Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Tranexamic Acid for the Management of Bleeding: A Review of the Clinical Effectiveness and Guidelines

DATE: 24 June 2013

CONTEXT AND POLICY ISSUES

Bleeding or hemorrhage indicates a blood loss from the circulatory system which can occur internally or externally, through either natural orifices (e.g. nose) or organic lesions.[1] Hemorrhages are typically classified in four classes outlined in Table 1.

Table 1: Classes of Bleeding adapted from Lippi et al. 2013[1]

Class of Bleeding	Characteristics
Class I	Non-shock, mostly asymptomatic condition characterized by a blood loss lower than 15% of total blood volume (e.g. a loss of 0.75L out of 5L for a 70 kg person)
Class II	Blood loss of between 15 to 30% of total blood volume (e.g. between 0.75 and 1.5 L), anxious state with modestly decreased blood pressure and increased pulse rate of between 100 and 120 (bpm)
Class III	Blood loss of between 30 to 40% of total blood volume (e.g. between 1.5 to 2.0L), confused state, significantly decreased blood pressure, and increased pulse rate (between 120 and 140 bpm)
Class IV	Pre-death event, blood losses greater than 40% of the total blood volume (i.e. >2.0 L), lethargic state, dramatically increased pulse rate (>140 bpm) and important hypotension along with very low to absent urine output

bpm= beats per minute

In Canada, trauma or injury is a leading cause of death for patients between 1 to 44 years of age and the fourth leading cause of death for Canadians of all ages.[2] In addition, in 2003, injuries were the second leading cause of potential life years lost (after cancer) before the age of 70.[3]

The relationship between posttraumatic bleeding and poor clinical outcomes has been widely acknowledged for several decades.[1] Massive bleeding is the second leading cause of trauma-related mortality (after head injury) in patients with severe trauma, accounting for 30 to 40% of deaths[1,4]. Furthermore, the majority of these deaths occur during the first 48 hours.[1]

Tranexamic acid (TXA) is a compound which some experts have suggested may be an important treatment for the treatment of bleeding caused by trauma.[2] However, it is unclear the degree it is being utilized in this setting in Canada, as the drug is not indicated for trauma-related bleeding.[5] The drug is indicated for hereditary angioneurotic oedema and "increased local fibronylysis when the diagnosis is indicative of hyperfibrnolysis, as with conization of the cervix, dental extraction in patients with coagulopathies (in conjunction with antihaemophilic factor) epistaxis, hyphaema, and menorrhagia (hypermennorrhea)".[5] As a result, the purpose of this report is to examine the clinical-effectiveness and evidence-based guidelines for tranexamic acid for the treatment of trauma patients with bleeding.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of tranexamic acid for the management of bleeding in patients who have experienced traumatic injuries?

2. What are the evidence-based guidelines regarding the use of tranexamic acid for the management of bleeding in patients who have experienced traumatic injuries?

KEY FINDINGS

Overall, there is evidence to suggest treatment with tranexamic acid reduces mortality from trauma related bleeding. In addition, subgroup analysis suggests treatment with 3 hours of trauma is associated with decreased mortality. However, treatment beyond three hours of trauma may be associated with an increased risk of death.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and May 27, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for final article selection (see Table 2).

Table 2: Selection Criteria

Population	patients with bleeding following trauma (pre-hospital and in-hospital)
Intervention	tranexamic acid (IV or oral)
Comparator	none, other antifibrolytic drugs
Outcomes	clinical effectiveness, evidence-based guidelines
Study Designs	Health Technology Assessments, Systematic Reviews, Meta-Analyses, Randomized Controlled-Trials, and Evidence-Based Guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in a selected systematic review or health technology assessment, or were published prior to 2008. Narrative reviews, editorials, case series or case studies, and guidelines with unclear or incomplete methods were also excluded.

Critical Appraisal of Individual Studies

The included randomized controlled trial (RCTs), reported in an HTA, and pre-specified subgroup analysis were critically appraised using the Downs and Black Checklist.[6] A numeric score for each study was not calculated, instead a narrative summary of study strengths and limitations was provided.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 165 citations. From these, 23 articles were selected for further examination. Three additional guidelines were identified from grey literature searching. Of the 26 articles, one RCT reported in a health technology assessment and one pre-specified subgroup analysis met the inclusion criteria upon full text review. No relevant systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies were identified. The study selection process is outlined in a PRISMA flowchart (Appendix 1). However, it should be noted that six reports were excluded because they included data on the CRASH-2 trial already reflected in the included HTA. Additional references of potential interest that did not meet inclusion criteria are provided in the Appendix 2.

