleeding to date. By capturing detailed information on patient characteristics, outcomes and the timing of events, they are also some of the most comprehensive. As such, the data can be used for more than simply assessing treatment effects – it can tell us not only if a treatment works, but how it works, when, and in whom. Analysing trial datasets as cohort studies can deepen our understanding of the mechanism of action of tranexamic acid, and the pathophysiology and natural history of bleeding.[4,20,25,31,32] I incorporate this prior knowledge into the design of subsequent trials, using an iterative approach to refine the outcome measures in each trial. During this process we have gained valuable insights and built an evidence base on outcome measures in trials of haemostatic treatments, the biological effect of tranexamic acid and the natural history of acute bleeding.

1.2 Aim and objectives

This project aims to inform the choice of outcome measures by exploring the effects of tranexamic acid on acute bleeding in large clinical trial datasets. The objectives are to:

i) Use data from trials to better understand the natural history of acute bleeding
ii) Use treatment effect dilution from outcome misclassification to refine assumptions about the empirical induction period of the cause-effect relationship
iii) Use evidence on the natural history of bleeding and the biological effects of tranexamic acid to inform the selection of outcome measures in clinical trials
iv) Propose and apply criteria for selecting outcome measures

1.3 Main findings

'*All diseases have a sort of natural life; that is, they begin, grow, attain maturity, decline, and terminate*.' William Farr (1862)

1.3.1 The biology of bleeding and tranexamic acid

Haemostasis comprises a set of physiological responses to various stimuli, including bleeding. When blood vessels are ruptured, vasoconstriction reduces blood flow to the site of injury, a platelet plug forms, and tissue factor activates the coagulation cascade. Thrombin converts fibrinogen into fibrin and a cross-linked fibrin mesh binds platelets and red blood cells together to form a clot. Coagulation is regulated in a process called fibrinolysis, where tissue plasminogen activator (tPA) converts plasminogen to the enzyme plasmin. tPA and plasminogen bind to fibrin at lysine binding sites, which localises plasmin formation. Plasmin then cleaves fibrin into fibrin degradation products, promoting further fibrinolysis.[33,34] Later, rising levels of plasminogen activator inhibitor-1 (PAI-1) inhibit tPA and regulate fibrinolysis. The coagulation and fibrinolytic systems work in parallel to maintain haemostasis but sometimes the balance shifts towards fibrinolysis. In acute bleeding, this can manifest as hyperfibrinolysis characterized by consumption of clotting factors, depletion of fibrinogen, high levels of fibrin degradation products such as D-dimers, and worsened bleeding. Fibrinolysis is an early feature of acute bleeding, with initial high levels of tPA that decline as levels of PAI-1 slowly rise,[34,35] making fibrinolysis an appropriate therapeutic target.

Tranexamic acid is a molecular analogue of the amino acid lysine. It competitively inhibits the activation and proteolytic action of plasmin on fibrin by binding to lysine binding sites on plasminogen.[13] Pharmacological studies demonstrate that a plasma concentration of around 10mg/L of tranexamic acid is needed to inhibit fibrinolysis.[36] Tranexamic acid is rapidly absorbed by intravenous and intramuscular injection, reaching therapeutic levels in minutes.[37] It has a short half-life of around 2 hours so around 98% is excreted within 12 hours of administration.[38,39] Tranexamic acid works mainly by reducing bleeding on day of onset and the timing of treatment administration is important. Early treatment is most effective, with treatment beyond 3 hours of bleeding onset being ineffective or potentially harmful.[20,22]

1.3.2 Cause and effect

Clinical trials provide information about both association and causality - is the trial treatment associated with the outcome of interest, and why? The latter is often an afterthought, with trialists and clinicians inferring causality based on statistical significance of the primary outcome alone. Clinical trials have demonstrated that tranexamic acid is a safe and effective treatment for bleeding. There is a strong association between being allocated tranexamic acid and having a reduced risk of death due to bleeding, particularly when tranexamic acid is given early.[18,19,22,24,40] Information from trials can also deepen our understanding of the cause-effect relationship being studied.[41] Longitudinal data on baseline characteristics of participants, clinical features and timing of events in trials offers important insights into the aetiology, natural history and pathophysiology of bleeding. This knowledge informs hypotheses about its biological effects, including when we are most likely to detect them, in which patients, and with what outcome measure(s).

1.3.3 Detecting the biological effect of a treatment in a clinical trial

Treatment effects are often modest and hard to detect. First, we must first make assumptions about when and in whom the treatment is likely to work. We should consider the time from causation to initiation (the aetiologic process or induction period) and from initiation to detection (the disease process or latent period), together termed the 'empirical induction period'.[42] When a participant is exposed to the trial treatment, it takes time to exert its effects on a biological pathway and for those effects to be detected. For example, tranexamic acid must be absorbed by the body, reach the required plasma concentration, bind to lysine binding sites on plasminogen and inhibit fibrinolysis before a clinical benefit can be observed. From a causation perspective, a trial treatment is a component cause but not a sufficient cause.[43] Other conditions need to be met for it to exert effects. There is a window of opportunity for the treatment to confer benefit. If we intervene too late in the disease process when the outcome is inevitable or when the targeted biological pathways have ceased, there will be no potential for benefit. Also, because many trial treatments have a mechanism of action that targets a specific biological pathway, the treatment is unlikely to affect a wide range of outcomes and may not be safe and effective in all patients.

1.3.4 Using outcome misclassification and dilution to examine treatment effects

Misclassification occurs when a value or attribute is categorised incorrectly. Non-differential misclassification is a common issue in clinical trials. Even when a trial has proper random sequence generation, allocation concealment, and blinding, some random measurement error is usually inevitable, though the extent of misclassification should be similar between groups. Because exposed and unexposed groups appear more alike, the association between exposure and outcome is diluted.[44,45] Unless there is considerable non-compliance with treatment, arguably the most important source of dilution in a trial is outcome misclassification, which can arise through measurement error. While some outcomes lend themselves to unequivocal assessment (e.g. death), others are not always clear cut (e.g. cause of death) and some can be prone to measurement error (e.g. postpartum blood loss). Inappropriate assumptions about aetiology and the empirical induction period of the cause-effect relationship can also dilute the effect estimate. As such, dilution even occurs when using unequivocal outcomes like death. If the outcome comprises components that are not etiologically relevant i.e. outcome events that fall outside of the etiologically relevant period or biological pathway, the estimate of the biological effect of the intervention on the outcome is diluted.

When measuring an outcome, there is usually a trade-off between sensitivity and specificity, which impact the effect estimate in different ways. An outcome with low specificity (many false positives) dilutes the effect estimate towards the null, whereas an outcome with low sensitivity will reduce precision but the effect estimate remains the same.[45] An outcome with high specificity for the biological effect of the treatment will therefore have fewer outcome events but a less diluted estimate of the treatment effect, whereas an outcome with high sensitivity will have more events but more dilution. For example, let's consider a trial to assess the effects of tranexamic acid for PPH prevention in 10,000 women, assuming 6% of 5,000 women in the placebo group have a PPH and tranexamic acid reduces this risk by 25%. if we can capture the outcome with 100% sensitivity and specificity using a gold standard measure (unlikely in reality) there will be 225 and 300 events in the tranexamic acid and placebo groups, respectively, (RR = 0.75, 95% CI 0.62-0.88). With 100% sensitivity but only 80% specificity, there would be 1,180 and 1,240 events in the tranexamic acid and placebo groups,

respectively (RR = 0.95, 95% CI 0.90-1.00). On the other hand, with 100% specificity but only 80% sensitivity, there would be 180 and 240 events in the tranexamic acid and placebo groups, respectively (RR = 0.75, 95% CI 0.59-0.91). Sometimes, dilution masks real treatment benefits and harms completely. Despite being a limitation, outcome misclassification can be used as a tool to inform assumptions about the empirical induction period, and therefore outcome measures, in subsequent trials. Dilution from outcome misclassification and inappropriate assumptions about the induction period acts like a sort of radar, allowing us to locate the signal of the treatment effect amongst the noise. My research identifies etiologically relevant outcomes by exploring the impact of outcome misclassification and using this information to refine assumptions about the biological effects of tranexamic acid.

1.3.5 The natural history of acute bleeding in trials of tranexamic acid

In 2010, researchers at an NIH trauma research roundtable stated that 'understanding the timing and sequence of events on the patient level leading to the progression of injury is fundamental to the conduct of successful studies and generation of high-quality data… understanding of the longitudinal course of injury progression (from seconds to minutes to hours) is extremely limited for acute injury'.[46] Until recently there were few large studies that examined the natural history of traumatic bleeding. There has been even less research into the natural history of postpartum and gastrointestinal bleeding. Early research in trauma revealed a trimodal distribution of death, with a peak of immediate deaths in the first hour due to unsurvivable injuries and massive haemorrhage, a peak of early deaths due to bleeding and traumatic brain injury a few hours later, and a peak of late deaths several days after injury due to multiorgan failure and sepsis.[47] As resuscitation, prehospital and critical care improved over time, polytrauma deaths have shifted to a bimodal or unimodal distribution, with an increase in the relative contribution of brain injury and haemorrhage deaths creating a peak of early deaths, and a decrease in the relative contribution of late deaths due to multiorgan failure and sepsis.[48–52]

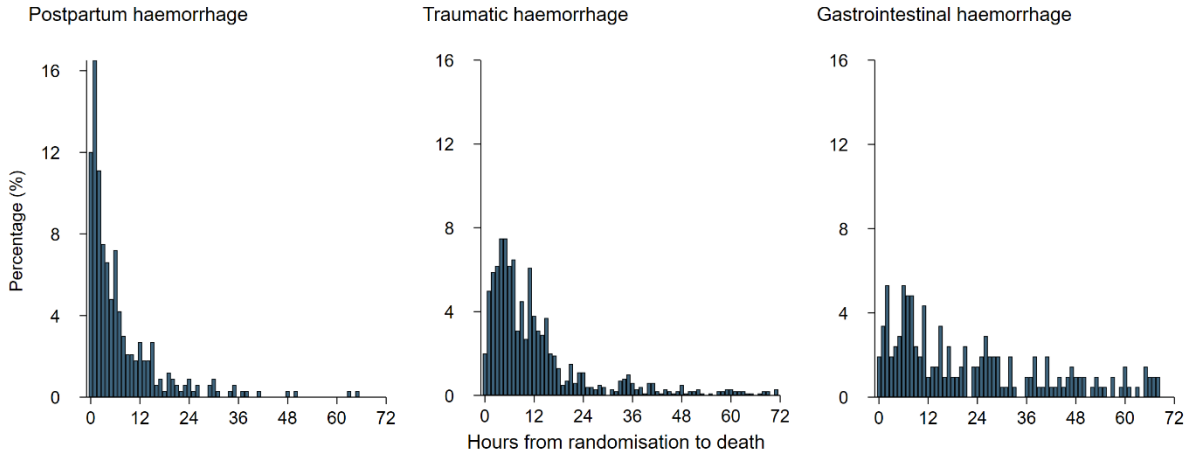

Figure 1. Temporal distribution of deaths due to bleeding by type of haemorrhage in the a) WOMAN, b) CRASH-2, and c) HALT-IT trials.

Trials of tranexamic acid have collected data on some of the largest cohorts of patients with acute haemorrhage. By analysing the CRASH-2, CRASH-3, WOMAN, WOMAN-2 and HALT-IT trials as longitudinal datasets, I have generated new knowledge on the natural history of different types of acute bleeding. Baseline data on participant characteristics, time of randomisation, cause and time of death, and time of other outcome events of interest are recorded along with a narrative describing the sequence of events. Regardless of the site of bleeding, the disease course is remarkably similar. Firstly, bleeding happens early, usually starting immediately after the causal event. Patients who exsanguinate tend to do so quickly, with a large proportion of deaths due to bleeding on the day of bleeding onset, particularly in postpartum haemorrhage (see Figure 1).[4] Some patients die from causes other than bleeding, which tend to happen later. Most bleeding deaths occur within 48 hours of admission, followed by deaths from vascular occlusion and multi-organ failure, with sepsis deaths about 1 week later. Because time and cause of death are correlated, the temporal distribution of death tells us about the likely cause. The relative contribution of different causes of death varies by the site of bleeding (see Figure 2), as well as population and setting, which impacts the extent to which the treatment effect on all-cause mortality is diluted by etiologically irrelevant outcome events.

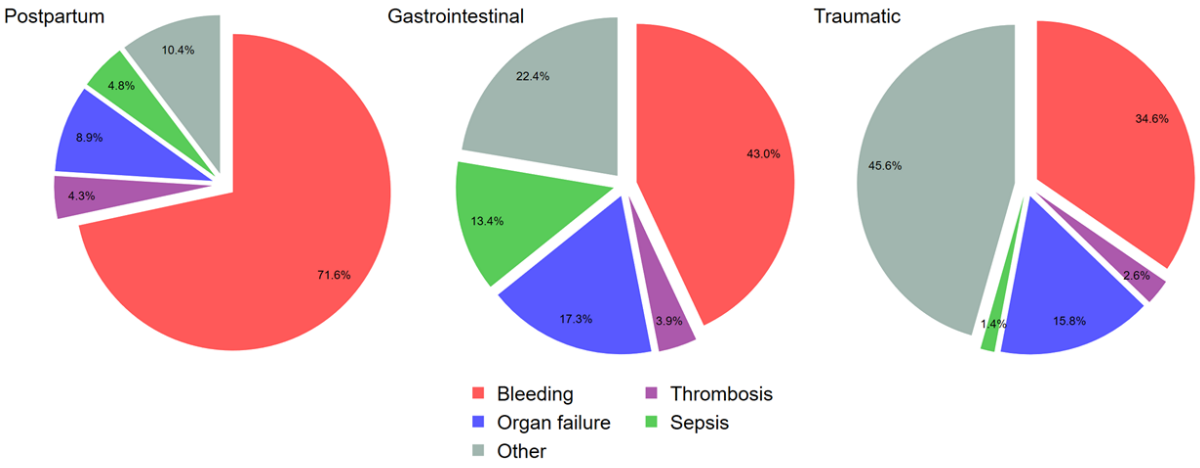

Figure 2. Cause of death by type of haemorrhage

1.3.6 Dilution from aetiologically irrelevant events

Composite outcomes fail to accurately capture the biological treatment effect when some components are not etiologically relevant, causing misclassification. All-cause mortality is a composite outcome because it comprises different causes of death. Many deaths following acute severe haemorrhage are due to patient comorbidities or complications rather than the failure to control bleeding. For example, patients with severe postpartum bleeding may survive the acute bleed but die from sepsis within the trial follow-up period.[4] Tranexamic acid is an antifibrinolytic drug that saves lives by reducing bleeding. While a haemostatic treatment might affect deaths from bleeding or thrombosis, it would be unrealistic to expect similar, if any, effects on other causes of death.

The effect on all-cause mortality is a weighted average of the effects on specific causes of death, weighted by their relative frequency (see Figure 3). If a large proportion of deaths are caused by mechanisms that are etiologically unrelated to the intervention, and therefore unaffected by it, this will dilute the effect estimate considerably and the trial will have low power for all-cause mortality, even if there was a significant reduction in deaths due to an etiologically relevant cause. For example, for a haemostatic treatment like tranexamic acid which targets bleeding, assuming 40% of all deaths are due to bleeding and tranexamic acid reduces the risk of bleeding deaths by 25% (RR 0.75) but has no effect on other causes of death (RR 1.00), the effect on all-cause mortality will be diluted (RR 0.90). Because the relative contribution of different components of a composite outcome will vary between populations, the treatment effect on a composite outcome is not generalisable. The only generalisable measure is the undiluted biological effect of the trial treatment. Researchers previously noted the importance of disease pathophysiology in guiding the choice of outcome measure in traumatic haemorrhage, suggesting early mortality as an appropriate outcome because early deaths are more likely to be due to bleeding.[53]

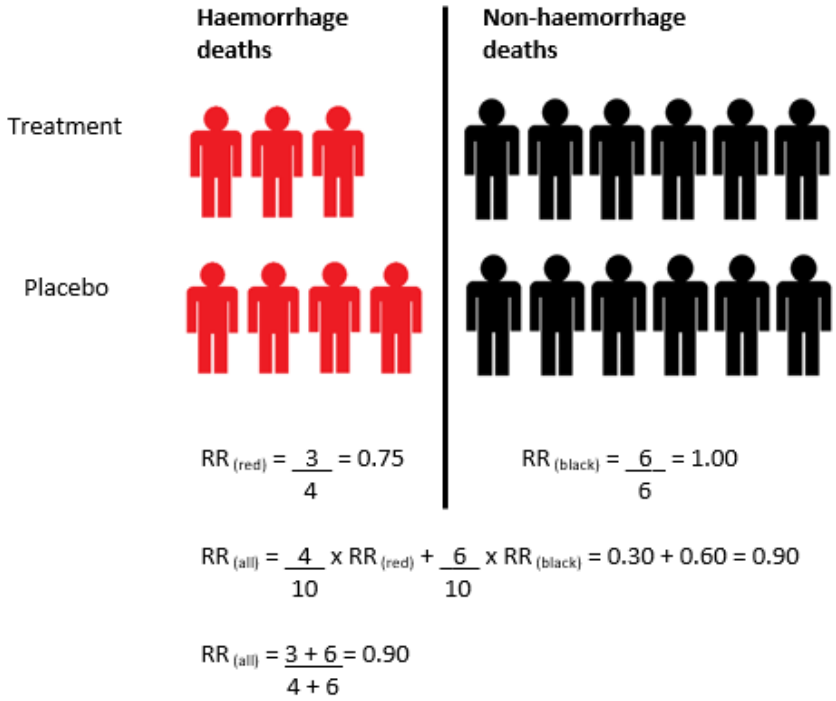

Figure 3. The impact of dilution from etiologically irrelevant outcome events (non-haemorrhage deaths) on the treatment effect for all-cause mortality. The relative risk (RR) can be estimated as the ratio of outcome events in the treatment group relative to the placebo group, because the total number of participants in each group should be approximately equal and so the denominators cancel out.

1.3.7 Dilution from inappropriate assumptions about the empirical induction period

To capture the biological effect of a treatment, outcome measures need to incorporate appropriate assumptions about the empirical induction period. When a sufficient cause is present, the disease

process begins, and some degree of disease is inevitable. Thereafter, a trial treatment may be ineffective, with some outcomes inevitable at the point of randomisation. This issue is particularly common in emergency care trials where eligible patients are critically ill and everything happens rapidly. For example, in patients who experience unsurvivable brain damage, the extent of the injury at the point of randomisation means it is unlikely the patient would survive. The inclusion of such patients will dilute the effect on head injury death because a proportion of deaths will be unaffected by treatment. This phenomenon has been documented in several head injury trials, with researchers recommending the exclusion of critically ill patients, although it can be difficult to identify such patients at baseline and may make recruitment more difficult.[54] In patients with massive haemorrhage, very early outcome events such as death due to bleeding may be inevitable regardless of treatment. In the WOMAN trial, when early deaths due to bleeding were excluded, there was a larger reduction in the risk of death due to bleeding with tranexamic acid (RR 0.41; 99% CI 0.19–0.89), suggesting some dilution from early, inevitable deaths entrained before randomisation.[31]

In patients with acute severe bleeding at baseline, many interventions are initiated pre-hospital or on arrival at hospital. Clinicians prioritise interventions with established effectiveness prescribed by treatment protocols over the administration of a trial intervention. Because the extent of blood loss prior to randomisation determines the use of interventions for bleeding, their use lacks the potential to be affected by a trial treatment in patients with acute bleeding at baseline.[4] For example, blood transfusions are triggered by estimated blood loss or blood pressure on presentation to emergency services, with the number and ratio of blood components transfused dictated by major haemorrhage protocols. Indeed, there was no evidence of an effect on transfusion in trials of tranexamic acid for the treatment of postpartum or traumatic haemorrhage.[18,40] Whereas in elective surgery trials, perioperative tranexamic acid reduced blood transfusion by about 25-30% because patients are exposed to the intervention prior to bleeding onset.[15,55] Interventions for bleeding are more appropriate as outcome measures in prevention trials where patients are recruited before the onset of bleeding.

Hysterectomy is listed as a core outcome for trials of treatments for severe postpartum bleeding, but not deemed critically important for prevention trials due to rarity in lower risk populations.[56] Yet there may be limited potential for hysterectomy to be affected in treatment trials. The decision to do an emergency hysterectomy in women with severe postpartum bleeding is often made at or before randomisation. This issue is demonstrated in the WOMAN trial, where over a quarter of hysterectomies were done within an hour of randomisation.[40] Because the treatment effect on the primary outcome (a composite of death or hysterectomy) would be diluted by the inclusion of early pre-planned hysterectomies, the sample size was increased to provide enough power for a key secondary outcome, death due to bleeding.[21] The inclusion of hysterectomies done at the same time as randomisation appeared to dilute the treatment effect, with no reduction in death or hysterectomy (RR 0.97, 95% CI 0.87-1.09).[40] But tranexamic acid reduced death due to bleeding, as well as re-operation to control bleeding (RR 0.64, 95% CI 0.49-0.85). Unlike hysterectomy, the decision to re-operate is made after randomisation and so could be influenced by tranexamic acid.

Blood transfusion and hysterectomy are particularly prone to dilution. Blood transfusion may be indicated for reasons other than bleeding (e.g. anaemia), in some countries blood shortages limit availability, and if the trial treatment improves survival, patients in the treatment arm have more

opportunity to receive interventions for bleeding. The decision to do a hysterectomy is affected by several factors other than bleeding. Emergency hysterectomy is more common among women with placenta praevia and accreta, older women, Caesarean section births, and women giving birth in Asia.[57] Clinicians may be more likely to conduct a hysterectomy for bleeding if a woman already has several children and her uterus is readily accessible during Caesarean section. Hysterectomy is also important in the management of abnormal placentation. Evidence on the effect of tranexamic acid on blood transfusion in women at risk of severe postpartum bleeding is mixed, with the TRAAP trials finding no evidence of a reduction (although transfusion was rare) and others finding some evidence of one.[58,5960]

Outcomes can also occur after the relevant biological pathway has ended. Just as early deaths or interventions initiated before randomisation lack potential to be affected by the trial intervention, so too do late deaths initiated after the intervention has stopped exerting an effect. Intracranial bleeding starts soon after impact and continues for several hours, with most of the haematoma expansion occurring within 1–1.5 h of injury.[61] Patients with an isolated TBI are unlikely to exsanguinate and head injury deaths can be caused by pathologies other than bleeding, which tend to occur later.[25,62,63] Patients with gastrointestinal bleeding may survive their initial bleed but die from re-bleeding during follow-up.[29] It may be unrealistic to expect a treatment to influence these late deaths and so their inclusion will dilute the treatment effect.

1.3.8 Key criteria for selecting an outcome measure

Based on the above concepts and findings, there are some general criteria that an outcome measure must satisfy to achieve a trial's primary objective of obtaining a valid and reliable estimate of the treatment effect.

First, the outcome should have the potential to be affected by the trial intervention, such that it is etiologically relevant. The etiologic mechanisms of both the disease and intervention should be considered, including the natural history and pathophysiology of the disease, the intervention's mechanism of action and the timing of its hypothesised effect.[42] The inclusion of outcome events that are i) etiologically unrelated to the intervention, ii) initiated at or before exposure to the intervention, or iii) induced after the intervention's effect ceases, will cause dilution.

Second, the outcome must be amenable to relatively unbiased assessment to provide a valid and reliable measure of the treatment effect. High specificity is particularly important. Outcomes with low specificity will contribute false positive cases that bias the effect estimate towards the null, whereas outcomes with low sensitivity will contribute false negative cases that reduce power rather than biasing the effect estimate. Still, the outcome must be sufficiently common for the trial to be adequately powered by a realistic number of participants. Trials are costly and resources are limited, so a rare outcome is not viable, no matter how etiologically relevant or accurately measured it is.

Finally, the outcome should be clinically relevant and important to patients, relating to how a patient feels, functions or survives. Although some endpoints such as biomarkers might be etiologically relevant, interventions that exert an effect on such outcomes may not confer real patient benefit. While an intervention may have a biological effect, we need patient-centred outcomes that are clinically important. On the other hand, not all patient-centred outcomes are appropriate as they may

not meet the other criteria. Sometimes the outcome that is important to patients is not the etiologically relevant outcome, although it might contain the etiologically relevant outcome (e.g. all-cause mortality), or may not be amenable to unbiased assessment.

1.4 Impact of work to date

1.4.1 Design and analysis of trials of tranexamic acid

Randomised trials comprising tens of thousands of patients have provided robust evidence that early tranexamic acid treatment safely reduces bleeding deaths in traumatic injury and postpartum haemorrhage.[12,18,22,24,40] By applying epidemiologic concepts like misclassification and causality to secondary analyses of these trial datasets, my research has provided new insights into the pathophysiology of bleeding, mechanism of action of tranexamic acid, the timing of its effects, and the utility of different outcome measures. Our team uses this mounting knowledge to inform the design and analysis of subsequent clinical trials of tranexamic acid, enabling the pre-specification of more appropriate outcome measures and analyses targeted at identifying the biological treatment effect, and further deepening our understanding. We are now assessing the role of tranexamic acid in the prevention of severe postpartum bleeding (WOMAN-2 trial) and the treatment of mild head injury (CRASH-4 trial), as well as finding alternative routes of administration (I'M WOMAN trial), for which my research has informed the trial design.[37,58,59,64–67]

Primary outcomes and statistical analysis plans

In both the CRASH-2 and WOMAN trials, when given within 3 hours of bleeding onset (injury or childbirth) tranexamic acid reduced the risk of death due to bleeding by a third. The effect on all-cause mortality was smaller, with no effect on non-bleeding causes of death. There is a relatively narrow time window for the treatment to be effective because most bleeding deaths happen early and most of the effect occurs on the day of bleeding onset.[19,20,40] Some early bleeding-related outcomes events may be inevitable, while other outcomes may happen too late to be affected, both contributing to misclassification.[20,29,31] These insights informed the outcomes and statistical analysis of the CRASH-3 and HALT-IT trials.[23,29]

In the CRASH-3 trial, over 90% of deaths were due to head injury. Early head injury deaths are more likely to result from intracranial haemorrhage so have the greatest potential to be reduced by tranexamic acid.[23] We expected later head injury deaths to be due other mechanisms such as oedema and diffuse axonal injury, and their inclusion would dilute the treatment effect. We also expected inevitable deaths in severe head injury patients to dilute the treatment effect. By prespecifying the outcome of head injury death within 24 hours and a sensitivity analysis excluding the most severely injured patients, we were able to test these hypotheses and target the biological treatment effect. Indeed, there was a large reduction in early head injury death (RR 0.81, 95% CI 0.69-0.95), particularly when the most severely injured patients were excluded (RR 0.72, 95% CI 0.56-0.92). This effect is consistent with the effect of early tranexamic acid on death due to bleeding in polytrauma patients in the CRASH-2 trial (RR 0.72, 95% CI 0.63-0.83) and women with postpartum haemorrhage in the WOMAN trial (RR 0.69, 95% CI 0.52-0.91).

