

# Antifibrinolytic drugs for acute traumatic injury (Review)

Roberts I, Shakur H, Ker K, Coats T, on behalf of the CRASH-2 Trial collaborators



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[Intervention Review]

## Antifibrinolytic drugs for acute traumatic injury

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### ABSTRACT

#### Background

Uncontrolled bleeding is an important cause of death in trauma victims. Antifibrinolytic treatment has been shown to reduce blood loss following surgery and may also be effective in reducing blood loss following trauma.

#### Objectives

To quantify the effect of antifibrinolytic drugs in reducing blood loss, transfusion requirement and mortality after acute traumatic injury.

#### Search strategy

We searched the Cochrane Injuries Group's Specialised Register, CENTRAL, MEDLINE, PubMed, EMBASE, Science Citation Index, National Research Register, Zetoc, SIGLE, Global Health, LILACS, and Current Controlled Trials. The Cochrane Injuries Group Specialised Register, CENTRAL, MEDLINE and EMBASE searches were updated in July 2010.

#### Selection criteria

We included all randomised controlled trials of antifibrinolytic agents (aprotinin, tranexamic acid [TXA] and epsilon-aminocaproic acid) following acute traumatic injury.

#### Data collection and analysis

The titles and abstracts identified in the electronic searches were screened by two independent authors to identify studies that had the potential to meet the inclusion criteria. The full reports of all such studies were obtained. From the results of the screened electronic searches, bibliographic searches, and contacts with experts, two authors independently selected trials meeting the inclusion criteria, with any disagreements resolved by consensus.

#### Main results

Four trials met the inclusion criteria. Two trials with a combined total of 20,451 patients assessed the effects of TXA on mortality; TXA reduced the risk of death by 10% (RR=0.90, 95% CI 0.85 to 0.97; p=0.0035). Data from one trial involving 20,211 patients found that TXA reduced the risk of death due to bleeding by 15% (RR=0.85, 95% CI 0.76 to 0.96; p=0.0077). There was no evidence that TXA increased the risk of vascular occlusive events or need for surgical intervention. There was no substantial difference in the receipt of blood transfusion between the TXA and placebo groups. The two trials of aprotinin provided no reliable data.

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## Authors' conclusions

TXA safely reduces mortality in bleeding trauma patients without increasing the risk of adverse events. Further trials are needed to determine the effects of TXA in patients with isolated traumatic brain injury.

## PLAIN LANGUAGE SUMMARY

### Blood-clot promoting drugs for acute traumatic injury

Injury is the second leading cause of death for people aged five to 45 years. Over three million people worldwide die of injuries, usually because of extensive blood loss. Antifibrinolytic drugs promote blood clotting by preventing blood clots from breaking down. Some examples of antifibrinolytic drugs are aprotinin, tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA). Doctors sometimes give these drugs to patients having surgery to prevent blood loss. They appear to have few complications. These drugs might also stop blood loss in seriously injured patients and, as a result, save lives.

The authors of this review searched for randomised trials assessing the effects of antifibrinolytics in trauma patients. When the review was first done in 2004 the results of the research were inconclusive. Since then, two new trials of TXA, one involving over 20,000 patients, have been completed. The results of this new research show that TXA reduces the risk of death compared to patients who receive no treatment without increasing the risk of adverse events.

Two small trials of aprotinin were also found although they provided no reliable data. Furthermore, since May 2008 aprotinin has been withdrawn from world markets in light of safety concerns.

The authors conclude that TXA can safely reduce death in bleeding trauma patients. They suggest that future trials should explore the effects of TXA in patients with traumatic brain injury with no other trauma.

## BACKGROUND

### Description of the condition

For people aged five to 45 years, trauma is second only to HIV/AIDS as a cause of death. Each year, worldwide, about three million people die as a result of trauma (Murray 1996), many after reaching hospital. Among trauma patients who do survive to reach hospital, exsanguination is a common cause of death, accounting for nearly half of in-hospital trauma deaths in some settings (Sauaia 1995). Central nervous system injury and multi-organ failure account for most of the remainder, both of which can be exacerbated by severe bleeding (BTF 2000).

Clotting helps to maintain the integrity of the circulatory system after vascular injury, whether traumatic or surgical in origin (Lawson 2004). Major surgery and trauma trigger similar haemostatic responses and the consequent massive blood loss presents an extreme challenge to the coagulation system. Part of the response to surgery and trauma in any patient, is stimulation of clot breakdown (fibrinolysis) which may become pathological (hyper-fibrinolysis) in some cases. Antifibrinolytic agents have been shown to reduce blood loss in patients with both normal and exaggerated

fibrinolytic responses to surgery, without apparently increasing the risk of post-operative complications.

