Tranexamic acid in trauma care: who should be treated, when and where?

Francois-Xavier Dominique AGERON

Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy
of the University of London

June 2021

Department of Population Health

Faculty of Epidemiology and Population Health

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

No funding received
Research group affiliation(s): Clinical Trials Unit

Author’s declaration

I, Francois-Xavier Ageron, 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

Introduction

Early tranexamic acid (TXA) treatment reduces bleeding deaths in trauma patients. Guidelines recommend the use of TXA for trauma patients who are bleeding or who are at risk of significant haemorrhage within 3 hours of the injury. However, many trauma patients who might benefit from TXA are either not treated or not treated soon enough. Early identification of haemorrhage is challenging and could explain this poor implementation. The purpose of the thesis is to determine who should be treated, when and where.

Methods

First, I developed and validated a prognostic model to predict traumatic death due to bleeding using multivariate logistic regression. Second, I conducted an IPD meta-analysis of randomised trials to assess whether the effectiveness of TXA varies by baseline risk of death due to bleeding. Third, I assessed the health impact of TXA treatment in terms of deaths avoided using the Trauma Audit and Research Network registry. Finally, I developed and validated a simple score (BATT score) that could be used by paramedics to identify patients at risk of haemorrhage and suggested treatment criteria that maximise the number of deaths avoided with TXA.

Results

The relative risk reduction with TXA did not appear to vary by baseline risk. Treating all major trauma patients prior to hospital arrival avoided more deaths and with a lower number needed to treat than with in-hospital treatment. The BATT score had a high discrimination (C-stat=0.90; 95% confidence interval 0.89-0.91). Treating patients with a BATT score ≥2 (60% of major trauma patients) would allow to avoid many deaths compared to current practice.

Conclusion

TXA should be given at the scene of the injury. It should be administered to a wide range of trauma patients and not only restricted to the most severely injured. A BATT score ≥2 represents a simple guidance for paramedics to initiate TXA treatment.

Acknowledgements

I am very grateful to Ian Roberts, my supervisor, for his support and advice. His guidance during the past three years was a tremendous chance for me. I will always remember our great moments of discussion and debate about trauma and epidemiology.

I am also grateful to Haleema Shakur-Still to have accepted to co-supervise this work, for her help and support.

I am grateful to Tim Coats for his advice.

Thanks to all the Clinical Trials Unit team for all the help I have received. Thanks to Katharina Kerr for her help in the systematic review and literature search.

I am grateful to David Prieto-Merino for his advice in medical statistics. I am also grateful to Liam Smeeth and David Prieto-Merino to examine my upgrading.

Thanks to Loic Belle, my mentor in the Northern French Alps Emergency Network, for supporting me in this project. Thanks to all the team of the Northern French Alps Emergency Network.

Thanks to Ewout Steyerberg for his advice in methodology of prognostic model.

Thanks to all the team of the TARN for the data being held in the UK TARN registry.

Thanks to Angèle for her advice and great support during these past three years.

Thanks to Hippolyte to accept to move in London and support his father.

Dedication

To Angèle, Hippolyte and my parents

Abbreviations

AIS:	Abbreviated Injury Scale
ATC:	acute traumatic coagulopathy
ATLS:	advanced trauma life support
BATT (score):	Bleeding Audit and Triage Trauma (score)
CI:	confidence interval
CRASH-2 trial:	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage
CRASH-3 trial:	Clinical Randomisation of an Antifibrinolytic in Significant Head Injury
DIC:	disseminated intravascular coagulation
GCS:	Glasgow Coma Scale
HALT-IT trial:	Haemorrhage Alleviation with Tranexamic acid – Intestinal system
HR:	heart rate
IPD:	individual patient-level data (meta-analysis)
IQR:	interquartile range
ISS:	Injury Severity Score
OR:	odds ratio
PAI-1:	plasminogen activator inhibitor 1
PATCH trial:	Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy & Haemorrhage Study
PPH:	postpartum haemorrhage
PTr:	prothrombin time ratio

ROC:	receiver operating characteristic (curve)
SBP:	systolic blood pressure
SD:	standard deviation
STAAMP trial:	Study of Tranexamic Acid during Air and Ground Medical Prehospital Transport trial
TAFI:	thrombin activatable fibrinolytic inhibitor
TBI:	traumatic brain injury
TICH-2 trial:	Tranexamic Acid for Hyperacute Primary IntraCerebral Haemorrhage
t-PA:	tissue plasminogen activator
TRENAU:	Trauma system of the Northern French Alps Emergency Network
TXA:	tranexamic acid
UK TARN:	United Kingdom Trauma Audit and Research Network
USA:	United States of America
WHO:	World Health Organization
WOMAN trial:	World Maternal Antifibrinolytic trial

Table of contents

List of Figures

List of Tables

Introduction

Trauma is a leading cause of death and disability worldwide.[1] Deaths from injury have increased during the last 20 years to reach more than 5 million deaths each year.[2] Injuries account for 10% of deaths worldwide, which is one-third more than deaths due to malaria, tuberculosis and HIV/AIDS combined. The injury death rate in low- and middle-income countries is twice that in high-income countries. There are approximately 100 injury deaths per 100,000 population per year in low-income and middle-income countries.[3] Bleeding is responsible for 20% to 30% of all trauma deaths [4,5] and is considered to be the leading cause of preventable death.[6,7]

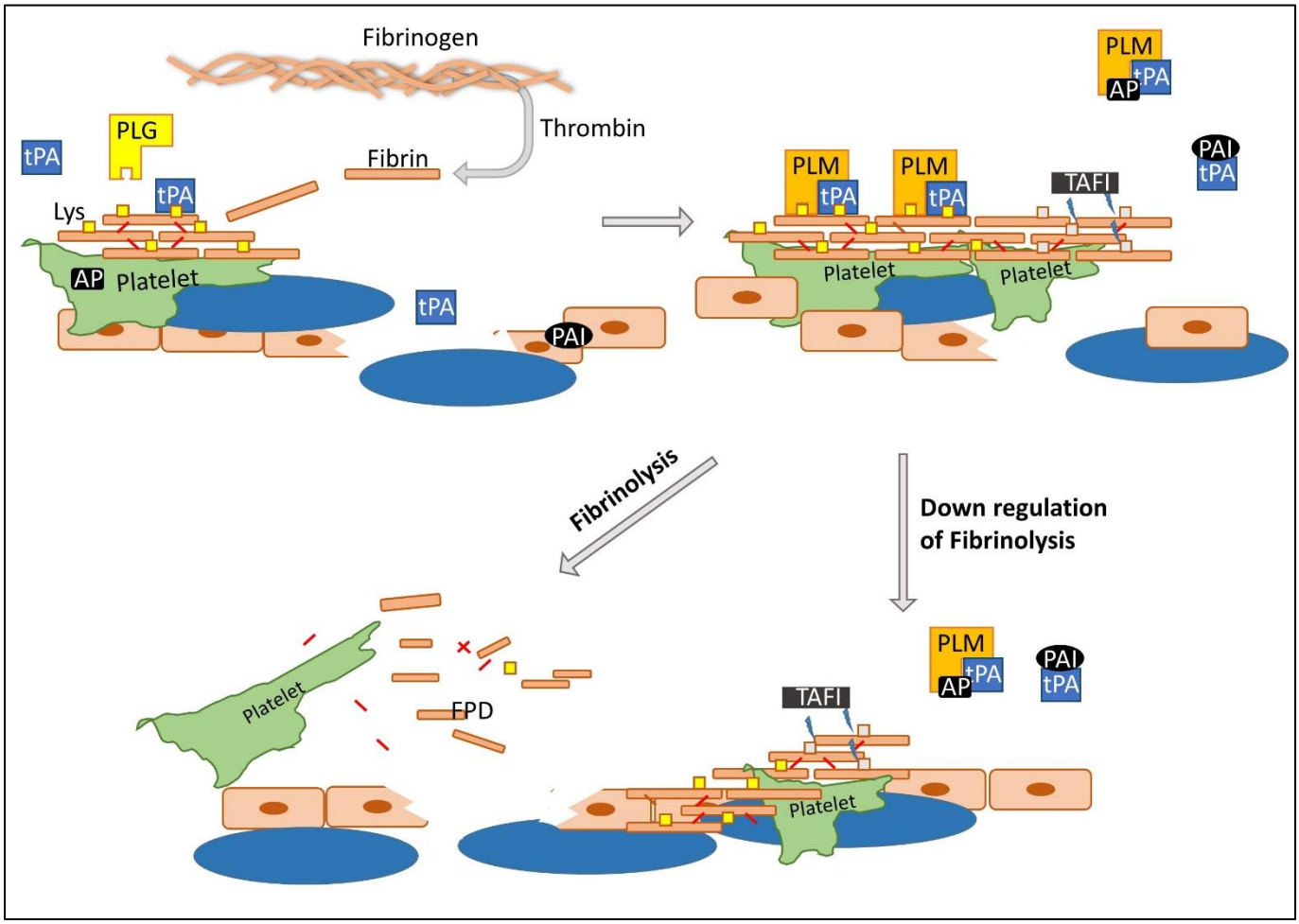
Tranexamic acid (TXA) reduces surgical blood loss and decreases deaths from bleeding in trauma patients.[8,9] It is more effective when given early and every 15 minutes of treatment delay decreases treatment effectiveness by around 10%.[10] Consequently, clinical guidelines recommend the use of TXA as soon as possible for trauma patients who are bleeding or at risk of significant haemorrhage.[11] However, early identification of traumatic bleeding is challenging. Indeed, identification of the source of bleeding is a major part of hospital management. A definitive diagnosis can take up to 1 hour, even in the best trauma systems. Unfortunately, many trauma patients who might benefit from TXA are either not treated or not treated soon enough.[12] The purpose of this thesis is to determine who should be treated, when and where.

Chapter I – Literature review

1. Fibrinolysis

The dissolution of polymerized fibrin chains was first described by Dastre in 1893 and named “fibrinolysis”. Fibrinolysis is a permanent process that is believed to prevent unnecessary intravascular accumulation of fibrin and facilitate blood clot dissolution. In 1946, Macfarlane et al. recognized the roles of plasmin, plasminogen and anti-plasmin in fibrinolysis.[13] Endothelial cells release tissue plasminogen activator (t-PA) in response to tissue damage and other factors, such as thrombin, adrenaline, histamine, vasopressin and physical exercise (Figure 1).[14] Plasminogen is released from the liver into the plasma. In the clot, plasminogen binds to fibrin and is converted to plasmin by t-PA. The complex t-PA-plasmin binds to fibrin by fixation to the lysine binding sites on the fibrin chain. Here, the active enzyme plasmin lyses the fibrin clot, releasing fibrin degradation products and D-dimers. This system is down-regulated by many factors and cofactors. Plasminogen activator inhibitor 1 (PAI-1) is released by endothelial cells and platelets. PAI-1 binds to t-PA, which forms a stable t-PA/PAI-1 complex. PAI-1 inhibits fibrinolysis by preventing t-PA from binding to plasminogen and fibrin. Alpha-2 anti-plasmin is a constituent of platelet granules and is the principal inhibitor of plasmin in the circulation. The thrombin-thrombomodulin complex activates thrombin activatable fibrinolytic inhibitor (TAFI), which removes lysine residues from the fibrin chain.

Figure 1-1 Fibrinolysis system



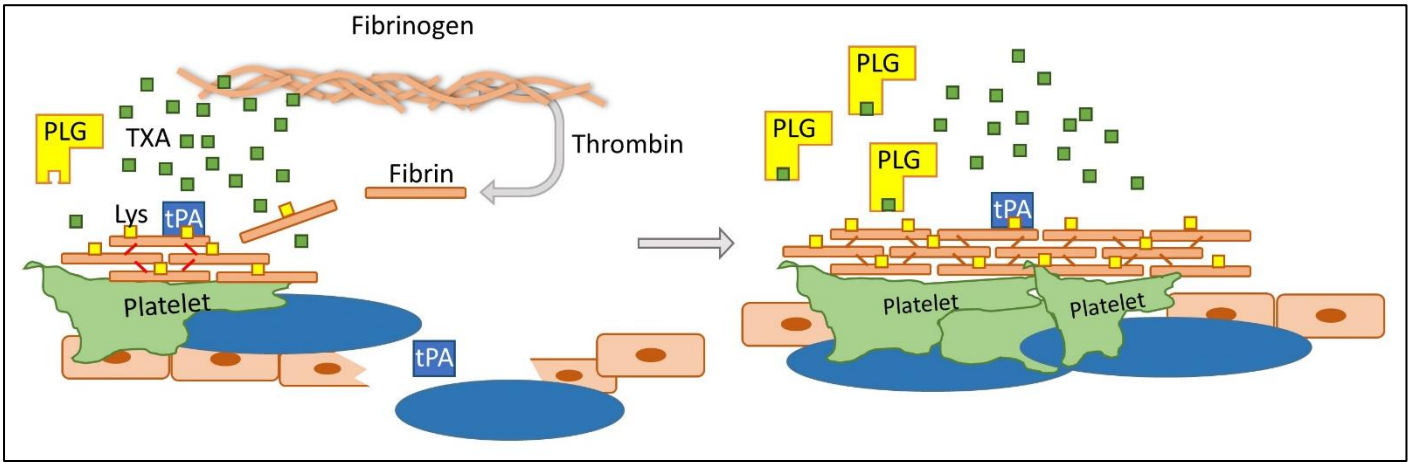
FDP: fibrin product degradation; Lys: lysine residue; PLG: plasminogen; PLM: plasmin; PAI-1: plasminogen activator inhibitor 1; AP: alpha-2 anti-plasmin; TAFI: thrombin activable fibrinolysis inhibitor; t-PA: tissue plasminogen activator.

2. Mechanism of tranexamic acid (TXA)

Fibrinolysis in bleeding and trauma has been studied since the 1950s. In 1964, Innes et al. suggested that a breakdown in the regulation of fibrinolysis might lead to “irreversible shock”. In the late 1950s, Shosuke and Utako Okamoto, a Japanese husband and wife research team, developed the antifibrinolytic drug TXA to treat postpartum haemorrhage (PPH).[15,16] TXA is a synthetic analogue of the amino acid lysine and inhibits plasmin formation by binding to the lysine site of plasminogen (Figure 2).[17] It prevents plasminogen binding to fibrin and inhibits plasminogen

activation to plasmin.[18,19] TXA enhances clot stability during clot formation and when thrombin generation is impaired.[20] D-dimer and viscoelastic assays have confirmed that TXA decreases fibrinolytic activity, thereby increasing clot firmness and stability.[20,21] TXA might therefore be considered as a clot stabiliser.

Figure 1-2 Mechanism of action of TXA



Lys: lysine residue; PLG: plasminogen; t-PA: tissue plasminogen activator.

Some authors have highlighted an anti-inflammatory mechanism of TXA as a potential explanation of the observed benefit. Plasmin is involved in the inflammatory cascade.[22] Plasmin activates complement proteins C3 to C5 and is involved in cytokine production.[23] TXA, as a plasmin inhibitor, may downregulate the inflammatory response observed in haemorrhagic shock in animal studies.[24] In clinical practice, TXA was shown to decrease inflammatory response, with decrease of expression of cytokines, in cardiac surgery.[25,26] In trauma, in-vitro and animal studies confirm that TXA reduces the inflammatory response observed in shock.[27,28] However, because the main effect of TXA is to reduce early death due to bleeding, preventing exsanguination seems to be the primary mechanism of action.[29]

3. TXA effectiveness and safety

3.1 TXA effectiveness

More than 100 randomised trials have studied the effectiveness of TXA in different settings from hereditary bleeding disorders, heavy menstrual bleeding and nose bleeds to surgery.[18,19] TXA reduces blood loss in surgery.[9] Cardiac and orthopaedic surgery have been particularly well studied.[30,31] In acute bleeding, TXA reduces death due to bleeding in trauma and postpartum haemorrhage (PPH).[8,32] The CRASH-2 trial is the largest clinical trial conducted in bleeding trauma patients and included 20,127 patients with or at risk of significant haemorrhage from 40 countries.[8] The trial showed a significant reduction in death due to bleeding with TXA. More recently, another randomised trial assessed the role of prehospital TXA in bleeding trauma patients. The STAAMP trial included 903 patients and showed a relative reduction in 30-day all-cause mortality of 20%. Although the result was imprecise and not statistically significant at $p<0.05$, it was consistent with the results of the CRASH-2 trial.[33] The authors observed a larger and statistically significant reduction of 40% of the risk of death in favour of TXA for patients treated within 1 hour of injury and in those with severe shock (SBP <70mmHg). The PATCH trial is an ongoing randomised trial assessing TXA in traumatic haemorrhage in the prehospital setting and is still recruiting.[34] This trial plans to recruit about 1000 trauma patients. Although there are several retrospective observational studies assessing TXA in traumatic haemorrhage, many have small sample sizes and are vulnerable to confounding, which limits their usefulness. Apart from traumatic haemorrhage, the effectiveness of TXA has been assessed in patients with traumatic brain injury (TBI). The CRASH-3 trial included 12,737 TBI patients

from 175 hospitals in 29 countries. TXA reduced the risk of head injury-related death, mainly in patients with mild to moderate head injury. Further analyses have shown that TXA reduces deaths on the day of the injury in mild, moderate and severe head injury. However, due to dilution from deaths unaffected by TXA treatment, there is a smaller reduction of deaths at 28 days in severe TBI.[35,36] In non-traumatic acute bleeding, the WOMAN trial showed that TXA reduced death due to bleeding for PPH.[37] In primary intracerebral haemorrhage, the TICH-2 trial showed that TXA reduced early deaths, haematoma expansion and serious adverse events, but failed to decrease the primary outcome of function outcome at day 90.[38] The HALT-IT trial found no evidence that TXA reduces death from gastrointestinal bleeding.[39]

3.2 Adverse events of TXA

Minor adverse events including hypersensitivity reactions, itching, skin rash, double or blurred vision, nausea, diarrhoea and vomiting have been reported as potential side-effects in pharmacovigilance reports. However, large randomised double-blind placebo trials of TXA did not observe any increased risk of such adverse events.[31,32] An increased risk of seizures was observed in trials using a high dose of TXA, especially in cardiac surgery and gastrointestinal bleeding.[40,41] Although an increase in vascular occlusive events might be expected with TXA, there is no evidence of any increase of these events in large randomised trials.[8,30,35,37,38,41–43] One large study, the HALT-IT trial, reported an increase of deep venous thrombosis and pulmonary embolism.[39] The authors suggested that the high dose and longer duration of treatment compared to other trials in acute bleeding might explain the increased risk of non-fatal venous thrombotic events. In trauma, controversy has been raised by some North American authors over the wide

use of TXA based on uncertainty about the fibrinolysis biological mechanism and the theoretical increased risk of vascular occlusive events.[44] Based on small retrospective observational studies or expert opinions, these studies failed to provide any significant scientific evidence.[45–47] Indeed, randomised trials of TXA in trauma patients have not found evidence of any increased risk of thrombosis.[8,33,35,48]

4. Influence of time to treatment

Coagulation and fibrinolysis appear to happen at the same time. In normal conditions, fibrinolysis and coagulation are balanced by their own regulation systems.[49] Wu et al. showed that t-PA, plasminogen, plasmin and d-dimer rise rapidly in the blood 30 minutes after polytrauma in the rat.[50] The rise of plasmin activity reaches a maximum at 1 hour, suggesting that fibrinolysis occurs soon after trauma. Levels of PAI-1 start to increase in the plasma from about 2 hours and reach a maximum at 4 hours. TAFI does not seem to initially affect plasmin activity as its blood concentration does not change after trauma. The immediate rise of plasmin activity with a late release of its inhibitors suggests that fibrinolysis is maximal in the first few hours after injury and decreases over time. Observational studies in trauma patients show that coagulation disorders occur soon after the onset of injury.[51,52] In keeping with these biological results, an exploratory analysis of the CRASH-2 trial shows that early treatment is more effective.[53] An individual patient-level data (IPD) meta-analysis on the effect of treatment delay of antifibrinolytics showed that every 15 minutes of treatment delay decreased its effectiveness in reducing death due to bleeding by approximately 10% with no benefit after 3 hours since the onset of bleeding.[10] These results suggest that TXA is best seen as an intervention to prevent bleeding, rather than a treatment for severe haemorrhage. An experimental

study in rats with polytrauma and haemorrhage and *in vitro* human blood assessed the effect of TXA administration prior to trauma or at 45 minutes following bleeding onset.[21] TXA administration prior to trauma showed more inhibition of systemic fibrinolysis than TXA administered at 45 minutes. This study confirmed the competitive mechanism of action of TXA on the plasmin lysine binding site. The maximum competitive inhibition of plasmin by TXA has to start prior to clot initiation as plasmin activity starts immediately. These observations in rats might explain the effectiveness of TXA in clinical trials in elective surgery and confirmed that TXA is preventive rather than curative. The authors concluded that TXA administration 45 minutes after trauma will not reverse established severe coagulopathy, but it is beneficial for the stabilization of the clot at the local wound. This biological mechanism emphasises time to treatment as a key issue observed in acute bleeding trials.

5. Influence of dose regimen and route

The CRASH-2 trial used an intravenous bolus of 1 gr over 10 minutes followed by an infusion of 1 gr over 8 hours. The choice of the dose was based on studies in cardiac surgery and the need for a fixed dose in emergency situation.[54,55] Fiechtner et al. showed that a dose of 10 mg/kg followed by an infusion of 1 mg/kg/hour was sufficient to inhibit fibrinolysis in-vitro. Horrow et al. showed that the same dose reduced bleeding in extra-corporeal circulation and that higher dose did not provide any additional benefit. Recently, two trials in trauma have used alternative TXA dose regimens. The STAAMP trial used three different dose regimens: (1) 1 gr bolus (abbreviated regimen); (2) 1 gr bolus followed by 1 gr over 8 hours (standard regimen); (3) 2 gr bolus followed by 1 gr over 8 hours (repeated bolus regimen).[33]

Rowell and al. in a clinical trial in traumatic brain injury used two dose regimens: the standard of 1 gr bolus followed by 1 gr over 8 hours, and a bolus only regimen with 2 gr.[48] Neither of these small trials provides reliable evidence to compare the different dose regimens of an initial bolus of 1 gr versus 2 gr. All trials in the emergency setting used the intravenous route for TXA administration. However, TXA is well tolerated and rapidly absorbed after intramuscular injection reaching therapeutic plasma concentration within 15 minutes in shocked trauma patient.[56] Intramuscular route makes it use easier for paramedics in prehospital and may increase the number of patient treated.

6. Trauma guidelines and existing strategies for using TXA

After the publication of the CRASH-2 trial, trauma guidelines recommended the use of TXA in trauma. Table 1 summarises TXA trauma guidelines in different countries. Most guidelines recommend TXA as soon as possible in trauma patients with or at risk of significant haemorrhage. However, guidelines do not recommend the use of TXA beyond 3 hours. In Europe, guidelines recommend treatment of all patients at risk of significant bleeding. In North America, some guidelines limit the use of TXA to when the massive transfusion protocol is activated. The World Health Organization (WHO) has published a model List of Essential Medicines since 1977, with the inclusion of TXA since 2011.[57]

Table 1-1 TXA trauma guidelines

	Who	When	Where
EUROPE			
European (Task Force for Advanced Bleeding Care in Trauma) [11]	Patient who is bleeding or at risk of significant haemorrhage (Grade 1A)	As soon as possible Within 3 hours	En route to the hospital (Grade 1C)
UK (National Institute for Health and Care Excellence) [58]	Major trauma	As soon as possible (do not use after 3 hours)	Prehospital and hospital
USA			
American College of Surgeons Trauma Quality Improvement Program [59]	Patient with massive transfusion protocol only	Within 3 hours	Hospital
American College of Surgeons, American College of Emergency Physicians, National Association of EMS Physicians [60]	Patient with non-compressible bleeding and HR >120 bpm and SBP <90 mmHg	Prehospital, but TXA use should never supersede field bleeding control techniques, rapid transport or blood-plasma administration	
AFRICA			
South Africa (Western Cape Emergency Care) [61]	Patient who is bleeding (SBP <90 or HR >110) or at risk of significant haemorrhage (ISS ≥9)		
Military use			
US Army (2011) (Joint Trauma System- Committee on Tactical Combat Casualty Care [62]	Casualty anticipated to need significant blood transfusion	As soon as possible, no later than 3 hours post-injury	Battlefield
British Army (2010) [63]	All casualties	As soon as possible	Battlefield
French Army (2011) [64]	All casualties	As soon as possible, Within 3 hours	Battlefield
Israeli Army (2011) [65]	All casualties	As soon as possible	Battlefield

SBP: systolic blood pressure; HR: heart rate; ISS: Injury Severity Score.

CHAPTER II – Research question and methods

1. Rationale

Clinical guidelines recommend the early administration of TXA in trauma patients with or at risk of significant bleeding, based on the inclusion criteria of the CRASH-2 trial. The CRASH-2 trial was a pragmatic randomised trial that used simple physiologic criteria and clinical judgment at hospital admission. There is no definition of "significant bleeding" and who is at risk. Inevitably, different interpretations and different treatment strategies have been adopted in different countries. The UK and most European countries recommend giving TXA as soon as possible after injury in the prehospital setting for patients with significant bleeding (Table 1). US guidelines recommend TXA administration in hospital and only when severe bleeding is confirmed (i.e. with massive transfusion protocol activation). As uncertainty exists about who to treat, paramedics and physicians have to decide for themselves for each individual patient. As a result, TXA is not sufficiently used or used too late. Only 10% of major trauma patients included in the UK Trauma Audit Research Network (TARN) received TXA in 2016.[12] Prehospital use of TXA is even lower with only 5% of trauma patients treated. The Department of health in England provides financial incentives for each trauma patient treated with TXA who also received blood transfusion (a proxy of significant bleeding). Sixty-nine percent of trauma patients requiring blood transfusion were treated with TXA, suggesting that the decision to treat is strongly influenced by reimbursement incentives. By contrast, trauma patients with a low risk of significant bleeding were not treated (less than 5%).[12] Similar results were observed in Europe, Africa and North America.[61,66,67]

Some barriers for TXA implementation can be identified. First, the extent to which the effectiveness of TXA varies by baseline risk has not been studied. A consensus seems to exist to treat trauma patients presenting with obvious signs of bleeding and a high risk of death due to bleeding. On the other hand, treatment for low-risk trauma patients is not considered by many clinicians and the effectiveness of TXA in these patients remains unknown. Second, the identification of bleeding in trauma patients can be challenging. Clinicians often use a systolic blood pressure (SBP) <90 mmHg, pulse character, and mental status as indicators of bleeding. These parameters are included in the advanced trauma life support (ATLS) classification of blood loss, but show poor discrimination.[68] Haemorrhage with hypovolemia does not necessarily result in a reduced haemoglobin concentration at hospital admission.[69] Thus, trauma guidelines recommend the use of point-of-care ultrasonography and whole-body computed tomography for the initial assessment and identification of a potential source of bleeding.[11] Clinical examination, imaging studies, laboratory tests and coagulation assays take up to 1 hour after hospital admission in experienced tertiary hospital and lead to a delay in the confirmation of bleeding and TXA administration. A number of trauma scores predicting traumatic haemorrhage have been developed.[70–75] However, these scores did not predict death due to bleeding, but rather transfusion requirements and coagulopathy. Of note, all of these scores were developed and validated in the same population and setting and lack external prospective validation. Proxies for death due to bleeding, such as massive transfusion or coagulopathy, suffer from problems of survival bias and outcome misclassification and there is currently no accurate tool to determine the risk of significant haemorrhage in the prehospital setting.

2. Objectives

The purpose of this thesis is to determine who should be treated with TXA, when and where. I have assessed the health impact of TXA treatment according to different treatment strategies and the target trauma population with the aim to develop a tool to identify patients at risk of significant bleeding and to propose rule for decision-making for TXA administration.

3. Methods

First, to assess TXA effectiveness by baseline risk, I developed a prognostic model predicting traumatic death due to bleeding. By using two large trauma databases, i.e. the CRASH-2 trial and the Northern French Alps trauma registry, I included 23,430 trauma patients admitted to hospital within 3 hours since the injury in 40 countries worldwide. Multivariate regression with random effects by country was used to identify predictors of death due to bleeding. Model performance was assessed in terms of discrimination and calibration. I performed internal validation to estimate the optimism of the model in 200 bootstrapped samples and conducted an internal-external validation with a cross-validation procedure by country to assess heterogeneity of performance indicators.

Second, I assessed TXA effectiveness according to baseline risk and conducted an IPD meta-analysis including large randomised trials of antifibrinolytic drugs. I included any randomised trial with more than 1000 patients with acute bleeding that assessed antifibrinolytic drugs between January 1, 1946 and July 5, 2018 (registered in PROSPERO, no. 42016052155). Three reviewers independently extracted data. Trials recruiting patients with acute bleeding at the time of randomisation were selected. Patients randomised more than 3 hours after bleeding onset were

excluded. I estimated the baseline risk of death due to bleeding separately for each trial and used the prognostic model developed previously for trauma. As there were no suitable prognostic models for PPH, I developed a prognostic model based on the same methodology. I assigned patients to four baseline risk categories of death due to bleeding: 0-5% (low); 6-10% (intermediate); 11-20% (high); and >20% (very high). All analyses were done on an intention-to-treat basis. I tested the homogeneity of treatment effect across these risk categories using the χ^2 test. The treatment effect within categories of the baseline risk were reported with crude risk ratios and 95% confidence intervals (CI). The homogeneity of the treatment effect between trials and by time to treatment was tested. I reported the P-value for the interaction term between treatment and baseline risk and plotted treatment effects with odds ratios (OR) according to the baseline risk as a continuous variable.

Third, using the results assessing the TXA treatment effect by baseline risk and by time to treatment, I assessed the health consequences of using TXA in patients included in a large trauma registry in England and Wales (TARN). I developed a simple clinical score (Bleeding Audit and Triage Trauma score [BATT]) based on the prognostic model predicting death due to bleeding previously developed and validated. External validation of The BATT score was performed using data from the UK TARN. This score allowed me to stratify the baseline risk of death due to bleeding in trauma patients both prehospital and in-hospital. Then, I assessed two different TXA treatment strategies: (1) prehospital treatment of all trauma patients at the scene of the injury with an ISS ≥9; and (2) hospital treatment of all trauma patients at hospital admission with an ISS ≥9. I modelled the net benefit of TXA treatment as the number of deaths avoided by TXA, including treatment effect interaction with time to treatment and baseline risk. Finally, I compared each treatment strategy according to

different thresholds of the BATT score to assess its clinical usefulness and treatment criteria.

CHAPTER III – Development and validation of a prognostic model predicting death due to bleeding

1. Introduction

Guidelines recommend TXA treatment for trauma patients with significant haemorrhage.[11] Many trauma patients who might benefit from TXA are either not treated or not treated soon enough. Trauma patients with a high risk of death are more likely to be treated than those with a low risk of death.[12] Early identification of traumatic haemorrhage is challenging. Because bleeding is the leading cause of preventable death, trauma system are dedicated to identify the source of bleeding.[6,11,76] Most of the injured patients did not present obvious bleeding. Identification of bleeding by ultrasonography and computed tomography takes time and may delay TXA administration. Given the lack of clear treatment criteria in guidelines, clinicians are more likely to treat trauma patients with obvious bleeding. Furthermore, the extent to which the effectiveness of TXA varies by baseline risk is unknown and the benefits of treating ‘low’ risk patients is uncertain.

Prognostic models can estimate the risk of death for each patient and allow to stratify a population by their baseline risk. A valid prognostic model is needed to assess TXA effectiveness by baseline risk. Prognostic models that identify patients at risk of death due to bleeding can be useful for trauma triage or trauma audit. To address this issue, I developed and validated a prognostic model to predict the risk of death due to bleeding based on information available at the first clinical assessment.

2. Methods

2.1 Study population

I used data from the following two large multicentre studies to develop a widely applicable prognostic model for death due to bleeding in trauma patients: an international randomised trial (the CRASH-2 trial) and the Northern French Alps Trauma registry.[8,77]

The CRASH-2 trial included patients from 274 hospitals in 40 countries from 2005 to 2010. Patients with or at risk of significant bleeding within 8 hours of injury were included. Since TXA is effective only within 3 hours of injury, I excluded patients treated beyond 3 hours.

The Northern French Alps Trauma Registry is part of the Northern French Alps Trauma system (TRENAU) and includes 24 hospitals, 16 prehospital mobile intensive care units from three emergency medical service systems. Patients with major trauma according to the triage rules of the American College of Surgeons were included from 2009 to 2016.[78] I excluded patients with cardiac arrest at the scene of the injury.

The CRASH-2 trial was approved by ethics committees in all participating hospitals and by the London School of Hygiene and Tropical Medicine. The Northern French Alps Trauma Registry was approved by the ethics committee of the University Hospital of Clermont-Ferrand, Clermont Ferrand, France.

2.2 Outcome and variable selection

The primary outcome was in-hospital death due to bleeding within 28 days. In the CRASH-2 trial, the responsible clinician recorded the cause of death. In the Northern

French Alps Registry, two trauma surgeons and two emergency physicians reviewed the records of all patients who died to determine the cause of death. I selected potential predictors from the CRASH-2 trial data collected before randomisation. I focused on data available in the prehospital setting or on hospital admission in the Northern French Alps Trauma Registry. These data included demographic characteristics (age, sex), physiological parameters (SBP, heart rate [HR], respiratory rate, Glasgow Coma Scale [GCS]) and the mechanism of injury (blunt or penetrating). All variables could be assessed at the first clinical assessment and were available in hospital records. Physiological variables were the first measure recorded, either in prehospital or at hospital admission. Physiological variables were measured prehospital in the Northern French Alps Registry and at admission for the CRASH-2 trial. I also included treatment by TXA and country income level (high-, middle- or low-income). Treatment by TXA was included in the equation for statistical adjustment. The coefficient for TXA treatment was constrained in the model equation to obtain a prediction before treatment at the first clinical assessment. Therefore, I used the entire dataset and not only the placebo arm of the CRASH-2 randomised trial. I assessed the importance of each predictor with the partial R^2 statistic that estimates the variability of the outcome explained by the predictor. I developed two models. A full model that included all potential predictors and a simple model.

2.3 Model development

I used multivariable logistic regression with random effect by country to identify predictors of death due to bleeding. Continuous variables were included in the model as linear terms. I assessed any departures from linearity by plotting the risk of death against continuous variables and I added quadratic and cubic terms to the model for

all continuous variables that did show a non-linear relationship graphically. The GCS was used as a continuous variable. I used a backward stepwise method by including all variables, quadratic and cubic terms and plausible interactions between the mechanism of injury and SBP, between the mechanism of injury and GCS, and between age and SBP. I then removed, one at a time, variables for which there was no evidence of an association (P >0.05) from the Wald test. I also used the LASSO method (Least Absolute Shrinkage and Selecting Operator) to check that variable selection obtained by the ordinary least square method was similar.[79]

2.4 Model performance

I assessed model performance in terms of discrimination and calibration. Discrimination was assessed with the C-statistic and receiving operating characteristic (ROC) curve.[80] Calibration was assessed as the difference between mean observed and predicted probabilities (calibration-in-the-large) and by plotting observed outcome and predicted probabilities by decile of the predicted risk of death and with a non-parametric smooth function.[81] I estimated the calibration slope based on the linear predictor of each model. A calibration slope of 1 and an intercept of 0 indicates perfect calibration. The overall calibration was summarized by the ratio of expected and observed number of events (E/O) with an ideal value of 1.[82] A value less than 1 indicates an underprediction and a value above 1 indicates an overprediction.

2.5 Model validation

I performed internal validation to estimate the statistical optimism of the final model. I drew 200 bootstrapped samples of 23,402 patients. I developed a model in each bootstrapped sample including variable selection. I estimated the C-statistic in each bootstrapped sample and assessed the performance of each model in the original sample. Optimism was estimated as the mean of the difference between the C-statistic of the bootstrap sample and the C-statistic in the original sample. I subtracted optimism from the C-statistic of the model developed in the original sample to obtain the optimism-corrected C-statistic.

I also conducted an internal-external validation.[83–85] I performed a cross-validation procedure where I selected countries with a sample size greater than 300.[84,86] I left out one country in turn and developed models using the same predictors in the remaining countries and estimated the discrimination and calibration in the omitted country. C-statistics, calibration slope and overall calibration for each country were pooled with random effect. I assessed heterogeneity with I^2 statistics and by testing interaction between the calibration slope and country.

2.6 Missing data

There was no loss to follow-up in the CRASH-2 trial and less than 0.3% in the Northern French Alps Trauma Registry. There was between 0% and 2% missing values for predictors in the CRASH-2 trial and between 0% and 5% in the Northern French Alps Trauma Registry. I performed a multiple imputation by chained equations to fill in the missing value of predictors.[87] I generated 20 imputed datasets and imputed 2253 missing values (1.6%) for 1317 incomplete observations.

All analyses were performed using STATA software (version 14.0; Stata Corp, College Station, TX, USA) and R software (version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

I included 23,430 trauma patients in the study (13,485 in the CRASH-2 trial and 9945 in the Northern French Alps Registry; Tables 3-1 and 3-2). In both the CRASH-2 and Northern French Alps cohorts, patients were mainly men with a median age of 30 and 35 years, respectively. Patients who died from bleeding had lower SBP, lower GCS scores and higher HRs.

Table 3-1 Characteristics of the CRASH-2 patients

	Missing (%)	All patients n=13,485	Alive n=11,404	All causes of death n=2081	Death due to bleeding n=815
Age, median [IQR]	0	30 [24-42]	30 [23-41]	34 [25-46]	32 [25-45]
SBP, median [IQR]	2	90 [80-110]	95 [80-110]	80 [70-100]	77 [60-90]
HR, median [IQR]	1	106 [92-120]	105 [90-120]	112 [98-128]	116 [100-130]
RR, median [IQR]	1	22 [20-26]	22 [20-26]	24 [20-30]	24 [20-30]
GCS, n (%)	0				
3-8		2125 (16%)	1030 (9%)	1094 (53%)	360 (35%)
9-12		1784 (13%)	1451 (13%)	332 (16%)	171 (21%)
13-15		9578 (71%)	8918 (78%)	654 (31%)	360 (44%)
Penetrating injury, n (%)	0	6874 (51%)	5958 (52%)	916 (44%)	485 (60%)

SBP, systolic blood pressure (mmHg); HR, heart rate (bpm); RR, respiratory rate (bpm), GCS, Glasgow Coma Scale; IQR, interquartile range. ISS was not collected in the CRASH-2 trial.

Penetrating injury was more frequent in CRASH-2 trial patients (51%) than in the Northern French Alps (5%). Eight hundred and fifteen patients (6%) died from bleeding in the CRASH-2 trial and 102 (1%) in the Northern French Alps Trauma Registry (Table 3-3). One-half of the Northern French Alps patients had an ISS of 16 or more and three-quarters had an ISS of 9 or more.

Table 3-2 Characteristics of the Northern French Alps Registry

	Missing (%)	All patients n=9945	Alive n=9256	All causes of death n=661	Death due to bleeding n=102
Age, median [IQR]	<1	36 [22-53]	35 [22-51]	58 [31-73]	51 [31-68]
SBP, median [IQR]	3	124 [110-140]	125 [111-140]	116 [80-140]	83 [60-110]
HR, median [IQR]	4	84 [74-100]	85 [75-100]	84 [60-110]	97 [60-120]
RR, median [IQR]	4	16 [15-20]	16 [15-20]	15 [14-20]	17 [11-25]
GCS, n (%)	3				
3-8		1170 (12)	718 (8)	449 (70)	51 (52)
9-12		500 (5)	452 (5)	48 (7)	10 (10)
13-15		7984 (83)	7813 (87)	148 (23)	37 (38)
Penetrating injury	<1	554 (6)	508 (6)	45 (7)	16 (16)
ISS, mean (sd)	2	16.2 (0.12)	14.9 (0.11)	33.4 (0.61)	36.6 (1.92)
0-8		2738 (28)	2723 (30)	14 (2)	1 (1)
9-15		2480 (26)	2450 (27)	26 (4)	6 (6)
16-24		2081 (21)	2008 (22)	68 (11)	15 (15)
25-34		1778 (18)	1,453 (16)	316 (49)	36 (36)
>35		686 (7)	465 (5)	221 (34)	41 (41)

SBP, systolic blood pressure (mmHg); HR, heart rate (bpm); RR, respiratory rate (bpm), GCS, Glasgow Coma Scale; IQR, interquartile range; ISS: Injury Severity Score.

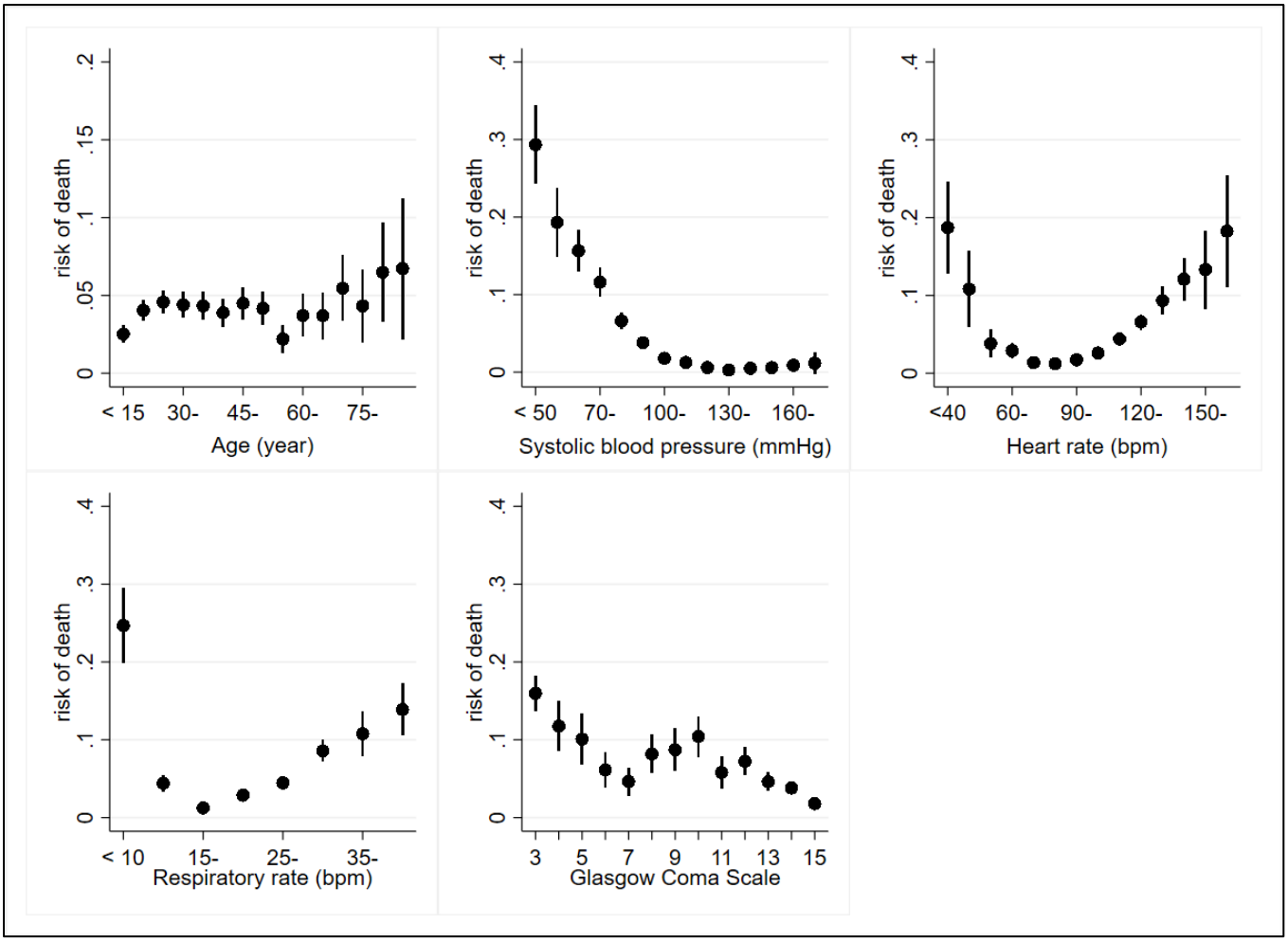
Table 3-3 Risk of death and intervention

	CRASH-2 n (%)	Northern French Alps Trauma Registry n (%)
Death due to bleeding	815 (6)	102 (1)
Overall death	2081 (15)	661 (7)
Admission in ICU	5354 (40)	4205 (42)
Surgical procedure	6608 (49)	2691 (27)
Surgical procedure for bleeding	916 (7)	1251 (12)*
Blood transfusion,	6506 (48)	1054 (11)
ICU median days [IQR]	3 [1-7]	4 [2-10]

*(including embolisation); ICU, intensive care unit; IQR, interquartile range.

Figure 3-1 shows the relationships between the potential predictors and death due to bleeding. The risk of death due to bleeding was higher with older age, lower SBP, and a lower GCS. Heart and respiratory rate showed U-shape relations. The predictors included in the full model were age, SBP, GCS, HR, respiratory rate and mechanism of injury. Sex and country income were not associated with death due to bleeding in the multivariable analysis (Appendix 3). The LASSO method gave similar results.

Figure 3-1 Relationship between death due to bleeding and potential predictors



Age, SBP and the GCS had the strongest prognostic value according to partial R^2. The models showed good discrimination with C-statistics of 0.88 (0.87 to 0.89] and 0.87 (0.86 to 0.88) for the full and simple models, respectively (Table 3-4). The calibration was good with no difference between observed and predicted death due to bleeding, except for high-risk patients (n=138) in whom the risk was overestimated above a predicted probability of 0.5 (Figure 3-2). Bootstrap resampling showed negligible model optimism of 0.0023 and gave an optimism-corrected performance that was unchanged with a C-statistic of 0.88 and 0.87 for the full and simple models, respectively.

Table 3-4 Model performance, internal and internal-external validation

	Full model		Simple model	
	Development	Internal-external validation[#]	Development	Internal-external validation[#]
	n=23,402	n=22,422	n=23,402	n=22,422
C- statistic (AUC)	0.88 (0.87-0.89)	0.85 (0.81-0.88)	0.87 (0.86-0.88)	0.84 (0.80-0.88)
Calibration-in-the-large*	<0.1	<0.1	<0.1	0.3 (0.1-0.6)
Calibration slope	1.01 (0.96-1.07)	1.07 (0.91-1.14)	1.04 (0.98-1.09)	1.12 (0.95-1.29)
E/O	1.02 (0.96-1.08)	0.93 (0.71-1.15)	0.98 (0.92-1.04)	0.91 (0.82-0.99)

AUC: area under the curve (C-statistic); E/O: expected/observed number of deaths due to bleeding.
*Calibration-in-the-large showed a difference between observed and predicted death due to bleeding.
[#]Internal-external validation based on pooled data with random effect obtained by cross-validation from 13 countries (each with n≥ 300). Every country is left out once for validation of a model based on the remaining countries.

At internal-external cross-validation, the C-statistics ranged from 0.80 to 0.94, except for India with a C-statistic of 0.72 (Figure 3-3). The pooled C-statistics were 0.85 (0.81 to 0.88) and 0.84 (0.80 to 0.88) for the full and simple models, respectively (Table 5). The pooled calibration slope was 1.07 (0.91 to 1.24) and 1.12 (0.95 to 1.29). Calibration slope and overall calibration showed heterogeneity, especially for Iraq, Georgia and Indonesia (Figures 3-4 and 3-5). I found a significant interaction between the calibration slope and country (P<0.001).