In the HALT-IT trial statistical analysis plan, I prespecified analyses of outcome measures that were thought to be aetiologically relevant based on findings from previous trials. Yet there was no effect on early death due to bleeding or rebleeding and thus analyses to assess the impact of dilution yielded little information.[30] The lack of treatment effect may suggest key differences in the natural history and aetiology of gastrointestinal (GI) bleeding compared to obstetric and traumatic bleeding studied in the previous trials. Late treatment, reduced fibrinolysis, or elevated portal pressure in liver disease

patients may have rendered tranexamic acid ineffective in GI bleeding. The effect of tranexamic acid declines with increasing time from bleeding onset and GI bleeding can start hours prior to symptom onset, unlike in PPH and trauma. Adrenaline activates the release of tPA from the endothelium resulting in fibrinolysis,[68,69] so a haemorrhage caused by an intensely painful event like childbirth or traumatic injury may have increased fibrinolysis compared to GI bleeding. A large proportion (41%) of HALT-IT trial participants had liver disease and their gastrointestinal bleeding was caused by portal hypertension and ruptured oesophageal varices, a biological pathway that is unlikely to be influenced by tranexamic acid.[29,30] These patients had a greater risk of death, accounting for nearly three quarters of deaths in the trial. However, a prespecified subgroup analysis of suspected variceal bleeding and comorbid liver disease compared with other or unknown causes of bleeding found no evidence of heterogeneity. The HALT-IT trial had about 85% power to detect a 25% reduction in early death due to bleeding, so a more modest effect could have been missed. Interestingly, the longer duration and higher dose of tranexamic acid in the HALT-IT trial compared to the CRASH and WOMAN trials (4 g over 24 hours compared to 1-2 g over 8 hours) may explain the increased risk of vascular occlusive events and seizures, respectively.

Interpretation of trial results

My research into dilution from outcome misclassification enables us to understand apparent inconsistencies in clinical trial results. The overall effect of tranexamic acid on all-cause mortality at 28 days in the CRASH-3 trial was smaller than in the CRASH-2 trial (RR 0.93, 95% CI 0.83-1.03 vs RR 0.84, 95% CI 0.77-0.92). Although there was no evidence of heterogeneity (p=0.18), many interpreted the CRASH-3 trial result as 'negative', failing to consider the evidence in context of what came before. A larger proportion of late (non-bleeding) deaths, and perhaps more inevitable deaths, meant that the outcome was more misclassified in the CRASH-3 trial than the CRASH-2 trial (see Figure 4).[25] When excluding patients with the most severe head injuries who are unlikely to benefit, the effect of tranexamic acid on death on the day of injury is remarkably similar in both trials (RR 0.79, 95% CI 0.70-0.90; RR 0.74, 95% CI 0.58-0.94), with no evidence of heterogeneity by trial (p=0.60). In the HALT-IT trial of tranexamic acid for gastrointestinal bleeding, the study population was older with more comorbidities, so a large proportion of deaths were due to non-bleeding causes such as cancer and liver disease. Many patients also experienced rebleeding episodes soon after their index bleed. To minimise outcome misclassification, we chose early death due to bleeding as the primary outcome, and early rebleeding as a major secondary outcome; however, there was no evidence of a treatment benefit as discussed above.

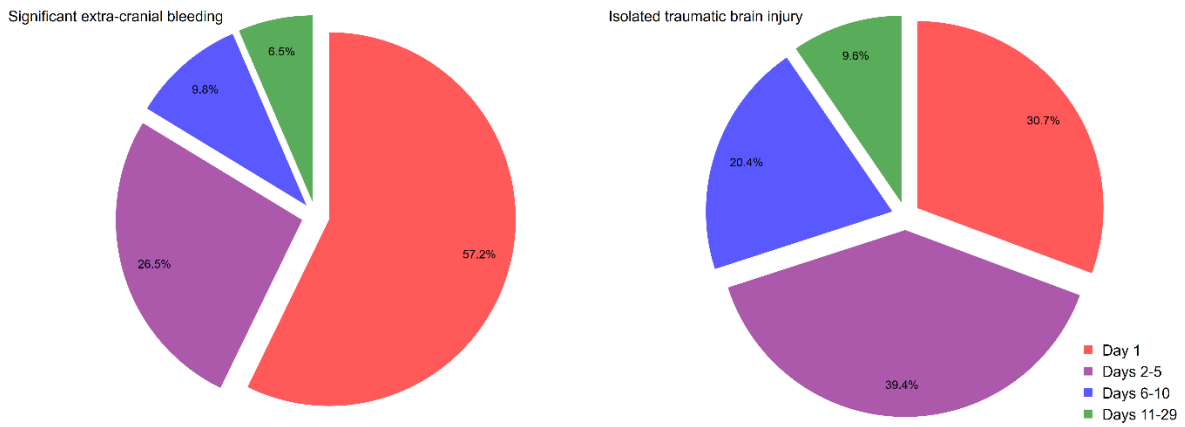

Figure 4. Distribution of time to death in patients with significant extracranial bleeding (CRASH-2 trial) versus isolated traumatic brain injury (CRASH-3 trial)

Validating outcome measures for postpartum haemorrhage

Postpartum blood loss is prone to measurement error and does not always predict poor maternal outcomes.[70] Improving the accuracy of blood loss measurement does not lead to earlier detection of postpartum haemorrhage.[71] Using an arbitrary cut-off of 500ml to define a 'postpartum haemorrhage' (PPH) is flawed, not only because it is hard to measure accurately, but also because a woman's ability to tolerate blood loss depends on many factors including her haemoglobin level. There is a need for an alternative definition of PPH in women with anaemia, which affects a third of pregnant women. Some proposed alternative definitions include those based on physiological changes or the receipt of interventions for PPH.[72] The WOMAN-2 trial is assessing the effects of tranexamic acid for postpartum bleeding in women with moderate or severe anaemia. I used data from this ongoing trial to assess the suitability of several PPH definitions as outcome measures in anaemic women, comparing each outcome's frequency, specificity for significant bleeding, and association with maternal functioning after birth.[32] This is the first study to assess outcome measures for severe postpartum bleeding in anaemic women - its findings have informed the primary outcome of the WOMAN-2 trial and might inform the choice of outcome measures for subsequent trials in this field.

1.4.2 Wider research on haemostatic treatments

As of June 2022, the five first author papers that form the basis of this PhD had been cited 63 times in total. Overall, my work has been cited over 400 times in the last 5 years, with eight first author or co-authored publications having at least 10 citations each. My research contributed to discussions and outputs from the NIH National Heart Lung and Blood Institute Haemostasis Clinical Trial Outcomes Symposium in 2019. During this two-day workshop, I met with an international panel of experts to establish clinically relevant outcome measures for trials evaluating haemostatic treatments across several disciplines including trauma, obstetrics, gastroenterology, neurosurgery, surgery and oncology.[73] The output from the trauma working group incorporates concepts from my research, recognising the need for an etiologically relevant outcome measure that captures the treatment effect on bleeding while minimising misclassification from non-bleeding causes of death.[74] The authors

recommended a primary outcome of 3 to 6-hour all-cause mortality in trials of treatments for traumatic bleeding. While this outcome should be highly specific for death due to bleeding, the timeframe may be too small to yield enough outcome events, and trials using this endpoint will likely lack statistical power unless the study population has a high baseline risk of death, or the treatment effect or sample size is large. In the CRASH-2 trial, among 13,493 injured trauma victims randomised within 3 hours of injury we estimated that 327 patients died within 6 h (time of death approximated from time of randomisation and date of death). Despite its large size, the trial would have had under 80% power to detect a 25% reduction in 6-hour all-cause mortality with tranexamic acid, assuming a baseline event rate of 3% (191 events in placebo group), and under 45% power to detect a 30% reduction in 3h mortality assuming a baseline event rate of 0.6% (42 events in placebo group). Cause-specific mortality or all-cause mortality within 24h may be more appropriate, striking a balance between specificity for bleeding and statistical power. In trials of polytrauma patients, power for such early outcomes will be even lower due to the increased proportion of late head-injury deaths.

1.4.3 Clinical practice

The impact of my work extends beyond guiding the choice of outcome measures in clinical trials of haemostatic treatments and providing insights into acute bleeding and tranexamic acid. By aiding the detection of the biological treatment effect and the understanding of trial results, my work has potentially impacted clinical practice and may have improved patient care. The latest British Society for Haematology guideline for major haemorrhage recommends the use of tranexamic acid in trauma and postpartum haemorrhage based on the WOMAN, CRASH-2 and CRASH-3 trial results, and states that patients with gastrointestinal bleeding should not receive tranexamic acid based on the HALT-IT trial results.[75] The CRASH-3 trial provides evidence of the first drug that prevents death following TBI. Tranexamic acid was recommended for the treatment of moderate to severe TBI in the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) Clinical Practice Guidelines for Head Trauma following the CRASH-3 trial. The NICE head injury guidance is being updated to include the latest evidence, with publication due in early 2023.[76,77] To increase implementation, I have disseminated the CRASH-2 and CRASH-3 trial results and my research findings to clinicians and the public via several means, including social media, a whiteboard animation, and presentation at the Trauma Care Virtual Conference in 2021.[78]

1.5 Strengths and Weaknesses

The trials that form the basis of this PhD provide a rich resource for exploring the natural history of bleeding and the mechanism of action of tranexamic acid. They represent some of the largest trials in patients with acute bleeding, comprising data on over 70,000 patients to date. The large number of outcome events provide reliable estimates of the treatment effect and make it possible to conduct meaningful subgroup and sensitivity analyses and explore different outcome measures. However, some trial results are imprecise, and while we believe this lack of statistical power is caused by dilution from outcome misclassification, chance cannot be ruled out as a potential alternative explanation.

Rigorous data collection and cleaning procedures such as central monitoring, on site monitoring, source data verification and staff training have generated high-quality datasets with almost complete follow-up and little missing data. Because the trials collected data on the time of bleeding onset, randomisation, death and other outcome events, as well as patient death narratives, it is possible to discern a detailed sequence of events. That said, the validity of these findings depends on the accuracy of data on the timing of events, and some measurement error is inevitable. Errors in the estimation of the time of injury could result in the inclusion of patients outside the early treatment or early death time window, and because late treatment is less effective and late outcomes are less likely to be due to bleeding, this will cause dilution.[79] Accurate estimation of time from injury to treatment is challenging, particularly in low resource settings with less well established prehospital emergency services, because patients are often taken to hospital by bystanders or family members in private vehicles with no record of the time of injury. Time of death can also be misclassified as there is often an interval between death and its formal confirmation. In the CRASH-2 trial, time of death was estimated from date and time of randomisation and date of death because time of death was not recorded, however, misclassification should not differ by group.

The biological effect of tranexamic acid and the impact of dilution from outcome misclassification is consistent across multiple trials and with biology. Activation of fibrinolysis occurs early in patients with acute bleeding,[80–82] and bleeding-related outcome events such as exsanguination tend to happen early.[4] It therefore seems reasonable that tranexamic acid would be most effective when given soon after bleeding onset and most likely to influence early, bleeding-related outcome events. When demonstrated mathematically, the impact of dilution from aetiologically irrelevant events aligns with biology and trial findings. For example, if tranexamic acid reduces the risk of early (bleeding) deaths by one quarter (RR = 0.75) but has no effect on late (non-bleeding) deaths (RR = 1.00), the overall relative risk for all-cause mortality at the end of follow-up is a weighted average of these relative risks, weighted by their relative frequency i.e. the proportion of deaths in the placebo group that are early or late: relative risk = (0.75 x 0.33) + (1.0 x 0.67) = 0.92. This diluted RR is almost identical to that observed for all-cause mortality at 28 days in the CRASH-3 trial (RR 0.93), with around a third of deaths occurring within 24 hours of injury (see Figure 4). Though less likely to affect non-bleeding related outcomes or outcomes occurring several days after treatment administration, it is possible for a drug with a short duration of action to have long term effects. Haemorrhage is usually not the proximate cause of death but rather a symptom of the ultimate cause, such as an injury. By reducing bleeding, tranexamic acid could potentially influence the risk of causes of death resulting from prolonged hypotension such as hypoxic brain damage, acute renal failure, disseminated intravascular coagulation,

or iatrogenic causes of death like surgery complications. As such, excluding late or non-bleeding causes of death from the outcome might miss possible 'secondary haemorrhage' deaths and underestimate the potential benefit.

While some of the epidemiological concepts are complex, the analytical methods I have used are relatively straightforward which aids interpretation and dissemination of findings but has some statistical limitations. Time-to-event data in clinical trials can be explored using survival analysis. For example, I used period-specific hazard ratios to explore the impact of early outcome events in the WOMAN trial, but these are susceptible to selection bias because post-randomisation exclusions based on time-to-outcome are not independent of treatment.[31,83] Competing risks are another issue in survival analysis, arising when the occurrence of one type of outcome event precludes or modifies the occurrence of the primary outcome event. Patients with acute bleeding are at risk of various causes of death that compete with one another. If a woman dies from eclampsia during childbirth, she is no longer at risk of death due to postpartum bleeding, for example. While competing risks affect cause-specific mortality, they are absent from all-cause mortality and so my analyses of death within 24 hours or 28 days should be minimally impacted. But when competing risks are present, such as in analyses of cause-specific death, the Kaplan Meier function will result in biased estimates of incidence over time, tending to overestimate it. A survival analysis can account for competing risks by using cumulative incidence functions to estimate the probability of the outcome over time, and using Gray's test in place of the log-rank test for equality in survival between groups.[84] These methods will be applied to future analyses to assess the potential impact of competing risks.

The global trials that form the basis of this research were conducted in hundreds of hospitals in many countries. One aspect not explored here is the potential need for different outcome measures in different settings. The study setting might reasonably influence the chronology of events, from the length of the empirical induction period to the timing of trial treatment administration, as well as the timing, type and frequency of interventions given such as blood transfusion, hysterectomy or additional therapies. Some outcomes may be more susceptible to misclassification and treatment effect dilution, and therefore less appropriate in certain settings. In analyses of the CRASH-2 and CRASH-3 trials, although the rate of the primary outcome varied significantly between centres and countries, there was no evidence of a difference in treatment effect between centres or countries, or by country income level.[25,85] There is some evidence that the extent of misclassification of time to treatment, an important effect modifier, varies by setting, although this appeared to have little impact on the overall trial result.[79] Depending on the research question and trial design, it may be important to consider if the outcome is appropriate in all settings in terms of frequency and potential for misclassification. Future analyses could investigate whether the extent of outcome misclassification and treatment effect dilution vary by setting.

The trials that form the basis of this research were also conducted over a period of several years. Patient outcomes may improve over time as a study progresses due to advances in care or may be impacted by global events. Descriptive analyses and multivariable modelling could be used to investigate temporal changes in the frequency of outcome events. However, even if the event rate changed over time, this should not have impacted the effect of tranexamic acid. In an individual patient data meta-analysis of the CRASH-2 and WOMAN trials, the effect of tranexamic acid did not

vary by baseline risk of death.[86] Understanding time-dependent treatment effects is perhaps more important for interventions given over a long period such as cancer therapies, or for screening or vaccination programmes that may have waning effects.

1.6 Implications for future research

1.6.1 Applying the concept of treatment effect dilution to other disease areas

The concepts presented in this PhD could be applied widely, beyond trials of haemostatic treatments. Dilution from inevitable outcome events is common in emergency care trials in general because patients are critically ill and everything happens rapidly. The concepts from this PhD could help inform the choice of outcome measures.

One example is heart failure trials. Despite several large trials of therapeutic interventions for heart failure over the past decade, most have failed to demonstrate patient benefit. One reason for this is the inclusion of patients with undertreated heart disease and comorbidities such as hypertension and diabetes in whom inevitable outcome events are common, as well as early cardiovascular outcomes that occur before the intervention has time to exert an effect.[87] Despite the high event rates, any treatment benefit is drowned out by noise from the large number of inevitable events. Heart failure trials also often use composite endpoints. There is a common misconception that by increasing the baseline event rate, using a composite measure will increase statistical efficiency.[88] A key assumption is that all components of the composite will be affected by the treatment to a similar extent.[89] While components of a composite may add events, if increased or unaffected by the treatment they will also add noise. Gains in power may well be offset by dilution of the treatment effect. Because sample size depends inversely on the square of the effect size, a small reduction in the treatment effect has a large impact on power. This is well demonstrated in the CAPRICORN trial, which switched its primary outcome from all-cause mortality to a composite of death or cardiovascular hospital admissions following a lower than expected mortality rate. Although the treatment reduced mortality, because there was no effect on hospital admissions, the composite endpoint did not achieve statistical significance and the trial was labelled as 'neutral'.[89]

Another example is COVID-19 trials. Despite the scale of the research response to the pandemic, many clinical trials of treatments for COVID-19 infection were too small and failed to provide reliable evidence of benefit or harm.[90] Death in patients with COVID-19 infection can result from diverse pathophysiological processes. In open-label COVID-19 trials, all-cause mortality is a common primary outcome because outcome assessment can be influenced by knowledge of treatment allocation. However, all-cause mortality inevitably includes deaths unaffected by the trial treatment that dilute any treatment effect towards the null. The prioritization of direct or indirect acting antiviral therapeutics by the World Health Organization early in the pandemic limited rapid recruitment of patients into trials evaluating supportive care interventions aimed at other important diseases processes. Because the timing of treatment in relation to the COVID-19 disease process is critical, clinical trials of antiviral drugs needed to recruit patients with ongoing viral replication before they became critically ill. Instead, most trials took place in a hospital setting, recruiting patients from intensive care units, late in the disease course, with high death rates, in whom viral replication may have ceased. The inclusion of such patients would dilute any antiviral effect and reduce statistical power.

1.6.2 Clinical trial methodology

With the current global economic crisis, limited funding and rising cost of research, the need to design efficient, cost effective trials has never been greater.[91] To find new effective treatments and improve

global public health, there is a need for large, simple trials with appropriate outcome measures.[92] It is critical to select outcome measures that capture the biological effect of a treatment to minimise dilution and maximise statistical power. In 2014, a survey of UK CRC Clinical Trial Units found that the choice of appropriate outcome measures was in the top three trial methodology priorities.[93] Trial methodology guidance recognises the importance of randomisation, blinding and complete follow-up to minimise bias, yet there is little emphasis on outcome selection to minimise dilution from misclassification.

As well as choosing relevant outcome measures, trials should aim to recruit participants for whom there is a reasonable possibility of benefit, such that the balance of risks and benefits is likely to be acceptable. Medical interventions often carry risks and clinical trials are very costly, so selecting an appropriate study population is important from an ethical standpoint, putting the wellbeing of participants first and using resources efficiently. To reduce dilution from inevitable outcome events, one option is to exclude patients in whom the treatment is unlikely to be effective, but this is not always known upfront. Having more exclusion criteria also makes recruitment more complicated, potentially leading to slower recruitment. Instead, we could have broad eligibility criteria and examine the impact of inevitable events using a sensitivity analysis that excludes critically ill patients. However, the tendency to dichotomise trials as positive or negative based on a single p-value from the primary analysis without trying to understand the data or its biases limits this approach at present.[94] Secondary outcomes and sensitivity analyses hold valuable information, yet the 'success' of a trial often hinges solely on the primary outcome, despite it being quite arbitrary. If we are to make progress, the evidence should be interpreted in its totality, considering all outcomes and what has come before, otherwise the supposed success of a trial will continue to rest on the primary outcome alone.[94] To avoid post hoc selection of findings, all outcomes and sensitivity analyses should be set out in a statistical analysis plan prior to unblinding of the trial, with the biological rationale for secondary analyses clearly presented.

Traditional clinical trial designs are inflexible, failing to take advantage of new information generated by trials as they are underway. Trial design can be improved by considering all relevant research, including accumulating data which should be reviewed at interim analyses. Adaptive trial designs have a degree of in-built flexibility and need not be complex. Rather, making adaptations to a trial's design while it is ongoing can make the trial more efficient and more ethical.[95,96] Designs that allow sample size re-estimation and population enrichment can prevent an initially underpowered trial from wasting resources. Tightening the inclusion criteria can focus recruitment on patients that are most likely to benefit or are at highest risk of the outcome, which in turn can boost the event rate and treatment effect, enhancing study power. Outcome measures can also be informed by accumulating evidence. Outcome switching is not an issue so long as the new outcome is prespecified before unblinding and there is a strong rationale to support its use. New evidence leading to changes in guideline recommendations may also necessitate changes to the primary outcome of ongoing trials, for example, researchers changed the definition of the primary outcome for the STREAM stage 2 trial to accommodate the rapidly evolving treatment landscape for rifampicin-resistant tuberculosis.[97] Adaptive platform trials offer another way to make the most efficient use of resources, by studying multiple interventions sequentially in a single trial with a master protocol.[98,99]

Finally, when designing trials, it is worth noting that dilution has different implications in superiority trials compared to equivalence or non-inferiority trials.[100] In superiority trials, dilution can lead to a false negative result, with researchers wrongly concluding that the trial intervention is ineffective because the effect is masked. But because it makes treatments appear more similar, dilution increases the chance of declaring non-inferiority or equivalence, therefore increasing the risk of false positive result in such trials. Wrongly concluding that an active and control treatment are equally effective may lead to wasted resources, no patient benefit and even possible harm.[101]

1.7 Conclusions

In this thesis, I explored the effects of tranexamic acid on acute bleeding, applying a range of methodological approaches to large clinical trial datasets. My work informed the selection of the primary outcome measure in the CRASH-3, HALT-IT and WOMAN-2 trials. By generating new insights into the natural history of acute bleeding and the mechanism of action of tranexamic acid, it also helped the implementation of the trial results, potentially contributing to improvements in patient care, and has influenced research on haemostatic treatments more generally. Whenever possible, I prespecified my hypotheses in statistical analyses plans and conducted my analyses prior to unblinding of the trial data.

The tendency for non-differential misclassification of outcomes to cause bias towards the null was exploited as a tool to study the biological effects of tranexamic acid. When an outcome measure includes events that fall outside of the etiologically relevant period or biological pathway, the effect estimate is diluted and biased towards the null. I assessed the impact of misclassification by varying assumptions about the empirical induction period and locating the least diluted measure of effect. This allowed me to refine hypotheses about the biological effects of tranexamic acid and select outcome measures better able to capture these effects.

I conducted descriptive and multivariable analyses of clinical trial data on baseline characteristics and the timing and frequency of various outcome events in many thousands of patients with acute bleeding. By deepening our understanding of the natural history of acute bleeding, the knowledge generated could facilitate the interpretation of trial results, suggest new hypotheses, and inform the design of clinical trials.

I proposed key criteria for selecting outcome measures: the outcome must 1) have the potential to be affected by the trial intervention; 2) be amenable to unbiased measurement; 3) be sufficiently common; and 4) be clinically relevant and important to patients. I applied these criteria when assessing the suitability of different outcomes in trials of tranexamic acid. For example, I validated the primary outcome for the WOMAN-2 trial by assessing frequency, specificity for significant bleeding, and association with maternal functioning.

These criteria and the concepts presented in this thesis could be applied to clinical trials in other disease areas and might help to inform the choice of outcome measures and generate knowledge on the cause-effect relationship between study interventions and outcomes.

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RESEARCH ARTICLE Open Access

The impact of early outcome events on the effect of tranexamic acid in post-partum haemorrhage: an exploratory subgroup analysis of the WOMAN trial

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Abstract

Background: In severe post-partum haemorrhage, death can occur within hours of bleeding onset so interventions to control the bleeding must be given immediately. In clinical trials of treatments for life-threatening bleeding, established treatments are given priority and the trial treatment is usually given last. However, enrolling patients in whom severe maternal morbidity or death is imminent or inevitable at the time of randomisation may dilute the effects of a trial treatment.

Methods: We conducted an exploratory analysis of data from the WOMAN trial, an international, randomised placebo-controlled trial of the effects of tranexamic acid on death and surgical intervention in 20,060 women with post-partum haemorrhage. We assessed the impact of early maternal death or hysterectomy due to exsanguination on the effect of tranexamic acid on each of these respective outcomes. We conducted repeated analyses excluding patients with these outcomes at increasing intervals from the time of randomisation. We quantified treatment effects using risk ratios (RR) and 99% confidence intervals (CI) and prepared cumulative failure plots.

Results: Among 14,923 women randomised within 3 h of delivery (7518 tranexamic acid and 7405 placebo), there were 216 bleeding deaths (1.5%) and 383 hysterectomies due to bleeding (2.8%). After excluding deaths from exsanguination at increasing time intervals following randomization, there was a significant reduction in the risk of death due to bleeding with tranexamic acid (RR = 0.41; 99% CI 0.19–0.89). However, after excluding hysterectomies at increasing time intervals post-randomization, there was no reduction in the risk of hysterectomy due to bleeding with tranexamic acid (RR = 0.79; 99% CI 0.33–1.86).

Conclusions: Findings from this analysis provide further evidence that tranexamic acid reduces the risk of death from exsanguination in women who experience postpartum haemorrhage. It is uncertain whether tranexamic acid reduces the risk of hysterectomy for bleeding after excluding early hysterectomies.

Trial registration: ISRCTN trial registration number ISRCTN76912190, 8 Dec 2008; ClinicalTrials.gov number NCT00872469, 30 March 2009; PACTR number PACTR201007000192283, 9 Feb 2010; EudraCT number 2008–008441-38, 8 Dec 2010 (retrospectively registered).

Keywords: Postpartum haemorrhage, Tranexamic acid, WOMAN trial, Hysterectomy, Death, Bleeding

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Background

Tranexamic acid reduces bleeding by inhibiting the breakdown of fibrin blood clots. When given prior to incision, tranexamic acid reduces blood loss in elective surgery by about one third [1]. The CRASH-2 trial showed that early tranexamic acid administration reduces death due to bleeding in trauma patients with or at risk of significant haemorrhage [2]. The WOMAN trial assessed the effects of tranexamic acid on death, hysterectomy and other outcomes in 20,060 women with post-partum haemorrhage (PPH). There was a significant reduction in death due to bleeding with tranexamic acid (RR = 0·81, 95% CI 0·65–1·00; p = 0·045) [3]. As in traumatic haemorrhage, the reduction was greatest when treatment was given early (within 3 h of delivery), (RR 0·69, 95% CI 0·53–0·90; p = 0·007), with no apparent reduction after 3 h [3, 4]. There was also a decrease in laparotomy to control bleeding in women who received tranexamic acid (RR 0·64, 95% CI 0·49–0·85; p = 0·002). Based on these results, the World Health Organization has recommended the early use (within 3 h of birth) of tranexamic acid for the treatment of PPH [5].

In the WOMAN trial, tranexamic acid did not prevent hysterectomy due to bleeding (RR = 0.95 95%CI 0.78–1.16, p = 0.611). During the trial, we noticed that clinicians sometimes decided to perform a hysterectomy at or prior to the time of randomisation and so tranexamic acid could not influence the decision. We predicted that including such hysterectomies as 'outcome measures' in the trial would reduce or obscure the effect of tranexamic acid [6].

Inappropriate assumptions about the timing of an exposure's effect can cause bias towards the null [7]. Even when outcome events occur after randomisation, some will be imminent or inevitable at the time of randomisation and so cannot be prevented by the trial treatment. This is a particular problem in trials in life threatening emergencies when the trial treatment is usually given after the established treatments. Although a trial would ideally evaluate a treatment as it would be used in clinical practice, it is difficult to ensure that a treatment of uncertain effectiveness is given urgently, particularly when clinicians know that half of the patients will receive a placebo.

Given the extent of blood loss in PPH, many of the women enrolled in the WOMAN trial were probably critically ill at the time of randomisation: 59% of women had haemodynamic instability. As such, hysterectomy or death may have been imminent or inevitable in some women. Such outcomes would likely have occurred soon after randomisation. We hypothesised that the inclusion of imminent or inevitable outcome events in the analysis would dilute the treatment effect towards the null. To estimate an undiluted measure of effect, Rothman proposed repeated analyses with varying assumptions about the timing of an exposure's effect [7]. We aimed to examine whether early outcome events diluted the effect of tranexamic acid on death due to bleeding and hysterectomy due to bleeding by conducting repeated analyses excluding outcomes at increasing intervals from randomisation.

