

# Significant haemorrhage following trauma: tranexamic acid

## Evidence summary

Published: 16 October 2012

[nice.org.uk/guidance/esuom1](https://www.nice.org.uk/guidance/esuom1)

## Key points from the evidence

The content of this evidence summary was up-to-date in October 2012. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Tranexamic acid is an antifibrinolytic agent used to prevent, stop or reduce unwanted bleeding. It is licensed for use as a tablet or injection to prevent or reduce bleeding for a range of other indications such as menorrhagia.

Following trauma, tranexamic acid can be administered as an intravenous bolus injection followed by an infusion over 8 hours. However, it does not currently have a UK marketing authorisation for the prevention or treatment of significant haemorrhage following trauma. Use of tranexamic acid in trauma patients will be off-label.

Evidence from a large, high-quality international randomised controlled trial (RCT) shows that a short course of tranexamic acid given within 8 hours of injury to adult trauma patients with, or at risk of, significant bleeding, improved all cause mortality.

A further, exploratory analysis found that death due to bleeding was reduced if tranexamic acid was administered up to 3 hours from injury. However, death due to bleeding seemed to increase with administration later than 3 hours after injury.

A health economic analysis has found that tranexamic acid for the prevention and treatment of significant haemorrhage in trauma patients has an incremental cost of \$64 international dollars (£43) per life saved.

#### About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

## Overview for healthcare professionals

Tranexamic acid is an antifibrinolytic agent used to prevent, stop or reduce unwanted bleeding. It can be administered by injection or taken orally as a tablet. Following trauma it is administered as an intravenous bolus injection followed by an 8-hour infusion.

### *Regulatory status of tranexamic acid*

When tranexamic acid is used in major trauma, it is being used off-label because it does not currently have UK marketing authorisation for the prophylaxis and treatment of significant haemorrhage following trauma. In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using tranexamic acid outside its authorised indications.

Tranexamic acid is available for oral and intravenous administration: these preparations differ in their licensed indications. Tranexamic acid injection (Cyclokapron, Pfizer) is a prescription-only medicine licensed in the UK for administration as a slow intravenous injection for short-term use in<sup>[1]</sup>:

- prophylaxis and treatment in patients at high risk of pre- and post-operative haemorrhage following:
  - prostatectomy
  - conisation of the cervix
  - surgical procedures and dental extractions in people with haemophilia
- haemorrhage complications in association with thrombolytic therapy
- haemorrhage associated with disseminated intravascular coagulation with predominant activation of the fibrinolytic system.

## *Evidence statements*

- A large high-quality international RCT found that administration of tranexamic acid reduces mortality in patients with or at risk of significant haemorrhage following trauma<sup>[2]</sup>.
- A health economic analysis has found that tranexamic acid for the prevention and treatment of significant haemorrhage in trauma patients has an incremental cost of \$64 international dollars (£43) per life saved<sup>[3]</sup>.
- An exploratory analysis of the trial data indicates that overall benefit may apply only to people treated within 3 hours of injury<sup>[4]</sup>.

## *Summary of the evidence*

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence Review](#) section.

## **Efficacy**

The main evidence published to date comes from the CRASH-2 study<sup>[2]</sup>, a large, high-quality international [randomised controlled trial](#) (RCT) which is relevant to UK practice. This recruited 20,211 adult trauma patients with or at risk of significant haemorrhage in whom treatment could commence within 8 hours of when the injury occurred. They were randomised to receive a 1 g loading dose of tranexamic acid infused intravenously over 10 minutes followed by a further 1 g infused over 8 hours, or placebo.

CRASH-2 showed that a short course of intravenous tranexamic acid given to trauma patients with, or at risk of, significant bleeding increases survival without an increased risk of adverse events (see table 1).