### Description of the intervention

Antifibrinolytic agents are widely used in major surgery to prevent fibrinolysis and reduce surgical blood loss. A recent systematic review (Henry 2011) of randomised controlled trials of antifibrinolytics (mainly aprotinin or tranexamic acid [TXA]) in elective surgical patients showed that antifibrinolytics reduced the numbers needing transfusion by one third, reduced the volume needed per transfusion by one unit, and halved the need for further surgery to control bleeding. These differences were all statistically significant at the  $P < 0.01$  level. Specifically, aprotinin reduced the rate of blood transfusion by 34% (relative risk [RR]=0.66; 95% confidence interval [95% CI] 0.60 to 0.72) and TXA by 39% (RR=0.61; 95% CI 0.53 to 0.70). Aprotinin use saved 1.02 units of red blood cells (RBCs) (95% CI 0.79 to 1.26) in those requiring transfusion, and TXA use saved 0.87 units (95% CI 0.53 to 1.20). There was a non-significant reduction in mortality with both aprotinin (RR=0.81; 95% CI 0.63 to 1.06) and TXA (RR=

0.60; 95% CI 0.33 to 1.10). However, concerns regarding an apparent increased risk of death compared to other antifibrinolytics lead to the removal of aprotinin from world markets in May 2008.

### How the intervention might work

Because the coagulation abnormalities that occur after injury are similar to those after surgery, it is possible that antifibrinolytic agents might also reduce blood loss, the need for transfusion, and mortality following trauma. A simple and widely practicable intervention that reduced blood loss following trauma might prevent hundreds of thousands of premature deaths. A reduction in the need for transfusion would also have important public health implications. Blood is a scarce and expensive resource and major concerns remain about the risk of transfusion-transmitted infection. Trauma is particularly common in parts of the world where the safety of blood transfusion cannot be assured. A recent study in Uganda estimated the population-attributable fraction of HIV acquisition as a result of blood transfusion to be around two percent (Kiwunuka 2004) although some estimates are much higher (Heymann 1992).

## OBJECTIVES

To quantify the effect of antifibrinolytic drugs on mortality, vascular occlusive events, surgical intervention and receipt of blood transfusion after acute traumatic injury.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCT), as per the following definition.

RCT: A study involving at least one intervention and one control treatment, concurrent enrolment and follow-up of the intervention and control groups, and in which the interventions to be tested are selected by a random process, such as the use of a random numbers table (coin flips are also acceptable). If the study author(s) state explicitly (usually by using some variant of the term 'random' to describe the allocation procedure used) that the groups compared in the trial were established by random allocation, then the trial is classified as an 'RCT'.

### Types of participants

People of any age following acute traumatic injury.

### Types of interventions

The interventions considered are the antifibrinolytic agents: aprotinin, tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA).

### Types of outcome measures

#### Primary outcomes

- Mortality at the end of the follow up.

#### Secondary outcomes

- Number of patients experiencing an adverse event, specifically vascular occlusive events (myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism).
- Number of patients undergoing surgical intervention.
- Number of patients receiving blood transfusion.
- Volume of blood transfused (units).

### Search methods for identification of studies

Searches were not restricted by date, language or publication status.

#### Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group's Specialised Register (searched July 2010)
- Cochrane Central Register of Controlled Trials Issue 3, 2010 (*The Cochrane Library*)
- MEDLINE (1966 to July week 2, 2010)
- PubMed (searched March 17, 2004)
- EMBASE (1980 to week 28, July 2010)
- Science Citation Index (searched March 17, 2004)
- National Research Register (issue 1, 2004)
- Zetoc (searched March 17, 2004)
- SIGLE (searched March 17, 2004)
- Global Health (searched March 17, 2004)
- LILACS (searched March 17, 2004)
- Current Controlled Trials (searched March 17, 2004)

The search strategies used in the latest update are listed in full in [Appendix 1](#).

### Searching other resources

All references in the identified trials and background papers were checked and study authors contacted to identify relevant published and unpublished data. Pharmaceutical companies were contacted to obtain information on ongoing trials.

## Data collection and analysis

### Selection of studies

The titles and abstracts identified in the electronic searches were screened by two independent authors to identify studies that had the potential to meet the inclusion criteria. The full reports of all such studies were obtained. From the results of the screened electronic searches, bibliographic searches, and contacts with experts, two authors independently selected trials meeting the inclusion criteria, with any disagreements resolved by consensus.

### Data extraction and management

Two authors independently extracted information on the following: number of randomised participants, types of participants and types of interventions. The outcome data sought were: numbers of deaths in each group, numbers with vascular occlusive events, numbers requiring surgical intervention, and the amount of blood transfused. The authors were not blinded to the authors or journal when doing this. Results were compared and any differences resolved by discussion. Where there was insufficient information in the published report, we attempted to contact the authors for clarification.

### Assessment of risk of bias in included studies

Since there is evidence that the quality of allocation concealment particularly affects the results of studies (Schulz 1995), two authors scored this quality on the scale used by Schulz 1995 as shown below, assigning C to poorest quality and A to best quality.

- A (low risk of bias) = trials deemed to have taken adequate measures to conceal allocation (that is, central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment).
- B = (unclear risk of bias) trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories.
- C = (high risk of bias) trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth).

Information on loss to follow-up, the use of blinding, and whether an intention-to-treat analysis was also extracted.

### Assessment of heterogeneity

The presence of heterogeneity of the observed treatment effects were assessed using the I-squared statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity; substantial heterogeneity is considered to exist when  $I^2 > 50\%$  (Higgins 2008). The following were specified a-priori as factors that could explain any observed heterogeneity: adequacy of allocation concealment; injury severity based on the injury severity score (an ISS of greater than or equal to 16 defines the severely injured strata); and according to whether the study population included predominantly blunt or penetrating trauma.

### Assessment of reporting biases

We planned to investigate the presence of reporting (publication) bias using funnel plots, however there were too few included studies to enable meaningful analysis.