Summary of Study Characteristics

A summary of individual study characteristics is presented in Appendix 3

Study Design

Two articles discussing a single RCT are included in the review. No evidence-based guidelines were identified for inclusion in the review. One report[7] is a health technology assessment of the

CRASH-2 [Clinical Randomisation of an Antifibrolytic in Significant Haemorrhage-2] RCT and one report is a pre-specified stratified subgroup analysis of data of the same RCT.[8] Patients were included if the responsible doctor was substantially uncertain about whether or not to treat with TXA. Patients in whom the responsible doctor considered that there was a clear indication for TXA were not randomly assigned. Similarly, patients in whom there was considered to be a clear contraindication to TXA treatment were not randomly assigned. However, for patients where the choice of treatment with TXA was uncertain, they were considered eligible for randomization.

The pre-specified stratified subgroup analysis was based on the CRASH-2 trial subgroup of patients whose treatment was initiated no more than 3 hours after injury. The patients were divided into four strata for risk of mortality (<6%, 6% to 20%, 21% to 50%, > 50%). The strata were chosen based on a previously developed simple risk chart to classify patients into these risk categories developed using the full population of the CRASH-2 trial (n= 20127) and validated using patients from the Trauma Audit and Research Network (n= 14220).[8,9]

Country of Origin

The included RCT was conducted in 40 countries around the world including Canada.[10]

Population

Patients in the included RCT were required to be adult trauma patients with significant hemorrhage (systolic BP < 90 mm Hg, > 110 BPM or both) or who were considered to be at significant risk of hemorrhage within 8 hours of injury.

Intervention and Comparators

Tranexamic acid was administered as a treatment in the included trial (loading dose 1 g over 10 minutes then infusing of 1 g over 8 hours).The comparator was a matched placebo (0.9% saline solution).

Outcomes

The primary outcome of the CRASH-2 trial was mortality within 28 days of injury. The pre-specified stratified subgroup analysis had outcomes that included all-cause mortality within 28 days of injury, mortality due to bleeding at 28 days, fatal and non-fatal thrombotic events. Additional outcomes reported in HTA of the included RCT were mortality due to bleeding within four weeks, and dependence at hospital discharge or day 28 using a modified version of the Oxford Handicap Scale. The scale was dichotomized into dead, dependent (fully dependent requiring attention day and night or dependent but not needing constant attention) or independent (some restriction in lifestyle but independent, minor symptoms or no symptoms).

Summary of Critical Appraisal

A detailed summary of the critical appraisal of the individual included reports can be found in Appendix 4. Overall, the HTA and pre-specified stratified subgroup analysis of the CRASH-2 trial were well designed. Strengths of the HTA of the CRASH-2 trial included the large sample size (n=20127), indistinguishable TXA and placebo, random allocation and allocation concealment with explicit description of methods for both, a clearly stated objective and

hypothesis, and a justification for the dose selected. Limitations of the HTA include the lack of information provided on patients lost to follow-up; the inclusion of only one RCT in the HTA; lack of a search of the literature to determine if additional studies on TXA for trauma related bleeding were available; the study was not powered to detect a difference between TXA and placebo for subgroups so results from these analyses are uncertain; and it is unclear if patients were balanced at baseline for injury severity a factor that may have influenced clinical outcomes.

A pre-specified subgroup analysis of CRASH-2 patients treated within three hours of injury was included. Strengths of this analysis include the large sample size, clearly stated objectives, justification was provided for the strata used for the analysis. Limitations of the prespecified subgroup analysis of CRASH-2 include the lack of clarity around AEs from the intervention, and lack of reporting of characteristics for patients lost to follow-up.

Summary of Findings

The results of the HTA of the CRASH-2 trial and the prespecified subgroup analysis of the CRASH-2 trial are reported in Appendix 5.