**Table 1: Summary of the CRASH-2 trial**

	Tranexamic acid	Placebo	Analysis
CRASH-2 <sup>[2]</sup>			
Modified ITT group <sup>a</sup>	n=10060	n=10067	
Primary outcome <sup>b</sup>	14.5%	16.0%	RR 0.91, 95% CI 0.85 to 0.97, p=0.0035
Death due to bleeding	4.9%	5.7%	RR 0.85, 95% CI 0.76 to 0.96, p=0.0077
Vascular occlusion <sup>c</sup>	0.3%	0.5%	RR 0.69, 95% CI 0.44 to 1.07, p=0.096
Primary outcome by estimated time from injury <sup>d</sup>			
<1 hour	509/3747 (13.6%)	581/3704 (15.7%)	RR 0.87, 99% CI 0.75 to 1.00 <sup>d</sup>
>1 hour to ≤3 hours	463/3037 (15.2%)	528/2996 (17.6%)	RR 0.87, 99% CI 0.75 to 1.00 <sup>d</sup>
>3 hours	491/3272 (15.0%)	502/2262 (14.9%)	RR 1.00, 99% CI 0.86 to 1.17 <sup>d</sup>

Abbreviations: CI, confidence interval; ITT, intention to treat; n, number of patients; RR, relative risk

<sup>a</sup> 20,211 patients were randomised. 3 patients in the tranexamic acid group and 1 patient in the placebo group withdrew consent. Primary outcome data were not available for 33 patients in the tranexamic acid group and 47 patients in the placebo group. Analysis is based on the remaining 20127 patients (99.6% of those randomised)

<sup>b</sup> All cause in-hospital mortality within 4 weeks of injury

<sup>c</sup> Includes myocardial infarction, stroke, and pulmonary embolism

<sup>d</sup> Note that these results are given with 99% confidence intervals. A subsequent analysis found that tranexamic acid significantly reduced the relative risk of all-cause death compared with placebo if administered within 3 hours of injury but not if administered more than 3 hours after injury (see the Evidence Review section)

In an exploratory analysis of the CRASH-2 results, early treatment (within 3 hours of injury) was found to be significantly more effective than treatment given after 3 hours<sup>[4]</sup>. Early treatment has been estimated to have the potential to save 755 life-years per 1,000 trauma patients in the UK<sup>[3]</sup>.

## Safety

No statistically significant increase in the risk of vascular occlusive events (including myocardial infarction, stroke and pulmonary embolism) was observed in the CRASH-2 trial<sup>[2]</sup>.

## Cost-effectiveness and cost

A cost-effectiveness analysis based on the results of the CRASH-2 trial found administering tranexamic acid to have an incremental cost of \$64 international dollars (£43) per life saved in a variety of settings<sup>[3]</sup>.

The cost of tranexamic acid at the dosage used in the trial is estimated at £6.20 per patient, excluding VAT and disposables (October 2012)<sup>[3]</sup>.

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<sup>[1]</sup> Electronic Medicines Compendium (eMC). Summary of Product Characteristics: Tranexamic acid. Available from [www.medicines.org.uk](http://www.medicines.org.uk) [Accessed on 24 September 2012]

<sup>[2]</sup> CRASH-2 trial collaborators. (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial *Lancet* 376: 23–32.

<sup>[3]</sup> Guerriero C, Cairns J, Perel P et al. (2011) Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS one*; 6(5).

<sup>[4]</sup> CRASH-2 trial collaborators. (2011) The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 377: 1096–101.

<sup>[5]</sup> [MIMS October 2012](#)

## Relevance to NICE guidance programmes

Tranexamic acid for preventing or treating significant bleeding in trauma patients may be included within the scope of the [NICE Clinical Guideline on the assessment and management of major trauma](#). This guideline has an estimated publication date of June 2015.

