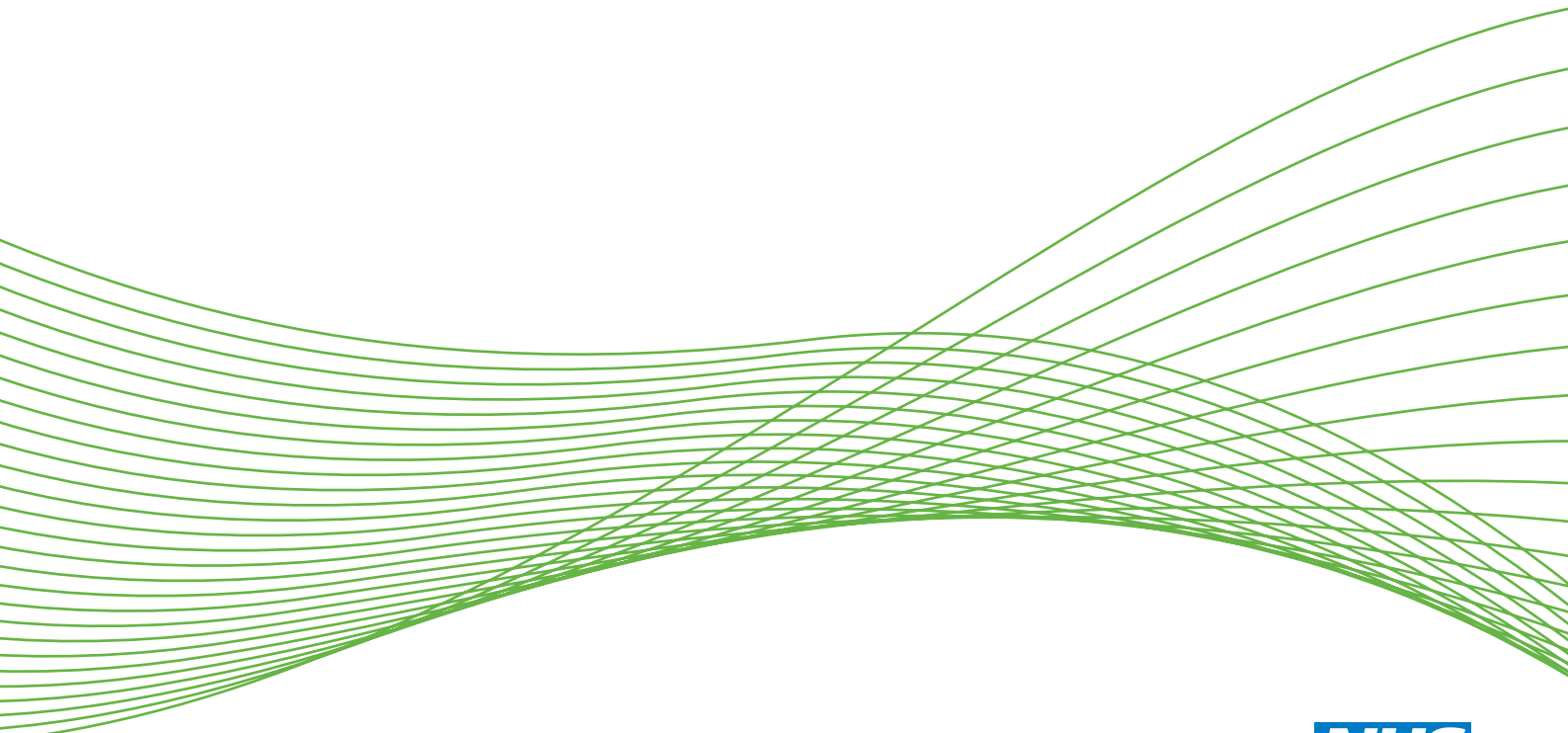Development and validation of a prognostic model to predict death in patients with traumatic bleeding, and evaluation of the effect of tranexamic acid on mortality according to baseline risk: a secondary analysis of a randomised controlled trial

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This report

Abstract

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

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Background: Severe bleeding accounts for about one-third of in-hospital trauma deaths. Patients with a high baseline risk of death have the most to gain from the use of life-saving treatments. An accurate and user-friendly prognostic model to predict mortality in bleeding trauma patients could assist doctors and paramedics in pre-hospital triage and could shorten the time to diagnostic and life-saving procedures such as surgery and tranexamic acid (TXA).

Objectives: The aim of the study was to develop and validate a prognostic model for early mortality in patients with traumatic bleeding and to examine whether or not the effect of TXA on the risk of death and thrombotic events in bleeding adult trauma patients varies according to baseline risk.

Design: Multivariable logistic regression and risk-stratified analysis of a large international cohort of trauma patients.

Setting: Two hundred and seventy-four hospitals in 40 high-, medium- and low-income countries.

Participants: We derived prognostic models in a large placebo-controlled trial of the effects of early administration of a short course of TXA [Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial]. The trial included 20,127 trauma patients with, or at risk of, significant bleeding, within 8 hours of injury. We externally validated the model on 14,220 selected trauma patients from the Trauma Audit and Research Network (TARN), which included mainly patients from the UK. We examined the effect of TXA on all-cause mortality, death due to bleeding and thrombotic events (fatal and non-fatal myocardial infarction, stroke, deep-vein thrombosis and pulmonary embolism) within risk strata in the CRASH-2 trial data set and we estimated the proportion of premature deaths averted by applying the odds ratio (OR) from the CRASH-2 trial to each of the risk strata in TARN.

Interventions: For the stratified analysis according baseline risk we considered the intervention TXA (1 g over 10 minutes followed by 1 g over 8 hours) or matching placebo.

Main outcome measures: For the prognostic models we included predictors for death in hospital within 4 weeks of injury. For the stratified analysis we reported ORs for all causes of death, death due to bleeding, and fatal and non-fatal thrombotic events associated with the use of TXA according to baseline risk.

Results: A total of 3076 (15%) patients died in the CRASH-2 trial and 1705 (12%) in the TARN data set. Glasgow Coma Scale score, age and systolic blood pressure were the strongest predictors of mortality. Discrimination and calibration were satisfactory, with C-statistics > 0.80 in both CRASH-2 trial and TARN data sets. A simple chart was constructed to readily provide the probability of death at the point of care, while a web-based calculator is available for a more detailed risk assessment. TXA reduced all-cause mortality and death due to bleeding in each stratum of baseline risk. There was no evidence of heterogeneity in the effect of TXA on all-cause mortality (p-value for interaction $= 0.96$) or death due to bleeding ($p = 0.98$). There was a significant reduction in the odds of fatal and non-fatal thrombotic events with TXA (OR $= 0.69$, 95% confidence interval 0.53 to 0.89; $p = 0.005$). There was no evidence of heterogeneity in the effect of TXA on the risk of thrombotic events ($p = 0.74$).

Conclusions: This prognostic model can be used to obtain valid predictions of mortality in patients with traumatic bleeding. TXA can be administered safely to a wide spectrum of bleeding trauma patients and should not be restricted to the most severely injured. Future research should evaluate whether or not the use of this prognostic model in clinical practice has an impact on the management and outcomes of trauma patients.

Contents

List of abbreviations

A&E	accident and emergency	IQR	interquartile range
AUC	area under curve	LIC	low-income country
CI	confidence interval	MIC	middle-income country
CRASH-2	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage trial	OR	odds ratio
		RR	respiratory rate
GCS	Glasgow Coma Scale	SBP	systolic blood pressure
HIC	high-income country	TARN	Trauma Audit and Research Network
HR	heart rate	TNF-α	tumour necrosis factor alpha
HSI	hours since injury	TXA	tranexamic acid
IL	interleukin		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Each year, around 4 million people die worldwide from unintentional injury and violence, with tens of millions more left permanently disabled. Although many of these deaths occur at the scene of the injury, it is estimated that 44% of deaths occur after hospital admission.

Severe bleeding accounts for about one-third of in-hospital trauma deaths and is an important contributory factor in other causes of death, in particular head injury and multiorgan failure. Failure to initiate appropriate early management in bleeding trauma patients is a leading cause of preventable trauma death. Recent evidence that the early administration of tranexamic acid (TXA) substantially reduces mortality in bleeding trauma patients further emphasises the clinical importance of the timely identification of life-threatening bleeding. The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial showed that a short course of TXA given to bleeding trauma patients within 3 hours of injury significantly reduces all-cause mortality with no apparent increase in the risk of thrombotic adverse events. As a result, TXA is being incorporated into trauma protocols around the world. These protocols generally focus on the care of the most severely injured. Patients with a high baseline risk of death have the most to gain from the use of life-saving treatments because the absolute benefits of an effective treatment tend to increase as the baseline risk increases, whereas adverse effects can be independent of baseline risk. On the other hand, there are more low-risk trauma patients than high-risk patients and it is possible that a large number of patients at low risk might contribute more deaths than a smaller number of patients at high risk.

An accurate and user-friendly prognostic model to predict mortality in bleeding trauma patients could assist doctors and paramedics in pre-hospital triage whether in civilian or battlefield settings; its use could shorten the time to diagnostic and life-saving procedures such as surgery and TXA.

Objectives

We aimed to develop a simple prognostic model that could be used at the point of care to estimate risk of death in patients with traumatic bleeding and to examine how TXA treatment effects vary according to the baseline risk of death in bleeding trauma patients.

Methods

We derived prognostic models in a large placebo-controlled trial of the effects of early administration of a short course of TXA (CRASH-2 trial). Analyses included predictors for death in hospital within 4 weeks of injury. We externally validated the model on the Trauma Audit and Research Network (TARN) data set. The derivation sample included 20,127 CRASH-2 trial trauma patients with, or at risk of, significant bleeding, within 8 hours of injury, and was undertaken in 274 hospitals in 40 high-, medium- and low-income countries. For the external validation we used 14,220 TARN adult patients presenting between the years 2000 and 2008, with an estimated blood loss of at least 20%.

We then used the prognostic model to stratify the patients in the CRASH-2 trial who were treated within 3 hours of injury into four mortality risk strata (<6%, 6–20%, 21–50% and >50%) and examined the effect of TXA on all-cause mortality, death due to bleeding and thrombotic events (fatal and non-fatal myocardial infarction, stroke, deep-vein thrombosis and pulmonary embolism) within these strata.

Results

A total of 3076 (15%) patients died in the CRASH-2 trial and 1705 (12%) in the TARN data set. Glasgow Coma Scale score, age and systolic blood pressure were the strongest predictors of mortality. Other predictors included in the final model were geographical region (low-, middle- or high-income countries), heart rate, time since injury and type of injury. Discrimination and calibration were satisfactory, with *C*-statistics > 0.80 in both CRASH-2 and the TARN data set. A simple chart was constructed to readily provide the probability of death at the point of care, while a web-based calculator is available for a more detailed risk assessment (www.crash2.lshtm.ac.uk).

We found that TXA reduced all-cause mortality and death due to bleeding in each stratum of baseline risk. There was no evidence of heterogeneity in the effect of TXA on all-cause mortality (*p*-value for interaction = 0.96) or death due to bleeding (*p* = 0.98). There was a significant reduction in the odds of fatal and non-fatal thrombotic events with TXA [odds ratio (OR) = 0.69; 95% confidence interval (CI) 0.53 to 0.89; *p* = 0.005]. There was a statistically significant reduction in arterial thrombotic events (OR = 0.58; 95% CI 0.40 to 0.83; *p* = 0.003) and a reduction in venous thrombotic events that was not statistically significant (OR = 0.83; 95% CI 0.59 to 1.17; *p* = 0.295). There was no evidence of heterogeneity in the effect of TXA on the risk of thrombotic events (*p* = 0.74).

Conclusions

This prognostic model can be used to obtain valid predictions of mortality in patients with traumatic bleeding, assisting in triage and potentially shortening the time to diagnostic and life-saving procedures. Age is an important prognostic factor, and this is of particular relevance in high-income countries with ageing trauma populations. TXA can be administered safely to a wide spectrum of bleeding trauma patients and should not be restricted to the most severely injured. The observed reduction in the risk of arterial events with TXA suggests that the absolute benefits from TXA administration are likely to be greatest in older trauma patients, who at any given level of injury severity have a higher baseline risk of haemorrhage death and thrombotic events.

Recommendations for research

The relationship between age and mortality needs further exploration; a better understanding of the mechanism underlying the association between age and increasing mortality could lead to effective interventions to improve the outcome in this vulnerable population.

As we were able to validate the model only in patients from high-income regions, future studies should also explore its performance in low- and middle-income country settings. Finally, future research should evaluate whether or not the use of this prognostic model in clinical practice has an impact on the management and outcomes of trauma patients.

Funding

Chapter 1 Introduction

Each year, around 4 million people die worldwide from unintentional injury and violence, with tens of millions more left permanently disabled. Most of the victims are from low-income countries (LICs) and middle-income countries (MICs).[1] Although many of these deaths occur at the scene of the injury, it is estimated that 44% of deaths occur after hospital admission.[2]

Severe bleeding accounts for about one-third of in-hospital trauma deaths and is an important contributory factor in other causes of death, in particular head injury and multiorgan failure.[3] Failure to initiate appropriate early management in bleeding trauma patients is a leading cause of preventable trauma death.[4] Triage criteria that allow the rapid identification of high-risk patients have the potential to reduce trauma mortality, and recent evidence that the early administration of tranexamic acid (TXA) substantially reduces mortality in bleeding trauma patients further emphasises the clinical importance of the timely identification of life-threatening bleeding.[5] However, any such early prediction would have to be based on variables that can be readily measured soon after injury.

Several clinical variables related to the physiological response to reduced intravascular volume predict the risk of death in bleeding trauma patients. These include blood pressure, capillary refill time, level of consciousness [Glasgow Coma Scale (GCS) score], heart rate (HR) and respiratory rate (RR).[6] Because all of these variables are of limited predictive value when considered in isolation, prognostic models that combine variables are required for better predictive accuracy.[7–9] An accurate and user-friendly prognostic model to predict mortality in bleeding trauma patients could assist doctors and paramedics in pre-hospital triage whether in civilian or battlefield settings; its use could shorten the time to diagnostic and life-saving procedures such as surgery and TXA. The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial showed that a short course of TXA given to bleeding trauma patients within 3 hours of injury significantly reduces all-cause mortality with no apparent increase in the risk of thrombotic adverse events. As a result, TXA is being incorporated into trauma protocols around the world. These protocols generally focus on the care of the most severely injured. Patients with a high baseline risk of death have the most to gain from the use of life-saving treatments because the absolute benefits of an effective treatment tend to increase as the baseline risk increases, whereas adverse effects can be independent of baseline risk. On the other hand, there are more low-risk trauma patients than high-risk patients and it is possible that a large number of patients at low risk might contribute more deaths than a smaller number of patients at high risk.

We have previously published a prognostic model for traumatic brain injury patients which is accurate, user-friendly and clinically useful for supporting physicians' decision-making.[10,11]

Existing prognostic models for bleeding trauma patients are limited.[12] Most were developed using data collected many decades ago and have methodological limitations. There is a need for models based on contemporary data because treatment practices have changed and the age of trauma patients has increased in high-income countries (HICs). Furthermore, although most trauma deaths occur in LICs and MICs, most prognostic models are based on data from HICs.[12]

We aimed to develop a simple prognostic model which could be used at the point of care to estimate risk of death in patients with traumatic bleeding. In addition, we report further analysis of the CRASH-2 trial data to examine how TXA treatment effects vary according to the baseline risk of death in bleeding trauma patients. We then use data from a large hospital-based trauma audit to assess the extent to which current trauma protocols maximise the patient benefits of TXA treatment.

