

**The effects of anti-fibrinolytic drugs in patients with or at risk of bleeding: a protocol for a systematic review and individual patient data meta-analysis**



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## SUMMARY

### Introduction

Bleeding is a major cause of mortality and morbidity worldwide. Anti-fibrinolytic agents are a group of drugs that inhibit clot breakdown (fibrinolysis) and have a potentially important role in the management of excessive bleeding. There is good evidence from clinical trials that a type of anti-fibrinolytic drug called tranexamic acid (TXA) improves outcomes in many bleeding patients. However, important uncertainties remain such as the effects on thromboembolic events as well as whether the effects vary by baseline risk, site of bleeding, and dose. We will undertake a systematic review and individual patient data (IPD) meta-analysis to assess the effects of anti-fibrinolytic drugs in patients with or at risk of bleeding.

### Methods

We have established the Anti-fibrinolytics Trialists Collaboration (ATC). Investigators representing eligible randomised trials of anti-fibrinolytics will be invited to join the collaboration and submit IPD for analysis. The primary outcome is death due to bleeding. Secondary outcomes include death (cause described), vascular occlusive events, seizures, and sepsis. We will collate anonymised, IPD into a single database, and carry out appropriate data checks. A one-stage IPD model will be used to explore how the effects of anti-fibrinolytics vary by baseline risk, site of bleeding, time to treatment, and dose.

### Discussion

This IPD meta-analysis will allow us to examine how the effects of anti-fibrinolytics vary by time to treatment, site of bleeding, baseline risk and dose, so that we gain a better understanding of the balance of benefits and harms upon which we can base recommendations for practice.

## BACKGROUND

Bleeding is a major cause of mortality and morbidity worldwide. In particular, surgical, traumatic, intracranial, gastrointestinal, and obstetric haemorrhage, account for an enormous disease burden and cause many premature deaths.

**Surgical haemorrhage:** Over 300 million surgical procedures are performed worldwide each year.<sup>1</sup> Bleeding and blood transfusion are common complications of surgery and are associated with poor outcomes. Severe surgical haemorrhage strongly predicts adverse patient outcomes and is associated with an eightfold increase in the odds of death.<sup>2</sup>

**Traumatic haemorrhage:** Trauma is a leading cause of death in children and young adults, with excessive bleeding responsible for about 40% of deaths.<sup>3</sup> In those who survive, bleeding is associated with complications such as organ failure and sepsis, with greater blood loss associated with poorer outcomes.<sup>4,5</sup>

**Intracranial haemorrhage:** Worldwide, over 10 million people are killed or hospitalised because of traumatic brain injury (TBI) each year and it is the most common cause of death and disability in those aged 1-40 years.<sup>6,7</sup> TBI is often accompanied by intracranial haemorrhage which is associated with increased mortality and disability, with the larger the bleed the worse the outcome.<sup>8</sup> Haemorrhagic stroke affects about six million people every year worldwide.<sup>9</sup> About three million die and many survivors are permanently disabled.<sup>9</sup> Continuation of bleeding can occur for many hours after onset in both traumatic and spontaneous intracranial bleeding, although it is most common during the first few hours.<sup>10,11</sup>

**Gastrointestinal (GI) haemorrhage:** GI haemorrhage is a common medical emergency. In the UK for example, about 50,000 people are admitted to hospital with upper GI bleeding each year, about 14% of whom die.<sup>12</sup> A further 20,000 patients are admitted to UK hospitals with lower GI bleeding, 3.5% of whom die while in hospital. GI bleeding is also common in low and middle income countries, where patients are usually young and poor.

**Obstetric haemorrhage:** Postpartum haemorrhage (PPH) follows about 6% to 10% of births and worldwide accounts for 50,000 to 100,000 maternal deaths each year.<sup>13,14</sup> Ninety-nine percent of deaths are in low and middle income countries.<sup>15</sup> Although death from PPH is relatively rare in high income countries, it is a common cause of morbidity. For women who survive, many require costly, urgent care, and a prolonged hospital stay. It can also have a significant psychological impact and adversely affect a mother's ability to breast-feed and bond with her baby.<sup>16</sup>

Blood transfusion is a common intervention for the management of excessive bleeding, which places enormous pressure on donor blood supplies. Blood for transfusion is a scarce and costly resource and most people in the world do not have access to donor blood. Furthermore, blood transfusion is not without risk and exposes the recipient to several infectious and non-infectious risks. The identification of a safe and effective treatment and an alternative to blood transfusion for the management of excessive bleeding is a public health priority. Indeed better understanding of the best drug alternatives to blood transfusion to reduce and prevent bleeding, has been ranked as one of the top 10 priority areas by the James Lind Alliance Blood Donation Priority Setting Partnership.<sup>17</sup> Anti-fibrinolytic drugs are potentially such an alternative.