NICE guidance exists for other indications and routes of administration for tranexamic acid (licensed indications):

- [Heavy menstrual bleeding](#), NICE clinical guideline 44
- [Long acting reversible contraception](#), NICE clinical guideline 30

## Intervention and alternatives

Tranexamic acid is a synthetic derivative of the amino acid lysine. It inhibits fibrinolysis by blocking the lysine binding sites on plasminogen<sup>[6]</sup>.

## Condition

Serious bleeding (significant haemorrhage) and its complications are a considerable cause of death following severe trauma and are responsible for 80% of deaths in the operating theatre and up to 50% of deaths in the first 24 hours after injury<sup>[7]</sup>.

## Alternative treatment options

A European guideline provides some advice on alternative treatments<sup>[8]</sup>. This guideline was published in 2010, before the reports on the CRASH-2 study. It is due to be updated and it is not yet known what the recommendations for tranexamic acid will be in the updated guideline.

The guideline advises that appropriate care for a patient with significant haemorrhage from trauma includes early identification of potential bleeding sources followed by prompt measures to minimise blood loss, restore the circulating blood volume and achieve stability. Resuscitation and surgical intervention can be a major part of this. The options for coagulation management discussed guideline include:

- calcium, if ionised calcium is low
- fresh frozen plasma for coagulopathy
- platelet concentrates to maintain platelet levels
- fibrinogen or cryoprecipitate
- recombinant activated coagulation factor VII (in specific circumstances)
- prothrombin complex concentrate (in specific circumstances).

Blood transfusions can also be given to the patient if required and the European Guideline recommends a target haemoglobin of 7 to 9 g/dl.

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<sup>[6]</sup> CRASH-2 trial collaborators. (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 376: 23–32.

<sup>[7]</sup> Association of Anaesthetists of Great Britain and Ireland (AAGBI). (2010) Blood transfusion and the anaesthetist: management of massive haemorrhage. *Anaesthesia* 65: 1153–61.

<sup>[8]</sup> Rossaint R, Bouillon B, Cerny V et al. (2010) Management of bleeding following major trauma: an updated European Guideline. *Critical Care* 14: R52.

## Evidence review: efficacy

### *CRASH-2 trial*

The efficacy of tranexamic acid has been assessed by an international randomised controlled trial (CRASH-2)<sup>[9]</sup>. In this study more than 20,000 patients with trauma who had significant haemorrhage (systolic blood pressure <90 mmHg or heart rate >110 beats per minute, or both) or who were considered to be at risk of significant haemorrhage were assigned to treatment with

tranexamic acid or placebo. The primary outcome was death in hospital due to any cause within 4 weeks of injury. Secondary outcomes were vascular occlusive events, receipt of blood transfusion and surgical intervention.

Initiating tranexamic acid in adult trauma patients with or at risk of significant haemorrhage within 8 hours of injury resulted in statistically significant and clinically important reductions in death from any cause. All-cause mortality within 4 weeks of injury was 14.5% with tranexamic acid compared with 16.0% with placebo: an absolute risk reduction of 1.5% and a relative risk reduction of 9% (relative risk [RR] 0.91, 95% confidence interval [CI] 0.85 to 0.97). This risk difference indicates that for every 1000 people in the study overall, there were 160 deaths among people who received placebo, compared with 145 deaths among people who were treated with tranexamic acid. However, in clinical practice, the effectiveness of tranexamic acid in preventing death in absolute terms will depend on the patients' characteristics and risk of death at baseline.

The risk of death due to bleeding was reduced with tranexamic acid (4.9% versus 5.7%, RR 0.85, 95% CI 0.76 to 0.96). No significant differences for other (non-bleeding) causes of death were seen between tranexamic acid and placebo (RR 0.94, 95% CI 0.86 to 1.02).