Methods

The WOMAN trial was a randomised, placebo-controlled trial of the effect of tranexamic acid on death, hysterectomy and other morbidities in women with PPH. It included 20,060 women aged 16 years and older with a clinical diagnosis of PPH recruited from 193 hospitals in 21 countries between 2010 and 2016. We randomly allocated women to receive 1 g of tranexamic acid or placebo by slow intravenous injection. If bleeding continued after 30 min or restarted within 24 h of the first dose, we gave a second dose of 1 g of tranexamic acid or placebo. We obtained follow-up data for 99.8% of patients. We have published full details of the trial rationale, design, methods and results elsewhere [3, 6].

We conducted the trial in accordance with good clinical practice guidelines. The relevant ethics committees and regulatory agencies approved the consent procedures. We obtained informed consent from women if their physical and mental capacity allowed. If a woman could not give consent, we obtained proxy consent from a relative or representative. If no proxy was available, then if local regulation allowed, we deferred or waived the consent. In these cases, we told the woman about the trial as soon as possible and obtained consent for use of the data collected.

Analysis

We conducted exploratory analyses of the WOMAN trial dataset using the method proposed by Rothman [7]. Our primary outcome was death due to bleeding and our secondary outcome was hysterectomy due to bleeding. We prepared frequency bar charts of the time intervals between randomisation and death due to bleeding and between randomisation and hysterectomy due to bleeding in the treatment and placebo groups to show the time course of bleeding-related outcomes. We then examined the effect of tranexamic acid on these outcomes among women treated within 3 h of delivery since tranexamic acid only appears to be effective when given within this timeframe [3, 4]. We hypothesised that maternal deaths or hysterectomies due to bleeding that occurred soon after randomisation were imminent or inevitable at the time of randomisation. As such, we assessed the impact of early deaths or hysterectomies due to bleeding on the treatment effect by conducting repeated analyses excluding patients with these

outcomes at increasing intervals from randomisation. We also excluded patients who died from any cause within the relevant exclusion period, as they could not contribute to the denominator. We increased the length of the exclusion period by one hour at a time, up to 10 h for deaths due to bleeding but 5 h for hysterectomy due to bleeding since there were few hysterectomies beyond 5 h. We excluded hysterectomies completed before randomisation. We conducted intention-to-treat and per-protocol analyses and quantified treatment effects using risk ratios and 99% confidence intervals. We used 99% rather than 95% confidence intervals due to the multiple number of between-group comparisons. We prepared plots of the cumulative percentage of death due to bleeding and hysterectomy due to bleeding in order to supplement the period-specific risk ratios, which can be susceptible to selection bias [8]. We assessed the proportional hazards assumption using the Grambsch-Therneau global test.

To assess the risk of selection bias from post-randomisation exclusions we examined the distribution of baseline characteristics by treatment group. We used stratified analyses to assess potential confounding factors including age, time to treatment, type and place of delivery, cause of haemorrhage, use of uterotonic prophylaxis, estimated blood loss, blood transfusion, and second dose of the trial treatment (or placebo). We adjusted for relevant factors using multivariable log binomial regression and selected a final model using likelihood ratio tests. We also conducted sensitivity analyses of women treated within an hour of delivery, women with uterine atony as the primary cause of haemorrhage, and women who underwent caesarean section.

Results

In the WOMAN trial, 20,060 women were randomly assigned to receive tranexamic acid (n = 10,051) or placebo (n = 10,009). After excluding 39 women who did not fulfil the eligibility criteria, withdrew consent or were lost to follow up, data on 20,021 women were available for analysis. Ten women (< 0.1%) had missing data on time of delivery or time of randomisation, so time to treatment was calculated in the remaining 20,011 women. Of these, 14,923 women were randomised within 3 h of delivery (7518 tranexamic acid and 7405 placebo), with a mean time from delivery to randomisation of 1 h (interquartile range = 0.4–1.5 h). Data on time of haemorrhage death were available for all women. Data on time of hysterectomy for bleeding or hysterectomy status were missing for 45 women (0.3%), leaving 14,878 patients for the hysterectomy analyses. Among women randomised within 3 h of delivery, there were 216 deaths due to bleeding (1.5%) and 383 hysterectomies due to bleeding (2.8%). Here we present the results of intention-to-treat analyses. In per-protocol analyses, we excluded 19 women who did not receive tranexamic acid (n = 9) or placebo (n = 10). The results of the per-protocol analysis were almost identical (see Additional file 1: Tables S1 and S2). The trial arms remained balanced by baseline characteristics (see Additional file 1: Tables S3 and S4), and there was no evidence of confounding (see Additional file 1: Tables S5 and S6).

Figure 1 shows a frequency bar chart of the interval between randomisation and death due to bleeding for the placebo group (n = 173) and tranexamic acid group (n = 138) over the 24 h after randomisation. The distribution was positively skewed, with 42% of all deaths from exsanguination occurring within 3 h of randomisation, 58% within 5 h, and 80% within 10 h. Thirty-five (10%) deaths from exsanguination occurred more than 24 h after randomisation.

Table 1 shows risk ratios for death due to bleeding in women treated within 3 h of delivery, excluding women who died at increasing intervals from randomisation. When all women were included, there was a 31% reduction in the risk of death due to bleeding with tranexamic acid (RR = 0.69, 99% CI 0.48–0.98). Excluding women who died soon after randomisation increased the treatment effect. The effect was largest after excluding women who died within 9 h of randomisation, with a 59% reduction in death due to bleeding (RR = 0.41, 99% CI 0.19–0.89). Although there was a decreasing trend in risk ratios, the 99% confidence intervals were wide and overlapping. In sensitivity analyses of women treated within an hour of delivery, women with uterine atony and women who underwent caesarean section, we observed the same decreasing trend in risk ratios (see Additional file 1: Tables S7-S9).

Figure 2 shows a plot of the cumulative percentage of deaths from bleeding by time from randomisation in the tranexamic acid and placebo groups. For the first few hours after randomisation the curves overlap but later they separate. The Grambsch-Therneau test for proportional hazards gave p = 0.06.

Figure 3 shows a frequency bar chart of the interval between randomisation and hysterectomy due to bleeding in the placebo group (n = 263) and tranexamic acid group (n = 245) for the 24 h after randomisation. Again, the distribution was positively skewed with 38% of hysterectomies for bleeding occurring within one hour of randomisation and 82% within 3 h. Less than 2% of hysterectomies for bleeding (n = 9) occurred more than 24 h after randomisation.

Table 2 shows risk ratios for hysterectomy due to bleeding for women treated within 3 h of delivery, excluding women who underwent hysterectomy at

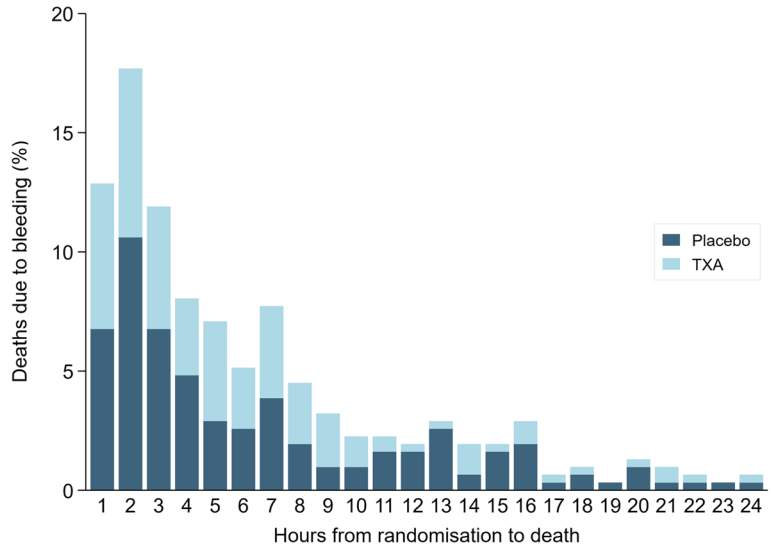

Fig. 1 Deaths due to bleeding within 24 h of randomisation by treatment group and hours since randomisation

increasing intervals from randomisation. When all women were included, there was no reduction in the risk of hysterectomy due to bleeding with tranexamic acid (RR = 0.95, 99% CI 0.73–1.23). Excluding women who had a hysterectomy for bleeding soon after randomisation resulted in a decrease in the risk ratio (RR = 0.79; 99% CI 0.33–1.86), however, the 99% confidence intervals overlapped the null at each exclusion interval.

Figure 4 shows a plot of the cumulative percentage of hysterectomy for bleeding by time from randomisation in the tranexamic acid and placebo groups. In the first hours after randomisation the curves were similar but with minimal separation later. The Grambsch-Therneau test for proportional hazards gave $p = 0.17$.

Discussion

In the original WOMAN trial, women who experienced PPH were randomized to receive tranexamic acid vs placebo. In the WOMAN trial, we observed a 19% reduction in the risk of death from exsanguination in women who received tranexamic acid compared to placebo, with a 31% reduction in women treated within 3 h of giving birth. In this secondary analysis of WOMAN trial data, after excluding deaths due to bleeding that occurred soon after randomisation, we observed a lower risk of death from exsanguination in women who received early tranexamic acid compared to placebo (RR = 0.41; 99% CI 0.19–0.89). Some women may have been so critically ill at the time of randomisation that death was imminent

Table 1 Impact of early deaths due to bleeding on the effect of tranexamic acid

Exclusion interval (hours from randomisation)	Exclusions[a]		N		Death due to bleeding		
	TXA (%)	Placebo (%)	TXA	Placebo	TXA (%)	Placebo (%)	Risk ratio (99% CI)
None	–	–	7518	7405	89 (1.2)	127 (1.7)	0.69 (0.48–0.98)
1	14 (0.2)	15 (0.2)	7504	7390	76 (1.0)	114 (1.5)	0.66 (0.45–0.96)
2	30 (0.4)	38 (0.5)	7488	7367	61 (0.8)	92 (1.3)	0.65 (0.43–1.00)
3	42 (0.6)	57 (0.8)	7476	7348	50 (0.7)	75 (1.0)	0.66 (0.41–1.05)
4	53 (0.7)	70 (1.0)	7465	7335	42 (0.6)	64 (0.9)	0.64 (0.39–1.07)
5	62 (0.8)	77 (1.0)	7456	7328	33 (0.4)	59 (0.8)	0.55 (0.31–0.96)
6	66 (0.9)	85 (1.2)	7452	7320	29 (0.4)	53 (0.7)	0.54 (0.30–0.97)
7	73 (1.0)	94 (1.3)	7445	7311	23 (0.3)	44 (0.6)	0.51 (0.26–0.99)
8	80 (1.1)	97 (1.3)	7438	7308	18 (0.2)	41 (0.6)	0.43 (0.21–0.89)
9	83 (1.1)	101 (1.4)	7435	7304	16 (0.2)	38 (0.5)	0.41 (0.19–0.89)
10	84 (1.1)	104 (1.4)	7434	7301	16 (0.2)	37 (0.5)	0.42 (0.20–0.91)

[a]% is the proportion of the original trial arm excluded ($N = 7518$ TXA, $N = 7405$ placebo). TXA = tranexamic acid. Includes women treated within 3 h of delivery only

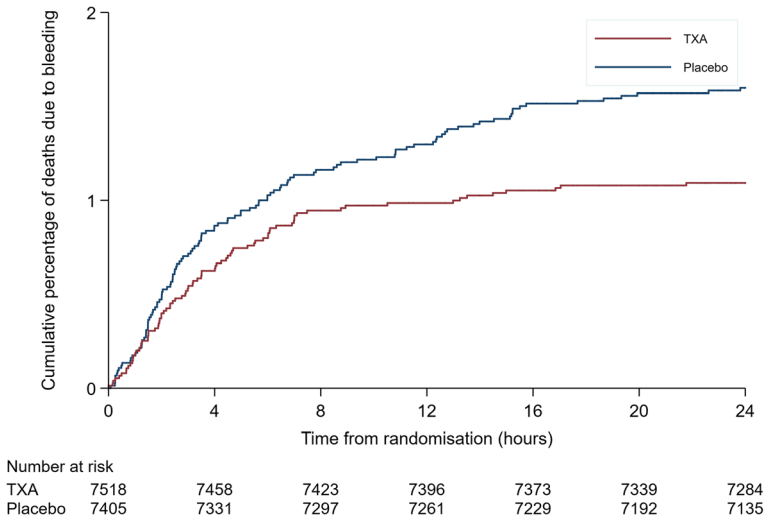

Fig. 2 Cumulative percentage of deaths due to bleeding by time from randomisation in the tranexamic acid and placebo group

and inevitable regardless of treatment. The findings of this secondary analysis extend those of the original WOMAN trial by further highlighting the importance of tranexamic acid as an early life-saving intervention for women who experience PPH.

The plasma concentration of tranexamic acid needed to inhibit fibrinolysis is around 5–15 mg/L and tranexamic acid has a half-life of 2–3 h [9–14]. After an intravenous injection of 1 g of tranexamic acid, the plasma concentration should exceed this range for several hours [13, 15]. Because it is eliminated by the kidneys, the concentration could remain elevated for much longer in women with severe bleeding and renal impairment [16]. Further research on the pharmacokinetics and pharmacodynamics of tranexamic acid in obstetric bleeding will help to determine the optimal dosing regimen.

Our analysis has important limitations. Although the statistical analysis plan, which we prepared before seeing the trial results, anticipated that outcomes determined prior to randomisation would dilute the treatment effect, the exploratory analyses presented here were not pre-specified and comprise multiple between-group comparisons. The possibility of a type 1 error cannot be excluded and so our results require cautious interpretation. That said, in keeping with our hypothesis, we observed an increase in the treatment effect on death due to bleeding with an increasing exclusion interval. This

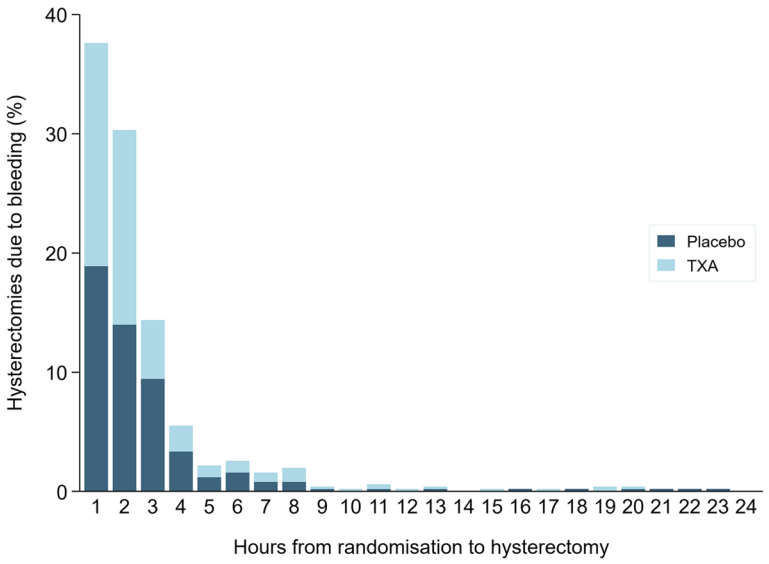

Fig. 3 Hysterectomies due to bleeding within 24 h of randomisation by treatment group and hours since randomisation

Table 2 Impact of early hysterectomies due to bleeding on the effect of tranexamic acid

Exclusion interval (hours from randomisation)	Exclusions[a]		N		Death due to bleeding		
	TXA (%)	Placebo (%)	TXA	Placebo	TXA (%)	Placebo (%)	Risk ratio (99% CI)
None	–	–	7494	7384	188 (2.5)	195 (2.6)	0.95 (0.73–1.23)
1	90 (1.2)	93 (1.3)	7404	7291	112 (1.5)	117 (1.6)	0.94 (0.67–1.32)
2	175 (2.3)	167 (2.3)	7319	7217	42 (0.6)	64 (0.9)	0.65 (0.39–1.08)
3	205 (2.7)	214 (2.9)	7289	7170	23 (0.3)	34 (0.5)	0.67 (0.33–1.33)
4	217 (2.9)	236 (3.2)	7277	7148	19 (0.3)	25 (0.4)	0.75 (0.34–1.63)
5	227 (3.0)	246 (3.3)	7267	7138	16 (0.2)	20 (0.3)	0.79 (0.33–1.86)

[a]% is the proportion of the original trial arm excluded (*N* = 7494 TXA, *N* = 7384 placebo). TXA = tranexamic acid. Includes women treated within 3 h of delivery only

finding was consistent in several sensitivity analyses. The temporal distribution of haemorrhage deaths allowed us to exclude women who died soon after randomisation. We did not observe a statistically significant decrease in the risk of hysterectomy for bleeding associated with tranexamic acid compared with placebo after excluding hysterectomies performed early after randomization. Although this finding suggests that tranexamic acid may not decrease the need for hysterectomy as a life-saving surgical intervention for PPH, it is possible that our sample size was inadequate to show a true treatment benefit when excluding early hysterectomies.

Period-specific risk ratios are susceptible to selection bias [8]. Because tranexamic acid reduces deaths due to bleeding, post-randomisation exclusions based on time-to-outcome are not independent of treatment. Indeed, we excluded 20 more deaths from the placebo group than from the treatment group. Although this might be expected to obscure rather than inflate the delayed effects of treatment, because we do not have data on patient characteristics at each time point selection bias remains a concern. Figure 2 provides some unbiased evidence of a lack of treatment benefit early on, in line with our hypothesis that early deaths due to bleeding may dilute the treatment effect, but this may be a spurious finding.

The validity of our results also depend on the accuracy of data on the time of randomisation (treatment) and the time of death but measurement error is inevitable. Although we urged investigators to give the trial treatment as soon as possible after randomisation, some outcomes would have occurred before the treatment was completed. Time of death could have been misclassified since there is often an interval between death and its formal confirmation.

Because maternal death can occur soon after major uncontrolled PPH, interventions to compensate for blood loss (e.g. blood transfusion) and control the bleeding (e.g. hysterectomy) may occur early after PPH diagnosis, often prior to administration of the trial

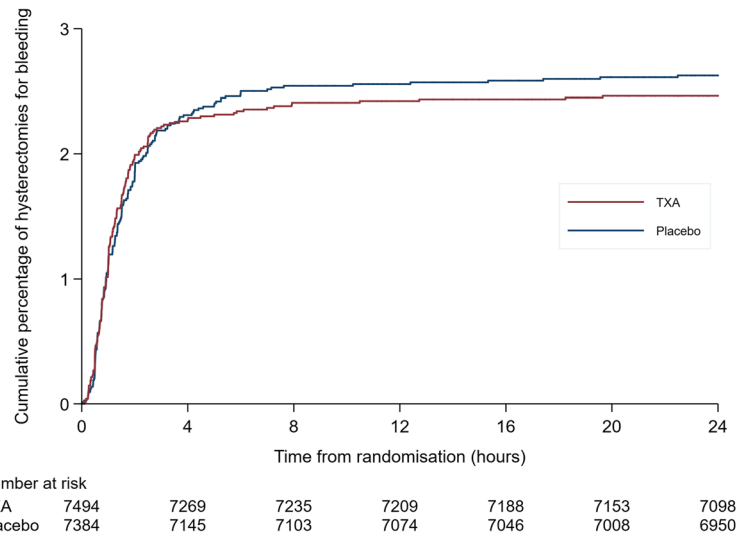

Fig. 4 Cumulative percentage of hysterectomies for bleeding by time from randomisation in the tranexamic acid and placebo groups

treatment. We conjecture that this may potentially explain the lack of any effect of tranexamic acid on blood transfusion and hysterectomy in the WOMAN trial. However, the results for hysterectomy were inconclusive and we did not have data on time of transfusion. Future studies are needed to examine the effect of tranexamic acid on haemorrhage-related morbidity, and should report the timing of relevant medical and surgical interventions, such as time to first transfusion, uterine balloon tamponade, interventional radiology, and surgical intervention (including hysterectomy and laparotomy).

Conclusions

In this secondary analysis of data from the WOMAN trial, we observed that tranexamic acid was associated with a reduced risk of maternal death from exsanguination after excluding early maternal deaths from the analysis. This finding is in line with the main findings from the WOMAN trial. Our results suggest that the inclusion of early deaths in the analysis may have diluted the treatment effect of tranexamic acid towards the null. Early outcome events could represent those that are imminent and inevitable. Therefore, the outcomes of some women with life-threatening PPH occurring soon after delivery may not be influenced by exposure to the study drug. These findings also raise the possibility that if we give women tranexamic acid as a first line treatment for PPH rather than a last resort, as now recommended by the World Health Organization [5], its effect on reducing the risk of death due to bleeding may exceed that observed in the WOMAN trial. However, these results should be viewed with caution due to the exploratory nature of this analysis. It remains uncertain whether tranexamic acid reduces the risk of hysterectomy for bleeding after excluding early hysterectomies post-randomisation. Further studies are needed to examine the effect of tranexamic acid on morbidity in PPH.

Additional file

Additional file 1: Supplementary data analyses. This file provides per protocol analyses (Tables S1 and S2); an assessment of potential selection bias (Tables S3 and S4); an assessment of potential confounding (Tables S5 and S6); a sensitivity analysis of women treated within an hour of delivery (Table S7); a sensitivity analysis of women with uterine atony as the primary cause of haemorrhage (Table S8); a sensitivity analysis of women who underwent caesarean section (Table S9). (DOCX 39 kb)

Abbreviations

PPH: Post-partum haemorrhage; TXA: Tranexamic acid; WOMAN trial: World Maternal Antifibrinolytic trial

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Availability of data and materials

The datasets generated and/or analysed during the current study are not yet publicly available due to ongoing analyses of this recently completed trial. After publication of the planned primary and secondary analyses, the trial data will be made available via our data-sharing portal, The Free Bank of Injury and Emergency Research Data (freeBIRD) website at https://ctu-app.lshtm.ac.uk/freebird/.

Authors' contributions

IR and HS conceived and designed the WOMAN trial. The WOMAN Trial Collaborators were responsible for conducting the study and for data collection. RC, BF, IR and HS contributed to the conception of this analysis. AB conducted the analysis. AB and IR drafted the manuscript. AB, HS, RC, BF, SA and IR participated in the interpretation of the data and the revising of the manuscript.

Ethics approval and consent to participate

Ethical approval was obtained from the London School of Hygiene and Tropical Medicine Ethics Committee and Berkshire Research Ethics Committee, in addition to the following local and national research ethics committees.

Albania: Komiteti Kombetar i Etikes.

Bangladesh: Ad-din Women's Medical College Ethics Committee; Ethical Review Committee Chittagong Medical College; Ethical Committee of Dhaka Medical College; Ethics Committee Ibn Sina Medical College Hospital; Rajshahi Medical College Hospital Ethical Committee.

Burkina Faso: Centre Hospitalier Regional de Dedougou; Centre Hospitalier Universitaire Yalgado Ouedraogo.

Cameroon: Comite d'Ethique de l'Hopital de District de Banyo; Comite d'ethique de l'hopital gyneco-obstetrique et pediatrique de Yaounde; Dschang District Hospital; Hopital Laquintinie de Douala; Kumba District Hospital; Limbe Regional Hospital; Le Comite d'ethique de l'Hopital de District de Sa'a; St Theresa's Catholic Hospital Local Ethics Committee; Yaounde Central Hospital; Comite d'ethique de l'hopital gyneco-obstetrique et pediatrique de Yaounde.

Colombia: Ethical and Biomedical Research Committee, Fundacion Valle del Lili.

Cote d'Ivoire: Direction Departementale d'Abobo-Est.

Democratic Republic of Congo: Le Comite d'Ethique du CSR Albert Barthel; Centre de Sante de Reference Kahembe; Centre Hospitalier Notre Dame d'Afrique; Le Comite d'Ethique Institutionnel, Centre Medical Abedeco; Le Comite d'Ethique du Centre Medical VUHE; Comite d'Ethique de CSR Carmel; Comite d'Ethique de GESOM; Comite d'Ethique de Hope Medical Center; Le Comite d'Ethique du Centre de l'Hopital Provincial du Nord Kivu/Goma; Le Comite d'Ethique du Centre de l'Hopital General de Reference Virunga.

Egypt: General Organisation for Teaching Hospitals and Institutes.

Ethiopia: Jimma University Ethics Committee; St. Paul's Hospital Millennium Medical College Ethics Committee.

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Nepal: Biratnagar Aspataal & Research Center Ethics Committee; Institutional Ethical Review Board BPKIHS; Mid Western Regional Hospital Ethics Committee; Nepal Medical College Institutional Research/Review Committee.

Nigeria: Abubakar Tafawa Balewa University Teaching Hospital; Oyo State Research Ethical Review Committee; Aminu Kano Teaching Hospital; Ahmadu

Bello University Teaching Hospital Faculty of Medicine Ethical Committee; Braithwaite Memorial Specialist Hospital Ethics Committee; Delta State University Teaching Hospital Research Ethics Committee; University Teaching Hospital Ado-Ekiti Ethics and Research Committee; Federal Capital Territory Health Research Ethics Committee; Federal Medical Centre Abeokuta Research Ethics Committee; Federal Medical Centre Azare Health Research Ethics Committee; Federal Medical Centre Bida Ethical Committee; Federal Medical Centre Birnin-Kebbi Research Ethics Committee; Federal Medical Centre Gusau Ethic and Research Committee; Federal Medical Centre Ido-Ekiti Ethics and Research Committee; Federal Medical Centre Katsina Medical Research Ethics Committee; Federal Medical Centre Keffi Health Research Ethics Committee; Federal Medical Centre Lokoja Ethical Review Committee; Federal Medical Centre Makurdi Committee on Medical Ethics; Federal Medical Centre Owerri Ethical Committee; Federal Medical Centre Owo Ethical Review Committee; Federal Medical Centre, Umuahia; Federal Medical Centre, Yenagoa; Federal Teaching Hospital Abakaliki Research Ethics Committee; Irrua Specialist Teaching Hospital Research Ethics Committee; Jos University teaching Hospital Institutional Health Research Ethics Committee; Kogi State Specialist Hospital Research and Ethical Committee; Ladoke Akintola University of Technology Teaching Hospital Ethical Committee; Lagos Island Maternity Hospital Ethical Committee; Lagos State University Teaching Hospital Health Research and Ethics Committee; Lagos University Teaching Hospital Research & Ethics Committee; Mother & Child Hospital Akure Research Ethics Committee; National Hospital Abuja Ethics Committee; Nigeria National Health Research Ethics Committee; Nnamdi Azikiwe UTH Ethical Committee; Obafemi Awolowo University Teaching Hospital Ethics & Research Committee; Plateau State Specialist Hospital Health Research Ethics Committee; Seventh Day Adventist Hospital Internal Review Board and Ethics Committee; University of Ibadan/University College Hospital Ethics Committee; University of Abuja Teaching Hospital Health Research Ethics Committee; University of Calabar Teaching Hospital Ethical Committee; University of Ilorin Teaching Hospital Ethical Reveiw Committee; University of Maiduguri Teaching Hospital Ethics and research Committee; University of Nigeria Hospital Research Ethics Committee; University of Uyo teaching Hospital Institutional Review Committee; Usmanu Danfodiyo University Teaching Hospital Sokoto Ethical Research Committee; Obafemi Awolowo University Teaching Hospital Ethics & Research Committee.