### Anti-fibrinolytic drugs

Epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA) are potent inhibitors of plasmin that inhibit fibrinolysis. A third anti-fibrinolytic agent is aprotinin, a non-specific, serine protease inhibitor, derived from bovine lung. Anti-fibrinolytics reduce bleeding by inhibiting the enzymatic breakdown of fibrin blood clots. Plasminogen, a glycoprotein pro-enzyme produced by the liver, is converted into the active fibrinolytic enzyme plasmin by tissue plasminogen activator (TPA).<sup>18</sup> Plasminogen binds to fibrin via lysine-binding sites.<sup>19</sup> If the lysine residues on fibrin are removed, the binding of plasminogen is inhibited. Fibrin binds plasminogen and TPA thus localising and enhancing plasmin formation. Plasmin splits fibrin into fibrin degradation products. EACA and TXA are molecular analogues of lysine that inhibit fibrinolysis by reducing the binding of plasminogen to fibrin.<sup>18</sup> Aprotinin has a direct inhibitory action on plasmin.

There is evidence that anti-fibrinolytic drugs reduce bleeding. Most evidence originates from randomised trials assessing the effects of TXA. A systematic review of 129 randomised trials in surgery found that TXA reduces the probability of receiving a blood transfusion (RR=0.62, 95% CI 0.58 to 0.68) and average blood loss (RR=0.66, 95% CI 0.65 to 0.67) regardless of the type of surgery and the extent of bleeding.<sup>20, 21</sup> This evidence that TXA reduces surgical bleeding is further supported by the results of the more recently published ATACAS trial involving over 4631 cardiac surgery patients.<sup>22</sup>

Two large trials have also shown that TXA reduces the risk of bleeding to death after trauma and PPH. In the CRASH-2 trial,<sup>23</sup> 20,211 adult trauma patients with significant bleeding, who were within 8 hours of their injury, were randomly allocated to receive TXA (1 g over 10 min followed by an infusion of 1 g over 8 hours) or matching placebo. TXA reduced death due to bleeding (RR=0.85, 95% CI 0.76 to 0.96) and all-cause mortality (RR=0.91, 95% CI 0.85 to 0.97). In the WOMAN trial,<sup>24</sup> 20,060 women with a clinical diagnosis of PPH after a vaginal birth or caesarean section, were randomly allocated to receive 1 g TXA or matching placebo. If bleeding continued after 30 minutes, or stopped and restarted within

24 hours of the first dose, a second dose of 1 g of TXA or placebo could be given. The results showed that TXA reduced death due to bleeding (RR=0.81, 95% CI 0.65 to 1.00).

The TICH-2 trial<sup>25</sup> assessed the effects of TXA in 2325 patients with intracerebral haemorrhage from acute stroke. Patients were randomly allocated to receive 1 g TXA bolus followed by an 8 hour infusion of 1 g TXA or a matching placebo, within 8 hours of symptom onset. There was no statistically significant difference in functional status at day 90 (aOR=0.88, 95% CI 0.76 to 1.03) between groups although there were fewer deaths at day 7 in patients who received TXA (aOR=0.73, 0.53 to 0.99).

Despite this evidence, there remains several important questions that cannot be answered reliably by considering each trial in isolation.