Chapter 2 Methods

Model development

For the development of the prognostic model, we involved potential users from three settings: pre-hospital, battlefield and emergency departments. We held separate meetings with paramedics, military doctors and emergency medicine consultants to identify variables and interactions that they considered important and convenient for their settings and to obtain information on how to present the prognostic model in a user-friendly format. In each of these meetings we conducted a semistructured interview following a prespecified questionnaire (see *Appendix 1*).

Sample
We included patients from the CRASH-2 trial.[13] The trial included 20,127 trauma patients with, or at risk of, significant bleeding, within 8 hours of injury, and was undertaken in 274 hospitals in 40 countries.

Outcome
The primary outcome was all-cause mortality. Patient outcomes were recorded as discharge, death in hospital or death 28 days after injury, whichever occurred first.

Predictors
Variables analysed as potential predictors were taken from the patient entry form completed prior to randomisation. Variables included in the CRASH-2 trial entry form can be divided into:

1. Patient demographic characteristics: age and sex.
2. Injury characteristics: type of injury and time from injury to randomisation.
3. Physiological variables: GCS score, systolic blood pressure (SBP), HR, RR and central capillary refill time.

Variable definitions
Age was recorded as a continuous variable measured in years. Type of injury had three categories: (1) penetrating, (2) blunt or (3) blunt and penetrating. However, it was analysed as penetrating, and blunt and penetrating. Time from injury was recorded as a continuous variable measured in hours. The five physiological variables were recorded according to usual clinical practice. For each of these variables, the value given on the entry form was the first measurement taken at hospital admission.

Multivariable analysis
We conducted complete-case analyses, as the number of missing data was very low in the CRASH-2 trial. All candidate predictors were included initially in the multivariable logistic regression. Analyses were adjusted for treatment by including treatment allocation as a covariate in the models. We also included a variable for economic region (i.e. LIC, MIC or HIC as defined by the World Bank).[14] We used logistic regression models with random intercepts by country. Continuous variables were initially analysed as linear terms. Departure from linearity was assessed graphically and by adding quadratic and cubic terms into the model. We also explored other variable transformations using fractional polynomial and splines; however, none of these provided a better fit to the data and they were discarded because they had a more difficult interpretation, and because splines require some arbitrary decisions about the number and placement of knots. Interactions by age and by type of injury were specifically explored. Time since injury was dichotomised into <3 hours or >3 hours, as the effect of this variable was reasonably well captured by using it as binary.

We conducted a backward stepwise approach. We first included all potential prognostic factors and interaction terms that were considered plausible by users. These interactions included all potential

predictors with type of injury, time since injury and age. We then removed, one at a time, terms for which there was no strong evidence of an association, judged according to the *p*-values (<0.05) from the Wald test. Each time, we calculated a log-likelihood ratio test to check that the term removed did not have a big impact in the model. Eventually, we reached a model where all terms were statistically significant. We used the R software environment (version 2.13.1, The R Foundation for Statistical Computing, Vienna, Austria).

Performance

The predictive ability of the prognostic model was assessed in terms of calibration and discrimination. Calibration indicates whether or not observed risks agree with predicted risks and was assessed graphically by plotting the observed outcomes compared with the predicted probabilities of the outcomes. Discrimination indicates whether or not low-risk patients can be separated from high-risk patients and was assessed using a concordance (*C*) statistic.[15] For the CRASH-2 trial data, the predictions were estimated by setting the random effect of country to 0.

Optimism in the performance was assessed by bootstrap resampling. We drew 200 samples with replacement from the original data, with the same size as the original derivation data. In each bootstrap sample we repeated the entire modelling process, including variable selection. We averaged the *C*-statistics of those 200 models in the bootstrap samples. We then estimated the average *C*-statistic when each of the 200 models was applied in the original sample. The difference between the two average *C*-statistics indicated the 'optimism' of the *C*-statistic in our prognostic model.[15]

External validation

For the external validation we used the data from TARN. Membership of TARN is voluntary and includes 60% of hospitals receiving trauma patients in England and Wales and some hospitals in Europe. Data are collected on patients who arrive at hospital alive and meet any of the subsequent criteria: death from injury at any point during admission, stay in hospital for longer than 3 days, require intensive or high-dependency care or require interhospital transfer for specialist care.

Patients with isolated closed-limb injuries and patients of >65 years old with isolated fractures of the neck of femur or pubic ramus were excluded. The physiological data available in TARN are identical to those in the CRASH-2 trial, in that for every patient the HR, SBP, GCS score, RR and capillary refill time on arrival are entered by the hospital data co-ordinators. For each patient the volume of blood loss is estimated. This is done by allocating an estimated percentage of total volume of blood lost to each injury code in the abbreviated injury scale dictionary by blinded, then consensus, agreement from two emergency physicians. This estimation is based on previous work on blood loss in specific injuries.[16]

Adult patients (aged >15 years at the time of injury) presenting between the years 2000 and 2008 to TARN-participating hospitals were selected. The definition used in the CRASH-2 trial of significant haemorrhage was not available; therefore, we selected only patients with an estimated blood loss of at least 20% who we considered would be clinically comparable with the CRASH-2 trial patients.

For the validation in the TARN data set we conducted multiple imputations to substitute the missing values of the predictors included in the prognostic model using the procedure of imputation by chained equations in Stata (release 11, 2009; StataCorp LP, College Station, TX, USA). For the imputation model the following variables were included: injury severity score, age, sex, outcome (alive/dead), intubation/ventilation (yes/no), transfer status, mechanism of injury, head injury (yes/no), treatment at neurocentre (yes/no) and pre-existing condition (yes/no). We applied the coefficients of the model developed in the CRASH-2 trial with the estimated UK intercept to the five imputed data sets of TARN, obtaining five predictions of mortality for each patient in TARN. We then averaged over these five predictions to calculate calibration and discrimination.[15]

Simple prognostic model

For ease of use at point of care, we developed a simple prognostic model. For this model we included the strongest predictors with the same quadratic and cubic terms as used in the full model, adjusting for TXA. The prognostic model was presented as a chart that cross-tabulates these predictors, but each of them recoded in a number of categories. The categories were made considering clinical and statistical criteria. In each cell of the chart we estimated the risk for an individual with values of each predictor at the mid-point of the predictor's range for that cell. We then coloured the chart cells in four groups according to ranges in the probability of death: <6%, 6–20%, 21–50% and >50%. We decided these cut-offs based on the feedback from the potential simple prognostic model users and by looking at previous publications.[17,18]

Evaluation of the effect of tranexamic acid according to baseline risk

For these analyses, we used the prognostic model to stratify the patients in the CRASH-2 trial who were treated within 3 hours of injury into four mortality risk strata (<6%, 6–20%, 21–50% and >50%). We then examined the effect of TXA on all-cause mortality, death due to bleeding and thrombotic events (fatal and non-fatal myocardial infarction, stroke, deep-vein thrombosis and pulmonary embolism) within these strata. We prespecified that unless there was strong evidence against the null hypothesis of homogeneity of effects (i.e. $p < 0.001$), the overall OR would be considered the most reliable guide to the approximate relative risks in all risk strata. We examined the effect of TXA on arterial (myocardial infarction and stroke) and venous (deep-vein thrombosis and pulmonary embolism) thrombotic events separately and combined.

We also used the prognostic model to estimate the number and cumulative proportion of deaths at different levels of baseline risk in UK trauma patients using TARN data. For each TARN patient we used the prognostic model described above to estimate the predicted risk of death and then estimated the proportion of premature deaths averted by applying the OR from the CRASH-2 trial to each of the risk strata. For these analyses we included only patients within 3 hours of injury. The discussion on what type of patients should receive TXA was further informed by a consultation meeting with accident and emergency (A&E) consultants with whom we discussed the results about the effect of TXA according to baseline risk.

The original protocol is included in *Appendix 2*.

Ethical approval

Ethical approval for this study and the use of the CRASH-2 trial data was obtained from the London School of Hygiene and Tropical Medicine, London, UK. TARN already has ethical approval (PIAG section 60; PIAG3-4(e)/2006) for research on the anonymised data that are stored securely on the University of Manchester server.

Chapter 3 Results

General characteristics

Tables 1 and *2* show the characteristics of the patients in the CRASH-2 trial and TARN data sets respectively.

TABLE 1 Characteristics of CRASH-2 trial patients

| Characteristics | All patients (*n* = 20,127) | | Alive (*n* = 17,051) | Dead (*n* = 3076) |
	Missing (%)	Median (IQR)	Median (IQR)	Median (IQR)
Age (years)	*<1*	30 (24–43)	30 (23–42)	35 (25–48)
SBP (mmHg)	*<1*	91 (80–110)	100 (84–110)	84 (70–100)
HR (beats per minute)	*<1*	105 (90–120)	104 (90–120)	111 (96–126)
RR (breaths per minute)	*<1*	22 (20–26)	22 (20–26)	24 (20–30)
GCS score (total)	*<1*	15 (11–15)	15 (13–15)	8 (4–14)
Capillary refill time (seconds)	*3*	3 (2–4)	3 (2–4)	4 (3–5)
HSI	*0*	2 (1–4)	2 (1–4)	2 (1–4)
PIN	*0*	6522 (32%)	5813 (34%)	709 (23%)

HSI, hours since injury; IQR, interquartile range; PIN, penetrating injury.

TABLE 2 Characteristics of TARN patients

| Characteristics | All patients (*n* = 14,220) | | Alive (*n* = 12,455) | Dead (*n* = 1765) |
	Missing (%)	Median (IQR)	Median (IQR)	Median (IQR)
Age (years)	*0*	39 (25–57)	38 (25–55)	43 (27–70)
SBP (mmHg)	*16*	129 (110–145)	130 (112–145)	111 (88–140)
HR (beats per minute)	*16*	88 (75–105)	87 (75–102)	103 (80–126)
RR (breaths per minute)	*29*	19 (16–24)	18 (16–23)	22 (17–30)
GCS score (total)	*21*	15 (15–15)	15 (15–15)	12 (3–15)
Capillary refill time (seconds)	*84*	1 (1–1)	1 (1–1)	1 (1–1)
HSI	*64*	1 (1–2)	1 (1–2)	1 (1–1)
PIN	*0*	1993 (14.0%)	1785 (14.3%)	208 (11.8%)

HSI, hours since injury; IQR, interquartile range; PIN, penetrating injury.

In the CRASH-2 trial, the majority of patients were male and the median age was 30 years. Patients who died were on average older, had lower SBP, higher HR and lower GCS score. There were few missing data for all of the variables. There were 3076 deaths (15%) among the 20,127 CRASH-2 trial patients, and 1765 deaths (12%) in the 14,220 TARN patients. In comparison, the patients from TARN were older (median age 39 years), they had fewer penetrating injuries and they had a higher SBP.

Relationship between predictors and overall mortality

Age showed a positive and increasing association with risk of death. SBP, HR and RR showed a U-shape relationship, and GCS score showed a negative association with risk of death (*Figure 1*).

Table 3 shows that in the CRASH-2 trial, age of patient was positively associated with mortality for each of the described causes of death, with the highest relative increase for vascular occlusive death.
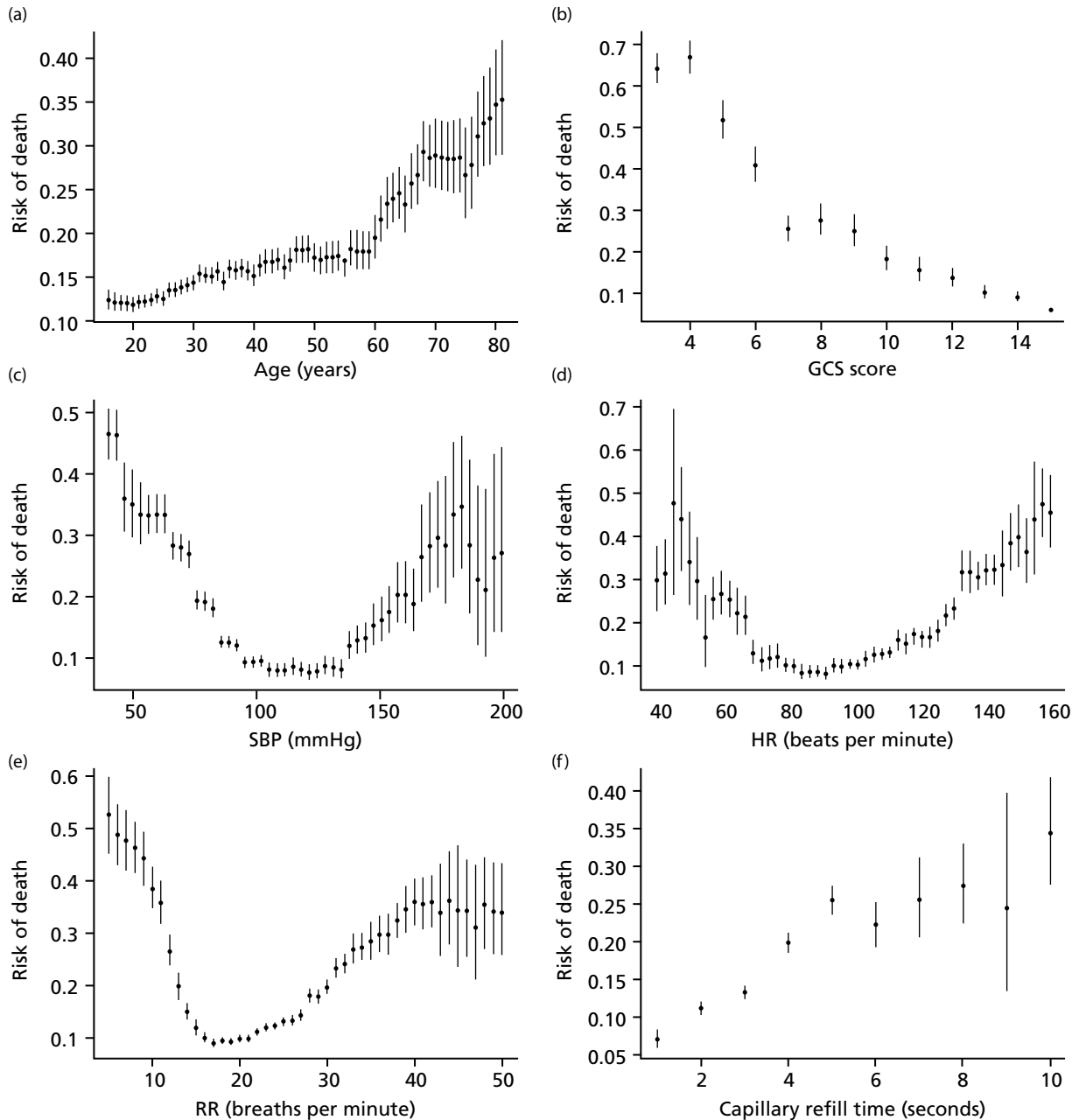
FIGURE 1 Association between continuous predictors and death among CRASH-2 trial patients. The error bars represent the 95% CI of that observed unadjusted risk in that level of the biomarkers.