### Data synthesis

Relative risk (RR) of death and 95% confidence interval (95% CI) were calculated, such that a relative risk of more than 1 indicates a higher risk of death (or surgery or re-operation) in the first group named. Relative risk was chosen because it is more readily applied to the clinical situation. For transfusion volumes, the mean difference (MD) in the volume of blood transfused were calculated with 95% CIs.

### Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses to explore whether effect sizes vary according to the type of antifibrinolytic agent and the dosing regimen. However there were too few trials for such analyses.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Searches conducted in April 2004 identified a total of 819 records. These were screened by two authors and the full texts of nine potentially eligible reports were obtained for closer examination. Of the nine potentially eligible reports, two trials met the inclusion criteria. Two further trials were identified in an updated search conducted in July 2010. In summary, four randomised controlled

trials have been identified that meet the inclusion criteria and these are included in this review.

### Tranexamic acid

Two trials compared TXA with placebo in trauma patients. The [CRASH-2 2010](#) recruited 20,211 trauma patients with, or at risk of, significant haemorrhage. A trial in Thailand ([Yutthakasemsunt 2010](#)) recruited 240 trauma patients with moderate to severe traumatic brain injury. At the time of writing (November 2010), the Thai trial [Yutthakasemsunt 2010](#) was only available as an abstract with publication of the full trial report pending. The trial has been included based on the data reported in the abstract. The full trial data will be incorporated into this systematic review once the full trial report is available.

### Aprotinin

Two trials compared the effects of aprotinin with placebo in trauma patients. One trial ([Auer 1979](#)) involved 20 patients with severe head injury, and one ([McMichan 1982](#)) involved 77 patients with combination of hypovolaemic shock and major fractures of the lower limb and/or pelvis.

See 'Characteristics of included studies' for further details.

### Risk of bias in included studies

The [CRASH-2 2010](#) trial was judged to be at low risk of bias. It was a large randomised controlled trial involving 20,211 adult trauma patients who were randomly allocated to receive TXA or placebo. TXA and placebo were packaged in identical ampoules. Hospitals with a reliable telephone access used a telephone randomisation service, hospitals without used a local pack system; allocation concealment was adequate. Participants and trial staff were blinded to treatment allocation. Over 99% of patients were followed up.

There was insufficient information presented in the abstract to assess the risk of bias of the trial by [Yutthakasemsunt 2010](#).

The trial by [Auer 1979](#) was described as double blind. The adequacy of allocation concealment was unclear. However, after randomly allocating the first 20 patients, five patients were added to the aprotinin group. Because it was not possible to separate the outcome data for the 20 randomised and the five non-randomised patients, this study provided no useable outcome data.

In the randomised controlled trial by [McMichan 1982](#) the aprotinin and placebo were prepared in "similar ampoules". All ampoules were in boxes of 50, with a code number assigned to each box. The nature of the content of the ampoules was not known to any of the investigators nor to the attending physicians. The codes were not broken until the end of the study. There were seven post-randomisation exclusions from the study in which there were three deaths. These three deaths were excluded because they occurred

within the first 24 hours (it is not clear whether or not this was specified in the study protocol). Three patients refused the trial investigations, and one patient was transferred to another hospital for specialist treatment of quadriplegia and later died.

## Effects of interventions

### Tranexamic acid versus placebo

#### Mortality

Both [CRASH-2 2010](#) and the trial by [Yutthakasemsunt 2010](#) reported mortality data.

All-cause mortality was significantly reduced with tranexamic acid (pooled relative risk (RR)=0.90, 95% CI 0.85 to 0.97;  $p=0.003$ ; [Analysis 1.1](#)). There was no evidence of statistical heterogeneity ( $\text{Chi}^2=0.77$ ,  $df=1$  ( $p=0.38$ );  $I^2=0\%$ ).

The [CRASH-2 2010](#) also presented mortality data by cause according to the following categories: bleeding, vascular occlusion (myocardial infarction, stroke, pulmonary embolism), multi-organ failure, head injury and other. The risk of death due to bleeding and myocardial infarction were significantly reduced (bleeding:  $RR=0.85$ , 95% CI 0.76 to 0.96;  $p=0.0077$ ; myocardial infarction:  $RR=0.32$ , 95% CI 0.14 to 0.75;  $p=0.0053$ ).

There were no statistically significant differences in the risk of death from vascular occlusion ( $RR=0.69$ , 95% CI 0.44 to 1.07;  $p=0.096$ ), stroke ( $RR=1.60$ , 95% CI 0.52 to 4.89;  $p=0.40$ ), pulmonary embolism ( $RR=0.86$ , 95% CI 0.46 to 1.61;  $p=0.63$ ), multi-organ failure ( $RR=0.90$ , 95% CI 0.75 to 1.08;  $p=0.25$ ), head injury ( $RR=0.97$ , 95% CI 0.87 to 1.08;  $p=0.60$ ), or from 'other' causes ( $RR=0.94$ , 95% CI 0.74 to 1.20;  $p=0.63$ ).