## *CRASH-2: exploratory analyses*

### **Effect of time of treatment**

The investigators performed an exploratory analysis on pre-specified subgroups from the CRASH-2 study population to examine the effects of time to treatment on outcomes. This analysis suggested that treatment within 3 hours of injury was more effective than later treatment<sup>[10]</sup>. If administered within 3 hours of injury, tranexamic acid reduced the relative risk of death by 13% compared with placebo (RR 0.87, 95% CI 0.81 to 0.95)<sup>[11]</sup>. When administered more than 3 hours after injury, tranexamic acid did not reduce the risk of all-cause death (RR 1.00, 95% CI 0.90–1.13). The relative risk of death from bleeding was increased in the group given tranexamic acid 3 hours after injury (RR 1.44, 95% CI 1.12 - 1.84)<sup>[10]</sup>.

### **Effect of severity of injury**

A further exploratory analysis was conducted on a pre-specified subgroup of participants in CRASH-2 who were treated within 3 hours of injury<sup>[12]</sup>. These were stratified according to risk of death at baseline (<6%, 6–20%, 21–50%, >50%), estimated from a model derived from the CRASH-2 data and validated in a large sample of trauma patients from the UK Trauma and Audit Research Network registry database<sup>[13]</sup>. These data suggest a similar effect from tranexamic acid on all-cause mortality and deaths from bleeding in all groups in relative terms, and that use should not

be restricted to the most severely injured. However, in the lowest risk group the precision of the estimated effect is low, and therefore there remains some uncertainty about the benefits of tranexamic acid in this group<sup>[12]</sup>.

## *Cochrane review*

A Cochrane systematic review of antifibrinolytic drugs following acute traumatic injury found 4 trials that met the inclusion criteria, including the CRASH-2 trial.<sup>[14]</sup> One small additional trial (n=240) of tranexamic acid added data to the CRASH-2 results on mortality.

The Cochrane review's conclusions were similar to those of CRASH-2. It found that tranexamic acid reduced the relative risk of death by 10% (RR 0.90, 95% CI 0.85 to 0.97). There was no evidence that tranexamic acid increased the risk of vascular occlusive events or need for surgical intervention. There was no substantial difference in the receipt of blood transfusion between tranexamic acid and placebo.

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<sup>[9]</sup> CRASH-2 trial collaborators. (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 376: 23–32.

<sup>[10]</sup> CRASH-2 trial collaborators. (2011) The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 377: 1096–101.

<sup>[11]</sup> Guerriero C, Cairns J, Perel P et al. (2011) Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS one*; 6(5).

<sup>[12]</sup> Roberts I, Perel P, Prieto-Merino D et al. (2012) Effects of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial. *BMJ* 345: e5839.

<sup>[13]</sup> Perel P, Prieto-Merino D, Shakur H et al. (2012) Predicting early death in patients with traumatic bleeding: development and validation of prognostic model. *BMJ* 345: e5166.

<sup>[14]</sup> Roberts I, Shakur H, Ker K et al. (2011) Antifibrinolytic drugs for acute traumatic injury (Review). *The Cochrane Collaboration* 1.

## Evidence: safety

In the CRASH-2 study, tranexamic acid reduced the risk of death in trauma patients with bleeding with no statistically significant increase in the risk of vascular occlusive events (including myocardial infarction, stroke and pulmonary embolism)<sup>[15]</sup>.

No adverse events in the CRASH-2 trial were regarded by clinicians as serious, unexpected and suspected to be related to the study treatment<sup>[15]</sup>.

An exploratory analysis of CRASH-2 data suggested that administration of tranexamic acid more than 3 hours after injury was not significantly effective in reducing the risk of all-cause death (RR 1.00, 95% CI 0.90–1.13) and increased the risk of death due to bleeding (RR 1.44, 95% CI 1.12–1.84)<sup>[16]</sup>.

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<sup>[15]</sup> CRASH-2 trial collaborators. (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 376: 23–32.

<sup>[16]</sup> CRASH-2 trial collaborators. (2011) The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 377: 1096–101.