The HTA of the CRASH-2 trial[7] reported treatment with TXA compared to placebo statistically significantly reduced all-cause mortality [relative risk (RR)=0.91; 95% confidence interval (CI): 0.85 to 0.97, P = 0.0035]. The risk of death due to bleeding was statistically significantly reduced when TXA was compared to placebo (RR=0.85; 95% CI 0.76 to 0.96, P = 0.0077). In addition, treatment within one hour of injury was associated with a statistically significant reduction in the risk of death due to bleeding compared to placebo (RR=0.68; 95% CI 0.57 to 0.82; P < 0.0001). Treatment given between one and three hours of injury also reduced the risk of death due to bleeding compared to placebo (RR= 0.79; 95% 0.64 to 0.97; P = 0.03). In addition, treatment with TXA greater than three hours after injury was associated with an increased risk of bleeding death compared to placebo. (RR=1.44; 95% CI 1.12 to 1.84; P<0.00). Results on dependence reported a statistically significantly increased number of patients of having no symptoms (RR=1.09; 95% 1.02 to 1.17); and a decreased risk of death for the comparisons of TXA to placebo (RR=0.91; 0.85 to 0.97). There were no statistically significant difference for TXA compared to placebo on minor symptoms (RR=0.98; 95% 0.94 to 1.02); and for full dependence (RR=0.96; 95% CI 0.91 to 1.01).

The pre-specified stratified subgroup analysis of CRASH-2 of all patients treated within three hours of injury reported numerous findings.[8] Only study results as they pertain to the research questions are reported here. Tranexamic acid, when compared to placebo, was associated with statistically significantly lower odds of patients experiencing any fatal and/or non-fatal thrombotic events [odds ratio (OR)=0.69; 95% CI 0.53 to 0.89]. When examining individual fatal and non-fatal thrombotic events, TXA appeared to have the largest decrease in the odds of myocardial infarction compared to placebo (OR= 0.49; 95% CI: 0.30 to 0.81). For patients receiving treatment with TXA within three hours of injury, there was a significantly reduced odds of all-cause mortality compared to placebo (OR= 0.85; 95% CI 0.78 to 0.93). For patients treated within three hours of injury a comparison of TXA to placebo was associated with a statistically significant reduction in odds of death from bleeding (OR= 0.71; 95% 0.61 to 0.82).

Limitations

There were few limitations to the included HTA of CRASH-2 and the pre-specified subgroup analysis of the trial. Both publications included subgroup analyses when the original trial was not powered to detect differences between subgroups. In addition, no information was provided for the TXA or placebo arms related to injury severity. It is possible that injury severity may have had an impact on mortality; however, it is unclear why this was not considered as a stratification factor in the study design.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There is limited evidence regarding the use of tranexamic acid for the treatment of patients bleeding following trauma. The available evidence suggests tranexamic acid may be a viable option to treat trauma related bleeding as it may lead to reductions in all-cause mortality or death due to bleeding. The findings based on the CRASH-2 trial are similar to those of the MATTERs (Military application of Tranexamic Acid in Trauma Emergency Resuscitation) Study[11] that suggest treatment with TXA in combination with blood transfusions was associated with a statistically significantly reduction in mortality when compared to blood transfusions alone. One study suggested the initiation of treatment within three hours may reduce the risk of all-cause mortality or mortality due to bleeding. However, there is some evidence to suggest treatment beyond three hours may increase the risk of mortality both all-cause and due to bleeding. The findings related to timing must be considered cautiously because they are based on subgroup analysis. More studies are needed to determine how timing may impact the treatment of trauma related bleeding with TXA. In addition, there is some evidence to suggest TXA may reduce the risk of thrombotic events (fatal and non-fatal). Overall, the included study suggests there may be some clinical benefit to treating patients with bleeding due to trauma with TXA.