*Do anti-fibrinolytics such as TXA increase the risk of thromboembolic events?* A key concern regarding anti-fibrinolytics is whether they increase the risk of thromboembolic events. Although no increased risk of thromboembolic events was observed in the systematic review of surgery trials, the ATACAS trial, the CRASH-2 trial, the WOMAN trial, or in the TICH-2 trial, such events are relatively rare and none of these trials were sufficiently powered to confirm or refute an increase or decrease in risk. On pathophysiological grounds, we might expect drugs that inhibit fibrinolysis to increase the risk of thrombosis. Indeed, the summary of product characteristics, which serves as the basis of information for clinicians on how to use TXA, lists arterial and venous thrombosis as potential adverse events and details specific warning regarding its use in patients at risk of thromboembolic events.<sup>26</sup> However, there is also reason to hypothesise that TXA may in fact decrease the risk of such events.<sup>27</sup> Bleeding is itself a risk factor for vascular occlusive events. In patients at risk of myocardial infarction, bleeding can worsen the imbalance between myocardial oxygen demand and supply, precipitating myocardial ischemia. By preventing bleeding, TXA could reduce the risk of death due to bleeding without increasing (and possibly reducing) the risk of vascular occlusive events.

Concerns over the risk of thrombosis is likely to dissuade clinicians from giving TXA to all bleeding patients, thus resolving this uncertainty is essential if we are to maximise patient benefit.

*How do the effects of anti-fibrinolytics such as TXA, vary by site of bleeding?* The evidence from trials in surgery, trauma, and PPH, provides reason to hope that TXA could have similar effects for other types of bleeding. However, whether it is appropriate to generalise the effects of anti-fibrinolytics across different types of bleeding is open to question. Although the effect of anti-fibrinolytics on fibrinolysis may be similar, the pathophysiological mechanisms responsible for adverse patient outcomes may be different depending on the site of bleeding. The extent to which the effectiveness and safety of anti-fibrinolytics depend on the site and cause of bleeding is therefore a critically important question.

*How do the effects of anti-fibrinolytics such as TXA, vary by time to treatment?* Both the CRASH-2 and WOMAN trials found that TXA was most effective when given early. Treatment within three hours of injury or giving birth reduced the risk of death due to bleeding by around 30% (CRASH-2 trial: RR=0.72, 95% CI 0.63 to 0.83; WOMAN trial: RR=0.69, 95% CI 0.52 to 0.91).<sup>24, 28</sup> However, treatment initiated after three hours of injury or giving birth did not appear to reduce the risk of death due to bleeding in either trial, and may even increase the risk of death. The extent to which the effects of TXA depend on time to treatment in other haemorrhage scenarios (e.g. gastrointestinal and intracranial) is an important question since late treatment might also be ineffective or harmful.

*How do the effects of anti-fibrinolytics such as TXA, vary by baseline risk?* We might expect that patients with severe bleeding would have most to gain from the use of anti-fibrinolytics (if shown to be effective) because absolute benefits tend to increase as baseline risk increases. On the other hand, there are many more patients with mild or moderate bleeding and a large number of patients at low or intermediate risk of death might contribute more deaths than the smaller number of patients at high risk. Although an analysis of data from the CRASH-2 trial did not find any evidence that the effect varies by baseline risk,<sup>29</sup> this analysis is limited by a lack of statistical power and it appears that clinicians are unconvinced. For example, a recent analysis of data collected by the Trauma Audit and Research Network of major trauma care in England & Wales, shows that only 10% of trauma patients receive TXA, with administration largely limited to those judged to be at high risk.<sup>30</sup> This suggests that doctors are uncertain about the balance of benefits and harms in low risk patients. This uncertainty could mean that many patients are dying unnecessarily. In terms of the number of deaths that could be prevented with TXA, most are in patients at low risk of death as they account for the greatest number of patients. By not treating these patients with TXA, we could therefore be failing to realise much of the potential benefit of TXA. It is therefore critical that we undertake robust analyses to determine the effects of anti-fibrinolytics by baseline risk.

*How do the effects of anti-fibrinolytics such as TXA, vary by dose?* The reduction in the risk of death due to bleeding observed in the CRASH-2 and WOMAN trials were observed after administration of a fixed dose of 1-2 g of TXA. An analysis based on aggregate data from surgery trials suggests that there may not be any additional benefit on bleeding associated with doses greater than 1 g<sup>21</sup> although many surgery patients receive doses higher than this. Furthermore, high doses (i.e. 5-10 g) of TXA have been found to be associated with an increased risk of seizures in surgical patients.<sup>22, 31, 32</sup> A better understanding of the benefit and harms of varying doses of anti-fibrinolytics is crucial for informing clinical practice.