Prognostic model

We included quadratic or cubic transformations in the prediction model to accommodate the departures from linearity. In the multivariable analysis, GCS score, SBP and age were the three strongest predictors. HR, RR and hours since injury (HSI) were associated with mortality and also included in the final model. All of these variables were considered important by users. Patients in LICs and MICs were more likely to die than patients in HICs. Although capillary refill time was weakly associated with mortality, it was not included in the prognostic model because in situations with poor visibility, such as on the battlefield, it is difficult to measure. In addition, capillary refill time was missing in >80% of the TARN patients. There was some evidence for statistical interaction between GCS score and type of injury. Low GCS scores were associated with worse prognosis for blunt injuries (*Table 4*).

Validation

The model showed a good internal validity, with a *C*-statistic of 0.84 (*Figure 2*) and good calibration except in very high-risk patients for whom the model over-predicted risk (*Figure 3*).

Internal validation using bootstrapping showed a minimal decrease of the *C*-statistic from 0.836 to 0.835. This indicates that there is very low over-optimism in the model development.

For the external validation we used the same variables as included in the derivation model except HSI, as this variable had a very large number of patients with missing data. Discrimination was good (*C*-statistic 0.88) and calibration satisfactory (see *Figures 2* and *3*).

Model presentation

The prognostic model is available online (www.crash2.lshtm.ac.uk), so risk of death can be obtained for individual patients. By entering the values of the predictors, the expected risk of death at 28 days is displayed. For example, a 70-year-old patient from a LIC, with a GCS score of 14, SBP of 100 mmHg, HR of 110 beats per minute and a RR of 35 breaths per minute, has a 32% probability of death at 28 days (*Figure 4*).

Users also highlighted the importance of a simple prognostic model that could be used at the bedside. The simple prognostic model included the three strongest prognostic variables (GCS score, SBP and age). We developed different prognostic models for patients within 3 hours of injury in LICs, MICs and HICs, and presented them as charts (*Figure 5*).

TABLE 3 Causes of death according to age in CRASH-2 trial patients

Age (years) (*n*)	Causes of death (%)					
	Bleeding	Vascular occlusion	Multiorgan failure	Head injury	Other causes	Any cause of death
<25 (5615)	4.6	0.1	1.5	4.4	1.1	11.8
25–44 (9874)	5.3	0.3	2.1	5.9	1.2	14.8
45–59 (3188)	5.6	0.6	2.8	6.9	1.6	17.4
≥60 (1449)	7.2	1.3	4.3	11.9	2.6	27.3

TABLE 4 Final multivariable model for predicting death

Variable	OR (95% CI)	*p*-value	Deviance	df
Intercept	0.012 (0.006 to 0.023)			
MICs	2.14 (1.03 to 4.44)	0.0405	18	2
LICs	3.59 (1.30 to 9.89)	0.0134		
TXA before 3 hours	0.81 (0.72 to 0.90)	0.0002	13	2
TXA after 3 hours	1.02 (0.87 to 1.20)	0.8158		
>3 HIS	0.75 (0.65 to 0.87)	0.0001	13	2
Age (linear component)	1.37 (1.16 to 1.62)	0.0002	223	3
Age^2	0.91 (0.84 to 0.99)	0.0228		
Age^3	1.02 (1.01 to 1.03)	0.0015		
SBP (linear component)	0.90 (0.87 to 0.93)	<0.0001	292	3
SBP^2	1.03 (1.02 to 1.03)	<0.0001		
SBP^3	1.00 (1.00 to 1.00)	0.0008		
RR (linear component)	0.74 (0.59 to 0.92)	0.0069	171	3
RR^2	1.48 (1.24 to 1.77)	<0.0001		
RR^3	0.93 (0.90 to 0.97)	0.0004		
HR (linear component)	0.97 (0.92 to 1.02)	0.1915	24	2
HR^2	1.02 (1.01 to 1.02)	<0.0001		
GCS score (linear component)	0.84 (0.80 to 0.88)	<0.0001	1993	4
$GCS score^2$	1.01 (1.00 to 1.01)	<0.0001		
PIN	0.91 (0.77 to 1.07)	0.2414	41	3
PIN $\times$ GCS score	0.92 (0.84 to 1.01)	0.0930	37	2
PIN $\times$ GCS $score^2$	0.99 (0.98 to 0.99)	0.0012		
Total			3126	21

df, degrees of freedom; PIN, penetrating injury.

These simple charts also showed good internal and external calibration (*Figure 6*). The area under the curve (AUC) for the simpler model was 0.82 for CRASH-2 trial data and 0.86 for TARN data.

Effect of tranexamic acid according to baseline risk

Table 5 shows the characteristics of CRASH-2 trial patients who were treated within 3 hours of injury according to baseline risk. Patients with higher baseline risk of death were older, had lower SBP and GCS scores, higher HRs and RRs, and were more likely to have blunt trauma than patients with a lower risk. Most patients (97%) were from MICs and this frequency distribution was similar for all of the risk strata.

Figure 7 shows the effect of TXA on all-cause mortality by baseline risk. TXA reduced all-cause mortality in each stratum of baseline risk. There was no evidence of heterogeneity in the effect of TXA on all-cause mortality (*p*-value for interaction = 0.96).
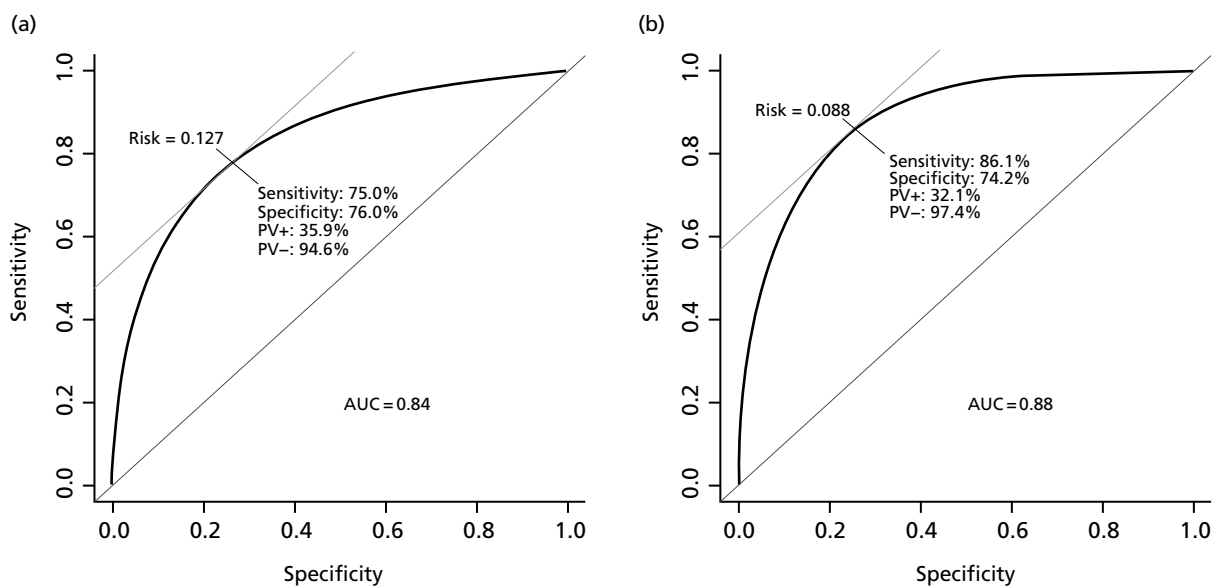
FIGURE 2 Internal and external discrimination displayed by the receiving operating characteristic. AUC, area under the curve; PV, predictive value. (a) CRASH-2 trial data (internal discrimination); (b) TARN data (external discrimination). Curves showing point where the addition of sensitivity and specificity is maximum and corresponding cut-points of risk.
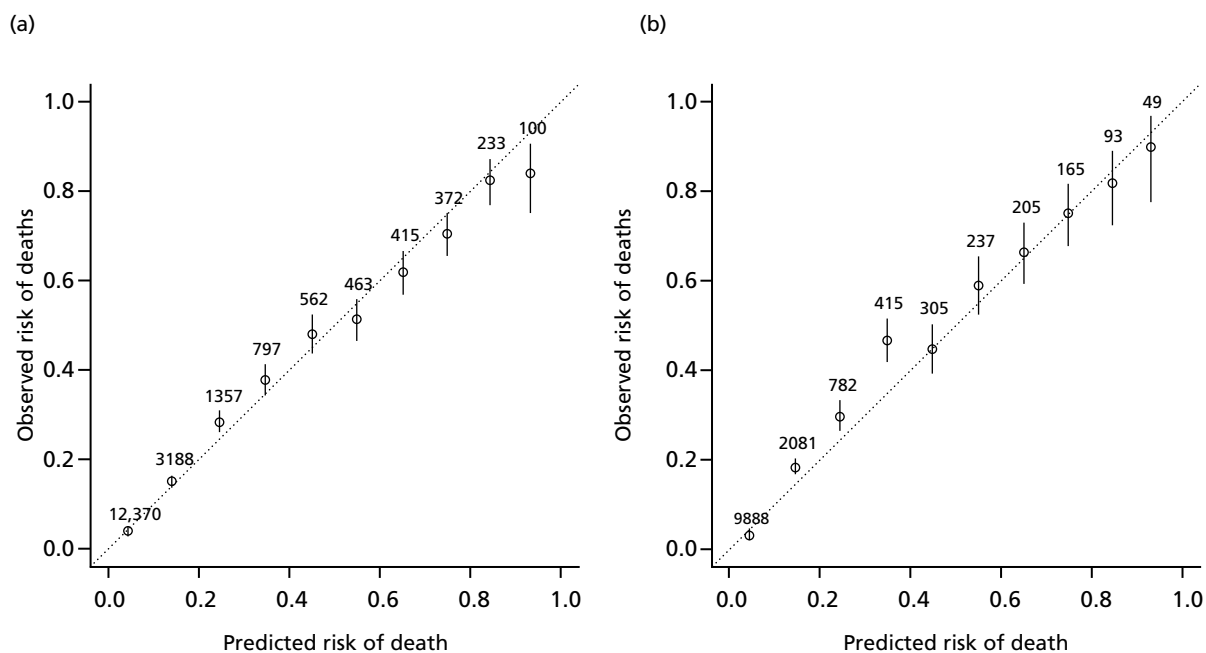
FIGURE 3 Goodness of fit and external calibration of the prognostic model by levels of predicted risk. (a) CRASH-2 trial data (goodness of fit); (b) TARN data (external validation).
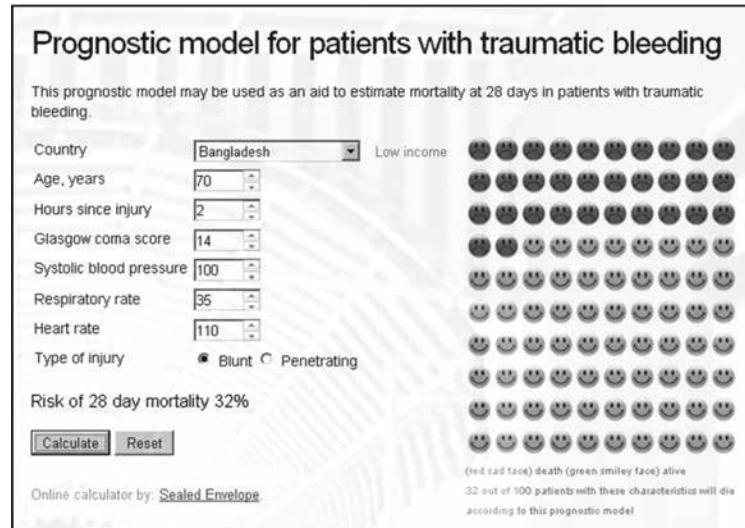
FIGURE 4 Snapshot of the web-based prognostic model.
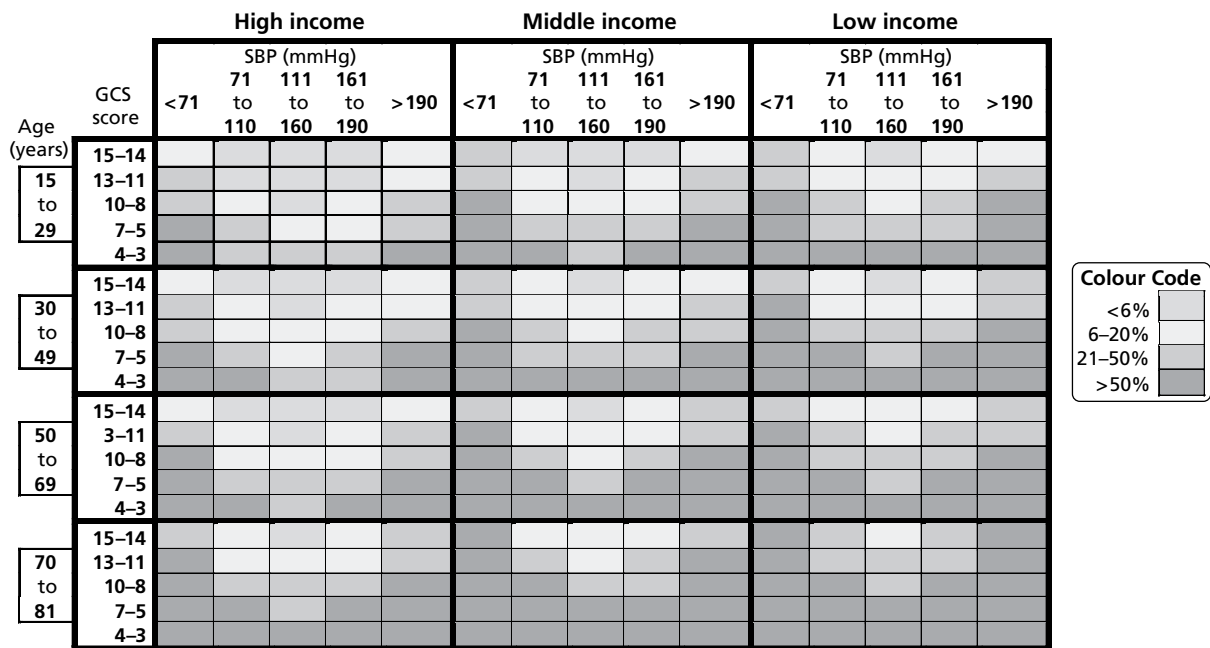
FIGURE 5 Chart to predict death in trauma bleeding patients.

Figures 8 and *9* show the effects of TXA on death due to bleeding, and on fatal and non-fatal thrombotic events by baseline risk of death.