#### Vascular occlusive events

The [CRASH-2 2010](#) trial reported data on vascular occlusive events. There was no difference in the risk of experiencing one or more vascular occlusive events (fatal or non-fatal; myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis) between the TXA and placebo groups ( $RR=0.84$ , 95% CI 0.68 to 1.02;  $p=0.084$ ). TXA reduced the risk of myocardial infarction ( $RR=0.64$ , 95% CI 0.42 to 0.97;  $p=0.035$ ). There was no difference in the risk of stroke ( $RR=0.86$ , 95% CI 0.61 to 1.23;  $p=0.42$ ), pulmonary embolism ( $RR=1.01$ , 95% CI 0.73 to 1.41;  $p=0.93$ ) or deep vein thrombosis ( $RR=0.98$ , 95% CI 0.63 to 1.51;  $p=0.91$ ).

#### Surgical intervention

Data from the [CRASH-2 2010](#) trial suggest that there is no statistically significant difference in the risk of receiving one or more

surgical intervention (neurosurgery, chest, abdominal or pelvic surgery) (RR=1.00, 95% CI 0.97 to 1.03; p=0.79).

### Receipt of blood transfusion

Of the patients allocated to TXA in the [CRASH-2 2010](#) trial, 5067 (50.4%) received a blood product transfusion versus 5160 (51.3%) of the patients allocated to placebo (RR=0.98, 95% CI 0.96 to 1.01; p=0.21). Those allocated to TXA received a mean of 6.06 (SD=9.98) [median=3] blood units, compared to a mean of 6.29 (SD=10.31) [median=3] for those allocated to placebo.

### Aprotinin versus placebo

The study by [Auer 1979](#), with 20 randomised patients, provided no useable outcome data for the reasons outlined above. The study by [McMichan 1982](#), with 77 randomised patients (seven post-randomisation exclusions), was reported in four separate reports (Rosengarten 1977; Rosengarten 1979 and McMichan 1977 in 'included studies' reference [McMichan 1982](#)).

### Mortality

[McMichan 1982](#) reported mortality data; there was no difference in the risk of death between the aprotinin or placebo groups (RR=0.14, 95% CI 0.01 to 2.67; p=0.19).

### Vascular occlusive events

Data on vascular occlusive events were not reported.

### Surgical intervention

[McMichan 1982](#) reported data on the number of patients undergoing a surgical intervention; there was no difference between the aprotinin or placebo groups (RR=1.07, 95% CI 0.87 to 1.33; p=0.53).

### Receipt of blood transfusion

Data on the number of patients receiving a blood transfusion or the volume transfused were not reported.

## DISCUSSION

### Summary of main results

Tranexamic acid reduces all-cause mortality in bleeding trauma patients, with no apparent increase in the risk of vascular occlusive events. This conclusion is based on the results of the [CRASH-2 2010](#) which recruited 20,211 bleeding trauma patients from 274 hospitals in 40 countries.

### Overall completeness and applicability of evidence

The large numbers of patients in a wide range of different health care settings around the world studied in the [CRASH-2 2010](#) trial help the result to be widely generalised. The treatment is effective in patients with blunt and penetrating trauma. Because TXA is inexpensive and easy to administer, it could readily be added to the normal medical and surgical management of bleeding trauma patients in hospitals around the world.

Each year, world-wide, about four million people die as a result of traumatic injuries and violence. Approximately 1.6 million of these deaths occur in hospital and about one third of these deaths (480,000) are from haemorrhage. The [CRASH-2 2010](#) trial has shown that TXA reduces mortality from haemorrhage by about one sixth. If this widely practicable intervention was used world-wide in the treatment of bleeding trauma patients, it could prevent over 70,000 deaths each year (see [Table 1](#)).

**Table 1. Deaths that could be avoided by the administration of TXA to bleeding trauma patients (ten countries with the highest numbers of avoided deaths shown)**

Country	Trauma deaths	Haemorrhage deaths	Deaths averted with TXA
India	714,730	85,768	12,865
China	667,277	80,073	12011
Indonesia	279,499	33,534	5030
Russia	246,836	29,620	4443
Brazil	122,953	14,754	2206



**Table 1. Deaths that could be avoided by the administration of TXA to bleeding trauma patients (ten countries with the highest numbers of avoided deaths shown) (Continued)**

USA	122,529	14,703	2206
Iraq	99,968	11,996	1799
Nigeria	87,811	10,537	1581
Bangladesh	76,938	9233	1385
DRC	73,579	8829	1324
World	4,100,645	492,077	73,812

Trauma and haemorrhage death estimates taken from the WHO Global Burden of Disease Study: <http://www.who.int/healthinfo/global-burden-disease/en/>

Many trauma patients suffer a brain injury. Traumatic brain injury (TBI) is commonly accompanied by intracranial bleeding which can develop or worsen after hospital admission. Traumatic intracranial haemorrhage is associated with an increased risk of death and disability, and regardless of location, haemorrhage size is strongly correlated with outcome. If TXA reduced intracranial bleeding after isolated TBI then this could improve patient outcomes. Although, many of the bleeding trauma patients included in the [CRASH-2 2010](#) trial also suffered a brain injury, it is possible that the effects of TXA may differ in patients with isolated TBI. The trial by [Yurthakasemsunt 2010](#) provides some promising evidence for the beneficial effect of TXA on mortality in patients with isolated TBI; however, further evidence is required from larger trials which also assess the effect on disability.

There is no evidence for the effect of aprotinin for trauma. Furthermore since publication of the original version of this review, aprotinin has been withdrawn from world markets in response to safety concerns.