Figure 3-2 Calibration curves for model development

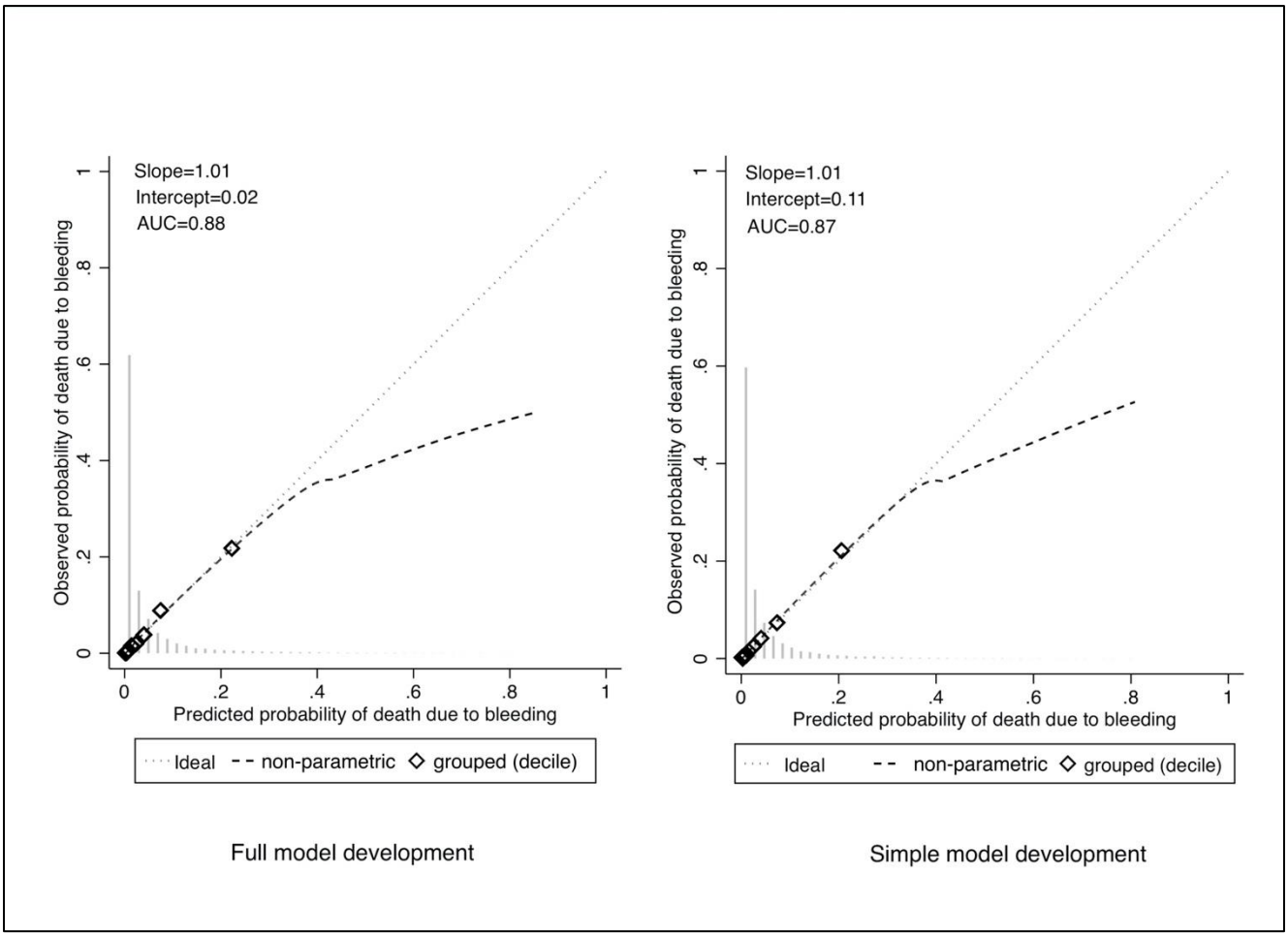


Figure 3-3 Internal-external cross-validation C-statistics by country

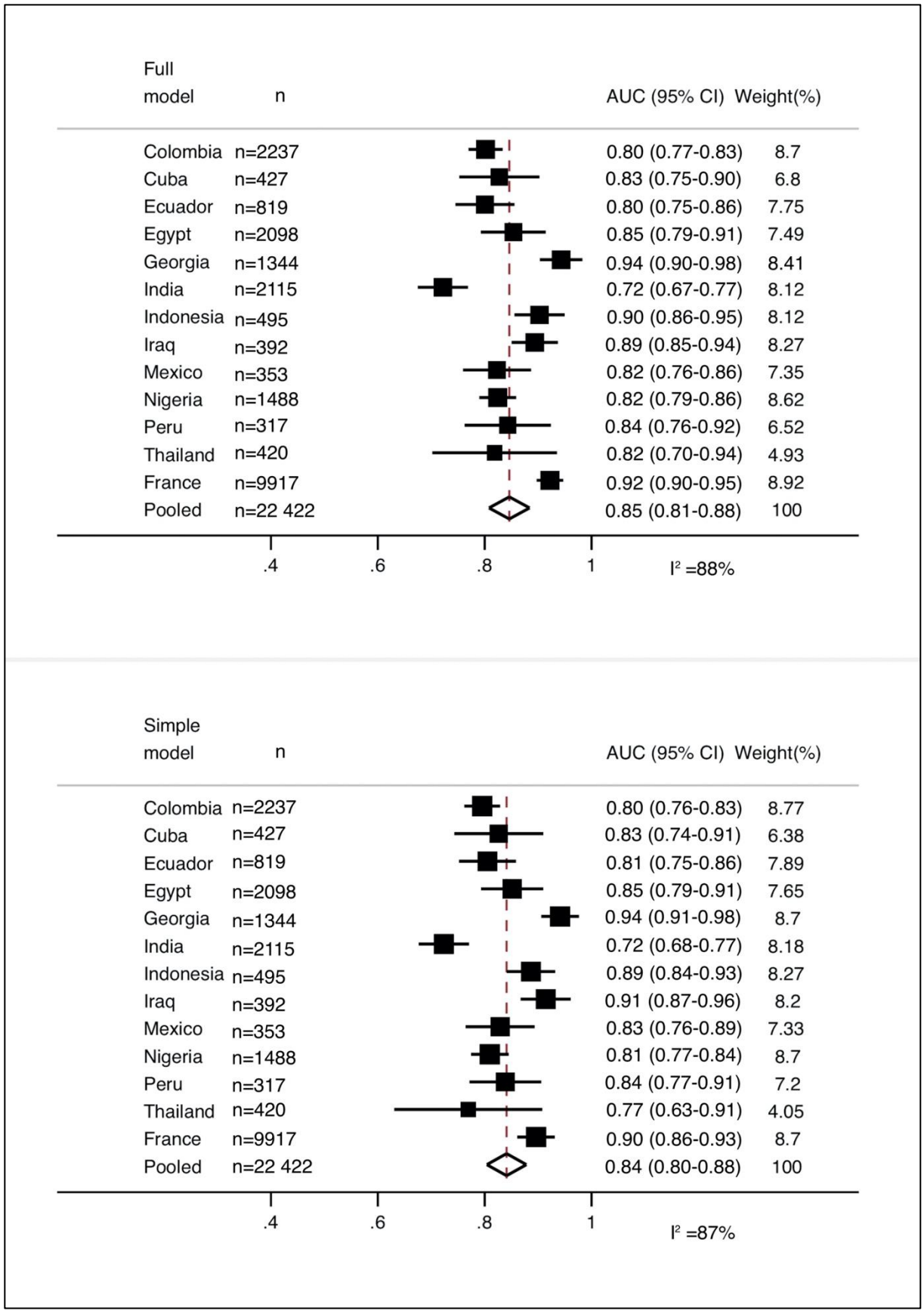


Figure 3-4 Internal-external cross-validation calibration slope by country

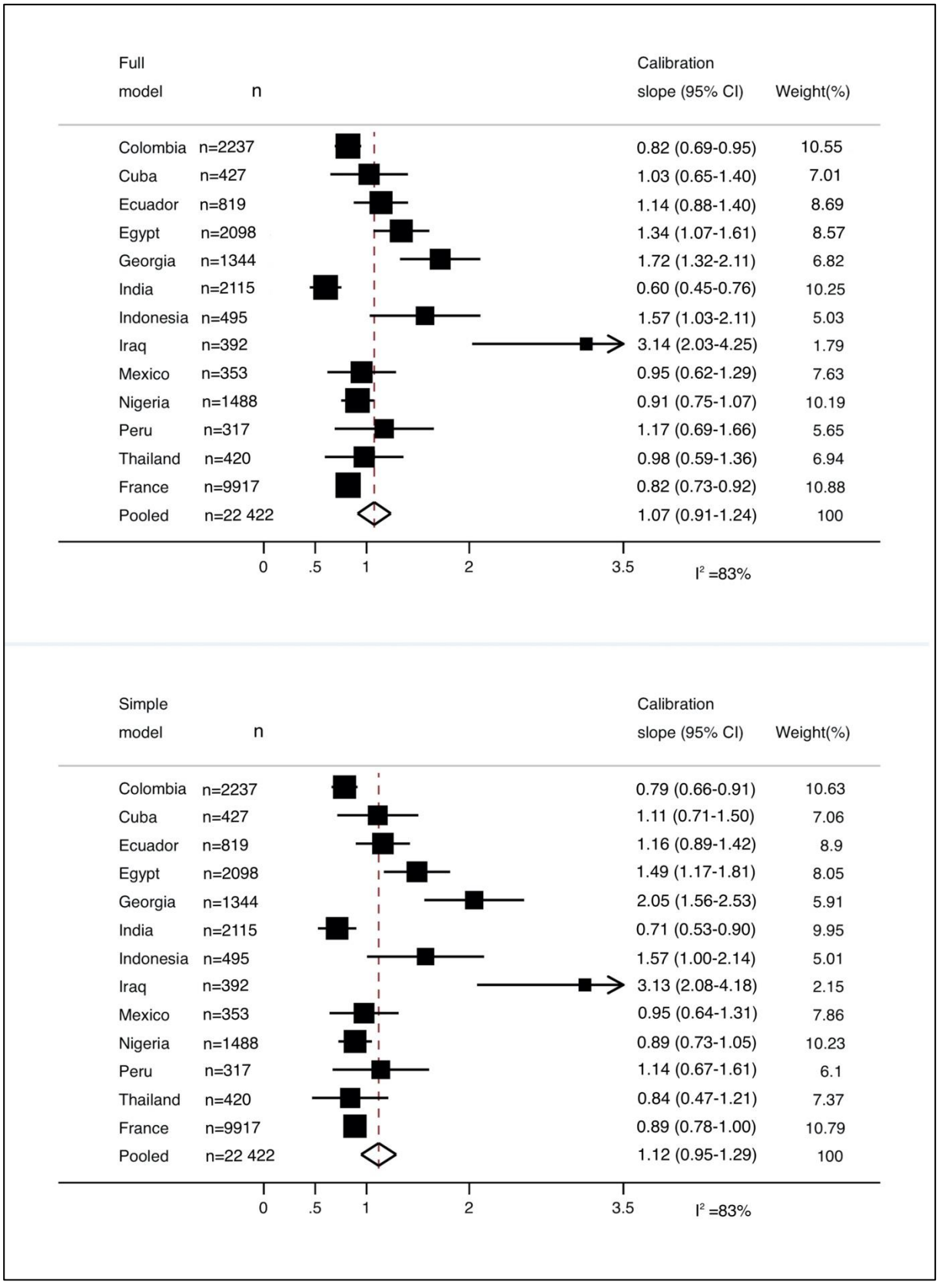
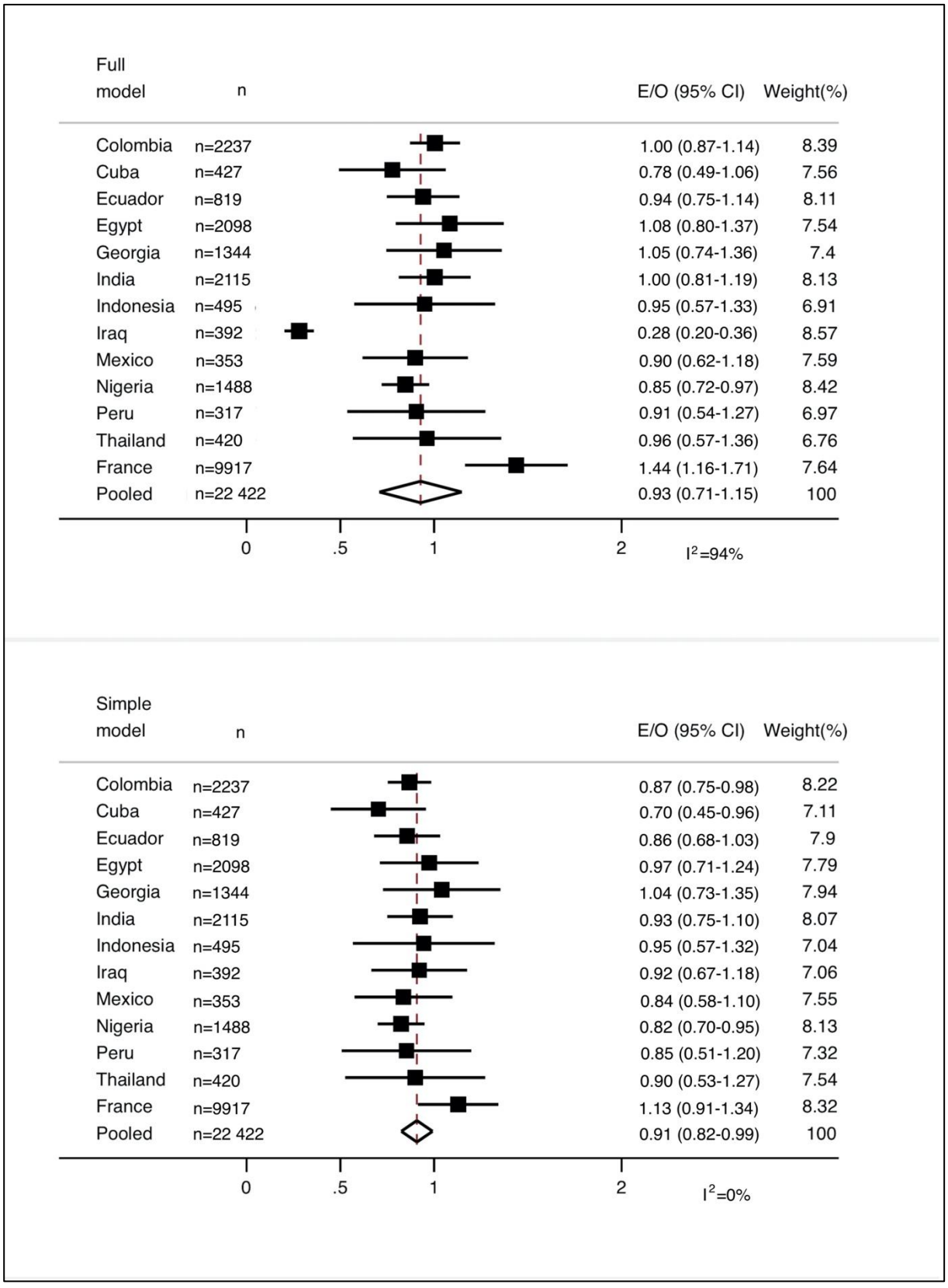


Figure 3-5 Internal-external cross-validation overall calibration E/O by country



4. Discussion

4.1 Main findings

I developed and internationally validated a prognostic model to predict death due to bleeding in trauma patients. The model showed good discrimination and calibration in a wide range of settings. By using clinical parameters that can be assessed at the site of injury and available in hospital records, I can accurately estimate the risk of death due to bleeding in a population with major trauma.

4.2 Strengths and limitations

This study has several strengths. I used data from well-described inception cohorts of bleeding trauma patients with or at risk of significant haemorrhage. Prognostic factors collected correspond to the first measure recorded after injury. Unlike previous studies, loss to follow up was minimal.[88] I used a well-defined outcome at a fixed time point after injury. These strengths helped to ensure the internal validity of the model.

I developed this model in a large international cohort with patients from 40 countries and a large trauma registry. This helps to ensure that my results are widely applicable. I did not split the data randomly or use separate derivation and validation cohorts. As the number of outcome events is the limiting factor in prognostic studies, I used the full dataset with more than 900 traumatic deaths due to bleeding to ensure accurate prediction and strengthen internal validity. Splitting the data could have led to a pessimistic and unstable estimate of performance.[89] For this reason, I did not perform split sample validation and preferred to perform internal-external cross-validation that has been recommended for assessing generalizability.[83] I also

performed bootstrapping that helps to estimate the model optimism. However, I welcome further external validation in different trauma cohorts by different authors.[90]

This study has some limitations. I cannot rule out misclassification of the outcome. Cause of death can be difficult to determine, especially for late bleeding deaths that could be confused with thrombotic, disseminated, intravascular coagulation (DIC).[91] If deaths due to DIC were misclassified as deaths due to bleeding, this might underestimate the effect of SBP, HR or respiratory rate in this model. Another limitation was the potential for the measurement error of prognostic factors. The use of a single measurement for blood pressure, rather than the average of several measurements, could lead to error and regression dilution bias.[92] The regression line between outcome and predictor is fitted in order to minimise the distance between each point and the line. The random error in the measurement of a predictor increases the distance to the regression line and underestimates the effect of the predictor by flattening the regression line.[93] This may explain the overprediction in high-risk patients. Patients with haemorrhagic shock and haemodynamic instability are more likely to have blood pressure variation and hence measurement error. This overprediction only occurred for trauma patients with a very high predicted risk of death due to bleeding (above 0.45) which represents <0.6% of the study population (n=138). In these very high-risk patients, precise quantification of the risk of death is unlikely to influence clinical decisions. On the other hand, accurate prediction is clinically important in low-risk patients, e.g. it may determine who receives TXA. Finally, I observed heterogeneity of performance across countries and noted that the discriminative ability was affected by miscalibration and case-mix.[85] The relative poor C-statistic in India could be explained by the combination of a calibration slope

<1 and a relatively homogenous case-mix. By contrast, the high C-statistic in France reflected that the Northern French Alps Trauma Registry selected a more heterogeneous case-mix population with major trauma. I acknowledge that this model is suitable for a population similar to those used in this study, such as a population with major trauma.

4.3 Study implications

Our prognostic model provides a way to identify trauma patients with or at risk of significant haemorrhage based on predicted probabilities of death due to bleeding. Quality improvement programmes could use this model to estimate the individual risk of death due to bleeding in a trauma population. Based on these predictions, trauma audit could determine a threshold for patients with “significant haemorrhage” who should be treated with TXA. The threshold used may depend on effectiveness, cost and safety considerations. According to European guidelines for the management of traumatic bleeding, TXA is supported by the highest level of evidence (Grade 1A).[94] TXA costs approximately £1 per patient and has no serious adverse effects. For these reasons, a low predicted risk of bleeding death might be used in trauma audit.

An internet application using the simple model could be developed for use in the prehospital setting. This could help paramedics decide who should receive TXA at the scene of injury. It could also be useful in prehospital triage. Some previously proposed trauma scores predict all-cause mortality or massive transfusion.[88,95,72] To the best of my knowledge, this is the only model that predicts death due to bleeding. As bleeding is the leading cause of preventable death, the model might become an essential tool to identify patients needing urgent interventions, such as damage control surgery and multi-specialised critical care. It could also help to

identify patients who need to be transported directly to a regional trauma centre or for whom the massive transfusion protocol needs to be activated before they arrive at the hospital.

A prognostic model predicting all-cause mortality was developed previously using CRASH-2 data.[96] However, traumatic deaths can result from many different pathophysiological mechanisms. For example, both high and low SBP predict death from all-causes, but only low blood pressure predicts death due to bleeding. The association of high blood pressure with all-cause mortality is likely to reflect deaths from TBI. By combining different mechanisms of death, predictions based on all-cause mortality could misclassify the risk of death from bleeding.

4.4 Future studies

These models may facilitate stratification of clinical trial populations into risk categories at baseline. The following chapters examine if and how the effect of TXA varies by baseline risk and model the health impact of different treatment strategies.

CHAPTER IV - The effect of tranexamic acid on death due to bleeding by baseline risk

1. Introduction

In the previous chapter, I developed and validated a prognostic model predicting death due to bleeding. Many guidelines, especially those for trauma, focus on the use of TXA in severely injured patients with a high risk of death from bleeding.[58,59] Although these patients have much to gain from TXA treatment, they are few in number and many die at the scene of injury.[97] As there are many more patients with less severe injuries and a lower risk of death from bleeding, if TXA was similarly effective, prompt treatment of these patients could prevent many deaths. In this chapter, I examine how the effectiveness and safety of anti-fibrinolytic drugs varies by the baseline risk of death due to bleeding.

2. Methods

2.1 Design and selection criteria

I conducted an IPD meta-analysis of randomised placebo trials conducted between January 1, 1946 and July 5, 2018. The methods and the selection criteria have been described previously.[10] The study protocol was registered in November 2016 (Prospero, no. 42016052155).[98] Any randomised trial with more than 1000 patients that assessed the effects of anti-fibrinolytic drugs (aprotinin, TXA, aminocaproic acid and aminomethylbenzoic acid) in patients with acute bleeding was eligible for inclusion. I identified trials from a permanent register of anti-fibrinolytic trials maintained by the London School of Hygiene & Tropical Medicine Clinical Trials Unit.

The register is based on searches of MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, PubMed, Popline, and the WHO International Clinical Trials Registry Platform (Appendix 4-1). Three reviewers independently extracted data. We selected trials recruiting patients with acute bleeding at the time of randomisation (treatment trials). I excluded patients who were randomised more than 3 hours after bleeding onset since previous studies have shown that anti-fibrinolytics are ineffective after this period. I prepared a statistical analysis plan before searching for trials. Patients and the public were not involved in the research.

2.2 Outcome

The primary outcome was death due to bleeding. This is the most relevant primary outcome given the mechanism of action of anti-fibrinolytic drugs. All-cause mortality includes non-bleeding-related deaths, such as sepsis, that should not be affected by anti-fibrinolytics. Given that these deaths could dilute the treatment effect, important benefits or harms could be obscured in all-cause mortality.[99] Moreover, because the relative contributions of non-bleeding deaths will vary between populations, all-cause mortality is not widely generalizable. Secondary outcomes were fatal and non-fatal vascular occlusive events (myocardial infarction, stroke, pulmonary embolism and deep venous thrombosis).

2.3 Data analysis

I evaluated the quality of included trials by assessing sequence generation, allocation concealment, blinding, data completeness and risk of selective reporting. Analysis

was IPD-based. I estimated the baseline risk of death due to bleeding separately for each trial. I used prognostic models to predict the baseline risk using multivariate logistic regression. I used the prognostic model for trauma developed in the previous chapter.[100] As there were no suitable prognostic models for PPH, I used the same method to develop a prognostic model for this condition. I only used baseline characteristics collected before randomisation as predictors. To improve the precision of our models, I included all trial participants from the treatment and placebo groups.[101] I included all potential predictors at baseline and adjusted for the use of anti-fibrinolytic drugs. I included linear and polynomial terms for continuous variables. I used a backward stepwise method and removed variables for which there was no evidence of association one at a time (p-value for the Wald test >0.05). To estimate the risk at baseline, the coefficient for anti-fibrinolytic drugs was constrained at 0 in the equation. I performed sensitivity analysis that estimated the baseline risk in the placebo arm and present the result in Appendix 4-9. The estimates would be less precise, but may avoid misclassification from assuming a constant effect of TXA. Predicted baseline risk of death due to bleeding was estimated for each trial participant in both treatment groups. For each prognostic model, I assessed performance by estimating discrimination and calibration. Discrimination represents the ability of the model to identify a patient with the outcome of interest and is evaluated by the concordance statistic (C-statistic). Calibration represents the agreement between predicted and observed risk. On the basis of the predicted baseline risk, participants were assigned to one of the four baseline categories of risk of death due to bleeding: 0% to 5% (low); 6% to 10% (intermediate); 11% to 20% (high) and >20% (very high). The categories were chosen because they were

clinically relevant, easy to understand (using a base of 5 or 10) and were consistent with previous studies.[95,102]

All analyses were done according to the intention-to-treat principle. I reported continuous variables as mean (standard deviation [SD]) and median (interquartile range [IQR]). I reported categorical variables as numbers and proportions. I plotted frequency distributions for the baseline risk in all participants and in patients who died from bleeding. I estimated the effect of anti-fibrinolytics on death due to bleeding within categories of baseline risk and provided crude risk ratios. I tested the homogeneity of treatment effect between these categories of risk using the χ^2 test. I used logistic regression to assess the effect of anti-fibrinolytics on death due to bleeding and reported treatment effects with OR and 95% CI. First, I tested homogeneity of the treatment effect between trials by including an interaction term between treatment and trial and reporting the p value (model 1, Appendix 4-2). I hypothesized that the treatment effect does not vary by baseline risk, unlike time to treatment for which treatment delay reduces the treatment benefit.[10] To verify the homogeneity of the effect of baseline risk on treatment effect by time to treatment, I performed a second model with a triple interaction between the terms for baseline risk, the treatment group, and time to treatment (model 2, Appendix 4-2). Once homogeneity of the treatment effect with baseline risk and time to treatment was verified, I ran a third model to assess homogeneity between the treatment effect and baseline risk, adjusting for trial and time to treatment (model 3, Appendix 4-2). I reported the p value for the interaction term between treatment effect and baseline risk and plotted the treatment effects with OR and 95% CI according to the baseline risk.

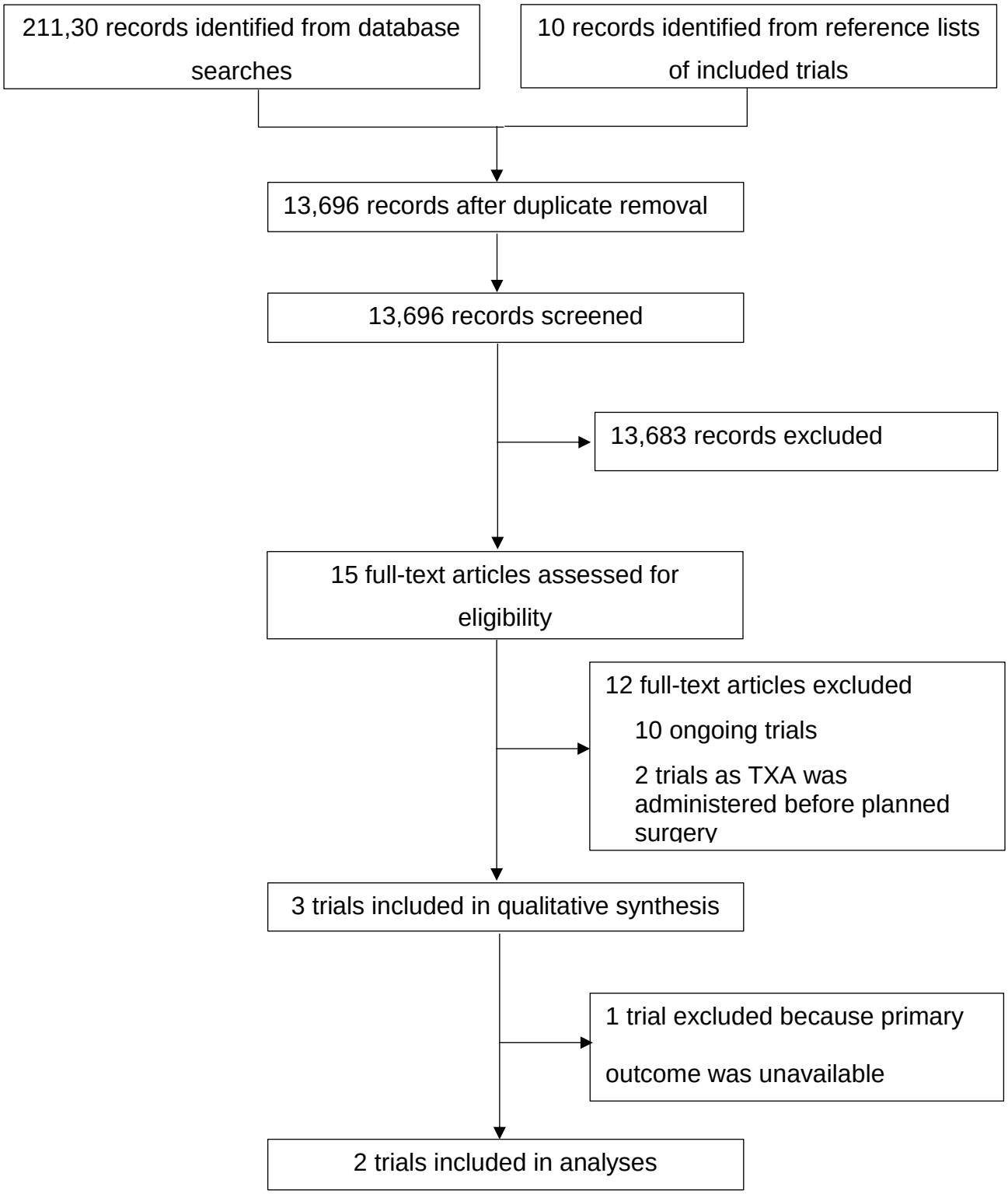
2.4 Missing values

There were no missing outcome data, but there were missing values for some predictor variables. In order to estimate baseline risks on the full dataset, I replaced missing predictors using multiple imputation with 20 imputed datasets and adjustment of the imputation model for death due to bleeding, age, SBP, respiratory rate and the GCS. All analyses were performed using STATA software (version 14.0; Stata Corp, College Station, TX, USA).

3. Results

Figure 4-1 shows the number of records identified and the reasons for exclusions. We found five completed [8,37,38,41,42] and 10 ongoing trials (Appendix 4-3).[34,103–111] All trials used TXA. Three trials met our inclusion criteria. The CRASH-2 trial included 20,211 trauma patients and assessed the effects of TXA on death and vascular occlusive events. The WOMAN trial assessed the effects of TXA on death and serious morbidity in 20,060 women with PPH. The TICH-2 trial assessed the effect of TXA on death and dependency in non-traumatic intracerebral haemorrhage. Exsanguination does not normally occur in adults with cerebral haemorrhage and death usually arises due to cerebral injuries and high intracranial pressure. The TICH-2 trial was excluded from the analysis as it did not meet the inclusion criteria. Included trials had a low risk of bias in all domains (Appendix 4-4).

Figure 4-1 Study selection



I obtained individual patient data for 28,333 participants randomised within 3 hours of bleeding onset: 13,485 from the CRASH-2 trial and 14,848 from the WOMAN trial (Table 4-1). Among these, 14,270 participants received TXA and 14,067 received placebo. Baseline risk predictors for both models are detailed in Appendix 4-5. The pooled discrimination of the prognostic models was good: C-statistic=0.88; 95% CI 0.87-0.89. The predicted risk was similar to the observed risk in the placebo group (ratio predicted/observed risk=1.00; 95% CI 0.92-1.07) (Appendix 4-6). The baseline risk was higher in trauma patients than in women with PPH. Most patients had a baseline risk <5% (Figure 4-2).

Figure 4-2 Number of patients and number of deaths according to baseline risk

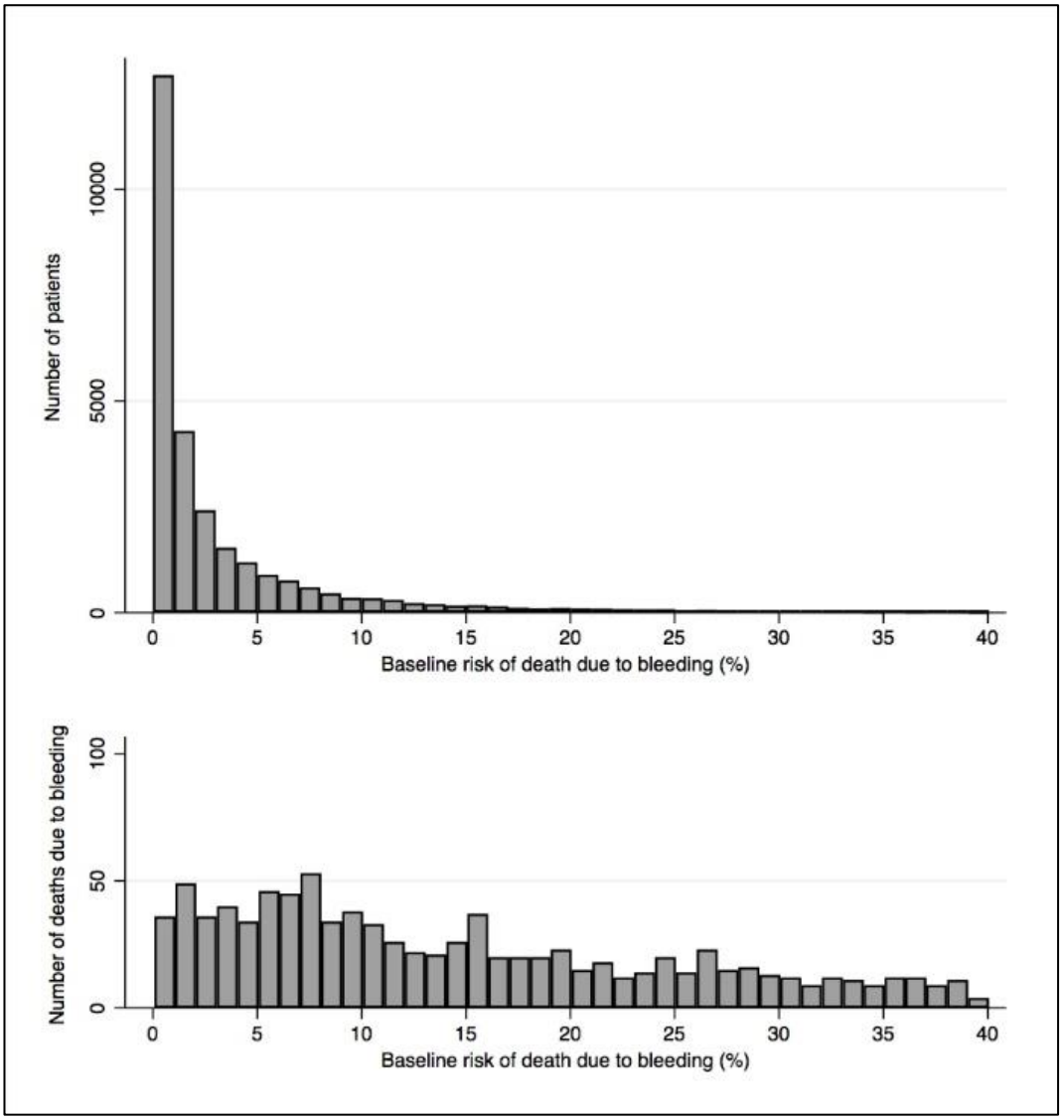


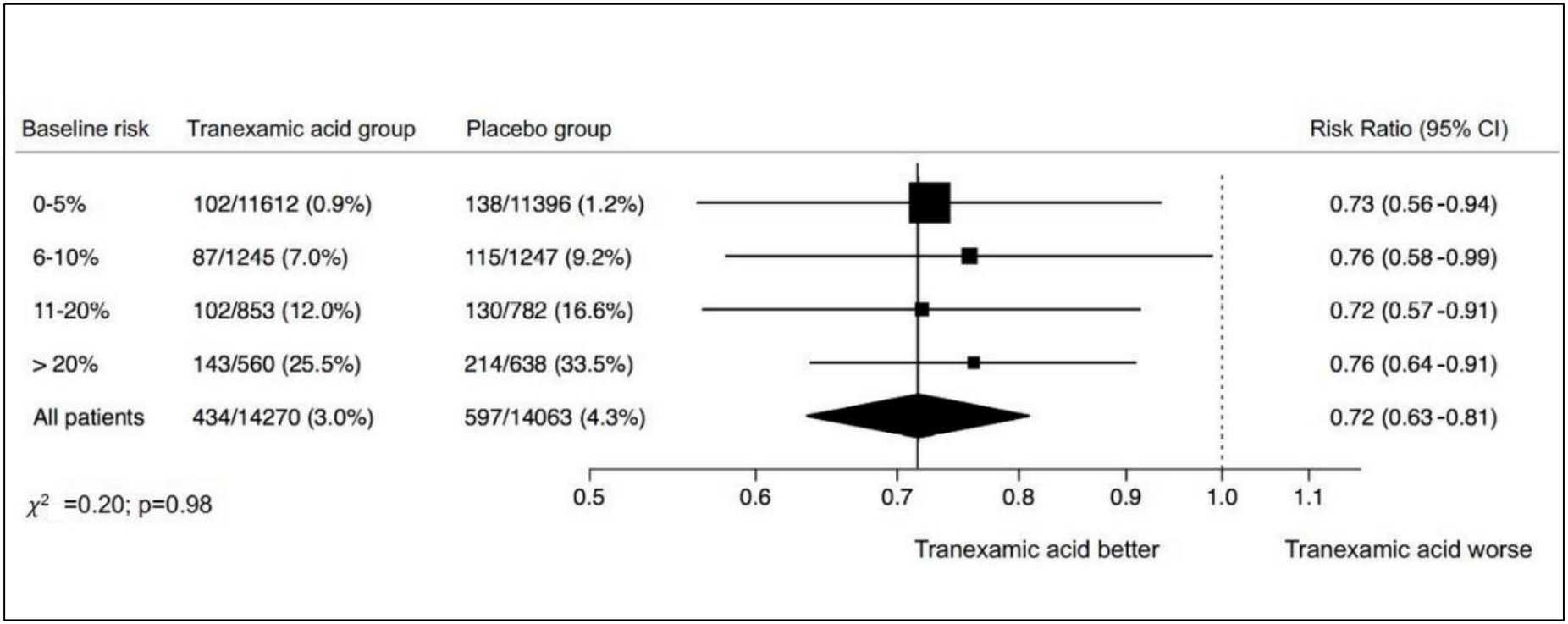
Table 4-1 Baseline characteristics of patients in participating trials

	CRASH-2 trial (n=13,485)	WOMAN trial (n=14,848)	Total (n=28,333)
Predicted baseline risk, n (%)			
0-5	9063 (67.2%)	13,945 (93.9%)	23,008 (81.2%)
6-10	2011 (14.9%)	481 (3.2%)	2492 (8.8%)
11-20	1373 (10.2%)	262 (1.8%)	1635 (5.8%)
> 20	1038 (7.7%)	160 (1.1%)	1198 (4.2%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean baseline risk (SD)	6.9 (9.5)	1.6 (4.4)	4.1 (7.7)
Median baseline risk (IQR)	3.3 (1.4-7.9)	0.4 (0.1-1.3)	1.3 (0.3-4.2)
Age (years), n (%)			
< 25	3840 (28.5)	3973 (26.8%)	7813 (27.6%)
25-29	2400 (17.8)	4590 (30.9%)	6990 (24.7%)
30-34	1792 (13.3)	3802 (25.6%)	5594 (19.8%)
≥ 35	5453 (40.4)	2478 (16.7%)	7931 (28.0%)
Missing	0 (0.0%)	5 (0.0%)	5 (0.0%)
Mean age (SD)	34.1 (14.0)	28.4 (5.7)	31.1 (10.9)
Median age (IQR)	30 (24-42)	28 (24-32)	29 (24-35)
Systolic blood pressure (mmHg), n (%)			
< 75	2074 (15.7%)	1011 (6.8%)	3085 (11.0%)
75-89	2360 (17.8%)	1563 (10.5%)	3923 (14.0%)
≥ 90	8813 (66.5%)	12,269 (82.7%)	21,082 (75.1%)
Missing	238 (1.8%)	5 (0.0%)	243 (0.9%)
Mean systolic blood pressure (SD)	96.6 (25.3)	101.5 (21.4)	99.2 (23.5)
Median systolic blood pressure (IQR)	90 (80-110)	100 (90-110)	100 (90-110)
Time to treatment (h), n (%)			
≤1	7452 (55.3%)	9220 (62.1%)	16,672 (58.8%)
1-3	6033 (44.7%)	5628 (37.9%)	11,661 (41.2%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean time to treatment (SD)	1.5 (0.8)	1.0 (0.8)	1.3 (0.8)
Median time to treatment (IQR)	1 (1-2)	0.7 (0.4-1.5)	1 (0.5-2)

SD: standard deviation; IQR: interquartile range.

Deaths due to bleeding occurred in all baseline risk categories with almost the same number of deaths due to bleeding. I reported 240 (1%), 202 (8%), 232 (14%) and 357 (30%) deaths in the low, intermediate, high and very high-risk categories, respectively. Deaths due to bleeding occurred in all categories of blood loss among women with PPH (Appendix 4-7). The effect of TXA did not vary between trials (model 1: P=0.82). I found no heterogeneity in the interaction between treatment effect, baseline risk and time to treatment (model 2: P=0.62 for the triple interaction). I did not find any significant interaction between the effect of TXA on death due to bleeding and the baseline risk (model 3: P=0.51). Figure 4-3 shows crude risk ratios by categories of baseline risk. The treatment effect did not vary by baseline risk (Figure 4-4). The risk of vascular occlusive events was similar according to baseline risk categories (Table 4-2). There was no increase in fatal and non-fatal occlusive events with TXA in any of the baseline risk categories (Appendix 4-8).

Figure 4-3 Effect of TXA on death due to bleeding by baseline risk



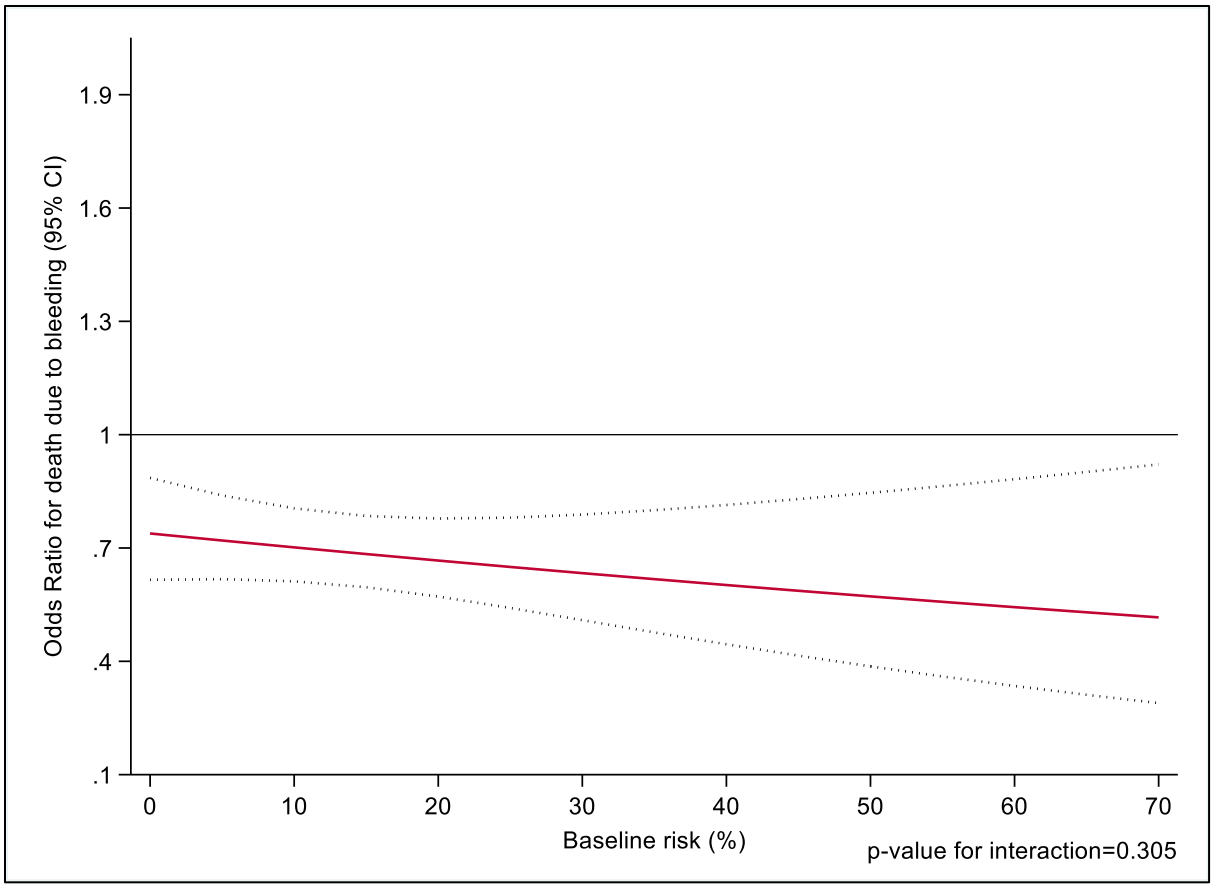
χ^2 corresponds to chi-squared test of homogeneity within-stratum weight (Mantel-Haenszel).

Table 4-2 Vascular occlusive events by treatment allocation according to baseline risk

Baseline risk	0-5%		6-10%		11-20%		> 20%		
	Tranexamic acid	Placebo	Tranexamic acid	Placebo	Tranexamic acid	Placebo	Tranexamic acid	Placebo	P value
	n=11,612	n=11,396	n=1245	n=1247	n=853	n=782	n=560	n=638	
Any vascular occlusive events	64 (0.6%)	65 (0.6%)	17 (1.4%)	22 (1.8%)	23 (2.7%)	38 (4.9%)	14 (2.7%)	27 (4.2%)	0.255
Fatal occlusive events	16 (0.1%)	15 (0.1%)	6 (0.5%)	4 (0.3%)	4 (0.5%)	14 (1.8%)	1 (0.2%)	7 (1.1%)	0.058
Myocardial infarction*	8 (0.1%)	14 (0.1%)	3 (0.2%)	7 (0.6%)	6 (0.7%)	13 (1.7%)	7 (1.3%)	12 (1.9%)	0.909
Stroke*	19 (0.2%)	14 (0.1%)	3 (0.2%)	6 (0.5%)	6 (0.7%)	15 (1.9%)	4 (0.7%)	7 (1.1%)	0.152
Pulmonary embolism*	28 (0.2%)	23 (0.2%)	6 (0.5%)	8 (0.6%)	14 (1.6%)	16 (2.1%)	6 (1.1%)	9 (1.4%)	0.739
Deep vein thrombosis*	12 (0.1%)	19 (0.2)	7 (0.6%)	2 (0.2%)	6 (0.7%)	4 (0.5%)	3 (0.5%)	5 (0.8%)	0.214

*Includes both fatal and non-fatal events

Figure 4-4 Effect of baseline risk on treatment benefit



4. Discussion

4.1 Main findings

Results show that many deaths from bleeding are in patients at low or intermediate risk and that the mortality reduction from TXA does not vary by baseline risk. I found no evidence of any increase in vascular occlusive events in any of the risk categories.

4.2 Strengths and limitations

This study has important strengths and some limitations. First, I selected only randomised trials with over 1000 patients to reduce selection bias. Small trials contribute very little evidence, but could increase the risk of selection bias.[112]

Second, I used a rigorous method to develop prognostic models to predict baseline risk.[113] Specifically, baseline risk was estimated using the entire dataset and not just the placebo group. By increasing the sample size and constraining the treatment effect in the regression equation, it improves both precision of prediction and calibration.[83] Third, I performed logistic regression with baseline risk as a continuous variable since an on-off step function is biologically implausible. There was no interaction between treatment effect, trial and time to treatment. Even though I restricted my analyses to patients treated within 3 hours of bleeding onset as recommended in clinical practice, I included trial and time to treatment in the model to avoid any residual confounding. Fourth, there were no missing outcome data and very few missing data for predictors of baseline risk (<1%). Nevertheless, I performed multiple imputation and used the whole dataset for analysis.

I cannot exclude some measurement error in the predictors used to estimate baseline risk and this could lead to regression dilution bias and over- or underprediction in some patients.[93] Misclassification of death due to bleeding is also possible as death from thrombotic DIC could be confused with death from bleeding. In addition, I cannot exclude some misclassification due to optimism of the model affecting calibration. I am reassured that optimism was low in the model developed for trauma and the selection of a limited number of predictors limits overfitting.[100,101] Finally, the large sample size with over 28,000 patients with acute bleeding treated within 3 hours of onset yields precise results. However, estimates of the effects on adverse events are much less precise. The study included data from 38 countries across several continents and thus the results should be widely generalizable to patients presenting to hospitals with PPH, as well as trauma patients with or at risk of significant haemorrhage.

4.3 Study implications

The main clinical implication of these results is that TXA treatment should be considered as an early preventive measure, rather than a treatment for severe coagulopathic bleeding. Because of the large number of patients in the low and intermediate risk groups, these groups contribute a large number of bleeding deaths. Indeed, approximately one-quarter of deaths from bleeding occurred in patients who initially appeared to have a low risk of death. Early identification of bleeding can be challenging, especially in trauma. Patients without obvious bleeding sometimes have concealed bleeding and can suddenly deteriorate. Although early identification of bleeding by a computed tomography (CT) or a focused assessment with sonography for trauma (FAST) scan is a priority, a definitive diagnosis can take up to 1 hour, even in the best trauma systems. Hence, many major trauma patients without clinically apparent bleeding will not receive TXA soon enough unless early treatment is given to all major trauma patients, irrespective of their apparent risk. Major trauma is usually defined as an injury or a combination of injuries that are potentially life-threatening or could lead to long-term disability. Given that the full extent of the patient's injuries are unknown at initial assessment, trauma team activation criteria represent a pragmatic alternative definition of major trauma in the prehospital setting. For obstetric bleeding, WHO guidelines recommend TXA in addition to standard care for all women with clinically-diagnosed PPH. However, if "in addition to" is taken to mean that TXA should be given after standard care has been found to be insufficient to stop the bleeding, this will result in an unnecessary treatment delay. Instead, we believe that early TXA treatment should be considered integral to standard care.

4.4 Future studies

I found 13 ongoing trials of anti-fibrinolytic drugs in acute severe bleeding. Three of these could provide additional data on treatment effect by baseline risk in extracranial bleeding, but these studies are small and their inclusion is very unlikely to change our conclusions. However, additional trials could increase the power to detect adverse effects. In addition, further IPD meta-analyses that consider vascular occlusive events are needed.

5. Conclusion

TXA appears to be safe and effective, regardless of the baseline risk for a patient treated within 3 hours since injury. Many deaths are in patients at low and intermediate risk and TXA use should not be restricted to the most severely injured or bleeding patients. As TXA is safe, it should be considered as an early preventive measure, rather than a treatment for severe coagulopathic bleeding.

CHAPTER V - Validation of the BATT score for prehospital risk stratification of traumatic haemorrhagic death and the health impact of tranexamic acid according to different treatment strategies

1. Introduction

TXA must be given urgently, preferably by paramedics, at the scene of the injury or in the ambulance.[11] Many bleeding deaths occur soon after injury and there is a 10% reduction in treatment effectiveness for every 15 minutes of treatment delay.[10] Paramedics need clear criteria that can be applied at the scene to guide who to treat. I previously developed a prognostic model to predict death from bleeding as detailed in Chapter III.[100] In Chapter IV, I demonstrated that the relative reduction in mortality with TXA does not vary with the baseline risk.[114] In this chapter, I show how I derived a simple score that paramedics can use at the scene to help decide who to treat with TXA. I have conducted an external validation of the score and explore different TXA treatment thresholds and strategies.