There was no evidence of heterogeneity in the effect of TXA on death due to bleeding ($p = 0.98$) or on thrombotic events ($p = 0.74$). There was a reduction in non-bleeding deaths that was not statistically significant (OR = 0.97; 95% CI 0.86 to 1.09), with no evidence of heterogeneity according to baseline risk ($p = 0.99$).
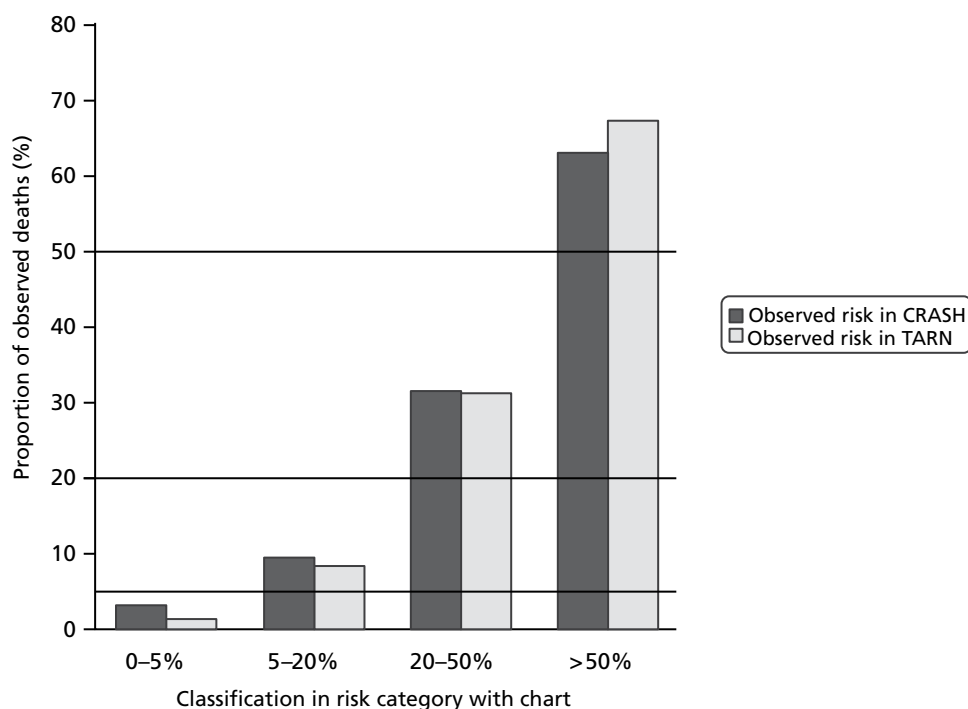
FIGURE 6 Internal and external calibration of the simple chart.

TABLE 5 Characteristics of CRASH-2 trial patients by risk strata

Characteristics	Risk strata			
	<6%	6–20%	21–50%	>50%
Total number of patients, n (%)	4840 (36)	5395 (41)	1848 (14)	1190 (9)
Male, n (%)	4111 (85)	4457 (83)	1533 (83)	1002 (84)
Age (years), mean (IQR)	27 (22–36)	32 (25–44)	35 (25–48)	35 (25–49)
Blunt injury, n (%)	2761 (57)	3186 (59)	1316 (71)	980 (82)
SBP (mmHg), mean (IQR)	100 (90–120)	90 (80–110)	80 (70–100)	80 (60–90)
HR (beats per minute), mean (IQR)	100 (90–112)	106 (92–120)	110 (97–124)	118 (98–130)
RR (breath per minute), mean (IQR)	20 (18–24)	24 (20–28)	24 (20–30)	24 (16–30)
GCS score (total), mean (IQR)	15 (15–15)	15 (13–15)	10 (7–13)	4 (3–6)

IQR, interquartile range.

Table 6 shows the effect of TXA on fatal and non-fatal thrombotic events in patients treated within 3 hours of injury. There was a significant reduction in the risk of fatal and non-fatal thrombotic events with TXA (OR = 0.69; 95% CI 0.53 to 0.89; p = 0.005).

There was a statistically significant reduction in arterial thrombotic events with TXA (OR = 0.58; 95% CI 0.40 to 0.83; p = 0.003). There was no evidence of heterogeneity in the effect of TXA on arterial thrombotic events (p = 0.91). There was a reduction in the risk of venous thrombotic events with TXA that was not statistically significant (OR = 0.83; 95% CI 0.59 to 1.17; p = 0.295). There was no evidence of heterogeneity in the effect of TXA on venous thrombotic events by baseline risk (p = 0.85).

Risk strata	TXA	Placebo		OR (95% CI)
<6%	33/2478 (1%)	40/2353 (2%)		0.78 (0.49 to 1.23)
6–20%	223/2682 (8%)	266/2713 (10%)		0.83 (070 to 1.00)
21–50%	281/908 (31%)	337/940 (36%)		0.80 (0.69 to 0.94)
>50%	392/607 (65%)	410/583 (70%)		0.77 (0.68 to 0.87)
All	929/6684 (14%)	1053/6589 (16%)		0.85 (0.78 to 0.93)

p=0.9606

TXA better   TXA worse

0.6 0.7 0.8 0.9 1.0 1.1
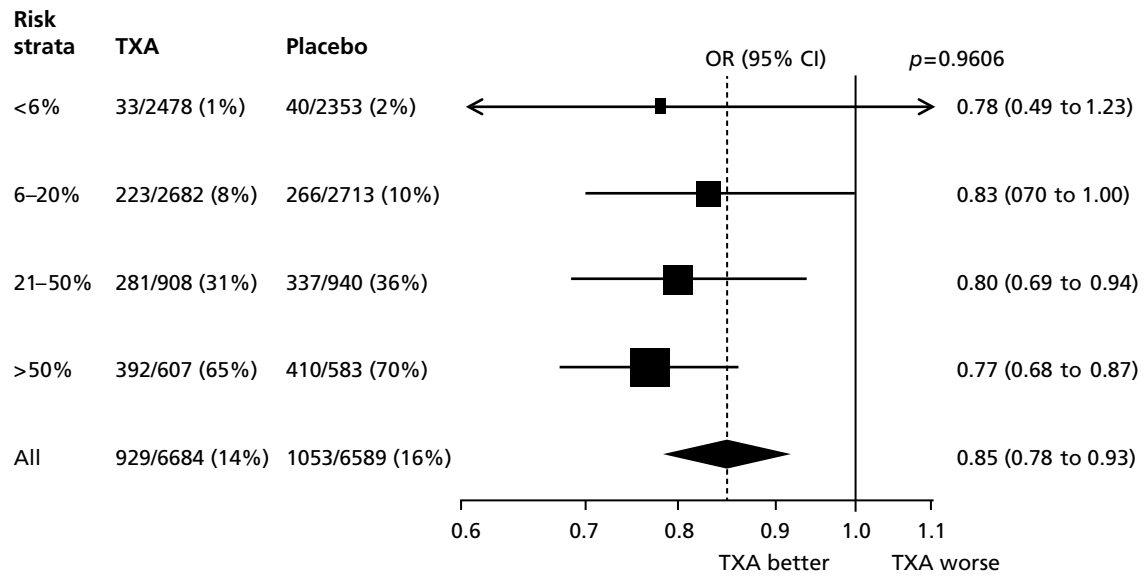
FIGURE 7 Death from all causes.

Risk strata	TXA	Placebo		OR (95% CI)
<6%	14/2487 (1%)	40/2353 (2%)		0.63 (0.32 to 1.24)
6–20%	96/2682 (4%)	134/2713 (5%)		0.71 (0.55 to 0.93)
21–50%	98/908 (11%)	142/940 (15%)		0.68 (0.53 to 0.88)
>50%	106/607 (17%)	132/583 (23%)		0.72 (0.56 to 0.93)
All	314/6684 (5%)	429/6589 (7%)		0.71 (0.61 to 0.82)

p=0.9759

TXA better   TXA worse

0.6 0.7 0.8 0.9 1.0 1.1
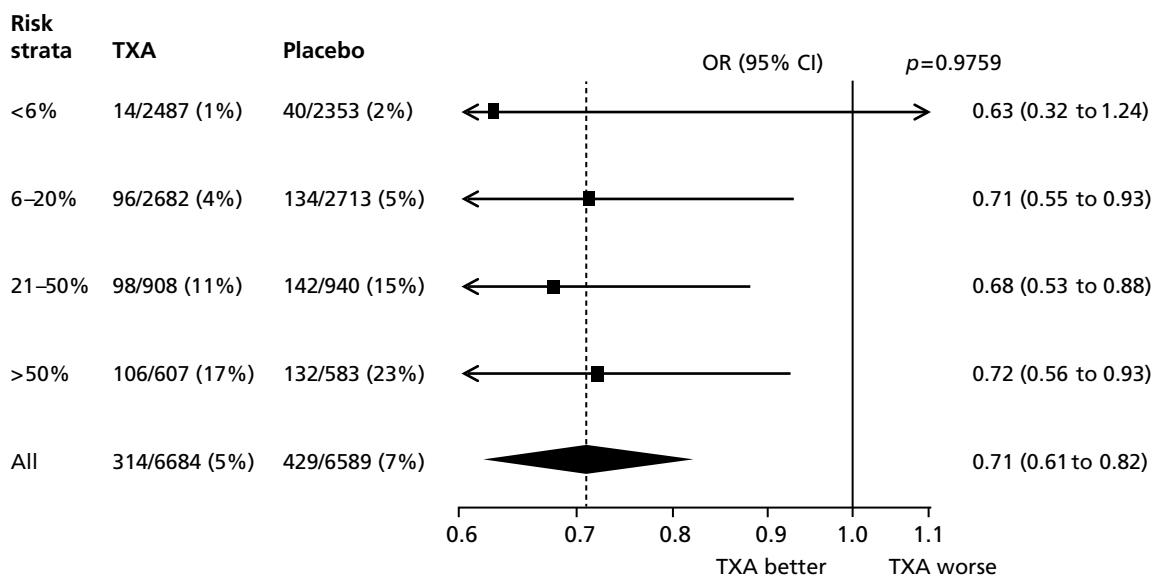
FIGURE 8 Death due to bleeding.

Estimation of lives saved if tranexamic acid given to different risk strata

Assuming that the effect of TXA is the same in all risk strata (constant OR), the percentage of premature deaths that could be averted in TARN by administering TXA within 3 hours of injury in each risk stratum (<6%, 6–20%, 21–50% and >50%) is 17%, 36%, 30% and 17% respectively. *Figure 10* shows the distribution of patients according to baseline risk in TARN, and *Figure 11* shows the absolute number of deaths that could potentially be averted through the use of TXA in patients in the UK TARN by baseline risk of death.
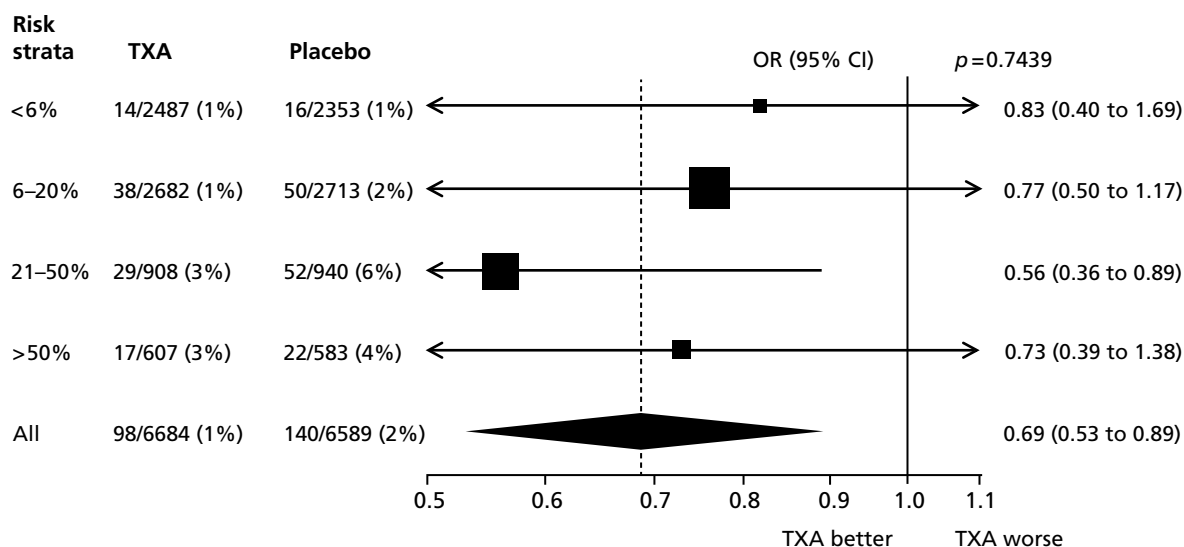
FIGURE 9 Fatal and non-fatal thrombotic events.

TABLE 6 Effect of TXA on fatal and non-fatal thrombotic events

Thrombotic events[a]	TXA (N = 6684), n (%)	Placebo (N = 6589), n (%)	OR (95% CI)	p-value
Any event	98 (1.5)	140 (2.1)	0.69 (0.53 to 0.89)	0.005
Any arterial event	47 (0.7)	80 (1.2)	0.58 (0.40 to 0.83)	0.003
Myocardial infarction	23 (0.3)	46 (0.7)	0.49 (0.30 to 0.81)	0.005
Stroke	28 (0.4)	40 (0.6)	0.69 (0.43 to 1.11)	0.128
Any venous event	60 (0.9)	71 (1.1)	0.83 (0.59 to 1.17)	0.295
Pulmonary embolism	42 (0.6)	47 (0.7)	0.88 (0.58 to 1.33)	0.548
Deep-vein thrombosis	25 (0.4)	28 (0.4)	0.88 (0.52 to 1.50)	0.641

a Fatal or non-fatal events.
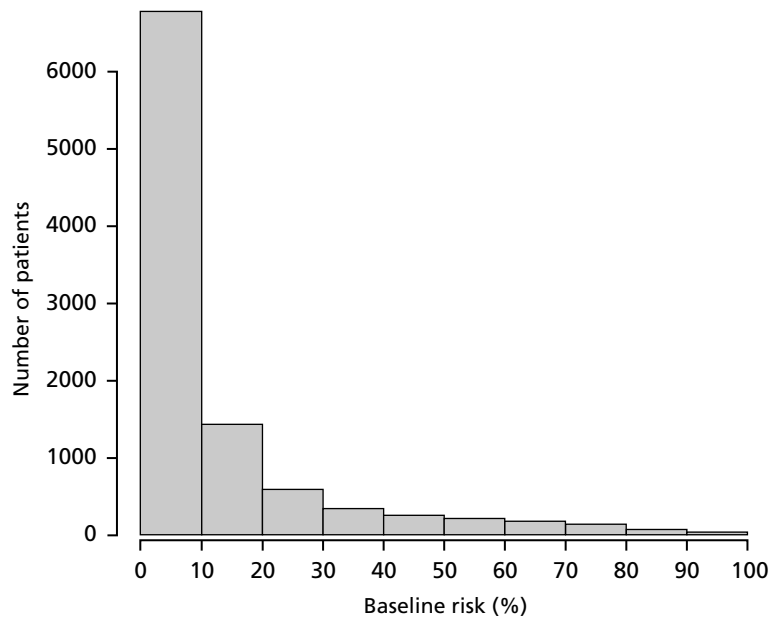
FIGURE 10 Trauma Audit and Research Network: distribution of patients by baseline risk.
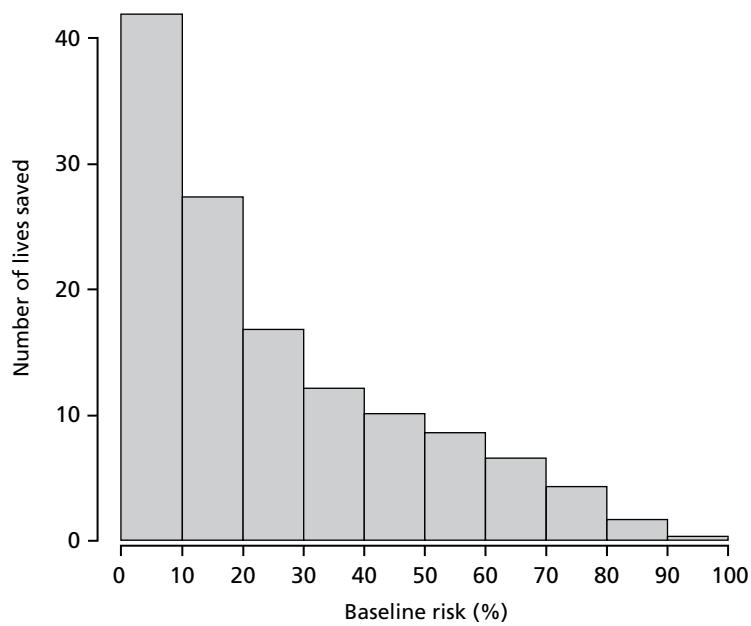
FIGURE 11 Trauma Audit and Research Network: distribution of lives saved if TXA was given to everyone (with constant OR –0.85).