Pakistan: Ayub Teaching Hospital Ethical Committee; Institutional Ethical Review Committee Bolan Medical College; Cantonment General Hospital Rawalpindi Ethics Committee; Institutional Ethics Committee, Combined Military Hospital Kharian; Combined Military Hospital Lahore Ethics Committee; Rawalpindi Medical College and Allied Hospitals Research and Ethics Committee; Fatima Bai Hospital Ethical Review Committee; Institutional Review Board Fatima Memorial Hospital; Ethical Committee Federal Government PolyClinic; Institutional Review Board Services Institute of Medical Sciences; Isra University Hospital Ethical Committee; AIMC/Jinnah Hospital Lahore Ethical Review Board; Ethical Review Committee Kahota Research Laboratory Hospital Islamabad; Institutional Review Board King Edward Medical University; Institutional Research & Ethics Board Lady Reading Hospital; Institutional Review Board King Edward Medical University; Liaquat Ethics Review Committee; Ethics Review Committee Liaquat University Hospital; Ethics Commitee MCH PIMS; Mian Muhammad Trust Hospital Ethics Committee; Research and Ethic Committee Islamabad Medical Complex Nescom; Institutional Ethical Review Committee Nishtar Medical College & Hospital Multan; Islamic International College Trust Pakistan Railway Hospital; Ethics Committee Patel Hospital; Ethical Review Committee People's University of Medical and Health Sciences; Rehman Medical Institute Peshawar Institutional Review Committee; Ethics Committee Shalamar Hospital; Ethical Committee Sharif Medical and Dental College; Institutional Review Board and Ethics Committee Shifa International Hospital; Sir Ganga Ram Hospital Lahore Ethics Committee; Zainab Panjwani Memorial Hospital Ethics Committee; Ziauddin Medical College.

Papua New Guinea: School of Medicine Research and Ethics Committee.

Sudan: National Medicines and Poisons Board.

Tanzania: Prime Ministers Office, Regional Administration and Local Government; Muheza Designated District Hospital; Muhimbili National Hospital; Mwananyamala Hospital; Temeke Municipal Council.

Uganda: Makerere University; Ugandan National Council of Science and Technology.

United Kingdom: Nottingham University Hospitals NHS Trust Research & Development Department; Liverpool Women's NHS Foundation Trust R&D Department; Central Manchester University Hospitals NHS Foundation Trust R&D; Guys and St Thomas NHS Foundation Trust Research and Development; City Hospitals Sunderland NHS Foundation Trust Research and Development; The Newcastle Upon Tyne NHS Foundation Trust Research and Development.

Zambia: Chipata General Hospital; Kabwe General Hospital Ethics Committee; University of Zambia Biomedical Ethics Committee; Livingstone General Hospital; St Paul's Mission Hospital, Kashikishi; St Francis Hospital Research Ethics Committee; University of Zambia Biomedical Ethics Committee.

The relevant ethics committees and regulatory agencies approved the consent procedures at each site. We obtained informed consent from women if their physical and mental capacity allowed. For fully competent women, an information sheet was provided, the study was discussed and written consent obtained. If the woman was unable to read or write then the information sheet was read to her and she then marked the consent form with either a cross or thumbprint. In this event, a witness not associated with the trial provided a full signature confirming the mark. If a woman could not give consent, we obtained proxy consent from a relative or representative in the same manner. If no proxy was available, then if local regulation allowed, we deferred or waived the consent. In these cases, we told the woman about the trial as soon as possible and obtained consent for use of the data collected. The consent procedures are described in detail in the trial protocol.

Competing interests

The authors declare that they have no competing interests.

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Trials

COMMENTARY Open Access

Outcome measures in clinical trials of treatments for acute severe haemorrhage

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Abstract

Background: Acute severe haemorrhage is a common complication of injury, childbirth, surgery, gastrointestinal pathologies and other medical conditions. Bleeding is a major cause of death, but patients also die from non-bleeding causes, the frequency of which varies by the site of haemorrhage and between populations. Because patients can bleed to death within hours, established interventions inevitably take priority over randomisation into a trial. These circumstances raise challenges in selecting appropriate outcome measures for clinical trials of haemostatic interventions.

Main body: We use data from three large randomised controlled trials in acute severe haemorrhage (CRASH-2, WOMAN and HALT-IT) to explore the strengths and limitations of outcome measures commonly used in trials of haemostatic treatments, including all-cause and cause-specific mortality, blood transfusion and surgical interventions. Many deaths following acute severe haemorrhage are due to patient comorbidities or complications rather than bleeding. If non-bleeding deaths are unaffected by a haemostatic intervention, even large trials will have low power to detect an effect on all-cause mortality. Due to the dilution from deaths unaffected or reduced by the trial treatment, all-cause mortality can also obscure important harmful effects. Additionally, because the relative contributions of different causes of death vary within and between patient populations, all-cause mortality is not generalisable. Different causes of death occur at different time intervals from bleeding onset, with bleeding deaths generally occurring early. Time-specific mortality can therefore be used as a proxy for cause in un-blinded trials where bias is a concern or in situations where cause of death cannot be assessed. Urgent treatment is critical, and so post-randomisation blood transfusion and surgery are often planned before or at the time of randomisation and therefore cannot be influenced by the trial treatment.

Conclusions: All-cause mortality has low power, lacks generalisability and can obscure harmful effects. Cause-specific mortality, such as death due to bleeding or thrombosis, avoids these drawbacks. In certain scenarios, time-specific mortality can be used as a proxy for cause-specific mortality. Blood transfusion and surgical procedures have limited utility as outcome measures in trials of haemostatic treatments.

Keywords: Blood transfusion, Clinical trial, Haemorrhage, Haemostasis, Mortality, Outcome measure, Trial methodology

Background

Acute severe haemorrhage is a common complication of injury, childbirth, surgery, gastrointestinal pathologies and other medical conditions. Regardless of the cause, serious bleeding often has similar pathophysiological consequences, such as those mediated by hypovolemic shock. Although efforts to achieve haemostasis depend on the site of bleeding, treatments to support coagulation and maintain vital organ perfusion are not site specific and are often included in generic major haemorrhage protocols [1]. For these reasons, clinical trials assessing the risks and benefits of haemostatic treatments often evaluate the same patient outcomes regardless of the cause or site of bleeding [2–4].

Outcomes in clinical trials should be relevant to patients, amenable to unbiased assessment and have the potential to be influenced by the trial treatment. Because trial results inform the care of different patients, in different places and at different times, we must also consider generalisability when selecting outcomes. We use data from large randomised placebo-controlled trials of tranexamic acid in acute severe bleeding (postpartum,

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traumatic and gastrointestinal) to assess the extent to which commonly used outcome measures meet these criteria. The CRASH-2 trial is a randomised trial of tranexamic acid in 20,211 trauma patients with, or at risk of, significant bleeding, within 8 h of injury [5]. The WOMAN trial is a randomised trial of tranexamic acid in 20,060 women with postpartum haemorrhage [6]. The HALT-IT trial is a randomised trial of tranexamic acid in 12,000 patients with significant gastrointestinal bleeding [7]. The methods are described in detail elsewhere [5–7]. The HALT-It trial is ongoing, but blinded data on 8699 patients are used in these analyses.

All-cause or cause-specific mortality?

Because death is important to patients, easy to quantify and may be affected by treatment, it is an important outcome measure in clinical trials in life-threatening bleeding. All-cause mortality is unequivocal and avoids any uncertainties in correctly ascribing the cause of death [8, 9]. Nevertheless, all-cause mortality has important disadvantages as an outcome measure in clinical trials [8, 10, 11].

Lower power for all-cause mortality

Many deaths following acute severe haemorrhage are due to patient comorbidities or complications rather than the failure to control bleeding. For example, patients with acute upper gastrointestinal bleeding secondary to gastric cancer may survive the acute bleed but die from cancer within the trial follow-up period. Although a haemostatic treatment might affect deaths from bleeding or thrombosis, it would be unrealistic to expect similar, if any, effects on other causes of death. This can lead to low power for all-cause mortality, even in large trials [11].

Table 1 shows the causes of death in patients with postpartum, traumatic and gastrointestinal haemorrhage. Although bleeding is important in each scenario, the contribution of non-bleeding deaths to all-cause mortality varies between 30 and 65% (see Fig. 1). Since there is usually no reason why a haemostatic intervention would reduce non-bleeding deaths, the effect of the intervention on all-cause mortality will be smaller than the effect on death from bleeding. More precisely, the effect on all-cause mortality will be a weighted average of the effects on specific causes of death, weighted according to their relative contribution to all-cause mortality (see Fig. 2). If non-bleeding deaths are common and are unaffected by the trial treatment, the dilution will be considerable, and a trial would have low power for all-cause mortality, even if there was a significant reduction in bleeding deaths. Sample size depends inversely on the square of the effect size, so a bigger sample is needed to achieve the same power for all-cause mortality as for cause-specific mortality [12]. For example, four times as many patients are needed if only 50% of deaths are due to the cause being affected by the trial medication (i.e. bleeding), and nine times as many are needed if a third of deaths are due to the relevant cause.

Important safety signals may be obscured in all-cause mortality

Due to the dilution from deaths unaffected or reduced by the trial treatment, all-cause mortality can also obscure important harmful effects, which are typically rarer and also need to be considered on a cause-specific basis [10, 11]. For example, there is strong evidence that the effect of tranexamic acid on bleeding deaths varies by time to treatment, with a 10% decrease in survival benefit for every 15-min delay [13]. Treatment given more than 3 h from bleeding onset is ineffective and possibly harmful [14]. However, this strong time-to-treatment interaction is obscured in analyses of all-cause mortality (see Fig. 3). For the same reason, we must assess separately any potential adverse effects of haemostatic treatments (e.g. increased risk of thrombotic deaths). These are often missed in all-cause endpoints due to the effect being swamped and obscured by other causes of death. Risk-benefit decisions in individuals also require separate assessment of benefits and harms because the baseline risks vary between patients. A haemostatic drug might reduce all-cause mortality in a young patient at low baseline risk of thrombosis but not in an older patient with cardiovascular comorbidity.

Generalisability

Because the relative contribution of different causes of death varies within and between patient populations, all-cause mortality is not generalisable. For example, in the CRASH-2 trial, bleeding accounted for 60% of deaths in patients with penetrating trauma compared to 25% of deaths in patients with blunt trauma. There was a substantial reduction in death due to bleeding with tranexamic acid, with no heterogeneity by type of injury, but no reduction in non-bleeding deaths (see Table 2). Consequently, although the effect of tranexamic acid on death due to bleeding is essentially the same in blunt and penetrating injury, it will have a larger effect on all-cause mortality in populations where penetrating trauma is common.

Misclassification of cause of death

The main concern with cause-specific mortality is that cause of death is determined subjectively and can be misclassified [15, 16]. For blinded trials, any misclassification would be unrelated to treatment allocation and so will not introduce bias. Although misclassification of cause of death might dilute the effect of the treatment on cause-specific mortality, the power of a trial to detect a slightly diluted measure of the relevant (generalisable) outcome should be higher than that for all-cause mortality. When cause of

Table 1 Cause of death and time from randomisation to death in postpartum, gastrointestinal and traumatic haemorrhage

Cause of death	Postpartum haemorrhage		Gastrointestinal haemorrhage		Traumatic haemorrhage[b]	
	N = 20,021		*N* = 8,699		*N* = 20,127	
	n (%)	Days (hours)	*n* (%)	Days (hours)	*n* (%)	Days (hours)
Bleeding	346 (1.7)	0 (5)	350 (4.0)	1 (28)	1063 (5.3)	0 (10)
Thrombosis[a]	21 (0.1)	0 (11)	32 (0.4)	4 (94)	81 (0.4)	4 (88)
Organ failure	43 (0.2)	2 (47)	141 (1.6)	5 (127)	486 (2.4)	3 (83)
Sepsis	23 (0.1)	5 (118)	109 (1.3)	6 (140)	44 (0.2)	9 (219)
Other	50 (0.2)	1 (13)	182 (2.1)	5 (114)	1402 (7.0)	1 (35)
All-cause	483 (2.4)	0 (7)	814 (9.4)	3 (66)	3076 (15.3)	1 (22)

Time to death is the median time from randomisation to death in days and hours
[a]Includes stroke, myocardial infarction and pulmonary embolism
[b]Time to death estimated using date and time of randomisation and date of death

death is ascertained by methods with very low sensitivity and specificity, the power of a trial to detect a treatment effect on cause-specific and all-cause mortality may be similar [17]. This also occurs when most of the deaths are due to the cause under study. Although independent, blinded event adjudication by an endpoint review committee is thought to provide an unbiased and systematic method for evaluating causes of death in clinical trials, there is little empirical evidence that this has any substantial effect on trial accuracy [18–20].

Time-specific mortality

Misclassification of cause of death is a particular concern in un-blinded trials, where knowledge of group allocation might influence decisions about cause of death and introduce bias. Because different causes of death occur at different time intervals from bleeding onset, time-specific mortality can help maintain objectivity whilst avoiding the drawbacks of all-cause mortality. Table 1 shows the time interval between hospital admission and death by cause of death and site of haemorrhage. Most bleeding deaths occur within 48 h of admission, followed by deaths from vascular occlusion and multi-organ failure, with sepsis deaths about 1 week later. Table 2 shows the effect of tranexamic acid on death due to bleeding and death within 48 h of admission in traumatic and postpartum haemorrhage. The results are similar, suggesting deaths within 48 h of admission might be used as a proxy for bleeding deaths in non-blinded trials. Although some misclassification is inevitable, especially if there are many early non-bleeding deaths, misclassification rates should not differ by allocated group.

In some scenarios, re-bleeding is common and can cause death. More than half of patients with liver disease who survive an episode of variceal bleeding will re-bleed within a year, and one fifth of these patients will die [21]. Re-bleeding also occurs after spontaneous intracranial haemorrhage. A patient enrolled in a trial of a haemostatic

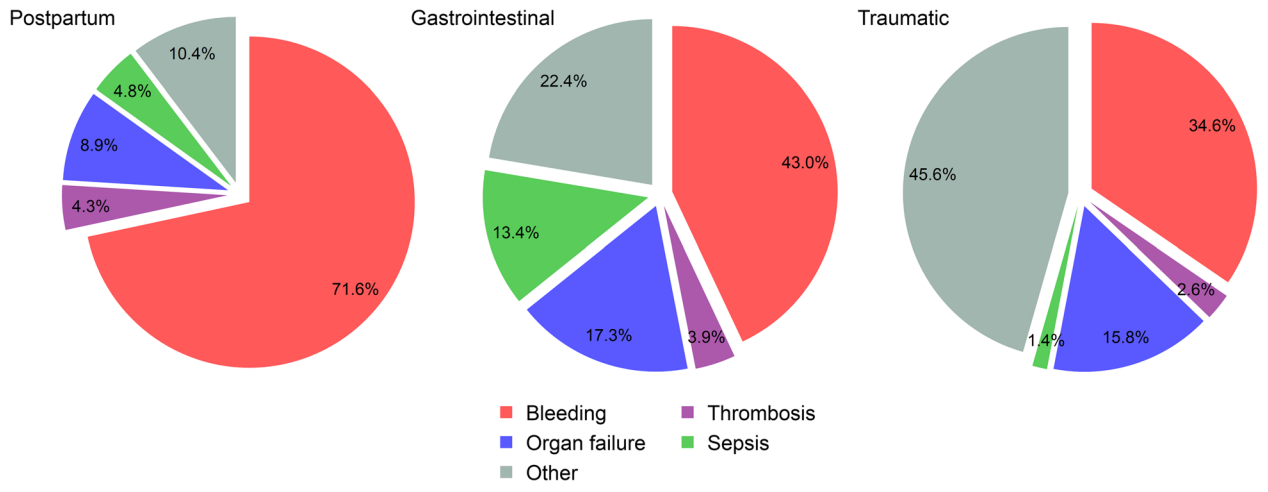

Fig. 1 Primary cause of death by site of acute severe haemorrhage. Other causes of death in traumatic haemorrhage include head injury (39.8%). Other causes of death in gastrointestinal haemorrhage include cancer (10.3%) and liver disease (2.3%). Other causes of death in postpartum haemorrhage include eclampsia (2.1%) and pulmonary oedema (1.5%)

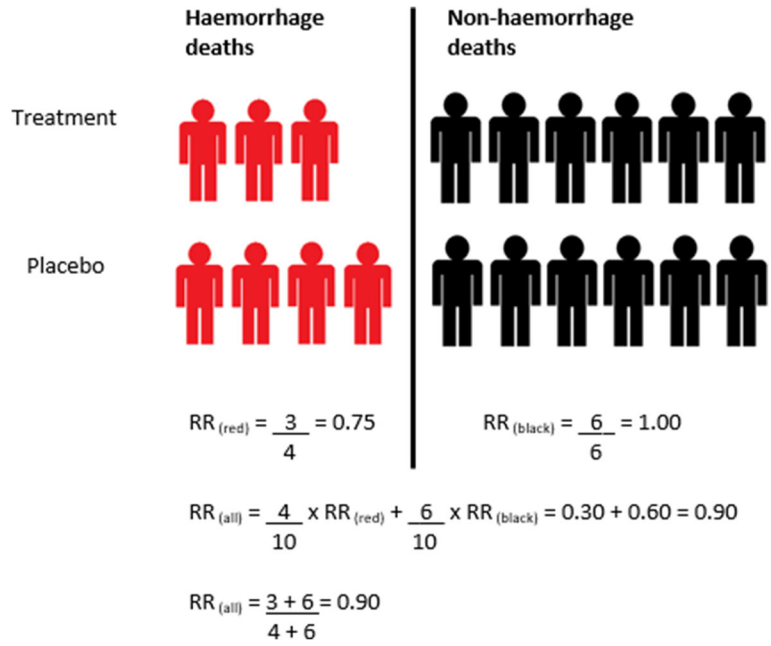

Fig. 2 Hypothetical model of the effect of a haemostatic treatment on all-cause and cause-specific mortality. The treatment reduces the risk of death due to bleeding by 25% (relative risk (*RR*) = 0.75) but has no effect on non-bleeding deaths (RR = 1.00). The effect on all-cause mortality (RR = 0.90) is a weighted average of the effect on cause-specific deaths, weighted according to the relative contributions of each cause. Assuming the same number of patients in each trial arm, the RR can also be calculated as the ratio of events in the treatment and placebo groups

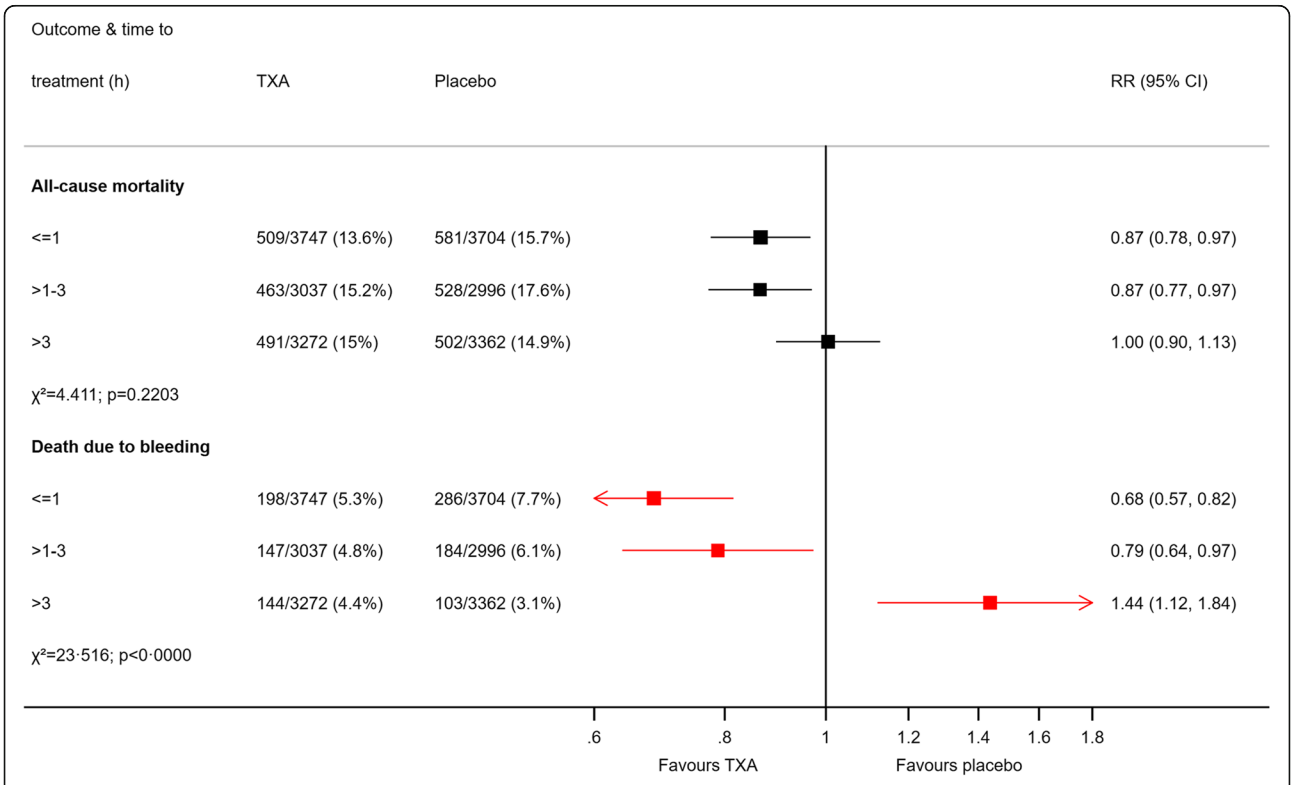

Fig. 3 Effect of tranexamic acid on all-cause mortality and death due to bleeding in traumatic haemorrhage by time to treatment

Table 2 Effect of early tranexamic acid on all-cause, cause-specific and time-specific mortality in postpartum and traumatic haemorrhage

Cause/time of death	Postpartum haemorrhage		Traumatic haemorrhage[b]		All	
	(*N* = 14,923)		(*N* = 13,484)		(*N* = 28,407)	
	RR (95% CI)	*p* value	RR (95% CI)	*p* value	RR (95% CI)	*p* value
All-cause	0.83 (0.66–1.04)	0.099	0.87 (0.80–0.94)	< 0.001	0.86 (0.80–0.93)	< 0.001
Cause-specific						
Haemorrhage	0.69 (0.53–0.90)	0.007	0.72 (0.63–0.83)	< 0.001	0.72 (0.63–0.81)	< 0.001
Thrombosis[a]	1.15 (0.39–3.42)	0.803	0.56 (0.31–0.99)	0.043	0.65 (0.39–1.07)	0.090
Other	1.35 (0.84–2.15)	0.213	0.99 (0.89–1.10)	0.867	1.01 (0.90–1.12)	0.908
Time-specific (hours from randomisation)						
< 48	0.74 (0.58–0.95)	0.015	0.83 (0.75–0.91)	< 0.001	0.81 (0.74–0.89)	< 0.001
≥ 48	1.81 (0.92–3.55)	0.080	0.94 (0.81–1.10)	0.457	0.98 (0.85–1.15)	0.844

Includes patients treated within 3 h of delivery/injury only
[a]Includes stroke, myocardial infarction and pulmonary embolism
[b]Time of death estimated using time and date of randomisation and date of death
CI confidence interval, *RR* relative risk

agent may survive the initial bleed but die from re-bleeding during the follow-up. Depending on the duration of the trial treatment and the half-life of the drug, it may be unrealistic to expect a treatment given for the initial bleed to influence re-bleeding deaths many days or weeks later, and the inclusion of these re-bleeding deaths could dilute the effect. In this situation, cause-specific mortality within a specified interval of the index bleed may be more appropriate.

Time-specific death can also be a useful endpoint when cause-specific mortality cannot be assessed. For example, in patients with spontaneous and traumatic intracranial bleeding it is difficult to determine the pathophysiological process (e.g. haemorrhage, oedema, infarction) leading to death [22–26]. However, because most intracranial bleeding occurs within hours of symptom onset with significant haematoma expansion being rare after 24 h, early deaths are more likely to be affected by a haemostatic agent than late deaths [24, 25]. The TICH-2 trial of tranexamic acid in spontaneous intracranial bleeding found a significant reduction in deaths within 7 days with less haematoma expansion, but no reduction in death at 90 days [27]. Whilst this cannot be taken as evidence of efficacy, it suggests the need for larger adequately powered trials.

Surgical intervention and blood transfusion as outcome measures

Surgical interventions to control bleeding and receipt of blood transfusion are common outcome measures in trials of haemostatic treatments. At first sight, they appear to satisfy our three criteria. Patients would prefer not to undergo surgery or receive allogenic blood; these outcomes are well documented; and both could be reduced by an effective haemostatic treatment. However, whilst surgery and transfusion may be suitable in bleeding prevention trials, they are less appropriate in treatment trials, where urgent treatment is critical and trial recruitment can often take second place. The activation of major haemorrhage protocols and decisions regarding established interventions are likely to happen before or around the same time as the administration of a trial treatment. Indeed, trials in elective surgery show that tranexamic acid reduces blood transfusion by about one third, whereas there was no effect on transfusion in trials of tranexamic acid for the treatment of postpartum or traumatic haemorrhage [5, 6, 28].

Death or hysterectomy was the primary outcome in the WOMAN trial of tranexamic acid treatment for postpartum haemorrhage. However, during the trial the investigators noticed that the decision to conduct an emergency peripartum hysterectomy was often made at the time of randomisation. For example, in response to life-threatening bleeding, a clinician might elect to do a hysterectomy and then enrol the woman into the trial. Although tranexamic acid might prevent death in these women, it could not prevent hysterectomy. In response, investigators increased the sample size from 15,000 to 20,000 patients to provide enough power to detect a reduction in bleeding deaths. On the other hand, there was a substantial reduction in re-operation to control bleeding with tranexamic acid. Unlike hysterectomy, the decision to re-operate is made after randomisation and so could be influenced by tranexamic acid.

Similarly, the receipt of blood transfusion after randomisation is mostly determined by blood lost prior to randomisation (see Additional file 1: Tables S1 and S2). Major haemorrhage protocols triggered by estimated blood loss or blood pressure on admission (i.e. before randomisation) largely dictate the amount of blood transfused through generic blood protocols, which specify the number and ratio of blood components transfused. Although administered post-randomisation, transfusions given in response to presenting clinical signs and symptoms caused

by blood lost before randomisation cannot be affected by the trial treatment, and this will dilute the treatment effect. For example, if we assume 80% of post-randomisation transfusions are given for blood lost before randomisation (relative risk (RR) = 1.00) and 20% are given for blood lost afterwards (RR = 0.70), the overall effect on transfusion, the weighted average of the two, will be severely diluted (RR = 0.94). It is also important to bear in mind that in some countries receipt of transfusion does not reflect blood loss due to blood shortages. Finally, if the trial treatment improves survival, there will be a greater opportunity to receive a transfusion in the treatment arm. For these reasons, we should not expect a substantial reduction in the need for transfusion in trials of treatments for acute severe haemorrhage.

Conclusions

When a patient has acute severe bleeding, time is of the essence, and urgent care inevitably takes priority over the administration of a trial treatment. As such, blood transfusion and surgery are often planned before or at the time of randomisation, and so cannot be prevented by the trial treatment. Indeed, the only patient outcome that can be clearly established as following the administration of the trial treatment is death. However, because many deaths in patients with acute severe bleeding are from comorbidities that may be unaffected by the trial treatment, even large trials will have low power to detect changes in all-cause mortality. Both benefit and harm can be obscured in all-cause mortality, and because the relative contributions of different causes of death vary within and between patient populations, all-cause mortality is not generalisable. Cause-specific mortality, such as death due to bleeding or thrombosis, avoids the drawbacks of all-cause mortality. Although assigning cause involves judgement, this will not cause bias in blind placebo-controlled trials. Time-specific mortality can be a proxy for cause in un-blinded trials or when cause of death cannot be assessed. Core outcome sets for trials evaluating treatments for life-threatening bleeding [29, 30] should consider the results of these analyses.