### Quality of the evidence

The quality of the evidence supporting the use of tranexamic acid for trauma is high. The findings of this review are based primarily on the results of the [CRASH-2 2010](#) trial. This was a large, high quality randomised trial with low risk of bias. Sequence generation was appropriately randomised, allocation was concealed and participants, trial personnel and outcome assessors were all blinded. Furthermore, there were minimal missing data with over 99% of patients followed up.

### Potential biases in the review process

This systematic review addresses a focused research question and

uses pre-defined inclusion criteria and methodology to select and appraise eligible trials.

As with all systematic reviews, the possibility of publication bias should be considered as a potential threat to validity. However, in light of our extensive and sensitive searching we believe that the risk of such a bias affecting the results is minimal.

### Agreements and disagreements with other studies or reviews

A systematic review of randomised trials assessing the effects of TXA in patients undergoing elective surgery has been conducted ([Henry 2011](#)). This review found that compared to control, TXA reduced the need for blood transfusion without any apparent increase in the risk of adverse events. Unlike the [Henry 2011](#) review, we found no evidence of any substantial reduction in the receipt of a blood transfusion or the amount of blood transfused in trauma patients. One possible explanation is that in the [CRASH-2 2010](#) trial, following the loading dose, TXA was infused over a period of eight hours, whereas decisions about transfusion are made very soon after hospital admission. The absence of any large effect on blood transfusion may also reflect the difficulty of accurately estimating blood loss in trauma patients when assessing the need for transfusion. Finally, the absence of any substantial reduction in transfusion requirements in patients treated with TXA acid may reflect the fact that there were fewer deaths in patients allocated to TXA acid than to placebo and patients who survive as a result of TXA administration would have had a greater opportunity to receive a blood transfusion (competing risks).

## AUTHORS' CONCLUSIONS

### Implications for practice

Tranexamic acid (TXA) safely reduces mortality in bleeding trauma patients. Because most deaths from traumatic haemorrhage occur in the first few hours after injury, every effort should be made to treat patients as soon as possible.

### Implications for research

The knowledge that TXA safely reduces the risk of death from traumatic bleeding raises the possibility that it might also be effective in other situations where bleeding can be life threatening or

disabling and further research is warranted to explore this potential. Randomised trials involving patients with isolated traumatic brain injury that assess both mortality and disability outcomes are required before TXA can be recommended for use in these patients.

## ACKNOWLEDGEMENTS

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Auer 1979

Methods	Probable RCT: "Twenty patients were included in a double-blind study; nine patients were treated with Trasylol. Eleven received a placebo drug." Five additional (non-randomly allocated) patients were added to the study and received aprotinin treatment. These patients were not separated out in the analysis.
Participants	Patients with severe head injury who had remained comatose for seven days. Most of them had clinical brain stem signs.
Interventions	Aprotinin group: 500,000 IE initially thereafter 200,000 IV every four hours.
Outcomes	Death. Range of biochemical end points.
Notes	Because it was not possible to separate the 5 non-randomised patients from the 20 probably randomised patients, this study provides no useable outcome data.

#### *Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Schulz rating = B (unclear).

#### CRASH-2 2010

Methods	RCT: Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Participants and study staff were blind to treatment allocation.
Participants	20,211 adult (>16 years) trauma patients with, or at risk of, significant bleeding.
Interventions	Tranexamic acid group: loading dose 1g over 10 minutes then infusion of 1g over 8 hours. Matching placebo.
Outcomes	Death. Vascular occlusive events. Blood transfusion requirements. Disability.
Notes	

#### *Risk of bias*

Item	Authors' judgement	Description
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**CRASH-2 2010** (Continued)

Allocation concealment?	Yes	Schulz rating = A (Adequate)
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**McMichan 1982**

Methods	RCT: Aprotinin and placebo were supplied in identical coded ampoules. Ampoules were in boxes of 50 with a code number assigned to each box. These numbers were randomised in groups of 20 and each batch was assigned in numerical order. The codes were not broken until the end of the study. Patients excluded after randomisation were those who died within the first 24 hours or refused continuing investigation.
Participants	Patients with a combination of hypovolaemic shock and major fractures of the lower limb and or pelvis. Patients seen 12 or more hours after injury and those with major head or chest injuries were excluded.
Interventions	Aprotinin group: 500,000 Kallikrein Inhibitor Units (KIU) IV statim followed by 300,000 KIU at 6-hour intervals for 96 hours.
Outcomes	Death. Mean blood transfusion. Respiratory function.
Notes	77 patients were randomised but there were 7 post-randomisation exclusions. Among the 7 excluded patients, there were 3 deaths within the first 24 hours of injury. One patient was transferred to another hospital because of quadriplegia and died later, and three patients refused investigation. It was noted in the results that the data on transfusion requirement was found to have a non-normal distribution. Nevertheless, the mean and standard deviation were presented.

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Yes	Schulz rating = A (Adequate)

**Yutthakasemsunt 2010**

Methods	RCT
Participants	240 adults patients (>16 years) with moderate to severe traumatic brain injury (Glasgow Coma Scale 4 to 12) within 8 hours of injury.
Interventions	Tranexamic acid group: 2g. Matching placebo.
Outcomes	Death. Progressive intracranial haemorrhage. Disability (GOS). Thromboembolic events.