Chapter 4 Discussion

Main findings

We have developed and validated a prognostic model for trauma patients with clinical parameters that are easy to measure. The model is available as a web calculator and can be used at the point of care in its simplified form. Separate models are available for patients from LICs, MICs and HICs. This simple prognostic model could inform doctors about the risk of death and guide them in the early assessment and management of trauma patients.

The ORs for all-cause mortality and death due to bleeding with TXA do not appear to vary by baseline risk. TXA reduced the odds of death due to bleeding by approximately 30% in each of the risk strata. TXA also appeared to reduce the odds of thrombotic events by 30%. Once again, this reduction does not appear to vary by baseline risk. Taken together, these data suggest that TXA can be administered safely to a wide spectrum of trauma patients and that its use should not be restricted to the most severely injured. However, although we did not find evidence of heterogeneity for the effect of TXA according to baseline risk, in the lowest-risk group the precision of the estimated effect is low.

Strengths and limitations

Our study has several strengths. Our models were based on a prospective cohort of bleeding trauma patients, with standardised collection of data on prognostic factors, very few missing data and low loss to follow-up. Unlike previous prognostic models, we explored more complex relationships between continuous predictors and mortality, and captured non–linear relationships. All of these factors provide reassurance about the internal validity of our models. The large sample size in relation to the number of prognostic variables is also an important strength. As most previous models were derived from single-centre studies in HICs, we developed separate models for LICs, MICs and HICs. Unlike most previous models, we conducted an external validation in a large cohort of trauma patients. This confirmed the discriminatory ability of the model in patients from HICs and showed good calibration. Another methodological strength was our use of imputation to address missing data, which has rarely been done in previous model validation studies. To the best of our knowledge this is the only prognostic model for this population that is available in a web-based calculator and a simplified chart that can be used at point of care. Importantly, we obtained advice from the potential users of the model throughout its development.

There are also some limitations. The data from which the models were developed come from a clinical trial and this could therefore limit external validity. For example, patients were recruited within 8 hours of injury, and we cannot estimate the accuracy of the models for patients evaluated beyond this time. Nevertheless, the CRASH-2 trial was a pragmatic trial that did not require any additional tests and, therefore, included a diversity of real-life patients. In addition, the relationship between predictors and outcome could be different in patients included in a clinical trial and in routine practice. The TARN data included a larger proportion of patients with blunt injuries than in the CRASH-2 trial; however, that the model's performance was very good in a trauma registry population provides reassurance that any potential bias (if present) was small. Another limitation was that for the validation we used a cohort of trauma patients that were not equally defined and we included them using an estimation of the blood loss. In any case, this weakness would have underestimated the accuracy of the model. Other potentially important variables such as pre-existing medical conditions, previous medications and laboratory measurement were not collected in the CRASH-2 trial and, therefore, were not available for inclusion into the model. However, these are variables that are usually unavailable in the acute care trauma setting in which the model is intended to be used. The prognostic model predicts overall death rather than death due to bleeding,

as death due bleeding was not available in the TARN data set. However, it is expected that bleeding contributes to the other main causes of death in trauma patients. In addition, some deaths classified as non-bleeding could in fact be due to bleeding.

Regarding the effect of TXA according to baseline risk, it is important to note that the data examined here are a subset of the entire CRASH-2 trial. As most trauma protocols restrict TXA use to patients within 3 hours after injury, we restricted our analyses to these patients. Given that our results are based on a subgroup analysis, they should be interpreted cautiously. On the other hand, there was also a reduction in the risk of fatal and non-fatal myocardial infarction (relative risk = 0.64; 95% CI 0.42 to 0.97; $p = 0.035$) in the main trial analysis of patients treated up to 8 hours from injury, and there were fewer thrombotic events in TXA-treated patients. Although there may be grounds for scepticism about the reduction in arterial thrombotic events with TXA, the data provide reassurance that there is no increased risk.

The absence of evidence of an interaction between the effect of TXA and baseline risk could be due to a lack of statistical power for the interaction tests; however, graphically it seems unlikely that the findings are due to lack of power and they suggest that the effect of TXA is not influenced by baseline risk. We used a multivariable approach that has been shown to improve the power of subgroup analysis in comparison with individual predictor subgroup analyses.[19] Simulation studies have shown that the power to detect an interaction is increased from 23% to 83% when a multivariable approach is used. Nevertheless, the absence of evidence of interaction should not be taken as evidence of absence of an interaction.

That we analysed data from a randomised controlled trial using a prognostic model derived from the same trial might be considered a weakness. On the other hand, the prognostic model we used has good external calibration and discrimination, and there are few models available that can be reliably applied to the trauma population included in the CRASH-2 trial. The revised trauma score, one of the most widely used scores, was developed many years ago, has several methodological limitations, and showed poor calibration in the CRASH-2 trial and TARN data sets (*Figure 12*).[20]

Establishing cause of death in trauma patients can be difficult and any inaccuracy might have affected our estimate of the effect of TXA on fatal thrombotic events. There may also have been inaccuracy in the diagnosis of non-fatal events. The diagnosis of myocardial infarction is particularly challenging in trauma patients, many of whom are anaesthetised or sedated. Elevations in creatine kinase-MB isoenzyme are hard to interpret because of muscle injury and we did not collect data on troponin. However, diagnostic inaccuracy tends to obscure treatment effects and would not readily explain the observed reduction in thrombotic events with TXA.

Implications of the study

Many trauma protocols use blood pressure as the main criterion for determining which patients should receive urgent intervention. However, according to our model, a 75-year-old patient with blunt trauma and a SBP of 110 mmHg, HR of 80 beats per minute, RR of 15 breaths per minute and a GCS score of 15 has a similar risk of death as a 45-year-old patient with exactly the same parameters but with a SBP of 60 mmHg. These findings have important practical implications. According to many trauma protocols, only the younger patient would receive urgent interventions such as TXA, whereas the older patient would be denied this life-saving intervention. The effect of age is particularly important bearing in mind that in HICs the average age of trauma patients is increasing. Data from TARN show that one-quarter of trauma deaths in England and Wales occur in patients >70 years. The effect of age is likely to reflect the increased incidence of co-existing diseases, in particular cardiovascular diseases. Elderly patients are more likely to have coronary heart disease and the decrease in oxygen supply associated with traumatic bleeding can increase the risk of myocardial ischaemia.[21] Another potential explanation for the increased risk of vascular occlusive death is related to the inflammation process trigger after trauma. It is known that after trauma there is a potent inflammatory response that involves increased serum levels of interleukin 1 (IL-1), IL-2,
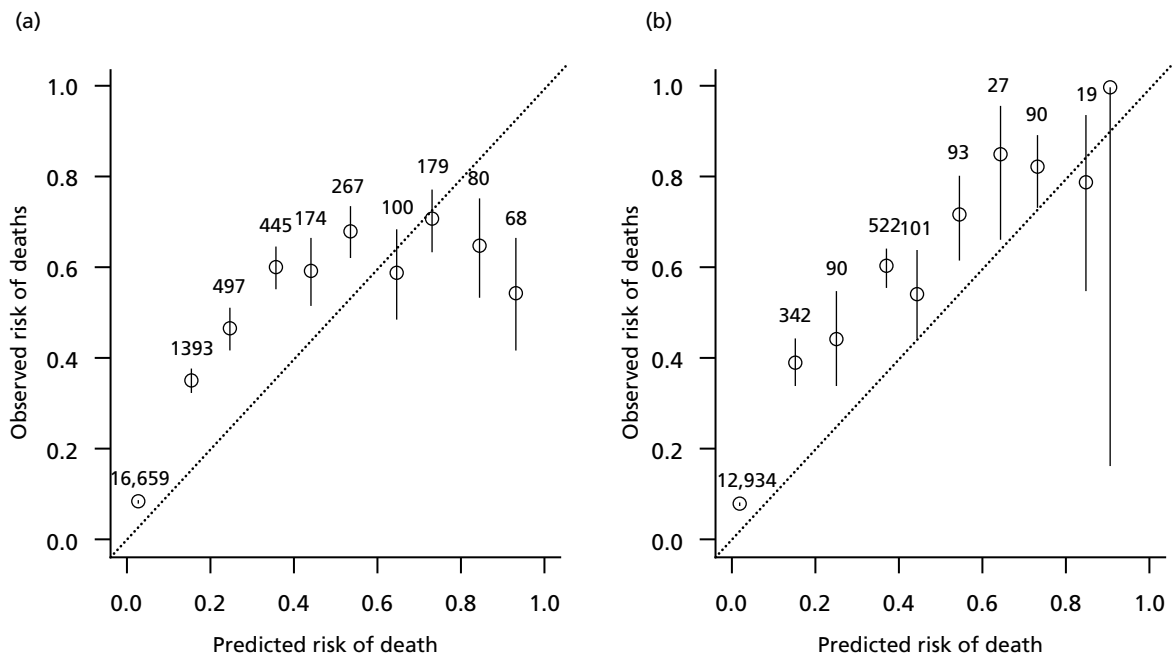
FIGURE 12 Calibration of the revised trauma score in CRASH-2 trial and TARN data. (a) CRASH-2 trial data (prediction with revised trauma score); (b) TARN data (prediction with revised trauma score).

tumour necrosis factor alpha (TNF-α), IL-6, IL-12 and interferon-gamma.[22] In patients with traumatic bleeding there is activation of plasmin which plays a key role in the fibrinolytic response in the early hours after injury. Plasmin also has pro-inflammatory effects through the activation of cytokines, monocytes, neutrophils, platelets and endothelial cells.[23] It has been suggested that vascular risk rises in short time periods of inflammatory responses to exposures such as infections or major surgery.[24] It is possible that some of the observed prognostic role of age in trauma patients is due to the acute trauma inflammatory response, which might trigger acute vascular events, particularly in those older patients who have a more widespread atherosclerotic condition. Furthermore, the prognostic role of age could be explained partially by a self-fulfilling prophecy phenomenon, as age has been shown to be positively associated with do-not-resuscitate orders.[25]

We found that trauma patients in LICs and MICs were at higher risk of death than patients from HICs. It is important to emphasise that the income classification refers to the country and not to individual patients. Some of the effect of income classification might be the consequence of the differences on health-care settings. Other studies have shown similar results, but to our knowledge this is the first one to include a large number of LICs and MICs.[26] Although we did not have enough information to explore the causes of these differences, it is likely that the rapid increase in the number of trauma patients and the lack of resources in poorer countries are among the most important reasons. Scaling up cost-effective interventions in these settings could save hundreds of thousands of lives every year.

Potential biological mechanisms

The effect of TXA in arterial events was unexpected. Treatments to reduce haemorrhage often increase thrombosis risk and the use of anticoagulants tends to increase the risk of bleeding. However, TXA reduces the risk of haemorrhage death and appears to also reduce the risk of arterial thrombotic events. What mechanisms might account for this? Trauma marks the onset of a period of greatly increased myocardial oxygen demand as pain and hypovolaemia lead to a rapidly increased HR. At the same time, blood loss results in hypotension and anaemia, which reduces myocardial oxygen delivery. The imbalance between increased oxygen demand and reduced supply may be sufficient to cause myocardial infarction,

particularly in patients with pre-existing coronary artery stenosis. Cohort studies have shown that even a modest reduction in haemoglobin is a strong risk factor for death in patients with stable angina. In this respect, the pathophysiology of myocardial ischaemia in trauma patients may be similar to stress-induced myocardial infarction in perioperative patients (type 2 perioperative myocardial infarction).[27] By reducing traumatic blood loss and anaemia, an early short course of TXA could reduce myocardial oxygen demand and increase oxygen supply.

Tranexamic acid might also play a role in the prevention of acute coronary thrombosis following trauma.[28] Traumatic injury triggers an acute inflammatory state with increases in TNF-α, IL-1 and IL-6. These inflammatory mediators have been implicated in coronary plaque fissuring and acute coronary thrombosis. TXA reduces bleeding through the inhibition of plasmin, the enzyme responsible for fibrinolysis. However, plasmin also has a wide spectrum of pro-inflammatory effects, raising the possibility that the observed reduction in the risk of arterial thrombotic events in trauma patients treated with TXA may be mediated via an anti-inflammatory effect.[29]

Implications for clinical practice

The result that the effect of TXA does not vary by baseline risk has important implications for the care of trauma patients. First, it suggests that TXA can be used safely in all trauma patients with or at risk of significant bleeding, as per the inclusion criteria used in the CRASH-2 trial, and not just in those with massive haemorrhage. Second, the observed reduction in the risk of arterial events with TXA suggests that the absolute benefits from TXA administration are likely to be greatest in older trauma patients, who at any given level of injury severity have a higher baseline risk of haemorrhage death and thrombotic events. Clinical concern about an increased risk of ischaemic cardiac events may be a reason to give rather than to withhold TXA. It is worth noting that trials of TXA in cardiac surgery patients, a group at high risk of cardiac events, provide no evidence of any increased risk with TXA.[30] We acknowledge that estimating the risk of significant bleeding is a challenging ongoing process that uses not only physiological variables but also other variables such as laboratory measurements and response to treatments. Physicians will use all of this information and their clinical judgement when deciding whether or not to use TXA. However, in situations of uncertainty physicians can use the prognostic model to support the decision-making process and should certainly consider administering TXA to patients with a risk of death >5%.

Future research

The relationship between age and mortality needs further exploration; a better understanding of the mechanism underlying the association between age and increasing mortality could lead to effective interventions to improve the outcome in this vulnerable population.

As we were able to validate the model only in patients from high-income regions, future studies should also explore its performance in LIC and MIC settings.

Finally, future research should evaluate whether or not the use of this prognostic model in clinical practice has an impact on the management and outcomes of trauma patients.

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Contribution of authors

Pablo Perel (Senior Lecturer), **Haleema Shakur** (Senior Lecturer) and **Ian Roberts** (Professor) designed the study.

David Prieto-Merino (Lecturer) analysed the data.

All authors contributed to writing the paper.

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Appendix 1 Semistructured interviews

We held separate meetings with three potential user groups: paramedics ($n = 1$), military personnel ($n = 4$) and emergency medicine consultants ($n = 5$).

In each meeting we first provided information about the purpose of the study and made a short presentation. We then explained what the CRASH-2 trial was, the data available from the CRASH-2 trial cohort and what prognostic models are.