2. Method

I developed a simple score (Bleeding Audit and Triage Trauma [BATT] score) to predict death due to bleeding in trauma patients. I conducted an external validation of this score using data from the UK TARN from 1 January, 2017 to 31 December, 2018. Finally, I evaluated the impact of TXA treatment thresholds in trauma patients.

2.1 Development of the BATT score

In Chapter III, I previously developed and validated a prognostic model to predict death due to bleeding in trauma patients.[100] Briefly, data on bleeding trauma patients from 298 hospitals in 41 countries were used to derive the model. I validated the model using an internal–external cross-validation method based on data from 41 countries to ensure that the results are widely applicable. The final prognostic model included age, SBP, GCS, HR, respiratory rate and mechanism of injury. To develop the BATT score, I assigned points for each predictor that were proportional to the coefficients of the regression equation. I added the criterion of high-energy trauma as the intercept of the regression equation corresponding to the inclusion criteria of the trauma registry used for the development of the prognostic model. High-energy trauma is routinely assessed at the scene and corresponds to injury from a road traffic crash (with intrusion, ejection, death in same passenger compartment, and motor vehicle versus pedestrian or cyclist), fall from a high height (>3 metres), a blow or blast.[115] An electronic version of the score is available for computer or smartphone at: https://www.evidencio.com/models/show/1393.

2.2 Validation of the BATT score

I used data from the TARN from 1 January, 2017 to 31 December, 2018 to validate the BATT score for use in England and Wales. The TARN database includes data on patients with an Injury Severity Score (ISS) of nine or more who were admitted to hospital in England and Wales for at least three nights, died in hospital, or were transferred to another hospital for specialist care.[116] Exclusion criteria were isolated mild traumatic brain injury with loss of consciousness, superficial scalp injury, patients 65 years or older with femoral neck or single pubic rami fracture, fracture or

dislocation of the foot or hand, closed fracture or dislocation of an isolated limb, or simple skin laceration with blood loss <20%.

As death due to bleeding is not recorded in the TARN database, I used early deaths and early deaths with evidence of haemorrhage as a proxy for death due to bleeding.[117] Specifically, I included deaths from all causes within 12 hours of injury (excluding asphyxia, drowning, hanging, or massive destruction of the skull or brain) and deaths between 12 to 24 hours with evidence of bleeding (activation of massive transfusion protocol or blood within 6 hours or an abbreviated injury scale (AIS) diagnosis associated with haemorrhage (Appendix 5-1)).

I assessed the accuracy, discrimination and calibration of the BATT score. Accuracy was assessed using the Brier score. Given that the Brier score depends on the prevalence of the outcome, we also calculated the scaled Brier score to account for the baseline risk of death due to bleeding (Appendix 5-2). The scaled Brier score ranges from 0% to 100% and indicates the degree of error in prediction.[81] A scaled Brier score of 0% shows perfect accuracy. Discrimination is the ability of the score to correctly identify patients with the outcome. I estimated the sensitivity, specificity, positive and negative likelihood ratio for each threshold of the BATT score. The likelihood ratio is the likelihood of a positive score in a patient with the outcome compared to the likelihood of a positive score in a patient without the outcome.[118] The positive likelihood ratio is the ratio of sensitivity to 1-specificity. The negative likelihood ratio is the ratio of 1-sensitivity to specificity. A positive likelihood ratio of 10 or above will result in a large increase in the probability of the outcome. A negative likelihood ratio of 0.1 or less will result in a large decrease in the probability of the outcome. I plotted the ROC curve, which is the sensitivity (true positives) on 1-specificity (false positives), for different thresholds of the BATT score.[119] An ideal

score will reach the upper-left corner (all true positives with no false positive). We estimated the area under the ROC curve (AUROC) that corresponds to the concordance statistic (C-statistic) for binary outcome. A C-statistic of 1.0 shows perfect discrimination ability. Calibration is the agreement between observed and predicted outcomes. I estimated calibration-in-the-large as the difference between the mean predicted and observed probabilities and the ratio of the predicted and observed number of events. I also plotted the observed and predicted probabilities of death by decile of the score and with local regression based on the LOESS algorithm.[81] I estimated the calibration intercept and slope of the calibration plot as a measure of the spread between the predicted and observed outcome. Ideally, the intercept would be zero, indicating that the predictions are neither systematically too low or too high and the slope would be 1.[120] There were missing values for some predictors, but no missing outcome data. To estimate the baseline risk for the full dataset, I replaced missing predictors using multiple imputation by chained equations on early death, age, SBP, respiratory rate, HR, GCS, time for injury, time for prehospital ambulance arrival, and time for hospital admission with 20 imputed datasets.

2.3 Evaluation of TXA treatment criteria

I evaluated two different TXA treatment strategies: (1) prehospital treatment of all trauma patients with an ISS ≥9 at the scene of the injury and (2) hospital treatment of all trauma patients with an ISS>9 in the emergency department. I compared each treatment strategy according to different thresholds of the BATT score in order to assess its clinical usefulness and treatment criteria.

I estimated the impact of TXA treatment for each treatment criteria. Since randomised trials of TXA in trauma patients report no increase in deaths from adverse events, the net impact of TXA was estimated by the number of deaths due to bleeding avoided by the treatment.[114,121] To estimate the number of deaths avoided by TXA, I predicted the baseline risk of death due to bleeding using our previously-published prognostic model.[100] To estimate post-treatment probabilities, I applied the treatment effect to these baseline risks, taking into account time to treatment.[10] The risk difference was used to estimate the number of deaths avoided. To account for miscalibration of predicted baseline risks, I conducted a sensitivity analysis using observed early deaths with evidence of haemorrhage as baseline risks. The details of both modelling methods and equations are described in Appendix 5-3. I plotted the cumulative number of deaths due to bleeding avoided by the BATT score threshold in a decision curve analysis as described by Vickers et al.[122] I compared the decision curve analysis for each scenario. I estimated the number needed to treat to save one life for each BATT score threshold and each scenario. The registry-based study design predetermines the sample size.

All analyses were performed using STATA software (version 16.0; Stata Corp, College Station, TX, USA).

3. Results

Table 5-1 shows the BATT Score. The minimum score is 0 and the maximum score is 27.

Table 5-1 BATT score

Age	≥ 65 years old	+ 1
	≥ 75 years old	+2
Systolic blood pressure	< 60 mmHg	+ 14
	≥ 60 and < 100 mmHg	+ 5
Glasgow Coma Scale	≤ 8	+ 4
	> 8 and ≤ 12	+ 3
Respiratory rate	< 10 or ≥ 30/min	+ 2
	Alt: Oxygen saturation < 90	+ 2
Heart rate	> 100/min	+ 1
Penetrating injury	Yes	+ 2
High-energy trauma	Yes	+2

The score is not suitable for isolated limb trauma or isolated neck femoral fracture in inividuals >65 years.

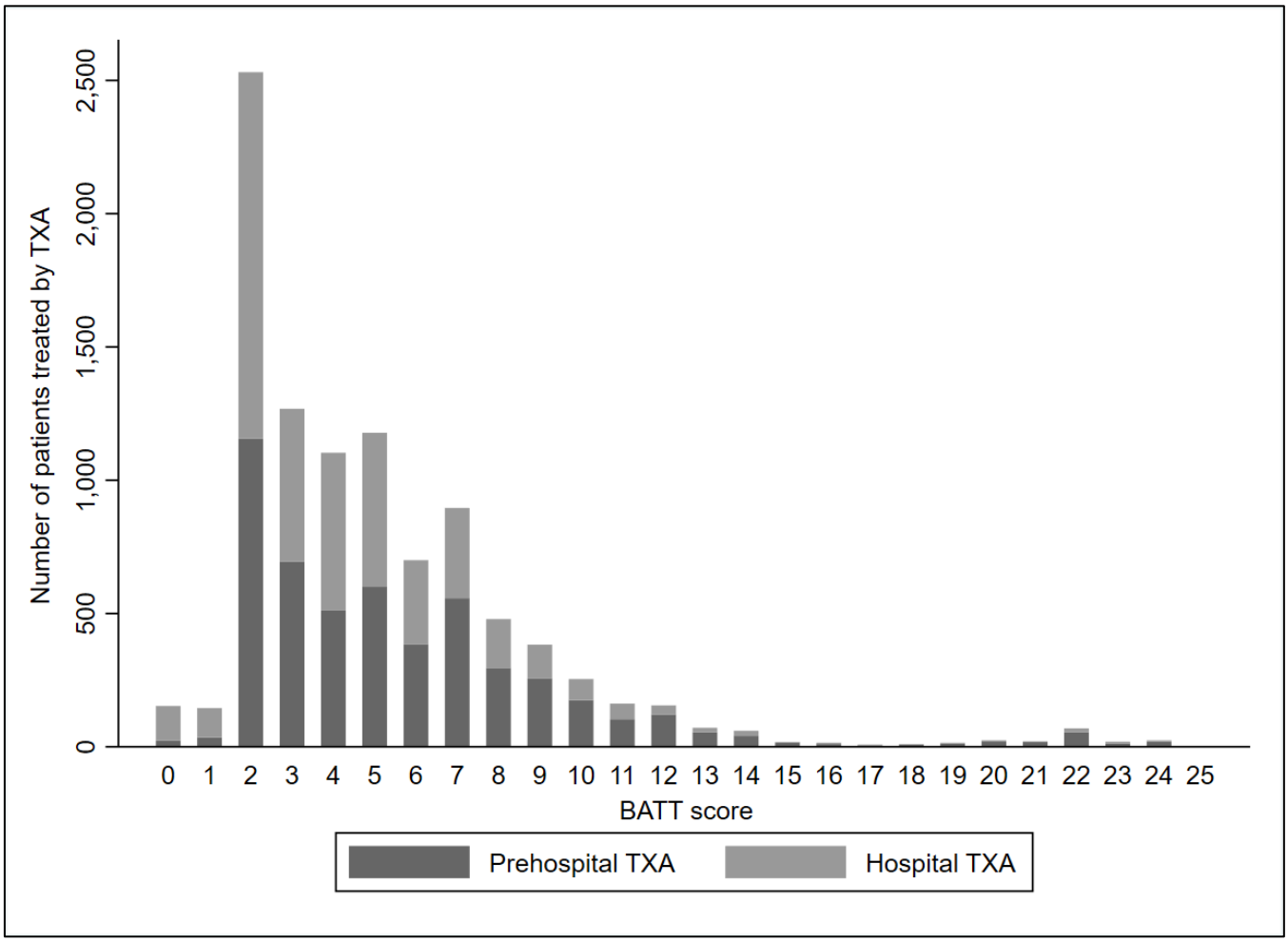
3.1 External validation - patient characteristics

I validated the score in 104,862 trauma patients with an ISS ≥9 who were transported to hospital by ambulance in England and Wales between 2017 and 2018. Patient characteristics are summarized in Table 5-2. Mean age was 62 years and 3189 (3%) had penetrating injuries. Median time from injury to ambulance arrival was 69 minutes, (IQR 24-174). Mean ISS was 16 (± 9) and 46% of patients had an ISS ≥16. TXA was administered in 9915 (9%) patients. Of these, 5185 (52%) received TXA prehospital. Median time from injury to treatment was 48 minutes (IQR 35-68) when TXA was given prehospital and 148 minutes (IQR 103-251) when given in hospital. 2760 (3%) of trauma patients received TXA within 1 hour and 5727 (6%) received TXA within 3 hours of injury. The mean ISS of patients treated with TXA was 23 (±13) compared with 14 (±7) for patients who were not treated (P <0.001). Most patients treated with TXA had a low or intermediate risk of death due to bleeding (Figure 5-1). Most patients treated had a BATT score of 2. The proportion of patients who received prehospital TXA increased with the BATT score. There was no loss to follow-up at 30 days. A total of 2517 (2.4%) patients died within 24 hours and 8874 (8.5%) died within 30 days. Early death with evidence of haemorrhage was reported for 1219 (1.2%) patients.

Table 5-2 Characteristics of trauma patients used to validate the BATT score

	n=104,862	Missing
Mean age (SD)	62 (24)	0
<18, n (%)	5616 (5)	-
18-44, n (%)	19,744 (19)	-
45-64, n (%)	26,354 (25)	-
65 -74, n (%)	13,123 (13)	-
≥75, n (%)	40,025 (38)	-
Sex female, n (%)	47,346 (45)	0
Penetrating injury, n (%)	3189 (3)	0
Circumstances, n (%)		0
Motor vehicle crash	19,709 (19)	-
Fall <2 metres	65,573 (62)	-
Fall > 2 metres	10,604 (10)	-
Blast – blow – crush	5266 (5)	-
Shooting	234 (0)	-
Stabbing	2538 (2)	-
Other	1938 (2)	-
First systolic blood pressure, mean (SD)	138 (28)	12,450 (12)
First systolic blood pressure <90 mmHg, n (%)	3033 (3)	
First Glasgow Coma Scale, n (%)		12,695 (12)
14-15	90,579 (86)	-
9-13	8566 (8)	-
3-8	5717 (6)	-
First heart rate, mean (SD)	86 (20)	11,479 (11)
Heart rate > 120 bpm, n (%)	5475 (5)	
Time from injury to ambulance arrival <3 hours, n (%)	79,430 (76)	50,496 (48)
Time from injury to hospital admission <3 hours, n (%)	63,246 (60)	50,465 (48)
Injury Severity Score (ISS), mean (SD)	16 (9)	0
ISS 9-15, n (%)	58,695 (56)	-
ISS 16-24, n (%)	24,635 (23)	-
ISS 25-34, n (%)	17,682 (17)	-
ISS≥ 35, n (%)	3850 (4)	-
TXA treatment	9915 (9)	13,115 (13)
Prehospital	5185 (5)	-
Hospital	4576 (4)	-
Unknown	176 (0.1)	
Any blood product received	4922 (5)	0
Massive transfusion protocol activated	2487 (2)	-
Blood received within 6 hours of injury	2277 (2)	-

Figure 5-1 Number of patients treated with tranexamic acid by BATT score in UK TARN data



3.2 External validation

Table 5-3 shows the performance of the BATT score. The scaled Brier score was 6%. The ROC curve, as well as the sensitivity and specificity at different thresholds of the BATT score, are shown in Appendices 5-4 and 5-5. A threshold of 2 or more had a sensitivity of 99% and a negative likelihood ratio of 0.03. The C-statistic was 0.90; 95% CI 0.89-0.91). The observed (1.16%) and predicted (1.15%) probabilities of death due to bleeding were similar (P=0.81). The calibration curve showed a slight overprediction in low-risk patients and underprediction in intermediate and high-risk patients

(Appendix 5-6). The calibration intercept was close to zero (0.00032) with a calibration slope of 1.09 (Table 5-3).

Table 5-3 Performance of the BATT score

	BATT score	95% CI
Overall performance		
Brier score	0.0107	
Scaled Brier score (%)	6	
Discrimination		
C-statistic	0.90	0.89-0.91
Mean predicted death due to bleeding		
If patient died from bleeding (%)	6.5	
If patient did not die from bleeding (%)	1.1	1.1-1.1
Discrimination slope (%)	5.4	0.053-0.056
Calibration		
Observed deaths due to bleeding (%)	1.16	1.1-1.2
Predicted deaths due to bleeding (%)	1.15	1.1-1.2
Calibration-in-the-large (%)	0.01	0.00-0.01
Ratio Predicted/Observed	0.99	0.94-1.05
Calibration Intercept	0.00032	
Calibration slope	1.09	1.07-1.11

3.3 Clinical usefulness

Figure 5-2 is a decision curve analysis showing the number of deaths due to bleeding avoided by TXA treatment by BATT score threshold. Treating all trauma patients as soon as possible at the scene of injury or in the ambulance prevented more deaths than in hospital treatment. The cumulative number of deaths avoided decreased as the BATT score threshold increased.

Figure 5-2 Impact of tranexamic acid treatment by BATT score threshold

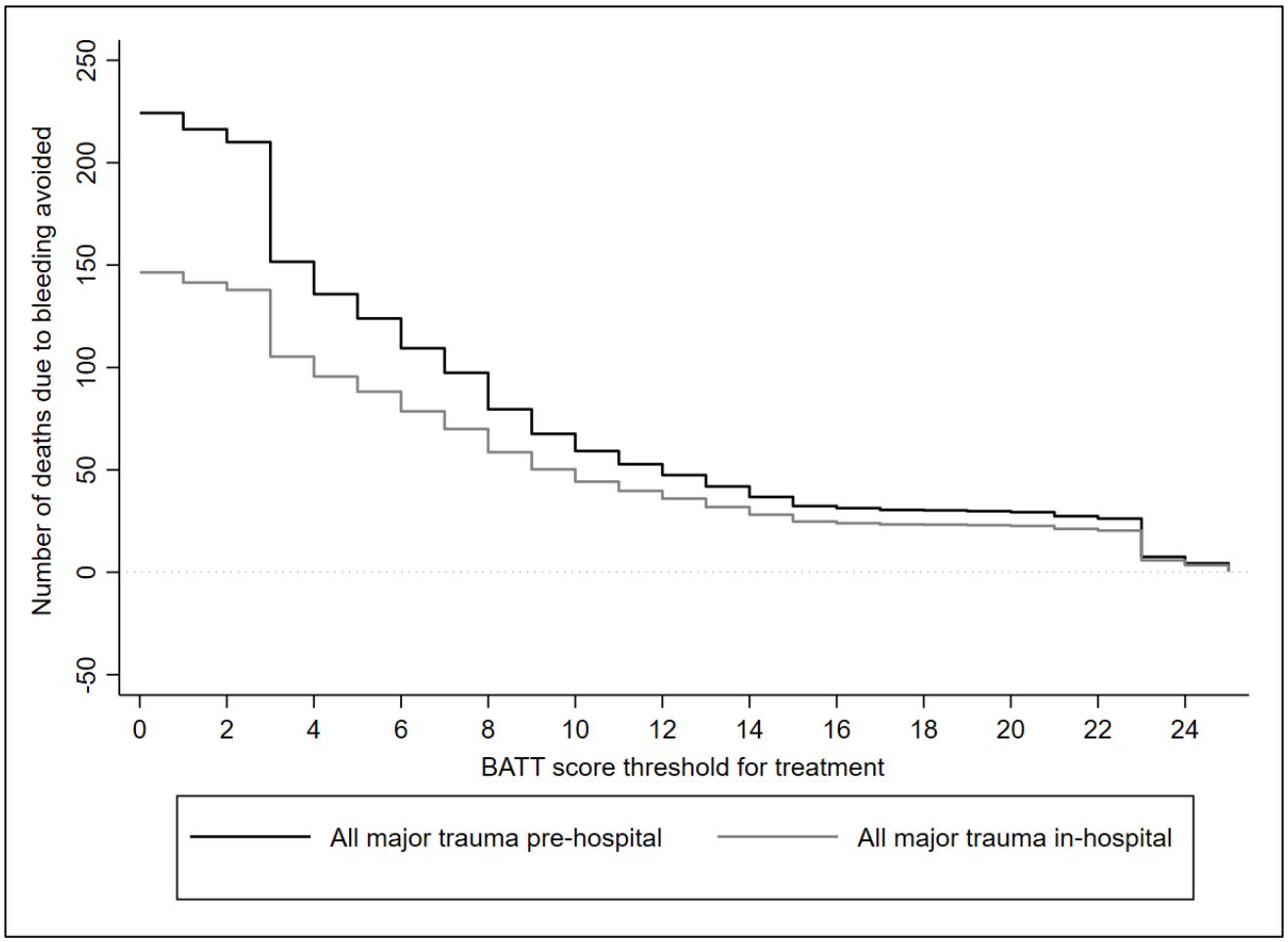


Table 5-4 shows the number of deaths avoided for the different scenarios and the sensitivity analysis based on observed early deaths in 2017 and 2018 in England and Wales. The sensitivity analysis confirms that prehospital treatment provides the maximum benefit with a lower number needed to treat than hospital treatment. Table

5-5 shows the number of deaths avoided and the number needed to treat for each BATT score threshold when patients are treated as soon as possible in the prehospital setting and within 3 hours of injury. A BATT score treatment threshold of 2 corresponds to the treatment of 61,598 patients (59% of major trauma patients included in the TARN registry with ISS ≥9) and results in 210 deaths avoided (Table 5-5). A BATT score treatment threshold <2 resulted in 6 to 14 additional deaths avoided with an additional number needed to treat for one death avoided more than 1000 patients (Table 5-5; Appendix 5-7).

Table 5-4 Comparison of number of deaths due to bleeding avoided by tranexamic acid treatment

	Patients treated n (%) n=104,862	Deaths avoided n (95% CI)	Deaths avoided per 10,000 patients n (95% CI)	Number needed to treat to avoid one death
Based on predicted probabilities				
Current strategy*	9,915 (11)	55 (54-57)	5 (5-5)	180
All prehospital	79,430 (76)	224 (220-228)	21 (21-22)	355
All in hospital	63,246 (60)	146 (144-149)	14 (14-14)	430
Based on observed probabilities (sensitivity analysis)**				
Current strategy*	9,915 (11)	168 (157-178)	16 (15-17)	59
All prehospital	79,430 (76)	323 (305-341)	31 (29-33)	244
All in hospital	63,246 (60)	240 (226-253)	22 (21-24)	273

Table 5-5 Number of deaths due to bleeding avoided and number needed to treat with prehospital treatment within 3 hours of injury according to the BATT score threshold as treatment criteria

BATT score threshold for TXA treatment	Total patients included in TARN n (%)	Number of patients considered for treatment* n (%)	Number of deaths avoided by the BATT score threshold	Standardised number of deaths avoided per 10,000	Number needed to treat**	Additional NNT*** for change of one point of BATT score
≥ 14	586 (<1)	534 (<1)	37	4.7	14	-
≥ 13	737 (<1)	671 (<1)	42	5.3	16	27
≥ 12	960 (1)	883 (1)	47	5.9	19	42
≥ 11	1266 (1)	1150 (1)	53	6.7	22	45
≥ 10	1727 (2)	1557 (2)	59	7.4	27	23
≥ 9	2533 (2)	2272 (2)	68	8.6	34	79
≥ 8	3859 (4)	3420 (3)	80	10.1	43	128
≥ 7	6879 (7)	5898 (6)	97	12.2	61	146
≥ 6	10,071 (10)	8584 (8)	109	13.7	78	224
≥ 5	16,032 (15)	13,335 (13)	124	15.6	108	317
≥ 4	22,946 (22)	18,769 (18)	136	17.1	138	452
≥ 3	33,483 (32)	27,062 (26)	152	19.1	179	518
≥ 2	80,071 (76)	61,598 (59)	210	26.4	293	595
≥ 1	89,948 (86)	68,452 (65)	216	27.2	316	1142
≥ 0	104,862 (100)	79,430 (76)	224	28.2	354	1372

TXA: tranexamic acid; NNT: number needed to treat.
*Number of trauma patients within 3 hours of injury and the arrival of the first ambulance. Proportions are based on all patients included in the TARN registry with an ISS ≥9.
**Standardised number of deaths avoided per 10,000 trauma patients within 3 hours included in the TARN registry with an ISS ≥9.
*** Additional trauma patients needed to treat for each death avoided compared to the BATT score threshold above.

4. Discussion

4.1 Main Findings

In 2017 and 2018, only 9% of trauma patients in England and Wales received TXA and only 3% received it within 1 hour of injury. Prehospital treatment of trauma patients with a BATT score of 2 or more would substantially increase the number of premature deaths that could be avoided with TXA.

4.2 Strengths and limitations

This study has important strengths. My prognostic score was derived using multivariable methods within a large international prospective cohort study with minimal missing data. I then validated the score in a second large cohort that was not used to derive the score.[83] I validated the BATT score using data from a large national trauma registry that includes trauma patients with a wide range of bleeding severity, thus providing a heterogeneous case-mix that allows accurate assessment of discrimination.[123] The score is based on variables recorded by paramedics at the scene of the injury when the decision to treat with TXA must be made. The large number of patients in this study increases the precision of the results. There were few missing values for predictor variables and no missing outcome data. The outcome was well defined and recorded at a fixed time point. These strengths help to ensure the validity of the results.

This study has some limitations. The measurement error of predictor variables could affect discrimination and calibration. Random error could arise for all predictors (SBP, HR, GCS, respiratory rate) and lead to reduced discrimination and calibration. Systematic errors arising from the use of monitoring devices is more likely to affect

calibration.[124] For example, a blood pressure measuring device may systematically overestimate SBP due to device engineering problems. As the outcome “death due to bleeding” was not available in the TARN database, we used early death as a proxy for death due to bleeding.[99] However, any outcome misclassification would be expected to decrease the C-statistic and reduce model performance, but since the C-statistic was high and model performance was excellent, misclassification is unlikely to be an important weakness.[125] Given that time from injury to ambulance arrival and hospital admission was missing for almost one-half of the patients, I imputed these data. Misclassification of time to treatment could therefore affect our estimate of the net benefit.[126] Estimates of deaths avoided are unlikely to be generalizable since they depend on the risk of death, which may vary in different settings. To model the number of deaths avoided, I used treatment effect estimates from randomised trials and so the estimates should be unconfounded. However, confounders in this observational study might affect my estimates of the absolute number of deaths avoided and this must be considered with caution. Nevertheless, I used the same method to estimate the impact of each strategy and it is thus unlikely that the comparison between different strategies was adversely affected by potential confounders. In addition, I considered that there were no adverse events to estimate the net benefit. This assumption was made because randomised trials in trauma and in emergency setting have not reported any increase in adverse events. I modelled the effect on death due to bleeding because there is no compelling evidence that TXA affects other causes of death. Of course, patients that do not die from bleeding may die from other causes and this will reduce the impact of the reduction of bleeding deaths on all-cause mortality. Furthermore, we are reassured by the result of the STAAMP trial assessing TXA in trauma patient in the prehospital setting.[33] The

magnitude of the treatment effect observed on all causes of death in this trial is similar to that observed in the CRASH-2 trial although the estimate was more imprecise.

4.3 Relation to other studies

To the best of our knowledge, the BATT score is the only score that predicts traumatic death due to bleeding. Existing haemorrhage scores predict massive transfusion, which is an imperfect surrogate of death due to bleeding and vulnerable to survival bias (i.e. the Trauma Associated Severe Hemorrhage [TASH] or Assessment of Blood Consumption [ABC] Scores).[70,72]

4.4 Clinical implications

Clinical guidelines recommend TXA treatment for patients with or at risk of significant bleeding and that treatment is given as soon as possible.[11] Due to the lack of clear treatment criteria, many trauma patients are not receiving TXA or else receive it too late. A study on paramedic perceptions concerning TXA use in bleeding in trauma patients showed that lack of self-confidence, uncertainty about the haemorrhage risk, and the need to give TXA by slow intravenous injection (over 10 minutes) were the main barriers to TXA administration.[127] These data suggest that using a BATT score threshold of 2 or more would improve outcomes with a four-fold increase in bleeding deaths prevented by TXA. This clear criterion could improve prehospital administration of TXA by paramedics. Although the use of this threshold would increase the number of patients treated, TXA is safe and inexpensive and is likely to be highly cost-effective.[128,129] Randomised trials of TXA in trauma and surgery

have included over 50,000 patients and no increase in vascular occlusive events has been found.[10,38,41,42,121] Recent trials in prehospital trauma did not find any increase in vascular occlusive events associated with TXA and provide evidence for the applicability of TXA treatment in the prehospital setting.[33,48]

Recent research has found that TXA is well tolerated and rapidly absorbed after intramuscular injection, reaching therapeutic concentrations within 15 minutes in bleeding trauma patients.[56] Further research is needed to assess the cost-effectiveness of different treatment thresholds and whether the use of the BATT score and intramuscular TXA administration by paramedics increases the prehospital administration of TXA to patients at risk of bleeding from trauma.

5. Conclusion

The BATT score is a validated tool and easy to perform at the scene of injury to identify trauma patients at risk of death from bleeding. A score of 2 or more would be an appropriate threshold for prehospital TXA treatment.

CHAPTER VI – Discussion

1. Principal findings

The relative risk reduction from TXA treatment does not appear to vary by baseline risk. TXA appears safe and effective in low-risk patients who represent more than three-quarters of all major trauma. Even though their case-fatality is relatively low, as there are so many low-risk patients, there are a substantial share of deaths in patients who appear to be at low risk on initial assessment. Prehospital TXA administration minimises time to treatment and saves more lives. Treating all trauma patients prehospital would maximise the number of deaths averted and the use of the BATT score would allow paramedics and emergency care providers to accurately identify patients at risk of “significant bleeding” both prehospital and in-hospital. A BATT score ≥2 identifies trauma patients at risk of significant haemorrhage who should be treated. A BATT score ≥2 represents one-half of all major trauma patients included in the UK TARN database. This means treating five times more patients than we are treating at present and would maximise the number of deaths averted, whilst optimizing the number needed to treat.

2. Strengths and weaknesses

2.1 Prognostic model

The strengths and weaknesses of this work have been highlighted in individual chapters. Importantly, this model was developed in a large international cohort of trauma patients and this helps to ensure that the results are widely applicable. I used a rigorous method that did not split the data in derivation and validation cohorts. The

method used ensures accurate prediction, strengthens internal validity, and avoids pessimistic and unstable estimates of model performance. However, I did observe some heterogeneity in the model performance across countries. Case-mix and miscalibration could have affected the discrimination of the model. Some countries included in the CRASH-2 trial showed a homogenous case-mix that decreased the C-statistic. On the other hand, the Northern French Alps Trauma Registry presented a heterogeneous case-mix that increased the C-statistic. However, I acknowledge that this model is most applicable to a population similar to the one used in this study, such as trauma patients with or at risk of bleeding and those that would typically be included in European trauma registries.

2.2 Baseline risk

To reduce selection bias, I selected only randomised trials with more than 1000 patients. Baseline risk was estimated using the entire dataset and not just the placebo group. By increasing the sample size, this improved precision of the prediction. However, I cannot exclude the possibility of some misclassification due to optimism of the model affecting calibration. I am reassured that optimism was low in the model developed for trauma and the selection of a limited number of predictors limits overfitting.[100,101] The large sample size with over 28,000 patients with acute bleeding gives precise results, but I acknowledge that the estimates of the effects on adverse events are less precise. I am reassured that evidence from randomised trials in surgery shows that TXA appears safe in a wide range of different types of surgery. Two randomised trials in trauma that were not completed at the time of the study have recently been published.[33,48] These studies did not report any increase of adverse events associated to TXA compared to placebo. Despite their small sample

size (both trials had less than 1000 patients), they provide additional safety information. The results of the STAAMP trial in extracranial traumatic bleeding found a similar treatment effect magnitude to the one I observed in this chapter and the addition of this trial in the meta-analysis would therefore have very little impact.

2.3 BATT score and TXA criteria

The strengths and weaknesses of my approach to developing the BATT score and the treatment criteria are reported in detail in Chapter 5 of the thesis. It is worth highlighting that the BATT score is based on a prognostic model built using multivariate methods within a large international prospective cohort with minimal missing data. I performed an internal and an internal-external validation of the prognostic model presented in Chapter III. The results presented in Chapter V provide the essential part of the validation process with an external validation of the prognostic model and the score. The external validation was performed in a population independent of the derivation cohort and with different geographical and temporal characteristics. This ensures that this score is widely applicable. The estimates of the number of deaths avoided with TXA was modelled using TXA benefit and harm observed in randomised trials. Consequently, estimates should be unconfounded. However, confounders in this observational study might affect the absolute number of deaths avoided and this must be considered with caution. As we used the same method to model TXA benefit and harm for each strategy, it is unlikely that the comparison between different strategies and criteria was affected by confounders. The recent published STAAMP trial confirms the feasibility and the magnitude of the treatment effect in the prehospital setting.[33]

3. Comparison with other studies

2.1 Prognostic model study

This is the first prognostic model predicting the risk of death due to haemorrhage. The only existing model predicting death in trauma patients was published by Perel at al. who developed and validated a prognostic model to predict all-cause mortality in patients with traumatic bleeding.[96] The model developed in this thesis and the model of Perel were both developed in the CRASH-2 trial cohort. The main differences are in the relationship between SBP and death, where Perel found a U-shape relationship. In my model, a high SBP was not associated with an increase of death due to bleeding. The model developed in this thesis more accurately identifies patients at risk of haemorrhage.

2.2 Baseline risk study

TXA reduces bleeding in surgery, regardless of the baseline risk.[43] The Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial showed a reduction in bleeding complications and blood transfusion with TXA in 4662 patients undergoing cardiac surgery.[41] The trial included a wide range of baseline risk with one-half of patients having a low-to-intermediate risk of death as defined by an Euroscore ≤4. Effectiveness and safety did not vary by baseline risk. Patients included in orthopaedic surgery trials are also at low risk of death due to bleeding.[130] Indeed, no deaths were reported in orthopaedic surgery trials.[43] TXA reduces bleeding and blood transfusion after knee or hip arthroplasty in these low-

risk patients. The effectiveness in low-risk patients in elective surgery showed that TXA reduces bleeding, even in the absence of evidence of systemic coagulopathy or hyperfibrinolysis.

Experimental studies in rats confirm this preventive effect. Wu et al. showed that TXA given prior to trauma (similar to the use of TXA in elective surgery) reduced fibrinolysis at the site of tissue injury and reduced circulating d-dimer levels.[21] However, TXA given 45 minutes after trauma was not as effective and did not prevent a rise in D-dimers. This suggests that a competitive binding of TXA and plasminogen is required during clot initiation. Time to treatment is a key issue for TXA effectiveness in acute bleeding. TXA effectiveness decreases by 10% for every 15 minutes of treatment delay.[10] Another animal model of polytrauma found an imbalance between plasmin activators and inhibitors at the onset of bleeding.[50] Following polytrauma, t-PA increases rapidly over the first 30 minutes. Plasmin and d-dimer follow the same trend, reaching a maximum within 1 hour. On the other hand, levels of PAI-1, the main inhibitor of plasmin, starts increasing from 2 hours after trauma, reaching a peak at 4 hours. This imbalance in favour of plasmin activation in the first 3 hours after injury is likely to explain the benefit of early TXA use observed in the CRASH-2 trial.[53] Recently, the STAAMP trial also found a time to treatment interaction in trauma with a strong survival benefit when TXA was given within 1 hour of injury.[33] Animal studies and trials in surgery help us to understand why TXA is as effective in low-risk as in high-risk patients, with the same strong time to treatment interaction. When given early and regardless of the baseline risk, TXA is a clot stabiliser that prevents worsening of bleeding until definitive care. TXA given in a low-risk trauma patient could be considered as preventive treatment for ongoing bleeding. Surgery, particularly orthopaedic surgery, are common in major trauma

patients. TXA could also be considered as a preventive treatment prior to surgery in major trauma patients with or without significant bleeding.

2.3 TXA treatment criteria and BATT score

Apart from the BATT score, there are no clinical scores to predict the risk of death from bleeding. Existing scores identify patients that need massive transfusion. Among the many scores, the TASH score was developed and validated with an appropriate methodology in the German Trauma Registry and has a good ability to discriminate patients requiring a massive transfusion.[72] As it includes laboratory test and imaging, it is not suitable for use in the prehospital setting for early identification of haemorrhage. Another score frequently cited is the ABC score. This was not developed using multivariate regression analysis, but was based on expert opinion. This score is not a prediction tool but, nevertheless, it has good discrimination since it corresponds to the criteria for activating the massive transfusion protocol. All trauma scores predicting massive transfusion are subject to misclassification. Patients without massive transfusion could have severe haemorrhage. They are also subject to survival bias. Furthermore, these scores only identify patients with a very high risk of bleeding and are not able to stratify the risk of death due to bleeding as permitted by the BATT score.

The BATT score is suitable for use in the prehospital setting by paramedics and allows them to stratify the risk of death due to bleeding as null, low, intermediate and high. Currently, there are no clear treatment criteria for prehospital TXA use in trauma patients. To the best of my knowledge, only the US National Association of Emergency Medical Service Physicians has published treatment criteria for prehospital use.[60] They recommend TXA treatment within 3 hours of injury for non-

compressible bleeding (e.g., penetrating thoraco-abdominal trauma or unstable pelvis fracture) along with a HR >120 bpm and a SBP < 90 mmHg, provided that TXA use does not delay rapid transport to a trauma centre. This thesis shows that restricting TXA treatment to very high-risk patients in this manner would miss one-half of deaths due to bleeding observed in the UK TARN major trauma registry.

4. Clinical Implications

TXA has been studied in many randomised trials. There is a considerable volume of evidence in surgery and acute bleeding. In trauma, TXA has to be used as soon as possible in the prehospital setting to decrease time to treatment and increase the number of deaths avoided. TXA should be given to a wide range of those at risk of haemorrhagic death to increase the number of deaths avoided. Patients at low or intermediate risk of death due to bleeding represent the majority of major trauma patients and contribute importantly to the number of traumatic deaths. Low-risk patients include patients with an unrecognised source of bleeding at an early stage, without abnormal vital signs. Prehospital TXA use appears to be safe and this has been confirmed by recent trials from North America.[33,48]

Using the BATT score as treatment criteria might avoid uncertainty in clinical decision-making and allow an early stratification of the risk of death due to bleeding. The BATT score is based on the main criteria used in trauma triage (physiologic criteria, mechanism of injury, special consideration of age). A BATT score ≥ 2 allows to identify trauma patients at risk of significant haemorrhage and allows to maximise the number of lives saved, but with an acceptable number needed to treat. In addition, TXA use is highly cost effective. The key issue with using the BATT score in clinical practice is specifying the targets population in which the BATT score will be

applied. The trauma registry considered major trauma with an ISS ≥ 9 as the inclusion criterion. In prehospital care, such criterion cannot be used. The BATT score could be used in trauma patients with high energy trauma, patients with life-threatening injury or patients with multiple injuries. The BATT score is not suitable for patients with isolated limb trauma or older people with isolated femoral neck fracture. Clinical experience and common sense combined with the prognostic score is likely to be better for risk identification than use of the score alone.

5. Future research

Research on paramedic perceptions on the use of TXA in trauma found several different barriers to TXA use.[127] In addition to uncertainties about the patient's risk of death due to bleeding, the need for an intravenous line and the need to inject TXA slowly over 10 minutes were important disincentives to TXA use. Recent research has found that TXA is well tolerated and rapidly absorbed after intramuscular injection, reaching therapeutic concentrations within 15 minutes in bleeding trauma patients.[56] Further research is needed to assess the cost-effectiveness of different treatment thresholds and whether the use of the BATT score and intramuscular TXA administration by paramedics increases prehospital administration of TXA to patients at risk of traumatic bleeding.

REFERENCES

1 James SL, Abate D, Abate KH, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2018;**392**:1789–858. doi:10.1016/S0140-6736(18)32279-7

2 WHO. Injuries and violence: The facts. https://www.who.int/violence_injury_prevention/key_facts/VIP_key_facts.pdf?ua=1 (accessed 21 Aug 2020).

3 Peden M, McGee K, Sharma G. The injury chart book: a graphical overview of the global burden of injuries. *Geneva: World Health Organization* 2002;**5**.https://www.who.int/violence_injury_prevention/publications/other_injury/chartb/en/ (accessed 19 Oct 2020).

4 Søreide K, Krüger AJ, Vårdal AL, *et al.* Epidemiology and contemporary patterns of trauma deaths: changing place, similar pace, older face. *World J Surg* 2007;**31**:2092–103. doi:10.1007/s00268-007-9226-9

5 Evans JA, van Wessem KJP, McDougall D, *et al.* Epidemiology of traumatic deaths: comprehensive population-based assessment. *World J Surg* 2010;**34**:158–63. doi:10.1007/s00268-009-0266-1

6 Girard E, Jegousso Q, Boussat B, *et al.* Preventable deaths in a French regional trauma system: A six-year analysis of severe trauma mortality. *J Visc Surg* Published Online First: 25 May 2018. doi:10.1016/j.jviscsurg.2018.05.002

7 Kleber C, Giesecke MT, Tsokos M, *et al.* Trauma-related preventable deaths in Berlin 2010: need to change prehospital management strategies and trauma management education. *Journal of Surgery* 2013;**37**:1154–61. doi:10.1007/s00268-013-1964-2

8 CRASH-2 trial collaborators, Shakur H, Roberts I, *et al.* Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;**376**:23–32. doi:10.1016/S0140-6736(10)60835-5

9 Ker K, Edwards P, Perel P, *et al.* Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012;**344**:e3054. doi:10.1136/bmj.e3054

10 Gayet-Ageron A, Prieto-Merino D, Ker K, *et al.* Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *The Lancet* 2018;**391**:125–32. doi:10.1016/S0140-6736(17)32455-8

11 Spahn DR, Bouillon B, Cerny V, *et al.* The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care* 2019;**23**:98. doi:10.1186/s13054-019-2347-3

12 Coats TJ, Fragoso-Iñiguez M, Roberts I. Implementation of tranexamic acid for bleeding trauma patients: a longitudinal and cross-sectional study. *Emerg Med J* 2019;**36**:78–81. doi:10.1136/emermed-2018-207693

13 Macfarlane RG, Pilling J. OBSERVATIONS ON FIBRINOLYSIS PLASMINOGEN, PLASMIN, AND ANTIPLASMIN CONTENT OF HUMAN BLOOD. *The Lancet* 1946;**248**:562–5. doi:10.1016/S0140-6736(46)91017-3

14 Cesarman-Maus G, Hajjar KA. Molecular mechanisms of fibrinolysis. *British Journal of Haematology* 2005;**129**:307–21. doi:10.1111/j.1365-2141.2005.05444.x

15 Watts G. Utako Okamoto. *The Lancet* 2016;**387**:2286. doi:10.1016/S0140-6736(16)30697-3

16 Okamoto S, Okamoto U. Amino-Methyl-Cyclohexane-Carboxylic Acid: Amcha. *The Keio Journal of Medicine* 1962;**11**:105–15. doi:10.2302/kjm.11.105

17 Okamoto S, Sato S, Takada Y, *et al.* AN ACTIVE STEREO-ISOMER (TRANS-FORM) OF AMCHA AND ITS ANTIFIBRINOLYTIC (ANTIPLASMINIC) ACTION IN VITRO AND IN VIVO. *Keio J Med* 1964;**13**:177–85. doi:10.2302/kjm.13.177

18 Mannucci PM, Levi M. Prevention and treatment of major blood loss. *N Engl J Med* 2007;**356**:2301–11. doi:10.1056/NEJMra067742

19 Tengborn L, Blombäck M, Berntorp E. Tranexamic acid – an old drug still going strong and making a revival. *Thrombosis Research* 2015;**135**:231–42. doi:10.1016/j.thromres.2014.11.012

20 Hvas A-M, Sørensen HT, Norengaard L, *et al.* Tranexamic acid combined with recombinant factor VIII increases clot resistance to accelerated fibrinolysis in severe hemophilia A. *Journal of Thrombosis and Haemostasis* 2007;**5**:2408–14. doi:10.1111/j.1538-7836.2007.02755.x

21 Wu X, Benov A, Darlington DN, *et al.* Effect of tranexamic acid administration on acute traumatic coagulopathy in rats with polytrauma and hemorrhage. *PLoS ONE* 2019;**14**:e0223406. doi:10.1371/journal.pone.0223406

22 Heissig B, Salama Y, Takahashi S, *et al.* The multifaceted role of plasminogen in inflammation. *Cell Signal* 2020;**75**:109761. doi:10.1016/j.cellsig.2020.109761

23 Shimazu H, Munakata S, Tashiro Y, *et al.* Pharmacological targeting of plasmin prevents lethality in a murine model of macrophage activation syndrome. *Blood* 2017;**130**:59–72. doi:10.1182/blood-2016-09-738096

24 Draxler DF, Yep K, Hanafi G, *et al.* Tranexamic acid modulates the immune response and reduces postsurgical infection rates. *Blood Adv* 2019;**3**:1598–609. doi:10.1182/bloodadvances.2019000092

25 Jimenez JJ, Iribarren JL, Lorente L, *et al.* Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of

fibrinolysis: a case control study followed by a randomized double-blind controlled trial. *Critical Care* 2007;**11**:R117. doi:10.1186/cc6173

26 Later AFL, Sitniakowsky LS, van Hilten JA, *et al.* Antifibrinolytics attenuate inflammatory gene expression after cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery* 2013;**145**:1611-1616.e4. doi:10.1016/j.jtcvs.2012.11.042

27 Walker PF, Foster AD, Rothberg PA, *et al.* Tranexamic acid decreases rodent hemorrhagic shock-induced inflammation with mixed end-organ effects. *PLoS One* 2018;**13**. doi:10.1371/journal.pone.0208249

28 Barrett CD, Moore HB, Kong Y-W, *et al.* Tranexamic acid mediates proinflammatory and anti-inflammatory signaling via complement C5a regulation in a plasminogen activator-dependent manner. *J Trauma Acute Care Surg* 2019;**86**:101–7. doi:10.1097/TA.0000000000002092

29 Roberts I, Prieto-Merino D, Manno D. Mechanism of action of tranexamic acid in bleeding trauma patients: an exploratory analysis of data from the CRASH-2 trial. *Crit Care* 2014;**18**:685. doi:10.1186/s13054-014-0685-8

30 Wei Z, Liu M. The effectiveness and safety of tranexamic acid in total hip or knee arthroplasty: a meta-analysis of 2720 cases. *Transfus Med* 2015;**25**:151–62. doi:10.1111/tme.12212

31 Myles PS, Smith JA, Forbes A, *et al.* Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. *N Engl J Med* 2017;**376**:136–48. doi:10.1056/NEJMoa1606424

32 Shakur H, Roberts I, Fawole B, *et al.* Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *The Lancet* 2017;**389**:2105–16. doi:10.1016/S0140-6736(17)30638-4

33 Guyette FX, Brown JB, Zenati MS, *et al.* Tranexamic Acid During Prehospital Transport in Patients at Risk for Hemorrhage After Injury: A Double-blind, Placebo-Controlled, Randomized Clinical Trial. *JAMA Surg* Published Online First: 5 October 2020. doi:10.1001/jamasurg.2020.4350

34 Mitra B, Mazur S, Cameron PA, *et al.* Tranexamic acid for trauma: filling the 'GAP' in evidence. *Emerg Med Australas* 2014;**26**:194–7. doi:10.1111/1742-6723.12172

35 Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *The Lancet* 2019;**394**:1713–23. doi:10.1016/S0140-6736(19)32233-0

36 Brenner A, Belli A, Chaudhri R, *et al.* Understanding the neuroprotective effect of tranexamic acid: an exploratory analysis of the CRASH-3 randomised trial. *Crit Care* 2020;**24**:560. doi:10.1186/s13054-020-03243-4

37 Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017;**389**:2105–16. doi:10.1016/S0140-6736(17)30638-4

38 Sprigg N, Flaherty K, Appleton JP, *et al.* Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet* 2018;**391**:2107–15. doi:10.1016/S0140-6736(18)31033-X

39 Roberts I, Shakur-Still H, Afolabi A, *et al.* Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. *The Lancet* 2020;**395**:1927–36. doi:10.1016/S0140-6736(20)30848-5

40 Zhang Y, Bai Y, Chen M, *et al.* The safety and efficiency of intravenous administration of tranexamic acid in coronary artery bypass grafting (CABG): a meta-analysis of 28 randomized controlled trials. *BMC Anesthesiol* 2019;**19**:104. doi:10.1186/s12871-019-0761-3

41 Myles PS, Smith JA, Forbes A, *et al.* Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. *N Engl J Med* 2017;**376**:136–48. doi:10.1056/NEJMoa1606424

42 Sentilhes L, Winer N, Azria E, *et al.* Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. *N Engl J Med* 2018;**379**:731–42. doi:10.1056/NEJMoa1800942

43 Ker K, Edwards P, Perel P, *et al.* Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012;**344**. doi:10.1136/bmj.e3054

44 Moore EE, Moore HB, Gonzalez E, *et al.* Rationale for the selective administration of tranexamic acid to inhibit fibrinolysis in the severely injured patient. *Transfusion* 2016;**56 Suppl 2**:S110-114. doi:10.1111/trf.13486

45 Benipal S, Santamarina J-L, Vo L, *et al.* Mortality and Thrombosis in Injured Adults Receiving Tranexamic Acid in the Post-CRASH-2 Era. *West J Emerg Med* 2019;**20**:443–53. doi:10.5811/westjem.2019.4.41698

46 Erramouspe PJ, García-Pintos MF, Benipal S, *et al.* Mortality and Complication Rates in Adult Trauma Patients Receiving Tranexamic Acid: A Single-center Experience in the Post-CRASH-2 Era. *Acad Emerg Med* 2020;**27**:358–65. doi:10.1111/acem.13883

47 Moore HB, Moore EE, Gonzalez E, *et al.* Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg* 2014;**77**:811–7; discussion 817. doi:10.1097/TA.0000000000000341

48 Rowell SE, Meier EN, McKnight B, *et al.* Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury. *JAMA* 2020;**324**:961–74. doi:10.1001/jama.2020.8958

49 Kolev K, Machovich R. Molecular and cellular modulation of fibrinolysis. *Thromb Haemost* 2003;**89**:610–21.

50 Wu X, Darlington DN, Cap AP. Procoagulant and fibrinolytic activity after polytrauma in rat. *Am J Physiol Regul Integr Comp Physiol* 2016;**310**:R323-329. doi:10.1152/ajpregu.00401.2015

51 Floccard B, Rugeri L, Faure A, *et al.* Early coagulopathy in trauma patients: an on-scene and hospital admission study. *Injury* 2012;**43**:26–32. doi:10.1016/j.injury.2010.11.003

52 Theusinger OM, Baulig W, Seifert B, *et al.* Changes in Coagulation in Standard Laboratory Tests and ROTEM in Trauma Patients Between On-Scene and Arrival in the Emergency Department. *Anesthesia & Analgesia* 2015;**120**:627–635. doi:10.1213/ANE.0000000000000561

53 CRASH-2 collaborators, Roberts I, Shakur H, *et al.* The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011;**377**:1096–101, 1101.e1-2. doi:10.1016/S0140-6736(11)60278-X

54 Fiechtner BK, Nuttall GA, Johnson ME, *et al.* Plasma tranexamic acid concentrations during cardiopulmonary bypass. *Anesth Analg* 2001;**92**:1131–6. doi:10.1097/00000539-200105000-00010

55 Horrow JC, Van Riper DF, Strong MD, *et al.* The dose-response relationship of tranexamic acid. *Anesthesiology* 1995;**82**:383–92. doi:10.1097/00000542-199502000-00009

56 Grassin-Delyle S, Shakur-Still H, Picetti R, *et al.* Pharmacokinetics of intramuscular tranexamic acid in bleeding trauma patients: a clinical trial. *British Journal of Anaesthesia* 2020;**Accepted for publication**.