Additional file

Additional file 1: Supplementary data analyses. This file provides two tables showing the relationship between baseline characteristics and blood transfusion in postpartum and traumatic haemorrhage. (DOCX 27 kb)

Abbreviations

CRASH-2: Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage; HALT-IT: Haemorrhage Alleviation with Tranexamic Acid - Intestinal System; WOMAN: World Maternal Antifibrinolytic

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Availability of data and materials

The datasets generated and/or analysed during the CRASH-2 trial are publicly available on our data-sharing portal, The Free Bank of Injury and Emergency Research Data (freeBIRD) website at https://ctu-app.lshtm.ac.uk/freebird/. The WOMAN trial dataset is not yet publicly available due to ongoing analyses of this recently completed trial. The HALT-IT trial is ongoing. After trial completion and publication of the planned primary and secondary analyses, the WOMAN and HALT-IT datasets will be made available on freeBIRD.

Authors' contributions

HS-S and IR conceived and designed the CRASH-2, WOMAN and HALT-IT trials. JC inspired the conception of this manuscript. AB and IR developed the concepts and conceived the analyses. AB conducted the analyses. AB and IR interpreted the data and drafted the manuscript. MA, JC, VJ, SS, KK and HS-S provided important feedback, revised the manuscript and contributed to the final version. All authors read and approved the final manuscript.

Ethics approval and consent to participate

We conducted the CRASH-2, WOMAN and HALT-IT trials in accordance with good clinical practice guidelines. The relevant ethics committees and regulatory agencies approved the consent procedures. We obtained informed consent from the patient if physical and mental capacity allowed. If a person could not give consent, we obtained proxy consent from a relative or representative. If no proxy was available, then if local regulation allowed, we deferred or waived the consent. In these cases, we told the patient about the trial as soon as possible and obtained consent for use of the data collected.

Competing interests

The authors declare that they have no competing interests.

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Trials

UPDATE Open Access

Tranexamic acid for acute gastrointestinal bleeding (the HALT-IT trial): statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial

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Abstract

Background: Acute gastrointestinal (GI) bleeding is an important cause of mortality worldwide. Bleeding can occur from the upper or lower GI tract, with upper GI bleeding accounting for most cases. The main causes include peptic ulcer/erosive mucosal disease, oesophageal varices and malignancy. The case fatality rate is around 10% for upper GI bleeding and 3% for lower GI bleeding. Rebleeding affects 5–40% of patients and is associated with a four-fold increased risk of death. Tranexamic acid (TXA) decreases bleeding and the need for blood transfusion in surgery and reduces death due to bleeding in patients with trauma and postpartum haemorrhage. It reduces bleeding by inhibiting the breakdown of fibrin clots by plasmin. Due to the methodological weaknesses and small size of the existing trials, the effectiveness and safety of TXA in GI bleeding is uncertain. The Haemorrhage ALleviation with Tranexamic acid – Intestinal system (HALT-IT) trial aims to provide reliable evidence about the effects of TXA in acute upper and lower GI bleeding.

Methods: The HALT-IT trial is an international, randomised, double-blind, placebo-controlled trial of tranexamic acid in 12,000 adults (increased from 8000) with acute upper or lower GI bleeding. Eligible patients are randomly allocated to receive TXA (1-g loading dose followed by 3-g maintenance dose over 24 h) or matching placebo. The main analysis will compare those randomised to TXA with those randomised to placebo on an intention-to-treat basis, presenting the results as effect estimates (relative risks) and confidence intervals. The primary outcome is death due to bleeding within 5 days of randomisation and secondary outcomes are: rebleeding; all-cause and cause-specific mortality; thromboembolic events; complications; endoscopic, radiological and surgical interventions; blood transfusion requirements; disability (defined by a measure of patient's self-care capacity); and number of days spent in intensive care or high-dependency units. Subgroup analyses for the primary outcome will consider time to treatment, location of bleeding, cause of bleed and clinical Rockall score.

(Continued on next page)

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(Continued from previous page)
Discussion: We present the statistical analysis of the HALT-IT trial. This plan was published before the treatment allocation was unblinded.

Trial registration: Current Controlled Trials, ID: ISRCTN11225767. Registered on 3 July 2012; Clinicaltrials.gov, ID: NCT01658124. Registered on 26 July 2012.

Keywords: Gastrointestinal haemorrhage, Tranexamic acid, Clinical trial, Statistical analysis,

Background

Acute gastrointestinal (GI) bleeding is a common medical emergency and an important cause of mortality worldwide. Bleeding can occur from the upper or lower GI tract, with upper GI bleeding accounting for most cases. The incidence varies widely depending on the population prevalence of risk factors, with a reported incidence of upper GI bleeding of 50–140 per 100,000 across the US, Europe and Scandinavia [1–9]. The case fatality rate is around 10% for upper GI bleeding [1, 10] and 3% for lower GI bleeding [11]. Despite evidence suggesting improvements in survival in recent decades, the case fatality rate for upper GI bleeding varies from 3 to 15%, with the highest risk of death in patients with upper GI malignancies and varices [1, 3, 4, 8, 10, 12–16]. In addition to cause of bleeding, other factors associated with mortality include older age, signs of shock, severe bleeding, active bleeding, rebleeding and extent of comorbid disease [16–20].

The main causes of GI bleeding are peptic ulcer disease, erosive mucosal disease, oesophageal varices and malignancy [10]. Peptic ulcer disease and erosions due to *Helicobacter pylori* infection and non-steroidal anti-inflammatory drug (NSAID) use are common causes of GI bleeding worldwide [1, 6, 10, 12, 18, 21–25]. Bleeding from gastro-oesophageal varices due to liver cirrhosis is an increasing cause of bleeding in the West, but is also a major cause in parts of South America, Asia, Africa and the Middle East where there is high prevalence of hepatitis or schistosomiasis [26–33]. Symptoms of GI bleeding include haematemesis and coffee ground vomitus, melaena and the passage of fresh red blood in the stool, and clinical signs of shock such as hypotension and tachycardia.

Some patients with GI bleeding initially stop bleeding and have a brief period of haemodynamic stability before starting to bleed again. This phenomenon, known as rebleeding, is common and can affect between 5 and 40% of patients with acute GI bleeding. Rebleeding is associated with a four-fold increased risk of death [10, 11, 16, 17, 34]. Some of the variation in rebleeding rates may be explained by the use of different definitions, including fresh haematemesis or melaena and recurrent hypotension or tachycardia within varying timeframes of the index bleed [18]. The risk of rebleeding is highest in the days immediately after the index bleed and declines rapidly with time [35–37]. The risk factors for rebleeding are related to the lesion responsible for bleeding, but also influenced by age, comorbidity and concomitant medication use. [16, 17].

Tranexamic acid (TXA) reduces clot breakdown by inhibiting the degradation of fibrin by plasmin. It decreases bleeding and the need for blood transfusion in surgery and reduces death due to bleeding in patients with traumatic and postpartum haemorrhage [38–40]. A systematic review and meta-analysis of TXA in patients with upper GI bleeding included eight randomised trials with a total of 1702 patients [41]. Although there was a statistically significant reduction in mortality with TXA (RR 0.60, 95% CI 0.42–0.87; $p = 0.007$) and a non-significant reduction in rebleeding (RR 0.72, 95% CI 0.50–1.03), because of methodological weaknesses in the included trials and the imprecise effect estimates from meta-analyses, the effectiveness and safety of TXA in GI bleeding remains uncertain [41]. Moreover, the included trials were too small to assess the effect of TXA on thromboembolic events. The Haemorrhage ALleviation with Tranexamic acid – Intestinal system (HALT-IT) trial aims to provide reliable evidence about the effects of TXA in acute GI bleeding [42].

Methods

Trial design

The HALT-IT trial is an international, randomised, double-blind (participants and trial staff), placebo-controlled trial to quantify the effects of TXA on morbidity and mortality in adults with significant upper or lower GI bleeding.

Blinding and randomisation

Pfizer Manufacturing, Marketing Authorisation number PL 00057/0952, manufactures the TXA. Torbay and South Devon NHS Foundation Trust, Manufacturing Authorisation number MIA (IMP) 13079, manufactures the placebo (sodium chloride 0.9%). Sharp Clinical Services (UK) Ltd., Manufacturing Authorisation number MIA (IMP) 10284, manufactures the study drug treatment packs containing either the active drug TXA or placebo. The Marketing Authorisation guarantees that

the product is manufactured and released in accordance with the UK's Good Manufacturing Practice (GMP) regulations. Ampoules and packaging are identical in appearance.

An independent statistician from Sealed Envelope Ltd. (UK) generates randomisation codes to be sent to Sharp Clinical Services UK Limited, a GMP-certified clinical trial supplies company that prepares trial treatment packs in accordance with the randomisation list. Sharp Clinical Services conduct the blinding process and first-stage Qualified Person (QP) release, which involves complete removal of the original manufacturer's label and replacement with the clinical trial label bearing the randomisation number for use as the pack identification. Other pack-label text are identical for TXA and placebo treatments and in compliance with requirements for investigational medicinal products. Sharp Clinical Services UK are also responsible for maintaining the Product Specification File (PSF) until final database lock and unblinding of the trial data. Quality control checks to assure the blinding process are performed on a random samples of final QP released drug packs. High-performance liquid chromatography (HPLC) separation of known TXA is assessed against blinded samples to confirm which ampoule contains the placebo and active treatment. The tested samples are unblinded to assure accuracy of blinding.

The Trial Coordinating Centre (TCC) is responsible for assuring that all relevant approvals are available at the TCC before release of the trial treatment to a site. A separate Manual of Operating Procedures details the drug accountability system. The Investigator's Brochure details labelling of the trial treatment and other processes for assuring adherence to GMP.

Eligible patients are randomised to receive either TXA or placebo as soon as possible and the study treatment started immediately. The next consecutively numbered treatment pack is taken from a box of eight packs. A fixed loading dosage of 1 g TXA or placebo (sodium chloride 0.9%) is administered, followed by a maintenance dose of 3 g TXA or placebo (sodium chloride 0.9%) infused over 24 h.

Ethics approval and consent

The trial was approved by the UK NRES Committee East of England (reference number 12/EE/0038), as well as national and local research ethics committees of participating countries outside of the UK.

Acute severe GI bleeding can be a frightening condition for the patient and the ensuing blood loss may have adverse impact on the patient's mental and emotional state, impairing their decision-making ability. The consent procedures consider this together with the need to randomise and treat urgently. If the patient is fully competent, written consent is sought. If the patient's capacity is impaired and a personal or professional representative is available, consent is sought from the representative. If neither are able to provide informed consent, consent is waived and the patient is informed about the trial as soon as it is possible.

Data collection

The entry form (Additional file 1) is used to assess eligibility and collect baseline information. Once a patient has been randomised, the outcome in hospital is collected even if the trial treatment is interrupted or is not actually given. No extra tests are required but a short outcome form (Additional file 1) is completed from the medical records 28 days after randomisation or on discharge from the randomising hospital or on death (whichever occurs first). Any adverse events that become known to the investigator are reported up to 28 days after randomisation.

Change in primary outcome

We originally specified all-cause mortality as the primary outcome because we believed that most deaths would be due to bleeding. However, as the trial was underway we observed that over half of all deaths were due to non-bleeding causes such as cancer and sepsis (see Fig. 1). Tranexamic acid reduces bleeding by inhibiting fibrinolysis. Based on this mechanism of action, we do not expect any substantial reduction in non-bleeding deaths. This hypothesis is supported by evidence from trials of TXA in trauma and postpartum haemorrhage [39, 40, 43]. As such, the treatment effect on all-cause mortality will be diluted by non-bleeding causes of death, reducing statistical power [43].

Death due to bleeding is the relevant endpoint for the HALT-IT trial because it has the potential to be reduced by the trial treatment. Fibrinolysis may play an important role in GI bleeding: gastric vein blood samples from patients with peptic ulcers contain high concentrations of plasmin and many patients with acute upper GI bleeding have elevated levels of fibrin degradation products (a biomarker for fibrinolysis) which is associated with worse outcomes [44–46].

Cause of death is assigned by local investigators and a narrative of the events leading to death is reviewed by the principal investigator (who is blind to treatment allocation) and queried as necessary to verify cause of death. Due to the double-blind nature of the trial, the coding of the cause of death cannot be affected by the patient's randomised group.

We also originally specified that the primary outcome would be measured up to 28 days after randomisation.

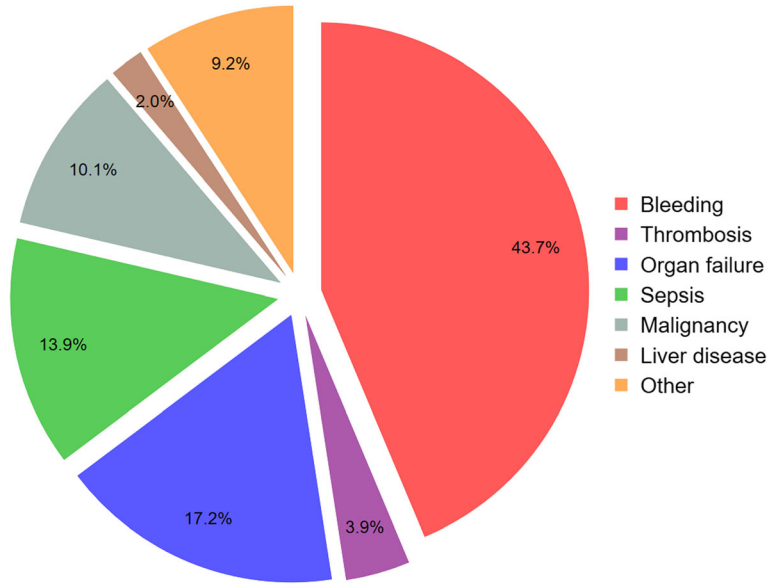

Fig. 1 Causes of death in the Haemorrhage ALleviation with Tranexamic acid – Intestinal system (HALT-IT) trial during recruitment (November 2018)

However, patients receive TXA (or placebo) for their initial bleed but not for rebleeding episodes. Tranexamic acid has a half-life of 2–3 h so 99% will be eliminated within about 2 days of randomisation [47, 48]. We do not expect TXA to reduce deaths from a rebleeding episode for several weeks after the drug has been fully eliminated, therefore the primary outcome will consider early deaths due to bleeding only, defined as those that occur within 5 days of randomisation.

The rationale for refining the primary outcome from all-cause mortality to death due to bleeding was published in October 2018 [43]. The decision was supported by the Trial Steering Committee and was made prior to the end of the trial and prior to unblinding and so was not a data-dependent change.

Sample size

The sample size calculation for the trial was based on the original primary outcome of all-cause mortality [42]. While the trial was underway, accumulating evidence from other large trials of TXA showed no apparent effect on non-bleeding causes of death [39, 40]. Because a considerable proportion of deaths in the HALT-IT trial are due to non-bleeding causes, the sample size was increased from 8000 to 12,000 to retain sufficient power for all-cause mortality. However, our assumptions were too generous – we assumed that 60% of deaths would be due to bleeding by the end of the trial rather than 40% (assuming a control group event rate of 10%, a study with 12,000 participants would have over 80% power to detect a 15% (RR = 0.6 × 0.75 + 0.4 × 1.0 = 0.85) reduction in all-cause mortality). Based on the refined primary outcome, assuming a cumulative incidence of death due to bleeding of 4%, a study with 12,000 patients will have about 85% power (two-sided alpha = 5%) to detect a clinically important 25% relative reduction in death due to bleeding from 4 to 3%. Loss to follow-up is expected to be less than 1% (it was 0.16% in the World Maternal Antifibrinolytic (WOMAN) trial) so was not taken into consideration when calculating the sample size. This power calculation is based on the primary analysis and refers to the unadjusted chi-squared test.

Trial population

Eligibility

Patients with significant GI bleeding to whom the uncertainty principle applies are eligible. Specifically, a patient can be enrolled if the responsible clinician is substantially uncertain as to whether the trial treatment is appropriate for that particular patient. Significant bleeding is diagnosed clinically and implies a risk of bleeding to death. Patients with significant bleeding may include those with hypotension, tachycardia, signs of shock, or those needing urgent transfusion, endoscopy or surgery. Patients with a clear indication (e.g. traumatic haemorrhage) or contraindication (e.g. history of convulsions, thromboembolic disease) for TXA are excluded.

Recruitment, withdrawal and loss to follow-up

We will display the flow of study participants using a Consolidated Standards of Reporting Trials (CONSORT) Diagram (see Additional file 1: Figure S1). For each trial arm, we will present the total number randomised, the number with baseline data, the number lost to follow-

up, the number who withdrew consent, and the number of participants with outcome data.

Baseline patient characteristics

We collect data on the following baseline characteristics: age, biological sex, time from onset of GI bleeding symptoms to randomisation, suspected location of bleeding, clinical symptoms (e.g. haematemesis, melaena), suspected variceal bleeding, systolic blood pressure (SBP) , heart rate (HR), signs of shock, suspected active bleeding, major comorbidities, anticoagulation therapy and type of admission. We will present the distribution of baseline characteristics (*n* and %) in the treatment and placebo groups to check that randomisation was successful in producing similar groups (see Additional file 1: Table S1).

Analysis

Primary analysis

The main analyses will compare those allocated TXA with those allocated placebo on a modified intention-to-treat basis, excluding patients who received neither dose of the allocated trial treatment. We will present the results as effect estimates (relative risks) with a measure of precision (95% confidence intervals) (see Additional file 1: Table S2). Additionally, we will present results of the primary analysis adjusted for all baseline covariates. If baseline covariates are associated with the outcome, adjusting for any chance imbalances in baseline risk will increase statistical power. We will not present risk differences because they are not a generalisable measure of the treatment effect and are dependent on baseline risk. The effect of TXA will also be examined graphically using cumulative incidence curves presented with their associated hazard ratios and log-rank *p* values (see Additional file 1: Figure S2) [49]. The effects of TXA on death due to bleeding in the HALT-IT trial will be set in the context of other trials of TXA for acute severe haemorrhage (the CRASH-2 and WOMAN trials).

Primary outcome

Death due to bleeding within 5 days of randomisation is the primary outcome. As outlined in the section 'Change in primary outcome' above, cause of death is assigned by local investigators who provide a narrative of the events leading to death. The cause of death narratives are reviewed by the principal investigator (who is blind to treatment allocation) and queried if more information is needed to confirm whether death is due to bleeding or another cause. Furthermore, due to double-blind nature of the trial, the coding of the cause of death cannot be affected by the patient's randomised group. For more details, please see accompanying information in the section 'Change of primary outcome'.

Secondary outcomes

We will assess the effect of TXA on the following secondary outcomes. Unadjusted analyses will be presented in the main text and although we do not expect any baseline imbalances, to complement the unadjusted analyses and potentially increase statistical power (if covariates are associated with the outcome) we will present results of the analyses adjusted for all baseline covariates in an appendix.

Rebleeding

Rebleeding generally occurs in approximately 10–25% of patients with acute GI haemorrhage and is associated with an increased risk of death due to bleeding [50]. A clinical diagnosis of rebleeding is made by the treating clinician based on the presence of any of the following criteria, as defined in a data collection guide. These criteria for rebleeding were recommended by a methodological framework for trials in GI bleeding following an international consensus conference [51]:

- Haematemesis or bloody nasogastric aspirate > 6 h after endoscopy
- Melaena after normalisation of stool colour
- Haematochezia after normalisation of stool colour or after melaena
- Development of tachycardia (HR > 110 beats per min) or hypotension (SBP ≤ 90 mmHg) after ≥ 1 h of haemodynamic stability (i.e. no tachycardia or hypotension) in the absence of an alternative explanation for haemodynamic instability such as sepsis, cardiogenic shock, or medication
- Haemoglobin drop of > 2 g/dl after two consecutive stable values (< 0.5 g/dl decrease) ≥3 h apart
- Tachycardia or hypotension that does not resolve within 8 h after index endoscopy despite appropriate resuscitation (in the absence of an alternative explanation) associated with persistent melaena or haematochezia
- Persistently dropping haemoglobin of > 3 g/dl in 24 h associated with persistent melaena or haematochezia

It should be noted that patients may continue to have haemodynamic instability, falling haemoglobin levels or persistent melaena or rectal bleeding for hours and even days after bleeding has stopped, making these patients difficult to categorise; however, these criteria are more likely to indicate rebleeding than equilibration [51].

Most rebleeding tends to occur within 5 days of the index bleed [35–37]. We believe that TXA will be most effective at reducing the risk of rebleeding soon after the index bleed when blood plasma concentrations of the drug are above the level needed to inhibit

fibrinolysis [52]. To assess whether TXA reduces rebleeding, we will analyse the effect on early rebleeding within 5 days of randomisation (see Additional file 1: Table S2).

Although rebleeding is most common within the first 5 days after the index bleed, TXA will have been metabolised within about 2 days of randomisation, with the blood plasma concentration falling below the level needed to inhibit fibrinolysis within around 24 h. As such, we will examine the effect on rebleeding within 24 h of randomisation. We hypothesise that TXA will be less effective for late rebleeding occurring days or weeks after the drug has been eliminated. To investigate this we will assess the effect of TXA on rebleeding within 28 days (see Additional file 1: Table S2). If our hypothesis is correct, the inclusion of late rebleeding events should dilute the treatment effect.

Death due to bleeding within 24 h and 28 days

Tranexamic acid will be eliminated within about 2 days of randomisation, with blood plasma levels falling below those needed to inhibit fibrinolysis within around 24 h. Furthermore, patients with acute GI haemorrhage bleed to death quickly, with many deaths due to bleeding occurring within the first day. Evidence from other trials suggests that this is where the greatest treatment benefit will be observed. As such, we will analyse the effect of TXA on deaths due to bleeding within 24 h of randomisation. Conversely, because there may be a weaker treatment effect on late deaths due to bleeding that occur several days or weeks after randomisation, we will also analyse the effect on death due to bleeding within 28 days of randomisation (see Additional file 1: Table S2). We expect to observe a smaller treatment effect when including late bleeding deaths due to dilution towards the null.

Mortality

We will analyse the effect of TXA on all-cause and cause-specific mortality at 28 days. Specific causes of death to be analysed include death due to bleeding, thrombosis, organ failure, pneumonia, sepsis, malignancy and other causes (see Additional file 1: Table S3). We will also examine the temporal distribution of causes of death by days since randomisation using a frequency bar chart (see Additional file 1: Figure S3). Based on its mechanism of action and data from large randomised trials, we do not expect TXA to reduce deaths from non-bleeding causes like cancer or sepsis or to reduce late deaths from bleeding.

Endoscopic, radiological and surgical procedures for GI bleeding

We will assess the effect of TXA on diagnostic and therapeutic endoscopic and radiological procedures and surgical interventions (see Additional file 1: Table S5). It remains unclear whether TXA reduces the need for surgery in GI bleeding [41]. In large trials of TXA for postpartum and traumatic haemorrhage, there was no evidence of an effect on surgical interventions except for laparotomy for bleeding [39, 40]. If TXA reduces GI bleeding, it has the potential to reduce the need for some endoscopic, radiological and surgical procedures. While we do not expect TXA to influence diagnostic endoscopic and radiological procedures planned around the time of hospital admission and randomisation, there is potential to reduce the need for diagnostic procedures planned after resuscitation, and, therefore, after randomisation [43]. Similarly, therapeutic procedures and surgical interventions planned and undertaken after diagnosis also have the potential to be influenced by TXA. It is not possible to look at procedures by time as this information was not recorded, and although type of procedure can be used as a rough indication of timing, therapeutic or surgical procedures planned around the time of randomisation could still dilute the effect estimates towards the null.

Blood transfusion

Since blood transfusion is mostly determined by blood loss prior to randomisation, we do not expect to see a marked reduction in the need for blood transfusion with the use of TXA [43]. Major haemorrhage protocols dictate the type and volume of blood components that patients receive based on presenting clinical signs such as blood pressure and estimated blood loss. Furthermore, survivor bias could lead to higher transfusion rates in the TXA group. In keeping with this, a systematic review of TXA for GI bleeding found no reduction in transfusion [41]. Although TXA has the potential to reduce transfusion for blood lost after randomisation, e.g. after rebleeding, we did not collect data on date and time of transfusion. Any effect on late transfusions is likely to be obscured by early transfusions for blood lost pre-randomisation. We will assess the effect of TXA on the use of whole blood or packed red cells, frozen plasma and platelets comparing the frequency of transfusion and the mean number of (adult-equivalent) units transfused (see Additional file 1: Table S5).

Thromboembolic events

An individual patient data meta-analysis of the WOMAN and CRASH-2 trials found evidence of a reduction in myocardial infarction with TXA (OR = 0·64, 95% CI 0·43–0·97; $p = 0·037$) and no evidence of an increased risk of fatal vascular occlusive events (OR 0·73,

95% CI 0·49–1·09; $p = 0·120$) or other non-fatal events [53]. While this finding is reassuring, we cannot exclude the possibility of some increased risk with TXA, particularly as patients with GI bleeding are older than those with traumatic or postpartum haemorrhage and many have multiple comorbidities. Older age is associated with a pro-coagulation haemostatic profile including elevated fibrinogen and plasminogen activator inhibitor 1 and reduced clotting time [54–56]. A systematic review of TXA for the treatment of upper GI bleeding found no evidence for a difference in the risk of thromboembolic events but lacked power [41]. We will examine the effect of TXA on fatal and non-fatal pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction (see Additional file 1: Table S6).

Complications

We will analyse the effect of TXA on renal, hepatic and respiratory failure, cardiac events, sepsis, pneumonia and seizures (see Additional file 1: Table S6). If TXA reduces death due to bleeding, patients in the tranexamic group will survive for longer on average and may, therefore, be at greater risk of complications such as sepsis, pneumonia and organ failure. Generally, death due to bleeding tends to occur soon after bleeding onset whereas infections and organ failure take several days to occur. On the other hand, if TXA reduces bleeding it may reduce liver failure because bleeding can lead to the deterioration of liver function. Although there is evidence that high-dose TXA can cause seizures, we do not expect to see an increase in seizures with the low dose given in the trial.

Self-care capacity

Patients self-care capacity will be measured using the Katz Index of Independence in Activities of Daily Living (Katz ADL) [57]. Participants' performance in six functions (bathing, dressing, toileting, transferring, continence and feeding) is assessed at the time of discharge from the randomising hospital or in hospital 28 days after randomisation. A score of 1 is assigned to each function the individual can perform independently and they are summed to produce a total score. A score of 6 suggests full function, 4 suggests moderate impairment, and 2 or less suggests severe functional impairment. We expect that reduced blood loss in patients who receive TXA will result in less functional impairment. That said, it is possible that patients in the treatment group will be discharged faster which could mask improvements in self-care capacity at the time of discharge. To assess this hypothesis we will compare the difference in mean Katz ADL score in survivors in the TXA and placebo groups as well as the proportion of patients with no impairment (6), mild to moderate impairment (3–5) or severe impairment (0–2), (see Additional file 1: Table S6).

Days spent in the intensive care or high-dependency unit

We will analyse the effect of TXA on number of days spent in the intensive care unit (ICU) or high-dependency unit (HDU). We will compare the difference in mean number of days spent in the ICU or HDU in the TXA and placebo groups (see Additional file 1: Table S6). Because beds in these units can be limited, we may not see an effect on this outcome measure.

Adverse events

Data on the number of adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) reported up to 28 days after randomisation will be presented. We will present a summary table in an Additional file 1 to describe the type of AE, Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT), MedDRA system organ class (SOC) and the number of occurrences and outcomes (completely recovered, recovered with sequelae, or died) in the TXA and placebo groups. With events grouped by MedDRA SOC, we will compare the frequency of events between trial arms using an unadjusted modified Poisson regression model (see Additional file 1: Table S7). AEs with evidence that they may be increased by TXA (i.e. seizures and thromboembolic events), will be analysed on an individual basis as well as recurrent episodes of GI bleeding reported as AEs.