## Evidence: economic issues

### *Cost effectiveness*

The cost-effectiveness of tranexamic acid for significant haemorrhage following trauma was analysed for 3 countries based on the results of the CRASH-2 trial: in Tanzania, India and the UK. Costs were considered from a health service perspective and included cost of administering tranexamic acid and cost of additional days in hospital. The analysis took into account the life expectancy of different age groups in each country<sup>[17]</sup>.

In the UK, the incremental cost per life year saved was \$64 international dollars (converted using [Purchasing Power Parities](#) which, using 2011 data, equates to around £43). Administering tranexamic acid to trauma patients with bleeding within 3 hours of injury was estimated to save 755 life-years per 1,000 trauma patients in the UK<sup>[11]</sup>.

On the basis of the CRASH-2 trial results, tranexamic acid has been included on the World Health Organization's (WHO) list of essential medicines, and incorporated into trauma treatment guidelines worldwide<sup>[18]</sup>. It has been estimated that the widespread use of tranexamic acid could save more than 100,000 lives per year around the world<sup>[19]</sup>.

## Cost

The price of tranexamic acid injection quoted in MIMS (October 2012) is £1.55 per 5 mL vial (100 mg/mL), excluding VAT<sup>[20]</sup>. The cost of tranexamic acid given at the doses in the CRASH-2 trial (initial treatment of 1 g infused intravenously over 10 minutes followed by intravenous infusion of 1 g over 8 hours) is £6.20.

## Current drug usage

No recent information on tranexamic acid usage following acute trauma in the UK was available at the time this evidence summary was prepared.

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<sup>[17]</sup> Guerriero C, Cairns J, Perel P et al. (2011) Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS one*; 6(5).

<sup>[18]</sup> Ker K, Kiriya J, Perel P et al. (2012) Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial. *BMC Emergency Medicine* 12(3).

<sup>[19]</sup> Roberts I, Perel P, Prieto-Merino D et al. (2012) Effects of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial. *BMJ* 345: e5839.

<sup>[20]</sup> MIMS October 2012

## Evidence strengths and limitations

The evidence for use of tranexamic acid for significant haemorrhage following trauma comes from a large high-quality RCT with a relatively low risk of bias<sup>[21]</sup>.

- The CRASH-2 RCT was well-conducted study with more than 99% of patients followed up and high internal validity.

- Participants in the trial were appropriately randomised with allocation concealed and assessors and patients all blinded to treatment group.

<sup>[21]</sup> Roberts I, Shakur H, Ker K et al. (2011) Antifibrinolytic drugs for acute traumatic injury (Review). The Cochrane Collaboration 1.

## Summary for patients

A [summary written for patients](#) is available on the NICE website.

## References

Association of Anaesthetists of Great Britain and Ireland (AAGBI). (2010) Blood transfusion and the anaesthetist: management of massive haemorrhage. *Anaesthesia* 65: 1153–61.

CRASH-2 trial collaborators. (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 376: 23–32.

CRASH-2 trial collaborators. (2011) The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 377: 1096–101.

Electronic Medicines Compendium (eMC). Summary of Product Characteristics: Tranexamic acid. Available from: [www.medicines.org.uk](http://www.medicines.org.uk) [Accessed on 24 September 2012]

Guerriero C, Cairns J, Perel P et al. (2011) Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS one*; 6(5).

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Roberts I, Shakur H, Ker K et al. (2011) Antifibrinolytic drugs for acute traumatic injury (Review). *The Cochrane Collaboration* 1.

Rossaint R, Bouillon B, Cerny V et al. (2010) Management of bleeding following major trauma: an updated European Guideline. *Critical Care* 14: R52.

## Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [Interim process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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### *Declarations of interest*

No relevant interests declared.