These questions represent unresolved uncertainties which are limiting the use of TXA in practice and need to be resolved to ensure that TXA is used to achieve maximum patient benefit.

## **Rationale**

There is good evidence that anti-fibrinolytics are effective in bleeding patients but important uncertainties remain, including the risk of thromboembolic events and how the effects vary by baseline risk, the timing of treatment, site of bleeding and dose. Such uncertainties are a serious problem as they limit the use of anti-fibrinolytics in clinical practice and therefore need to be resolved. However, such uncertainties cannot be reliably resolved by individual trials or by standard meta-analyses based on aggregate data. We have therefore established the Anti-fibrinolytics Trialists Collaboration (ATC) to undertake individual patient data (IPD) meta-analyses of the effects of anti-fibrinolytics in bleeding patients. Systematic reviews and meta-analyses of IPD are the 'gold standard' for systematic reviews.<sup>33</sup> IPD reviews allows for more flexible analysis of outcomes and the increased statistical power facilitates more reliable subgroup analyses.

## **OBJECTIVES**

To conduct a systematic review and IPD meta-analyses to assess the effects of anti-fibrinolytic drugs on death, thromboembolic events, sepsis, and seizures in patients with or at risk of bleeding and to answer the following questions;

- i) Does the effectiveness and safety of anti-fibrinolytic treatment vary by the site of bleeding?
- ii) Does the effectiveness and safety of anti-fibrinolytic treatment vary by time to treatment?
- iii) Does the effectiveness and safety of anti-fibrinolytic treatment vary by baseline risk?
- iv) Does the effectiveness and safety of anti-fibrinolytic treatment vary by dose?

## **METHODS**

### **General approach**

The systematic review will be conducted by a review team based at the LSHTM CTU that will not include the principal investigators of any of the eligible trials.

## Systematic review

### *Trial eligibility criteria*

#### Types of trials

Randomised controlled trials. To be included a randomised trial must:

- be prospectively registered (i.e. before the first participant is enrolled) in a trial registry according to the ICMJE definition;
- randomise 500 patients or more; and
- be judged to be at low risk of bias for sequence generation, allocation concealment and blinding of outcome assessment.

Inclusion will also be contingent on receipt of a copy of the ethics approval and protocol for each trial.

All eligible trials will be included irrespective of language or publication status.

#### Types of participants

Patients with, or at risk of, bleeding.

#### Types of interventions

Anti-fibrinolytics drugs including aprotinin, tranexamic acid, epsilon-aminocaproic acid and p-aminomethylbenzoic acid. All of modes of administering the drug (e.g. intravenous, intramuscular, oral, topical) will be eligible.

#### Types of comparator

Control group not treated with an anti-fibrinolytic (placebo or standard care).

#### Types of outcomes

##### Primary

- Death due to bleeding (in the case of trials in intracranial bleeding, this includes death due to head injury or haemorrhagic stroke).

##### Secondary

- Death (cause described: all-cause, multi-organ failure, thromboembolic events, sepsis, other)
- Dependency (in trials of intracranial haemorrhage only)
- Thromboembolic events (myocardial infarction, ischaemic stroke, pulmonary embolism, deep vein thrombosis)



- Sepsis
- Seizures

### *Search methods for identifying trials*

We will identify trials from a register of anti-fibrinolytic trials maintained by the LSHTM CTU. Records included in this register are identified by running regular searches of the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the WHO International Clinical Trials Registry Platform, using the search strategies shown in Appendix 1. We will also check reference lists of relevant articles and correspond with trialists to identify any further trials. The searches will not be restricted by language or publication status.

### *Selecting trials*

One review team member will examine (screening by title and abstract) the records to identify potentially eligible trials. The full texts of these potentially eligible trial reports will be retrieved and assessed against the inclusion criteria. Two review team members will independently extract aggregate data using an extraction form. Disagreements will be resolved through discussion or after consultation with a third review team member if required.

### *Assessing risk of bias*

Trials will be assessed as being at low, unclear, or high risk of bias for the following domains according to criteria adapted from Cochrane guidelines:<sup>34</sup>

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants, personnel (performance bias);
- blinding of outcome assessors (detection bias);
- incomplete outcome data (attrition bias);
- selective outcome reporting (reporting bias).

Only trials judged to be at low risk of bias for random sequence generation, allocation concealment and blinding of outcome assessment will be included.