Subgroup analyses

We will conduct the following subgroup analyses for the primary outcome of death due to bleeding: time to treatment, location of bleeding, cause of bleeding and clinical Rockall score. We will fit interaction terms with randomised group in a Poisson regression model with robust error variance from the sandwich estimator [58]. Interaction tests (the Wald test) will be used to explore whether the effect of treatment (if any) differs across these subgroups. Results will be presented as unadjusted and adjusted effect estimates with a measure of precision (95% confidence intervals) and p value for the test for interaction (see Additional file 1: Table S4). Except for time to treatment, statistically significant heterogeneity between subgroups is required, as determined by the test for interaction p value, and not just statistical significance of a result in a specific subgroup [59].

Although treatment group is randomised within subgroups, the factors defining subgroups are not randomised. Several baseline characteristics are associated with the subgroup variables. For example, early treatment is correlated with bleed characteristics and patient

characteristics (see Fig. 2), some of which confer a higher clinical Rockall score, suggesting that patients with more severe bleeding are treated earlier. Since these factors are also associated with mortality, they could potentially confound the interaction between time to treatment and the treatment effect.

If TXA is shown to be effective and the treatment effect varies by time to treatment, there is potential to intervene on time to treatment in order to increase the treatment effect. Although we cannot intervene on location of bleeding, cause of bleeding or clinical Rockall score, we are interested in ascertaining causal interaction of these factors with the treatment effect rather than simply assessing effect heterogeneity. As such, we will adjust all subgroup analyses for potential confounders [60]. Selection of potential confounders is based upon review of unblinded data within the trial to date in order to identify prognostic baseline characteristics that are associated with the subgroup variables. Potential confounders include age, time to treatment, SBP, HR, signs of shock, location of bleeding, suspected active bleeding, comorbid liver disease and suspected variceal bleeding. Signs of shock may be collinear with HR or blood pressure, and suspected variceal bleeding may be collinear with comorbid liver disease – if so, signs of shock and suspected variceal bleeding will not be included in the models. The final models remain to be determined because the outcome of interest is the treatment effect and the association between the potential confounders and the treatment effect cannot be assessed before unblinding.

Time to treatment (≤ 3 h, > 3 h)

Trials of TXA in traumatic and postpartum haemorrhage provide evidence that early treatment (within 3 h of bleeding onset) confers the most benefit, while late treatment is ineffective [39, 53, 61]. As such, we plan to conduct a subgroup analysis of the treatment effect stratified by time to treatment. Patients with GI bleeding may not experience symptoms immediately so time of symptom onset may not accurately reflect time of bleeding onset. Time to treatment may, therefore, be underestimated. Because few patients are treated early (within 3 h), there may be low power to detect an interaction if one exists. As such, we will analyse time to treatment as both a categorical (≤ 3 h, > 3 h) and continuous variable because the latter will preserve more information so should have more power. However, a limitation of modelling time to treatment as a continuous variable is the need to specify the form of the association. To assess non-linearities, we will fit a logistic regression model and use a likelihood ratio test. Any differences between the two approaches will be noted.

There is strong prior evidence to expect a time-to-treatment interaction, with early treatment conferring a greater benefit and late treatment being ineffective and possible even harmful [53, 61]. As such, for the

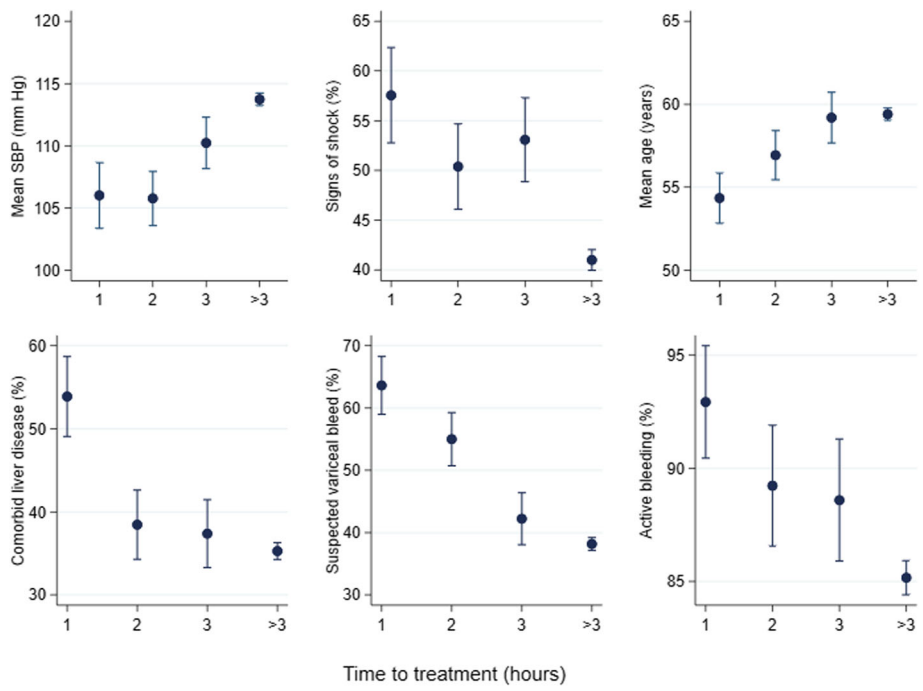

Fig. 2 Potential confounding factors in the subgroup analysis of time to treatment

subgroup analysis of time to treatment we do not require as strong evidence against the null hypothesis of homogeneity as we might usually require. Most trials lack power to detect heterogeneity in treatment effects and the lack of a statistically significant interaction does not mean that the overall treatment effect applies to all patients. Due to prior evidence that early treatment is more effective, we will consider the time to treatment subgroup analysis in the context of the existing data (in particular data from the CRASH-2 and WOMAN trials) on the time-to-treatment interaction and will rely more on scientific judgment than on statistical tests.

Location of bleeding (upper GI, lower GI)

We will examine the effect of TXA on death due to bleeding stratified by location (upper versus lower GI). Evidence suggests the rates of rebleeding and mortality after upper and lower GI bleeding are similar [34], and there is no reason to expect the effect of TXA to vary substantially by location of bleeding in the GI tract. Unless there is strong evidence against the null hypothesis of homogeneity of effects (i.e. $p < 0.01$), the overall relative risk will be considered the most reliable guide to the approximate treatment effect in all patients.

Suspected variceal bleeding and comorbid liver disease (yes, no/unknown)

Outcomes in acute GI bleeding vary by cause of haemorrhage. Variceal bleeding is associated with the highest risk of rebleeding and death. Oesophageal varices are dilated submucosal veins that usually develop because of portal hypertension, often due to cirrhosis. Haemostasis is disturbed in patients with liver disease because many of the pro- and anti-coagulation factors and components of the fibrinolytic system are produced by hepatic parenchymal cells in the liver, although the overall sum of effects are debated [62–64]. Any resulting imbalance in coagulation or fibrinolysis may alter the antifibrinolytic activity of TXA; however, the direction of this potential effect remains to be determined. We will examine the effects of TXA on death due to bleeding in patients with suspected variceal bleeding and comorbid liver disease compared to other or unknown causes of bleeding. Unless there is strong evidence against the null hypothesis of homogeneity of effects (i.e. $p < 0.01$), the overall relative risk will be considered the most appropriate measure of effect.

Clinical Rockall score (1–2, 3–4, 5–7)

We will assess the effect of TXA stratified by the clinical (pre-endoscopy) Rockall score, a widely used risk scoring system for GI bleeding. The score is derived from age, comorbidities, signs of shock, HR and SBP, all of which are independent predictors of mortality. Although originally developed for upper GI bleeding [17], the Rockall score has also been shown to be predictive of mortality in lower GI bleeding [34]. We do not expect the treatment effect to vary by Rockall score. Unless there is strong evidence of an interaction ($p < 0.01$), we will present the overall relative risk as the most appropriate measure of effect.

Missing data

Based on the data collected to date, we expect loss to follow-up to be minimal (i.e. less than 1% missing data on the primary outcome). Any missing values will be reported but not imputed.

Other analyses to be reported in separate publications

Survival analysis to investigate the timing and duration of the treatment effect

We will conduct a survival analysis to explore the effect of TXA on rebleeding and death due to bleeding in more detail. In large trials of TXA for traumatic (CRASH-2) and postpartum haemorrhage (WOMAN), there were few late-bleeding-related events. The precise timing and duration of TXA's antifibrinolytic effect remain to be determined. For example, it is unclear whether the treatment effect persists after the drug has been eliminated. Bleeding-related events occur later in acute GI bleeding, partly due to rebleeding, so the HALT-IT trial presents a unique opportunity to investigate this question.

We will report the median survival time and the cumulative incidence in the treatment and placebo groups, and model the treatment effect. Cox proportional hazards modelling assumes the hazards in the treatment and placebo groups are proportional over time. This assumption may be invalid if the antifibrinolytic effect of TXA declines over time as the drug is metabolised. We will formally assess this using the Royston-Palmer test for proportional hazards – a combined test with increased power when an early treatment effect is present [65]. If the treatment effect on death due to bleeding and rebleeding appears to change with time (non-proportional hazards), we will examine this in detail using various methods. We will estimate average cumulative hazard ratios for increasingly longer periods of follow-up. This method is preferred to period-specific hazard ratios, which can be susceptible to selection bias [66]. Nevertheless, we will also use Lexis expansion to calculate period-specific hazard ratios and test for interactions between treatment group and period. If we are able to identify the average duration of the treatment effect, we will examine whether this varies by baseline characteristics including time to treatment, bleeding severity, cause of bleeding and age. We will also assess how the

treatment effect changes with time by including a time-by-treatment interaction term in the model. Residual methods will be used to test the assumption of linear time (first order trend) by plotting Martingale residuals against continuous covariates.

Death due to bleeding is a competing risk for non-bleeding causes of death and vice versa. Death is also a competing risk for rebleeding. We will estimate the treatment effect using a proportional cause-specific hazards model in which competing events are censored. The proportional cause-specific hazards model is preferred for aetiological research; however, both the cause-specific hazard and cumulative incidence can provide insights into a treatment's effects [67, 68]. As such, a subdistribution hazards model and Gray's test for comparing cumulative incidence functions will be presented as a supplementary analysis [69, 70]. Risk of rebleeding is highest immediately after the index bleed, death is a competing risk for rebleeding and some patients may experience more than one episode during the follow-up period. A survival analysis of the effect of TXA on rebleeding will take into account timing of events and competing risks.

Cost effectiveness analysis

If the trial demonstrates that TXA is an effective treatment for GI bleeding, we will conduct an economic evaluation to determine cost-effectiveness. Broadly speaking the methods will mirror those used by Li et al. who assessed the cost-effectiveness of TXA for the treatment of women with postpartum haemorrhage [71].

The analysis will compare TXA against clinical practice without TXA. A cost-utility analysis will be performed from a health services cost perspective with outcomes expressed as Quality-adjusted Life Years (QALYs). The analyses will be performed separately for a set of different countries, depending on where the majority of people have been recruited, but is likely to include at least the UK and Pakistan. A decision model will be used to extrapolate results from the trial into the longer term. Resource data, such as drugs and length of inpatient stay, are collected as part of the trial and will be analysed accordingly. Both deterministic and probabilistic sensitivity analysis will be undertaken. Results will also be presented by subgroups if considered appropriate.

Impact of baseline risk on treatment effectiveness

To assess whether the effect of TXA on death due to bleeding varies by baseline risk we will build a prognostic model using baseline characteristics identified as important predictors of death due to bleeding. Prognostic factors include age, SBP, HR, suspected location of bleeding, haemetamesis/coffee ground vomitus, suspected variceal bleeding, suspected active bleeding, comorbidities and country. The prognostic model will then be used to stratify patients by risk of mortality and stratum-specific effect estimates (relative risk) and 95% confidence intervals will be calculated. We do not expect the treatment effect to vary by baseline risk. Unless there is strong evidence against the null hypothesis of homogeneity of effects ($p < 0.01$), the overall relative risk will be considered the most reliable guide to the approximate treatment effect in all patients.

Adjustment for baseline risk

Due to the large size of the HALT-IT trial, baseline characteristics should be well balanced between the treatment and placebo groups so that any difference in outcomes is due to the treatment. There is still a small possibility, however, that some imbalance in baseline risk may have arisen by chance. If prognostic factors are distributed differently across the treatment and placebo groups, this could bias the treatment effect. To investigate this hypothesis, we will conduct an analysis of the treatment effect on death due to bleeding adjusted for baseline risk. Patients will be stratified by risk deciles based on the predicted probability of death due to bleeding and a pooled effect estimate (relative risk) will be calculated using inverse variance weighting. This will provide an estimate of the treatment effect where both groups have equal baseline risks.

Centre and country effects

Centre- and country-level characteristics can influence patient outcomes. Differences in outcome may be related to resource availability or clinical practice. To explore between-country differences we will present a graph showing the number of patients and bleeding deaths by country and will use multivariable regression modelling to examine the treatment effect by country, including an interaction term between country and treatment. We will not adjust for clustering as we expect the effects of clustering to be small. Because we aim to understand any between-country differences in the treatment effect, we will adjust for potential confounders including age, SBP, HR, comorbidities, location of bleeding, suspected variceal bleeding, suspected active bleeding and time to treatment. A comparison between low-, middle- and high-income countries will be included using the World Bank country groupings by income. We do not expect the effect of TXA on the risk of death due to bleeding to vary by country, even though the absolute risk will vary due to between-country differences in patient populations. Countries recruiting fewer than 100 patients will be omitted from the analysis as necessary.

Between-centre differences in outcome may also influence the estimation of the treatment effect. We will first use a mixed-effects regression model using restricted

maximum likelihood estimation to examine whether there are differences in death due to bleeding between centres. Results will be presented in the form of a forest plot. Prognostic patient characteristics (age, SBP, HR, comorbidities, location of bleeding, suspected variceal bleeding, suspected active bleeding), treatment group and time to treatment will be adjusted for. To take into account country-level effects we will also consider between-centre differences in outcome adjusted for country. We will then use mixed-effects regression to estimate the treatment effect before and after accounting for between-centre differences, assuming a constant treatment effect across centres. To assess whether the treatment effect differs by centre, we will fit a model with an interaction term between centre and treatment.

Data monitoring

The progress of the HALT-IT trial, including recruitment, data quality, outcomes and safety data, are reviewed by an independent Data Monitoring Committee, which can decide to reveal unblinded results to the Trial Steering Committee. To date, four interim analyses have been conducted.

Data sharing

To maximise data utilisation and improve patient care, the trial data will be made available via our online data-sharing portal – The Free Bank of Injury and Emergency Research Data (freeBIRD) (https://ctu-app.lshtm.ac.uk/freebird/) – once primary and secondary analyses have been published.

Trial status

The study has been actively recruiting since July 2013. End of recruitment is planned for 31 May 2019, with end of follow-up expected on 30 June 2019. Further information is available at http://haltit.Lshtm.ac.uk/.

Discussion

We present our plan for the statistical analysis of the HALT-IT trial prior to the end of recruitment, database lock and unblinding in order to avoid data-dependent analyses. We set out a-priori hypotheses and propose ways to test these. We also provide the rationale for changing the primary outcome from all-cause mortality to death due to bleeding within 5 days of randomisation.

Additional file

Additional file 1 **Figure S1** Trial profile. **Figure S2** Cumulative percentage of death due to bleeding in the tranexamic acid and placebo groups. **Figure S3** Distribution of cause of death by days since randomisation. **Table S1** Baseline characteristics of participants prior to randomisation. **Table S2** Death due to bleeding and rebleeding. **Table S3** Other causes of death and all-cause mortality. **Table S4** Death due to bleeding by subgroups. **Table S5** Need for surgical, endoscopic and radiological interventions and blood transfusion. **Table S6** Thromboembolic events, complications and self-care capacity. **Table S7** Adverse events. (DOC 355 kb)

Abbreviations

AE: Adverse event; CRASH-2: Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage; GI: Gastrointestinal; GMP: Good Manufacturing Practice; HALT-IT: Haemorrhage ALleviation with Tranexamic acid – Intestinal system; HDU: High-dependency unit; HPLC: High-performance liquid chromatography; HR: Heart rate; ICU: Intensive care unit; Katz ADL: Katz Index of Independence in Activities of Daily Living; MedDRA PT: Medical Dictionary for Regulatory Activities Preferred Term; MedDRA SOC: Medical Dictionary for Regulatory Activities system organ class; MedDRA: Medical Dictionary for Regulatory Activities; PSF: Product Specification File; QALYs: Quality-adjusted Life Years; QP: Qualified Person; SAE: Serious adverse event; SBP: Systolic blood pressure; SUSAR: Suspected unexpected serious adverse reaction; TCC: Trial Coordinating Centre; TXA: Tranexamic acid; UK: United Kingdom; US: United States; WOMAN: World Maternal Antifibrinolytic

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Authors' contributions

HS and IR conceived and designed the HALT-IT trial. AB conducted the analyses. MA is the HALT-IT trial manager. AB and IR drafted the manuscript. AA, SMA, MA, RC, TC, JC, IG, CH, DH, VJ, KJ, AK, MM, MAN, HSS, SS and AV provided important feedback and contributed to the final version of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not yet publicly available because the trial is ongoing. Once recruitment has stopped and after publication of the planned primary and secondary analyses, the trial data will be made available via our data-sharing portal, The Free Bank of Injury and Emergency Research Data (freeBIRD) website at https://ctu-app.lshtm.ac.uk/freebird/.

Ethics approval and consent to participate

The trial was approved by the UK NRES Committee East of England (reference number 12/EE/0038), as well as national and local research ethics committees of participating countries outside the UK. Informed consent will be obtained from all study participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Critical Care

RESEARCH Open Access

Understanding the neuroprotective effect of tranexamic acid: an exploratory analysis of the CRASH-3 randomised trial

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On behalf of the CRASH-3 trial collaborators

Abstract

Background: The CRASH-3 trial hypothesised that timely tranexamic acid (TXA) treatment might reduce deaths from intracranial bleeding after traumatic brain injury (TBI). To explore the mechanism of action of TXA in TBI, we examined the timing of its effect on death.

Methods: The CRASH-3 trial randomised 9202 patients within 3 h of injury with a GCS score ≤ 12 or intracranial bleeding on CT scan and no significant extracranial bleeding to receive TXA or placebo. We conducted an exploratory analysis of the effects of TXA on all-cause mortality within 24 h of injury and within 28 days, excluding patients with a GCS score of 3 or bilateral unreactive pupils, stratified by severity and country income. We pool data from the CRASH-2 and CRASH-3 trials in a one-step fixed effects individual patient data meta-analysis.

Results: There were 7637 patients for analysis after excluding patients with a GCS score of 3 or bilateral unreactive pupils. Of 1112 deaths, 23.3% were within 24 h of injury (early deaths). The risk of early death was reduced with TXA (112 (2.9%) TXA group vs 147 (3.9%) placebo group; risk ratio [RR] RR 0.74, 95% CI 0.58–0.94). There was no evidence of heterogeneity by severity ($p = 0.64$) or country income ($p = 0.68$). The risk of death beyond 24 h of injury was similar in the TXA and placebo groups (432 (11.5%) TXA group vs 421 (11.7%) placebo group; RR 0.98, 95% CI 0.69–1.12). The risk of death at 28 days was 14.0% in the TXA group versus 15.1% in the placebo group (544 vs 568 events; RR 0.93, 95% CI 0.83–1.03). When the CRASH-2 and CRASH-3 trial data were pooled, TXA reduced early death (RR 0.78, 95% CI 0.70–0.87) and death within 28 days (RR 0.88, 95% CI 0.82–0.94).

Conclusions: Tranexamic acid reduces early deaths in non-moribund TBI patients regardless of TBI severity or country income. The effect of tranexamic acid in patients with isolated TBI is similar to that in polytrauma. Treatment is safe and even severely injured patients appear to benefit when treated soon after injury.

Trial registration: ISRCTN15088122, registered on 19 July 2011; NCT01402882, registered on 26 July 2011.

Keywords: Traumatic brain injury, Tranexamic acid, CRASH-3 trial, Randomised controlled trial, Intracranial haemorrhage, Epidemiology, Emergence care

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Background

The acute management of traumatic brain injury (TBI) aims to avoid secondary brain damage and optimise conditions for recovery [1]. The day of the injury is the most hazardous, accounting for one third of in-hospital deaths [2]. Some TBI victims have brain damage that is incompatible with life and die shortly after admission. In many patients, intracranial bleeding starts soon after impact and continues for several hours, with the majority of haematoma expansion occurring within 1–1.5 h of injury [3, 4]. The accumulating blood can increase intracranial pressure, causing cerebral herniation and death. Tranexamic acid reduces bleeding in surgery and reduces death from bleeding in traumatic and post-partum haemorrhage [5–7]. The therapeutic premise of the CRASH-3 trial was that timely tranexamic acid treatment might curtail intracranial bleeding and prevent some of the early bleeding-related deaths. A 1-g bolus started within 3 h of injury was followed by an infusion of 1 g over 8 h. Tranexamic acid has a half-life of 2 h and by the second day is almost completely eliminated. By this time, the bleeding will have stopped, but other pathological processes, likely unaffected by tranexamic acid, will continue to cause deaths. Those who survive the first day run the risk of cerebral oedema, diffuse axonal injury, organ failure, sepsis, pneumonia and many other threats, some iatrogenic, that make up the remaining two thirds of in-hospital deaths.

The management of TBI is only partly based on results from randomised trials. In practice, doctors draw on pathophysiological knowledge, the available evidence and their clinical experience to identify mechanisms of brain damage and target physiologically based treatment accordingly [3]. Large randomised trials can reduce our therapeutic uncertainty, but to categorise them as positive or negative based on arbitrary p value thresholds is inappropriate [8–10]. The CRASH-3 trial results have variously been described as 'negative', 'neutral' or 'a win for patients with head injury' that will benefit patients [11–13]. We argue that randomised trials can deepen our understanding of pathophysiology and that mechanistic insights should inform their interpretation. To explore the mechanism of action of tranexamic acid in TBI patients, we examined the timing of its effect on death. We also set the results of our analysis in the context of other trials of tranexamic acid in TBI and polytrauma patients, taking into consideration current treatment guidelines that exclude patients with isolated TBI.

Methods

The background to the CRASH-3 trial, the methods, baseline characteristics and main results were previously reported [2, 6, 14]. Briefly, adults with TBI who were within 3 h of injury and had a Glasgow coma scale score (GCS) ≤ 12 or any intracranial bleeding on CT scan and no significant extra-cranial bleeding were eligible. The time window for eligibility was originally 8 h, but in 2016, the protocol was changed to limit recruitment to within 3 h of injury. Between July 2012 and January 2019, we randomly allocated 12,737 patients with TBI to receive tranexamic acid or placebo, of whom 9202 patients were treated within 3 h. Patients were assigned by selecting a numbered treatment pack from a box containing eight packs that were identical apart from the pack number. Patients, care givers and those assessing outcomes were masked to treatment allocation.

Based on previous research on the mechanism of tranexamic acid in bleeding trauma patients, we hypothesised that tranexamic acid would have a greater effect on deaths soon after injury, since early bleeding-related deaths have the most potential to be reduced by tranexamic acid [15]. We pre-specified this hypothesis in the statistical analysis plan that we published before unblinding [14]. We also anticipated that the treatment effect would be diluted by the inclusion of patients with a GCS score of 3 or unreactive pupils who have a very poor prognosis regardless of treatment [14]. The trial results were consistent with both of these hypotheses [2]. The pre-specified primary outcome in the CRASH-3 trial was death due to head injury within 28 days among patients treated within 3 h of injury. Although our scientific reasons for pre-specifying head injury death as the primary outcome were given in the statistical analysis plan and presented in detail elsewhere [16], there has been strong interest in the effects of tranexamic acid on all-cause mortality. As such, this analysis focusses on early deaths from any cause, excluding patients with a GCS score of 3 or bilateral unreactive pupils. Analyses of head injury deaths and analyses including patients with a GCS score of 3 or bilateral unreactive pupils are presented in the Additional file 1 for comparison with the results presented below and for cross-reference with the main trial results.

We examine the temporal distribution of deaths from any cause in the CRASH-3 trial. We explore the effects of tranexamic acid on deaths due to any cause within 24 h of injury and on deaths due to any cause within 28 days, stratified by severity and country income level. We use the baseline GCS score to define severity—mild to moderate (GCS 9–15) and severe (GCS 3–8)—and World Bank definitions to determine country income level (LMIC vs HIC). Because a subgroup analysis demonstrated effect modification by severity, we explore this further. Because most patients were from LMICs, the generalisability of the results to HICs has been questioned and so we explore how the treatment effects vary by country income level. To check if the effect on early deaths could be explained by undiagnosed extra-cranial

bleeding, we conducted a sensitivity analysis excluding patients with hypotension (SBP < 90 mmHg). We also examined the effects of tranexamic acid on vascular occlusive events (fatal and non-fatal) in all patients irrespective of time to treatment because theoretically the potential risk of vascular occlusive events would be greater with late treatment as there is a shift from a fibrinolytic to a coagulopathic state. We report risk ratios, 95% confidence intervals and heterogeneity p values. We excluded 98 patients with missing outcome data.

We prespecified an analysis setting the results of the CRASH-3 trial in the context of other evidence, including the CRASH-2 trial, in which 40% of deaths were due to head injury [14]. The CRASH-3 trial essentially represents a subgroup of patients with isolated TBI who were excluded from the CRASH-2 trial. Here, to set our results in the context of tranexamic acid in polytrauma patients, we pooled the data from the CRASH-2 and CRASH-3 trials in a one-step fixed effects individual patient data meta-analysis using a Poisson regression model with sandwich variance estimation, adjusted for time to treatment. In the main CRASH-3 trial publication, we updated a systematic search for randomised trials of tranexamic acid in TBI. We searched PubMed, Science Citation Index, National Research Register, Zetoc, SIGLE, Global Health, LILACS, Current Controlled Trials, the Cochrane Injuries Group Specialised Register, CENTRAL, MEDLINE and EMBASE. We identified three trials in addition to the CRASH-3 trial including the CRASH-2 intracranial bleeding study, a randomised trial of 283 TBI patients sponsored by Khon Kaen University [17] and a randomised trial of pre-hospital tranexamic acid in 967 TBI patients sponsored by the University of Washington (NCT01990768). The CRASH-2 intracranial bleeding study was omitted as this is already contained within the CRASH-2 trial dataset, and the small Thai study was omitted due to a lack of data on timing of death, cause of death and GCS score, and limitations in methodological quality including an unclear risk of selection bias from allocation concealment.

The model for the one-step meta-analysis was as follows:

$$\log \pi = \beta_0 + \beta_1 \text{trial} + \beta_2 \text{group} + \beta_3 \text{ttt}$$

where trial = 0 for CRASH-2 and 1 for CRASH-3, group = 0 for placebo and 1 for TXA, ttt is time to treatment and β_2 is the summary effect estimate across both trials.

We also consider the CRASH-3 trial results in the context of the CRASH-2 trial and the trial of pre-hospital tranexamic acid (NCT01990768) using an aggregate data meta-analysis with fixed effects to assess the effect of tranexamic acid on death at 28 days excluding patients with a GCS score of 3 or bilateral unreactive pupils, and on vascular occlusive events in all patients. An aggregate data meta-analysis was used because we did not have access to the individual patient data for trial NCT01990768.