57 World Health Organization. WHO Model Lists of Essential Medicines, 21th edition. 2017.https://www.who.int/medicines/publications/essentialmedicines/en/ (accessed 12 Sep 2020).

58 National Institute for Health and Care Excellence. Major trauma: assessment and initial management: NICE guideline [NG39]. 2016.https://www.nice.org.uk/guidance/ng39/resources/major-trauma-assessment-and-initial-management-1837400761285 (accessed 11 Sep 2020).

59 Committee on Trauma of the American College of Surgeons. ACS TQIP Massive Transfusion in Trauma Guidelines. https://www.facs.org/-/media/files/quality-programs/trauma/tqip/transfusion_guildelines.ashx (accessed 11 Sep 2020).

60 Fischer PE, Bulger EM, Perina DG, *et al.* Guidance Document for the Prehospital Use of Tranexamic Acid in Injured Patients. *Prehospital Emergency Care* 2016;**20**:557–9. doi:10.3109/10903127.2016.1142628

61 Wiese JGG, van Hoving DJ, Hunter L, *et al.* Poor adherence to Tranexamic acid guidelines for adult, injured patients presenting to a district, public, South African hospital. *Afr J Emerg Med* 2017;**7**:63–7. doi:10.1016/j.afjem.2017.04.006

62 Joint Trauma System (JTS), Committee on Tactical Combat Casualty Care (CoTCCC). Tactical Combat Casuality Care Guidelines 2019. https://learning-media.allogy.com/api/v1/pdf/40e98785-c0a1-4916-a892-ca7977355864/contents (accessed 11 Sep 2020).

63 Finlayson HW. The Role of Tranexamic Acid (TXA) in Military Trauma. *Traumatology (Tallahass Fla)* 2018;**0**.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7183734/ (accessed 13 Sep 2020).

64 Ausset S, Glassberg E, Nadler R, *et al.* Tranexamic acid as part of remote damage-control resuscitation in the prehospital setting: A critical appraisal of the medical literature and available alternatives. *Journal of Trauma and Acute Care Surgery* 2015;**78**:S70–5. doi:10.1097/TA.0000000000000640

65 Lipsky AM, Abramovich A, Nadler R, *et al.* Tranexamic acid in the prehospital setting: Israel Defense Forces' initial experience. *Injury* 2014;**45**:66–70. doi:10.1016/j.injury.2013.08.025

66 Wafaisade A, Lefering R, Bouillon B, *et al.* Prehospital administration of tranexamic acid in trauma patients. *Crit Care* 2016;**20**:143. doi:10.1186/s13054-016-1322-5

67 Napolitano LM. Prehospital tranexamic acid: what is the current evidence? *Trauma Surg Acute Care Open* 2017;**2**:e000056. doi:10.1136/tsaco-2016-000056

68 Guly HR, Bouamra O, Spiers M, *et al.* Vital signs and estimated blood loss in patients with major trauma: Testing the validity of the ATLS classification of hypovolaemic shock. *Resuscitation* 2011;**82**:556–9. doi:10.1016/j.resuscitation.2011.01.013

69 Shahi V, Shahi V, Mower WR. Using Serial Hemoglobin Levels to Detect Occult Blood Loss in the Early Evaluation of Blunt Trauma Patients. *The Journal of Emergency Medicine* 2018;**55**:307–12. doi:10.1016/j.jemermed.2018.06.017

70 Nunez TC, Voskresensky IV, Dossett LA, *et al.* Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? *J Trauma* 2009;**66**:346–52. doi:10.1097/TA.0b013e3181961c35

71 Ogura T, Nakamura Y, Nakano M, *et al.* Predicting the need for massive transfusion in trauma patients: the Traumatic Bleeding Severity Score. *J Trauma Acute Care Surg* 2014;**76**:1243–50. doi:10.1097/TA.0000000000000200

72 Yücel N, Lefering R, Maegele M, *et al.* Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. *J Trauma* 2006;**60**:1228–36; discussion 1236-1237. doi:10.1097/01.ta.0000220386.84012.bf

73 Tonglet ML, Minon JM, Seidel L, *et al.* Prehospital identification of trauma patients with early acute coagulopathy and massive bleeding: results of a prospective non-interventional clinical trial evaluating the Trauma Induced Coagulopathy Clinical Score (TICCS). *Critical Care* 2014;**18**:648. doi:10.1186/s13054-014-0648-0

74 Mitra B, Cameron PA, Mori A, *et al.* Early prediction of acute traumatic coagulopathy. *Resuscitation* 2011;**82**:1208–13. doi:10.1016/j.resuscitation.2011.04.007

75 Krumrei NJ, Park MS, Cotton BA, *et al.* Comparison of massive blood transfusion predictive models in the rural setting. *J Trauma Acute Care Surg* 2012;**72**:211–5. doi:10.1097/TA.0b013e318240507b

76 Huber-Wagner S, Lefering R, Qvick L-M, *et al.* Effect of whole-body CT during trauma resuscitation on survival: a retrospective, multicentre study. *Lancet* 2009;**373**:1455–61. doi:10.1016/S0140-6736(09)60232-4

77 Bouzat P, Ageron F-X, Brun J, *et al.* A regional trauma system to optimize the pre-hospital triage of trauma patients. *Crit Care* 2015;**19**. doi:10.1186/s13054-015-0835-7

78 Sasser SM, Hunt RC, Faul M, *et al.* Guidelines for field triage of injured patients: recommendations of the National Expert Panel on Field Triage, 2011. *MMWR Recomm Rep* 2012;**61**:1–20.

79 Tibshirani R. Regression Shrinkage and Selection via the Lasso. *Journal of the Royal Statistical Society Series B (Methodological)* 1996;**58**:267–88.

80 Royston P, Altman DG. Visualizing and assessing discrimination in the logistic regression model. *Stat Med* 2010;**29**:2508–20. doi:10.1002/sim.3994

81 Steyerberg EW, Vickers AJ, Cook NR, *et al.* Assessing the performance of prediction models: a framework for some traditional and novel measures. *Epidemiology* 2010;**21**:128–38. doi:10.1097/EDE.0b013e3181c30fb2

82 Riley RD, Ensor J, Snell KIE, *et al.* External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. *BMJ* 2016;**353**:i3140.

83 Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol* 2016;**69**:245–7. doi:10.1016/j.jclinepi.2015.04.005

84 Royston P, Parmar MKB, Sylvester R. Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer. *Stat Med* 2004;**23**:907–26. doi:10.1002/sim.1691

85 Austin PC, van Klaveren D, Vergouwe Y, *et al.* Validation of prediction models: examining temporal and geographic stability of baseline risk and estimated covariate effects. *Diagn Progn Res* 2017;**1**:12. doi:10.1186/s41512-017-0012-3

86 Steyerberg EW, Mushkudiani N, Perel P, *et al.* Predicting Outcome after Traumatic Brain Injury: Development and International Validation of Prognostic Scores Based on Admission Characteristics. *PLoS Med* 2008;**5**. doi:10.1371/journal.pmed.0050165

87 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in Medicine* 2011;**30**:377–99. doi:10.1002/sim.4067

88 Rehn M, Perel P, Blackhall K, *et al.* Prognostic models for the early care of trauma patients: a systematic review. [Review]. *Journal of Trauma* Published Online First: March 2011. doi:10.1186/1757-7241-19-17

89 Austin PC, Steyerberg EW. Events per variable (EPV) and the relative performance of different strategies for estimating the out-of-sample validity of logistic regression models. *Stat Methods Med Res* 2017;**26**:796–808. doi:10.1177/0962280214558972

90 Siontis GCM, Tzoulaki I, Castaldi PJ, *et al.* External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination. *J Clin Epidemiol* 2015;**68**:25–34. doi:10.1016/j.jclinepi.2014.09.007

91 Ciesla DJ, Pracht EE, Tepas JJ, *et al.* Measuring trauma system performance: Right patient, right place-Mission accomplished? *J Trauma Acute Care Surg* 2015;**79**:263–8. doi:10.1097/TA.0000000000000660

92 MacMahon S, Peto R, Collins R, *et al.* Blood pressure, stroke, and coronary heart disease. *The Lancet* 1990;**335**:765–74. doi:10.1016/0140-6736(90)90878-9

93 Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. *BMJ* 2010;**340**:c2289. doi:10.1136/bmj.c2289

94 Rossaint R, Bouillon B, Cerny V, *et al.* The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care* 2016;**20**:100. doi:10.1186/s13054-016-1265-x

95 Sartorius D, Le Manach Y, David J-S, *et al.* Mechanism, glasgow coma scale, age, and arterial pressure (MGAP): a new simple prehospital triage score to predict mortality in trauma patients. *Crit Care Med* 2010;**38**:831–7. doi:10.1097/CCM.0b013e3181cc4a67

96 Perel P, Prieto-Merino D, Shakur H, *et al.* Predicting early death in patients with traumatic bleeding: development and validation of prognostic model. *BMJ* 2012;**345**:e5166.

97 Pfeifer R, Teuben M, Andruszkow H, *et al.* Mortality Patterns in Patients with Multiple Trauma: A Systematic Review of Autopsy Studies. *PLoS One* 2016;**11**. doi:10.1371/journal.pone.0148844

98 Roberts, Ian. A systematic review and prospective individual patient data meta-analysis of the effects of anti-fibrinolytic drugs on mortality and the risk of thromboembolic events in acute severe bleeding. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=52155 (accessed 3 Apr 2019).

99 Brenner A, Arribas M, Cuzick J, *et al.* Outcome measures in clinical trials of treatments for acute severe haemorrhage. *Trials* 2018;**19**. doi:10.1186/s13063-018-2900-4

100 Ageron F-X, Gayet-Ageron A, Steyerberg E, *et al.* Prognostic model for traumatic death due to bleeding: cross-sectional international study. *BMJ Open* 2019;**9**:e026823. doi:10.1136/bmjopen-2018-026823

101 Burke JF, Hayward RA, Nelson JP, *et al.* Using internally developed risk models to assess heterogeneity in treatment effects in clinical trials. *Circ Cardiovasc Qual Outcomes* 2014;**7**:163–9. doi:10.1161/CIRCOUTCOMES.113.000497

102 Perel P, Prieto-Merino D, Shakur H, *et al.* Development and validation of a prognostic model to predict death in patients with traumatic bleeding, and evaluation of the effect of tranexamic acid on mortality according to baseline risk: a secondary analysis of a randomised controlled trial. *Health Technol Assess* 2013;**17**:1–45, v–vi. doi:10.3310/hta17240

103 Dewan Y, Komolafe EO, Mejía-Mantilla JH, *et al.* CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials* 2012;**13**:87. doi:10.1186/1745-6215-13-87

104 Roberts I, Coats T, Edwards P, *et al.* HALT-IT - tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial. *Trials* 2014;**15**. doi:10.1186/1745-6215-15-450

105 Shanghai First Maternity and Infant Hospital. Tranexamic Acid for Preventing Postpartum Hemorrhage After Cesarean Section (NCT02936661). https://clinicaltrials.gov/ct2/show/record/NCT02936661 (accessed 3 Apr 2019).

106 Brown JB, Neal MD, Guyette FX, *et al.* Design of the Study of Tranexamic Acid during Air Medical Prehospital Transport (STAAMP) Trial: Addressing the Knowledge Gaps. *Prehosp Emerg Care* 2015;**19**:79–86. doi:10.3109/10903127.2014.936635

107 Clifton, Rebecca. Tranexamic Acid for the Prevention of Obstetrical Hemorrhage After Cesarean. https://clinicaltrials.gov/ct2/show/NCT03364491

108 May, Susanne. Prehospital Tranexamic Acid Use for Traumatic Brain Injury (NCT01990768). https://clinicaltrials.gov/ct2/show/record/NCT01990768?term=NCT01990768&rank=1 (accessed 3 Apr 2019).

109 Ker K, Roberts I, Chaudhri R, *et al.* Tranexamic acid for the prevention of postpartum bleeding in women with anaemia: study protocol for an international, randomised, double-blind, placebo-controlled trial. *Trials* 2018;**19**. doi:10.1186/s13063-018-3081-x

110 Devereaux, PJ. PeriOperative ISchemic Evaluation-3 Trial (POISE-3). https://clinicaltrials.gov/ct2/show/study/NCT03505723?show_locs=Y#locn (accessed 3 Apr 2019).

111 NCT03431805. TRAnexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean Delivery. *TRAnexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean Delivery :a Multicenter Randomised, Double Blind Placebo Controlled Trial (TRAAP2)* Published Online First: 2018.https://clinicaltrials.gov/show/NCT03431805

112 Tierney JF, Vale C, Riley R, *et al.* Individual Participant Data (IPD) Meta-analyses of Randomised Controlled Trials: Guidance on Their Use. *PLoS Med* 2015;**12**. doi:10.1371/journal.pmed.1001855

113 Steyerberg EW, Uno H, Ioannidis JPA, *et al.* Poor performance of clinical prediction models: the harm of commonly applied methods. *J Clin Epidemiol* Published Online First: 24 November 2017. doi:10.1016/j.jclinepi.2017.11.013

114 Ageron F-X, Gayet-Ageron A, Ker K, *et al.* Effect of tranexamic acid by baseline risk of death in acute bleeding patients: a meta-analysis of individual patient-level data from 28 333 patients. *British Journal of Anaesthesia* 2020;**124**:676–83. doi:10.1016/j.bja.2020.01.020

115 van Laarhoven JJEM, Lansink KWW, van Heijl M, *et al.* Accuracy of the field triage protocol in selecting severely injured patients after high energy trauma. *Injury* 2014;**45**:869–73. doi:10.1016/j.injury.2013.12.010

116 Lecky F, Woodford M, Yates D. Trends in trauma care in England and Wales 1989–97. *The Lancet* 2000;**355**:1771–5. doi:10.1016/S0140-6736(00)02264-9

117 Lefering R, Paffrath T, Bouamra O, *et al.* Epidemiology of in-hospital trauma deaths. *Eur J Trauma Emerg Surg* 2012;**38**:3–9. doi:10.1007/s00068-011-0168-4

118 Peng P, Coyle A. Likelihood Ratios for the Emergency Physician. *Academic Emergency Medicine* 2018;**25**:958–65. doi:10.1111/acem.13439

119 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;**143**:29–36. doi:10.1148/radiology.143.1.7063747

120 Stevens RJ, Poppe KK. Validation of clinical prediction models: what does the “calibration slope” really measure? *Journal of Clinical Epidemiology* 2020;**118**:93–9. doi:10.1016/j.jclinepi.2019.09.016

121 Franchini M, Mengoli C, Marietta M, *et al.* Safety of intravenous tranexamic acid in patients undergoing major orthopaedic surgery: A meta-analysis of

randomised controlled trials. *Blood Transfusion* 2018;**16**:36–43. doi:10.2450/2017.0219-17

122 Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. *BMJ* 2016;**352**:i6.

123 Damen JAAG, Debray TPA, Pajouheshnia R, *et al.* Empirical evidence of the impact of study characteristics on the performance of prediction models: a meta-epidemiological study. *BMJ Open* 2019;**9**:e026160. doi:10.1136/bmjopen-2018-026160

124 Rosella LC, Corey P, Stukel TA, *et al.* The influence of measurement error on calibration, discrimination, and overall estimation of a risk prediction model. *Population Health Metrics* 2012;**10**:20. doi:10.1186/1478-7954-10-20

125 Jurek AM, Greenland S, Maldonado G, *et al.* Proper interpretation of non-differential misclassification effects: expectations vs observations. *Int J Epidemiol* 2005;**34**:680–7. doi:10.1093/ije/dyi060

126 van Doorn S, Brakenhoff TB, Moons KGM, *et al.* The effects of misclassification in routine healthcare databases on the accuracy of prognostic prediction models: a case study of the CHA2DS2-VASc score in atrial fibrillation. *Diagn Progn Res* 2017;**1**. doi:10.1186/s41512-017-0018-x

127 Nicholson H. Paramedic perceptions of bleeding in trauma and the use of tranexamic acid. 2020.https://uwe.cloud.panopto.eu/Panopto/Pages/Viewer.aspx?id=c673a0d2-e8e3-4cbf-8634-abf800b35828 (accessed 19 Aug 2020).

128 Meybohm P, Straub N, Füllenbach C, *et al.* Health economics of Patient Blood Management: a cost-benefit analysis based on a meta-analysis. *Vox Sanguinis* 2020;**115**:182–8. doi:10.1111/vox.12873

129 Guerriero C, Cairns J, Perel P, *et al.* Cost-Effectiveness Analysis of Administering Tranexamic Acid to Bleeding Trauma Patients Using Evidence from the CRASH-2 Trial. *PLoS One* 2011;**6**. doi:10.1371/journal.pone.0018987

130 Benoni G, Fredin H. Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. *J Bone Joint Surg Br* 1996;**78**:434–40.

131 Sentilhes, Loic. TRAnexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean Delivery :a Multicenter Randomised, Double Blind Placebo Controlled Trial (TRAAP2). https://clinicaltrials.gov/ct2/show/record/NCT03431805?term=TRAAP2&rank=1 (accessed 3 Apr 2019).

APPENDICES

Appendix 3-1 Equation for predicting death due to bleeding

Simple model:

Predicted probability of death due to bleeding$= \frac{1}{1+e^{-S}}$

Where S= 0.6037 + Intercept_by_country + 0.0561 x Age – 0.0014 x Age^2 + 1.18e-05 x Age^3 + 0.0104 x SBP – 4.71e-04 x SBP^2 + 1.46e-06 x SBP^3 – 0.6144 x GCS + 0.0713 x GCS^2 – 0.0029 x GCS^3

Full model

Predicted probability of death due to bleeding$= \frac{1}{1+e^{-F}}$

Where F= -0. 5344 + Intercept_by_country + 0.0605 x Age – 0.0014 x Age^2 + 1.12e-05 x Age^3 + 0.0235 x SBP – 5.36e-04 x SBP^2 + 1.58e-06 x SBP^3 – 0.6336 x GCS + 0.0738 x GCS^2 – 0.0029 x GCS^3 – 0.0086 x HR + 1.03e-04 x HR^2 – 0.1710 x RR + 0.0060 x RR^2 – 5.4e-05 x RR^3

Coefficient for treatment by tranexamic acid was not included in the equation at baseline.

To predict death due to bleeding after treatment by tranexamic acid add -0.33 X tranexamic acid (0=no treatment, 1= tranexamic acid).

Appendix 3-2 Multivariate analysis predicting death due to bleeding

Full model N=23,402	coefficient	(95% CI)		P-VALUE
Age	0.0605	-0.0022	0.1232	0.059
Age^2	0.0014	-0.0028	$2.e^{-5}$	0.053
Age^3	$1.2e^{-5}$	$2.38e^{-6}$	$2.2e^{-5}$	0.015
SBP	0.0235	0.0024	0.04452	0.029
SBP^2	0.0005	-0.0007	.0003	<0.001
SBP^3	1.6 e^{-6}	$1.09e^{-6}$	$2.06e^{-6}$	<0.001
GCS	0.6336	-1.0710	-0.1962	0.005
GCS^2	0.0738	0.0213	0.1264	0.006
GCS^3	0.0029	-0.0048	-0.0010	0.002
HR	0.0086	-0.0236	0.0065	0.263
HR^2	0.0001	$2.9e^{-5}$	0.0002	0.006
RR	0.1710	-0.2379	-0.1040	<0.001
RR^2	0.0060	0.0035	0.0084	<0.001
RR^3	5.4 e-5	$-8.2e^{-5}$	$-2.6e^{-5}$	<0.001
Penetrating injury	0.3056	0.1327	0.4785	0.001
TXA	-0.3295	-0.4856	-0.1735	<0.001
Constant	-0.5344	-0.8861	1.9550	0.461

SBP: systolic blood pressure (mmHg); GCS: Glasgow Coma Scale ; HR: heart rate (bpm); RR: respiratory rate (bpm); TXA: tranexamic acid; 95% CI: 95% confidence interval.

Appendix 4-1 MEDLINE search strategy

The searches used to identify trials for this study were conducted to 1 July, 2018 with no restriction by date, language or publication status.

Database: Ovid MEDLINE(R) <1946 to March Week 26 2018>

1 exp Antifibrinolytic Agents/

2 (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.

3 exp Aprotinin/

4 (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren).ab,ti.

5 exp Tranexamic Acid/

6 (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or

transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.

7 exp Aminocaproic Acids/ or exp 6-Aminocaproic Acid/

8 (((aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan).ab,ti.

9 exp 4-Aminobenzoic Acid/tu [Therapeutic Use]

10 (PAMBA or para-aminomethylbenzoic or p-aminomethylbenzoic or amino?methylbenzoic acid or Gumbix or Styptopur or H-4-AMB-OH or CAS:56-91-7

or H-4AMBZ-OH or NH2-CH2-PH4-COOH or TIMTEC-BB SBB006704 or "RARECHEM AL BW 0005" or Amino-p-toluicacid).ti,ab.

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 10

12 randomi?ed.ab,ti.

13 randomized controlled trial.pt.

14 controlled clinical trial.pt.

15 placebo.ab.

16 clinical trials as topic.sh.

17 randomly.ab.

18 trial.ti.

19 12 or 13 or 14 or 15 or 16 or 17 or 18

20 (animals not (humans and animals)).sh.

21 19 not 20

22 11 and 21

Appendix 4-2 Equations of the different models

Logistic regression assessing overall treatment effect and homogeneity of treatment effect across trials

$$\text{Logit}\,(p(Y = 1)) = \beta_0 + \beta_1 S + \beta_2 X + \beta_3 (X*S) \qquad \text{[model-1]}$$

With Y = 1, the outcome did not die from bleeding for patient i in trial j, S is the trial (CRASH-2 S=0, WOMAN S=1), X is treatment (tranexamic acid is X=1, placebo is X=0).

Then β_0 is the log(odds) in the placebo group in the CRASH-2 trial; β_1 is the difference between trials in placebo group; β_2 the effect of tranexamic acid in CRASH-2 trial; and β_3 is the interaction between treatment effect and trial.

Logistic regression estimating non-linear effect of intervention by baseline risk and its interaction with time to treatment (triple interaction).

$$\text{Logit}\,(p(Y = 1)) = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 BR + \beta_4 (X*T) + \beta_5 (BR*T) + \beta_6 (BR*X) + \beta_7 (BR*X*T) \qquad \text{[model-2]}$$

With Y, X coded as in [model-1]. T is the time to treatment in hours. BR is the baseline risk.

Then β_0 is the log(odds) in the placebo group when T=0 and BR=0; β_1 is the linear effect of time to treatment in the placebo group at BR=0; β_2 the effect of tranexamic acid at T=0 and BR=0; β_3 is the linear effect of baseline risk in the placebo group at T=0; β_4 is the interaction between treatment effect and time to treatment at BR=0; β_5 is the interaction between time to treatment and baseline risk in the placebo group; β_6

is the interaction of baseline risk with the treatment at T=0; β_7 is the triple interaction of baseline risk with the treatment and the time to treatment.

Logistic regression estimating linear effect of intervention by baseline risk (we assume this interaction is the same in both trials).

$$\text{Logit}\,(p(Y = 1)) = \beta_0 + \beta_1 S + \beta_2 X + \beta_3 BR + \beta_4 (BR*X) + \beta_5 T \qquad \text{[model-3]}$$

With Y, S, X, T, BR coded as in [model-1] and [model-2];

Then, β_0 is the log(odds) in the placebo group in the CRASH-2 trial when BR=0; β_1 is the difference between trials; β_2 is the effect of tranexamic when BR=0; $\beta_3$is the linear effect of baseline risk in the placebo group of both trials; β_4 is the interaction of baseline risk with the treatment; β_5 is the effect of time to treatment.

Appendix 4-3 Characteristics of included and ongoing trials

Trial ID	Title	Participants	Intervention	Outcomes
Included trials				
CRASH-2 [8]	A large randomised placebo controlled trial among trauma patients with, or at risk of, significant haemorrhage, of the effects of anti-fibrinolytic treatment on death and transfusion requirement.	n=20,211 Adult (>16 years) trauma patients with or at risk of significant bleeding.	A loading dose of 1 g tranexamic acid or placebo will be administered as soon possible, followed by a maintenance dose of 1 g TXA or placebo over 8 hours.	Primary: death. Secondary: vascular occlusive events, blood transfusion requirements, disability.
WOMAN [37]	Tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double-blind, placebo controlled trial	N=20,060 Women with clinically diagnosed PPH following vaginal delivery of a baby or caesarean section. Clinical diagnosis of PPH may be based on any of the following: estimated blood loss after	1g of tranexamic acid by intravenous injection or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. If after 30 minutes bleeding continues, or if it stops and restarts within 24 hours after	Primary: death or hysterectomy. Secondary: death, surgical intervention, blood transfusion, health status, thromboembolic events, other relevant medical events, length of stay at hospital/time spent at an intensive care unit, mechanical

		vaginal delivery of a baby >500 mL OR >1000 mL from caesarean section OR blood loss sufficient to compromise the haemodynamic status of the woman.	the first dose, a second dose may be given.	ventilation, status of breastfed baby/ies.
TICH-2[38]	Tranexamic acid for hyperacute primary Intracerebral haemorrhage	N=2325 Adult patients with acute primary intracerebral haemorrhage within 8 hours of stroke onset.	Tranexamic acid 1 g or placebo in 100 ml sodium chloride 0.9% infusion bag intravenously as a loading dose infusion over 10 min, followed by infusion of tranexamic acid 1 g or placebo in 250 ml sodium chloride 0.9% infusion bag over 8 h.	Primary: eath or dependency at day 90 Secondary: neurological impairment at day 7 or discharge if sooner, disability (Barthel index) at day 90, Quality of Life (EuroQol) at day 90, cognition at day 90, costs: length of stay in hospital, re-admission, institutionalisation, radiological efficacy/safety (computed tomography scan):

				change in haematoma volume from baseline to day 2, haematoma location and new infarction.
Excluded Trials				
ATACAS[41]	Aspirin and tranexamic acid for Coronary Artery Surgery Trial	N=4662 Adults undergoing coronary-artery surgery and at risk of perioperative complications.	Tranexamic acid (100 mg/kg) or saline administered 30 minutes after induction of anaesthesia (dose of tranexamic acid halved to 50 mg after 1392 patients enrolled)	Primary: composite outcome of all-cause 30 day mortality or thrombotic event Secondary: death, nonfatal myocardial infarction, pulmonary embolism, stroke, acute renal failure, bowel infarction), reoperation due to major haemorrhage or cardiac tamponade, blood transfusion.
TRAAP[42]	Tranexamic acid for Preventing Postpartum Haemorrhage Following a Vaginal Delivery: a Multicenter Randomised	N = 4079	1g tranexamic acid or placebo will be administered intravenously just after birth.	Primary: incidence of PPH, defined by blood loss ≥500 mL Secondary: Mean blood loss at 15 minutes after birth; mean

	Double Blind Placebo Controlled Trial	Women in labour for a planned vaginal singleton delivery, at a term ≥35 weeks.		total blood loss; incidence of severe PPH; need for supplementary uterotonic treatment; postpartum transfusion; need for invasive second-line procedures for PPH; haemoglobin, hematocrit; hemodynamic tolerance; mild adverse effects; tolerance lab tests; severe adverse effects
Ongoing trials				
CRASH-3 [103] (ISRCTN15088122) Completed after the study period inclusion	Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double-blind placebo controlled trial	N=13,000 (target) Adults with traumatic brain injury, who are within 8 hours of injury, with any intracranial bleeding on computed tomography scan or who have	Loading dose of tranexamic acid (1 g by intravenous injection) or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. Maintenance dose of tranexamic acid (1 g	Primary: death in hospital within 28 days of injury. Secondary: vascular occlusive events, disability, seizures, neurosurgical intervention, days in intensive care, other adverse events.

		a GCS of 12 or less, and have no significant extra-cranial haemorrhage.	by intravenous injection) or placebo (sodium chloride 0.9%) given after the loading dose is finished.	
HALT-IT[104] (ISRCTN11225767) Completed after the study period inclusion	Tranexamic acid for the treatment of gastrointestinal haemorrhage: an international randomised, double blind placebo controlled trial	N=8000 (target) Adults with acute significant upper or lower gastrointestinal bleeding.	Loading dose of tranexamic acid (1 g by intravenous injection) or placebo (sodium chloride 0.9%) will be given as soon as possible after randomisation, followed by an intravenous infusion of 3g of tranexamic acid or placebo (sodium chloride 0.9%) over 24 hours.	Primary: death in hospital (cause-specific mortality will also be recorded) Secondary: re-bleeding, need for salvage surgery or radiological intervention, blood transfusion, thromboembolic events, other adverse medical events, functional status, time spent at an intensive care unit, length of stay in hospital
Shanghai FMIH-TXA1[105] NCT02936661	Tranexamic acid for Preventing Postpartum Hemorrhage After Caesarean Section	N=6700 (target) Women giving birth by caesarean section.	Tranexamic acid or placebo	Primary: PPH Secondary: amount of postpartum bleeding

Expected completion date: March 2019				
PATCH[34] NCT02187120 Expected completion date: January 2021	A Multi-centre Randomised, Double-blinded, Placebo-controlled Trial of Pre-hospital Treatment With tranexamic acid for Severely Injured Patients at Risk of Acute Traumatic Coagulopathy.	N= 1184 (target) Adult patients (age ≥18 years); injured through any mechanism; COAST score≥3.	1 g tranexamic acid or placebo (0.9% NaCl) by slow intravenous injection as early as possible following injury. Soon after arrival to the emergency department, patients will be given 1g tranexamic acid or placebo infused intravenously for 8 hours.	Primary: favourable outcome at six months (moderate disability to good recovery, GOSE scores 5-8) compared to those who have died (GOSE 1), or have severe disability (GOSE 2-4). Secondary: units of blood products used in the first 24 hours; coagulation profile; ICU ventilator-free days in first 28 days; vascular occlusive events; mortality; proportion of deaths due to: bleeding, vascular occlusion, multi-organ

				failure and head injury; cumulative incidence of sepsis at 28 days or hospital discharge whichever occurs first; severity of chronic pain 6 months after injury and its interference with daily activities measured using the modified Brief Pain Inventory; Quality of Life (SF12® and EQ5D) at 6 months.
STAAMP [106] NCT02086500 Completed after the study period inclusion	Study of tranexamic acid During Air Medical Prehospital Transport Trial For Trauma Patients At Risk Of Hemorrhage	N=1000 (target) Adult (18-90 years) trauma patients within 2 hours of injury. Setting: USA	1 g tranexamic acid or placebo during air medical transport.	Primary outcome: 30 day mortality. Secondary outcomes: hyperfibrinolysis, acute lung injury, multiple organ failure, nosocomial infection, mortality, early seizures, pulmonary embolism, early resuscitation needs, early

				coagulopathy as measured by INR and rapid thromboelastography parameters, early inflammatory response, plasmin levels, leukocyte, platelet and complement activation.
NCT03364491[107] (MFMU Network) Expected completion date: December 2020	Tranexamic Acid for the Prevention of Obstetrical Hemorrhage After Caesarean Section	N=11000 (target) Women giving birth by scheduled or unscheduled caesarean section Setting: USA	1g tranexamic acid or placebo	Primary outcome: maternal death or transfusion of 1 or more units of packed red blood cells (up to hospital discharge or 7 days) Secondary outcome: blood loss, composite surgical or radiological intervention to control bleeding, composite maternal death and thromboembolic events, transfusion related acute lung

				injury, transfusion of other blood products, transfusion of more than 4 RBC, acute kidney injury, thromboembolic events, seizure, ingfection, admission to ICU, change in haemoglobin, TXA side-effects, length of stay, hospital re-admission, transfusion reaction
NCT01990768[108] Completed after the study period inclusion	Prehospital Tranexamic Acid Use for Traumatic Brain Injury	N=1002 (target) 967 recruited Moderate to severe TBI (GCS score ≤12) Setting: prehospital, Canada, USA	1 g tranexamic acid prior to hospital arrival followed by a 1 g infusion or 2 g tranexamic acid prior to admission or placebo	Primary outcome: Glasgow Outcome Scale Extended (GOS-e) at 6 months. Secondary outcome: Death at 28 days, disability rating scale at discharge and 6 months, Unfavourable outcome Dichotomized GOS-e, Number ICH, Marshall score CT,

				Rotterdam score CT, Neurosurgical intervention, Hospital free-days, ICU free-days, seizure, thromboembolic event (CVD, DVT, MI, PE).
TRAAP-2[131] NCT03431805 Expected completion date: June 2020	Tranexamic acid for Preventing Postpartum Haemorrhage Following a Cesarean Delivery	N=4524 (target) Women admitted for caesarean delivery before or during labour (term ≥34 weeks) Setting: France	1 g tranexamic acid or placebo with prophylactic uterotonic 3 minutes after birth.	Primary outcome: incidence of PPH, defined by blood loss >1000 mL at day 2. Secondary outcome: blood loss >500; >1500, mean blood loss, incidence of transfusion, mean red blood cells transfused, incidence embolization or surgery, change in haemoglobin, HR, SBP, DBP, nausea, vomiting, phosphenes, dizziness, vreat, urea, prothrombin, asat, alat, bilirubin, fibrinogen, DVP, PE,

				MI, any thrombotic event, seizure, women's satisfaction, shock, ICU, death from any cause
WOMAN-2[109] NCT03475342 Expected completion date: March 2022	World Maternal Antifibrinolytic Trial 2	N=10000 (target) Women with moderate or severe anemia (Hb <100g/L or packed cell volume <30%) planned to give birth vaginally Setting: international	1g tranexamic acid or placebo administered at delivery (no later than 15 minutes after umbilical cord is clamped)	Primary outcome: PPH at 24 hours (blood loss >500 or any blood loss sufficient to compromise haemodynamic stability). Secondary outcome: blood loss, Hb, Haemodynamic instability, shock index, quality of life (maternal), side-effects, exercise tolerance, intervention for control PPH, blood transfusion, vascular occlusive events, anaemia, organ dysfunction, in-hospital death, length of hospital stay,

				transfer to higher facility, status baby, thrombotic events in breastfed babies, adverse events.
POISE-3 trial[110] NCT03505723 Expected completion date: December 2022	PeriOperative ISchemic Evaluation-3 Trial	N=10000 (target) Patent undergoing non-cardiac surgery with ≥45 years of age and expected to require at least an overnight hospital admission after surgery. Setting: international		Primary outcome: a composite of life-threatening bleeding, major bleeding and critical organ bleeding at 30 days. A composite of myocardial infarction, non-haemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism at 30 days. For patients in the blood pressure management arm: a composite of vascular death, and non-fatal myocardial

				infarction, stroke, and cardiac arrest at 30 days.

References

1 CRASH-2 trial collaborators, Shakur H, Roberts I, *et al.* Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet Lond Engl* 2010; **376**: 23–32.

2 Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet Lond Engl* 2017; **389**: 2105–16.

3 Sprigg N, Flaherty K, Appleton JP, *et al.* Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet Lond Engl* 2018; **391**: 2107–15.

4 Myles PS, Smith JA, Forbes A, *et al.* Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. *N Engl J Med* 2017; **376**: 136–48.

5 Sentilhes L, Winer N, Azria E, *et al.* Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. *N Engl J Med* 2018; **379**: 731–42.

6 Dewan Y, Komolafe EO, Mejía-Mantilla JH, Perel P, Roberts I, Shakur H. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials* 2012; **13**: 87.

7 Roberts I, Coats T, Edwards P, *et al.* HALT-IT - tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial. *Trials* 2014; **15**. DOI:10.1186/1745-6215-15-450.

8 Shanghai First Maternity and Infant Hospital. Tranexamic Acid for Preventing Postpartum Hemorrhage After Cesarean Section (NCT02936661). https://clinicaltrials.gov/ct2/show/record/NCT02936661 (accessed April 3, 2019).

9 Mitra B, Mazur S, Cameron PA, *et al.* Tranexamic acid for trauma: filling the 'GAP' in evidence. *Emerg Med Australas EMA* 2014; **26**: 194–7.

10 Brown JB, Neal MD, Guyette FX, *et al.* Design of the Study of Tranexamic Acid during Air Medical Prehospital Transport (STAAMP) Trial: Addressing the Knowledge Gaps. *Prehospital Emerg Care Off J Natl Assoc EMS Physicians Natl Assoc State EMS Dir* 2015; **19**: 79–86.

11 Clifton, Rebecca. Tranexamic Acid for the Prevention of Obstetrical Hemorrhage After Cesarean. https://clinicaltrials.gov/ct2/show/NCT03364491.

12 May, Susanne. Prehospital Tranexamic Acid Use for Traumatic Brain Injury (NCT01990768). https://clinicaltrials.gov/ct2/show/record/NCT01990768?term=NCT01990768&rank=1 (accessed April 3, 2019).

13 Sentilhes, Loic. TRAnexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean Delivery :a Multicenter Randomised, Double Blind Placebo Controlled Trial (TRAAP2). https://clinicaltrials.gov/ct2/show/record/NCT03431805?term=TRAAP2&rank=1 (accessed April 3, 2019).

14 Ker K, Roberts I, Chaudhri R, *et al.* Tranexamic acid for the prevention of postpartum bleeding in women with anaemia: study protocol for an international, randomised, double-blind, placebo-controlled trial. *Trials* 2018; **19**. DOI:10.1186/s13063-018-3081-x.

15 Devereaux, PJ. PeriOperative ISchemic Evaluation-3 Trial (POISE-3). https://clinicaltrials.gov/ct2/show/study/NCT03505723?show_locs=Y#locn (accessed April 3, 2019).

Appendix 4-4 Results of risk of bias assessment

CRASH-2

Domain	Judgement	Justification
Sequence generation	Low	Computer-generated.
Allocation concealment	Low	Tranexamic acid and placebo were packaged in identical ampoules. Recruiting hospitals with reliable telephone access using a telephone randomisation service, hospitals without, using a local pack system.
Blinding	Low	Participants, clinicians and trial staff were blinded to treatment allocation.
Incomplete outcome data	Low	Over 99% of patients were followed up and contributed outcome data.
Selective outcome reporting	Low	Prospectively registered and data on all pre-specified outcomes available for analysis.

WOMAN

Domain	Judgement	Justification
Sequence generation	Low	Computer-generated.
Allocation concealment	Low	Tranexamic acid and placebo were packed in sequentially numbered, sealed, treatment boxes.
Blinding	Low	Participants, clinicians and trial staff were blinded to treatment allocation.
Incomplete outcome data	Low	Over 99% of patients were followed up and contributed outcome data.
Selective outcome reporting	Low	Prospectively registered and data on all pre-specified outcomes available for analysis.

Appendix 4-5 Prognosis model to estimate baseline risk of death due to bleeding

CRASH-2 trial

$Pr = 1/ (1+e^{-xb})$

$xb = 0.534 + RI + (0.061 * Age) – (1.4e^{-3} * Age^2) + (1.2e^{-05} * Age^3) + (0.023 * SBP) – (5.4e\text{-}04 * SBP^2) + (1.6e^{-06} * SBP^3) – (0.634 * GCS) + (0.074 * GCS^2) – (2.9e^{-3} * GCS^3) – (8.6e^{-3} * HR) + (1.0e\text{-}04 * HR^2) – (0.171 * RR) + (0.006 * RR^2) – (5.4e^{-05} * RR^3)$

RI: Random Intercept by country

Age (Year)

SBP: Systolic Blood Pressure (mmHg)

HR: Heart Rate (Beat per min)

RR: Respiratory Rate (Breath per minute)

GCS: Glasgow Coma Scale

Penetrating: Penetrating Injury

WOMAN trial

$Pr = 1/ (1+e^{-xb})$

$xb = -8.66 + RI + (Age * 0.06) – (SBP * 0.01) – (SBP^2 * 3\ e^{-4}) + (SBP^3 * 1.6\ e^{-6}) + (BL * 2\ e^{-3}) – (BL^2 * 3\ e^{-7}) – (PP * 1.05) – (UA * 0.32) + (HI * 1.56) - (Delivery * 0.72)$

RI: Random Intercept by country

Age (Year)

SBP: Systolic Blood Pressure (mmHg)

BL: Blood Loss (ml)

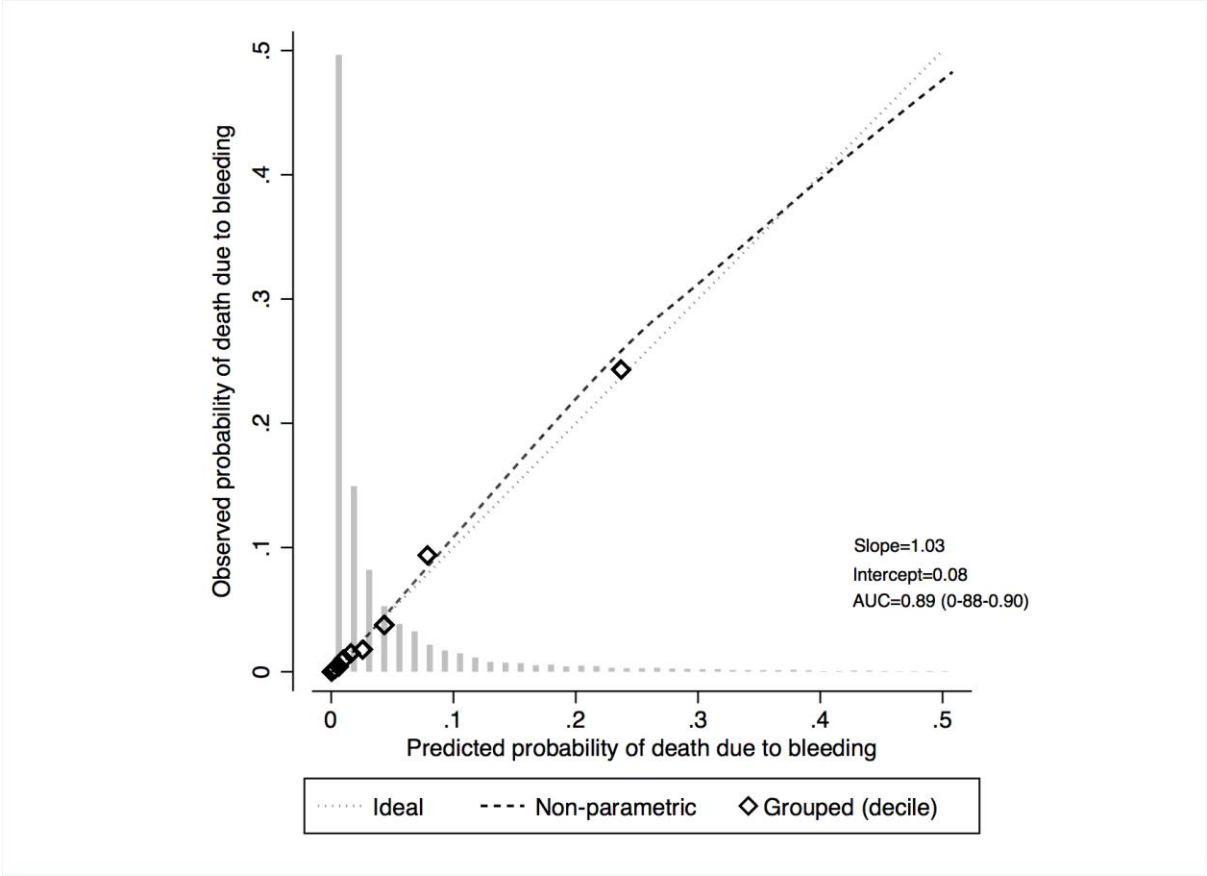
PP: Placenta Previa (Yes=1, No=0)

UA: Uterine Atony (Yes=1, No=0)

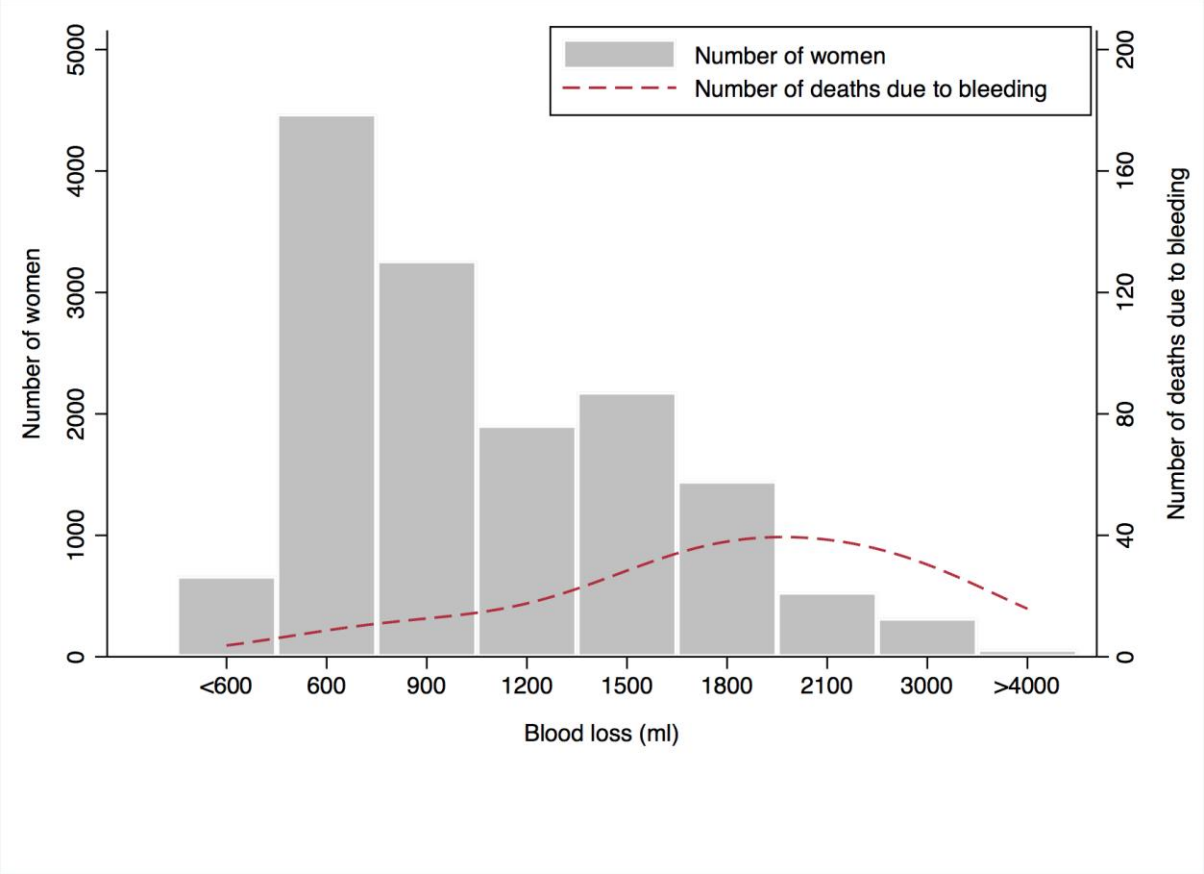
HI: Haemodynamic instability (Yes=1, No=0)

Delivery: 0=Vaginal delivery; 1=caesarean section

Appendix 4-6 Performance of prognosis model predicting baseline risk of death due to bleeding



Appendix 4-7 Frequency of women with postpartum hemorrhage and death due to bleeding according to blood loss



Appendix 4-8 Vascular occlusive events (fatal and non-fatal) by trial and overall

	CRASH-2 trial			WOMAN-trial			Overall trials		
Baseline risk	Tranexamic acid n (%)	Placebo n (%)	RR (95% CI)	Tranexamic acid n (%)	Placebo n (%)	RR (95% CI)	Tranexamic acid n (%)	Placebo n (%)	RR (95% CI)
0-5%	45 / 4587 (1.0)	55 / 4476 (1.2)	0.80 (0.54-1.18)	19 / 7003 (0.3)	10 / 6920 (0.1)	1.87 (0.87-4.02)	64 / 11612 (0.6%)	65 / 11396 (0.6%)	0.97 (0.69-1.36)
6-10%	15 / 988 (1.5)	22 / 1001 (2.2)	0.71 (0.36-1.35)	2 / 257 (0.8)	0 / 224 (0)	-	17 (1.4%)	22 (1.8%)	0.77 (0.41-1.45)
11-20%	22 / 731 (3.0)	36 / 642 (5.6)	0.54 (0.32-0.90)	1 / 122 (0.8)	2 / 140 (1.4)	0.57 (0.05-6.25)	23 (2.7%)	38 (4.9%)	0.55 (0.33-0.92)
>20%	13 / 478 (2.7)	25 / 560 (4.4)	0.61 (0.32-1.18)	1 / 82 (1.2)	2 / 78 (2.6)	0.48 (0.04-5.14)	14 (2.7%)	27 (4.2%)	0.59 (0.31-1.12)
Test for homogeneity, P-value			0.040			0.367			0.076

Appendix 4-9 Sensitivity analysis with baseline risk estimate based on models developed with placebo arm only

	Main analysis (baseline risk based on both arm)				Sensitivity analysis (baseline risk based on placebo arm)			
	Overall adjusted effect	P value	Test for homogeneity*	P value	Overall adjusted effect	P value	Test for homogeneity*	P value
Baseline risk by categories (RR)	0.74 (0.66-0.83)	<0.001	0.20	0.978	0.74 (0.66-0.83)	<0.001	4.44	0.218
Model 3 (interaction TXA-Baseline risk (OR)	0.74 (0.61-0.88)	0.001	-0.66	0.510	0.74 (0.62-0.89)	0.001	-1.03	0.305

*****by categories or for interaction

TXA: tranexamic acid; RR: risk ratio; OR: odds ratio

Appendix 5-1 Abbreviated Injury Scale (AIS) diagnosis associated with haemorrhage

- Blood loss > 20%.