We will only consider trials using a centralised method of allocation to be at low risk of bias for allocation concealment. We will judge the use of sealed envelopes to be at high risk of bias due to potential for the subversion of the randomisation process.<sup>35</sup>

We will only assess the risk of bias for incomplete outcome data and selective outcome reporting for trials for which IPD is not provided.

Two members of the review team will independently assess the risk of bias in each included trial. Disagreements will be resolved by discussion with involvement of a third review team member if required.

### Collecting individual patient data

We will contact the named investigator (as specified in the final trial publication or the trial registration record) for each trial and provide them with the IPD meta-analysis protocol and a cover letter explaining what the study is about. If we receive no response from the named investigator, we will contact another trial investigator. The investigators of the eligible trials will be invited to join the ATC and to contribute IPD for analysis.

We will request the anonymised, individual patient data from all eligible trials. The data items to be requested will include a limited number of baseline, treatment, and outcome variables. This will include baseline data recorded before randomisation, information on the randomly allocated treatments and information on the prospectively agreed outcomes occurring during the scheduled treatment period (i.e. intention-to-treat) for each randomised patient. We will also request the data dictionary for the dataset.

Trialists can provide the data in their preferred format for transfer to the co-ordinators based at LSHTM CTU by any secure method depending on the preference of the trialists' institutions.

### Data analysis

A separate statistical analysis plan will be prepared and published prior to any IPD being sought from the trialists. The following general approach is anticipated.

Before conducting analyses to estimate the effects of anti-fibrinolytic treatment, we will present descriptive analyses to show any differences in baseline characteristics between the types of patient enrolled in the included trials. We will present statistical comparisons of baseline means (t-tests) and prevalence measures (chi-squared tests) for patients enrolled in the included trials.

IPD meta-analysis will be conducted using a one-stage model. The one-stage approach combines IPD in a single meta-analysis based on a regression model stratified by trial. This approach allows for the investigation of within and between trial variances and estimation of the effect of anti-fibrinolytics in a single analytical model. We will use logistic regression to estimate the relationship between treatment effect with time to treatment, baseline risk, site of bleeding, and dose. We will report treatment effects using odds ratios and 95% confidence intervals.

Data on all randomised patients will be included regardless of whether or not they received the trial treatment (i.e. on an intention-to-treat basis).

A separate analysis limited to the subset of trials assessing the effects of anti-fibrinolytics in patients with intracranial haemorrhage is planned, the statistical analysis plan for which has been published.<sup>36</sup>

### **Inclusion of aggregate data**

For trials that do not provide IPD, we will extract aggregate data from the final trial reports which will be incorporated into sensitivity analyses as specified in the statistical analysis plan.

### **PUBLICATION POLICY**

Collaborating trialists will have the opportunity to contribute to the interpretation of results. Data will not be used in any publication without the permission of the responsible trialists.

All reports will be published in the name of the ATC. We aim to publish the main results of the analysis in a peer-reviewed journal under a CC-BY Licence. This licence will ensure the publication is freely available and can be distributed by others as long as they give credit to the original creation. All publications will follow the PRISMA-IPD statement.<sup>37</sup> Links to publications will be inserted into the PROSPERO registration record and the ATC website.

### **CONFIDENTIALITY, DATA STORAGE, AND HANDLING**

A separate data policy will be made available prior to any IPD being sought from the collaborating trialists. All IPD data supplied to the ATC will be held securely at the LSHTM CTU in adherence to all relevant legislation, guidelines, and regulatory requirements. The data will be used for the purposes of medical research only and within the constraints of consent under which the data were provided to the ATC. Supplied data will not be shared with others outside of the ATC management group without the permission of the responsible trialist. No individual patients will be identified in any publications or presentations prepared by the ATC.

Original data will be transferred and stored in a secure environment at the LSHTM CTU. Data will only be accessible by ATC staff and authorised personnel. Electronic data will be protected by any or all of the following: assigned log-ins, protected network areas and encryption.

We will check the data for consistency and completeness, referring any resultant queries back to the responsible trialists for clarification.

Trialists will be able to withdraw their data from the analyses at any time.

