

# 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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## Executive summary

Prediction of death in patients with traumatic bleeding and effect of TXA on mortality

Health Technology Assessment 2013; Vol. 17: No. 24

DOI: 10.3310/hta17240

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# 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](http://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

Funding for this study was provided by the Health Technology Assessment programme for the National Institute for Health Research.

## Publication

Perel P, Prieto-Merino D, Shakur H, Roberts I. Development and validation of a prognostic model to predict death in patients with traumatic bleeding, and evaluation of the effect of tranexamic acid on mortality according to baseline risk: a secondary analysis of a randomised controlled trial. *Health Technol Assess* 2013;**17**(24).

# Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Five-year impact factor: 5.596

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## This report

The research reported in this issue of the journal was funded by the HTA programme as project number 09/22/165. The contractual start date was in October 2010. The draft report began editorial review in July 2012 and was accepted for publication in November 2012. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

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