## Appendix: Search strategy and evidence selection

### Search strategy

The sources are:

1. [NHS Evidence](#) (including guidelines)
2. [NICE](#)
3. Broad internet search: [Google](#), for example: tranexamic acid AND (haemorrhage OR hemorrhage) AND ~guideline OR ~algorithm) filetype:pdf

### MEDLINE & Embase (via Ovid)

1. Tranexamic Acid/
2. (Tranexamic Acid or Cyklokapron or AMCA or AMCHA or Amchafibrin or Anvitoff or Exacyl or KABI 2161 or Spotof or t-AMCHA or Transamin or Ugurol or Lysteda).tw.
3. "trans-4-(Aminomethyl)cyclohexanecarboxylic".tw.
4. 1 or 2 or 3
5. (haemorrhage or hemorrhage or bleeding or blood loss).tw.
6. exp Hemorrhage/
7. 5 or 6
8. (injur\$ or trauma\$).tw.
9. exp Wounds/ and Injuries/
10. 8 or 9
11. 7 and 10
12. 4 and 11
13. exp review/
14. (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh.

15. ((hand adj2 search\$) or (manual\$ adj2 search\$)).ti,ab,sh.
16. ((electronic or bibliographic or computeri?ed or online) adj4 database\$).ti,ab.
17. (pooling or pooled or mantel haenszel).ti,ab,sh.
18. (peto or dersimonian or der simonian or fixed effect).ti,ab,sh.
19. or/14-18
20. 13 and 19
21. Meta Analysis/
22. (meta-analys\$ or meta analys\$ or metaanalys\$).ti,ab,sh.
23. ((systematic\$ or quantitativ\$ or methodologic\$) adj5 (review\$ or overview\$ or synthesis\$)).ti,ab,sh.
24. (integrative research review\$ or research integration).ti,ab,sh.
25. or/21-24
26. 20 or 25
27. clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/
28. (random\$ or placebo\$ or ((singl\$ or double\$ or triple\$ or treble\$) and (blind\$ or mask\$))).ti,ab,sh.
29. 27 or 28
30. (animal\$ not human\$).sh.
31. 29 not 30
32. 26 or 31
33. cost?.tw,hw.
34. (economic? or expenditure?).tw,hw.
35. 33 or 34

36. 32 or 35

37. 12 and 36

### CRD HTA, DARE and EED database

1. MeSH DESCRIPTOR Tranexamic Acid
2. (Tranexamic acid ) OR (Cyklokapron)
3. #1 OR #2
4. (haemorrhage OR hemorrhage OR bleeding OR blood loss)
5. MeSH DESCRIPTOR hemorrhage EXPLODE ALL TREES
6. #4 OR #5
7. #3 AND #6
8. (injur\* OR trauma\*)
9. MeSH DESCRIPTOR Wounds and Injuries EXPLODE ALL TREES
10. #9 OR #10
11. #7 AND #10

### Euroscan

Tranexamic acid OR Cyklokapron

### Grey literature and ongoing trials

1. [FDA](#)
2. [EMA](#)
3. [MHRA](#)
4. [Scottish Medicines Consortium](#)
5. [All Wales Medicine Strategy Group](#)
6. Manufacturers' websites as applicable

7. [metaRegister of Controlled Trials \(mRCT\)](#)

8. [ClinicalTrials.gov](#)

## Manufacturers' websites

Abbott <http://www.abbott.com/index.htm>

Fides Ecopharma n/a

Pfizer <http://www.pfizer.co.uk/sites/uk/Products/Pages/AllProducts.aspx>

Pharmygiène n/a

Sanofi <http://en.sanofi.com/>

## Evidence selection

Studies were included based on predetermined criteria for relevance to the question set at scoping. Individual studies were scored for validity using the methods and checklists described in the appendices of the NICE guidelines method manual. The highest quality research was selected as the basis for answering the questions set on efficacy, safety and cost. The CRASH-2 trial was the main reference used for this report, supplementary, sub-group or exploratory trials were also included if these have been published and were based on the CRASH-2 trial data.

## About 'Evidence summaries: unlicensed or off-label medicines'

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This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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