## ETHICAL APPROVAL

We judge that separate institutional review board (IRB) approval for this study is not required. This project involves the analysis of existing trial data. Each trial providing individual patient data will have received local ethical approval. The planned study will not require further recruitment or data collection from patients and the analysis will not include identifiable data. If, however, there is uncertainty about the use of data from any trial, we will seek approval from the IRB board that originally approved the trial before including the data in the analysis.

## FUNDING

The establishment and preliminary work of the ATC is supported by the LSHTM CTU. Additional funding from other sources is being sought.

## PROTOCOL DEVELOPMENT

This protocol has been prepared by the following members of the ATC management group with contributions from trial representatives including those present at the first meeting of the Anti-fibrinolytics Trialists Collaboration held in June 2018.

<b>Name, institution</b>	<b>Role</b>
Dr Francois-Xavier Ageron, Annecy Genevois Hospital	Clinical expert
Professor Philip Bath, University of Nottingham	Trialist (TICH-2)
Ms Amy Brenner, LSHTM	Research Fellow and epidemiologist
Professor Mike Clarke, Queen's University Belfast	Methodological expert
Catherine Deneux-Tharoux, National Institute for Health and Medical Research (INSERM)	Trialist (TRAAP)
Dr Angèle Gayet-Ageron, University Hospitals of Geneva	Clinician and methodologist
Professor Russell Gruen, Australian National University	Trialist (PATCH)
Dr Katharine Ker, LSHTM*	Methodologist and co-ordinator of ATC
Ms Abda Mahmood, LSHTM	PhD student
Dr Maura Marcucci, McMaster University	Trialist (POISE-3)
Professor Paul Myles, Monash University	Trialist (ATACAS)
Professor Ian Roberts, LSHTM	Trialist (CRASH-2, CRASH-3, HALT-IT)
Professor George Saade, University of Texas Medical Branch at Galveston	Trialist (NCT03364491)
Professor Loic Sentilhes, Bordeaux University Hospital	Trialist (TRAAP, TRAAP-2)

Professor Haleema Shakur-Still, LSHTM	Trialist (WOMAN, WOMAN-2)
Professor Nikola Sprigg, University of Nottingham	Trialist (TICH-2)
Dr Elizabeth Thom, The George Washington University	Trialist (NCT03364491)

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## AMENDMENTS

We anticipate that this will be an ongoing research project. New evidence will be incorporated as it becomes available and new hypotheses may emerge. Any consequent protocol amendments will be detailed in a revised protocol document that will be dated and assigned a new version number.

## REFERENCES

1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, *et al.* Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet* 2015;385 Suppl 2:S11.
2. Karkouti K, Wijesundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA, *et al.* The independent association of massive blood loss with mortality in cardiac surgery. *Transfusion* 2004;44(10):1453-1462.
3. Ker K, Kiriya J, Perel P, Edwards P, Shakur H, Roberts I. 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 Emerg Med* 2012;12:3.
4. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma* 2006;60(6 Suppl):S3-11.
5. Heckbert SR, Vedder NB, Hoffman W, Winn RK, Hudson LD, Jurkovich GJ, *et al.* Outcome after hemorrhagic shock in trauma patients. *J Trauma* 1998;45(3):545-549.
6. NICE. Head injury: assessment and early management. Clinical guideline [CG176] - <https://www.nice.org.uk/guidance/cg176>. 2014.
7. Bruns J, Jr., Hauser WA. The epidemiology of traumatic brain injury: a review. *Epilepsia* 2003;44 Suppl 10:2-10.
8. Perel P, Roberts I, Bouamra O, Woodford M, Mooney J, Lecky F. Intracranial bleeding in patients with traumatic brain injury: a prognostic study. *BMC Emerg Med* 2009;9:15.
9. Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, *et al.* Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. *Neuroepidemiology* 2015;45(3):161-176.
10. Homnick A, Sifri Z, Yonclas P, Mohr A, Livingston D. The temporal course of intracranial haemorrhage progression: how long is observation necessary? *Injury* 2012;43(12):2122-2125.
11. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, *et al.* Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* 1997;28(1):1-5.