- Aorta [OR] Vena Cava [OR]carotid [OR]femoral [OR]Major arteries [OR]veins AND laceration.

- Spleen [OR]liver [OR] Kidney [OR] Myocardium [AND] major laceration.

- Major haemothorax.

- Retroperitoneum haemorrhage.

Appendix 5-2 Formula for the Brier Score and Scaled Brier Score

Brier Score= $\frac{1}{N}\sum_{i=1}^{n}(Y-p)^2$

Where Y is the observed outcome and P the prediction of the model.

Brier Score$_{max}$= $P \times (1-P)^2 + (1-P) \times P^2$

Where P is the mean of the prediction p.

Scaled Brier score= $\frac{1-Brier}{Brier\ max}$

Scaled Brier score ranges from 0% to 100%

Appendix 5-3 Methods to model tranexamic acid treatment effect and death due to bleeding avoided.

First method

a) We estimated the baseline probabilities of death due to bleeding in the TARN population (P1).

P1= [0.5344157 - 0.5726779 + (0.0604783 * age) - (0.0013908 * age2) + (0.000012 * age3) + (0.0234826 * isbp) - (0.0005366 * isbp2) + (0.00000158 * isbp3) - (0.6336347 * igcs) + (0.0738416 * igcs2) - (0.0029216 * igcs3) - (0.0085677 * ihr) + (0.0001027 * ihr2) - (0.1709854 * irr) + (0.0059866 * irr2) - (0.000054 * irr3) + (0.3056116 * penetrating)] * 0.82

P1 (Baseline probabilities of death due to bleeding); ISBP (initial systolic blood pressure); IGCS (initial Glasgow coma scale); IHR (initial heart rate); IRR (initial respiratory rate); Penetrating injury.

b) We used previous studies exploring treatment effect by time and baseline risk (TE).

TE= OR txa/time * OR txa/baseline risk

TE (treatment effect); OR (odds ratio)

OR txa/time is function of delay from Accident to Ambulance Arrival (Prehospital treatment) or Delay from Accident to Hospital Arrival (In-hospital treatment).[10]

0.70235307 if delay=0 min	0.76495222 if delay ==65 min	0.83300851 if delay ==130 min
0.70698462 if delay=5 min	0.76998788 if delay ==70 min	0.83848272 if delay ==135 min
0.71164609 if delay ==10 min	0.77505601 if delay ==75 min	0.84399218 if delay ==140 min
0.71633767 if delay ==15 min	0.78015683 if delay ==80 min	0.84953709 if delay ==145 min
0.72105956 if delay ==20 min	0.78529054 if delay ==85 min	0.8551177 if delay ==150 min
0.72581194 if delay ==25 min	0.79045734 if delay ==90 min	0.86073421 if delay ==155 min
0.73059501 if delay ==30 min	0.79565744 if delay ==95 min	0.86638687 if delay ==160 min
0.73540897 if delay ==35 min	0.80089106 if delay ==100 min	0.87207589 if delay ==165 min
0.740254 if delay ==40 min	0.80615841 if delay ==105 min	0.87780151 if delay ==170 min
0.7451303 if delay ==45 min	0.81145969 if delay ==110 min	0.88356395 if delay ==175 min
0.75003808 if delay ==50 min	0.81679513 if delay ==115 min	0.88936344 if delay ==180 min
0.75497752 if delay ==55 min	0.82216493 if delay ==120 min	
0.75994883 if delay ==60 min	0.82756932 if delay ==125 min	

OR txa/baseline risk is constant=1 (Ref BJA)

c) We estimated post-treatment probabilities of death due to bleeding (P2)

$$P2=P1 * TE$$

d) We estimated the number of deaths due to bleeding avoided by tranexamic acid.

$$\text{number of deaths avoided}= \sum P1 \ - \sum P2$$

e) Net benefit

Net benefit= bumber of deaths avoided – number of deaths due to side-effects

We considered tranexamic acid treatment within 3 hours from injury. In this time interval, we did not find any randomised control trial reporting death due to side-effects or any increase of non-fatal vascular occlusive events.

$$\text{Net benefit} = \text{number of deaths avoided}$$

Sensitivity analysis (Second method)

a) We estimated the baseline probabilities of death due to bleeding in the TARN population ($P1_{obs}$).

We divided death due to bleeding by treatment effect for patient treated by tranexamic acid to estimate baseline probabilities.

$$P1_{obs}= (Death_{obs})_{if\ TXA=0} + \left(\frac{Death_{obs}}{TE}\right)_{if\ TXA==1}$$

$Death_{obs}$= early death with evidence of haemorrhage

b) We estimated post-treatment probabilities of deaths due to bleeding (P2)

$$P2=P1_{obs} * TE$$

c) We estimated the number of deaths due to bleeding avoided by tranexamic acid.

$$\text{number of deaths avoided} = \sum P1 \; - \sum P2$$

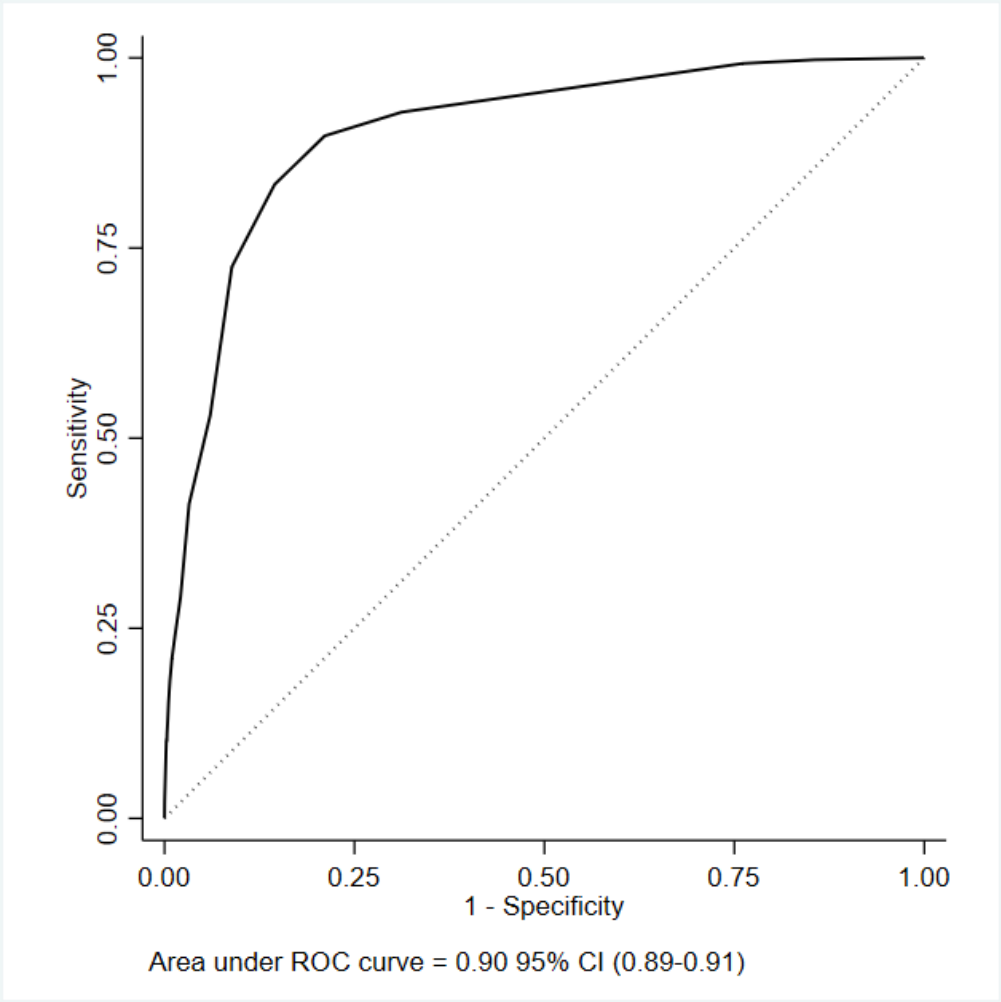
d) Net benefit

Net benefit = number of deaths avoided – number of deaths due to side-effects

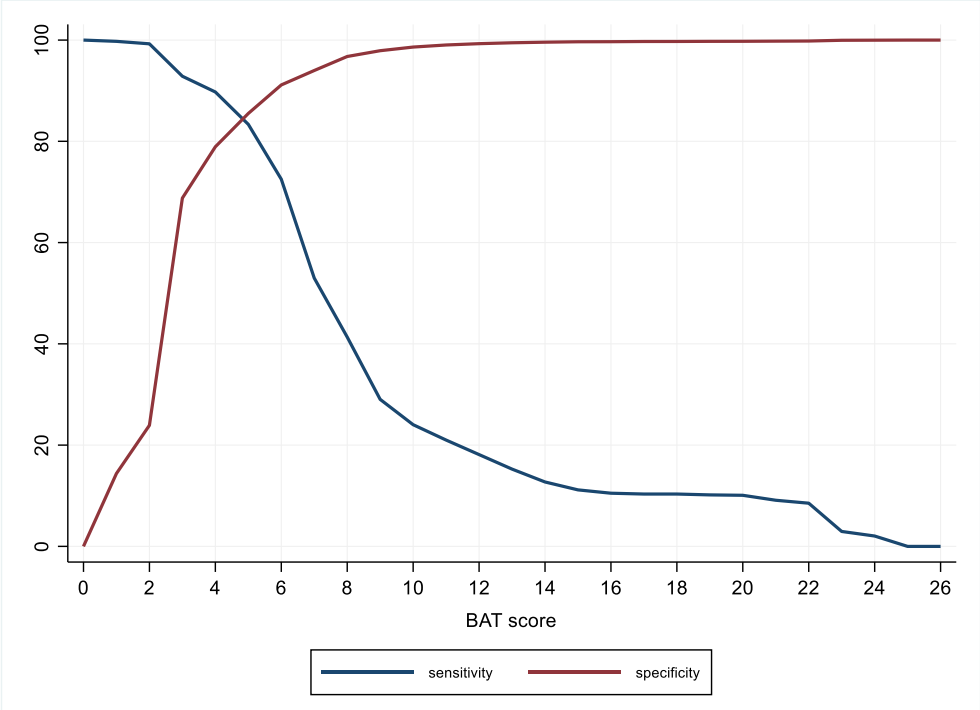
We considered tranexamic acid treatment within 3 hours from injury. In this time interval, we did not find any randomised control trial reporting death due to side-effects or any increase of non-fatal vascular occlusive events.

$$\text{net benefit} = \text{number of deaths avoided}$$

Appendix 5-4 Receiving operating characteristic curve for external validation of the BATT score

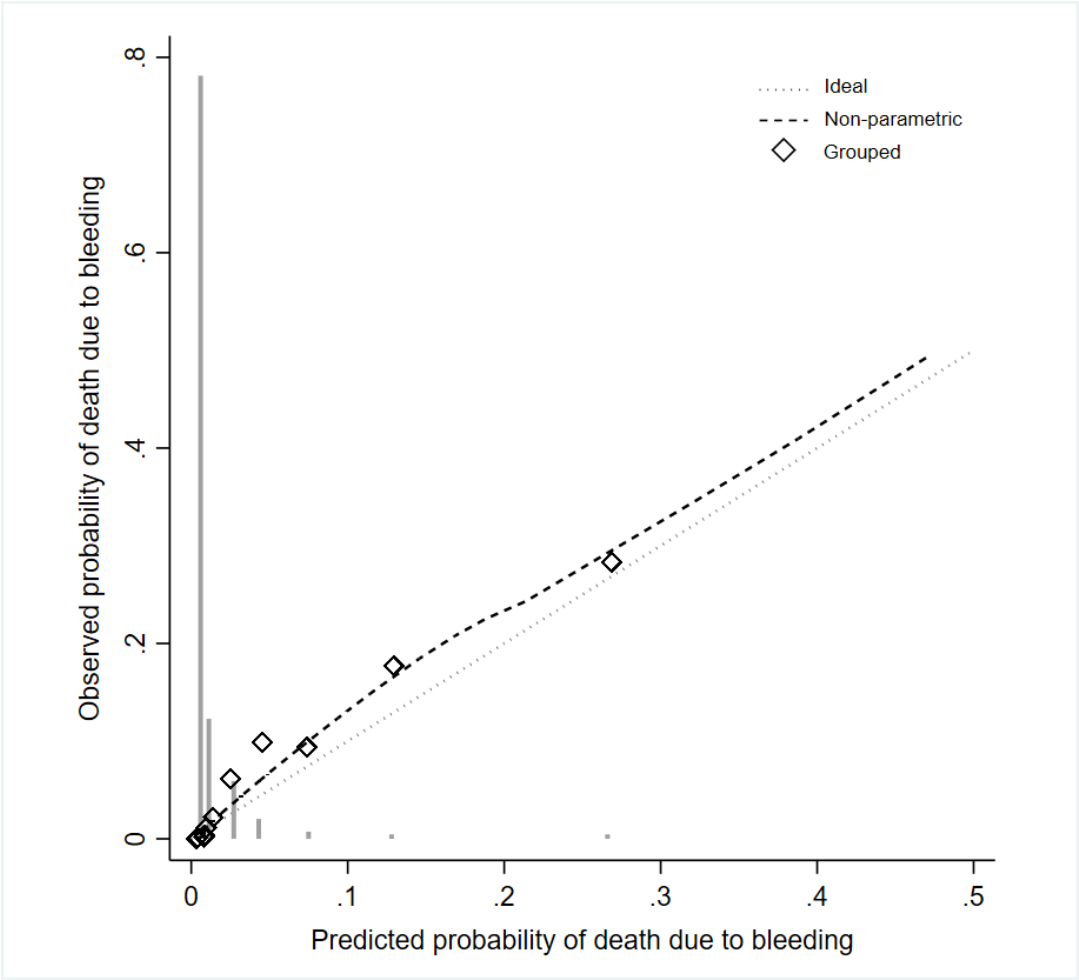


Appendix 5-5 Sensitivity and specificity according to the BATT score for death due to bleeding.

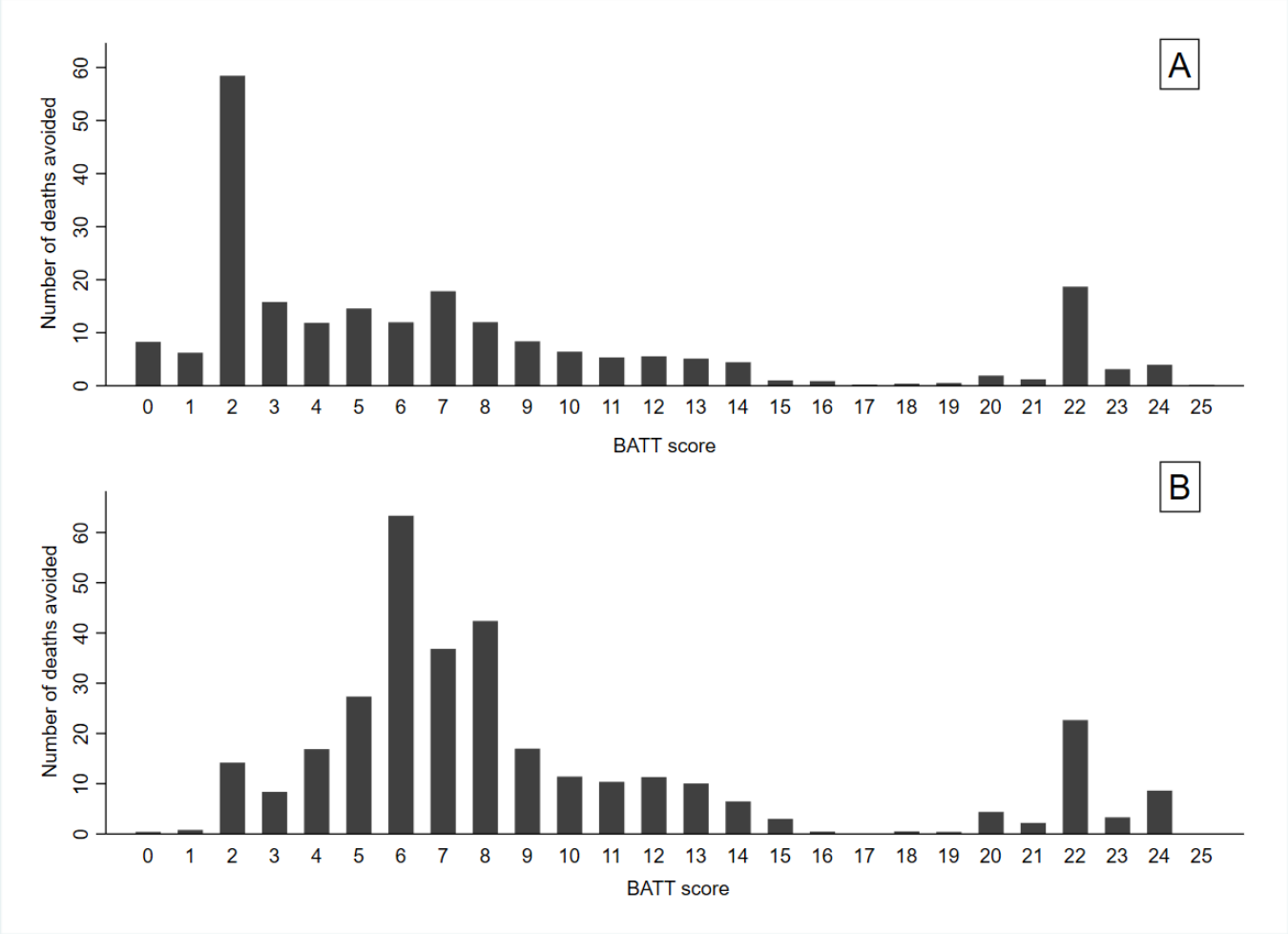


Threshold	Sensitivity (%)	Specificity (%)	Likelihood ratio +	Likelihood ratio -
0	100	0	1	-
≥ 1	100	14	1.17	0.017
≥ 2	99	24	1.31	0.031
≥ 3	93	69	2.98	0.104
≥ 4	90	79	4.26	0.130
≥ 6	73	91	8.18	0.302
≥ 8	41	97	12.77	0.606
≥ 10	24	99	17.37	0.770
≥ 12	18	99	25.42	0.825

Appendix 5-6 Calibration curve for external validation of the BATT score



Appendix 5-7 Number of deaths avoided due to prehospital tranexamic acid by BATT score



A: Estimated number of deaths avoided based on the predicted baseline risk.

B: Estimated number of deaths avoided based on observed probabilities of death (sensitivity analysis).

Appendix 6. Published papers

Ageron F. -X., Gayet-Ageron A., Steyerberg E., Bouzat P., & Roberts I. (2019). Prognostic model for traumatic death due to bleeding: cross-sectional international study.. *BMJ Open*, *9*(5), e026823. doi:10.1136/bmjopen-2018-026823 (Chapter III)

Ageron F. -X., Gayet-Ageron A., Ker K., Coats T. J., Shakur-Still H., Roberts I., & Antifibrinolytics Trials Collaboration. (2020). Effect of tranexamic acid by baseline risk of death in acute bleeding patients: a meta-analysis of individual patient-level data from 28 333 patients. *BRITISH JOURNAL OF ANAESTHESIA*, *124*(6), 676-683. doi:10.1016/j.bja.2020.01.020 (Chapter IV)

Ageron F-X, Coats T.J., Darioli V., Roberts I. (2020). Validation of the BATT score for prehospital risk strati123cation of traumatic haemorrhagic death: Usefulness for tranexamic acid treatment criteria. *SCANDINAVIAN JOURNAL OF TRAUMA RESUSCITATION & EMERGENCY MEDICINE,* doi:10.21203/rs.3.rs-64755/v2 (Undergoing minor revision) (Chapter V)

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1602524	**Title**	Dr
First Name(s)	Francois-Xavier		
Surname/Family Name	Ageron		
Thesis Title	Tranexamic acid in trauma care: Who should be treated, when and where?		
Primary Supervisor	Professor Ian Roberts		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	British Medical Journal Open access (1)		
When was the work published?	2019		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the study with Ian Roberts. I designed and monitored the data collectioon with Pierre Bouzat and Ian Roberts. I analysed the data with Angele Gayet. I wrote the manuscript.

SECTION E

Student Signature	[redacted]
Date	9 Dec 2020

Supervisor Signature	[redacted]
Date	9 12 20

BMJ Open

Prognostic model for traumatic death due to bleeding: cross-sectional international study

Francois-Xavier Ageron,[1,2] Angele Gayet-Ageron,[1,3] Ewout Steyerberg,[4,5] Pierre Bouzat,[6] Ian Roberts[1]

To cite: Ageron F-X, Gayet-Ageron A, Steyerberg E, *et al*. Prognostic model for traumatic death due to bleeding: cross-sectional international study. *BMJ Open* 2019;**9**:e026823. doi:10.1136/bmjopen-2018-026823

► Pre-publication history and additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-026823).

Received 21 September 2018
Revised 12 April 2019
Accepted 30 April 2019

For numbered affiliations see end of article.

Correspondence to
Francois-Xavier Ageron;
fxageron@gmail.com

ABSTRACT

Objective To develop and validate a prognostic model and a simple model to predict death due to bleeding in trauma patients.

Design Cross-sectional study with multivariable logistic regression using data from two large trauma cohorts.

Setting 274 hospitals from 40 countries in the Clinical Randomisation of Anti-fibrinolytic in Significant Haemorrhage (CRASH-2) trial and 24 hospitals in the Northern French Alps Trauma registry.

Participants 13 485 trauma patients in the CRASH-2 trial and 9945 patients in the Northern French Alps Trauma registry who were admitted to hospital within 3 hours of injury.

Main outcome measure In-hospital death due to bleeding within 28 days.

Results There were 815 (6%) deaths from bleeding in the CRASH-2 trial and 102 (1%) in the Northern French Alps Trauma registry. The full model included age, systolic blood pressure (SBP), Glasgow Coma Scale (GCS), heart rate, respiratory rate and type of injury (penetrating). The simple model included age, SBP and GCS. In a cross-validation procedure by country, discrimination and calibration were adequate (pooled C-statistic 0.85 (95% CI 0.81 to 0.88) for the full model and 0.84 (95% CI 0.80 to 0.88) for the simple model).

Conclusion This prognostic model can identify trauma patients at risk of death due to bleeding in a wide range of settings and can support prehospital triage and trauma audit, including audit of tranexamic acid use.

Strengths and limitations of this study

- While there are models that predict all-cause mortality for trauma, this prognostic model is the first to identify trauma patients from a wide range of settings at risk of death due to bleeding.
- We used a rigorous innovative method to develop and validate this prognostic model with an internal–external cross-validation method based on data from 41 countries to ensure that the result is widely applicable.
- This model can support clinical decision-making for prehospital triage and for identifying population to audit to help implementation of effective intervention such as tranexamic acid.
- As the objective of this model was to identify the population at risk of death due to bleeding, discrimination showed a good ability and homogenous results across countries.
- Due to narrow range in the case-mix of some countries, we observed statistical heterogeneity in terms of calibration.

INTRODUCTION

Traumatic haemorrhage is responsible for about 2 million deaths each year and is a leading cause of preventable death in trauma.[1–3] Early administration of tranexamic acid given within 3 hours of injury reduces death due to bleeding by about one-third.[4] Tranexamic acid is widely included in trauma care guidelines.[5 6]

Nevertheless, many trauma patients who might benefit from tranexamic acid are not treated or are not treated soon enough.[7] Despite an increase in tranexamic acid use after regionalisation of trauma services in England, 42% of bleeding trauma patients did not receive it.[8] There are many ways to increase adherence to guidelines, ranging from education to financial incentives and regulation.[9] Audit and feedback are particularly effective and have helped increase the timely use of reperfusion therapies in patients with myocardial infarction and stroke.[10–13] Audit and feedback are also important in trauma care.[14–16] Prognostic models estimate the risk of death for each patient and allow us to target the population to audit. We can also calculate a clinical score that can be used for initial triage. To allow the audit of tranexamic acid use in trauma patients, we developed and validated a prognostic model to predict the risk of death due to bleeding based on information available at the first clinical assessment.

METHODS

Study population

We used data from two large multicentre studies to develop a widely applicable

prognostic model for death due to bleeding in trauma patients: an international randomised control trial (The Clinical Randomisation of Anti-fibrinolytic in Significant Haemorrhage [CRASH-2] trial) and the Northern French Alps Trauma registry.[17 18]

The CRASH-2 trial included patients from 274 hospitals in 40 countries from 2005 to 2010. Patients with or at risk of significant bleeding within 8 hours of injury were included. Since tranexamic acid is effective only within 3 hours of injury, we excluded patients treated beyond 3 hours.

The Northern French Alps trauma registry, part of the Northern French Alps trauma system (TRENAU), includes 24 hospitals and 16 prehospital mobile intensive care units from 3 emergency medical service systems. Patients, from 2009 to2016, with major trauma according to the triage rules of the American College of Surgeons were included.[19] We excluded patients with cardiac arrest at the scene of the injury.

Outcome and variable selection

The primary outcome was in-hospital death due to bleeding within 28 days. In the CRASH-2 trial, the clinician responsible recorded the cause of death. In the Northern French Alps registry, two trauma surgeons and two emergency physicians reviewed the records of all patients who died to determine the cause of death. We selected potential predictors from the CRASH-2 trial data collected before randomisation. We focused on the data available in the prehospital setting or on hospital admission in the Northern French Alps Trauma registry. These data included demographic characteristics (age, sex), physiological parameters (systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR), Glasgow coma scale (GCS)) and the mechanism of injury (blunt or penetrating). All variables could be assessed at the first clinical assessment and were available in hospital records. Physiological variables were the first measures recorded. We also included treatment by tranexamic acid and country income level (high, middle or low income). Treatment by tranexamic acid was included in the equation for statistical adjustment. The coefficient for tranexamic acid treatment was constrained in the model equation to obtain a prediction before treatment at the first clinical assessment. Therefore, we used the entire dataset and not just the placebo arm of the CRASH-2 randomised trial. We assessed the importance of each predictor with the partial R^2 statistic that estimates the variability of the outcome explained by the predictor. We developed two models. A full model that included all potential predictors and a simple model.

Model development

We used multivariable logistic regression with random effects by country to identify predictors of death due to bleeding. Continuous variables were included in the model as linear terms. We assessed departures from linearity by plotting the risk of death against continuous variables and added quadratic and cubic terms to the model for all continuous variables that showed a non-linear relationship graphically. The GCS was used as a continuous variable. We used a backward stepwise method by including all variables, quadratic and cubic terms and plausible interactions between the mechanism of injury and SBP, between the mechanism of injury and GCS, and between age and SBP. We then removed, one at a time, variables for which there was no evidence of association ($p>0.05$) from the Wald test. We also used the Least Absolute Shrinkage and Selecting Operator (LASSO) method to check that variable selection obtained by the ordinary least squares method was similar.[20]

Model performance

We assessed the model performance in terms of discrimination and calibration. Discrimination was assessed with the C-statistic and the receiving operating characteristic curve.[21] Calibration was assessed as the difference between mean observed and predicted probabilities (calibration in the large) and by plotting observed outcome and predicted probabilities by decile of the predicted risk of death and with a non-parametric smooth function.[22] We estimated the calibration slope based on the linear predictor of each model. A calibration slope of 1 and an intercept of 0 indicates perfect calibration. The overall calibration was summarised by the ratio of expected and observed number of events (E/O) with an ideal value of 1.[23] A value <1 indicates an underprediction and a value > 1 indicates an overprediction.

Model validation

We performed internal validation to estimate the statistical optimism of the final model. We drew 200 bootstrapped samples of 23 402 patients. We developed a model in each bootstrapped sample including variable selection. We estimated the C-statistic in each bootstrapped sample and assessed the performance of each model in the original sample. Optimism was estimated as the mean of the difference between the C-statistic of the bootstrap sample and the C-statistic in the original sample. We subtracted optimism from the C-statistic of the model developed in the original sample to obtain the optimism-corrected C-statistic.

We also conducted an internal–external validation.[24–26] We performed a cross-validation procedure where we selected countries with a sample size > 300.[25 27] We left out one country in turn and developed models using the same predictors in the remaining countries and estimated the discrimination and calibration in the omitted country. C-statistics, calibration slope and overall calibration for each country were pooled with random effects. We assessed heterogeneity with I^2 statistics and by testing interaction between calibration slope and country.

Missing data

There was no loss to follow-up in the CRASH-2 trial and <0.3% in the Northern French Alps Trauma registry.

Table 1 Characteristics of the CRASH-2 trial patients

	Missing (%)	All patients n=13 485	Alive n=11 404	All causes of death n=2081	Death due to bleeding n=815
Age, median (IQR)	0	30 (24–42)	30 (23–41)	34 (25–46)	32 (25–45)
SBP, median (IQR)	2	90 (80–110)	95 (80–110)	80 (70–100)	77 (60–90)
HR, median (IQR)	1	106 (92–120)	105 (90–120)	112 (98–128)	116 (100–130)
RR, median (IQR)	1	22 (20–26)	22 (20–26)	24 (20–30)	24 (20–30)
GCS, n (%)	0				
3–8		2125 (16%)	1030 (9%)	1094 (53%)	360 (35%)
9–12		1784 (13%)	1451 (13%)	332 (16%)	171 (21%)
13–15		9578 (71%)	8918 (78%)	654 (31%)	360 (44%)
Penetrating Injury, n (%)	0	6874 (51%)	5958 (52%)	916 (44%)	485 (60%)

CRASH-2, Clinical Randomisation of Anti-fibrinolytic in Significant Haemorrhage; GCS, Glasgow Coma Scale; HR, heart rate (bpm); RR, respiratory rate (bpm); SBP, systolic blood pressure (mm Hg).

There were 0% to 2% missing values for predictors in the CRASH-2 trial and 0% to 5% in the Northern French Alps Trauma registry. We performed multiple imputation by chained equations to fill in the missing values of predictors.[28] We generated 20 imputed datasets. We imputed 2253 missing values (1.6%) for 1317 incomplete observations.

Patient and public involvement statement

Patients were not involved in the research question and in the design of the study.

All analyses were performed using STATA software V.14.0; and R software V.3.4.3 (R foundation for statistical computing).

RESULTS

We included 23 430 trauma patients in the study (13 485 in the CRASH-2 trial and 9945 in the Northern French Alps registry, tables 1 and 2). In both the CRASH-2 and Northern French Alps cohorts, the patients were mostly men with a median age of 30 and 35 years respectively. Patients who died from bleeding had lower SBP, lower GCS scores and higher HRs. Penetrating injury was more frequent in the CRASH-2 trial patients (51%) than in the Northern French Alps (5%). Eight hundred and fifteen patients (6%) died from bleeding in the CRASH-2 trial and 102 (1%) in the Northern French Alps cohorts (table 3). Half of the Northern French Alps patients had

Table 2 Characteristics of the Northern French Alps registry

	Missing (%)	All patients n=9945	Alive n=9256	All causes of death n=661	Death due to bleeding n=102
Age, median (IQR)	<1	36 (22–53)	35 (22–51)	58 (31–73)	51 (31–68)
SBP, median (IQR)	3	124 (110–140)	125 (111–140)	116 (80–140)	83 (60–110)
HR, median (IQR)	4	84 (74–100)	85 (75–100)	84 (60–110)	97 (60–120)
RR, median (IQR)	4	16 (15–20)	16 [15-–20]	15 (14–20)	17 (11–25)
GCS, n (%)	3				
3–8		1170 (12)	718 (8)	449 (70)	51 (52)
9–12		500 (5)	452 (5)	48 (7)	10 (10)
13–15		7984 (83)	7813 (87)	148 (23)	37 (38)
Penetrating injury	<1	554 (6)	508 (6)	45 (7)	16 (16)
Injury severity Score, n (%)	2				
0–8		2738 (28)	2723 (30)	14 (2)	1 (1)
9–15		2480 (26)	2450 (27)	26 (4)	6 (6)
16–24		2081 (21)	2008 (22)	68 (11)	15 (15)
25–34		1778 (18)	1453 (16)	316 (49)	36 (36)
>35		686 (7)	465 (5)	221 (34)	41 (41)

GCS, Glasgow Coma Scale; HR, heart rate (bpm); RR, respiratory rate (bpm); SBP, systolic blood pressure (mm Hg).

Table 3 Risk of death and intervention

	CRASH-2 n (%)	Northern French Alps Trauma registry n (%)
Death due to bleeding	815 (6)	102 (1)
Overall death	2081 (15)	661 (7)
Admission in ICU	5354 (40)	4205 (42)
Surgical procedure	6608 (49)	2691 (27)
Surgical procedure for bleeding	916 (7)	1251 (12)*
Blood transfusion,	6506 (48)	1054 (11)
ICU median day (IQR)	3 (1–7)	4 (2–10)

*including embolisation
CRASH-2, Clinical Randomisation of Anti-fibrinolytic in Significant Haemorrhage; ICU, intensive care unit.

an Injury Severity Score (ISS) of 16 or more and three quarters had an ISS of 9 or more.

Figure 1 shows the relationships between the potential predictors and death due to bleeding. The risk of death due to bleeding was higher with higher age, lower SBP and lower GCS. HR and RR showed U-shaped relations. The predictors included in the full model were age, SBP, GCS, HR, RR and the mechanism of injury. Sex and country income were not associated with death due to bleeding in multivariable analysis (online supplementary 1 and 2). The LASSO method gave similar results. Age, SBP and GCS had the strongest prognostic value according to partial R^2. The performance of the model development showed good discrimination with C-statistics of 0.88 (0.87 to 0.89) and 0.87 (0.86 to 0.88) for the full and simple models respectively (table 4). Calibration was good with no differences between observed and predicted deaths due to bleeding, except for high-risk

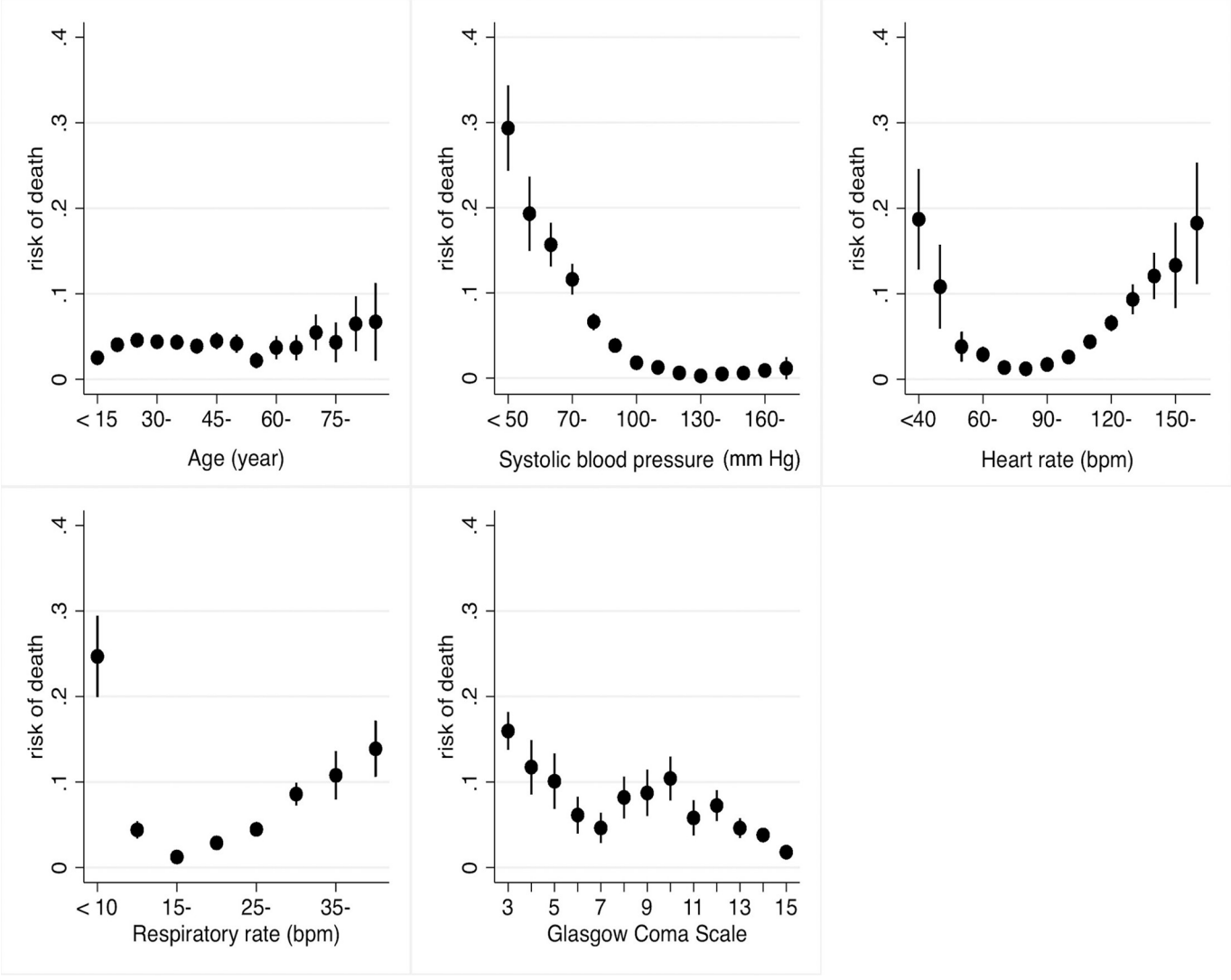


Figure 1 Relationship between death due to bleeding and potential predictors.

Table 4 Model performance, internal and internal–external validation.

	Full model		Simple model	
	Development	Internal–external validation*	Development	Internal–external validation*
	n=23 402	n=22 422	n=23 402	n=22 422
C- statistic (AUC)	0.88 (0.87–0.89)	0.85 (0.81–0.88)	0.87 (0.86–0.88)	0.84 (0.80–0.88)
Calibration-in-the-large†	<0.1	<0.1	<0.1	0.3 (0.1–0.6)
Calibration slope	1.01 (0.96–1.07)	1.07 (0.91–1.14)	1.04 (0.98–1.09)	1.12 (0.95–1.29)
E/O	1.02 (0.96–1.08)	0.93 (0.71–1.15)	0.98 (0.92–1.04)	0.91 (0.82–0.99)

*Internal–external validation based on pooled data with random effect obtained by cross validation from 13 countries (each with n≥300). Every country is left out once for validation of a model based on the remaining countries.
†Calibration-in-the-large showed difference between observed and predicted death due to bleeding.
AUC, area under the curve (C-statistic); E/O: expected/observed number of deaths due to bleeding.

patients (n=138) in whom the risk was over-estimated above a predicted probability of 0.5 (figure 2). Bootstrap resampling showed negligible model optimism of 0.0023 and gave an optimism-corrected performance that was unchanged with a C-statistic of 0.88 and 0.87 for the full and simple models. At internal–external cross-validation, the C-statistic ranged from 0.80 to 0.94, except for India with a C-statistic of 0.72 (figure 3). The pooled C-statistics were 0.85 (0.81 to 0.88) and 0.84 (0.80 to 0.88) for the full and simple models respectively (table 4). Pooled calibration slope was 1.07 (0.91 to 1.24) and 1.12 (0.95 to 1.29). Calibration slope and overall calibration showed heterogeneity, especially for Iraq, Georgia and Indonesia (figures 4 and 5). We found a significant interaction between calibration slope and country (p<0.001).

DISCUSSION

Main findings

We developed and internationally validated a prognostic model to predict death due to bleeding in trauma patients. The model showed good discrimination and calibration in a wide range of settings. By using clinical parameters that can be assessed at the site of injury and available in hospital records, we can accurately estimate the risk of death due to bleeding in a population with major trauma.

STRENGTHS AND LIMITATIONS

This study has several strengths. We used data from well-described inception cohorts of bleeding trauma

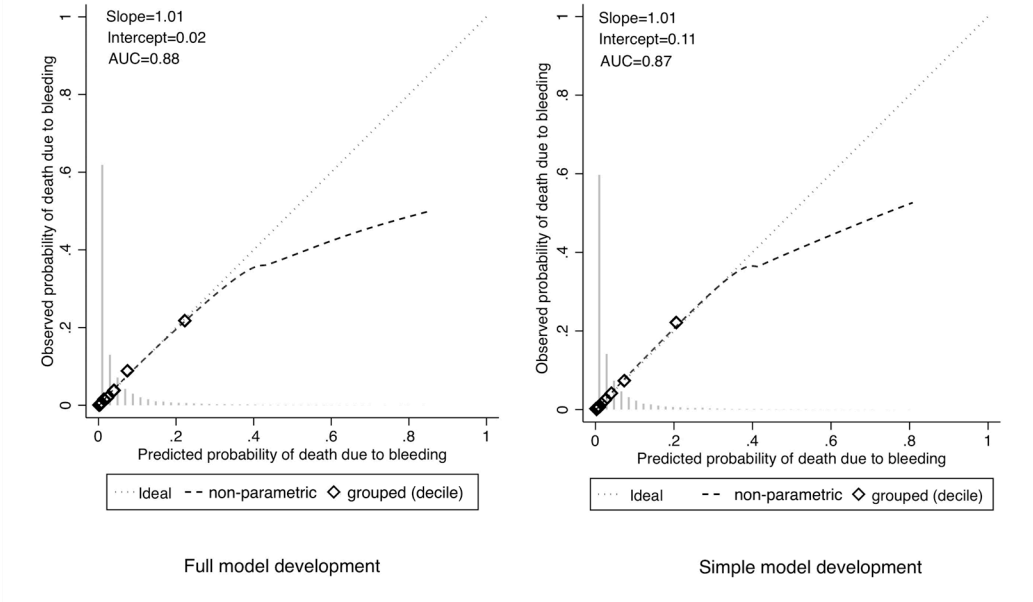
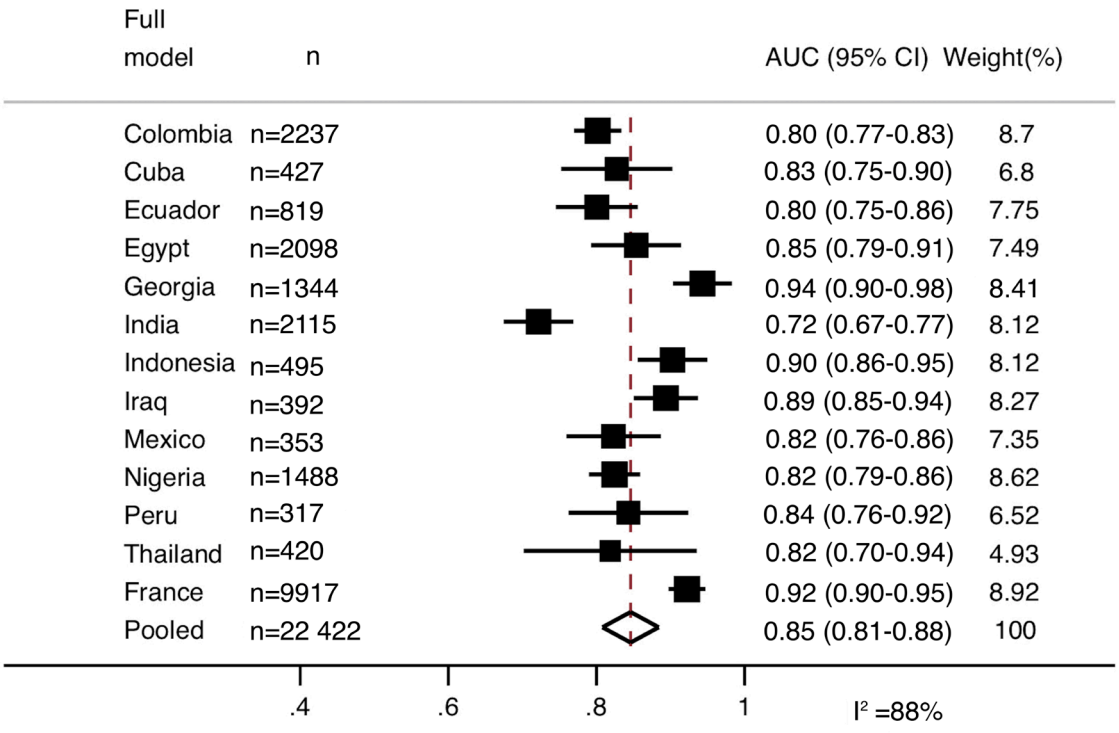


Figure 2 Calibration curves for model development. AUC, area under the curve.



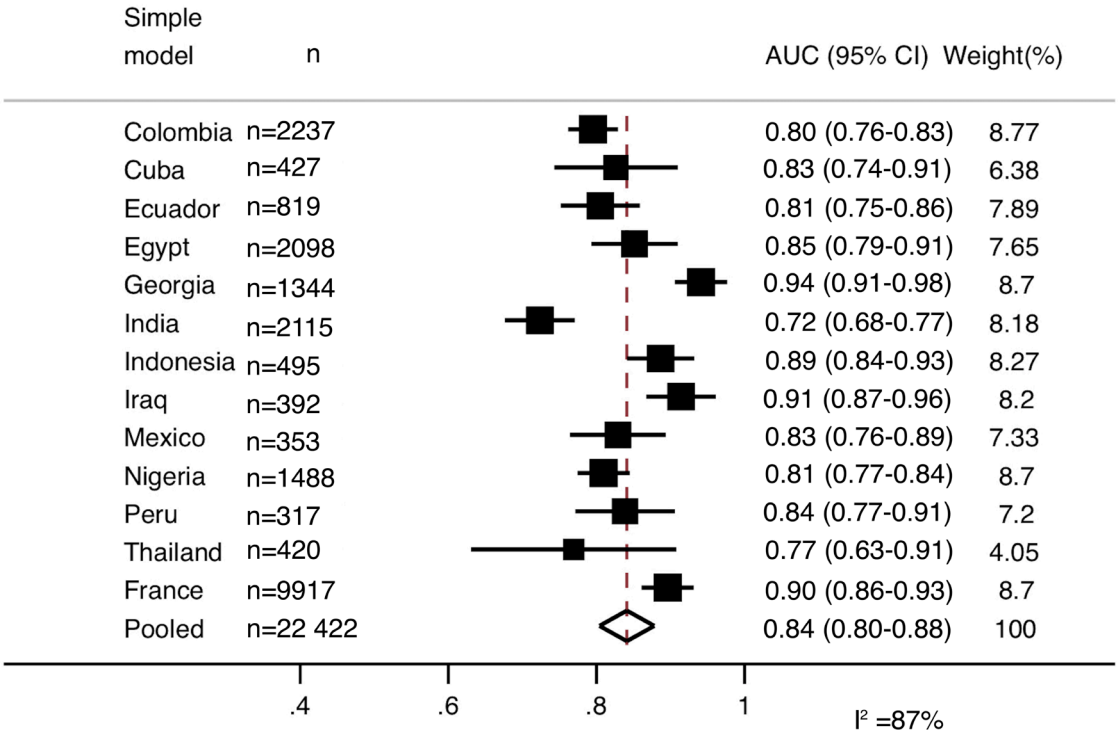


Figure 3 Internal–external cross-validation C-statistics by countries. AUC, area under the curve.