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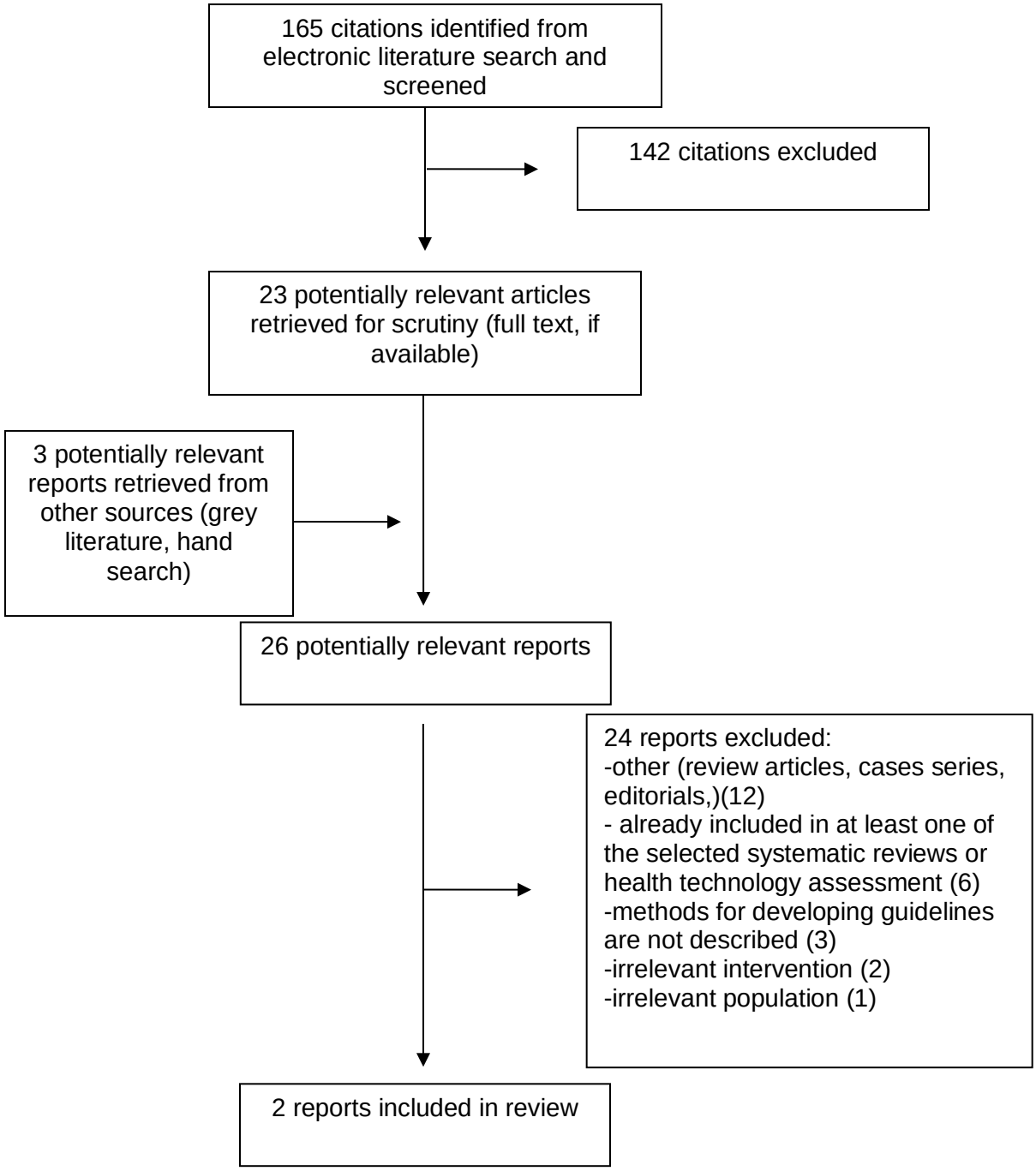
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional References of Potential Interest

Irrelevant Intervention (combination treatment)

1. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. Arch Surg. 2012 Feb;147(2):113-9.

Methods for Guideline Development Unclear/

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Appendix 3: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Roberts et al. (2013)[7] United Kingdom	HTA of RCT 4 weeks	Adults trauma patients with significant hemorrhage (systolic BP < 90 mm Hg, > 110 BPM or both) or who were considered to be at significant risk of hemorrhage within 8 hours of injury	TXA (loading dose 1 g over 10 minutes then infusing of 1g over 8 hours)	Matched placebo (0.9% saline)	All-cause mortality at 28 days, mortality due to bleeding, dependency at hospital discharge or day 28 (Modified Oxford Handicap Scale)
Roberts et al. (2012)[8] United Kingdom	RCT, prespecified stratified analysis 4 weeks	Subgroup of patients from the CRASH-2 Trial who were initiated on treatment within three hours of injury divided into four strata based on risk of death (<6%, 6 to 20%, 21 to 50%, > 50%)	TXA (loading dose 1 g over 10 minutes then infusing of 1g over 8 hours)	Matched placebo (0.9% saline)	All-cause mortality, mortality from bleeding, and thrombotic events

BP=blood pressure; **BPM=**beats per minute**; CRASH=** Clinical Randomisation of an Antifibrolytic in Significant Hemorrhage ;**HTA**= Health Technology Assessment; **RCT**= Randomized Controlled Trials; **TXA**= Tranexamic Acid;