12. Crooks C, Card T, West J. Reductions in 28-day mortality following hospital admission for upper gastrointestinal hemorrhage. *Gastroenterology* 2011;141(1):62-70.
13. Calvert C, Thomas SL, Ronsmans C, Wagner KS, Adler AJ, Filippi V. Identifying regional variation in the prevalence of postpartum haemorrhage: a systematic review and meta-analysis. *PLoS One* 2012;7(7):e41114.
14. Carroli G, Cuesta C, Abalos E, Gulmezoglu A. Epidemiology of postpartum haemorrhage: a systematic review. *Best practice and research in clinical obstetrics and gynaecology* 2008;epub(Accessed 9/10/08).
15. Say L, Pattinson R, Gulmezoglu A. WHO systematic review of maternal morbidity and mortality: the prevalence of severe acute maternal morbidity(near miss). *BioMed Central. Reproductive Health* 2004;1(3).
16. Thompson JF, Heal LJ, Roberts CL, Ellwood DA. Women's breastfeeding experiences following a significant primary postpartum haemorrhage: A multicentre cohort study. *Int Breastfeed J* 2010;5:5.
17. James Lind Alliance Blood Transfusion and Blood Donation Priority Setting Partnership. Final data sheet, March 2018 - <http://www.jla.nihr.ac.uk/priority-setting-partnerships/blood-transfusion-and-blood-donation/downloads/Blood%20Transfusion%20and%20Blood%20Donation%20PSP%20final%20data%20sheet.pdf>. 2018.
18. Cesarman-Maus G, Hajjar KA. Molecular mechanisms of fibrinolysis. *Br J Haematol* 2005;129(3):307-321.
19. Lucas MA, Fretto LJ, McKee PA. The binding of human plasminogen to fibrin and fibrinogen. *J Biol Chem* 1983;258(7):4249-4256.
20. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *Bmj* 2012;344:e3054.
21. Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. *Br J Surg* 2013;100(10):1271-1279.
22. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T, *et al.* Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery. *N Engl J Med* 2017;376(2):136-148.
23. The CRASH-2 Collaborators. 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* 2010;376(9734):23-32.
24. Woman Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017;389(10084):2105-2116.
25. Sprigg N, Flaherty K, Appleton JP, Al-Shahi Salman R, Bereczki D, Beridze M, *et al.* Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet* 2018;391(10135):2107-2115.
26. ADVANZ Pharma. Summary of product characteristics. Tranexamic Acid 100mg/ml Solution for Injection (<https://www.medicines.org.uk/emc/product/1220/smpc#companyDetails>). Updated 6 August 2018.

27. Pealing L, Perel P, Prieto-Merino D, Roberts I, Collaborators C-T. Risk factors for vascular occlusive events and death due to bleeding in trauma patients; an analysis of the CRASH-2 cohort. *PLoS One* 2012;7(12):e50603.
28. The CRASH-2 Collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011;377(9771):1096-1101, 1101 e1091-1092.
29. Roberts I, Perel P, Prieto-Merino D, Shakur H, Coats T, Hunt BJ, *et al.* Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial. *Bmj* 2012;345:e5839.
30. Coats TJ, Fragoso-Iniguez M, Roberts I. Implementation of tranexamic acid for bleeding trauma patients: a longitudinal and cross-sectional study. *Emerg Med J* 2018.
31. Kalavrouziotis D, Voisine P, Mohammadi S, Dionne S, Dagenais F. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. *The Annals of thoracic surgery* 2012;93(1):148-154.
32. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M. High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesthesia & Analgesia* 2010;110(2):350-353.
33. Stewart L, Tierney J, Clarke M, on behalf of the Cochrane Individual Patient Data Meta-analysis Methods Group, *Reviews of individual patient data in Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).*, J. Higgins and S. Green, Editors. 2011.
34. Higgins J, Green S, *Cochrane Handbook for Systematic Reviews of Interventions*. 2011, Chichester, UK: John Wiley & Sons Ltd.
35. Kennedy ADM, Torgerson DJ, Campbell MK, Grant AM. Subversion of allocation concealment in a randomised controlled trial: a historical case study. *Trials* 2017;18(1):204.
36. Ker K, Prieto-Merino D, Sprigg N, Mahmood A, Bath P, Kang Law Z, *et al.* The effectiveness and safety of antifibrinolytics in patients with acute intracranial haemorrhage: statistical analysis plan for an individual patient data meta-analysis. *Wellcome Open Res* 2017;2:120.
37. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, *et al.* Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA* 2015;313(16):1657-1665.