**Yutthakasemsunt 2010** (Continued)

Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Schulz rating = B (unclear)

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
Gierhake 1971	Types of patients: general surgery patients not trauma.
Husted 2003	Types of patients: orthopaedic patients not trauma.
Klobow 1977a	Types of interventions: trasylol compared with heparin.
Klobow 1977b	Types of interventions: trasylol compared with heparin.
Kuiian 1999	Types of studies: After Dr Vasily Vlassov, Director of the Russian Branch of the Nordic Cochrane Centre kindly translated the methods section it was clear that this study was not randomised.
Loew 1970	Types of studies: alternation used not random allocation.
Nissen 1989	Types of studies: review article not randomised controlled trial.
Schneider 1976	Types of studies: randomisation in this trial was by allocating patients to the treatment group according to the day of admission. However, this procedure was subverted for large numbers (813) of patients in which case the study cannot be considered to be a randomised controlled trial.

## DATA AND ANALYSES

### Comparison 1. Tranexamic acid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2	20367	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.85, 0.97]
2 Proportion undergoing surgical intervention	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Proportion receiving blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Volume of blood transfused	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

### Comparison 2. Aprotinin versus none

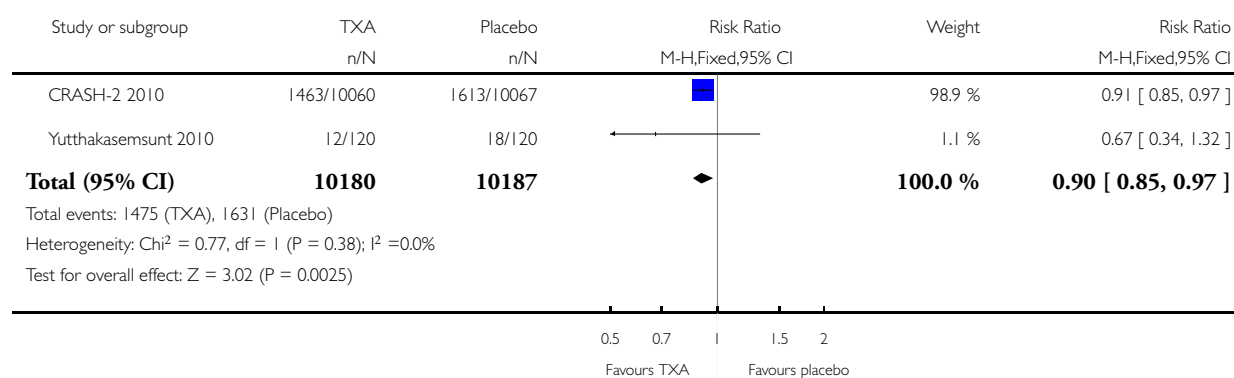
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Proportion undergoing surgical intervention	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Volume of blood transfused	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

#### Analysis 1.1. Comparison 1 Tranexamic acid versus placebo, Outcome 1 Death.

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 1 Tranexamic acid versus placebo

Outcome: 1 Death

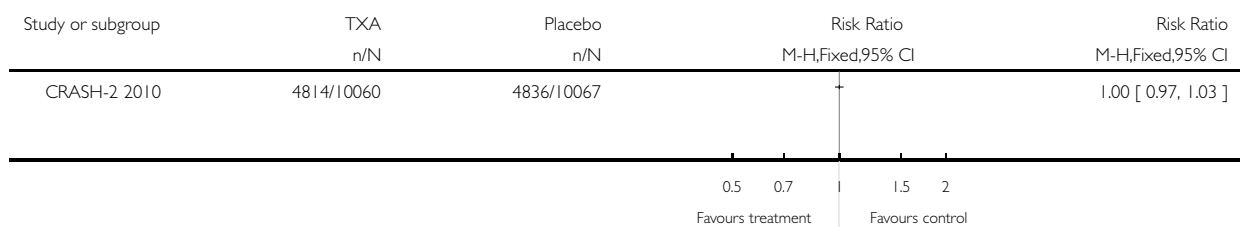


**Analysis 1.2. Comparison 1 Tranexamic acid versus placebo, Outcome 2 Proportion undergoing surgical intervention.**

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 1 Tranexamic acid versus placebo

Outcome: 2 Proportion undergoing surgical intervention



**Analysis 1.3. Comparison 1 Tranexamic acid versus placebo, Outcome 3 Proportion receiving blood transfusion.**

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 1 Tranexamic acid versus placebo

Outcome: 3 Proportion receiving blood transfusion



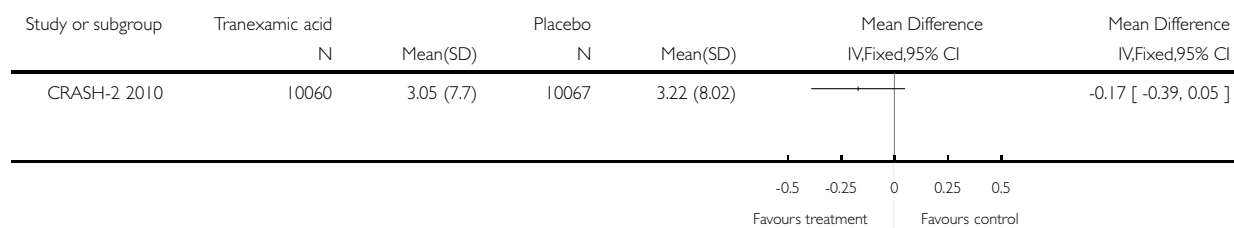


### Analysis 1.4. Comparison 1 Tranexamic acid versus placebo, Outcome 4 Volume of blood transfused.

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 1 Tranexamic acid versus placebo