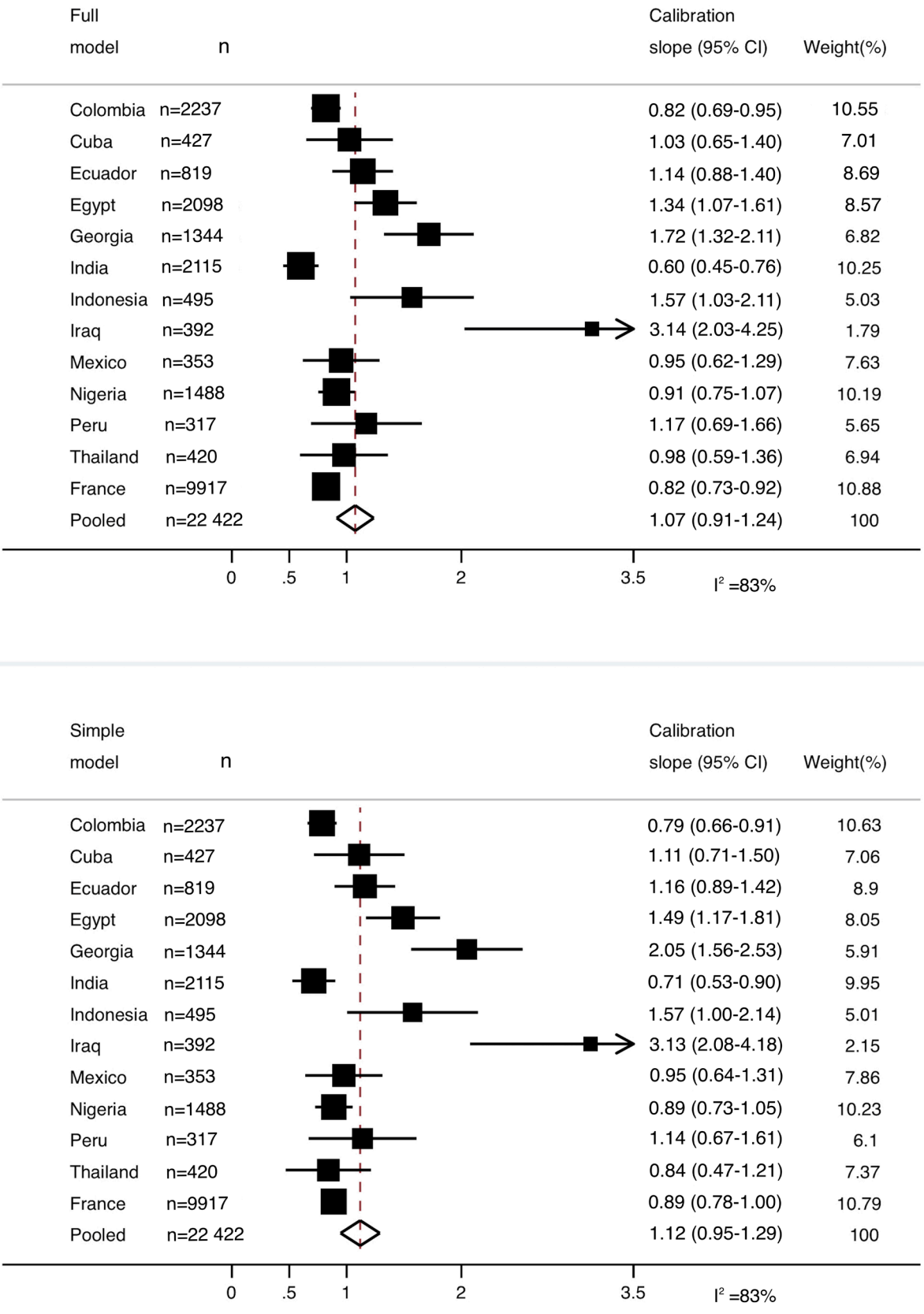
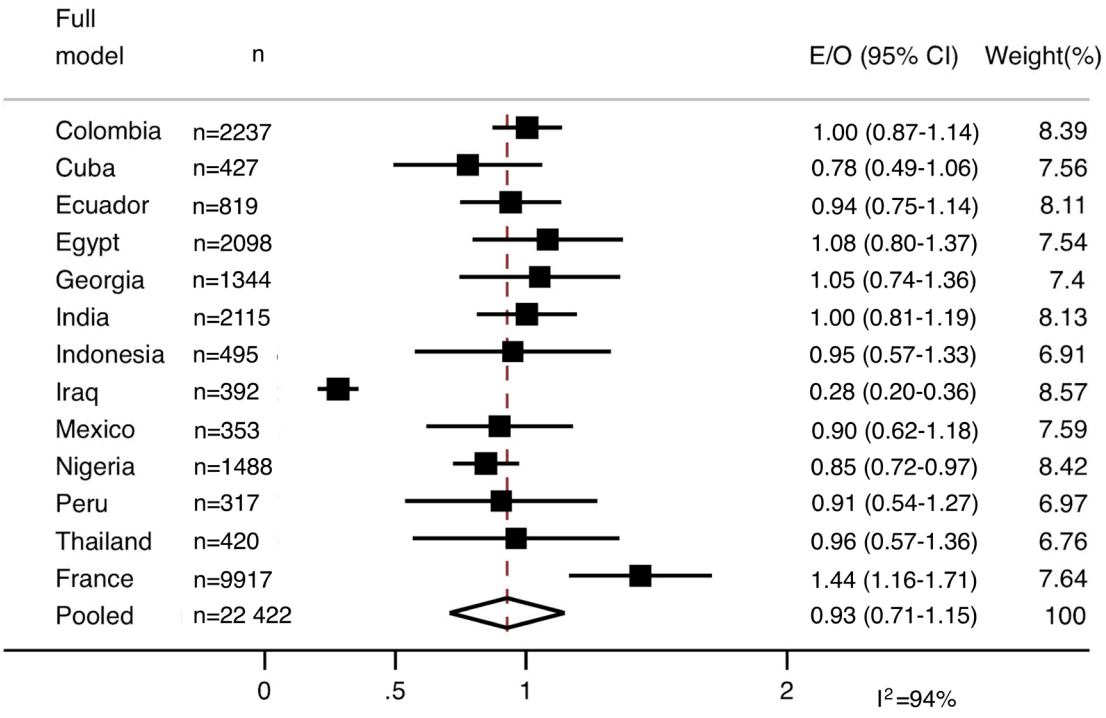


Figure 4 Internal–external cross-validation of calibration slope by countries.



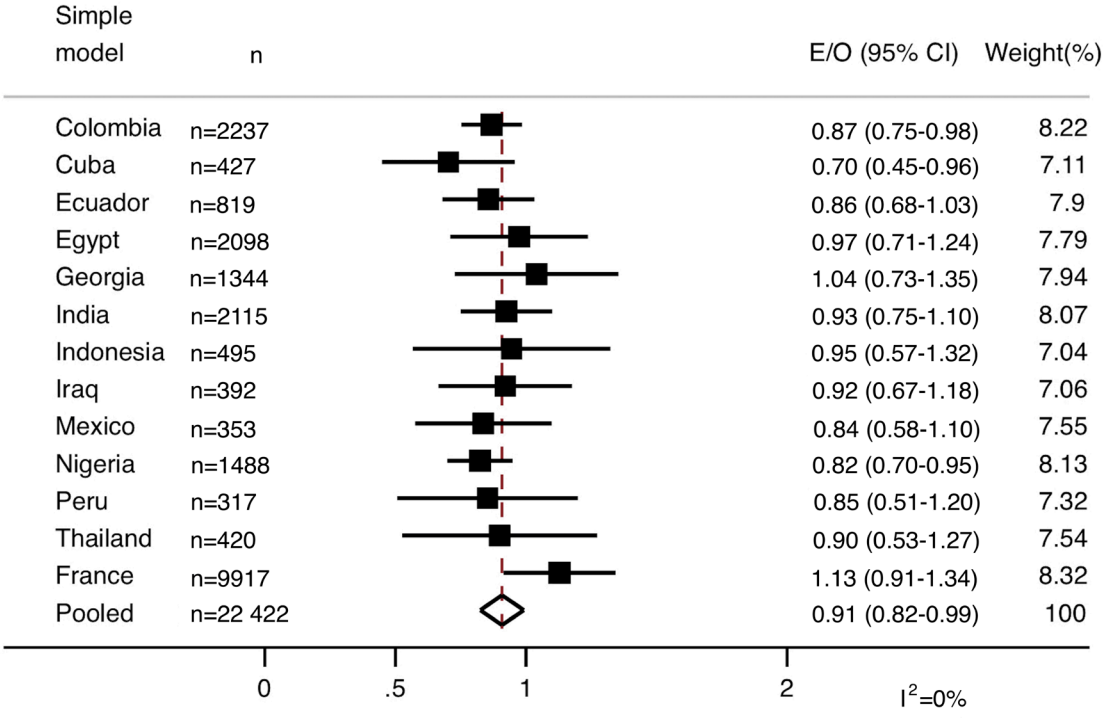


Figure 5 Internal–external cross-validation overall calibration expected and observed number of deaths due to bleeding (E/O) by countries.

patients with or at risk of significant haemorrhage. Prognostic factors collected correspond to the first measure recorded after injury. Unlike previous studies, loss to follow-up was minimal.[29] We used a well-defined outcome at a fixed time point after injury. These strengths help ensure the internal validity of the model.

We developed our model in a large international cohort with patients from 40 countries and a large trauma registry. This helps to ensure that our results are widely applicable. We did not split the data randomly or use separate derivation and validation cohorts. Because the number of outcome events is the limiting factor in prognostic studies, we used the full dataset with more than 900 traumatic deaths due to bleeding to ensure accurate prediction and strengthen internal validity. Splitting the data could have led to a pessimistic and unstable estimate of performance.[30] For this reason, we did not perform split-sample validation and preferred to perform internal-external cross-validation that has been recommended for assessing generalisability.[24] We also performed boostraping that helps to estimate the model optimism. However, we welcome further external validation in different trauma cohorts by different authors.[31]

Our study also has limitations. We cannot rule out misclassification of the outcome. The cause of death can be difficult to determine, especially in late bleeding deaths that could be confused with thrombotic disseminated intravascular coagulation (DIC).[6] If deaths due to DIC were misclassified as deaths due to bleeding, this might underestimate the effect of SBP, HR or RR in this model.

Another limitation was the potential for measurement error in prognostic factors. The use of a single measurement for blood pressure rather than the average of several measurements could lead to error and regression dilution bias.[32] The regression line between outcome and predictor is fitted in order to minimise the distance between each point and the line. The random error of the predictor increases the distance to the regression line and underestimates the effect of the predictor by flattening the regression line.[33] This may explain the over-prediction in high risk patients. Patients with haemorrhagic shock and haemodynamic instability are more likely to have blood pressure variation and, hence, measurement error. This over-prediction occurred only for trauma patients with a very high predicted risk of death due to bleeding (above 0.45), representing <0.6% of the study population (n=138). In these very high-risk patients, precise quantification of the risk of death is unlikely to influence clinical decisions. On the other hand, accurate prediction is clinically important in low-risk patients, as, for example, it may determine who receives tranexamic acid.

Finally, we observed heterogeneity of performance across countries. We note that the discriminative ability is affected by miscalibration and case-mix.[26] The relatively poor C-statistic in India could be explained by the combination of calibration slope below 1 and a relatively homogenous case-mix. On the other hand, the high C-statistic in France reflected that the Northern French Alps trauma registry selected a more heterogeneous case-mix population with major trauma. We acknowledge that this model is suitable for a population similar to that used in this study, such as a population with major trauma.

Implications of study

Our prognostic model provides a way of identifying trauma patients with or at risk of significant haemorrhage based on predicted probabilities of death due to bleeding. Quality improvement programmes could use this model to estimate the individual risks of death due to bleeding in a trauma population. Based on these predictions, a trauma audit could determine a threshold for patients with 'significant haemorrhage' who should be treated with tranexamic acid. The threshold used may depend on effectiveness, cost and safety considerations. According to European guidelines for the management of traumatic bleeding, tranexamic acid is supported by the highest level of evidence (grade 1A).[5] Tranexamic acid costs about one pound per patient and has no serious adverse effects. For these reasons, a low predicted risk of bleeding death might be used in trauma audit.

An internet application has been prepared using our simple model for use in the prehospital setting (www.evidencio.com). This could help paramedics decide who should receive tranexamic acid at the scene of injury. It could also be useful in prehospital triage. Some previously proposed trauma scores predict all-cause mortality or massive transfusion.[29 34 35] Ours is the only model that predicts death due to bleeding. Because bleeding is the leading cause of preventable death, the model might become an essential tool for identifying patients needing urgent interventions such as damage control surgery and multispeciality critical care. It could also help identify patients who need to be transported directly to a regional trauma centre or for whom massive transfusion protocol needs to be activated before they arrive at the hospital.

A prognostic model predicting all-cause mortality was developed previously using CRASH-2 data.[36] However, traumatic deaths can result from many different pathophysiological mechanisms. For example, both high and low SBP predict death from all causes but only low blood pressure predicts death due to bleeding. The association of high blood pressure with all-cause mortality is likely to reflect deaths from traumatic brain injury. By combining different mechanisms of death, predictions based on all-cause mortality could misclassify the risk of death from bleeding.

FUTURE STUDIES

Our models may facilitate stratification of clinical trial populations into risk categories at baseline. Future studies may examine if and how the effect of tranexamic acid varies with baseline risk and model the health impact of different treatment strategies.

Author affiliations
[1]Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK
[2]Emergency Department and Northern French Alps Emergency Network, Hospital Annecy Genevois, Annecy, France
[3]Clinical Research Center and Division of Clinical Epidemiology, Department of Health and Community Medicine, University Hospital Geneva, Geneva, Switzerland
[4]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, Rotterdam, The Netherlands
[5]Department of Public Health, Erasmus MC, Rotterdam, The Netherlands
[6]Grenoble Alpes Trauma Center, Pôle Anesthésie-Réanimation, CHU Grenoble Alpes, Grenoble, France

Contributors FXA, IR designed the study. FXA, PB, IR designed and monitored the data collection from which this paper was developed. FXA, AGA analysed the data. PB gave feedback about the clinical use. ES gave feedback and statistical advice. FXA, IR wrote the first draft. FXA, AGA, ES, PB, IR contributed to write and revised the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The CRASH-2 trial received ethics committee approval from the London School of Hygiene & Tropical Medicine, UK and the ethics committees of all participating hospitals. The Northern French Alps Trauma Registry was approved by the ethics committee of the university hospital of Clermont-Ferrand, France.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data from the CRASH-2 trial is available via freeBIRD (free bank of injury and emergency research data), hosted by the Clinical Trial Unit of the London School of Hygiene and Tropical Medicine. More information at .

REFERENCES

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* 2013;2015:117–71.
2. Esposito TJ, Sanddal TL, Reynolds SA, *et al*. Effect of a voluntary trauma system on preventable death and inappropriate care in a rural state. *J Trauma* 2003;54:663–70. discussion 669-670.
3. Kleber C, Giesecke MT, Tsokos M, *et al*. Trauma-related preventable deaths in Berlin 2010: need to change prehospital management strategies and trauma management education. *World J Surg* 2013;37:1154–61.
4. Roberts I, Shakur H, Afolabi A, *et al*. CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011;377:1096–101. 1101.e1-2.
5. Rossaint R, Bouillon B, Cerny V, *et al*. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care* 2016;20:100.
6. Ciesla DJ, Pracht EE, Tepas JJ, *et al*. Measuring trauma system performance: Right patient, right place-Mission accomplished? *J Trauma Acute Care Surg* 2015;79:263–8.
7. Coats TJ, Fragoso-Iñiguez M, Roberts I. Implementation of tranexamic acid for bleeding trauma patients: a longitudinal and cross-sectional study. *Emerg Med J* 2019;36:78–81.
8. Metcalfe D, Perry DC, Bouamra O, *et al*. Regionalisation of trauma care in England. *Bone Joint J* 2016;98-B:1253–61.
9. Angus DC, Black N. Improving care of the critically ill: institutional and health-care system approaches. *Lancet* 2004;363:1314–20.
10. Jamtvedt G, Young JM, Kristoffersen DT, *et al*. Does telling people what they have been doing change what they do? A systematic review of the effects of audit and feedback. *Qual Saf Health Care* 2006;15:433–6.
11. Ivers N, Jamtvedt G, Flottorp S, *et al*. Audit and feedback: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012:CD000259.
12. Ludman PF, de Belder MA, McLenachan JM, *et al*. The importance of audit to monitor applications of procedures and improve primary angioplasty results. *EuroIntervention* 2012;8(Suppl P):P62–P70.
13. Strbian D, Michel P, Ringleb P, *et al*. Relationship Between Onset-to-Door Time and Door-to-Thrombolysis Time. *Stroke* 2013;44:2808–13.
14. McDermott FT. Trauma audit and quality improvement. *Aust N Z J Surg* 1994;64:147–54.
15. Patel HC, Bouamra O, Woodford M, *et al*. Trends in head injury outcome from 1989 to 2003 and the effect of neurosurgical care: an observational study. *The Lancet* 2005;366:1538–44.
16. Shafi S, Barnes SA, Rayan N, *et al*. Compliance with recommended care at trauma centers: association with patient outcomes. *J Am Coll Surg* 2014;219:189–98.
17. Shakur H, Roberts I, Bautista R, *et al*. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet Lond Engl* 2010;376:23–32.
18. Bouzat P, Ageron FX, Brun J, *et al*. A regional trauma system to optimize the pre-hospital triage of trauma patients. *Crit Care* 2015;19:111.
19. Sasser SM, Hunt RC, Faul M, *et al*. Guidelines for field triage of injured patients: recommendations of the National Expert Panel on Field Triage, 2011. *MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep Cent Dis Control* 2012;61(RR-1):1–20.
20. Tibshirani R. Regression Shrinkage and Selection Via the Lasso. *J R Stat Soc Ser B Methodol* 1996;58:267–88.
21. Royston P, Altman DG. Visualizing and assessing discrimination in the logistic regression model. *Stat Med* 2010;29:2508–20.
22. Steyerberg EW, Vickers AJ, Cook NR, *et al*. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010;21:128–38.
23. Riley RD, Ensor J, Snell KI, *et al*. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. *BMJ* 2016;353:i3140.
24. Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol* 2016;69:245–7.
25. Royston P, Parmar MK, Sylvester R. Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer. *Stat Med* 2004;23:907–26.
26. Austin PC, van Klaveren D, Vergouwe Y, *et al*. Validation of prediction models: examining temporal and geographic stability of baseline risk and estimated covariate effects. *Diagn Progn Res* 2017;1:12.
27. Steyerberg EW, Mushkudiani N, Perel P, *et al*. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 2008;5:e165.
28. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30:377–99.
29. Rehn M, Perel P, Blackhall K, *et al*. Prognostic models for the early care of trauma patients: a systematic review. *Scand J Trauma Resusc Emerg Med* 2011;19:17.
30. Austin PC, Steyerberg EW, variable Eper. Events per variable (EPV) and the relative performance of different strategies for estimating the out-of-sample validity of logistic regression models. *Stat Methods Med Res* 2017;26:796–808.
31. Siontis GC, Tzoulaki I, Castaldi PJ, *et al*. External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination. *J Clin Epidemiol* 2015;68:25–34.
32. MacMahon S, Peto R, Collins R, *et al*. Blood pressure, stroke, and coronary heart disease. *The Lancet* 1990;335:765–74.
33. Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. *BMJ* 2010;340:c2289.
34. Sartorius D, Le Manach Y, David JS, *et al*. Mechanism, glasgow coma scale, age, and arterial pressure (MGAP): a new simple prehospital triage score to predict mortality in trauma patients. *Crit Care Med* 2010;38:831–7.
35. Yücel N, Lefering R, Maegele M, *et al*. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. *J Trauma* 2006;60:1228–37. discussion 1236-1237.
36. Perel P, Prieto-Merino D, Shakur H, *et al*. Predicting early death in patients with traumatic bleeding: development and validation of prognostic model. *BMJ* 2012;345:e5166.

Supplement 1. Equation for predicting death due to bleeding (Simple and full model).

Simple model:

Predicted probability of death due to bleeding$= \frac{1}{1+e^{-S}}$

Where S= 0.604 + Intercept_by_country + (0.056 x Age) – ($1.4e^{-3}$ x Age^2) + ($1.2e^{-5}$ x Age^3) + (0.010 x SBP) – ($4.7e^{-4}$ x SBP^2) + ($1.5e^{-06}$ x SBP^3) – (0.614 x GCS) + (0.071 x GCS^2) – ($2.8e^{-3}$ x GCS^3)

Full model

Predicted probability of death due to bleeding$= \frac{1}{1+e^{-F}}$

Where F= 0.534 + Intercept_by_country + (0.061 x Age) – ($1.4e^{-3}$ x Age^2) + ($1.2e^{-05}$ x Age^3) + (0.023 x SBP) – (5.4e-04 x SBP^2) + ($1.6e^{-06}$ x SBP^3) – (0.634 x GCS) + (0.074 x GCS^2) – ($2.9e^{-3}$ x GCS^3) – ($8.6e^{-3}$ x HR) + (1.0e-04 x HR^2) – (0.171 x RR) + (0.006 x RR^2) – ($5.4e^{-05}$ x RR^3)

NB: coefficient for treatment by tranexamic acid was not included in the equation at baseline.

To predict death due to bleeding after treatment by tranexamic acid, add (-0.325 x TXA) for simple model (S equation) and (-0.336 x TXA) for full model (F equation).

Supplement 2. Internal-external validation by study.

	CRASH-2 Trial		Northern French Alps Registry	
	OR (95%CI)	P-VALUE	OR (95%CI)	P-VALUE
Simple model[a]	N=13,245		N=9,296	
Age	1.09 (1.00-1.20)	0.049	1.01 (0.90-1.13)	0.814
Age^2	0.99 (0.99-1.00)	0.028	1.00 (1.00-1.00)	0.901
Age^3	1.00 (1.00-1.00)	0.009	0.99 (0.99-1.00)	0.908
SBP	1.03 (0.99-1.06)	0.115	1.03 (1.00-1.05)	0.040
SBP^2	0.99 (0.99-1.00)	<0.001	0.99 (0.99-1.00)	<0.001
SBP^3	1.00 (1.00-1.00)	<0.001	1.00 (1.00-1.00)	<0.001
GCS	0.62 (0.39-0.99)	0.050	0.34 (0.09-1.28)	0.111
GCS^2	1.05 (1.00-1.12)	0.066	0.99 (0.97-1.35)	0.104
GCS^3	0.99 (0.99-1.00)	0.038	0.99 (0.99-1.00)	0.074
TXA	0.72 (0.63-0.87)	<0..001	-	
Full model[a]	N=13,086		N=9 ,012	
Age	1.07 (0.98-1.17)	0.136	1.04 (0.92-1.18)	0.535
Age^2	0.99 (0.99-1.00)	0.095	0.99 (0.99-1.00)	0.881
Age^3	1.00 (1.00-1.00)	0.038	1.00 (1.00-1.00)	0.906
SBP	1.06 (1.02-1.10)	0.003	1.04 (1.00-1.09)	0.062
SBP^2	0.99 (0.99-1.00)	<0.001	0.99 (0.99-1.00)	0.001
SBP^3	1.00 (1.00-1.00)	<0.001	1.00 (1.00-1.00)	<0.001
GCS	0.62 (0.38-1.02)	0.062	0.54 (0.13-2.29)	0.403
GCS^2	1.05 (1.00-1.12)	0.089	1.08 (0.90-1.30)	0.383
GCS^3	0.99 (0.99-1.00)	0.068	0.99 (0.99-1.00)	0.303
HR	0.98 (0.96-1.00)	0.043	1.02 (0.99-1.05)	0.248
HR^2	1.00 (1.00-1.00)	0.001	1.00 (1.00-1.00)	0.840
RR	0.79 (0.71-0.87)	<0.001	0.65 (0.54-0.78)	<0.001
RR^2	1.01 (1.00-1.01)	<0.001	1.02 (1.01-1.03)	<0.001
RR^3	0.99 (0.99-1.00)	<0.001	0.99 (0.99-1.00)	0.002
Penetrating injury	1.14 (0.94-1.37)	0.188	2.54 (1.21-5.34)	0.689
TXA	0.72 (0.61-0.85)	<0.001	-	

SBP: Systolic blood pressure (mmHg); GCS: Glasgow Coma Scale ; HR: Heart Rate (bpm); RR: Respiratory Rate (bpm).

[a]: Simple and full model were applied using the model developed in the complete database.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1602524	**Title**	Dr
First Name(s)	Francois-Xavier		
Surname/Family Name	Ageron		
Thesis Title	Tranexamic acid in trauma care: Who should be treated, when and where?		
Primary Supervisor	Professor Ian Roberts		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	British Journal of Anaesthesia (2)		
When was the work published?	2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the study with Ian Roberts, Angele Gayet and Katahrine Ker. I designed and monitored the data collection with Hallema Shakur-Still and Katarine Ker. I analysed the data and wrote the manuscript.

SECTION E

Student Signature	[redacted]
Date	9 Dec 2020

Supervisor Signature	[redacted]
Date	9 12 20

BJA

British Journal of Anaesthesia, 124 (6): 676–683 (2020)

doi: 10.1016/j.bja.2020.01.020
Advance Access Publication Date: 19 March 2020
Cardiovascular

CARDIOVASCULAR

Effect of tranexamic acid by baseline risk of death in acute bleeding patients: a meta-analysis of individual patient-level data from 28 333 patients

Francois-Xavier Ageron[1,2,*], Angele Gayet-Ageron[3], Katharine Ker[1], Timothy J. Coats[4], Haleema Shakur-Still[1] and Ian Roberts[1], for the Antifibrinolytics Trials Collaboration[†]

[1]Clinical Trials Unit, London School of Hygiene and Tropical Medicine, London, UK, [2]Emergency Department, Lausanne University Hospital, CHUV, Lausanne, Switzerland, [3]Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland and [4]Emergency Medicine, University of Leicester, Leicester, UK

*Corresponding author. E-mail: fxageron@gmail.com

[†]The members of the Antifibrinolytics Trials Collaboration are listed in the Acknowledgments section.

This article is accompanied by an editorial: Tranexamic acid: the king is dead, long live the king! by Lier & Shander, *Br J Anaesth* 2020:124:659–662, doi: 10.1016/j.bja.2020.02.015

Abstract

Background: Early administration of the antifibrinolytic drug tranexamic acid reduces death from bleeding in trauma and postpartum haemorrhage. We examined how the effectiveness and safety of antifibrinolytic drugs varies by the baseline risk of death as a result of bleeding.

Methods: We performed an individual patient-level data meta-analysis of randomised trials including more than 1000 patients that assessed antifibrinolytics in acute severe bleeding. We identified trials performed between January 1, 1946 and July 5, 2018 (PROSPERO, number 42016052155).

Results: Two randomised trials were selected where 28 333 patients received tranexamic acid treatment within 3 h after the onset of acute bleeding. Baseline characteristics to estimate the risk of death as a result of bleeding were divided into four categories: Low (0–5%), intermediate (6–10%), high (11–20%), and very high (>20%). Most patients had a low baseline risk of death as a result of bleeding (23 008 [81%]). Deaths as a result of bleeding occurred in all baseline risk categories with 240 (1%), 202 (8%), 232 (14%), and 357 (30%) deaths in the low-, intermediate-, high-, and very high-risk categories, respectively. The effectiveness of tranexamic acid did not vary by baseline risk when given within 3 h after bleeding onset ($P=0.51$ for interaction term). There was no increased risk of vascular occlusive events with tranexamic acid and it did not vary by baseline risk categories ($P=0.25$).

Conclusions: Tranexamic acid appears to be safe and effective regardless of baseline risk of death. Because many deaths are in patients at low and intermediate risk, tranexamic acid use should not be restricted to the most severely injured or bleeding patients.

Keywords: antifibrinolytics; bleeding; coagulopathy; mortality; postpartum haemorrhage; trauma

Editor's key points

- This meta-analysis investigated how the effectiveness and safety of tranexamic acid varies by the baseline risk of death as a result of acute bleeding.
- The study shows that many deaths from bleeding are in patients at low or intermediate risk.
- The effectiveness of tranexamic acid seems not to vary by the baseline risk of patients.
- Tranexamic acid should therefore not be limited to the most severely injured or bleeding patients.

Received: 5 October 2019 **Accepted:** 27 January 2020

The Anti-Fibrinolytic Trials Collaboration previously published a meta-analysis of individual patient data showing that early administration of tranexamic acid safely reduces death from acute severe bleeding.[1] When given soon after bleeding onset, tranexamic acid reduces the relative risk of death as a result of bleeding by about one-third. Early tranexamic acid treatment is widely recommended in treatment guidelines for acute severe bleeding, including postpartum haemorrhage and major trauma.[2–4]

Many guidelines, especially those for trauma, focus on the use of tranexamic acid in severely injured patients with a high risk of death from bleeding.[5,6] Although these patients have much to gain from tranexamic acid treatment, they are few in number and many die at the scene.[7] Because there are many more patients with less severe injuries and a lower risk of death from bleeding, if tranexamic acid was similarly effective, prompt treatment of these patients could prevent many deaths. We examined how the effectiveness and safety of antifibrinolytic drugs vary by the baseline risk of death as a result of bleeding.

Methods

Design and selection criteria

We conducted an individual patient data meta-analysis of randomised, placebo-controlled trials conducted between January 1, 1946 and July 5, 2018. The methods and the selection criteria were described previously.[1] The study protocol was registered in November 2016 (PROSPERO, number 42016052155).[8] Any randomised trial with more than 1000 patients that assessed the effects of antifibrinolytic drugs (aprotinin, tranexamic acid, aminocaproic acid, and aminomethylbenzoic acid) in patients with acute bleeding was eligible for inclusion. We identified trials from a permanent register of antifibrinolytic trials maintained by the London School of Hygiene and Tropical Medicine Clinical Trials Unit. The register is based on searches of MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, PubMed, Popline, and the WHO International Clinical Trials Registry Platform (Supplementary file S1). Three reviewers (AG-A, KK, F-XA) independently extracted data. We selected trials recruiting patients with acute bleeding at the time of randomisation (treatment trials). We excluded patients who were randomised more than 3 h after bleeding onset, since previous studies have shown that antifibrinolytics are ineffective after this period. We prepared a statistical analysis plan before searching for trials. Patients and the public were not involved in the research.

Outcome

The primary outcome was death as a result of bleeding. This is the most relevant primary outcome given the mechanism of action of antifibrinolytic drugs. All-cause mortality includes non-bleeding related deaths, such as sepsis, that should not be affected by antifibrinolytics. Because these deaths could dilute the treatment effect, important benefits or harms could be obscured in all-cause mortality.[9] Moreover, because the relative contributions of non-bleeding deaths will vary between populations, all-cause mortality is not widely generalisable. Secondary outcomes were fatal and non-fatal vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, and DVT).

Data analysis

We evaluated the quality of included trials by assessing sequence generation, allocation concealment, blinding, data completeness, and risk of selective reporting. Analysis was based on individual patient-level data. We estimated the baseline risk of death as a result of bleeding separately for each trial. We used prognostic models to predict the baseline risk using multivariate logistic regression. We used a previously published prognostic model for trauma.[10] Because there were no suitable prognostic models for postpartum haemorrhage, we used the same method to develop a prognostic model for postpartum haemorrhage. We only used baseline characteristics collected before randomisation as predictors. To improve the precision of our models, we included all trial participants from the treatment and placebo groups.[11] We included all potential predictors at baseline and adjusted for the use of antifibrinolytic drugs. We included linear and polynomial terms for continuous variables. We used the backward stepwise method and removed one at a time, variables for which there was no evidence of association (P-value for the Wald test >0.05). To estimate the risk at baseline, the coefficient for antifibrinolytic drugs was constrained at 0 in the equation. We performed sensitivity analysis that estimated the baseline risk in the placebo arm and present the results in the supplementary files. The estimates would be less precise, but may avoid misclassification from assuming a constant effect of tranexamic acid. The predicted baseline risk of death as a result of bleeding was estimated for each trial participant in both treatment groups. For each prognostic model, we assessed the performance by estimating discrimination and calibration. Discrimination represents the ability of the model to identify a patient with the outcome of interest and is evaluated by the concordance statistic (C-Statistic). Calibration represents the agreement between predicted and observed risk. On the basis of the predicted baseline risk, participants were assigned to one of the four baseline categories of risk of death as a result of bleeding: 0–5% (low); 6–10% (intermediate); 11–20% (high), and >20% (very high). The categories were chosen because they were clinically relevant, easy to understand (using a base of 5 or 10), and consistent with previous studies.[12,13]

All analyses were done according to the intention-to-treat principle. We reported continuous variables as mean (standard deviation) and median (inter-quartile range). We reported categorical variables as numbers and proportions. We plotted frequency distributions for baseline risk in all participants and in patients who died from bleeding. We estimated the effect of antifibrinolytics on death as a result of bleeding within categories of baseline risk and provide crude risk ratios. We tested the homogeneity of treatment effect across these between categories of risk using the χ^2 test. We used logistic regression to assess the effects of antifibrinolytics on death as a result of bleeding and reported treatment effects with odds ratios and 95% confidence interval (CI). First, we tested the homogeneity of the treatment effect between trials by including an interaction term between treatment and trial and reporting the P-value (model 1, Supplementary file S2). We hypothesised that the treatment effect does not vary by baseline risk, unlike time to treatment for which treatment delay reduces the treatment benefit.[1] To verify the homogeneity of the effect of baseline risk on treatment effect by time to treatment, we performed a second model with a triple interaction between the terms for baseline risk, the treatment group, and the time to treatment (model 2, Supplementary file S2). Once the homogeneity of the

treatment effect with baseline risk and time to treatment was verified, we ran a third model to assess the homogeneity between the treatment effect and baseline risk adjusting for trial and time to treatment (model 3, Supplementary file S2). We reported the *P*-value for the interaction term between treatment effect and baseline risk and plotted the treatment effects with odds ratios and 95% CI according to baseline risk.

Missing values

There were no missing outcome data, but there were missing values for some predictor variables. In order to estimate baseline risks on the full dataset, we replaced missing predictors using multiple imputation with 20 imputed datasets and adjustment of the imputation model for death as a result of bleeding, age, systolic BP, ventilatory frequency, and Glasgow outcome scale.

Results

Figure 1 shows the number of records identified and the reasons for exclusions. We found five completed[14–18] and 10 ongoing trials[19–28] (Supplementary file S3). All trials used tranexamic acid. Three trials met our inclusion criteria. The CRASH-2 and WOMAN trials received ethics committee approval from the London School of Hygiene and Tropical Medicine, UK and the ethics committees of all participating hospitals. The CRASH-2 trial included 20 211 trauma patients and assessed the effects of tranexamic acid on death and vascular occlusive events. Data from the CRASH-2 trial are available via freeBIRD (free bank of injury and emergency research data), hosted by the Clinical Trial Unit (CTU) of the London School of Hygiene and Tropical Medicine (https://ctu-app.lshtm.ac.uk/freebird). The WOMAN trial assessed the effects of tranexamic acid on death and serious morbidity in 20

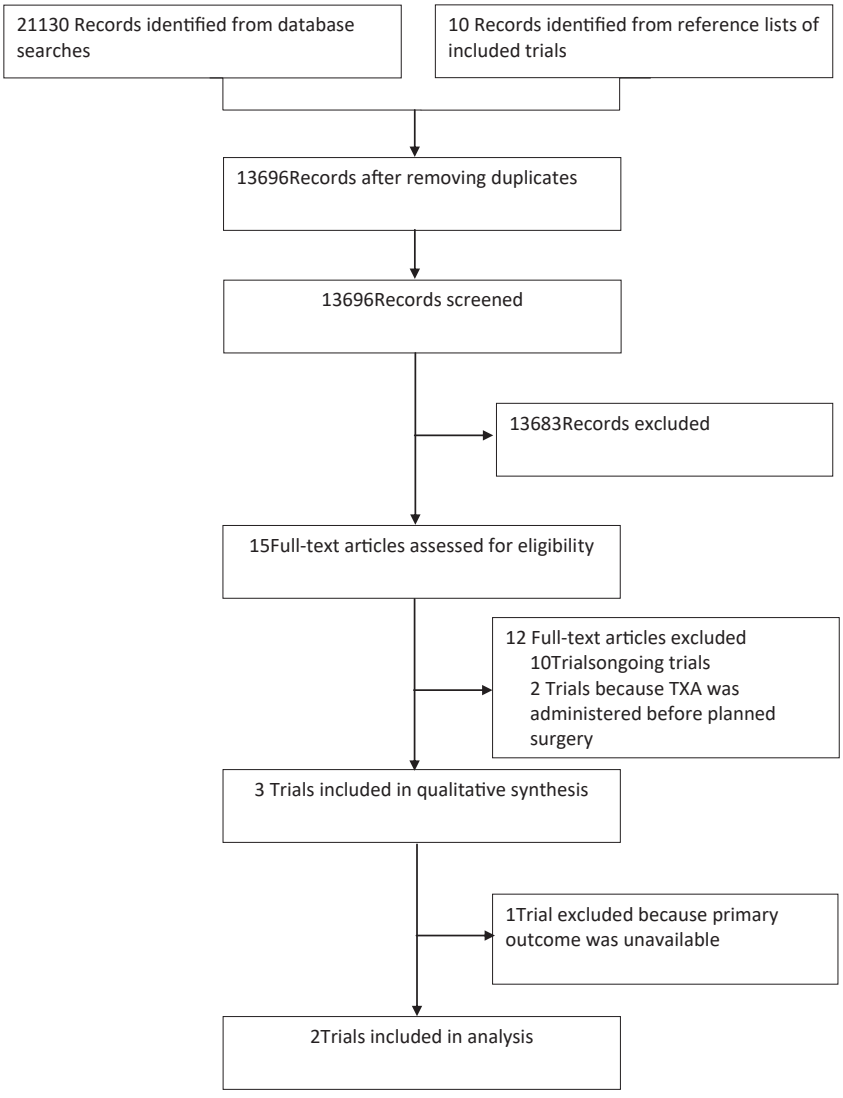


Fig 1. Study selection. TXA, tranexamic acid.

060 women with postpartum haemorrhage. The TICH-2 trial assessed the effect of tranexamic acid on death and dependency in non-traumatic intracerebral haemorrhage. Exsanguination does not normally occur in adults with cerebral haemorrhage. Death usually arises as a result of cerebral injuries and high ICP. The TICH-2 trial was excluded from analysis as it was not possible to collect the primary outcome death as a result of bleeding. Included trials had a low risk of bias in all domains (Supplementary file S4).

We obtained individual patient data for 28 333 participants randomised within 3 h of the bleeding onset: 13 485 from the CRASH-2 trial and 14 848 from the WOMAN trial (Table 1). Of these, 14 270 participants received tranexamic acid and 14 067 received placebo. The baseline risk predictors for both models are detailed in the Supplementary file S5. The pooled discrimination of the prognostic models was good; C-statistic=0.88, 95% CI (0.87–0.89). The predicted risk was similar to the observed risk in the placebo group (ratio predicted/observed risk=1.00; 95% CI (0.92–1.07)) (Supplementary file S6). The baseline risk was higher in trauma patients than in women with postpartum haemorrhage. Most patients had a baseline risk under 5% (Fig. 2). Deaths as a result of bleeding occurred in all baseline risk categories with almost the same number of deaths as a result of bleeding. We reported 240 (1%), 202 (8%), 232 (14%), and 357 (30%) deaths in the low-, intermediate-, high-, and very high-risk categories, respectively. Deaths as a result of bleeding occurred in all categories of blood loss among women with postpartum haemorrhage (Supplementary file S7). The effect of tranexamic acid did not vary between trials (model 1: P=0.82). We found no heterogeneity in the interaction between treatment effect, baseline risk, and time to treatment (model 2: P=0.62 for the triple interaction). We did not find any significant interaction between the effect of tranexamic acid on death as a result of bleeding and baseline risk (model 3: P=0.51). Figure 3 shows crude risk ratios by categories of baseline risk. The treatment effect did not vary by baseline risk (Fig. 4). The risk of vascular occlusive events was similar according to baseline risk categories (Table 2). There was no increase in fatal and non-fatal occlusive events with tranexamic acid in any of the baseline risk categories (Supplementary file S8).

Discussion

Main findings

Our results show that many deaths from bleeding are in patients at low or intermediate risk and that the mortality reduction from tranexamic acid does not vary by baseline risk. We found no evidence of any increase in vascular occlusive events in any of the risk categories. Our study has important strengths and some limitations. First, we selected only randomised trials with more than 1000 patients to reduce selection bias. Small trials contribute very little evidence but could increase the risk of selection bias.[29] Second, we used a rigorous method to develop prognostic models to predict baseline risk.[30] Specifically, baseline risk was estimated using the entire dataset and not just the placebo group. By increasing the sample size and constraining the treatment effect in the regression equation, it improves both

Table 1 Baseline characteristics of patients in participating trials.

	CRASH-2 trial (n=13 485)	Woman trial (n=14 848)	Total (n=28 333)
Predicted baseline risk, *n* (%)			
0–5	9063 (67.2)	13 945 (93.9)	23 008 (81.2)
6–10	2011 (14.9)	481 (3.2)	2492 (8.8)
11–20	1373 (10.2)	262 (1.8)	1635 (5.8)
>20	1038 (7.7)	160 (1.1)	1198 (4.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Mean baseline risk (SD)	6.9 (9.5)	1.6 (4.4)	4.1 (7.7)
Median baseline risk (IQR)	3.3 (1.4–7.9)	0.4 (0.1–1.3)	1.3 (0.3–4.2)
Age (yr), *n* (%)			
<25	3840 (28.5)	3973 (26.8)	7813 (27.6)
25–29	2400 (17.8)	4590 (30.9)	6990 (24.7)
30–34	1792 (13.3)	3802 (25.6)	5594 (19.8)
≥35	5453 (40.4)	2478 (16.7)	7931 (28.0)
Missing	0 (0.0)	5 (0.0)	5 (0.0)
Mean age (SD)	34.1 (14.0)	28.4 (5.7)	31.1 (10.9)
Median age (IQR)	30 (24–42)	28 (24–32)	29 (24–35)
Systolic BP (mm Hg), *n* (%)			
<75	2074 (15.7)	1011 (6.8)	3085 (11.0)
75–89	2360 (17.8)	1563 (10.5)	3923 (14.0)
≥90	8813 (66.5)	12 269 (82.7)	21 082 (75.1)
Missing	238 (1.8)	5 (0.0)	243 (0.9)
Mean systolic BP (SD)	96.6 (25.3)	101.5 (21.4)	99.2 (23.5)
Median systolic BP (IQR)	90 (80–110)	100 (90–110)	100 (90–110)
Time to treatment (h), *n* (%)			
≤1	7452 (55.3)	9220 (62.1)	16 672 (58.8)
1–3	6033 (44.7)	5628 (37.9)	11 661 (41.2)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean time to treatment (SD)	1.5 (0.8)	1.0 (0.8)	1.3 (0.8)
Median time to treatment (IQR)	1 (1–2)	0.7 (0.4–1.5)	1 (0.5–2)

IQR, inter-quartile range; SD, standard deviation.

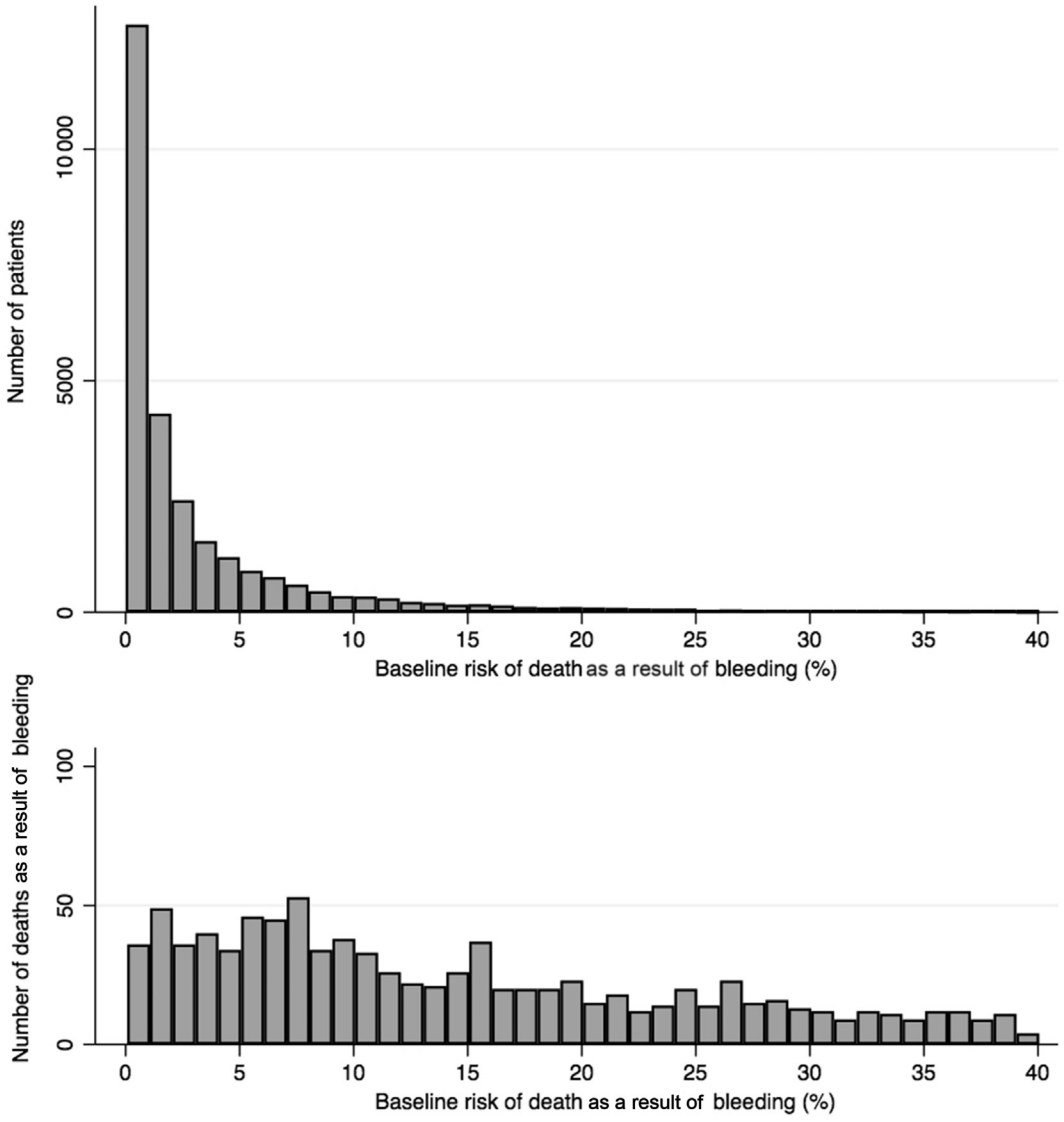


Fig 2. Number of patients and number of deaths according to baseline risk.

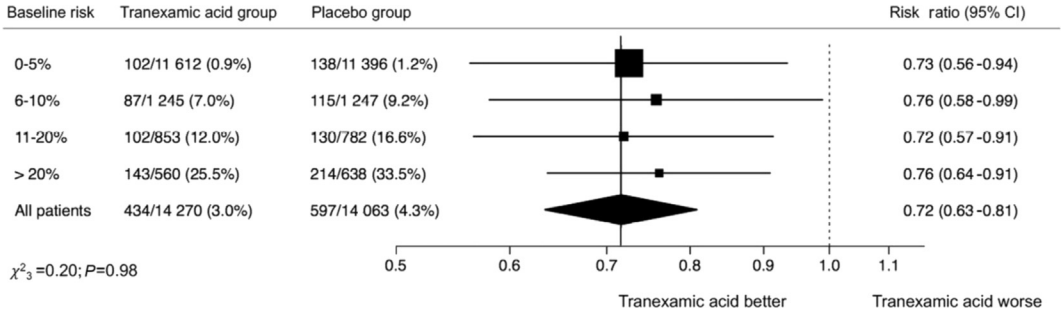


Fig 3. Effect of tranexamic acid on death as a result of bleeding by baseline risk. CI, confidence interval.

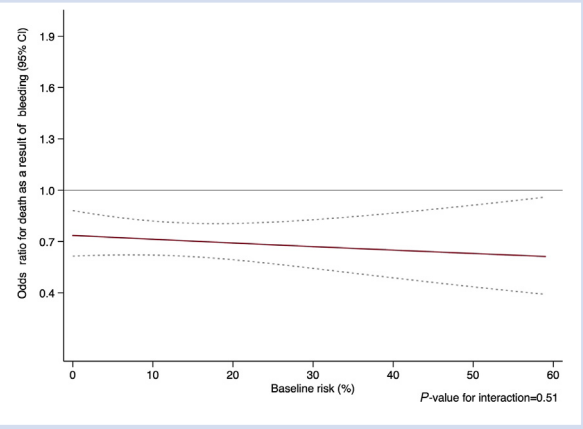


Fig 4. Effect of baseline risk on treatment benefit. CI, confidence interval.

the precision of prediction and the calibration.[31] Third, we performed logistic regression with baseline risk as a continuous variable since an on–off step function is biologically implausible. There was no interaction between treatment effect, trial, and time to treatment. Even though we restricted our analyses to patients treated within 3 h of bleeding onset, as recommended in clinical practice, we included trial and time to treatment in the model to avoid any residual confounding. Fourth, there were no missing outcome data and very few missing data for predictors of baseline risk (<1%). Nevertheless, we performed multiple imputation and used the whole dataset for analysis. We cannot exclude some measurement error in the predictors used to estimate the baseline risk and this could lead to regression dilution bias and over- or under-prediction in some patients.[32] Misclassification of death as a result of bleeding is also possible, as death from thrombotic disseminated intravascular coagulation could be confused with death from bleeding. We cannot exclude some misclassification as a result of optimism of the model affecting calibration. We are reassured that optimism was low in the model developed for trauma and the selection of a limited number of predictors limits overfitting.[10 11] Finally, the large sample size with more than 28 000 patients with acute bleeding treated within 3 h of onset gives precise results. However, estimates of the effects on adverse events are much less precise. The study included data from 38 countries across several continents and so the results should be widely generalisable to patients presenting to hospitals with postpartum haemorrhage and to trauma patients with, or at risk of, significant haemorrhage.