## APPENDIX 1: SEARCH STRATEGIES

### Ovid MEDLINE

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?9921 or 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-aminomethylcyclohexanecarboxylic acid\* or t-amcha or amca or kabi 2161 or transamin\* or exacyl or amchafibrin or anvitoff or spotof or cyklokapon 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 cyclokapon or cyklokapon 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 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.
9. exp 4-Aminobenzoic Acid/tu [Therapeutic Use]
10. (PAMBA or para-aminomethylbenzoic or p-aminomethylbenzoic or amino?methylbenzoic acid or Gumbix or Styptopur or H-4-AMB-OH or CAS:56-91-7 or H-4AMBZ-OH or NH2-CH2-PH4-COOH or TIMTEC-BB SBB006704 or "RARECHEM AL BW 0005" or Amino-p-toluicacid).ti,ab.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 10
12. randomi?ed.ab,ti.
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. placebo.ab.
16. clinical trials as topic.sh.
17. randomly.ab.
18. trial.ti.
19. 12 or 13 or 14 or 15 or 16 or 17 or 18



20. (animals not (humans and animals)).sh.
21. 19 not 20
22. 11 and 21

### Ovid EMBASE

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 kazaal 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 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-aminomethylcyclohexanecarboxylic 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 aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklokapron 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 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 ethaaminocaproic or emocaprol or hepin or ipilon or jd?177 or neocaprol or nsc?26154 or tachostyptan).ab,ti.
9. exp 4-Aminobenzoic Acid/tu [Therapeutic Use]
10. (PAMBA or para-aminomethylbenzoic or p-aminomethylbenzoic or amino?methylbenzoic acid or Gumbix or Styptopur or H-4-AMB-OH or CAS:56-91-7 or H-4AMBZ-OH or NH2-CH2-PH4-COOH or TIMTEC-BB SBB006704 or "RARECHEM AL BW 0005" or Amino-p-toluic acid).ti,ab.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 10
12. randomi?ed.ab,ti.
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. placebo.ab.
16. clinical trials as topic.sh.
17. randomly.ab.
18. trial.ti.

- 19. 12 or 13 or 14 or 15 or 16 or 17 or 18
- 20. (animals not (humans and animals)).sh.
- 21. 19 not 20
- 22. 11 and 21

## CENTRAL

- 1 MeSH descriptor: [Antifibrinolytic Agents] explode all trees
- #2 (anti-fibrinolytic\* or antifibrinolytic\* or antifibrinolysin\* or anti-fibrinolysin\* or antiplasmin\* or anti-plasmin\*):ti,ab,kw (Word variations have been searched)
- #3 ((plasmin or fibrinolysis) near/3 inhibitor\*)
- #4 #2 or #3
- #5 #1 or #4
- #6 MeSH descriptor: [Aprotinin] explode all trees
- #7 (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):ti,ab,kw (Word variations have been searched)
- #8 (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?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren or midran)
- #9 #7 or #8
- #10 ((Kunitz near/3 inhibitor\*) or (pancrea\* near/3 antitrypsin) or (pancrea\* near/3 trypsin next inhibitor\*)):ti,ab,kw (Word variations have been searched)
- #11 #6 or #9 or #10
- #12 MeSH descriptor: [Tranexamic Acid] explode all trees
- #13 (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 cyklokapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA):ti,ab,kw (Word variations have been searched)
- #14 #12 or #13
- #15 MeSH descriptor: [Aminocaproic Acids] explode all trees
- #16 MeSH descriptor: [6-Aminocaproic Acid] explode all trees
- #17 (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)
- #18 (aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic):ti,ab,kw (Word variations have been searched)
- #19 #15 or #16 or #17 or #18
- #20 (PAMBA or para-aminomethylbenzoic or p-aminomethylbenzoic).ti,ab,kw.

#21 #5 or #11 or #14 or #19 or #20

**WHO International Clinical Trials Registry Platform**

anti-fibrinolytic\* OR antifibrinolytic\* OR tranexamic OR TXA OR aprotinin OR epsilon-aminocaproic  
OR EACA OR p-aminomethylbenzoic OR PAMBA OR para-aminomethylbenzoic OR p-  
aminomethylbenzoic

Recruitment status = All

Terms in 'Title' OR 'Intervention'