Appendix 4: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Roberts et al. (2013)[7]	• Large sample size (n=20127) • Allocation concealed appropriately • Clearly stated objective and hypothesis • Justification for dose selected provided	• No information was provided on patients lost to follow-up • No justification was provided for the categorization selected for subgroup analyses • Some evidence to suggest an effect for the subgroups based on time (<3 hours), however study not powered to detect this effect so some evidence to suggest but it remains uncertain • Patients were not stratified based on injury severity at baseline and it was not reported as a baseline characteristics. As a result, there is some uncertainty whether treatment arms were balanced for this factor
Roberts et al. (2013)[8] United Kingdom	• The model was derived from the control group • Large sample size (n=13273) • Clearly state objectives • Prognostic model was validated in a separate administrative dataset	• Subgroup analysis results need to be interpreted with caution because trials were not powered to detect a difference in the prespecified sub population • Prognostic model was based solely on the CRASH-2 trial. A preferred approach may have been identifying this subgroups based on a meta-analysis of previous trials • Establishing cause of death in trauma is a difficult task and there is the possibility that some causes of death classifications may be inaccurate for individual patients • Baseline characteristics of the subgroup of patients were not reported in the context of the overall trial population to determine if they were similar. It is possible that the patients in this subgroup differ for on outcomes, which could affect the study results.
CRASH= Clinical Randomisation of an Antifibrolytic in Significant Hemorrhage		

Appendix 5: Summary of Findings

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Roberts et al. (2013)[7]	• The risk of all-cause mortality was statistically significantly reduced with TXA compared to placebo (RR= 0.91; 95% CI 0.85 to 0.97; P = 0.003) • The risk of death due to bleeding was statistically significantly reduced with TXA compared to placebo (RR=0.85; 95% CI 0.76 to 0.96;P = 0.007) • Early treatment (≤1 hour from injury) statistically significantly reduced the risk of death due to bleeding for treatment with TXA versus placebo (RR=0.68; 95% CI 0.57 to 0.82; P < 0.001). Treatment given between 1 and 3 hours also reduced the risk of death due to bleeding (RR= 0.79; 95% 0.64 to 0.97; P = 0.030) • Treatment with TXA greater than three hours after injury was associated with a statistically significantly increased risk of bleeding death compared to placebo. (RR=1.44; 95% CI 1.12 to 1.84) Dependency • There was a statistically significantly increased chance of having no symptoms for TXA compared to placebo (RR=1.09; 95% 1.02 to 1.17) • There was no statistically significant difference in minor symptoms for TXA compared to placebo (RR=0.98; 95% 0.94 to 1.02) • There was no statistically significant difference in having some restriction for TXA compared to placebo (RR=0.96; 95% CI 0.91 to 1.01) • There was no statistically difference in the risk of dependence (not requiring constant attention) for TXA compared to placebo (RR=1.00; 95% CI 0.93 to 1.07) • There was no statistically significant of full dependence for TXA compared to placebo (RR= 1.01; 95% 0.92 to 1.12) • There was a statistically significantly decreased risk of death for TXA when compared to placebo (RR=0.91; 0.85 to 0.97)	"Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study. TA appears most effective when given early after the trauma and should be given only within approximately 3 hours. Treatment beyond 3 hours of injury is unlikely to be effective." (p. xii)
Roberts et al. (2013)[8] United Kingdom	• The odds of fatal and non-fatal thrombotic events were statistically significantly reduced with TXA versus placebo (OR=0.69; 95% CI 0.53 to 0.89) • The odds of any arterial event were statistically significantly reduced with TXA compared to placebo (OR= 0.58, 95% CI 0.40 to 0.83) • The odds of MI were statistically significantly reduced with TXA compared to placebo (OR=0.49; 95%CI 0.30 to 0.81) • The was no statistically significant difference for the odds of stroke for TXA compared to placebo (OR= 0.69; 95% CI 0.43 to 1.11)	"Tranexamic acid can be administered safely to a wide spectrum of patients with traumatic bleeding and should not be restricted to the most severely injured." (p.1)

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	• There was no statistically significant difference for the odds of venous event for TXA compared to placebo (OR=0.83; 95% CI 0.43 to 1.11) • There was no statistically significant difference for the odds of pulmonary embolism for TXA compared to placebo (OR=0.88; 95% CI 0.58 to 1.33) • There was no statistically significant difference for the odds of deep vein thrombosis for TXA compared to placebo (OR=0.88; 95% CI 0.52 to 1.50) • For patients receiving treatment with TXA compared to placebo within three hours of injury, there was a significantly reduced odds of all-cause mortality (OR= 0.85; 95% CI 0.78 to 0.93). • For patients treated within three hours of injury a comparison of TXA to placebo was associated with a statistically significant reduction in odds of death from bleeding (OR= 0.71; 95% 0.61 to 0.82).	
CI= Confidence Interval; **OR**= odds ratio; **RR**= relative risk; **TXA**= Tranexamic Acid;		