The following questions were posed and used as triggers for discussion:

1. Which are the most important outcomes to predict?
2. Which are the most important variables that you consider when you want to predict death in trauma patients?
3. Do you think prognostic models should be different for different populations, and if so specify?
4. Do you usually use a prognostic model (or risk score) to assess prognosis in trauma patients?
5. Thinking about the day-to-day use of the model, would you prefer a paper-based one you can use on your computer or mobile telephone?

In general, there was agreement in the responses of the different user groups, whether they were from the pre-hospital, battlefield or hospital emergency setting. Most of them prioritised death as the overall main outcome. Regarding potential predictors there was also agreement that, among the physiological variables, capillary refill time was not very useful and was difficult to measure. Emergency consultants suggested that laboratory tests could be added, but unfortunately these variables were not available in the CRASH-2 trial data set. The interactions most commonly mentioned as important to explore were the ones regarding prognostic variables with different type of injuries and age. Almost all of the users confirmed not using a prognostic model currently, but most of them were positive about using one if it was accurate, user friendly and informative for clinical practice. There were mixed responses regarding the presentation; some preferred an electronic version that could be available online, whereas others were more inclined to a paper-based version of the prognostic model.

Appendix 2 Project submitted to Health Technology Assessment programme

1. Project title

Development and validation of a risk score for trauma patients with haemorrhage *The CRASH-2 score*

2. How the project has changed since the outline proposal was submitted (PR only)

Following feedback from the Board: 1) We have explained in detail how the CRASH-2 trial data are collected and justified why the use of these data are appropriate for developing a risk score. 2) We have described the quality of the CRASH-2 trial data which will be available and explained that there will be negligible missing data with a follow-up rate of about 99%. 3) We have described how we will tackle the problem of poor fit. Briefly, we will reduce the possibility of overfitting when developing the risk score because we will use a large sample size, with few key predictors, and large number of events. We will use a full model approach that minimises selection bias of predictors, and we will shrink the coefficients with bootstrapping if there is any evidence of overfitting. 4) We have explained that to overcome the potential problem of differences in care patterns we will update the estimates for the new setting (UK) following a Bayesian approach. 5) We have described in more detail the potential benefit to patients and impact on clinical practice. Briefly, failure to recognize the extent of haemorrhage is a leading cause of preventable deaths in trauma patients. A simple and accurate risk score, such as the proposed CRASH-2 trial score, will be useful to make triage decisions in the pre-hospital setting, the battlefield, and to initiate necessary diagnostic and therapeutic interventions at hospital admission. 6) We have described how we will involve three potential risk score users groups (ambulance crew, military personnel and A&E clinicians) to adapt the CRASH-2 trial score for each of these setting.7) We have added the Board recommendation that respiratory rate could not be practical, and 8) Included a more active public participation.

3. Planned investigation

Research objectives
To develop a practical risk score for use in the emergency setting to predict unfavourable outcomes in patients with trauma and haemorrhage.

Specifically:

(a) Develop a risk score for in-hospital mortality and disability in patients with trauma and significant haemorrhage using data from CRASH-2 trial patients;
(b) Validate the performance of the CRASH-2 trial score in a sample of patients with trauma and bleeding from the NHS (TARN dataset) and, if needed, re-calibrate and adjust the CRASH-2 trial score according to the validation results;
(c) Adapt the CRASH-2 trial score to the specific needs of the pre-hospital setting, battlefield, and A&E departments.

Existing research

Trauma

Trauma is a common cause of death and disability worldwide, causing 5 million deaths each year.(1) It is a leading cause of death in people younger than 35 years and causes approximately 10,000 deaths annually in England and Wales. Serious injuries result in 640,000 hospital admissions each year and more than 6 million attendances to accident and emergency (A&E) departments. It is estimated that trauma costs the NHS £1.2 billion annually.(2)

Traumatic haemorrhage

Haemorrhage is the second leading cause of death in trauma patients, exceeded only by traumatic brain injury. It is estimated that haemorrhage causes approximately 30% to 40% of trauma-related deaths.(3) Not only does haemorrhage itself contribute to mortality, but its associated hypotension is also a prognostic factor for poor outcome in patients with traumatic brain injury.(4) Much of the impact of haemorrhage occurs in the early hours after injury, when haemorrhage accounts for an even larger proportion of trauma deaths. Almost 50% of trauma deaths in the first 24 hours of medical care, and over 80% of deaths in the operating room, are estimated to be due to haemorrhage.(5)

The importance of early treatment in traumatic haemorrhage

The initial treatment of patients with haemorrhage has two objectives; to stop the haemorrhage and restore the volume.(6) Interventions should be implemented as soon as possible after the injury, as the probability of survival increases with shorter times between injury and the onset of medical care.(7) The recent European guidelines for the management of bleeding following major trauma recommend that the *"time elapsed between injury and operation be minimised for patients in need of urgent surgical bleeding control"*.(8) A joint report from the Royal College of Surgeons of England and the British Orthopaedic Association stresses the importance of early treatment and recommends that the time of on-scene care should not exceed ten minutes and that the start of the operation for visceral injuries must be within 60 minutes of admission.(9)

Traumatic haemorrhage is the leading cause of preventable death in trauma

The failure to initiate appropriate early management of trauma patients with haemorrhage is not unusual, and consequently uncontrolled haemorrhage is considered to be the leading cause of preventable death among trauma patients.(10) Most of these preventable deaths are associated with missed diagnosis or delayed interventions. For example, it has been shown that there were delays in treating the source of bleeding in 32% of the patients with blunt injuries, who later died from haemorrhage, and that 79% of patients whose deaths were considered preventable had received no, or delayed, operations for conditions that would normally require an operation.(11, 12) Similarly, another study showed that a delay in treatment or a misdiagnosis was reported in 75% of patients with preventable haemorrhage related deaths.(13)

Early assessment of traumatic haemorrhage

Estimation of blood loss is very challenging early after trauma. Different studies showed that medical personnel estimate of the amount of blood loss is generally inaccurate in the emergency situation.(14, 15) Furthermore the risk associated with the haemorrhage does not depend only on the amount of blood lost, but also on the speed of blood loss, and the patient's characteristics (e.g. previous clinical condition, age or weight). Therefore, for the early assessment of patients with trauma and haemorrhage what is really important is to evaluate the association of variables with poor outcome (i.e. their predictive ability).

Trauma patients with haemorrhage present a physiological response which is related with the extent of blood loss, and has been recognized as useful for predictive purposes. Part of this response, such as the reduction in blood pressure, the increase in capillary refill time, and the alteration of consciousness (Glasgow Coma Scale score), is a direct result of the loss of intravascular volume. Other variables are related with compensatory mechanisms, such as the increase of heart and respiratory rate as a

consequence of the sympathetic activation.(16) All these physiological variables have been considered as useful parameters for the initial assessment of patients with traumatic haemorrhage.(6, 17, 18)

Although these physiological variables have been shown to be useful, they have showed limitations when used as an isolated parameter. For example, hypotension has been shown to be a late marker of shock, which in this context can be defined as the inadequate tissue perfusion as a result of blood loss.(17, 19) Tachycardia, when used as an isolated predictor of shock, has shown low sensitivity and specificity.(20) To overcome the limitations of using isolated physiological parameters there have been many attempts to combine several variables into risk scores.

Risk scores, which can be defined as the mathematical combination of two or more patient or disease characteristics to predict outcome, have shown to be more accurate than clinical prediction.(21, 22) According to studies in cognitive psychology, the human brain is poorly prepared for making and updating precise quantitative prediction.(23) The difficulties in collecting and summarizing quantitative data to make predictions are even more extreme in emergency situations such as in the treatment of trauma patients.(24)

The potential use of risk scores

Most of the preventable deaths due to haemorrhage occur in the early hours after injury, during the pre-hospital period or in the initial hours after injury. It is therefore important to assess rapidly the extent of haemorrhage in order to identify those patients who require prompt referral to hospital and, at hospital admission, initiate the necessary diagnostic and therapeutic interventions. A simple and accurate method to assess the extent of bleeding in the early stages of trauma could guide doctors in their early evaluations of these patients and therefore reduce preventable deaths associated with delayed treatment in traumatic haemorrhage. This decision-making process is commonly called 'triage' and can be defined as the sorting of medical conditions into different categories to achieve a true priority of care.(25)

An accurate and simple risk score could be used as a triage tool in the pre-hospital setting. There is some evidence, from observational studies, that care provided to major trauma patients in specialized centres improves outcome.(26) Therefore, a simple risk score at the pre-hospital setting could stratify patients and be used for appropriate referral.

A risk score could be also used at hospital admission. As mentioned before, most of the preventable deaths are associated with missed or delayed diagnosis of traumatic bleeding, therefore an accurate risk score could rapidly trigger the appropriate diagnostic and therapeutic interventions, and ensure a fast and adequate response at hospital admission. Fisher and collaborators showed that the use of the Revised Trauma Score for triage at hospital admission reduced management errors in trauma patients.(27) However, this study had methodological limitations as it was a before after study from a single centre with several interventions introduced in the same period. Furthermore, as discussed below the Revised Trauma Score has some limitations.

An additional setting in which a simple risk score could be useful is for trauma in combat fields. Haemorrhage is also considered the leading cause of preventable death in the battlefield, and development of new triage methods is among the priorities of military medical research.(28) A further advantage of a simple risk score in this setting is that it could be used by non-medical personnel.

Finally, an important use of triage could be related with mass causalities in the context of terrorist incidents in urban settings, such as the bombing that occurred in London in 2005. In these situations large numbers of casualties may overwhelm existing medical resources and therefore prioritization of medical care according to risk becomes very relevant.(29)

Existing trauma scores

Trauma scores can include anatomical or physiological variables or a combination of the two types.(30) The physiological scores can be further divided into: simple, when only clinical data are included (e.g. heart rate), or complex, when laboratory test are added (e.g. lactic acid). Simple physiological scores are more useful in the early management of trauma patients when the extent and exact nature of the anatomical impact of the injury is still unclear, and data from more complex diagnostic tests are yet to be obtained. Although several trauma scores have been published, to date none of these have been widely accepted and none are without limitations.

The recent European Guideline for the Management of Bleeding following major trauma recommends the use of the '*American College of Surgeons Advanced Trauma Life Support classification of haemorrhage severity*' for initial assessment of the extent of traumatic haemorrhage.(8)

American College of Surgeons Advanced Trauma Life Support classification of haemorrhage severity

Haemorrhage severity according to ACS/ATLS classification[a]	Class I	Class II	Class III	Class IV
Blood loss (ml)	<750	750–1,500	1,500–2,000	>2,000
Pulse rate (per minute)	<100	>100	>120	>140
Blood pressure	Normal	Normal	Low	Low
Pulse pressure (mm Hg)	Normal	Low	Low	Low
Respiratory rate (per minute)	14–20	20–30	30–40	>40
Urine output (ml/hour)	>30	20–30	5–15	Negligible
Central nervous system (mental status)	Slightly anxious	Mildly anxious	Anxious, confused	Lethargic

a Values are estimated for a 70-kg adult. Table adapted from the American College of Surgeons. ACS/ATLS, American college of Surgeons/Advanced Trauma Life Support.

The development of this classification is unreferenced, and to the best of our knowledge there is no evidence to support the blood loss volumes used in each category of severity. In addition, some of its components, such as urine output measurement, require some time to evaluate, therefore it would not be practical for use in the pre-hospital setting or in the early stages of admission.

The Revised Trauma Score (RTS) is the most widely used physiologic score.(31) The RTS consists of the following variables: Glasgow Coma Scale (GCS) score, systolic blood pressure and respiratory rate. The RTS is calculated by adding the coded value for each variable.

Coding variables for the Revised Trauma Score

GCS score	SBP	RR	Coded value
13–15	>89	10–29	*4*
9–12	76–89	>29	*3*
6–8	50–75	6–9	*2*
4–5	1–49	1–5	*1*
3	0	0	*0*

For outcome prediction a weight for each individual component is added according to the following formula: 0.7326 SBP + 0.2908 RR + 0.9368 GCS score. Limitations of this score include the fact that the values for each of the variables is based on expert consensus and not empirical data, and that the weight for each component was derived from patients from a single hospital in the United States more than 20 years ago.(31) Furthermore, the weighted RTS is not presented in a simple way practical to use in the emergency setting. In addition, it has been shown that the RTS coded values do not accurately describe the relationship of the variables with mortality.(32)

A simple score, called shock index (SI) has also been proposed. The SI is calculated as the ratio of heart rate to systolic blood pressure. In some studies the SI has shown to have better discrimination than either systolic blood pressure or heart rate alone. Although this index has good specificity, its sensitivity is low. (33) Another limitation of this index is that it does not incorporate information from other important variables such as respiratory rate, capillary refill time or level of consciousness, as measured by the Glasgow Coma Scale.

Finally, there are other clinical aspects that have not been fully considered in the risk scores described above. It is plausible that some of the variables have different relationships with mortality in certain clinical subgroups. At least two subgroups should be considered when estimating the potential different prediction of the physiological variables, these are: type of injury (i.e. penetrating versus blunt), and presence of traumatic brain injury.

In blunt trauma there might be a different physiological response in blood pressure and heart rate in comparison with penetrating trauma due to greater nociceptive response.(34) In patients with traumatic brain injury, hypotension and GCS score have been shown to be strong predictors of poor outcome. (35, 36)

It is therefore plausible that risk prediction will differ according to the type of injury, or the presence of traumatic brain injury; therefore specific risk scores should be developed for these populations.

The CRASH-2 Trial

CRASH-2 is a large clinical trial evaluating the effect of tranexamic acid on mortality and the need for transfusion among trauma patients with significant haemorrhage.(37) The trial includes patients within eight hours of injury, collects clinical and demographic variables at entry (described below), shown to be predictors of poor outcome, and data on outcome at hospital discharge with a high follow-up rate (99%). Furthermore, approximately 30% of the recruited patients have a concomitant TBI, and patients with both types of injury (blunt or penetrating) are included. These data would allow us to explore the performance of a risk score in the relevant subgroup of patients. A total of 20,207 patients have been recruited in the CRASH-2 trial. The CRASH-2 cohort of patients represents a unique opportunity to develop a risk score (CRASH-2 score) for patients with traumatic bleeding. The large sample size will ensure precise predictions.

Trauma Audit & Research Network (TARN)

The CRASH-2 score will subsequently be validated in a large sample of trauma patients (12,358) included in TARN, which is the largest European trauma registry. TARN mainly includes patients from the UK. The evaluation of the CRASH-2 score on this sample will have practical implications for assessing its validity for NHS patients.

Research methods

This project will be divided into three phases

1. *Score development*: Development and internal validation of the CRASH-2 score using the CRASH-2 dataset

2. *Score validation*: External validation of the CRASH-2 score in the TARN database, recalibration and comparison with other trauma scores
3. *Score adaptation*: Adaptation of CRASH-2 score to pre-hospital setting, battlefield and A&E departments.

Phase 1: Score Development

Sample

The cohort of patients used to develop the model will be all patients recruited to the CRASH-2 trial. The sample includes 20,207 patients from 40 different countries. Patients eligible for inclusion in the trial are "adult trauma patients with ongoing significant haemorrhage, within 8 hours of injury."