Results

Among the 12,639 randomised patients with outcome data available, 9127 were treated within 3 h of injury. A total of 1490 patients had GCS score of 3 or bilateral unreactive pupils at baseline (16.3%), leaving 7637 patients for analysis. There were 1112 deaths from all causes within 28 days, of which 259 (23.3%) occurred within 24 h of injury (early deaths) and 853 (76.7%) were beyond 24 h of injury. Figure 1 shows the time interval from injury to death in placebo-treated patients overall and according to severity and country income. Overall, the proportion of early deaths was larger in severe head injury (28.1%) and in LMICs (24.1%).

Effect of tranexamic acid on early deaths

The risk of early death was lower in patients with mild-to-moderate head injury compared to severe head injury (1.1% vs 9.9%) and in HICs compared to LMICs (2.0% vs 3.8%). The risk of early death was reduced with tranexamic acid (112 (2.9%) deaths in the tranexamic acid group vs 147 (3.9%) deaths in the placebo group; risk ratio [RR] RR 0.74, 95% CI 0.58–0.94; see Table 1). There was no evidence that the effect of tranexamic acid on early deaths varied by severity (heterogeneity p = 0.64) or by country income (heterogeneity p = 0.68). When 114 (1.5%) patients with hypotension (SBP < 90 mmHg) at baseline were excluded from the analyses, the results were essentially the same (106 (2.8%) deaths in the tranexamic acid group vs 143 (3.9%) deaths in the placebo group; RR 0.72, 95% CI 0.56–0.92). The effect of tranexamic acid on early death was smaller (261 vs 315 events; RR 0.81, 95% CI 0.69–0.95) when we included patients who had a GCS score of 3 or bilateral unreactive pupils at baseline (see Appendix Table 1). The effect was larger when the analysis was restricted to head injury-related deaths only (Appendix Tables 2 and 3).

Effect of tranexamic acid on deaths after 24 h

The risk of death more than 24 h after injury was lower in patients with mild-to-moderate head injury compared to severe head injury (6.3% vs 25.2%) and in HICs compared to LMICs (8.2% vs 12.1%). The risk of death from all causes beyond 24 h of injury was similar in the tranexamic acid and placebo groups (432 (11.5%) deaths in the tranexamic acid group vs 421 (11.7%) deaths in the placebo group; RR 0.98, 95% CI 0.69–1.12; see Table 1). The effect on deaths beyond 24 h was similar by severity

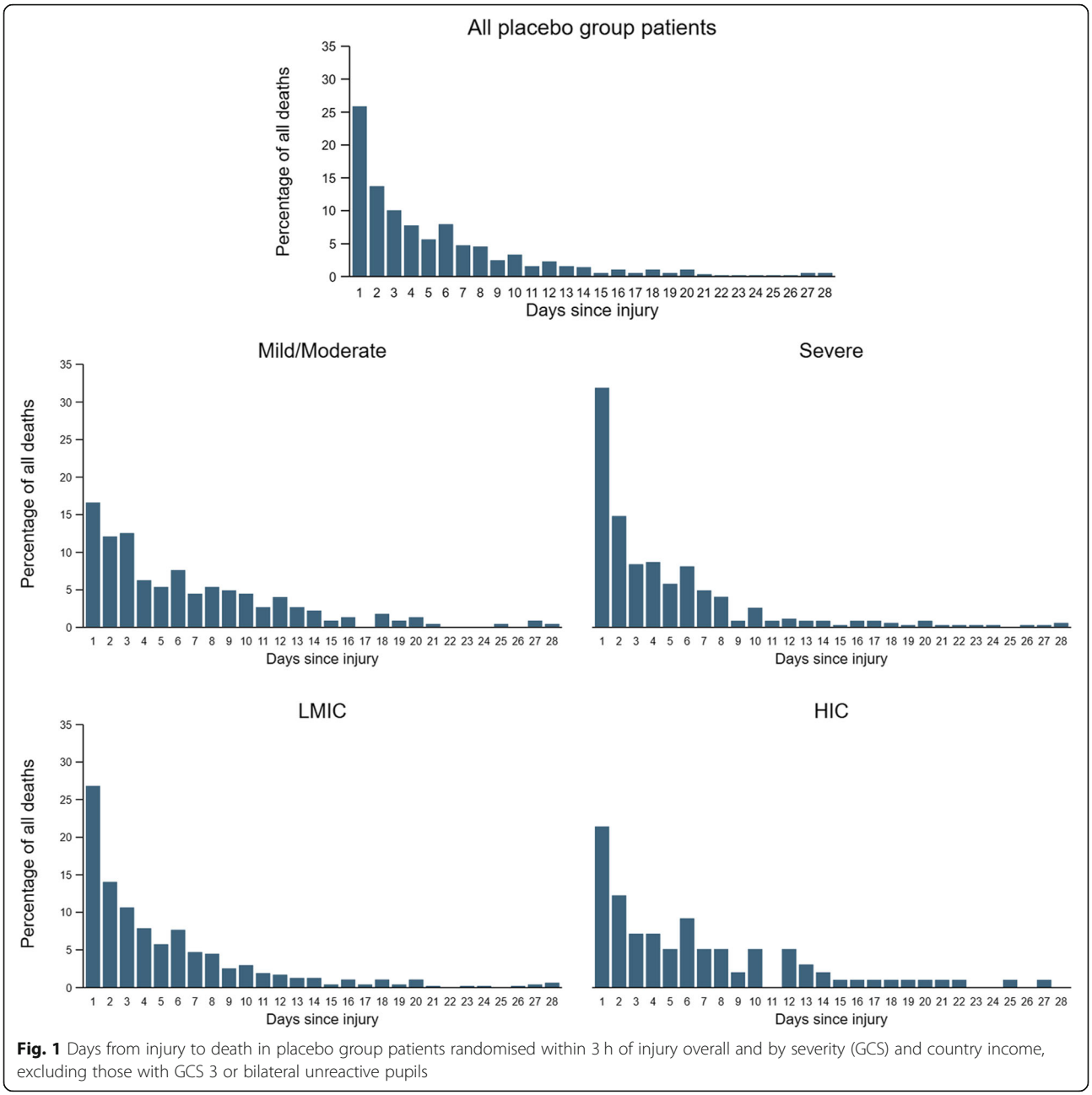

Fig. 1 Days from injury to death in placebo group patients randomised within 3 h of injury overall and by severity (GCS) and country income, excluding those with GCS 3 or bilateral unreactive pupils

(heterogeneity $p = 0.088$) and country income (heterogeneity $p = 0.36$).

Effect of tranexamic acid on deaths at 28 days

The risk of death at 28 days was lower in mild-to-moderate head injury compared to severe head injury (7.4% vs 35.1%) and in HICs compared to LMICs (10.1% vs 15.9%). The risk of death from any cause at 28 days was 14.0% in the tranexamic acid group versus 15.1% in the placebo group (544 vs 568 events; RR 0.93, 95% CI 0.83–1.03; see Table 1). The effect of tranexamic acid on all-cause mortality at 28 days was similar by severity (heterogeneity $p = 0.11$) and country income (heterogeneity $p = 0.35$).

Effect of tranexamic acid on vascular occlusive events

Among the 12,639 randomised patients with outcome data, there were 203 (1.6%) fatal or non-fatal vascular occlusive events. The absolute risk of vascular occlusive events in all patients was lower in mild-to-moderate head injury than in severe head injury (1.2% vs 2.4%) and in LMICs compared to HICs (1.0% vs 3.0%). The risk of vascular occlusive events was 1.6% in both the

Table 1 Effect of early tranexamic acid on all-cause mortality within 24 h of injury, after 24 h and at 28 days stratified by severity and country income level in patients randomised within 3 h of injury, excluding those with a GCS score of 3 or bilateral unreactive pupils

	Within 24 h			After 24 h			At 28 days		
	TXA	Placebo	RR (95% CI)	TXA	Placebo	RR (95% CI)	TXA	Placebo	RR (95% CI)
	n (%)	*n* (%)		*n* (%)	*n* (%)		*n* (%)	*n* (%)	
All patients	112 (2.9)	147 (3.9)	0.74 (0.58–0.94)	432 (11.5)	421 (11.7)	0.98 (0.69–1.12)	544 (14.0)	568 (15.1)	0.93 (0.83–1.03)
Severity									
Mild/moderate	25 (0.9)	37 (1.3)	0.66 (0.40–1.09)	163 (5.8)	186 (6.9)	0.85 (0.69–1.04)	188 (6.7)	223 (8.1)	0.82 (0.68–0.99)
Severe	87 (8.5)	110 (11.3)	0.75 (0.58–0.98)	269 (28.7)	235 (27.2)	1.05 (0.91–1.22)	356 (34.7)	345 (35.4)	0.98 (0.87–1.10)
Country income									
LMIC	98 (3.3)	126 (4.4)	0.75 (0.58–0.98)	363 (12.6)	344 (12.5)	1.01 (0.88–1.16)	461 (15.5)	470 (16.3)	0.95 (0.84–1.07)
HIC	14 (1.5)	21 (2.4)	0.65 (0.33–1.26)	69 (7.7)	77 (9.0)	0.86 (0.63–1.18)	83 (9.2)	98 (11.1)	0.82 (0.62–1.08)

tranexamic acid and placebo groups (101 vs 102 events; RR 0.98, 95% CI 0.74–1.28; see Table 2).

The results of the CRASH-3 trial in context

When the CRASH-2 and CRASH-3 trial data were pooled in a one-stage individual patient data meta-analysis, early tranexamic acid reduced death within 24 h of injury (RR 0.78, 95% CI 0.70–0.87) and death within 28 days (RR 0.88, 95% CI 0.82–0.94), with no evidence of heterogeneity by trial (death within 24 h $p = 0.60$; death within 28 days $p = 0.18$; see Fig. 2). Adjusting for time to treatment made no difference to the results. For deaths with 24 h of injury, the adjusted RR = 0.78 (95% CI 0.70–0.87), and for death within 28 days the adjusted RR = 0.88 (95% CI 0.82–0.94). When a US trial of pre-hospital tranexamic acid for isolated TBI was included in an aggregate data meta-analysis on death from any cause at 28 days, the results were identical (RR 0.88, 95% CI 0.82–0.94), with no evidence of heterogeneity by trial ($p = 0.41$). There was no difference in the risk of vascular occlusive events between treatment groups (RR 0.87, 95% CI 0.74–1.02), again with no heterogeneity by trial ($p = 0.42$).

Table 2 Effect of tranexamic acid on vascular occlusive events (fatal and non-fatal) at 28 days in all patients, stratified by severity and country income level

	TXA			Placebo			RR (95% CI)
	N	*n*	(%)	*N*	*n*	(%)	
All patients	6359	101	(1.6)	6280	102	(1.6)	0.98 (0.74–1.28)
Severity							
Mild/moderate	4066	41	(1.0)	3997	52	(1.3)	0.76 (0.52–1.16)
Severe	2264	60	(2.7)	2247	50	(2.2)	1.19 (0.82–1.73)
Country income							
LMIC	4375	50	(1.1)	4330	35	(0.8)	1.41 (0.92–2.17)
HIC	1984	51	(2.6)	1950	67	(3.4)	0.75 (0.52–1.07)

Discussion

Based upon this post hoc, exploratory analysis of the CRASH-3 trial, tranexamic acid reduces deaths on the day of the injury regardless of TBI severity and country income but has no apparent effect on deaths beyond the day of the injury. The effect of tranexamic acid on all-cause mortality at 28 days is a weighted average of these early and late effects and, although diluted toward the null, is similar to the results of the CRASH-2 trial and indicative of a survival benefit.

Because a larger proportion of deaths in the CRASH-3 trial occurred after 24 h (69% in CRASH-3 versus 43% in CRASH-2), the effect on mortality at 28 days is smaller (more diluted) in the CRASH-3 trial, although there is no evidence of heterogeneity. As anticipated in the statistical analysis plan, the effect is smaller when including patients with un-survivable injuries prior to treatment. Tranexamic acid did not increase the risk of adverse vascular occlusive events in trauma patients.

Because our choice of head injury death as the primary outcome measure was criticised, these analyses report all-cause mortality. The trial inclusion criteria were clinical and reflect the situation that doctors face in practice. We enrolled TBI patients within 3 h of injury if they had no significant extra-cranial bleeding. The effect of tranexamic acid on early deaths is not explained by undiagnosed extra-cranial bleeding. Only 1.5% of patients had hypotension (SBP < 90 mmHg) at baseline and only 11 of the 1112 deaths (six in the tranexamic acid group and five in the placebo group) were classified as extracranial bleeding deaths. When patients with hypotension are excluded, the results are the same. The reduction in all-cause mortality within 24 h strongly suggests that tranexamic acid reduces intracranial bleeding deaths.

We conducted the CRASH-3 trial because there was reason to believe that tranexamic acid could reduce bleeding-related head injury deaths. Increased fibrinolysis is common in TBI patients and worsens intracranial bleeding. The CRASH-2 trial in 20,211 polytrauma

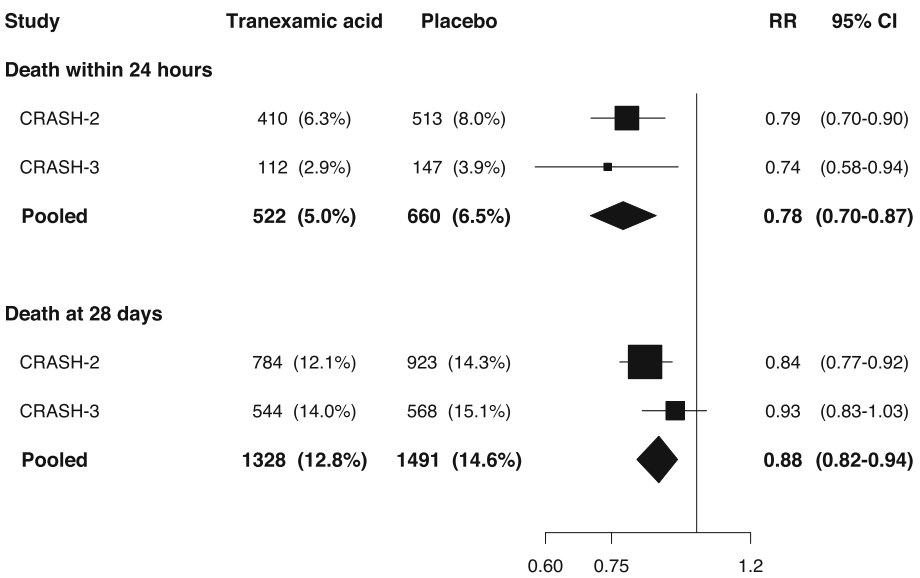

Fig. 2 Evidence on the effect of early tranexamic acid on all-cause mortality within 24 h and 28 days of injury, excluding patients with a GCS score of 3 or bilateral unreactive pupils at baseline

patients (extra-cranial and intra-cranial injury) with significant bleeding found that tranexamic acid reduces mortality, primarily by reducing bleeding deaths on the day of the injury [15]. Because the CRASH-2 trial was large, this early benefit was still apparent at 28 days, although 'diluted' by non-bleeding deaths. The CRASH-3 trial was smaller than the CRASH-2 trial, and so despite the higher mortality rate, there were fewer deaths and less statistical power to detect the diluted effect on all-cause mortality at 28 days. A non-significant difference between two groups in a randomised trial can be real difference that is not significant due to a lack of power, or it can be a difference that has occurred by chance. In this case (Table 1), there is a large reduction in deaths within 24 h with tranexamic acid (RR = 0.74) that is highly statistically significant and consistent with the expected biological effects of tranexamic acid but no apparent reduction in deaths beyond 24 h (RR = 0.98). Because the relative risk at 28 days is a weighted average of these effects, the modest reduction in death at 28 days (RR = 0.93) is not statistically significant. We believe the reduction in deaths at 28 days is a real reduction that is not significant due to a lack of statistical power. This interpretation is consistent with biology (intracranial bleeding occurs early, and there is little or no tranexamic acid in the body beyond 24 h) and as shown in the next paragraph is mathematically consistent with dilution. The reduction in deaths at 28 days in the CRASH-3 trial is similar to that seen in the larger (and more powerful) CRASH-2 trial, and when the results are pooled, the reduction in deaths at 28 days with tranexamic acid is highly significant. However, we accept that can never rule out chance as a potential explanation.

Because 'dilution' is key to understanding the CRASH-3 results, it is best considered quantitatively. Figure 3 shows results from a hypothetical trial in

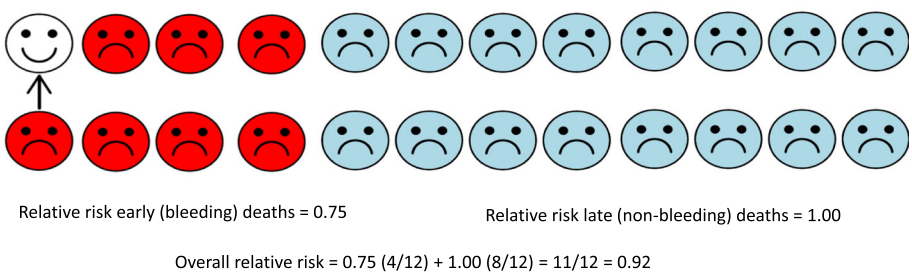

Fig. 3 Hypothetical trial in which the effect on all-cause mortality is a weighted average of the effect on cause-specific mortality. The trial treatment reduces the risk of early (bleeding) deaths by one quarter (RR = 0.75) but has no effect on late (non-bleeding) deaths (RR = 1.00). The overall relative risk for all-cause mortality at the end of follow-up is a weighted average of these relative risks (RR = 0.92)

which the treatment reduces the risk of early bleeding deaths (red circles) by one quarter (relative risk = 0.75), but has no effect (relative risk = 1.00) on later non-bleeding deaths (blue circles). The relative risk at the end of the follow-up period is a weighted average of these relative risks: relative risk = 0.75(4/12) + 1.0(8/12) = 11/12 = 0.92, where (4/12) and (8/12) are the proportions of deaths in the untreated group that are early or late. Because the relative risk at the end of follow-up is closer to the null (0.92 versus 0.75), and smaller effects are harder to detect, the treatment effect is less visible and, in this sense, is diluted. But the biological effect did not change. It was not offset by any harm but was simply obscured by deaths unrelated to its mechanism of action. Deaths that are inevitable before randomisation also dilute treatment effects. Many patients with a GCS score of 3 or unreactive pupils have un-survivable injuries and will die soon after admission regardless of treatment. Errors in the estimation of the time of injury could result in the inclusion of patients outside the eligibility time window, and because late treatment is less effective, this will also cause dilution. This is most relevant in LMICs where patients are often taken to hospital by bystanders or family members in private vehicles with no recording of the time of injury.

Because no treatment has effects on all causes of death, all-cause mortality at 28 days is a composite outcome that combines deaths affected by the trial treatment with those that are unaffected by it [16]. Using all-cause mortality to assess the 'true' effect of a treatment has counterintuitive consequences since it means that the effect of any given treatment depends on the effects of all the others. An antibiotic that reduces pneumonia deaths in week 2, by reducing the proportion of late deaths, will appear to increase the effectiveness of a treatment for early bleeding. Because the proportion of late deaths varies with injury severity and in different locations, all-cause mortality is not generalisable. The only generalisable measure is the undiluted biological effect of the trial treatment.

Conclusions

Tranexamic acid safely reduces early deaths in non-moribund TBI patients regardless of TBI severity or country income. The effect of tranexamic acid in patients with isolated TBI is similar to that in polytrauma, reducing deaths on the day of the injury by over 20% in the CRASH-2 and the CRASH-3 trials. Tranexamic acid is included in treatment guidelines for the pre-hospital care of bleeding trauma patients, but patients with isolated TBI were excluded. The CRASH-3 trial data support the reconsideration of tranexamic acid for administration in isolated TBI, and even severely injured patients appear to benefit when treated soon after injury.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13054-020-03243-4.

Additional file 1: Supplementary Table 1. Effect of tranexamic acid on all-cause mortality within 24 hours of injury, after 24 hours and at 28 days stratified by severity and country income in patients randomised within 3 hours of injury. **Supplementary Table 2.** Effect of tranexamic acid on head injury death within 24 hours, after 24 hours and at 28 days by severity and country income in patients randomised within 3 hours of injury, excluding those with GCS 3 or bilateral unreactive pupils. **Supplementary Table 3.** Effect of tranexamic acid on head injury death within 24 hours, after 24 hours and at 28 days by severity and country income in patients randomised within 3 hours of injury.

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Authors' contributions

Study conception: IR and HSS. Data collection: ABe, RC, TC, LF, SJ, LF, RJ, PS and TS. Trial management: LF. Data analysis: ABr and RM. Data interpretation: ABr, RM and IR. Drafting the manuscript: ABr and IR. All authors were responsible for reviewing and revising the manuscript and have approved the final version. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

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Availability of data and materials

Following publication of the primary and secondary analyses, individual de-identified patient data from the CRASH-3 trial will be made available via our data sharing portal, The Free Bank of Injury and Emergency Research Data (freeBIRD) website (http://freebird.Lshtm.ac.uk) indefinitely. The CRASH-2 trial data is already available. The trial protocols, statistical analysis plans and trial publications will be freely available online. The trial protocol, statistical analysis plan and trial publications will be freely available at http://www.txacentral.org/.

Ethics approval and consent to participate

Most patients with TBI are unable to provide informed consent to participate in a clinical trial due to the nature of their injury. As per the Declaration of Helsinki, patients who are incapable of giving consent are an exception to the general rule of informed consent in clinical trials. In the CRASH-3 trial, consent was sought from the patient's relative or a legal representative unless no such representative was available, in which case the study proceeded with the agreement of two clinicians. If the patient regained capacity, they were told about the trial and written consent was sought to continue participation. If either the patient or their representative declined consent, participation was stopped. If patients were included in the trial but did not regain capacity, consent was sought from a relative or legal representative. We adhered to the requirements of the local and national ethics committees.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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COMMENTARY Open Access

Postpartum haemorrhage in anaemic women: assessing outcome measures for clinical trials

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Abstract

Background: Postpartum haemorrhage (PPH) is a leading cause of maternal mortality worldwide. Maternal anaemia greatly increases the risk of PPH, and over a third of all pregnant women are anaemic. Because anaemia reduces the oxygen-carrying capacity of the blood, anaemic women cannot tolerate the same volume of blood loss as healthy women. Yet the same blood loss threshold is used to define PPH in all women. The lack of an established PPH definition in anaemic women means the most appropriate outcome measures for use in clinical trials are open to question. We used data from the WOMAN-2 trial to examine different definitions of PPH in anaemic women and consider their appropriateness as clinical trial outcome measures.

Main body: The WOMAN-2 trial is assessing tranexamic acid (TXA) for PPH prevention in women with moderate or severe anaemia at baseline. To obtain an accurate, precise estimate of the treatment effect, outcome measures should be highly specific and reasonably sensitive. Some outcome misclassification is inevitable. Low sensitivity reduces precision, but low specificity biases the effect estimate towards the null. Outcomes should also be related to how patients feel, function, or survive. The primary outcome in the WOMAN-2 trial, a 'clinical diagnosis of PPH', is defined as estimated blood loss > 500 ml or any blood loss within 24 h sufficient to compromise haemodynamic stability. To explore the utility of several PPH outcome measures, we analysed blinded data from 4521 participants. For each outcome, we assessed its: (1) frequency, (2) specificity for significant bleeding defined as shock index ≥1.0 and (3) association with fatigue (modified fatigue symptom inventory [MFSI]), physical endurance (six-minute walk test) and breathlessness. A clinical diagnosis of PPH was sufficiently frequent (7%), highly specific for clinical signs of early shock (95% specificity for shock index ≥1) and associated with worse maternal functioning after childbirth.

Conclusion: Outcome measures in clinical trials of interventions for PPH prevention should facilitate valid and precise estimation of the treatment effect and be important to women. A clinical diagnosis of PPH appears to meet these criteria, making it an appropriate primary outcome for the WOMAN-2 trial.

Trial registration: ClinicalTrials.gov NCT03475342, registered on 23 March 2018; ISRCTN62396133, registered on 7 December 2017; Pan African Clinical Trial Registry PACTR201909735842379, registered on 18 September 2019.

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Keywords: Anaemia, Bleeding, Haemoglobin, Outcome measure, Postpartum haemorrhage, Randomised controlled trial, Tranexamic acid, Treatment effect, WOMAN-2 trial

Background

Postpartum haemorrhage (PPH) is a leading cause of maternal mortality worldwide, responsible for over 70,000 deaths annually [1]. Maternal anaemia greatly increases the risk of PPH [2, 3]. Over a third of all pregnant women (around 30 million) are anaemic, with a high prevalence in sub-Saharan Africa and South Asia [4]. Because anaemia reduces the oxygen-carrying capacity of the blood, anaemic women are more vulnerable to tissue hypoxia, morbidity and death after PPH [5, 6].

Primary PPH is usually defined as blood loss ≥500 ml from the genital tract within 24 h of a vaginal birth [7]. This definition, proposed by a WHO working group in 1989, uses the same threshold for all women. Despite recognising the need for an alternative definition in anaemic women, no specific criteria were proposed [8]. The core outcome set for PPH prevention trials does not consider anaemia [9].

Given the lack of an established definition of PPH in anaemic women, the most appropriate outcome measures for use in clinical trials are open to question. We used data from the WOMAN-2 trial to examine different definitions of PPH in anaemic women and consider their appropriateness as clinical trial outcome measures.

Criteria to assess PPH outcome measures

The WOMAN-2 trial is examining tranexamic acid (TXA) for PPH prevention in women with moderate (Hb 70–99 g/L, *n* = 3714, 82%) or severe (Hb < 70 g/L, *n* = 805, 18%) anaemia at baseline. Women are randomly allocated to receive 1 g of TXA or matching placebo as soon as possible after cord clamping. The primary outcome, a 'clinical diagnosis of PPH', may be defined as estimated blood loss > 500 ml or any blood loss within 24 h sufficient to compromise haemodynamic stability. Haemodynamic instability is based on clinical judgement and assessed using clinical signs (low systolic blood pressure, tachycardia, reduced urine output) that require an intervention (e.g. intravenous fluids)) [10].

In a clinical trial, the primary outcome should facilitate valid and precise estimation of the treatment effect and be related to how patients feel, function or survive [11, 12]. Some outcome misclassification is inevitable. Table 1 shows the potential impact of sensitivity and specificity on the relative risk (RR) in the WOMAN-2 trial. Assuming 6% of the placebo group have a PPH and TXA reduces this risk by 25% (RR = 0.75), a sample size of 10,000 should provide 90% power [10]. Low sensitivity (many false negatives) reduces precision but the RR remains the same, whereas low specificity (many false positives) biases the RR towards the null [13].

To explore the utility of several PPH outcome measures, we analysed blinded data from 4521 participants recruited to 14th July 2021. For each outcome, we assessed its: (1) frequency, (2) specificity for significant bleeding and (3) importance to women. To assess frequency, we considered the sample size calculation for the trial—for 90% power to detect a 25% reduction in PPH with TXA, a minimum event rate of 6% in the placebo group is required, with an event rate of 4.5% in the TXA group and therefore 5.25% overall. To assess specificity, we used a shock index (postpartum heart rate/systolic blood pressure) ≥1.0 as the 'gold standard' for the cardiovascular impact of bleeding (see Table 2) [14–17]. To assess importance to women, we examined each outcome's association with fatigue (modified fatigue symptom inventory [MFSI]), physical endurance (6-min walk test) and breathlessness (patient-reported outcome post-walk test), (see Table 3).