Outcome: 4 Volume of blood transfused

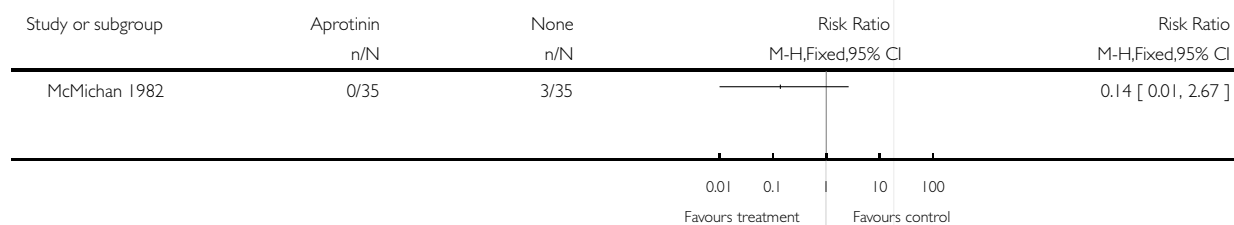


### Analysis 2.1. Comparison 2 Aprotinin versus none, Outcome 1 Death.

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 2 Aprotinin versus none

Outcome: 1 Death

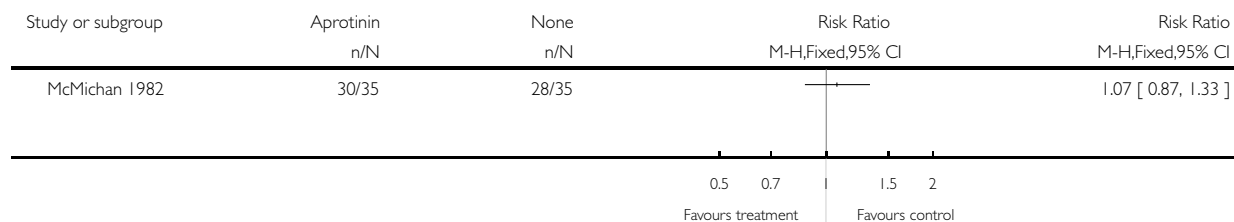


**Analysis 2.2. Comparison 2 Aprotinin versus none, Outcome 2 Proportion undergoing surgical intervention.**

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 2 Aprotinin versus none

Outcome: 2 Proportion undergoing surgical intervention

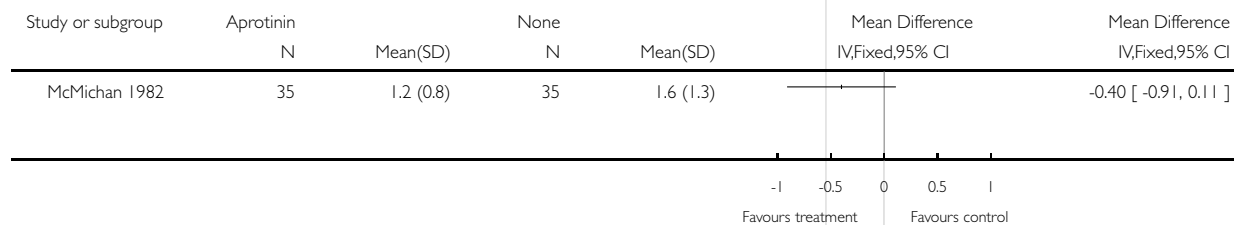


**Analysis 2.3. Comparison 2 Aprotinin versus none, Outcome 3 Volume of blood transfused.**

Review: Antifibrinolytic drugs for acute traumatic injury

Comparison: 2 Aprotinin versus none

Outcome: 3 Volume of blood transfused



## APPENDICES

### Appendix I. Search strategy

#### Cochrane Injuries Group Specialised Register (searched July 2010)

(Aprotinin\* or kallikrein-trypsin inactivator\* or bovine kunitz pancreatic trypsin inhibitor\* or bovine pancreatic trypsin inhibitor\* or basic pancreatic trypsin inhibitor\* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin\* or Trasylyl or Antilysin Spofa or rp:9921 or antagosan or antilysin or antily sine or apronitin\* or apronitrine or bayer a? 128 or bovine pancreatic secretory trypsin inhibitor\* or contrycal or frey inhibitor\* or gordox or kallikrein trypsin inhibitor\* or kazal type trypsin inhibitor\* or (Kunitz adj3 inhibitor\*) or midran or (pancrea\* adj2 antitrypsin) or (pancrea\* adj2 trypsin inhibitor\*) or riker?52g or rp:9921 or traclyol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren) or (tranexamic or Cyclohexanecarboxylic Acid\* or Methylamine\* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid\* or t-amcha or amca or kabi 2161 or transamin\* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol or amino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl:65336 or cl65336 or cyclo capron or cyclokapron or cyklokapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA) or (aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid\*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177 or neocaprol or nsc? 26154 or tachostyptan)