Outcome

The primary outcome is death at 28 days. Patient outcome is recorded at either discharge, death in hospital or 28 days after injury, whichever occurred first. (Appendix A of the protocol) Information on the date of death is collected and will be used to create a binary outcome: dead or alive.

The secondary outcome will be death or severe disability at 28 days. In patients who survived, dependency status at 28 days or prior to discharge is recorded on the outcome form using the Modified Oxford Handicap Scale.(38) This consists of five categories: no symptoms, minor symptoms, some restriction in lifestyle but independent, dependent but not requiring constant attention, and fully dependent requiring attention day and night. (Appendix A of the protocol) This scale has been shown to be predictive of poor outcome as measured with the Glasgow Outcome Scale in traumatic brain injury patients.(39)

A binary variable will be created combining information on survival and dependency at 28 days post injury, where outcome will be either favourable (alive with no symptoms, minor symptoms or independent with some restriction in lifestyle) or unfavourable (dead or alive but dependent).

Predictors

Variables analysed as potential predictors will be taken from the patient entry form completed prior to randomisation. (Appendix B of the protocol) Variables included in the CRASH-2 trial entry form can be divided into

1. Patient demographic characteristics: age and gender
2. Injury characteristics: type of injury, traumatic brain injury, and time from injury to randomization
3. Physiological variables: Glasgow Coma Scale score, systolic blood pressure, heart rate, respiratory rate, and central capillary refill time

Variable definitions:

- Age is recorded as a continuous variable measured in years
- Type of injury is recorded as a categorical variable with 3 categories – blunt injury, penetrating injury, or blunt and penetrating injury
- Traumatic brain injury is recorded a binary variable, presence or absence of significant traumatic brain injury as defined by the clinical criteria of the CRASH-2 collaborator (This variable is recorded in the outcome form.)
- Time since injury is recorded as a continuous variable measured in hours
- The five physiological variables are recorded on the patient entry form according to usual clinical definitions. For each of these variables the value given on the entry form is the first measurement available taken after injury.
  - Glasgow Coma Scale is measured as a categorical variable (3 to 15)
  - Systolic blood pressure is measured in millimetres of mercury
  - Heart rate is measured in beats per minute
  - Respiratory rate is measured in breaths per minute

    ◦   Central capillary refill time is measured in seconds

Because central capillary refill time is not universally measured in clinical practice, further guidance on how to measure it was provided. Collaborators were advised to *"Apply firm pressure with your fingertips to the selected area, e.g. chest for about 5 seconds. Timing starts on release of pressure and is counted in seconds. Timing stops when the blanched area of the skin returns to its normal colour. If skin is dark or there is injury to the chest, CRT can be measured by applying pressure to another area such as the base of the thumb, nail bed or gums"*.

Trial treatment (placebo or tranexamic acid) will be included as a separate predictor. Following the Board recommendation we will consider that respiratory rate might not be practical to consider as it is often not recorded in practice.

Why CRASH-2 data are appropriate for the development of a risk score

The characteristics of the CRASH-2 trial, a large pragmatic and simple trial, have many advantages for developing a risk score. It is a prospective cohort of patients with almost no missing data and high follow-up. The inclusion criteria are broad, there are not specific exclusion criteria and there are not additional tests required, so although it is a clinical trial it includes "real life" patients. Furthermore, the physiological variables are defined as usual practice so the definitions are fit for purpose; this means that the risk score will be used by physicians who will measure these variables in the usual way in the context of the emergency setting. A rigid and standard definition of variables (e.g. two readings of blood pressure with an automatic device) will not be practical to use in this context. Using data from the CRASH-1 trial, which has a similar design to the CRASH-2 trial, we have already shown that variables recorded in this way are useful for developing a risk score.(36) Finally, all the variables are measured at a similar time point: first measurement available after the injury. The outcomes are also measured at a pre-specified time.

Because of the characteristics of the CRASH-2 trial there is almost no missing data among the potential predictors. Age, type of injury, time since injury and Glasgow Coma Scale score are all mandatory variables and a patient cannot be included in the trial if any of these variables is not available in the entry form. The other physiological variables, except capillary refill time, are routinely measures in clinical practice. Furthermore, the practical design of the CRASH-2 trial and the minimum requirement of data will ensure very few missing data on these variables.

Analysis

Continuous variables

Continuous variables will be initially kept as continuous. This is to avoid loss of information and bias introduced by choosing cut points to group variables.(40) Continuous variables will be re-coded as categorical variables and plotted against log odds of each outcome variable to assess the relationship between variables and outcomes. Linearity and departure from linearity will be assessed by adding quadratic terms and cubic terms into the model and carrying out likelihood ratio tests. We will also explore more complex relationships using spline functions and fraction polynomial analysis.(41)

Correlation

In a multivariate prognostic model, variables which are highly correlated with each other provide little independent information. Several predictor variables, such as systolic blood pressure and heart rate, are likely to be correlated. The correlation between these variables will be assessed by drawing scatter plots of the relationship between each variable and calculating the correlation coefficient. If the correlation coefficient is less than 0.8, both variables will be included in the model.(41) If for any pair of variables it is greater than 0.8, a decision based on clinical importance will be made about which variable to keep as a predictor.

Interaction

Interactions will be considered between all the predictors and:

- Traumatic brain injury
- Type of injury

These two interactions will be considered because, a priori, it is possible that the effect of predictors of mortality may vary depending on the presence of traumatic brain injury and type of injury. Interactions will be assessed by likelihood ratio tests. If there is strong evidence of interaction between these variables and any of the predictors, additional models will be developed separately for the corresponding subgroup of patients.

Multivariable analysis

The variables considered for the risk score have been previously associated with prognosis in trauma patients, so all of them will be included in the multivariable logistic regression analysis. Analyses will be adjusted for trial treatment. We will include all the variables irrespective of their statistically significance, because selection of predictors according to their statistical significance has been shown to introduce selection bias and results in overfitting of models.(41) We will use random effect logistic regression models to take into account the variability among the different settings (hospitals). Random effect logistic regression model estimates random intercepts and coefficients. This implicitly assumes that the intercepts and estimates vary by centre and follow a normal distribution. With this approach we will establish the heterogeneity between settings, and this heterogeneity estimate will be used to update the model to the TARN setting.

Performance

Performance of the CRASH-2 score will be assessed in terms of calibration and discrimination. Discrimination will be assessed using the c statistic (an equivalent concept to area under the receiver operator characteristic curve). Calibration will be assessed graphically (plotting the observed versus expected probabilities of the outcomes by deciles of risk) and with the Hosmer-Lemeshow test.(42) We will also estimate the performance for each of the individual physiological variables, and their different combinations.

Internal validation and shrinkage of estimates

Internal validity of the final model will be assessed by using bootstrap re-sampling technique. Regression models will be estimated in 100 models. For each of the 100 bootstrap samples the model will be refitted and tested on the original sample to obtain an estimate of predictive accuracy corrected for overfitting. If there is evidence of overoptismism for the performance of the CRASH-2 score we will shrink the coefficients with bootstrapping methods.

Phase 2: Score Validation

Sample

For the external validation we will use the data from the Trauma Audit & Research Network (TARN). TARN was established in 1989 to benchmark and improve hospital trauma care (using case fatality measures). Membership is voluntary and includes 60% of hospitals receiving trauma patients in England and Wales and some hospitals in European centres. Data are collected on patients who arrive at hospital alive and meet any of the subsequent criteria:

- death from injury at any point during admission
- stay in hospital for longer than 3 days
- require intensive or high dependency care
- require inter-hospital transfer for specialist care.

Patients with isolated closed limb injuries are excluded, as are patients over 65 years old with isolated fractured neck of femur or pubic ramus fracture. All other isolated closed femoral injuries are included. Every TARN patient has each single injury described in terms of the abbreviated injury scale (AIS) dictionary where a descriptor and its corresponding numerical code is allocated. Hospitals submit data electronically to TARN via a secure website, data is held on the University of Manchester server. The physiological data available on TARN is identical to that on CRASH in that for every patient the HR, SBP, GCS score, RR and capillary refill on arrival is entered by the hospital data co-ordinators.

For each patient the volume of blood loss is estimated. This is done by allocating an estimated percentage of total volume of blood lost to each injury code in the AIS dictionary by blinded, then consensus, agreement from two emergency physicians. This estimation is based on previous work on blood loss in specific injuries.(43)

Adult (age >15 yrs at the time of injury) patients presenting between 2000 and 2008 to TARN participating hospitals will be selected if they had an estimated blood loss of at least 20%. A total of 12,358 patients fulfilling these criteria will be included in the validation. We will use this definition because the CRASH-2 definition is not available for the TARN dataset. We estimate that patients with blood loss of 20% or more would be comparable with the CRASH-2 patients. We will only include patients recruited from year 2000 onwards because trauma care in the UK has changed in terms of outcome significantly since then. (Fiona Lecky personal communication)

Outcome

We will validate the CRASH-2 score for in-hospital mortality at 28 days as this is the only outcome considered in this proposal for which TARN has data. TARN hospital patients are followed up for 93 days post admission or until the time the patient leaves hospital alive, whichever is first.

Predictors

TARN patients have data in all the predictors considered in the CRASH-2 score. Data are collated by trained staff in participating hospitals and submitted via the TARN Electronic Data Collection and Reporting (EDCR) system (ref www.tarn.ac.uk). Each submission is checked for consistency and accuracy by trained coders at the University of Manchester. The methods of measuring and recording the data within TARN are identical to those within CRASH 2 in that they reflect real measurements made by the clinical staff caring for patients on arrival in the Emergency Department.

Analysis

External validation

For the external validation process, we will apply the mean estimates from the random logistic regression model (obtained in the development phase with the CRASH-2 patients) to the validation sample (TARN dataset patients). If there are missing data in any of the predictors we will use multiple imputation to substitute the missing values.(41) We will estimate the performance (discrimination and calibration) in the new dataset.

Recalibration

If there is any evidence of poor performance in the validation set we will conduct an updating of the CRASH-2 score to improve the performance for the new setting. For this we will conduct a Bayesian updating approach.(41) For this analysis we need to know the estimate from the derivation sample (e_{ds}), the estimate from the validation sample (e_{vs}), the variance of the estimate in the validation sample (v_{vs}) and the variance between the different samples (v_{bs}). This latter estimate will be obtained with the random effect logistic regression model in phase 1. We will obtain the updated estimates ($\mathbf{e_u}$) with the following empirical Bayes formula.(41)

$$\mathbf{e_u} = e_{ds} + v_{bs}/(v_{bs} + v_{vs}) * (e_{vs} - e_{ds})$$

With this approach we will be able to obtain updated estimates for the new setting.

Comparison with other scores

We will compare the performance of the recalibrated CRASH-2 score with the Revised Trauma Score and with the Shock Index performance on the TARN data.

We will also estimate the performance for each of the individual physiological variables, and their different combinations. These results about the performance of individual predictors, their different combinations and the full model performance will inform the following phase of score adaptation in the different settings.

Phase 3: Score Adaptation

The previous two phases will ensure that we are following the necessary steps to obtain a valid risk score from a statistical perspective. But an important, and commonly neglected, aspect when developing a risk score is its clinical sensibility or acceptability.(44) The clinical acceptability of a risk score requires judgement, not statistical criteria, to select the predictors, and an adequate score presentation format for the specific setting where the score will be used. We identified three settings where CRASH-2 risk scores could be applied; the pre-hospital setting, the battlefield, and in A&E departments at hospital admission. Therefore, we will involve risk score users at these three levels: ambulance crew from the North West Ambulance Service, military personnel, and clinicians from A&E departments participating in TARN. We will work with these users to achieve two objectives: i) to identify the variables they consider important and practical for their respective setting, and ii) to obtain information on how to present the risk score in a practical way.

Selecting the variables appropriate for each setting

The first two phases will provide data about the performance of the full score, the individual predictors and different combinations of predictors. However the decision about which predictors should be included requires making a judgment about the trade off between the accuracy and practicality of the score. For example a score including Glasgow Coma Scale, respiratory rate, capillary refill time, and systolic blood pressure could be marginally more accurate than one excluding systolic blood pressure, but in the battlefield measurement of blood pressure might be complex and a risk score excluding that variable, at the expense of losing some accuracy, could be judged more convenient for that setting. On the other hand in the A&E department even if the increase of accuracy is marginal, clinicians could argue that a risk score for trauma patients and haemorrhage should always include systolic blood pressure.

Presentation of the risk score

A risk score allows the probability of the outcome for an individual patient to be estimated by combining the predictor values with the regression coefficients and obtaining the linear predictor for the model, which is then transformed to a predicted probability through the logistic transformation. However, even a valid risk score will not be used if the presentation to estimate the individual probability is inadequate or complicated. Methodological guidelines stress how important it is that prognostic models are easy and simple to use and well accepted by physicians.(45) Simplicity of presentation and ease of use is even more relevant in the context of the emergency situation when treating patients with trauma and bleeding. Risk score format presentation can be electronic or paper based. We have already developed an electronic calculator and a paper based risk score for patients with traumatic brain injury, using data from the CRASH-1 trial. The electronic calculator can be found at http://www.crash.lshtm.ac.uk.

We will conduct focus groups with all the relevant risk score users (ambulance crew, military personnel, and clinicians from A&E departments) at different stages of the study to inform us about their opinion regarding relevant predictors and to decide on the most suitable presentation for each setting.

For developing an appropriate presentation of the risk calculator we will work jointly with the *Winton programme for the public understanding of risk* based in the Statistical Laboratory in the University of

Cambridge. This programme aims to help improve the way that uncertainty and risk are presented, and they have experience in developing electronic risk calculators. (http://understandinguncertainty.org/) We contacted Professor David Spiegelhalter, leader of this programme, who confirmed his willingness to collaborate in this project.

Planned interventions (PR only)
NA

Planned inclusion/exclusion criteria
The CRASH-2 score will be developed using data from patients included in the CRASH-2 Trial. This trial recruits adult patients with trauma and significant haemorrhage.

Ethical arrangements
Ethics approval for this study and the use of the CRASH-2 trial data will be obtained from the London School of Hygiene and Tropical Medicine.

TARN already has ethical approval (PIAG section 60) for research on the anonymised data that is stored securely on the University of Manchester server.

Proposed sample size
We will include all the 20,207 patients recruited in the CRASH-2 Trial. It is recommended that for multivariable analyses there should be at least 10 events for each potential predictor evaluated.(46) The CRASH-2 trial has an overall mortality of approximately 15%. There were 3,076 events. As we are planning to consider 10 potential predictors, our study will have a ratio of 307 events for each predictor, so will have a very large sample for the multivariable analysis and therefore our estimates for predicting mortality will be very precise.

The validation will be conducted in the TARN database. We will include 12,358 adult trauma patients presenting after the year 2000 with an estimated blood loss of >20%.

Statistical analysis
The details of the statistical analysis have been included in the sections describing the phases of this study. In this section we explain why the statistical plan will minimize the potential poor fit.

There are two main causes of a poor fit of a risk score:

1. *Overfitting of the original score*: The possibility of overfitting will be low because i) We are using a large sample size with few predictors and high frequency of outcome; ii) We will follow a full model strategy for rmodel development which avoids selection bias of predictors; and iii) We will use bootstrapping to shrink the estimates if there is any evidence of overoptimism in the performance measures.
2. Differences between the derivation and validation sample (case mix and differences of the relationship between predictors and outcome): If there is any evidence of poor fit in the validation sample we will obtain updated estimates for this setting using a Bayesian approach.