Implications of the study

The main clinical implication of these results is that tranexamic acid treatment should be considered as an early preventive measure rather than a treatment for severe coagulopathic bleeding. Because of the large number of patients in the low- and intermediate-risk groups, these groups contribute a large number of bleeding deaths. Indeed, about one-quarter of deaths from bleeding occurred in patients who initially appeared to have a low risk of death. Early identification of bleeding can be challenging, especially in trauma. Patients without obvious bleeding sometimes have concealed bleeding and can suddenly deteriorate. Although early identification of bleeding by a CT scan or FAST (Focused Assement with Sonography for Trauma) vel is a priority, a definitive diagnosis can take up to 1 h, even in the best trauma systems. Hence, many major trauma patients without clinically apparent bleeding will not receive tranexamic acid soon enough unless early treatment is given to all major trauma patients whatever their apparent risk. Major trauma is usually defined as an injury or a combination of injuries that are potentially life-threatening or could lead to long-term disability. Because the full extent of the patient's injuries is unknown at initial assessment, trauma team activation criteria represent a pragmatic alternative definition of major trauma in the prehospital setting. As for obstetric bleeding, WHO guidelines recommend tranexamic acid in addition to standard care for all women with clinically diagnosed postpartum haemorrhage. However, if 'in addition to' is taken to mean that tranexamic acid should be given after standard care has been found to be insufficient to stop the bleeding, this will result in unnecessary treatment delay. Instead, we believe

Table 2 Vascular occlusive events by treatment allocation according to baseline risk.

Baseline risk, *n* (%)	0–5%		6–10%		11–20%		>20%		*P*-value
	Tranexamic acid N=11 612	Placebo N=11 396	Tranexamic acid N=1245	Placebo N=1247	Tranexamic acid N=853	Placebo N=782	Tranexamic acid N=560	Placebo N=638	
Any vascular occlusive events	64 (0.6)	65 (0.6)	17 (1.4)	22 (1.8)	23 (2.7)	38 (4.9)	14 (2.7)	27 (4.2)	0.255
Fatal occlusive events	16 (0.1)	15 (0.1)	6 (0.5)	4 (0.3)	4 (0.5)	14 (1.8)	1 (0.2)	7 (1.1)	0.058
Myocardial infarction*	8 (0.1)	14 (0.1)	3 (0.2)	7 (0.6)	6 (0.7)	13 (1.7)	7 (1.3)	12 (1.9)	0.909
Stroke*	19 (0.2)	14 (0.1)	3 (0.2)	6 (0.5)	6 (0.7)	15 (1.9)	4 (0.7)	7 (1.1)	0.152
Pulmonary embolism*	28 (0.2)	23 (0.2)	6 (0.5)	8 (0.6)	14 (1.6)	16 (2.1)	6 (1.1)	9 (1.4)	0.739
Deep vein thrombosis*	12 (0.1)	19 (0.2)	7 (0.6)	2 (0.2)	6 (0.7)	4 (0.5)	3 (0.5)	5 (0.8)	0.214

* Includes both fatal and non-fatal events.

that early tranexamic acid treatment should be considered integral to standard care.

Future studies

We found 13 ongoing trials of antifibrinolytic drugs in acute severe bleeding. Three of these could provide additional data on the treatment effect by baseline risk in extracranial bleeding. However, these ongoing trials are small and their inclusion is very unlikely to change our conclusions. However, additional trials could increase the power to detect adverse effects. Further individual patient level data meta-analyses that consider vascular occlusive events are needed.

Conclusions

Tranexamic acid appears to be safe and effective regardless of the baseline risk for patients treated within 3 h since injury. Because many deaths are in patients at low and intermediate risk, tranexamic acid use should not be restricted to the most severely injured or bleeding patients. As tranexamic acid is safe, it should be considered as an early preventive measure rather than a treatment for severe coagulopathic bleeding.

Authors' contributions

Designed the study: FXA, AGA, KK, IR
Designed and monitored the data collection from which this paper was developed: FXA, HSS, KK, IR
Analysed the data: FXA, AGA
Gave feedback about the clinical use: FXA, AGA
Wrote the first draft: FXA, IR
Contributed to writing and revising the paper: all authors

Declaration of interest

The authors declare that they have no conflicts of interest.

Funding

Wellcome Trust (grant 208870 to IR and HSS).

Acknowledgements

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

The Antifibrinolytic Trials Collaboration is an ongoing collaboration of any clinical trialists who wish to share data from relevant randomised trials with more than 1000 patients, coordinated by the Clinical Trials Unit at the London School of Hygiene & Tropical Medicine (London, UK).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.01.020.

References

1. Gayet-Ageron A, Prieto-Merino D, Ker K, et al. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *Lancet* 2018; **391**: 125–32
2. World Health Organization. *WHO model lists of essential medicines*. 21th edition 2019 Available from:. https://www.who.int/medicines/publications/essentialmedicines/en/
3. Vogel JP, Oladapo OT, Dowswell T, Gülmezoglu AM. Updated WHO recommendation on intravenous tranexamic acid for the treatment of post-partum haemorrhage. *Lancet Glob Health* 2018; **6**: e18–9
4. Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care* 2019; **23**: 98
5. Committee on Trauma of the American College of Surgeons. *ACS TQIP massive transfusion in trauma guidelines*. Chicago, Il: American College of Surgeons; 2019
6. National Institute for Health and Care Excellence. *Major trauma: assessment and initial management: NICE guideline*. Available from: https://www.nice.org.uk/guidance/ng39/resources/major-trauma-assessment-and-initial-management-1837400761285. [Accessed 6 March 2020]
7. Pfeifer R, Teuben M, Andruszkow H, Barkatali BM, Pape H-C. Mortality patterns in patients with multiple trauma: a systematic review of autopsy studies. *PLoS One* 2016; **11**, e0148844
8. Roberts I. *A systematic review and prospective individual patient data meta-analysis of the effects of anti-fibrinolytic drugs on mortality and the risk of thromboembolic events in acute severe bleeding*. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=128260. [Accessed 6 March 2020]
9. Brenner A, Arribas M, Cuzick J, et al. Outcome measures in clinical trials of treatments for acute severe haemorrhage. *Trials* 2018; **19**: 533
10. Ageron F-X, Gayet-Ageron A, Steyerberg E, Bouzat P, Roberts I. Prognostic model for traumatic death due to bleeding: cross-sectional international study. *BMJ Open* 2019; **9**, e026823
11. Burke JF, Hayward RA, Nelson JP, Kent DM. Using internally developed risk models to assess heterogeneity in treatment effects in clinical trials. *Circ Cardiovasc Qual Outcome* 2014; **7**: 163–9
12. Sartorius D, Le Manach Y, David J-S, et al. Mechanism, Glasgow coma scale, age, and arterial pressure (MGAP): a new simple prehospital triage score to predict mortality in trauma patients. *Crit Care Med* 2010; **38**: 831–7
13. Perel P, Prieto-Merino D, Shakur H, Roberts I. Development and validation of a prognostic model to predict death in patients with traumatic bleeding, and evaluation of the effect of tranexamic acid on mortality according to baseline risk: a secondary analysis of a randomised controlled trial. *Health Technol Assess* 2013; **17**: 1–45. v–vi
14. CRASH-2 trial collaborators, Shakur H, Roberts I. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet Lond Engl* 2010; **376**: 23–32
15. Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. *N Engl J Med* 2017; **376**: 136–48

16. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **389**: 2105–16
17. Sentilhes L, Winer N, Azria E, et al. Tranexamic acid for the prevention of blood loss after vaginal delivery. *N Engl J Med* 2018; **379**: 731–42
18. Sprigg N, Flaherty K, Appleton JP, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet* 2018; **391**: 2107–15
19. Brown JB, Neal MD, Guyette FX, et al. Design of the study of tranexamic acid during air medical prehospital transport (STAAMP) trial: addressing the knowledge gaps. *Prehosp Emerg Care* 2015; **19**: 79–86
20. Clifton R. *Tranexamic acid for the prevention of obstetrical hemorrhage after Cesarean*. Available from: https://clinicaltrials.gov/ct2/show/NCT03364491. [Accessed 6 March 2020]
21. Dewan Y, Komolafe EO, Mejía-Mantilla JH, Perel P, Roberts I, Shakur H. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials* 2012; **13**: 87
22. Ker K, Roberts I, Chaudhri R, et al. Tranexamic acid for the prevention of postpartum bleeding in women with anaemia: study protocol for an international, randomised, double-blind, placebo-controlled trial. *Trials* 2018; **19**: 712
23. May S. *Prehospital tranexamic acid use for traumatic brain injury (NCT01990768)*. University of Washington; 2019. Available from: https://clinicaltrials.gov/ct2/show/record/NCT01990768?term=NCT01990768&rank=1. [Accessed 6 March 2020]
24. Mitra B, Mazur S, Cameron PA, et al. Tranexamic acid for trauma: filling the 'GAP' in evidence. *Emerg Med Australas EMA* 2014; **26**: 194–7
25. Roberts I, Coats T, Edwards P, et al. HALT-IT - tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial. *Trials* 2014; **15**: 450
26. Sentilhes Loic. *TRAnexamic Acid for Preventing Postpartum hemorrhage following a Cesarean delivery: a multicenter randomised, double blind placebo controlled trial (TRAAP2)*. Bordeaux: University Hospital; 2019. Available from: https://clinicaltrials.gov/ct2/show/record/NCT03431805?term=TRAAP2&rank=1. [Accessed 6 March 2020]
27. Shanghai First Maternity and Infant Hospital. *Tranexamic acid for preventing postpartum hemorrhage after Cesarean section (NCT02936661)*. Available from: https://clinicaltrials.gov/ct2/show/record/NCT02936661. [Accessed 6 March 2020]
28. Devereaux PJ. *PeriOperative ISchemic evaluation-3 trial (POISE-3)*. Hamilton, Canada: Population Health Research Institute; 2019. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03505723?show_locs=Y#locn. [Accessed 6 March 2020]
29. Tierney JF, Vale C, Riley R, et al. Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use. *PLoS Med* 2015; **12**, e1001855
30. Steyerberg EW, Uno H, Ioannidis JPA, van Calster B, Collaborators. Poor performance of clinical prediction models: the harm of commonly applied methods. *J Clin Epidemiol* 2018; **98**: 133–43
31. Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol* 2016; **69**: 245–7
32. Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. *BMJ* 2010; **340**: c2289

Handling editor: Christa Boer

Supplementary material

Supplementary method S1. MEDLINE search strategy.

The searches used to identify trials for this study were run to 1 July 2018 and were not restricted by date, language or publication status.
Database: Ovid MEDLINE(R) <1946 to March Week 26 2018>

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

Supplementary method S2. Equations of the different models.

1) Logistic regression assessing overall treatment effect and homogeneity of treatment effect across trials

$$\text{Logit}\,(p(Y = 1)) = \beta_0 + \beta_1 S + \beta_2 X + \beta_3 (X*S) \qquad \text{[model-1]}$$

With Y = 1, the outcome did not die from bleeding for patient i in trial j, S is the trial (CRASH-2 S=0, WOMAN S=1), X is treatment (tranexamic acid is X=1, placebo is X=0).
Then β_0 is the log(odds) in the placebo group in the CRASH-2 trial, β_1 is the difference between trials in placebo group, β_2 the effect of tranexamic acid in CRASH-2 trial, and β_3 is the interaction between treatment effect and trial.

2) Logistic regression estimating non-linear effect of intervention by baseline risk and its interaction with time to treatment (triple interaction).

$$\text{Logit}\,(p(Y = 1)) = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 BR + \beta_4 (X*T) + \beta_5 (BR*T) + \beta_6 (BR*X) + \beta_7 (BR*X*T) \qquad \text{[model-2]}$$

With Y, X coded as in [model-1]. T is the time to treatment in hours. BR is the baseline risk.
Then β_0 is the log(odds) in the placebo group when T=0 and BR=0; β_1 is the linear effect of time to treatment in the placebo group at BR=0; β_2 the effect of tranexamic acid at T=0 and BR=0; β_3 is the linear effect of baseline risk in the placebo group at T=0; β_4 is the interaction between treatment effect and time to treatment at BR=0; β_5 is the interaction between time to treatment and baseline risk in the placebo group; β_6 is the interaction of baseline risk with the treatment at T=0; β_7 is the triple interaction of baseline risk with the treatment and the time to treatment.

3) Logistic regression estimating linear effect of intervention by baseline risk (we assume this interaction is the same in both trials).

$$\text{Logit}\,(p(Y = 1)) = \beta_0 + \beta_1 S + \beta_2 X + \beta_3 BR + \beta_4 (BR*X) + \beta_5 T \qquad \text{[model-3]}$$

With Y, S, X, T, BR coded as in [model-1] and [model-2];
Then, β_0 is the log(odds) in the placebo group in the CRASH-2 trial when BR=0; β_1 is the difference between trials; β_2 is the effect of tranexamic when BR=0;; $\beta_3$is the linear effect of baseline risk in the placebo group of both trials ; β_4 is the interaction of baseline risk with the treatment; β_5 is the effect of time to treatment.

Supplementary method S3. Characteristics of included and ongoing trials.

Trial ID	Title	Participants	Intervention	Outcomes
Included trials				
CRASH-2[1]	A large randomised placebo controlled trial among trauma patients with, or at risk of, significant haemorrhage, of the effects of anti-fibrinolytic treatment on death and transfusion requirement.	N=20,211 Adult (>16 years) trauma patients with, or at risk of, significant bleeding.	A loading dose of 1 g tranexamic acid or placebo will be administered as soon possible, followed by a maintenance dose of 1 g TXA or placebo over eight hours.	Primary: Death. Secondary: Vascular occlusive events, blood transfusion requirements, disability.
WOMAN[2]	Tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind, placebo controlled trial	N=20,060 Women with clinically diagnosed postpartum haemorrhage following vaginal delivery of a baby or caesarean section. The clinical diagnosis of PPH may be based on any of the following: estimated blood loss after vaginal delivery of a baby> 500 mL OR >1000 mL from caesarean section OR blood loss sufficient to compromise the haemodynamic status of the woman.	1g of T tranexamic acid by intravenous injection or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. If after 30 minutes bleeding continues, or if it stops and restarts within 24 hours after the first dose, a second dose may be given.	Primary: Death or hysterectomy. Secondary: Death, surgical intervention, blood transfusion, health status, thromboembolic events, other relevant medical events, length of stay at hospital/time spent at an intensive care unit, mechanical ventilation, status of breastfed baby/ies.
TICH-2[3]	Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage	N=2325 Adult patients with acute primary intracerebral haemorrhage within 8 hours of stroke onset.	Tranexamic acid 1 g or placebo in 100 ml sodium chloride 0.9% infusion bag intravenously as a loading dose infusion over 10 min, followed by infusion of tranexamic acid 1 g or placebo in 250 ml sodium chloride 0.9% infusion bag over 8 h.	Primary: Death or dependency at day 90 Secondary: Neurological impairment at day 7 or discharge if sooner, disability (Barthel index) at day 90, Quality of Life (EuroQol) at day 90, cognition at day 90, costs: length of stay in hospital, re-admission, institutionalisation, radiological efficacy/safety (CT scan): change in haematoma volume from baseline to day 2, haematoma location and new infarction.
Excluded Trials				
ATACAS[4]	Aspirin and tranexamic acid for Coronary Artery Surgery Trial	N=4662 Adults undergoing coronary-artery surgery and at risk of perioperative complications.	Tranexamic acid (100mg/kg) or saline administered 30 minutes after induction of anaesthesia (dose of tranexamic acid halved to 50mg after 1392 patients enrolled)	Primary: Composite outcome of all-cause 30 day mortality or thrombotic event Secondary: Death, nonfatal myocardial infarction, pulmonary embolism, stroke, acute renal failure, bowel infarction), reoperation due to major haemorrhage or cardiac tamponade, blood transfusion.
TRAAP[5]	Tranexamic acid for Preventing Postpartum Haemorrhage Following a Vaginal Delivery: a Multicenter Randomised Double Blind Placebo Controlled Trial	N = 4079 Women in labour for a planned vaginal singleton delivery, at a term ≥ 35 weeks.	1g tranexamic acid or placebo will be administered intravenously just after birth.	Primary: incidence of PPH, defined by blood loss ≥500 mL Secondary: Mean blood loss at 15 minutes after birth; mean total blood loss; incidence of severe PPH; need for supplementary uterotonic treatment;

				postpartum transfusion; need for invasive second-line procedures for PPH; haemoglobin, hematocrit; hemodynamic tolerance; mild adverse effects; tolerance lab tests; severe adverse effects
Ongoing trials				
CRASH-3[6] (ISRCTN15088122) Expected completion date: December 2018	Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind placebo controlled trial	N=13,000 (target) Adults with traumatic brain injury, who are within eight hours of injury, with any intracranial bleeding on CT scan or who have a GCS of 12 or less, and have no significant extra-cranial haemorrhage.	Loading dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. Maintenance dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) given after the loading dose is finished.	Primary: death in hospital within 28 days of injury. Secondary: vascular occlusive events, disability, seizures, neurosurgical intervention, days in intensive care, other adverse events.
HALT-IT[7] (ISRCTN11225767) Expected completion date: October 2017	Tranexamic acid for the treatment of gastrointestinal haemorrhage: an international randomised, double blind placebo controlled trial	N=8000 (target) Adults with acute significant upper or lower gastrointestinal bleeding.	Loading dose of tranexamic acid (1g by intravenous injection) or placebo (sodium chloride 0.9%) will be given as soon as possible after randomisation, followed by an intravenous infusion of 3g of tranexamic acid or placebo (sodium chloride 0.9%) over 24 hours.	Primary: death in hospital (cause-specific mortality will also be recorded) Secondary: Re-bleeding, need for salvage surgery or radiological intervention, blood transfusion, thromboembolic events, other adverse medical events, functional status, time spent at an intensive care unit, length of stay in hospital
Shanghai FMIH-TXA1[8] NCT02936661 Expected completion date: March 2019	Tranexamic acid for Preventing Postpartum Hemorrhage After Cesarean Section	N=6700 (target) Women giving birth by cesarean section.	Tranexamic acid or placebo	Primary: postpartum haemorrhage Secondary: the amount of postpartum bleeding
PATCH[9] NCT02187120 Expected completion date: January 2021	A Multi-centre Randomised, Double-blinded, Placebo-controlled Trial of Pre-hospital Treatment With tranexamic acid for Severely Injured Patients at Risk of Acute Traumatic Coagulopathy.	N= 1184 (target) Adult patients (age ≥18 years); injured through any mechanism; COAST score≥3.	1g tranexamic acid or placebo (0.9% NaCl) by slow intravenous injection as early as possible following injury. Soon after arrival to the emergency department, patients will be given 1g tranexamic acid or placebo infused intravenously for 8 hours.	Primary: Favourable outcome at six months (moderate disability to good recovery, GOSE scores 5-8) compared to those who have died (GOSE 1), or have severe disability (GOSE 2-4). Secondary: Units of blood products used in the first 24 hours; coagulation profile; ICU ventilator-free days in first 28 days; vascular occlusive events; mortality; proportion of deaths due to: bleeding, vascular occlusion, multi-organ failure and head injury; cumulative incidence of sepsis at 28 days or hospital discharge whichever occurs first; severity of chronic pain 6 months after injury and its interference with daily activities measured using the modified Brief Pain Inventory; Quality of life (SF12® and EQ5D) at 6 months.

STAAMP[10] NCT02086500 Expected completion date: March 2019	Study of tranexamic acid During Air Medical Prehospital Transport Trial For Trauma Patients At Risk Of Hemorrhage	N=1000 (target) Adult (18-90 years) trauma patients within 2 hours of injury. Setting: USA	1g tranexamic acid or placebo during air medical transport.	Primary outcome: 30 day mortality. Secondary outcomes: hyperfibrinolysis, acute lung injury, multiple organ failure, nosocomial infection, mortality, early seizures, pulmonary embolism, early resuscitation needs, early coagulopathy as measured by INR and rapid thromboelastography parameters, early inflammatory response, plasmin levels, leukocyte, platelet and complement activation.
NCT03364491[11] (MFMU Network) Expected completion date: December 2020	Tranexamic Acid for the Prevention of Obstetrical Hemorrhage After Cesarean	N=11000 (target) Women giving birth by scheduled or unscheduled cesarean section Setting: USA	1g tranexamic acid or placebo	Primary outcome: Maternal death or transfusion of 1 or more units of packed red blood cells (up to hospital discharge or 7 days) Secondary outcome: Blood loss, composite surgical or radiological intervention to control bleeding, composite maternal death and thromboembolic events, transfusion related acute lung injury, transfusion of other blood products, transfusion of more than 4 RBC, acute kidney injury, thromboembolic events, seizure, ingfection, admission to ICU, change in haemoglobin, TXA side-effects, length of stay, hospital re-admission, transfusion reaction
NCT01990768[12] Expected completion date: January 2019	Prehospital Tranexamic Acid Use for Traumatic Brain Injury	N=1002 (target) 967 recruited Moderate to severe TBI (GCS score ≤12) Setting: Prehospital, Canada, USA	1g tranexamic acid prior to hospital arrival followed by a 1g infusion or 2g tranexamic acid prior to admission or placebo	Primary outcome: Glasgow Outcome Scale Extended (GOS-e) at 6 months. Secondary outcome: Death at 28 days, disability rating scale at discharge and 6 months, Unfavourable outcome Dichotomized GOS-e, Number ICH, Marshall score CT, Rotterdam score CT, Neurosurgical intervention, Hospital free-days, ICU free-days, seizure, thromboembolic event (CVD, DVT, MI, PE).
TRAAP-2[13] NCT03431805 Expected completion date: June 2020	Tranexamic acid for Preventing Postpartum Haemorrhage Following a Cesarean Delivery	N=4524 (target) Women admitted for caesarean delivery before or during labor (term≥34) Setting: France	1g tranexamic acid or placebo with prophylactic uterotonic 3 minutes after birth.	Primary outcome: incidence of PPH, defined by blood loss >1000 mL at day 2. Secondary outcome: blood loss >500; >1500, mean blood loss, incidence of transfusion, mean RBC transfused, incidence embolization or surgery, change in haemoglobin, HR, SBP, DBP, nausea, vomiting, phosphenes, dizziness, vreat, urea, prothrombin, asat, alat,

				bilirubin, fibrinogen, DVP, PE, MI, any thrombotic event, seizure, women's satisfaction,m shock, ICU, death from any cause
WOMAN-2[14] NCT03475342 Expected completion date: March 2022	World Maternal Antifibrinolytic Trial 2	N=10000 (target) Women with moderate or severe anemia (Hb<100g/L or packed cell volume <30%) planned to give birth vaginally Setting: International	1g tranexamic acid or placebo administered at delivery (no later than 15 minutes after umbilical cord is clamped)	Primary outcome: PPH at 24H(blood loss>500 or any blood loss sufficient to compromise haemodynamic stability). Secondary outcome: blood loss, Hb, Haemodynamic instability, shock index, quality of life (maternal), side-effects, exercise tolerance, intervention for control PPH, blood transfusion, vascular occlusive events, anemia, organ dysfunction, in-hospital death, length of hospital stay, transfer to higher facility, status baby, thrombotic events in breastfed babies, adverse events.
POISE-3 trial[15] NCT03505723 Expected completion date: December 2022	PeriOperative ISchemic Evaluation-3 Trial	N=10000 (target) Patent undergoing noncardiac surgery with ≥ 45 years of age and expected to require at least an overnight hospital admission after surgery. Setting: International		Primary outcome : A composite of life-threatening bleeding, major bleeding, and critical organ bleeding at 30 days. A composite of myocardial infarction, non-hemorrhagic stroke, peripheral arterial thrombosis, and symptomatic proximal venous thromboembolism at 30 days. For patients in the blood pressure management arm: A composite of vascular death, and non-fatal myocardial infarction, stroke, and cardiac arrest at 30 days.

References

1 CRASH-2 trial collaborators, Shakur H, Roberts I, *et al.* Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet Lond Engl* 2010; **376**: 23–32.

2 Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet Lond Engl* 2017; **389**: 2105–16.

3 Sprigg N, Flaherty K, Appleton JP, *et al.* Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet Lond Engl* 2018; **391**: 2107–15.

4 Myles PS, Smith JA, Forbes A, *et al.* Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. *N Engl J Med* 2017; **376**: 136–48.

5 Sentilhes L, Winer N, Azria E, *et al.* Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. *N Engl J Med* 2018; **379**: 731–42.

6 Dewan Y, Komolafe EO, Mejía-Mantilla JH, Perel P, Roberts I, Shakur H. CRASH-3 - tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials* 2012; **13**: 87.

7 Roberts I, Coats T, Edwards P, *et al.* HALT-IT - tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial. *Trials* 2014; **15**. DOI:10.1186/1745-6215-15-450.

8 Shanghai First Maternity and Infant Hospital. Tranexamic Acid for Preventing Postpartum Hemorrhage After Cesarean Section (NCT02936661). https://clinicaltrials.gov/ct2/show/record/NCT02936661 (accessed April 3, 2019).

9 Mitra B, Mazur S, Cameron PA, *et al.* Tranexamic acid for trauma: filling the 'GAP' in evidence. *Emerg Med Australas EMA* 2014; **26**: 194–7.

10 Brown JB, Neal MD, Guyette FX, *et al.* Design of the Study of Tranexamic Acid during Air Medical Prehospital Transport (STAAMP) Trial: Addressing the Knowledge Gaps. *Prehospital Emerg Care Off J Natl Assoc EMS Physicians Natl Assoc State EMS Dir* 2015; **19**: 79–86.

11 Clifton, Rebecca. Tranexamic Acid for the Prevention of Obstetrical Hemorrhage After Cesarean. https://clinicaltrials.gov/ct2/show/NCT03364491.

12 May, Susanne. Prehospital Tranexamic Acid Use for Traumatic Brain Injury (NCT01990768). https://clinicaltrials.gov/ct2/show/record/NCT01990768?term=NCT01990768&rank=1 (accessed April 3, 2019).

13 Sentilhes, Loic. TRAnexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean Delivery :a Multicenter Randomised, Double Blind Placebo Controlled Trial (TRAAP2). https://clinicaltrials.gov/ct2/show/record/NCT03431805?term=TRAAP2&rank=1 (accessed April 3, 2019).

14 Ker K, Roberts I, Chaudhri R, *et al.* Tranexamic acid for the prevention of postpartum bleeding in women with anaemia: study protocol for an international, randomised, double-blind, placebo-controlled trial. *Trials* 2018; **19**. DOI:10.1186/s13063-018-3081-x.

15 Devereaux, PJ. PeriOperative ISchemic Evaluation-3 Trial (POISE-3). https://clinicaltrials.gov/ct2/show/study/NCT03505723?show_locs=Y#locn (accessed April 3, 2019).

Supplementary method S4. Results of risk of bias assessment.

CRASH-2

Domain	Judgement	Justification
Sequence generation	Low	Computer-generated.
Allocation concealment	Low	Tranexamic acid and placebo were packaged in identical ampoules. Recruiting hospitals with reliable telephone access used a telephone randomisation service, hospitals without, used a local pack system.
Blinding	Low	Participants, clinicians and trial staff were blinded to treatment allocation.
Incomplete outcome data	Low	Over 99% of patients were followed up and contributed outcome data.
Selective outcome reporting	Low	Prospectively registered and data on all pre-specified outcomes available for analysis.

WOMAN

Domain	Judgement	Justification
Sequence generation	Low	Computer-generated.
Allocation concealment	Low	Tranexamic acid and placebo were packed in sequentially numbered, sealed, treatment boxes.
Blinding	Low	Participants, clinicians and trial staff were blinded to treatment allocation.
Incomplete outcome data	Low	Over 99% of patients were followed up and contributed outcome data.
Selective outcome reporting	Low	Prospectively registered and data on all pre-specified outcomes available for analysis.

Supplementary method S5. Prognosis model to estimate baseline risk of death due to bleeding

CRASH-2 trial

$Pr = 1/(1+e^{-xb})$

$xb = 0.534 + RI + (0.061 * Age) - (1.4e^{-3} * Age^2) + (1.2e^{-05} * Age^3) + (0.023 * SBP) - (5.4e\text{-}04 * SBP^2) + (1.6e^{-06} * SBP^3) - (0.634 * GCS) + (0.074 * GCS^2) - (2.9e^{-3} * GCS^3) - (8.6e^{-3} * HR) + (1.0e\text{-}04 * HR^2) - (0.171 * RR) + (0.006 * RR^2) - (5.4e^{-05} * RR^3)$

RI: Random Intercept by country
Age (Year)
SBP: Systolic Blood Pressure (mmHg)
HR: Heart Rate (Beat per min)
RR: Respiratory Rate (Breath per minute)
GCS: Glasgow Coma Scale
Penetrating: Penetrating Injury

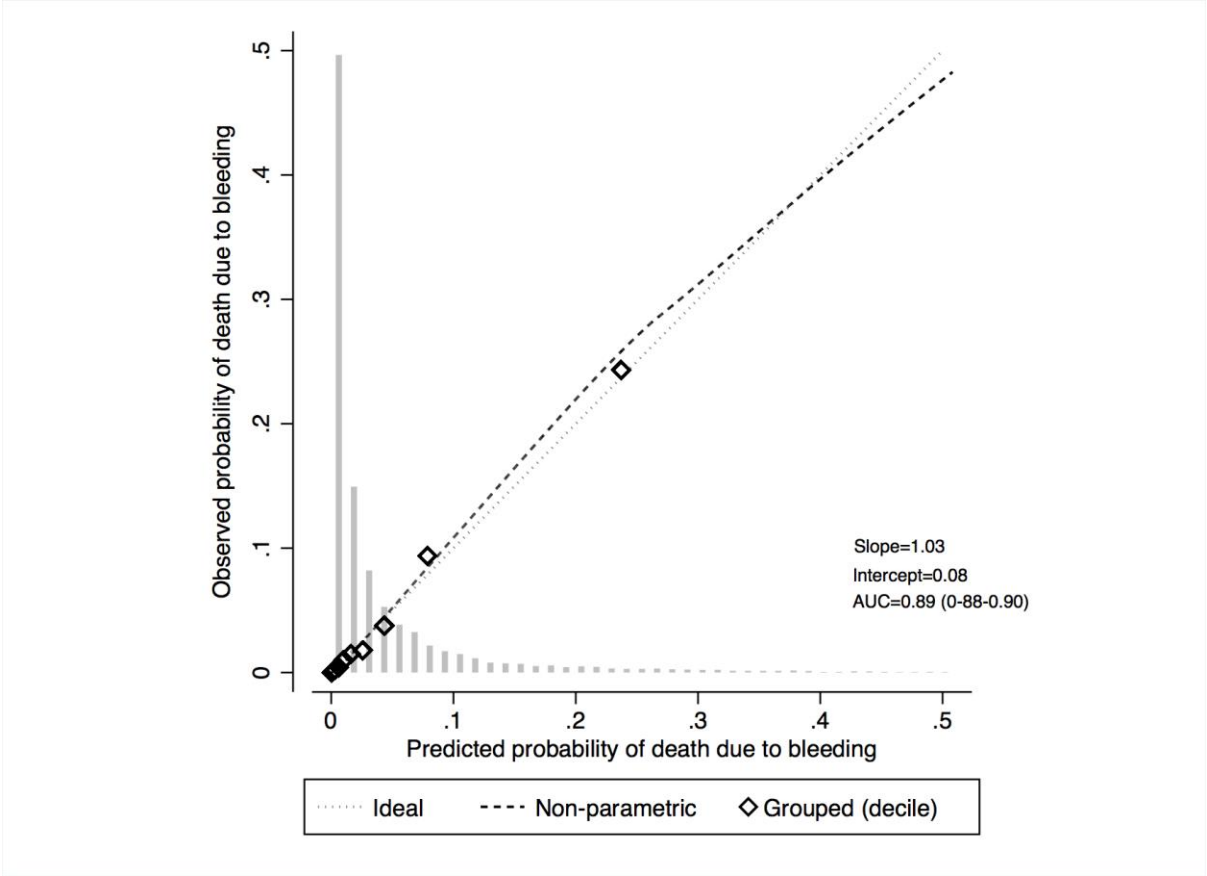
WOMAN trial

$Pr = 1/(1+e^{-xb})$

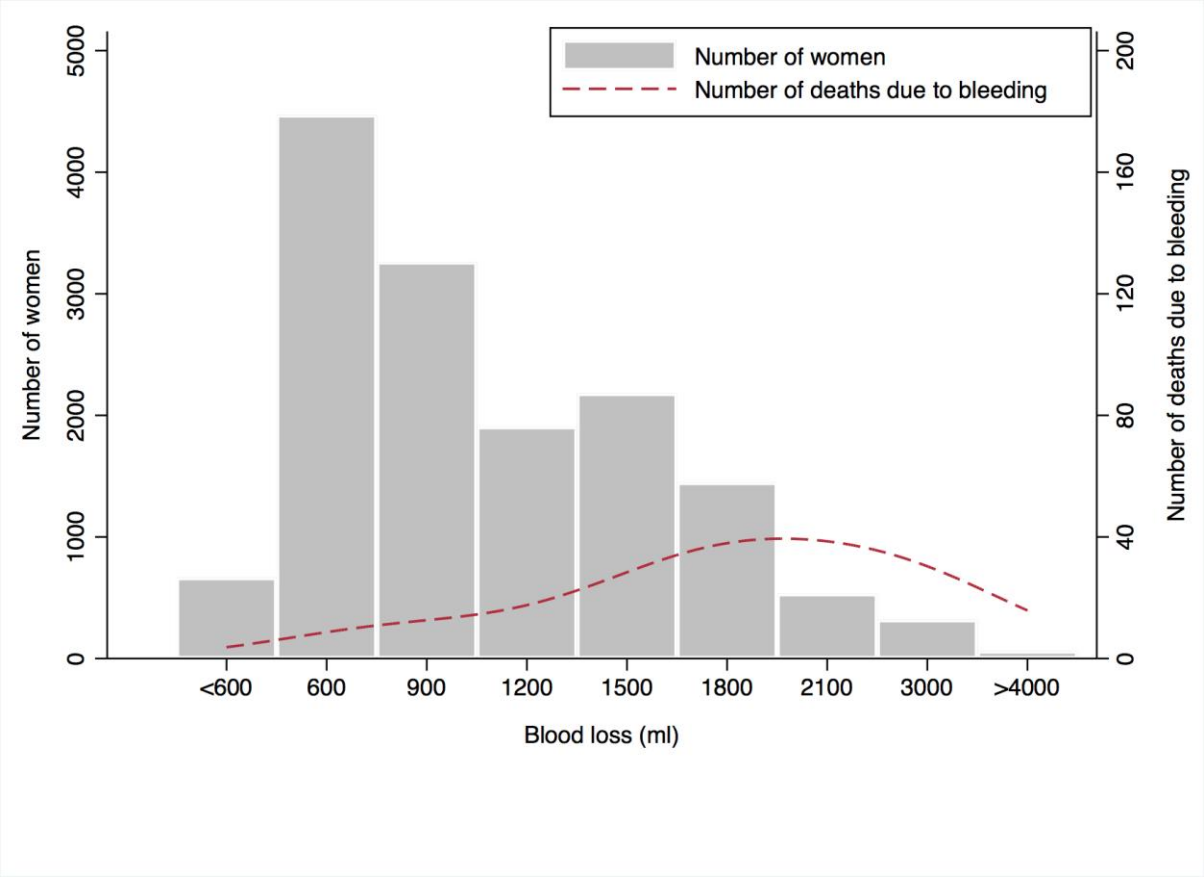
$xb = -8.66 + RI + (Age * 0.06) - (SBP * 0.01) - (SBP^2 * 3\ e^{-4}) + (SBP^3 * 1.6\ e^{-6}) + (BL * 2\ e^{-3}) - (BL^2 * 3\ e^{-7}) - (PP * 1.05) - (UA * 0.32) + (HI * 1.56) - (Delivery * 0.72)$

RI: Random Intercept by country
Age (Year)
SBP: Systolic Blood Pressure (mmHg)
BL: Blood Loss (ml)
PP: Placenta Previa (Yes=1, No=0)
UA: Uterine Atony (Yes=1, No=0)
HI: Haemodynamic instability (Yes=1, No=0)
Delivery: 0=Vaginal delivery; 1=caesarean section

Supplementary figure S6. Performance of prognosis model predicting baseline risk of death due to bleeding.



Supplementary figure S7. Frequency of women with post-partum hemorrhage and death due to bleeding according to blood loss.



Supplementary table S8. Vascular occlusive events (fatal and non-fatal) by trial and overall.

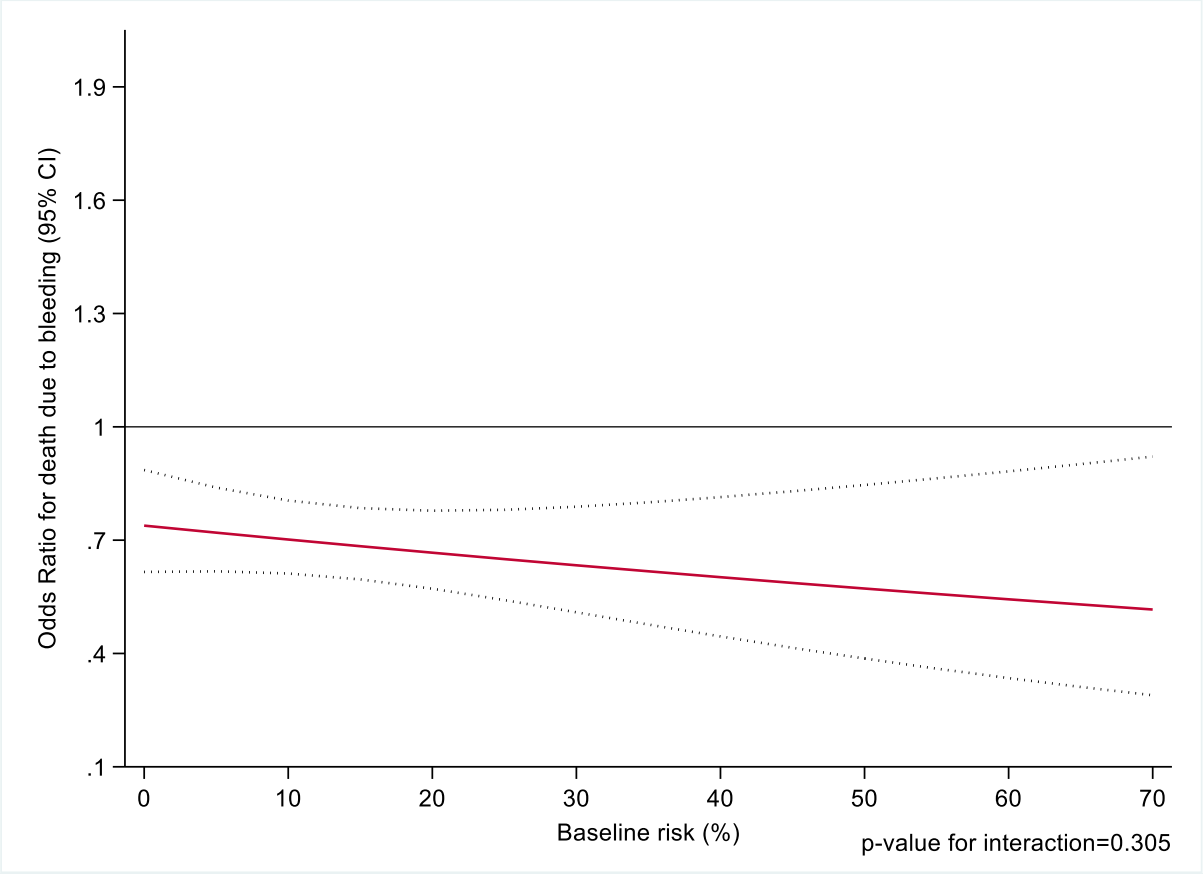
	CRASH-2 trial			WOMAN-trial			Overall Trials		
Baseline risk	Tranexamic acid n (%)	Placebo n (%)	RR (95% CI)	Tranexamic acid n (%)	Placebo n (%)	RR (95% CI)	Tranexamic acid n (%)	Placebo n (%)	RR (95% CI)
0-5%	45 / 4587 (1.0)	55 / 4476 (1.2)	0.80 (0.54-1.18)	19 / 7003 (0.3)	10 / 6920 (0.1)	1.87 (0.87-4.02)	64 / 11612 (0.6%)	65 / 11396 (0.6%)	0.97 (0.69-1.36)
6-10%	15 / 988 (1.5)	22 / 1001 (2.2)	0.71 (0.36-1.35)	2 / 257 (0.8)	0 / 224 (0)	-	17 (1.4%)	22 (1.8%)	0.77 (0.41-1.45)
11-20%	22 / 731 (3.0)	36 / 642 (5.6)	0.54 (0.32-0.90)	1 / 122 (0.8)	2 / 140 (1.4)	0.57 (0.05-6.25)	23 (2.7%)	38 (4.9%)	0.55 (0.33-0.92)
>20%	13 / 478 (2.7)	25 / 560 (4.4)	0.61 (0.32-1.18)	1 / 82 (1.2)	2 / 78 (2.6)	0.48 (0.04-5.14)	14 (2.7%)	27 (4.2%)	0.59 (0.31-1.12)
Test for homogeneity, P Value			0.040			0.367			0.076

Supplementary table S9. Sensitivity analysis with baseline risk estimate based on models developed with placebo arm only.

	Main analysis (baseline risk based on both arm)				Sensitivity analysis (baseline risk based on placebo arm)			
	Overall adjusted effect	P value	Test for homogeneity*	P Value	Overall adjusted effect	P value	Test for homogeneity*	P Value
Baseline risk by categories (RR)	0.74 (0.66-0.83)	<0.001	0.20	0.978	0.74 (0.66-0.83)	<0.001	4.44	0.218
Model 3 (interaction TXA-Baseline risk (OR)	0.74 (0.61-0.88)	0.001	-0.66	0.510	0.74 (0.62-0.89)	0.001	-1.03	0.305

*by categories or for interaction
TXA: Tranexamic acid; RR: Risk ratio; OR: Odds ratio

Supplementary Figure S10. Sensitivity analysis with baseline risk estimate based on models developed with placebo arm only: effect of baseline risk on treatment benefit.



London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1602524	**Title**	Dr
First Name(s)	Francois-Xavier		
Surname/Family Name	Ageron		
Thesis Title	Tranexamic acid in trauma care: Who should be treated, when and where?		
Primary Supervisor	Professor Ian Roberts		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Scandinavian Journal of Trauma and Emergency Medicine (3)
Please list the paper's authors in the intended authorship order:	Francois-Xavier Ageron; Timothy J. Coats; Vincent Darioli; Ian Roberts.
Stage of publication	**Undergoing revision**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the study with Ian Roberts. I designed and monitored the data collection. I analysed the data and wrote the manuscript.

SECTION E

Student Signature	[redacted]
Date	9 Dec 2020

Supervisor Signature	[redacted]
Date	9/12/20

Ageron et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine (2021) 29:6
https://doi.org/10.1186/s13049-020-00827-5

Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine

ORIGINAL RESEARCH Open Access

Validation of the BATT score for prehospital risk stratification of traumatic haemorrhagic death: usefulness for tranexamic acid treatment criteria

Francois-Xavier Ageron[1,2*], Timothy J. Coats[3], Vincent Darioli[2] and Ian Roberts[1]

Abstract

Background: Tranexamic acid reduces surgical blood loss and reduces deaths from bleeding in trauma patients. Tranexamic acid must be given urgently, preferably by paramedics at the scene of the injury or in the ambulance. We developed a simple score (Bleeding Audit Triage Trauma score) to predict death from bleeding.

Methods: We conducted an external validation of the BATT score using data from the UK Trauma Audit Research Network (TARN) from 1st January 2017 to 31st December 2018. We evaluated the impact of tranexamic acid treatment thresholds in trauma patients.

Results: We included 104,862 trauma patients with an injury severity score of 9 or above. Tranexamic acid was administered to 9915 (9%) patients. Of these 5185 (52%) received prehospital tranexamic acid. The BATT score had good accuracy (Brier score = 6%) and good discrimination (C-statistic 0.90; 95% CI 0.89–0.91). Calibration in the large showed no substantial difference between predicted and observed death due to bleeding (1.15% versus 1.16%, $P = 0.81$). Pre-hospital tranexamic acid treatment of trauma patients with a BATT score of 2 or more would avoid 210 bleeding deaths by treating 61,598 patients instead of avoiding 55 deaths by treating 9915 as currently.

Conclusion: The BATT score identifies trauma patient at risk of significant haemorrhage. A score of 2 or more would be an appropriate threshold for pre-hospital tranexamic acid treatment.

Keywords: Trauma, Tranexamic acid, Bleeding, Score, Prognostic model

Introduction

Tranexamic acid (TXA) reduces surgical blood loss and reduces deaths from bleeding in trauma patients [1, 2]. TXA must be given urgently, preferably by paramedics at the scene of the injury or in the ambulance [3]. Many bleeding deaths occur soon after injury and there is a 10% reduction in treatment effectiveness for every 15 min treatment delay [4]. Paramedics need clear criteria that can be applied at the scene to guide who to treat. We previously developed a prognostic model to predict death from bleeding and showed that the relative reduction in mortality with TXA does not vary with baseline risk [5, 6]. Because many deaths are in patients at low and intermediate risk, TXA use should not be restricted to the most severely injured [6]. In this study, we derive a simple score that paramedics can use at the scene to help decide who to treat with TXA. We conduct an external validation of the score and explore different TXA treatment thresholds.

* Correspondence: fxageron@gmail.com
[1]Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK
[2]Department of Emergency Medicine, Lausanne University Hospital, University of Lausanne, 1011 Lausanne, Switzerland
Full list of author information is available at the end of the article

Method

We developed a simple score (Bleeding Audit and Triage Trauma Score - BATT) to predict death due to bleeding in trauma patients. We conducted an external validation of this score using data from the UK Trauma Audit Research Network (TARN) from 1st January 2017 to 31st December 2018. Finally, we evaluated the impact of TXA treatment thresholds in trauma patients.

Development of the BATT score

We previously developed and validated a prognostic model to predict death due to bleeding in trauma patients. The methods are described in detail elsewhere [5]. Briefly, data on bleeding trauma patients from 298 hospitals in 41 countries were used to derive the model. We validated the model using an internal–external cross-validation method based on data from 41 countries to ensure that the results are widely applicable. The final prognostic model included age, systolic blood pressure, Glasgow Coma Scale, heart rate, respiratory rate and mechanism of injury. To develop the BATT score, we assigned points for each predictor that were proportional to the coefficients of the regression equation. We added the criterion high velocity trauma as the intercept of the regression equation corresponding to the inclusion criteria of the trauma registry used for the development of prognostic model. High velocity trauma is routinely assessed at the scene and corresponds to injury from road traffic crash (with intrusion, ejection, death in same passenger compartment, and motor vehicle versus pedestrian or bicyclist), fall from high height (> 3 m), blow or blast [7]. An electronic version of the score is available for computer or smartphone: https://www.evidencio.com/models/show/1393

Validation of the BATT score

We used data from the Trauma Audit Research Network (TARN) from 1st January 2017 to 31st December 2018 to validate the BATT score for use in England and Wales. The TARN database includes data on patients with an Injury Severity Score (ISS) of nine or more who are admitted to hospital in England and Wales for at least three nights, died in hospital or were transferred to another hospital for specialist care [8]. The exclusion criteria were isolated mild traumatic brain injury with loss of consciousness, superficial scalp injury, patients 65 years or older with femoral neck or single pubic rami fracture, fracture or dislocation of the foot or hand, closed fracture or dislocation of an isolated limb, simple skin laceration with blood loss < 20%.

Because death due to bleeding is not recorded in the TARN database, we used early deaths and early deaths with evidence of haemorrhage as a proxy for death due to bleeding. Causes of trauma deaths depend on time and location of death [9]. Prehospital immediate deaths are likely to be due to traumatic brain injury or cardiovascular injuries [10]. The main causes of in-hospital deaths are exsanguination and brain injury [11]. Two studies, one in North America and one including two large European registries (UK and Germany) showed that deaths due to exsanguination occurred within 24 h with a peak at 6 h after admission [9, 12]. Deaths due to head injuries occurred within 72 h with a peak at 24 h after admission. Consequently, we included deaths from all cause within 12 h of injury (excluding asphyxia, drowning, hanging, or massive destruction of skull or brain) and deaths between 12 to 24 h with evidence of bleeding (activation of massive transfusion protocol or blood within 6 h or an abbreviated injury scale (AIS) diagnosis associated with haemorrhage listed in the Supplementary file 1).

We assessed the accuracy, discrimination and calibration of the BATT score. Accuracy was assessed using the Brier score. Because the Brier score depends on the prevalence of the outcome, we also calculated the scaled Brier score to account for the baseline risk of death due to bleeding (Supplementary file 2). The scaled Brier score ranges from 0 to 100% and indicates the degree of error in prediction [13]. A scaled Brier score of 0% shows perfect accuracy. Discrimination is the ability of the score to correctly identify patients with the outcome. We estimated the sensitivity, specificity, positive and negative likelihood ratio for each threshold of the BATT score. The likelihood ratio is the likelihood of a positive score in a patient with the outcome compared to the likelihood of a positive score in a patient without the outcome [14]. The positive likelihood ratio is the ratio of sensitivity to 1-specificity. The negative likelihood ratio is the ratio of 1-sensitivity to specificity. A positive likelihood ratio of 10 or above will result in a large increase in the probability of the outcome. A negative likelihood ratio of 0.1 or less will result in a large decrease in the probability of the outcome. We plotted the Receiving Operating Characteristic (ROC) curve which is the sensitivity (true positives) on 1-specificity (false positives) for different threshold of the BATT score [15]. An ideal score will reach the upper left corner (all true positive with no false positive). We estimated the area under the ROC curve (AUROC) that corresponds to the concordance statistic (C-Statistic) for binary outcome. A C-statistic of 1.0 shows perfect discrimination ability. Calibration is the agreement between observed and predicted outcomes. We estimated calibration in the large as the difference between the mean predicted and observed probabilities and the ratio of the predicted and observed number of events (P/O). We also plotted the observed and predicted probabilities of death by decile of the score and with local regression based on LOESS

algorithm [13]. We estimated the calibration intercept and slope of the calibration plot as a measure of spread between predicted and observed outcome. Ideally, the intercept would be zero indicating that the predictions are neither systematically too low or too high and the slope would be 1 [16]. There were missing value for some predictors but no missing outcome data. To estimate baseline risk for the full dataset, we replaced missing predictors using multiple imputation by chained equations on early death, age, systolic blood pressure, respiratory rate, heart rate, Glasgow coma scale, time for injury, time for prehospital ambulance arrival, and time for hospital admission with 20 imputed datasets.

Evaluation of TXA treatment criteria

We evaluated two different TXA treatment strategies: (1) prehospital treatment of all trauma patients with an ISS ≥9 at the scene of the injury, (2) hospital treatment of all trauma patients with an ISS > 9 in the emergency department (ED). We compared each treatment strategy according to different thresholds of the BATT score to assess its clinical usefulness and treatment criteria.

We estimated the impact of TXA treatment for each treatment criteria. Since randomized trials of TXA in trauma patients report no increase in deaths from adverse events, the net impact of TXA was given by the number of deaths due to bleeding avoided by the treatment [6, 17]. To estimate the number of deaths avoided by TXA, we predicted the baseline risk of death due to bleeding using our previously published prognostic model [5]. To estimate post-treatment probabilities, we applied the treatment effect to these baseline risks taking into account time to treatment [4]. The risk difference was used to estimate the number of deaths avoided. To account for miscalibration of predicted baseline risks, we conducted a sensitivity analysis using observed early deaths with evidence of haemorrhage as baseline risks. The details of both modelling methods and equations are described in the Supplementary file 3. We plotted the cumulative number of death due to bleeding avoided by BATT score threshold in a decision curve analysis as described by Vickers et al. [18] We compared decision curve analysis for each scenario. We estimated the number needed to treat to save one life for each BATT score threshold and each scenario. The registry-based study design predetermines the sample size. All analyses were performed using STATA software (version 16.0; Stata Corp, College Station, TX, USA).

Results

Table 1 shows the BATT Score. The minimum score is 0 and the maximum score is 27.

Table 1 BATT score

Age	≥ 65 years old	+ 1
	≥ 75 years old	+ 2
Systolic Blood Pressure	< 60 mmHg	+ 14
	≥ 60 and < 100 mmHg	+ 5
Glasgow Coma Scale	≤ 8	+ 4
	> 8 and ≤ 12	+ 3
Respiratory rate	< 10 or ≥ 30/min	+ 2
	Alt: Oxygen saturation < 90	+ 2
Heart rate	> 100/min	+ 1
Penetrating injury	Yes	+ 2
High velocity trauma	Yes	+ 2

The score is not suitable for isolated limb trauma or isolated neck femoral fracture in people older than 65 years

External validation - patient's characteristics

We validated the score in 104,862 trauma patients with an ISS ≥ 9 who were transported to hospital by ambulance in England and Wales between 2017 and 2018. Their characteristics are summarized in Table 2. The mean age was 62 years and 3189 (3%) had penetrating injuries. The median time from injury to ambulance arrival was 69 min, IQR (24–174). Mean ISS was 16 (± 9) and 46% of patients had an ISS ≥ 16. TXA was administered in 9915 (9%) patients. Of these 5185 (52%) received it prehospital. The median time from injury to treatment was 48 min, IQR (35–68) when TXA was given prehospital and 148 min, IQR (103–251) when it was given in hospital. 2760 (3%) of the trauma patients received TXA within 1 h and 5727 (6%) received TXA within 3 h of injury. The mean ISS of patients treated with TXA was 23 (±13) compared with 14 (±7) for patients who were not treated ($P < 0.001$). Most patients treated with TXA had a low or intermediate risk of death due to bleeding (Fig. 1). Most patients treated had a BATT score of 2. The proportion of patients who received prehospital TXA increased with the BATT score. There was no loss to follow-up at 30 days. A total of 2517 (2.4%) patients died within 24 h and 8874 (8.5%) died within 30 days. Early death with evidence of haemorrhage was reported for 1219 (1.2%) patients.

External validation

The Table 3 shows the performance of the BATT score. The scaled Brier score was 6%. The receiving operator curve, the sensitivity and specificity at different thresholds of the BATT score are shown in Supplementary files 4 and 5. A threshold of 2 or more had a sensitivity of 99% and a negative likelihood ratio of 0.03. The C-statistic was 0.90; 95% CI (0.89–0.91). The observed (1.16%) and predicted (1.15%) probabilities of death due to bleeding were similar ($p = 0.81$). The calibration curve

Table 2 Characteristics of the trauma patients used to validate the BATT score

	***N* = 104,862**	**Missing**
Mean age (SD)	62 (24)	0
< 18, N (%)	5616 (5)	–
18–44, N (%)	19,744 (19)	–
45–64, N (%)	26,354 (25)	–
65–74, N (%)	13,123 (13)	–
≥75, N (%)	40,025 (38)	–
Sex female, N (%)	47,346 (45)	0
Penetrating injury, N (%)	3189 (3)	0
Circumstances, N (%)		0
Motor vehicle crash	19,709 (19)	–
Fall less than 2 m	65,573 (62)	–
Fall more than 2 m	10,604 (10)	–
Blast – Blow – Crush	5266 (5)	–
Shooting	234 (0)	–
Stabbing	2538 (2)	–
Other	1938 (2)	–
First systolic blood pressure, mean (SD)	138 (28)	12,450 (12)
First systolic blood pressure < 90 mmHg, N (%)	3033 (3)	
First Glasgow coma scale, N (%)		12,695 (12)
14–15	90,579 (86)	–
9–13	8566 (8)	–
3–8	5717 (6)	–
First heart rate, mean (SD)	86 (20)	11,479 (11)
Heart rate > 120 bpm, N (%)	5475 (5)	
Time from injury to ambulance arrival < 3 h, N (%)	79,430 (76)	50,496 (48)
Time from injury to hospital admission < 3 h, N (%)	63,246 (60)	50,465 (48)
Injury Severity Score, mean (SD)	16 (9)	0
ISS 9–15, N (%)	58,695 (56)	–
ISS 16–24, N (%)	24,635 (23)	–
ISS 25–34, N (%)	17,682 (17)	–
ISS ≥ 35, N (%)	3850 (4)	–
Tranexamic acid treatment	9915 (9)	13,115 (13)
Prehospital	5185 (5)	–
Hospital	4576 (4)	–
Unknown	176 (0.1)	
Any blood product received	4922 (5)	0
Massive transfusion protocol activated	2487 (2)	–
Blood received within 6 h of injury	2277 (2)	–

showed slight over-prediction in low risk patients and under-prediction in intermediate and high-risk patients (Supplementary file 6). The calibration intercept was close to zero (0.00032) with a calibration slope of 1.09 (Table 3).

Clinical usefulness

Figure 2 is a decision curve analysis showing the number of deaths due to bleeding avoided by TXA treatment by BATT score threshold. Treating all trauma patients as soon as possible at scene or in the ambulance prevented

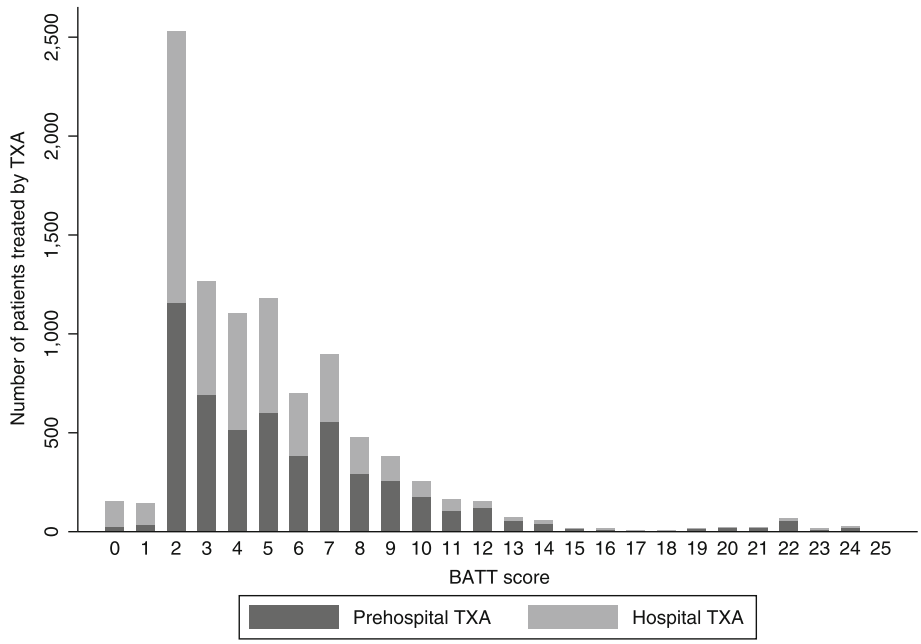


Fig. 1 Number of patients treated with tranexamic acid by BATT score in UK TARN data

more deaths than in hospital treatment. The cumulative number of deaths avoided decreased as the BATT score threshold increased. Table 4 shows the number of deaths avoided for the different scenarios and the sensitivity analysis based on observed early deaths in 2017 and 2018 in England and Wales. The sensitivity analysis confirms that prehospital treatment provides the maximum benefit with a lower number needed to treat than hospital treatment. Table 5 shows the number of deaths avoided and the number needed to treat for each BATT score threshold when patients are treated as soon as possible in the prehospital setting and within 3 h of injury. A BATT score treatment threshold of 2 corresponds to the treatment of 61,598 patients (59% of major trauma patients included in TARN registry with ISS ≥ 9) and results in 210 deaths avoided (Table 5). A BATT score treatment threshold below 2 resulted in 6 to 14 additional deaths avoided with an additional number needed to treat for one death avoided more than 1000 patients (Table 5, Fig. 3).

Table 3 Performance of the BATT score

	BATT score	95% CI
Overall performance		
Brier score	0.0107	
Scaled Brier score (%)	6	
Discrimination		
C-statistic	0.90	0.89–0.91
Mean predicted death due to bleeding (%)		
If patient died from bleeding	6.5	
If patient did not die from bleeding	1.1	1.1–1.1
Discrimination slope (%)	5.4	0.053–0.056
Calibration		
Observed deaths due to bleeding (%)	1.16	1.1–1.2
Predicted deaths due to bleeding (%)	1.15	1.1–1.2
Calibration-in-the-large (%)	0.01	0.00–0.01
Ratio Predicted/Observed	0.99	0.94–1.05
Calibration Intercept	0.00032	
Calibration slope	1.09	1.07–1.11

Discussion

Main findings

In 2017 and 2018, only 9% of trauma patients in England and Wales received TXA and only 3% received it within an hour of injury. Pre-hospital treatment of trauma patients with a BATT score of 2 or more would substantially increase the number of premature deaths that could be avoided with TXA.

Strengths and limitations

Our study has important strengths. Our prognostic score was derived using multivariable methods within a large international prospective cohort study with minimal missing data. We then validated the score in a second large cohort that was not used to derive the score [19]. We validated the BATT score in data from a large national trauma registry which includes trauma patients with a wide range of bleeding severity thus providing a heterogenous case-mix that allows accurate assessment

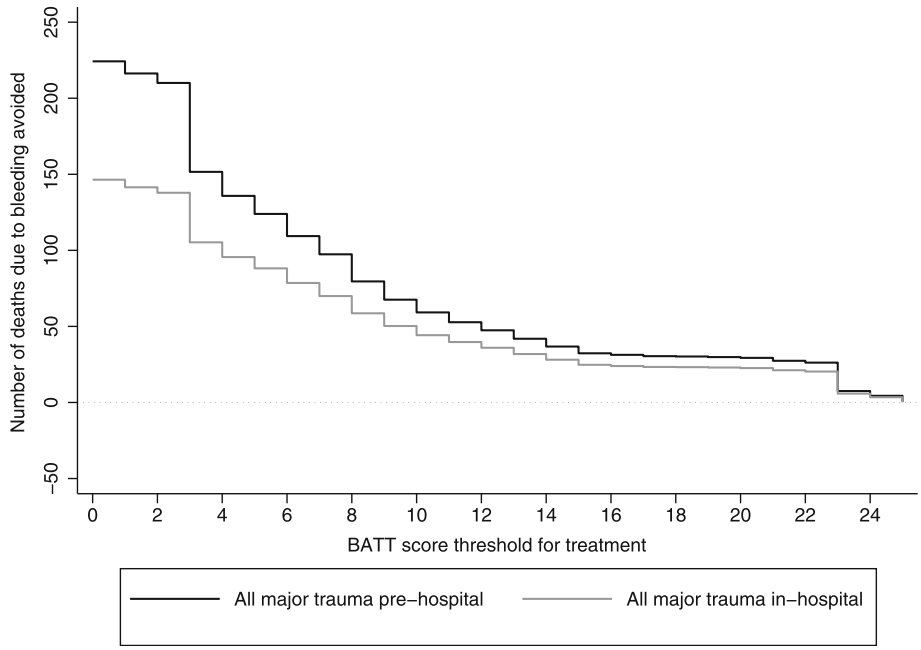


Fig. 2 Impact of tranexamic acid treatment by BATT score threshold

of discrimination [20]. The score is based on variables recorded by paramedics at the scene of the injury when the decision to treat with TXA must be made. The large number of patients in this study increases the precision of the results. There were few missing values for predictor variables and no missing outcome data. The outcome was well defined and recorded at fixed time point. These strengths help to ensure the validity of the results.

Our study also has limitations. Measurement error of predictor variables could affect discrimination and calibration. Random error could arise for all predictors (blood pressure, heart rate, Glasgow Coma scale, Respiratory rate) and lead to reduce discrimination and calibration. Systematic errors arising from the use of monitoring devices is more likely to affect calibration [21]. Because the outcome 'death due to bleeding' was not available in TARN database, we used early death as a proxy for death due to bleeding [22]. However, any outcome misclassification would be expected to decrease the C-statistic and reduce model performance [23] and

Table 4 Comparison of number of deaths due to bleeding avoided by tranexamic acid treatment

	Patients treated N (%) *N* = 104,862	Deaths avoided N (95% CI)	Deaths avoided per 10,000 patients N (95% CI)	Number needed to treat to avoid one death
Based on predicted probabilities				
Current strategy[a]	9915 (11)	55 (54–57)	5 (5–5)	180
All prehospital	79,430 (76)	224 (220–228)	21 (21–22)	355
All in hospital	63,246 (60)	146 (144–149)	14 (14–14)	430
Based on observed probabilities (sensitivity analysis)[b]				
Current strategy[a]	9915 (11)	168 (157–178)	16 (15–17)	59
All prehospital	79,430 (76)	323 (305–341)	31 (29–33)	244
All in hospital	63,246 (60)	240 (226–253)	22 (21–24)	273

NNT Number Needed to Treat
[a]Current strategy observed in the UK-TARN data based on clinical judgment and current guidelines in UK
[b]Sensitivity analysis based on observed deaths due to bleeding

Table 5 Number of deaths due to bleeding avoided and number needed to treat with pre-hospital treatment within 3 h of injury according to BATT score threshold as treatment criteria

BATT Score Threshold for TXA treatment	Total patients included in TARN N (%)	Number of patients considered for treatment[a] N (%)	Number of deaths avoided by BATT score threshold	Standardized number of deaths avoided per 10,000	Number needed to treat[b]	Additional NNT[c] for change of one point of BATT score
≥ 14	586 (< 1)	534 (< 1)	37	4.7	14	–
≥ 13	737 (< 1)	671 (< 1)	42	5.3	16	27
≥ 12	960 (1)	883 (1)	47	5.9	19	42
≥ 11	1266 (1)	1150 (1)	53	6.7	22	45
≥ 10	1727 (2)	1557 (2)	59	7.4	27	23
≥ 9	2533 (2)	2272 (2)	68	8.6	34	79
≥ 8	3859 (4)	3420 (3)	80	10.1	43	128
≥ 7	6879 (7)	5898 (6)	97	12.2	61	146
≥ 6	10,071 (10)	8584 (8)	109	13.7	78	224
≥ 5	16,032 (15)	13,335 (13)	124	15.6	108	317
≥ 4	22,946 (22)	18,769 (18)	136	17.1	138	452
≥ 3	33,483 (32)	27,062 (26)	152	19.1	179	518
≥ 2	80,071 (76)	61,598 (59)	210	26.4	293	595
≥ 1	89,948 (86)	68,452 (65)	216	27.2	316	1142
≥ 0	104,862 (100)	79,430 (76)	224	28.2	354	1372

TXA Tranexamic acid, *NNT* Number needed to treat

[a]Number of trauma patients within 3 h of injury and the arrival of the first ambulance. Proportions are based on all patients included in the TARN registry with ISS ≥ 9

[b]Standardized number of deaths avoided per 10,000 trauma patients within 3 h included in the TARN registry with an ISS ≥9

[c]Additional trauma patients needed to treat for each death avoided compared to the BATT score threshold above

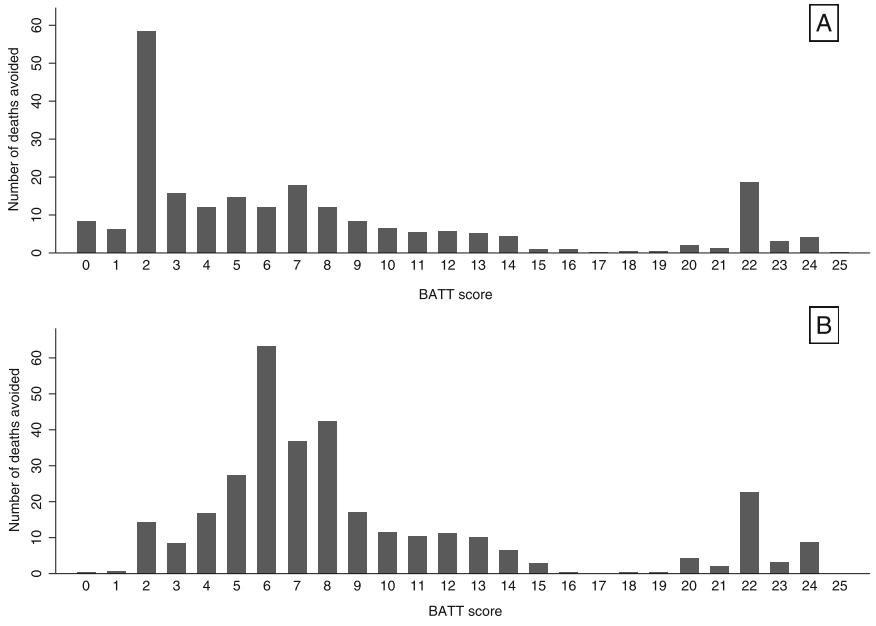


Fig. 3 Number of deaths avoided due to prehospital tranexamic acid by BATT score. **a**: Estimated number of deaths avoided based on predicted baseline risk. **b**: Estimated number of deaths avoided based on observed probabilities of death (Sensitivity analysis)

since the C-statistic was high and model performance was excellent, misclassification is unlikely to be an important weakness. Because time from injury to ambulance arrival and hospital admission was missing for nearly half of the patients, we imputed these data. Misclassification of time to treatment could affect our estimate of the net benefit [24]. The estimates of deaths avoided are unlikely to be generalizable since they depend on the risk of death, which may vary in different settings. To model the number of deaths avoided, we used treatment effect estimates from randomised trials and so the estimates should be unconfounded. However, confounders in this observational study might affect our estimates of the absolute number of deaths avoided and so this must be considered with caution. Because we used the same method to estimate the impact of each strategy, it is unlikely that the comparison between different strategies was adversely affected by potential confounders. Furthermore, we are reassured by the result of the STAAMP trial assessing TXA in trauma patient in the prehospital setting [25]. The magnitude of the treatment effect observed in this trial is similar to that observed in the CRASH-2 trial although the estimate was more imprecise.

Relation to other studies

To the best of our knowledge, ours is the only score that predicts traumatic death due to bleeding. Existing haemorrhage scores predict massive transfusion which is an imperfect surrogate of death due to bleeding and vulnerable to survival bias (i.e. TASH score, ABC score) [26, 27].

Clinical implications

Clinical guidelines recommend TXA treatment for patients with or at risk of significant bleeding and that treatment is given as soon as possible [3]. Due to the lack of clear treatment criteria, many trauma patients are not receiving TXA or else receive it too late. A study on paramedic perceptions concerning tranexamic acid use in bleeding in trauma patients showed that lack of self-confidence, uncertainty about haemorrhage risk and the need to give TXA by slow intravenous injection (over 10 min) were the main barriers to TXA administration [28]. Our data suggest that using a BATT score threshold of 2 or more would improve outcomes with a fourfold increase in bleeding deaths prevented by TXA. This clear criterion could improve prehospital administration of TXA by paramedics. Although the use of this threshold would increase the number of patients treated, TXA is safe and inexpensive and is likely to be highly cost-effective [29, 30]. Randomised trials of TXA in trauma and surgery have included over 50,000 patients and no increase in vascular occlusive events has been found [4, 17, 31–33]. Recent trials in prehospital trauma did not find any increase in vascular occlusive events associated with TXA and provide evidence for applicability of TXA treatment in the prehospital setting [25, 34].

Recent research has found that TXA is well tolerated and rapidly absorbed after intramuscular injection reaching therapeutic concentrations within 15 min in bleeding trauma patients [35]. Further research is needed to assess the cost-effectiveness of different treatment thresholds and whether use of the BATT score and intramuscular TXA administration by paramedics increases the pre-hospital administration of TXA to patients at risk of bleeding from trauma. Prospective validation of the BATT score would certainly increase its value for clinical use.

Conclusion

The BATT score is a validated tool, easy to perform at the scene of injury to identify trauma patients at risk of death from bleeding. A score of 2 or more would be an appropriate threshold for pre-hospital tranexamic acid treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13049-020-00827-5.

Additional file 1: Supplementary file 1. Abbreviated Injury Scale diagnosis associated with haemorrhage. **Supplementary file 2.** Formula for the Brier Score and Scaled Brier Score. **Supplementary file 3.** Methods to model tranexamic acid treatment effect and death due to bleeding avoided. **Supplementary file 4.** Receiving Operator Curve for external validation of the BATT score. **Supplementary Figure 5.** Sensitivity and specificity according to BATT score for death due to bleeding. **Supplementary file 6.** Calibration curve for external validation of the BATT score.

Acknowledgements

We thank TARN and all hospitals participating to the network; Professor Jonathan Benger for his support to develop the BATT score.

Authors' contributions

FXA, IR designed the study. TC designed and monitored the data collection from which this paper was developed. FXA analysed the data. VD, TC gave feedback about the clinical use. FXA, IR wrote the first draft. FXA, TC, VD, IR contributed to write and revised the paper. The author(s) read and approved the final manuscript.

Funding

This study did not receive any fund.

Availability of data and materials

Data are available on reasonable request and with agreement from TARN.

Ethics approval and consent to participate

The TARN Registry has ethical approval TARN from the UK Health Research Authority (section 251 PIAG) for analysis of the anonymized data.

Consent for publication

Not applicable.

Competing interests
All authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Author details
[1]Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK. [2]Department of Emergency Medicine, Lausanne University Hospital, University of Lausanne, 1011 Lausanne, Switzerland. [3]Emergency Medicine, University of Leicester, Leicester, UK.

Received: 24 August 2020 Accepted: 15 December 2020
Published online: 06 January 2021

References

1. CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376:23–32.
2. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ. 2012;344:e3054.
3. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care. 2019;23:98.
4. Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron F-X, Roberts I, et al. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. Lancet. 2018;391:125–32.
5. Ageron F-X, Gayet-Ageron A, Steyerberg E, Bouzat P, Roberts I. Prognostic model for traumatic death due to bleeding: cross-sectional international study. BMJ Open. 2019;9:e026823.
6. Ageron F-X, Gayet-Ageron A, Ker K, Coats TJ, Shakur-Still H, Roberts I, et al. Effect of tranexamic acid by baseline risk of death in acute bleeding patients: a meta-analysis of individual patient-level data from 28 333 patients. Br J Anaesth. 2020;124:676–83.
7. van Laarhoven JJEM, Lansink KWW, van Heijl M, Lichtveld RA, Leenen LPH. Accuracy of the field triage protocol in selecting severely injured patients after high energy trauma. Injury. 2014;45:869–73.
8. Lecky F, Woodford M, Yates D. Trends in trauma care in England and Wales 1989–97. Lancet. 2000;355:1771–5.
9. Demetriades D, Murray J, Charalambides K, Alo K, Velmahos G, Rhee P, et al. Trauma fatalities: time and location of hospital deaths. J Am Coll Surg. 2004;198:20–6.
10. Søreide K, Krüger AJ, Vårdal AL, Ellingsen CL, Søreide E, Lossius HM. Epidemiology and contemporary patterns of trauma deaths: changing place, similar pace, older face. World J Surg. 2007;31:2092–103.
11. Pfeifer R, Teuben M, Andruszkow H, Barkatali BM, Pape H-C. Mortality Patterns in Patients with Multiple Trauma: A Systematic Review of Autopsy Studies. PLoS One. 2016;11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4752312/ [cited 2020 Nov 27].
12. Lefering R, Paffrath T, Bouamra O, Coats TJ, Woodford M, Jenks T, et al. Epidemiology of in-hospital trauma deaths. Eur J Trauma Emerg Surg. 2012;38:3–9.
13. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. Epidemiology. 2010;21:128–38.
14. Peng P, Coyle A. Likelihood ratios for the emergency physician. Acad Emerg Med. 2018;25:958–65.
15. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982;143:29–36.
16. Stevens RJ, Poppe KK. Validation of clinical prediction models: what does the "calibration slope" really measure? J Clin Epidemiol. 2020;118:93–9.
17. Franchini M, Mengoli C, Marietta M, Marano G, Vaglio S, Pupella S, et al. Safety of intravenous tranexamic acid in patients undergoing majororthopaedic surgery: a meta-analysis of randomised controlled trials. Blood Transfus. 2018;16:36–43.
18. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. BMJ. 2016;352 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4724785/ [cited 2019 Apr 2].
19. Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal-external, and external validation. J Clin Epidemiol. 2016;69:245–7.
20. Damen JAAG, Debray TPA, Pajouheshnia R, Reitsma JB, Scholten RJPM, Moons KGM, et al. Empirical evidence of the impact of study characteristics on the performance of prediction models: a meta-epidemiological study. BMJ Open. 2019;9:e026160.
21. Rosella LC, Corey P, Stukel TA, Mustard C, Hux J, Manuel DG. The influence of measurement error on calibration, discrimination, and overall estimation of a risk prediction model. Popul Health Metrics. 2012;10:20.
22. Brenner A, Arribas M, Cuzick J, Jairath V, Stanworth S, Ker K, et al. Outcome measures in clinical trials of treatments for acute severe haemorrhage. Trials. 2018;19 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6167881/ [cited 2019 Apr 2].
23. Jurek AM, Greenland S, Maldonado G, Church TR. Proper interpretation of non-differential misclassification effects: expectations vs observations. Int J Epidemiol. 2005;34:680–7.
24. van Doorn S, Brakenhoff TB, Moons KGM, Rutten FH, Hoes AW, Groenwold RHH, et al. The effects of misclassification in routine healthcare databases on the accuracy of prognostic prediction models: a case study of the CHA2DS2-VASc score in atrial fibrillation. Diagn Progn Res. 2017;1 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6460749/ [cited 2020 Apr 17].
25. Guyette FX, Brown JB, Zenati MS, Early-Young BJ, Adams PW, Eastridge BJ, et al. Tranexamic Acid During Prehospital Transport in Patients at Risk for Hemorrhage After Injury: A Double-blind, Placebo-Controlled, Randomized Clinical Trial. JAMA Surg. 2020; Available from: https://jamanetwork.com/journals/jamasurgery/fullarticle/2771225 [cited 2020 Oct 22].
26. Nunez TC, Voskresensky IV, Dossett LA, Shinall R, Dutton WD, Cotton BA. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? J Trauma. 2009;66:346–52.
27. Yücel N, Lefering R, Maegele M, Vorweg M, Tjardes T, Ruchholtz S, et al. Trauma associated severe hemorrhage (TASH)-score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. J Trauma. 2006;60:1228–36 discussion 1236-1237.
28. Nicholson H. Paramedic perceptions of bleeding in trauma and the use of tranexamic acid. 2020. Available from: https://uwe.cloud.panopto.eu/Panopto/Pages/Viewer.aspx?id=c673a0d2-e8e3-4cbf-8634-abf800b35828 [cited 2020 Aug 19].
29. Meybohm P, Straub N, Füllenbach C, Judd L, Kleinerüschkamp A, Taeuber I, et al. Health economics of patient blood management: a cost-benefit analysis based on a meta-analysis. Vox Sang. 2020;115:182–8.
30. Guerriero C, Cairns J, Perel P, Shakur H, Roberts I. CRASH 2 trial collaborators. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. PLoS One. 2011;6:e18987.
31. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T, et al. Tranexamic acid in patients undergoing coronary-artery surgery. N Engl J Med. 2017;376:136–48.
32. Sentilhes L, Winer N, Azria E, Sénat M-V, Le Ray C, Vardon D, et al. Tranexamic acid for the prevention of blood loss after vaginal delivery. N Engl J Med. 2018;379:731–42.
33. Sprigg N, Flaherty K, Appleton JP, Salman RA-S, Bereczki D, Beridze M, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. Lancet. 2018;391:2107–15.
34. Rowell SE, Meier EN, McKnight B, Kannas D, May S, Sheehan K, et al. Effect of out-of-hospital Tranexamic acid vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe traumatic brain injury. JAMA. 2020;324:961–74.
35. Grassin-Delyle S, Shakur-Still H, Picetti R, Frimley L, Jarman H, Davenport R, et al. Pharmacokinetics of intramuscular tranexamic acid in bleeding trauma patients: a clinical trial. Br J Anaesth. 2020; Accepted for publication.

Publisher's Note

Web Appendix

Supplementary file 1. Abbreviated Injury Scale diagnosis associated with haemorrhage

- Blood loss > 20%.

- Aorta [OR] Vena Cava [OR]carotid [OR]femoral [OR]Major arteries [OR]veins AND laceration.

- Spleen [OR]liver [OR] Kidney [OR] Myocardium [AND] major laceration.

- Major haemothorax.

- Retroperitoneum haemorrhage.

Supplementary file 2. Formula for the Brier Score and Scaled Brier Score

Brier Score$= \frac{1}{N}\sum_{i=1}^{n}(Y-p)^2$

Which Y is the observed outcome and p the prediction of the model.

Brier Score$_{max}= P \times (1-P)^2 + (1-P) \times P^2$

Which P is the mean of the prediction p.

Scaled Brier score$= \frac{1-Brier}{Brier\ max}$

Scaled Brier score ranges from 0% to 100%

Supplementary file 3. Methods to model tranexamic acid treatment effect and death due to bleeding avoided.

First method

a) We estimated the baseline probabilities of death due to bleeding in the TARN population (P1).

P1= [0.5344157 - 0.5726779 + (0.0604783 * age) - (0.0013908 * age2) + (0.000012 * age3) + (0.0234826 * isbp) - (0.0005366 * isbp2) + (0.00000158 * isbp3) - (0.6336347 * igcs) + (0.0738416 * igcs2) - (0.0029216 * igcs3) - (0.0085677 * ihr) + (0.0001027 * ihr2) - (0.1709854 * irr) + (0.0059866 * irr2) - (0.000054 * irr3) + (0.3056116 * penetrating)] * 0.82

P1 (Baseline probabilities of death due to bleeding); ISBP (initial systolic blood pressure); IGCS (initial Glasgow coma scale); IHR (initial heart rate); IRR (initial respiratory rate); Penetrating injury.

b) We used previous studies exploring treatment effect by time and baseline risk (TE).

TE= OR txa/time * OR txa/baseline risk

TE (treatment effect); OR (Odds ratio)

OR txa/time is function of delay from Accident to Ambulance Arrival (Prehospital treatment) or Delay from Accident to Hospital Arrival (In-hospital treatment). (REF Lancet Gayet)

0.70235307 if delay=0 min	0.76495222 if delay ==65 min	0.83300851 if delay ==130 min
0.70698462 if delay=5 min	0.76998788 if delay ==70 min	0.83848272 if delay ==135 min
0.71164609 if delay ==10 min	0.77505601 if delay ==75 min	0.84399218 if delay ==140 min
0.71633767 if delay ==15 min	0.78015683 if delay ==80 min	0.84953709 if delay ==145 min
0.72105956 if delay ==20 min	0.78529054 if delay ==85 min	0.8551177 if delay ==150 min
0.72581194 if delay ==25 min	0.79045734 if delay ==90 min	0.86073421 if delay ==155 min
0.73059501 if delay ==30 min	0.79565744 if delay ==95 min	0.86638687 if delay ==160 min
0.73540897 if delay ==35 min	0.80089106 if delay ==100 min	0.87207589 if delay ==165 min
0.740254 if delay ==40 min	0.80615841 if delay ==105 min	0.87780151 if delay ==170 min
0.7451303 if delay ==45 min	0.81145969 if delay ==110 min	0.88356395 if delay ==175 min
0.75003808 if delay ==50 min	0.81679513 if delay ==115 min	0.88936344 if delay ==180 min
0.75497752 if delay ==55 min	0.82216493 if delay ==120 min	
0.75994883 if delay ==60 min	0.82756932 if delay ==125 min	

OR txa/baseline risk is constant=1 (Ref BJA)

c) We estimated Post-Treatment probabilities of death due to bleeding (P2)

P2=P1 * TE

d) We estimated the number of death due to bleeding avoided by tranexamic acid.

Number of death avoided= $\sum P1 \; - \sum P2$

e) Net benefit

Net benefit= Number of death avoided – Number of death due to side effect

We considered tranexamic acid treatment within 3 hours from injury. In this time interval, we did not find any randomized control trial reporting death due to side effect or any increase of non-fatal vascular occlusive event.

Net Benefit = Number of death avoided

Sensitivity analysis (Second method)

a) We estimated the baseline probabilities of death due to bleeding in the TARN population ($P1_{obs}$).

We divided death due to bleeding by treatment effect for patient treated by tranexamic acid to estimate baseline probabilities.

$$P1_{obs} = (Death_{obs})_{if\ TXA=0} + \left(\frac{Death_{obs}}{TE}\right)_{if\ TXA==1}$$

$Death_{obs}$=Early death with evidence of haemorrhage

b) We estimated Post-Treatment probabilities of death due to bleeding (P2)

$$P2 = P1_{obs} * TE$$

c) We estimated the number of death due to bleeding avoided by tranexamic acid.

$$\text{Number of death avoided} = \sum P1 - \sum P2$$

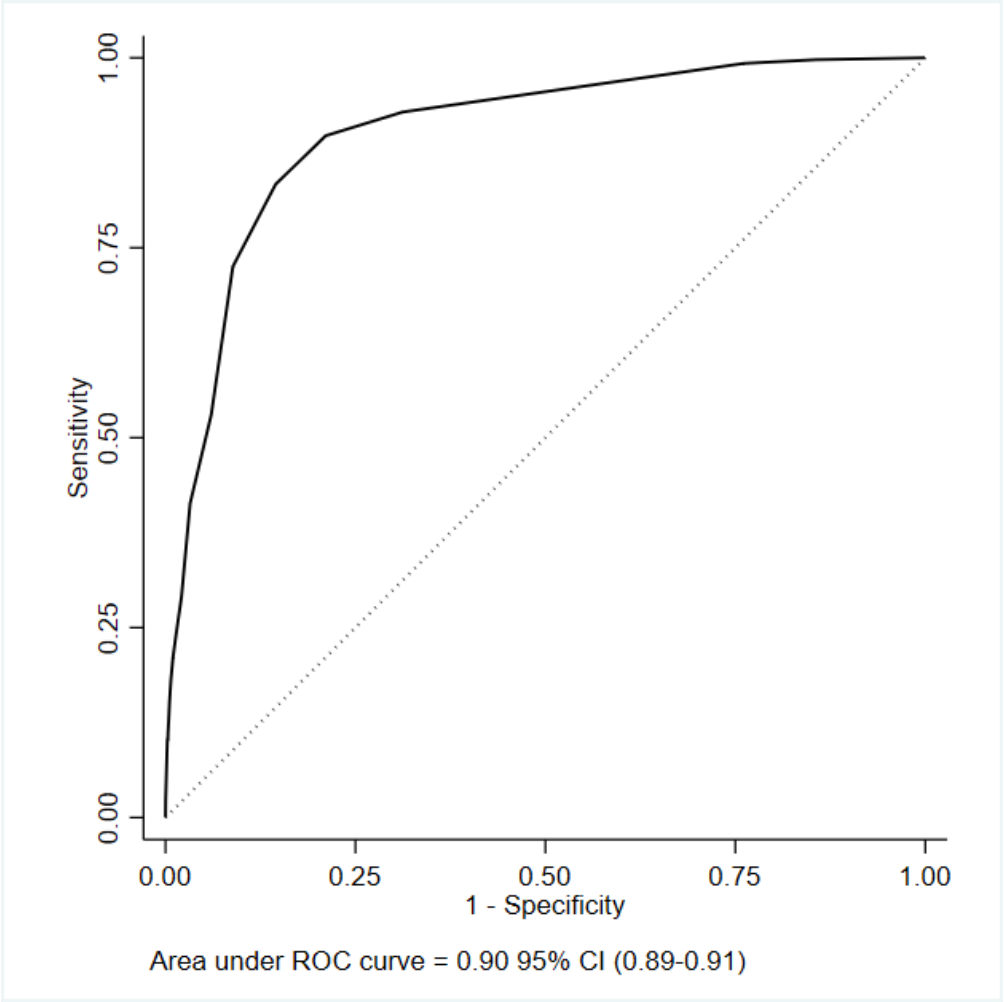
d) Net benefit

Net benefit= Number of death avoided – Number of death due to side effect

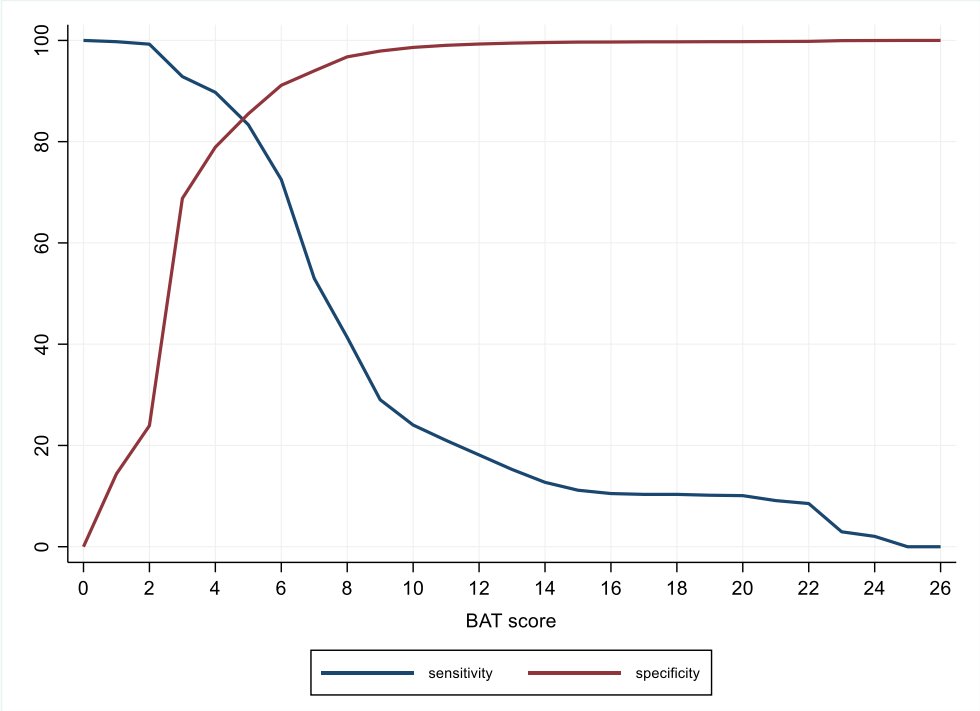
We considered tranexamic acid treatment within 3 hours from injury. In this time interval, we did not find any randomized control trial reporting death due to side effect or any increase of non-fatal vascular occlusive event.

Net Benefit = Number of deaths avoided

Supplementary file 4. Receiving Operator Curve for external validation of the BATT score.

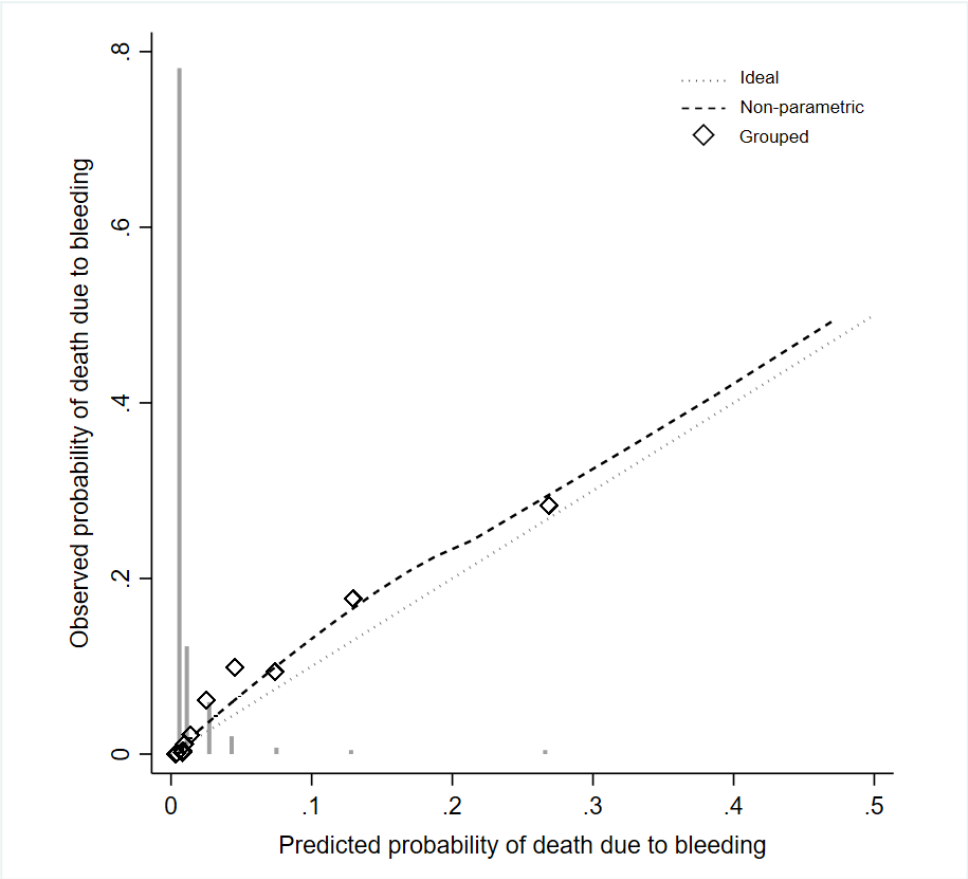


Supplementary figure 5. Sensitivity and specificity according to BATT score for death due to bleeding.

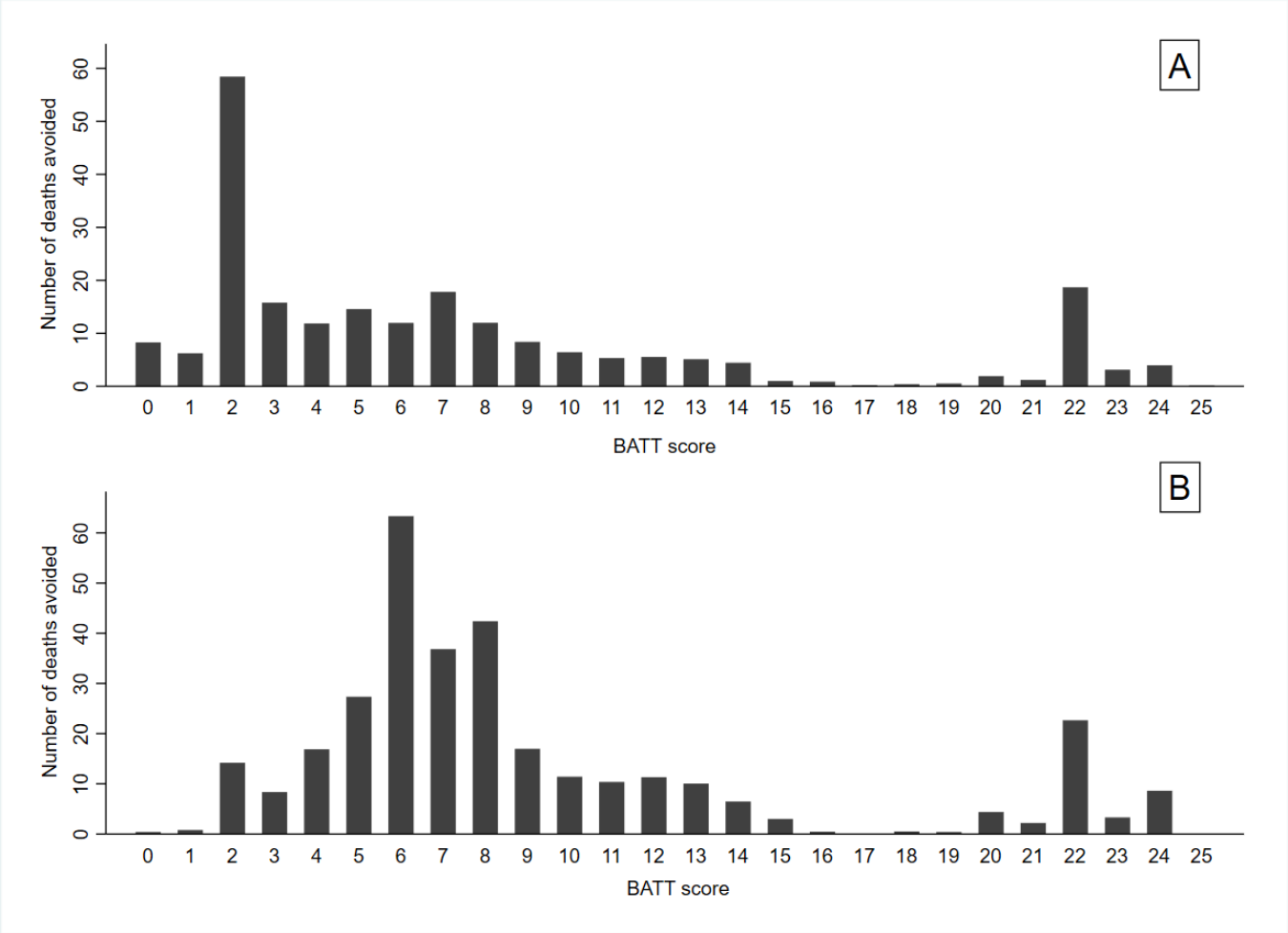


Threshold	Sensitivity (%)	Specificity (%)	Likelihood ratio +	Likelihood ratio -
0	100	0	1	-
≥ 1	100	14	1.17	0.017
≥ 2	99	24	1.31	0.031
≥ 3	93	69	2.98	0.104
≥ 4	90	79	4.26	0.130
≥ 6	73	91	8.18	0.302
≥ 8	41	97	12.77	0.606
≥ 10	24	99	17.37	0.770
≥ 12	18	99	25.42	0.825

Supplementary file 6. Calibration curve for external validation of the BATT score.



Supplementary file 7. Number of deaths avoided due to prehospital tranexamic acid by BATT score



A: Estimated number of deaths avoided based on predicted baseline risk.

B: Estimated number of deaths avoided based on observed probabilities of death (Sensitivity analysis).