#### Cochrane Central Register of Controlled Trials 2010, Issue 3 (*The Cochrane Library*)

#1 MeSH descriptor Antifibrinolytic Agents explode all trees

#2 (anti-fibrinolytic\* or antifibrinolytic\* or antifibrinolysin\* or anti-fibrinolysin\* or antiplasmin\* or anti-plasmin\* ):ab,ti or ((plasmin or fibrinolysis) near3 inhibitor\*):ab,ti

#3 MeSH descriptor Aprotinin explode all trees

#4 (Aprotinin\* or kallikrein-trypsin inactivator\* or bovine kunitz pancreatic trypsin inhibitor\* or bovine pancreatic trypsin inhibitor\* or basic pancreatic trypsin inhibitor\* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin\* or Trasylyl or Antilysin Spofa or rp:9921 or antagosan or antilysin or antily sine or apronitin\* or apronitrine or bayer a? 128 or bovine pancreatic secretory trypsin inhibitor\* or contrycal or frey inhibitor\* or gordox or kallikrein trypsin inhibitor\* or kazal type trypsin inhibitor or riker?52g or rp:9921 or traclyol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren or midran):ab,ti or ((Kunitz near3 inhibitor\*) or (pancrea\* near3 antitrypsin) or (pancrea\* near3 trypsin next inhibitor\*)):ab,ti

#5 MeSH descriptor Tranexamic Acid explode all trees

#6 (tranexamic or Cyclohexanecarboxylic Acid\* or Methylamine\* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid\* or t-amcha or amca or kabi 2161 or transamin\* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol or amino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl:65336 or cl65336 or cyclo capron or cyclokapron or cyklokapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA):ab,ti

#7 MeSH descriptor Aminocaproic Acids explode all trees

#8 MeSH descriptor 6-Aminocaproic Acid explode all trees

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

#10 (aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic):ab,ti

#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)

**MEDLINE(Ovid) 1950 to July Week 2 2010**

1.exp Antifibrinolytic Agents/

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

3.exp Aprotinin/

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

5.exp Tranexamic Acid/

6.(tranexamic or Cyclohexanecarboxylic Acid\* or Methylamine\* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid\* or t-amcha or amca or kabi 2161 or transamin\* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol or amino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.

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

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

9.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10.randomi?ed.ab,ti.

11.randomized controlled trial.pt.

12.controlled clinical trial.pt.

13.placebo.ab.

14.clinical trials as topic.sh.

15.randomly.ab.

16.trial.ti.

17.10 or 11 or 12 or 13 or 14 or 15 or 16

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

19.17 not 18

20.9 and 19

**EMBASE (Ovid) 1980 to 2010 (Week 28)**

1.exp Antifibrinolytic Agent/

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

3.exp Aprotinin/

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

5.exp Tranexamic Acid/

6.(tranexamic or Cyclohexanecarboxylic Acid\* or Methylamine\* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid\* or t-amcha or amca or kabi 2161 or transamin\* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol or amino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.

7.exp Aminocaproic Acid/

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

9.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10.exp Randomized Controlled Trial/

11.exp controlled clinical trial/

12.randomi?ed.ab,ti.

13.placebo.ab.

14.\*Clinical Trial/

15.randomly.ab.

16.trial.ti.

17.10 or 11 or 12 or 13 or 14 or 15 or 16

18.exp animal/ not (exp human/ and exp animal/)

19.17 not 18

20.9 and 19

## WHAT'S NEW

Last assessed as up-to-date: 13 July 2010.

Date	Event	Description
22 November 2010	New citation required and conclusions have changed	Two new trials ( <a href="#">CRASH-2 2010</a> - 20,211 bleeding trauma patients) and <a href="#">Yurthakasemsunt 2010</a> 2010 - 240 patients with traumatic brain injury) have been included. The objectives of the review have been amended. The Results, Discussion and Conclusions sections have been amended accordingly.

## HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 4, 2004

## CONTRIBUTIONS OF AUTHORS

TC helped design the protocol, identified the included trials, extracted data and drafted the final version of the review.

IR helped design the protocol, identified the included trials, extracted data and drafted the final version of the review.

HS helped design the protocol and draft the final version of the review.

KK helped identify the included trials, extract data and revise the text of the review for the November 2010 update.

## DECLARATIONS OF INTEREST

Tim Coats, Haleema Shakur and Ian Roberts are investigators in the CRASH-2 trial - a large scale multi-centre randomised controlled trial of effect of the antifibrinolytic agent tranexamic acid on mortality and transfusion requirements in trauma patients with significant haemorrhage.

## SOURCES OF SUPPORT

### Internal sources

- London School of Hygiene & Tropical Medicine, UK.

### External sources

- No sources of support supplied

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The objectives of the review have changed. Reducing blood loss has been removed, and vascular occlusive events and surgical intervention have been added as outcomes.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Antifibrinolytic Agents [\*therapeutic use]; Aprotinin [therapeutic use]; Blood Loss, Surgical [prevention & control]; Blood Transfusion [\*utilization]; Hemorrhage [\*drug therapy; etiology; mortality]; Randomized Controlled Trials as Topic; Tranexamic Acid [therapeutic use]; Wounds and Injuries [\*complications; mortality]

## **MeSH check words**

Humans