Proposed outcome measures
We will develop risk scores for the most clinically relevant outcomes: in-hospital mortality and disability at discharge. The outcomes are defined as per the CRASH-2 trial protocol. No economic analysis is planned.

Research governance (for PR only)
The use of the CRASH-2 trial data for the development of the risk score has been approved by the Trial Management Group. Only fully anonymized data will be used.

The use of the TARN data has been agreed and approved by Fiona Lecky

This research will be monitored and supervised by the CRASH-2 Score Committee whose responsibility will be to monitor and supervise the progress of the project to ensure the milestones are achieved. Membership will consist of Pablo Perel (Chair), Haleema Shakur, Ian Roberts, Fiona Lecky, Tim Clayton and Ewout Steyerberg.

4. Project timetable and milestones

We propose to conduct this study in 12 months from the time the contract is signed: Month 1 (Preparation database and staff in post) Month 1 to 4 (Development and internal validation of risk scores) Month 5 to 7 (External validation and recalibration) Month 8 to 10 (Focus group with risk score users to develop practical and clinically acceptable risk scores) Month 11 to 12 (Preparation of final report) We will submit the final amended form taking into account the Board recommendation by May 24th. If the contract is signed in June 2010 we will be able to start in July 2010.

July 2010:	Study coordinator and statistician in post
	Start preparing databases
August 2010:	Start developing statistical program for CRASH-2 score development
September 2010:	CRASH-2 database ready for analysis
October 2010:	Complete CRASH-2 score development
	Complete internal validation
November 2010:	TARN database ready for analysis
December 2010:	Complete external validation
	Complete recalibration
February 2011:	Start evaluation of CRASH-2 scores by users
	Start electronic calculator development
April 2011:	Complete electronic and paper based presentation of CRASH-2 scores
June 2011:	Complete final report and paper for peer reviewed journal

5. Expertise

Pablo Perel is a clinical lecturer with expertise in clinical trials, prognosis research and emergency medicine. He has worked extensively on prognostic models in trauma. He led the project that developed and validated practical risk scores for traumatic brain injury.

Haleema Shakur is a senior lecturer in clinical trials with expertise in clinical trials and trial management. She has experience in research in emergency medicine and she is the trial manager of the CRASH-2 trial.

Ian Roberts is a professor of epidemiology with expertise in epidemiology, systematic reviews, clinical trials and emergency medicine. He is the principal investigator of the CRASH-2 Trial.

Fiona Lecky is a senior lecturer / honorary consultant in emergency medicine at the University of Manchester and Research Director of TARN. She has experience in trauma and has led the development of a prognostic model used to compare case fatality after major injury in NHS Trusts.

Tim Clayton is a senior lecturer in medical statistics. He has experience in statistical analysis of clinical trials and has been involved in the analysis of several risk scores in emergency medicine.

Ewout Steyerberg is professor of medical decision making. He has extensive experience in prognosis research in general and prognostic models in particular. He has recently published a book on this topic called "Clinical Prediction Models".

6. Service users

In the context of this project we considered as service users, the personnel who will potentially be using the CRASH-2 score. We have identified three types of potential service users: ambulance crew, military personnel, and medical staff from A&E departments; each of these groups will be involved in the focus groups described in phase 3 of this proposal.

Ambulance crew: Professor Kevin Mackway Jones, Medical Director for North West Ambulance Service NHS Trust, has confirmed the participation of ambulance crew from the North West Ambulance Service.

A&E doctors: Doctor Fiona Lecky, Research Director of TARN, has confirmed the participation of A&E departments'clinicians participating in TARN.

Military personnel: We have discussed this proposal with leading clinicians from the Defence Medical Services of the UK Ministry of Defence and they are keen to collaborate.

We will work with each of these groups to better understand their needs and to obtain feedback about how to tailor the risk score for their respective setting.

Brigitte Chaudry, President of the European Federation of the Victims of Road Traffic Crashes represents service users on the Trial Steering Committee of the CRASH-2 Trial. As this project involves a secondary analysis of the CRASH-2 trial, we will have input from the public through the participation of this patient organization. In addition, following the Board recommendation, we will ensure to have an active public participation conducting a series of focus groups meetings with relatives of road traffic crashes. In these meetings we will evaluate public's perspective of important outcomes to predict and preferences to present risk estimation. We have already contacted Amy-Aeron Thomas, who is Director of Road Peace (the UK charity providing support for victims of road traffic crashes) who has agreed to involve this organization in this research project. We will follow the "*Good practice in active public involvement in research*" published by INVOLVE.
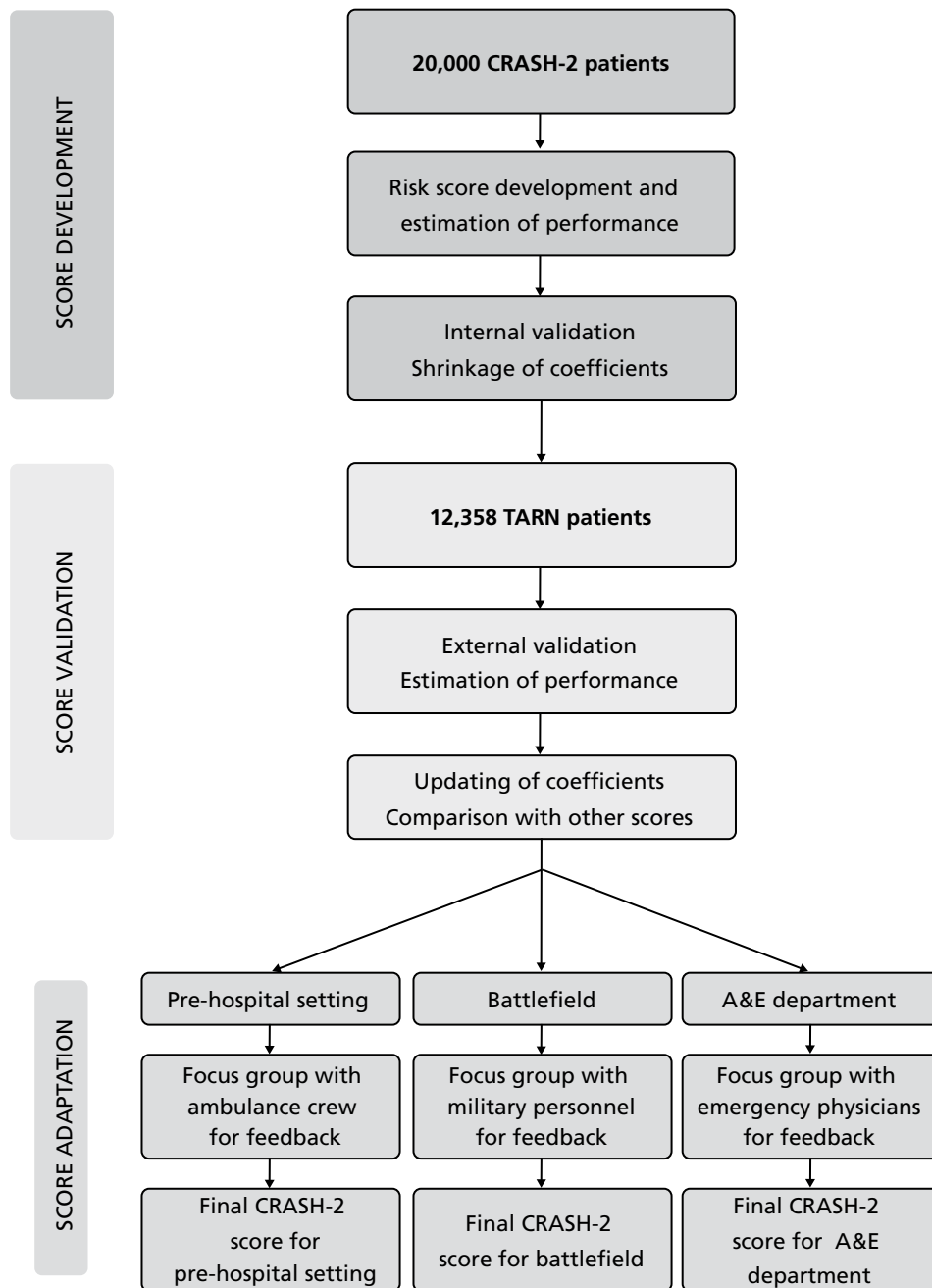
7. Justification of support required

LSHTM staff: A study coordinator (70%) is required to coordinate all the activities of the project to ensure a successful completion. A statistician (50%) is required to conduct the data cleaning and database development; he/she will also provide expertise in the statistical analysis of the study.

Other LSHTM costs: One new computer is needed plus the related departmental maintenance cost.

Other costs: Travel costs have been included to cover regular meetings in Manchester, Rotterdam, and for the welcome meeting in Southampton. It is anticipated that some focus group meetings will be held in London for a number of potential users of the score. TARN will provide the analysed patient data and the cost for obtaining this has been included as an FEC cost for University of Manchester. A consultancy fee will be paid to Ewout Steyerberg for his input as an expert in prognostic models. An electronic calculator will be provided by an external consultant. As suggested by the Board we will now ensure a more comprehensive participation of the public through focus group meetings. We included cost of the focus group meetings with the public.

8. Flow diagram (primary research only)

```
SCORE DEVELOPMENT

        ┌─────────────────────────────────┐
        │    20,000 CRASH-2 patients      │
        └─────────────────────────────────┘
                        │
                        ▼
        ┌─────────────────────────────────┐
        │   Risk score development and    │
        │    estimation of performance    │
        └─────────────────────────────────┘
                        │
                        ▼
        ┌─────────────────────────────────┐
        │      Internal validation        │
        │    Shrinkage of coefficients    │
        └─────────────────────────────────┘

SCORE VALIDATION

                        │
                        ▼
        ┌─────────────────────────────────┐
        │     12,358 TARN patients        │
        └─────────────────────────────────┘
                        │
                        ▼
        ┌─────────────────────────────────┐
        │      External validation        │
        │    Estimation of performance    │
        └─────────────────────────────────┘
                        │
                        ▼
        ┌─────────────────────────────────┐
        │    Updating of coefficients     │
        │   Comparison with other scores  │
        └─────────────────────────────────┘
```

SCORE ADAPTATION

Pre-hospital setting	Battlefield	A&E department
Focus group with ambulance crew for feedback	Focus group with military personnel for feedback	Focus group with emergency physicians for feedback
Final CRASH-2 score for pre-hospital setting	Final CRASH-2 score for battlefield	Final CRASH-2 score for A&E department

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Appendix A of the protocol: outcome form

CRASH2
Clinical Randomisation of an
Antifibrinolytic in Significant Haemorrhage

OUTCOME FORM

COMPLETE AT DISCHARGE FROM THE RANDOMISING HOSPITAL,
DEATH IN HOSPITAL OR 28 DAYS AFTER INJURY, WHICHEVER OCCURS FIRST

Attach
treatment
pack sticker
here

1. HOSPITAL   *(Hospital name or code)*

2. PATIENT

Patient Initials		Hospital ID Number		Sex	M	F
Date of Birth	YEAR / MONTH / DAY					

3. OUTCOME

3.1 DEATH IN HOSPITAL

Date of death YEAR / MONTH / DAY

Cause of death
☐ Bleeding
☐ Head injury
☐ Myocardial Infarction
☐ Stroke
☐ Pulmonary Embolism
☐ Multi organ failure
☐ Other – describe

3.2 PATIENT ALIVE

☐ **Discharged** – Date of discharge YEAR / MONTH / DAY

☐ **Still in this hospital now** *(28 days after injury)* – Date YEAR / MONTH / DAY

3.3 IF ALIVE TICK ONE BOX THAT BEST DESCRIBES THE PATIENT'S CONDITION *(at 28 days or prior discharge)*

☐ No symptoms
☐ Minor symptoms
☐ Some restriction in lifestyle but independent
☐ Dependent, but not requiring constant attention
☐ Fully dependent, requiring attention day and night

4. MANAGEMENT

a) **Days in Intensive Care Unit** *(if not admitted to ICU, write '0' here)*		
b) **Significant Head Injury**	YES	NO
c) **Operation site** - *Tick one box on every line*		
• Neurosurgical	YES	NO
• Chest	YES	NO
• Abdomen	YES	NO
• Pelvis	YES	NO

5. COMPLICATIONS

Tick one box on every line

• Pulmonary Embolism	YES	NO
• Deep Vein Thrombosis	YES	NO
• Stroke	YES	NO
• Operation for bleeding	YES	NO
• Myocardial Infarction	YES	NO
• Gastrointestinal bleeding	YES	NO

6. TRIAL TREATMENT

a) Complete **loading dose** given	YES	NO
b) Complete **maintenance dose** given	YES	NO

7. TRANSFUSION

a) Blood products transfusion	YES	NO
b) Units transfused in 28 days		
• Red cell products		units
• Fresh frozen plasma		units
• Platelets		units
• Cryoprecipitate		units
• Recombinant Factor VIIa	YES	NO

8. PERSON COMPLETING FORM

NAME	
POSITION	
DATE	

NOW SEND THIS FORM TO THE CO-ORDINATING CENTRE IN ONE OF THE FOLLOWING WAYS:
• SECURE WEBSITE
• ELECTRONIC DATA FORMS / EMAIL
• FAX +44 (0)20 7299 4663
SEE INSTRUCTIONS IN YOUR SITE FILE

ISRCTN86750102

Appendix B of the protocol: patient entry form

CRASH2 PATIENT ENTRY INTERNATIONAL

ALL QUESTIONS BELOW NEED TO BE ANSWERED BEFORE CALLING THE RANDOMISATION SERVICE

INFORMATION ABOUT YOUR HOSPITAL

1. Country	
2. Name of hospital (or your hospital code)	
3. Name of caller	

INFORMATION ABOUT THE PATIENT

4. Patient sex (please circle)	Male	Female	**5.** Patient initials	
6. Patient hospital identification number				
7. Do you know patient's date of birth?				
a. **YES** – date of birth YEAR MONTH DAY			b. **NO** – approximate age	

INFORMATION ABOUT THE INJURY

8. Estimated number of hours since injury	hours	
9. Type of injury (please circle) 1 Blunt 2 Penetrating 3 Both		

FIRST MEASUREMENT IN HOSPITAL OF THE FOLLOWING (IF UNKNOWN GIVE VALUE AT RANDOMISATION)

10. Systolic BP (mmHg)		**11.** Respiratory rate (per min)	
12. Central capillary refill time (sec)		**13.** Heart rate (per min)	

		EYE OPENING	**MOTOR RESPONSE**	**VERBAL RESPONSE**
14. Glasgow Coma Score (max 15)		4 Spontaneous 3 To sound 2 To pain 1 None	6 Obeys commands 5 Localising 4 Normal flexion 3 Abnormal flexion 2 Extending 1 None	5 Orientated 4 Confused speech 3 Words 2 Sounds 1 None

Now call **Randomisation Service** with these answers and write down the treatment pack number given at the end of the phone call

Box ☐☐☐☐ **Pack** ☐☐

Get this pack and follow the instructions on it carefully

Or paper randomise as per instructions in site file

EME
HS&DR
HTA
PGfAR
PHR

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