Table 1 Impact of sensitivity and specificity on the treatment effect estimate in a randomised trial. Hypothetical example based on the WOMAN-2 trial of 10,000 women (5000 per arm), assuming a true placebo group event rate of 6% and a true relative risk of 0.75

Varying specificity, 100% sensitivity				Varying sensitivity, 100% specificity			
Specificity	Outcome events (*n*)		RR (95% CI)	Sensitivity	Outcome events (*n*)		RR (95% CI)
	TXA	Placebo			TXA	Placebo	
100%	225	300	0.75 (0.62–0.88)	100%	225	300	0.75 (0.62–0.88)
95%	464	535	0.87 (0.78–0.96)	95%	214	285	0.75 (0.61–0.89)
90%	703	770	0.91 (0.84–0.98)	90%	203	270	0.75 (0.61–0.89)
85%	941	1005	0.94 (0.88–1.00)	85%	191	255	0.75 (0.60–0.90)
80%	1180	1240	0.95 (0.90–1.00)	80%	180	240	0.75 (0.59–0.91)

RR relative risk, *CI* confidence interval, *TXA* tranexamic acid

Table 2 Cumulative incidence of PPH outcome measures and their diagnostic accuracy for early shock defined as shock index ≥1

PPH definition	SI ≥ 1		SI < 1		Total		Sensitivity	Specificity
	n	(%)	*n*	(%)	*N*	(%)		
Clinical diagnosis of PPH								
Yes	109	(31)	208	(5)	317	(7)	31%	95%
No	240	(69)	3956	(95)	4196	(93)		
Total	349	(100)	4164	(100)	4513	(100)		
Estimated blood loss ≥ 500 ml								
Yes	95	(27)	274	(7)	369	(8)	27%	93%
No	254	(73)	3890	(93)	4144	(92)		
Total	349	(100)	4164	(100)	4513	(100)		
Total blood volume lost ≥ 15%								
Yes	48	(14)	69	(2)	117	(3)	14%	98%
No	301	(86)	4095	(98)	4396	(97)		
Total	349	(100)	4164	(100)	4513	(100)		
Peripartum Hb drop ≥ 20 g/L[a]								
Yes	47	(14)	111	(3)	158	(4)	14%	97%
No	297	(86)	3990	(97)	4287	(96)		
Total	344	(100)	4101	(100)	4445	(100)		
Peripartum Hb drop ≥ 10%[a]								
Yes	105	(31)	604	(15)	709	(16)	31%	85%
No	239	(69)	3497	(85)	3736	(84)		
Total	344	(100)	4101	(100)	4445	(100)		
Calculated blood loss ≥ 1000 ml[a]								
Yes	70	(20)	298	(7)	368	(8)	20%	93%
No	274	(80)	3799	(93)	4073	(92)		
Total	344	(100)	4097	(100)	4441	(100)		
RBC transfusion within 24 h after delivery								
Yes	119	(34)	1010	(24)	1129	(25)	34%	76%
No	226	(66)	3121	(76)	3347	(75)		
Total	345	(100)	4131	(100)	4476	(100)		
IV fluid within 24 h after delivery								
Yes	200	(58)	1716	(42)	1916	(43)	59%	58%
No	139	(40)	2331	(56)	2470	(55)		
Total	339	(98)	4047	(98)	4386	(98)		
TXA within 24 h after delivery								
Yes	87	(25)	169	(4)	256	(6)	25%	96%
No	262	(76)	3994	(97)	4256	(95)		
Total	349	(101)	4163	(101)	4512	(101)		
Postpartum uterotonics								
Yes	133	(39)	1174	(28)	1307	(29)	38%	72%
No	216	(63)	2990	(72)	3206	(72)		
Total	349	(101)	4164	(101)	4513	(101)		

PPH postpartum haemorrhage, *SI* shock index, *Hb* haemoglobin, *RBC* red blood cell, *IV* intravenous, *TXA* tranexamic acid
[a]Postpartum Hb corrected for RBC transfusions and IV fluids received between randomisation and postpartum Hb test

Table 3 Association of PPH with measures of maternal functioning after birth

PPH definition	Fatigue (MSFI score)			6-min walk test (metres)[a]			Moderate-extreme breathlessness			
	N	Mean ± SD	Dif. in means (95% CI)	*N*	Mean ± SD	Dif. in means (95% CI)	*n*	*N*	(%)	RR (95% CI)
Clinical diagnosis of PPH										
Yes	304	3.8 ± 20.3	8.0 (5.7–10.4)	291	154.1 ± 85.3	− 21.3 (− 31.6 to − 11.0)	46	281	(16)	1.97 (1.49–2.62)
No	4102	− 4.2 ± 15.5		3993	175.4 ± 97.7		327	3944	(8)	
Blood loss ≥ 500 ml										
Yes	353	2.0 ± 19.9	6.1 (4.0–8.3)	337	158.9 ± 85.5	− 16.7 (− 26.3 to − 7.0)	49	330	(15)	1.79 (1.35–2.37)
No	4052	− 4.1 ± 15.5		3946	175.3 ± 97.8		323	3894	(8)	
Total blood volume lost ≥ 15%										
Yes	111	4.4 ± 20.2	8.3 (4.4–12.1)	105	160.2 ± 87.7	− 14.2 (− 32.9 to 4.6)	16	102	(16)	1.82 (1.15–2.88)
No	4294	− 3.7 ± 15.8		4178	174.4 ± 97.2		356	3411	(10)	
Peripartum Hb drop ≥ 20 g/L [b]										
Yes	150	4.7 ± 22.8	8.7 (5.0–12.4)	147	187.8 ± 104.5	13.8 (− 2.2 to 29.8)	27	141	(19)	2.31 (1.62–3.29)
No	4211	− 4.0 ± 15.5		4093	174.0 ± 97.0		335	4040	(8)	
Peripartum Hb drop ≥ 10% [b]										
Yes	687	− 0.8 ± 19.7	3.5 (1.9–5.0)	670	180.9 ± 106.4	7.7 (− 1.0 to 16.3)	91	655	(14)	1.81 (1.45–2.26)
No	3674	− 4.3 ± 15.1		3570	173.2 ± 95.5		271	3255	(8)	
Calculated blood loss ≥ 1000 ml [b]										
Yes	353	2.2 ± 21.5	6.4 (4.1–8.7)	347	184.1 ± 108.1	10.6 (− 1.3 to 22.4)	51	337	(15)	1.87 (1.42–2.46)
No	4004	− 4.3 ± 15.2		3889	173.6 ± 96.3		311	3840	(8)	
RBC transfusion within 24 h after delivery										
Yes	1105	0.4 ± 17.7	5.5 (4.4–6.7)	1046	151.1 ± 88.4	− 30.6 (− 36.9 to − 24.2)	105	1032	(10)	1.20 (0.97–1.49)
No	3267	− 5.1 ± 15.0		3205	181.6 ± 98.6		267	3162	(8)	
IV fluid within 24 h after delivery										
Yes	1863	− 0.6 ± 17.3	5.5 (4.5–6.4)	1818	161.0 ± 90.1	− 24.0 (− 29.8 to − 18.2)	211	1785	(12)	1.82 (1.49–2.22)
No	2422	− 6.1 ± 14.4		2349	185.0 ± 100.3		151	2326	(6)	
TXA within 24 h after delivery										
Yes	245	4.8 ± 20.9	9.0 (6.3–11.7)	240	148.9 ± 83.5	− 26.5 (− 37.5 to − 15.5)	38	230	(17)	1.97 (1.45–2.68)
No	4160	− 4.2 ± 15.5		4043	175.4 ± 97.6		335	3994	(8)	
Postpartum uterotonics										
Yes	1274	− 0.5 ± 17.8	4.5 (3.4–5.6)	1157	144.6 ± 92.4	− 40.2 (− 46.7 to − 33.8)	117	1118	(10)	1.27 (1.03–1.56)
No	3132	− 5.0 ± 15.0		3127	184.9 ± 96.4		256	3107	(8)	
Shock index ≥ 1										
Yes	331	0.3 ± 19.9	4.3 (2.1 to 6.5)	334	191.7 ± 103.0	19.3 (7.8 to 30.7)	44	325	(14)	1.60 (1.20 to 2.15)
No	4075	− 4.0 ± 15.6		3950	172.5 ± 96.3		329	3900	(8)	

PPH postpartum haemorrhage, *MFSI* modified fatigue symptom inventory, *SD* standard deviation, *Dif* difference, *CI* confidence interval, *Hb* haemoglobin, *RBC* red blood cell, *IV* intravenous, *TXA* tranexamic acid

[a]Women who were too ill to do the walk test were coded as 0 m walked and those who did not complete it for other reasons were excluded from the analysis

[b]Postpartum Hb corrected for RBC transfusions and IV fluids received between randomisation and postpartum Hb test

Clinical diagnosis of PPH

In this population of anaemic women, 7% had a clinical diagnosis of PPH. When compared against shock index ≥1, this outcome measure had 95% specificity, meaning the false positive rate was 5% (see Table 2). Those with a clinical diagnosis of PPH had worse fatigue, reduced ability to exercise and were more breathless after exercise compared to those without this diagnosis (Table 3).

Estimated blood loss ≥500 ml

Blood loss was estimated to be ≥500 ml in 8% of women. When compared against shock index ≥1, this outcome had 93% specificity, meaning a false positive rate of 7% (see Table 2). Those with blood loss ≥500 ml had worse fatigue, reduced ability to exercise and were more breathless after exercise compared to those with blood loss < 500 ml (see Table 3).

Proportion of total blood volume lost

Height and weight determine total blood volume. The smaller the woman, the larger the proportion of total blood volume any given volume of blood loss represents. In pregnancy, blood volume per kilogram (kg) decreases with increasing body mass index (BMI) because fat tissue is relatively non-vascular [18]. BMI ranged from 13 to 68 kg/m^2 in our study population (mean 26, SD 4; see Fig. 1). Based on the Advanced Trauma Life Support classification of hypovolaemic shock, we defined PPH as ≥15% total blood volume lost, which occurred in 3% of women. When compared against shock index ≥1, this outcome had 98% specificity, meaning a false positive rate of 2% (see Table 2). Women who lost ≥15% of their total blood volume had worse fatigue and were more breathless after exercise, with weak evidence of a reduced ability to exercise (see Table 3).

Peripartum haemoglobin change

Studies suggest that postpartum blood loss ≥500 ml confers a Hb drop ≥20 g/L, although this may vary between women and is affected by red blood cell (RBC) transfusion and intravenous (IV) fluids [19–23]. In the WOMAN-2 trial, 25% (n = 1143) and 44% (n = 2000) of women received a RBC transfusion or IV fluids (mostly crystalloids) between randomisation and their postpartum Hb test, respectively. In a multivariable linear regression model, one unit of RBC increased peripartum Hb by 7.7 g/L (95% CI 7.0 to 8.3), while 1 L of IV fluids reduced it by 1.5 g/L (95% CI − 2.2 to − 0.8), adjusting for baseline Hb and estimated blood loss. Mean Hb increment per unit of RBC transfused increased with lower baseline Hb (9 vs 6 g/L for Hb of 30 and 99 g/L). To correct postpartum Hb for RBC transfusion, we used coefficients from a predictive model of mean Hb increment derived from 23,194 patients in US hospitals who received one unit of RBC, which adjusted for possible effect modification by baseline Hb, BMI and age [22]. To correct for IV fluids, we applied the model coefficient from the WOMAN-2 data.

After correcting for RBC transfusion and IV fluid, 4% of women had a peripartum Hb drop ≥20 g/L. When

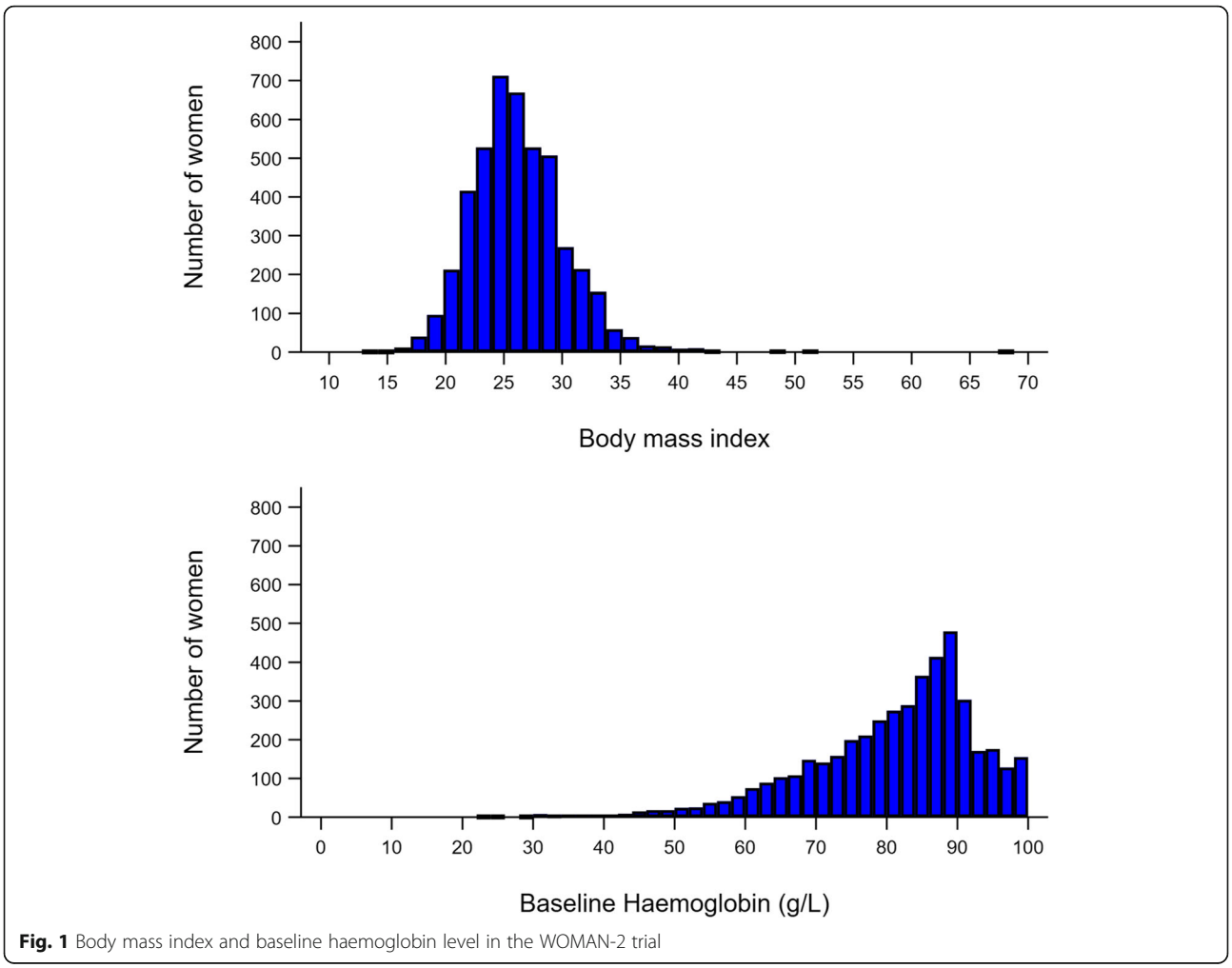

Fig. 1 Body mass index and baseline haemoglobin level in the WOMAN-2 trial

compared against shock index ≥1, this outcome had 97% specificity, or a false positive rate of 3% (see Table 2). Because baseline Hb varied (mean = 8.1 g/dL, SD 1.4, range = 2.3–9.9; see Fig. 1), we analysed a relative Hb drop ≥10%, which occurred in 16% of women and had 85% specificity for shock index ≥1 or a 15% false positive rate (see Table 2). Women with a Hb drop ≥20 g/L or ≥ 10% had worse fatigue and breathlessness after exercise, but weak evidence of an increased ability to exercise compared to those with Hb drop < 20 g/L or < 10% (see Table 3).

Calculated blood loss ≥1000 ml

Another way to define PPH is using calculated blood loss (estimated total blood volume × proportional change in peripartum Hb) [24]. After correcting postpartum Hb for RBC transfusions and fluid resuscitation, 8% of women had calculated blood loss ≥1000 ml. When compared against shock index ≥1, this outcome had 93% specificity, or a 7% false positive rate (see Table 2). Women with calculated blood loss ≥1000 ml had worse fatigue and breathlessness after exercise, but weak evidence of an increased ability to exercise compared to those with calculated blood loss < 1000 ml (see Table 3).

Interventions for blood loss

Blood transfusion, intravenous fluid, TXA and uterotonics are common interventions for postpartum blood loss but are also routinely given for anaemia, dehydration or PPH prophylaxis. Interventions within 24 h after birth are more likely to be for primary PPH. In total, 25% of women had a blood transfusion within 24 h after giving birth, which had 76% specificity for shock index ≥1 (see Table 2). A total of 44% of women received IV fluid within 24 h after birth, which had 58% specificity for shock index ≥1 (see Table 2). In total, 6% of women received TXA within 24 h after birth, which had 96% specificity for shock index ≥1 (see Table 2). A total of 29% of women received postpartum uterotonics (oxytocin, carbetocin, misoprostol, prostaglandins and/or ergometrine), which had 72% specificity for shock index ≥1 (see Table 2). Women who received a blood transfusion had worse fatigue and a reduced ability to exercise, with weak evidence of increased breathlessness compared to those who did not receive a blood transfusion, whereas women who received IV fluids, TXA or postpartum uterotonics had worse fatigue, reduced ability to exercise and worse breathlessness (see Table 3).

Shock index ≥1

Although shock index was used as a gold standard measure of the cardiovascular impact of bleeding, we assessed its frequency and importance to women as an outcome measure. Shock index was ≥1 in 8% of women. Those with a shock index ≥1 had worse fatigue and breathlessness after exercise, but some evidence of an increased ability to exercise compared to those with shock index < 1 (Table 3).

Discussion

To obtain an accurate, precise estimate of the treatment effect, outcome measures should be highly specific and reasonably sensitive. To ensure that evidence of effectiveness translates into real benefit for mothers, the outcome should also be important to women. A clinical diagnosis of PPH, the primary outcome in the WOMAN-2 trial, appears to meet these criteria—it was sufficiently frequent, highly specific for clinical signs of early shock and predictive of maternal functioning after birth. Estimated blood loss and receipt of TXA within 24 h of birth also performed well against our criteria.

High-quality data on over 4500 anaemic pregnant women provided reliable estimates of PPH and its association with various factors. We were able to assess several PPH definitions and discern the sequence of events. Blood loss was estimated visually rather than measured as it is more practical and no worse at predicting adverse maternal outcomes [25]. The formula to estimate total blood volume was derived from pregnant women (blood volume = weight (kg) × 95 if BMI < 30, or 73 if BMI ≥30) but we did not collect data on pre-pregnancy weight [18]. Hb was measured with the Haemocue Hb 201 system which has reasonable accuracy [26]. We corrected postpartum Hb for RBC transfusion and IV fluid but not for time to postpartum Hb test, which had only a small effect (0.03 g/L drop in postpartum Hb for 1 h increase in time from childbirth to Hb test) [22, 23]. Although unlikely, women could possibly receive a RBC transfusion between their baseline Hb test and randomisation, which is not recorded in the trial. While heart rate and blood pressure can be accurately measured, shock index is an imperfect physiological marker of postpartum blood loss with low sensitivity for PPH [27]. Maternal cardiovascular compensatory mechanisms like haemoconcentration and increased cardiac output after childbirth may obscure early physiologic signs of postpartum bleeding. Shock can be caused by other conditions like sepsis, although this affected < 1% of trial participants.

By combining clinical judgement, physical signs of haemodynamic instability and estimated blood loss, a clinical diagnosis of PPH may be more specific for significant bleeding than estimated blood loss alone, particularly in anaemic women [28]. The TRAAP trial of TXA for the prevention of blood loss after vaginal birth found a 17% reduction in blood loss ≥500 ml with TXA (RR = 0.83, 95% CI 0.68–1.01) but a 26% reduction in clinically diagnosed PPH (RR = 0.74, 95% CI 0.61–0.91)

[29]. Calculated blood loss combines peripartum Hb change and total blood volume. The TRAAP2 trial of TXA for PPH prevention in Caesarean births found a reduction in calculated blood loss ≥1000 ml or transfusion (RR = 0.84, 95% CI 0.75–0.94) [24]. However, surrogate measures of PPH based on Hb change may lack value to patients and clinical relevance. Of note, we found a non-significant increase in ability to exercise among women with PPH defined using peripartum Hb change. The relationship between Hb level and postpartum blood loss is not straightforward [20]. Dehydration during childbirth can cause haemoconcentration, increasing postpartum Hb [30]. Physiological adaptions of pregnancy like increased plasma volume and haemodilution may prevent a large drop in Hb with postpartum bleeding [20, 31]. Indeed, few women in the WOMAN-2 trial experienced a Hb drop ≥20 g/L.

Blood transfusion, IV fluid and uterotonics had low specificity, probably because some were given routinely for reasons other than bleeding or despite blood loss. The WOMAN trial of TXA for PPH showed that early treatment reduces death due to bleeding (RR = 0·69, 95% CI 0·52–0·91) but there was no effect on all-cause mortality or hysterectomy as TXA cannot influence non-bleeding causes of death (29% of all deaths) or hysterectomies planned before randomisation (38% of hysterectomies for bleeding occurred within an hour) [12, 32]. Careful consideration of the mechanism of action of the trial treatment, the natural history of the disease and potential sources of null bias is vital when selecting primary outcomes for clinical trials.

The WOMAN-2 trial will provide further insight into outcome measures for PPH research in anaemic women and evidence on the role of TXA for PPH prevention. Anaemia is a highly prevalent risk factor for PPH which needs more attention if we are to reduce the burden of PPH and its consequences for anaemic women and their babies [3, 6]. Large high-quality randomised trials are needed to find effective interventions for the treatment of anaemia in women of reproductive age.

Conclusions

Outcome measures in clinical trials of interventions for PPH prevention should facilitate valid and precise estimation of the treatment effect and be important to women. A clinical diagnosis of PPH is highly specific for the cardiovascular effects of significant postpartum bleeding, sufficiently common and associated with maternal functioning after birth, making it an appropriate primary outcome for the WOMAN-2 trial.

Abbreviations

CI: Confidence interval; Hb: Haemoglobin; MSFI: Modified fatigue symptom inventory; PPH: Postpartum haemorrhage; RR: Relative risk/risk ratio; TXA: Tranexamic acid; WHO: World Health Organization; WOMAN-2 trial: WOrld Maternal ANtifibrinolytic-2 trial

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Authors' contributions

HS-S and IR conceived and designed the WOMAN-2 trial. RC, KJ and AK coordinate the trial in Pakistan. FB and OO coordinate the trial in Nigeria. ML and BV coordinate the trial in Zambia. AB, IR and HS-S developed the concepts and conceived the analyses. AB and RM conducted the analyses. AB, IR and HS-S interpreted the data. AB and IR drafted the manuscript. EB, FB, RC, CF, KJ, AK, ML, RM, OO, DP, BV and HS-S provided important feedback, revised the manuscript and contributed to the final version. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available because the WOMAN-2 trial is ongoing. After trial completion and publication of the planned primary and secondary analyses, the dataset will be made publicly available on the Free Bank of Injury and Emergency Research Data (freeBIRD) website, our data-sharing portal at https://ctu-app.lshtm.ac.uk/freebird/.

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from the London School of Hygiene and Tropical Medicine (ref: 15194), as well as all relevant national and local ethics committees. If women are in the active stage of labour and able to give fully informed consent, written consent is obtained. However, many women arrive at hospital in the second stage of labour. Because these women are more likely to be anaemic and more likely to have a PPH, it is important to include them in the trial. However, they may not have the physical/mental capacity to give fully informed consent due to the pain of labour, poor health, or the urgency of the situation. In these cases, a clinician will assess the capacity of the woman and the most appropriate consent procedure is used, which includes giving brief verbal information, obtaining witnessed verbal agreement and delaying written consent until women regain capacity. The patient information sheet and consent form can be found at https://woman2.lshtm.ac.uk/trial-materials-2/protocol/.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

3 Proforma describing student's contributions

1 **Brenner A**, Shakur-Still H, Chaudhri R, Fawole B, Arulkumaran S, Roberts I. The impact of early outcome events on the effect of tranexamic acid in post-partum haemorrhage: an exploratory subgroup analysis of the WOMAN trial. *BMC Pregnancy Childbirth* 2018; 18: 215.

AB led the analysis and designed and produced all tables and figures. AB interpreted the data and took the lead in drafting the manuscript, with critical comment from IR.

2 **Brenner A**, Arribas M, Cuzick J, Jairath V, Stanworth S, Ker K, Shakur-Still H & Roberts I. Outcome measures in clinical trials of treatments for acute severe haemorrhage. *Trials* 2018; 19: 533.

AB developed the concepts and devised the methods to explore the strengths and limitations of outcome measures commonly used in trials of haemostatic treatments, with review and input from IR. AB led the analysis of the CRASH-2, WOMAN and HALT-IT trial data, and designed and produced all tables and figures. AB interpreted the data and took the lead in drafting the manuscript, with critical comment from IR.

3 **Brenner A**, Afolabi A, Ahmad SM, Arribas M, Chaudhri R, Coats T, Cuzick J, Gilmore I, Hawkey C, Jairath V, Javaid K, Kayani A, Mutti M, Nadeem M, Shakur-Still H, Stanworth S, Veitch S, Roberts I & HALT-IT Trial Collaborators. Tranexamic acid for acute gastrointestinal bleeding (the HALT-IT trial): statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial. *Trials* 2019; 20: 467.

AB developed the rationale for the HALT-IT statistical analysis plan (SAP), which was revised in discussion with IR and HSS. AB conducted interim data analyses of blinded HALT-IT trial data as well as secondary analyses of other trials to inform the choice of primary outcome, which was changed from all-cause mortality at 28 days to early death due to bleeding. This choice was based on concepts developed in the prior publication, which also informed some of the secondary outcomes. AB designed the shell tables and produced the figures. AB took the lead in drafting the manuscript.

4 **Brenner A**, Belli A, Chaudhri R, Coats T, Frimley L, Jamaluddin S, Jooma R, Mansukhani R, Sandercock P, Shakur-Still H, Shokunbi T & Roberts I On behalf of the CRASH-3 trial collaborators. Understanding the neuroprotective effect of tranexamic acid: an exploratory analysis of the CRASH-3 randomised trial. *Crit Care* 2020; 1–10.

AB developed the concepts and methods based on the CRASH-3 trial results and her prior publications, with revision following discussion with IR and HS-S. AB led the analysis and designed and produced the tables and figures, except for the IPD meta-analysis Poisson regression model and associated forest plot, which were produced by RM. AB interpreted the data and took the lead in drafting the manuscript, with critical comment from IR. AB also led the production of a whiteboard animation to disseminate these findings more effectively than through a journal alone (https://www.youtube.com/watch?v=l_SU41_mdec), the release of which was coordinated with World Day of Remembrance for Road Traffic Victims 2020.

5 **Brenner A**, Roberts I, Balogun E, Bello F, Chaudhri R, Fleming C, Javaid K, Lubeya M, Mansukhani R, Olayemi O, Prowse D, Vwalika B, Shakur-Still H. Postpartum haemorrhage in anaemic women: assessing outcome measures for clinical trials. *Trials* (under consideration)

AB developed the concepts and methods to investigate the appropriateness of different PPH definitions as outcome measures for clinical trials, with revision following in discussion with IR and HS-S. AB led the analysis of the WOMAN-2 trial data (statistician RM corrected postpartum haemoglobin for blood transfusion by applying model coefficients). AB designed and produced all tables and figures. AB interpreted the data and took the lead in drafting the manuscript, with critical comment from IR and HSS.

Applicant name: Amy Brenner Signature:

Lead co-author/PI name: Ian Roberts Signature: