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Haemostatic therapies for acute spontaneous intracerebral haemorrhage (Review)

Al-Shahi Salman R, Law ZK, Bath PM, Steiner T, Sprigg N

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[Intervention Review]

Haemostatic therapies for acute spontaneous intracerebral haemorrhage

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ABSTRACT

Background

Outcome after spontaneous (non-traumatic) intracerebral haemorrhage (ICH) is influenced by haematoma volume; up to one-third of ICHs enlarge within 24 hours of onset. Early haemostatic therapy might improve outcome by limiting haematoma growth. This is an update of a Cochrane Review first published in 2006, and last updated in 2009.

Objectives

To examine 1) the effectiveness and safety of individual classes of haemostatic therapies, compared against placebo or open control, in adults with acute spontaneous intracerebral haemorrhage, and 2) the effects of each class of haemostatic therapy according to the type of antithrombotic drug taken immediately before ICH onset (i.e. anticoagulant, antiplatelet, or none).

Search methods

We searched the Cochrane Stroke Trials Register, CENTRAL; 2017, Issue 11, MEDLINE Ovid, and Embase Ovid on 27 November 2017. In an effort to identify further published, ongoing, and unpublished randomised controlled trials (RCT), we scanned bibliographies of relevant articles and searched international registers of RCTs in November 2017.

Selection criteria

We sought randomised controlled trials (RCTs) of any haemostatic intervention (i.e. pro-coagulant treatments such as coagulation factors, antifibrinolytic drugs, or platelet transfusion) for acute spontaneous ICH, compared with placebo, open control, or an active comparator, reporting relevant clinical outcome measures.

Data collection and analysis

Two authors independently extracted data, assessed risk of bias, and contacted corresponding authors of eligible RCTs for specific data if they were not provided in the published report of an RCT.

Main results

We included 12 RCTs involving 1732 participants. There were seven RCTs of blood clotting factors versus placebo or open control involving 1480 participants, three RCTs of antifibrinolytic drugs versus placebo or open control involving 57 participants, one RCT of platelet transfusion versus open control involving 190 participants, and one RCT of blood clotting factors versus fresh frozen plasma involving five participants. We were unable to include two eligible RCTs because they presented aggregate data for adults with ICH and other types of intracranial haemorrhage. We identified 10 ongoing RCTs. Across all seven criteria in the 12 included RCTs, the risk of bias was unclear in 37 (44%), high in 16 (19%), and low in 31 (37%). Only one RCT was at low risk of bias in all criteria.

In one RCT of platelet transfusion versus open control for acute spontaneous ICH associated with antiplatelet drug use, there was a significant increase in death or dependence (modified Rankin Scale score 4 to 6) at day 90 (70/97 versus 52/93; risk ratio (RR) 1.29, 95% confidence interval (CI) 1.04 to 1.61, one trial, 190 participants, moderate-quality evidence). All findings were non-significant for blood clotting factors versus placebo or open control for acute spontaneous ICH with or without surgery (moderate-quality evidence), for antifibrinolytic drugs versus placebo (moderate-quality evidence) or open control for acute spontaneous ICH (moderate-quality evidence), and for clotting factors versus fresh frozen plasma for acute spontaneous ICH associated with anticoagulant drug use (no evidence).

Authors' conclusions

Based on moderate-quality evidence from one trial, platelet transfusion seems hazardous in comparison to standard care for adults with antiplatelet-associated ICH.

We were unable to draw firm conclusions about the efficacy and safety of blood clotting factors for acute spontaneous ICH with or without surgery, antifibrinolytic drugs for acute spontaneous ICH, and clotting factors versus fresh frozen plasma for acute spontaneous ICH associated with anticoagulant drug use.

Further RCTs are warranted, and we await the results of the 10 ongoing RCTs with interest.

PLAIN LANGUAGE SUMMARY

Treatments to help blood clotting to improve the recovery of adults with stroke due to bleeding in the brain

Review question

Do treatments to help blood clot reduce the risk of death and disability for adults with stroke due to bleeding in the brain?

Background

More than one-tenth of all strokes are caused by bleeding in the brain (known as brain haemorrhage). The bigger the haemorrhage, the more likely it is to be fatal. Roughly one-third of brain haemorrhages enlarge significantly within the first 24 hours. Therefore, treatments that promote blood clotting might reduce the risk of death or being disabled after brain haemorrhage by limiting its growth, if given soon after the bleeding starts. However, haemostatic drugs might cause unwanted clotting, leading to unwanted side effects, such as heart attacks and clots in leg veins.

Study characteristics

We found 12 randomised controlled trials, including 1732 participants, up to November 2017.

Key results

We found moderate-quality evidence of harm from platelet transfusion for people who had used antiplatelet drugs until they had a brain haemorrhage. We found no evidence of either benefit or harm from other haemostatic therapies for people with brain haemorrhage.

Quality of the evidence

Overall, the quality of the evidence was moderate to low.

More information will become available from the 10 trials that are ongoing.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Blood clotting factors compared with placebo or open control for acute spontaneous intracerebral haemorrhage

Patient or population: adults with acute spontaneous intracerebral haemorrhage
Settings: secondary care
Intervention: recombinant activated factor VII
Comparison: placebo or open control

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Death or dependence (mRS 4 to 6) at day 90	**RR 0.87** (0.70 to 1.07)	1390 (6)	⊕⊕⊕◯ **moderate**[1]	

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

CI: confidence interval; RR: risk ratio; mRS: modified Rankin Scale
[1]We downgraded the quality of the evidence once because of imprecision.

BACKGROUND

Description of the condition

The burden of haemorrhagic stroke is out of proportion to its frequency as a subtype of stroke. Although haemorrhagic stroke causes 11% to 22% of all new strokes (Feigin 2009), it caused 50% of all stroke deaths, and approximately 42% (47 million) of the disability-adjusted life years lost due to stroke in the 2013 Global Burden of Disease study (Feigin 2015). Spontaneous (non-traumatic) intracerebral haemorrhage (ICH) accounts for two-thirds of haemorrhagic stroke, amounting to more than two million strokes per year (Al-Shahi Salman 2009a). ICH is due to cerebral small vessel disease, and may be associated with the use of antithrombotic (i.e. anticoagulant or antiplatelet) drugs. The age-specific incidence of ICH - like the age-specific incidence of ischaemic stroke and myocardial infarction - rises with age (Feigin 2015). Two-thirds of people who have an ICH are 75 years or older (Lovelock 2007; Samarasekera 2015). Given that the number of people aged 75 years and older is projected to rise in many parts of the world, the burden due to ICH incidence, recurrence, and prevalence will rise.

Outcome after stroke due to ICH is poor: one-year survival is 46% (95% confidence interval (CI) 43% to 49%), five-year survival is 29% (95% CI 26% to 33%), and predictors most consistently associated with death are increasing age, decreasing Glasgow Coma Scale score, increasing ICH volume, presence of intraventricular haemorrhage, and deep or infratentorial ICH location (Poon 2014). Approximately one-third of acute ICHs (i.e. less than 24 hours after symptom onset or time last seen well) enlarge from three to 24 hours after onset (Brott 1997); ICH growth is independently associated with death and poor outcome (Davis 2006).

Description of the intervention

The three main components of haemostasis (the process that stops bleeding) are vasoconstriction, platelet plug formation, and coagulation.

Vascular smooth muscle cell vasoconstriction is a blood vessel's first response to injury. They constrict the damaged vessels, which reduces the amount of blood flow through the area and limits the amount of blood loss. Collagen is exposed at the site of injury, which causes platelets to adhere to the injury site.

Primary haemostasis is achieved by platelets, which adhere to damaged endothelium to form a platelet plug. Plug formation is activated by the Von Willebrand factor, which is found in plasma. When platelets are activated, they express glycoprotein receptors that interact with other platelets, producing aggregation and adhesion. Platelets release cytoplasmic granules that contain serotonin, adenosine diphosphate (ADP), and thromboxane A2, all of which increase the effect of vasoconstriction. ADP attracts more platelets to the affected area, serotonin is a vasoconstrictor, and thromboxane A2 assists in platelet aggregation, vasoconstriction, and degranulation.

Secondary haemostasis starts once a platelet plug has been formed. Blood plasma clotting factors are activated in a sequence of events known as the coagulation cascade. Inactive fibrinogen produces a fibrin mesh around the platelet plug to hold it in place. Red and white blood cells are trapped in the mesh to produce a thrombus, or clot. Tissue factor (also called platelet tissue factor, factor III, or thromboplastin) is a protein that is exposed after endothelial damage, which leads to thrombin formation and activation of the tissue factor pathway, as well as its circulating ligand factor VII.

Therapies that intervene in primary haemostasis (e.g. platelet transfusion) or secondary haemostasis (e.g. administration of clotting factors (fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC), or antifibrinolytic drugs) might promote clot formation, decrease bleeding, and thus improve outcomes by limiting ICH growth.

How the intervention might work

Theoretically, early interventions to reduce acute ICH volume might improve outcomes. Although surgical craniotomy to evacuate spontaneous supratentorial ICH and reduce ICH volume was found to reduce the odds of dying or becoming dependent compared with medical management alone, the result was not very robust, and surgical evacuation is not frequently used (Prasad 2008). Therefore, medical (non-surgical) interventions to promote haemostasis, and limit haematoma growth, have become the main focus of acute ICH therapeutic research.

Why it is important to do this review

Various haemostatic therapies have been investigated in a variety of spontaneous bleeding conditions with little evidence for their effectiveness in some settings (Johansen 2015: Stanworth 2012; Wikkelsø 2013), but clear benefit in others (Ker 2015). It is unclear whether they are effective for acute ICH. Therefore, we systematically reviewed the literature for randomised controlled trials (RCTs) of all potential haemostatic therapies for the treatment of acute spontaneous ICH.

OBJECTIVES

To examine 1) the effectiveness and safety of individual classes of haemostatic therapies, compared against placebo or open control, in adults with acute spontaneous intracerebral haemorrhage (ICH), and 2) the effects of each class of haemostatic therapy according to the type of antithrombotic drug taken immediately before ICH onset (i.e. anticoagulant, antiplatelet, or none).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, whether published or unpublished, regardless of the language of publication. Pseudo-randomised studies were not eligible.

Types of participants

People of any sex, aged 16 years or older. We restricted this review to people with radiographically-confirmed acute spontaneous intracerebral haemorrhage (ICH). Where possible, we grouped RCTs, or participant subgroups, by whether ICH was associated with antiplatelet drug use, anticoagulant drug use, or neither.

Types of interventions

Single or multiple haemostatic therapies (including antifibrinolytic drugs, blood coagulation factors, antidotes to specific antithrombotic drugs, platelet transfusion, or other platelet activation therapies), regardless of dosage or route of administration. Interventions could be compared against placebo, open control, or an active comparator.

Types of outcome measures

We assessed the following outcomes at 90 days after randomization (or at the end of scheduled follow-up, if not provided at 90 days).

Primary outcomes

- Death or dependence from any cause (measured on a standard rating scale, such as the modified Rankin Scale)

Secondary outcomes

- All serious adverse events (if possible, with a separate analysis of arterial and venous thromboembolic events, including deep vein thrombosis symptomatic pulmonary embolism, arterial embolism, myocardial infarction, ischaemic stroke, and disseminated intravascular coagulation)
- Change in volume of ICH on follow-up brain imaging
- Death from any cause (categorised into early (e.g. less than seven days) and late (e.g. between seven days and the end of follow-up) if possible)
- Quality of life
- Mood
- Cognitive function

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We searched for trials in all languages, and arranged for the translation of relevant articles when necessary.

Electronic searches

The Cochrane Stroke Group Information Specialist searched the Cochrane Stroke Group Trials Register (last searched 27 November 2017), the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 11) in the *Cochrane Library* (searched 27 November 2017; Appendix 1); MEDLINE Ovid (1946 to 27 November 2017; Appendix 2); and Embase Ovid (1974 to 27 November 2017; Appendix 3).

One review author (ZL) also searched the following international registers of RCTs on 27 November 2017.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) using the search strategy in Appendix 4;
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch) using the search strategy in Appendix 5.

Searching other resources

In an effort to identify further published, ongoing, and unpublished RCTs, three authors (RA-SS, NS, and ZL) scanned bibliographies of relevant articles.

Data collection and analysis

Selection of studies

Two authors independently checked the titles and abstracts of studies identified by the search strategy for RCTs meeting the selection criteria for the first version of this review (You 2006). Two authors (ZL or RA-SS) independently screened the results of the updated searches for potentially eligible studies for this updated review, and obtained the full published articles or trial registry entries for studies likely to be relevant RCTs. Two authors (NS and RA-SS) independently read these potentially eligible RCTs in full, and confirmed their inclusion according to the inclusion criteria.

Data extraction and management

Two authors (NS and RA-SS) used a standard data collection form to independently extract data on risk of bias, other RCT characteristics, participants, methods, interventions, outcomes, and results. If necessary, we sought additional data from the principal investigators of RCTs that met, or potentially met the inclusion criteria. We sought unpublished data that were not quantified in

the original publications, or not presented as stratified by intracranial haemorrhage type, from the principal investigators and pharmaceutical companies. In the one study for which these data were not forthcoming, RA-SS measured the numbers in the relevant groups in the stacked bar charts, using Adobe Acrobat Professional measuring tools on the PDF of the published study (Mayer 2008 (FAST)). In one phase II study, we could obtain only limited data from the Novo Nordisk website (F7ICH-1602 2007).

Assessment of risk of bias in included studies

Two authors (NS and RA-SS) independently assessed included RCTs' risk of bias, according to the seven criteria of the Cochrane 'Risk of bias' tool (Higgins 2011). The same two authors discussed and agreed on the overall quality of the evidence for each outcome, using the GRADE approach (Higgins 2011).

Measures of treatment effect

We calculated risk ratio (RR) for dichotomous data, and mean difference (MD), or standardized mean difference (SMD) for different measures of the same outcome, for continuous data.

Dealing with missing data

We sought missing data from studies' corresponding authors, and used all the data that were available to us.

Assessment of heterogeneity

We estimated inconsistency between RCTs using the I^2 statistic.

Assessment of reporting biases

We used funnel plots to assess publication bias where there were sufficient data.

Data synthesis

We used a random-effects model (because we expected studies of different drugs and doses to estimate different, yet related, treatment effects) to calculate RRs and 95% confidence intervals (CIs), with the inverse variance method.

Subgroup analysis and investigation of heterogeneity

We expected to find that the choice of intervention and comparator would be largely determined by the use and type of antithrombotic drug taken prior to a spontaneous acute ICH (e.g. fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC) for anticoagulant-associated ICH, platelet transfusion for antiplatelet-associated ICH). However, where interventions were used for ICH, whether it was associated with antithrombotic drug use or not (e.g. the clotting factor recombinant activated factor VII, antifibrinolytic drugs), and where ICH evacuation using craniotomy was performed, we stratified our analyses by pre-ICH antithrombotic drug use and use of surgery.

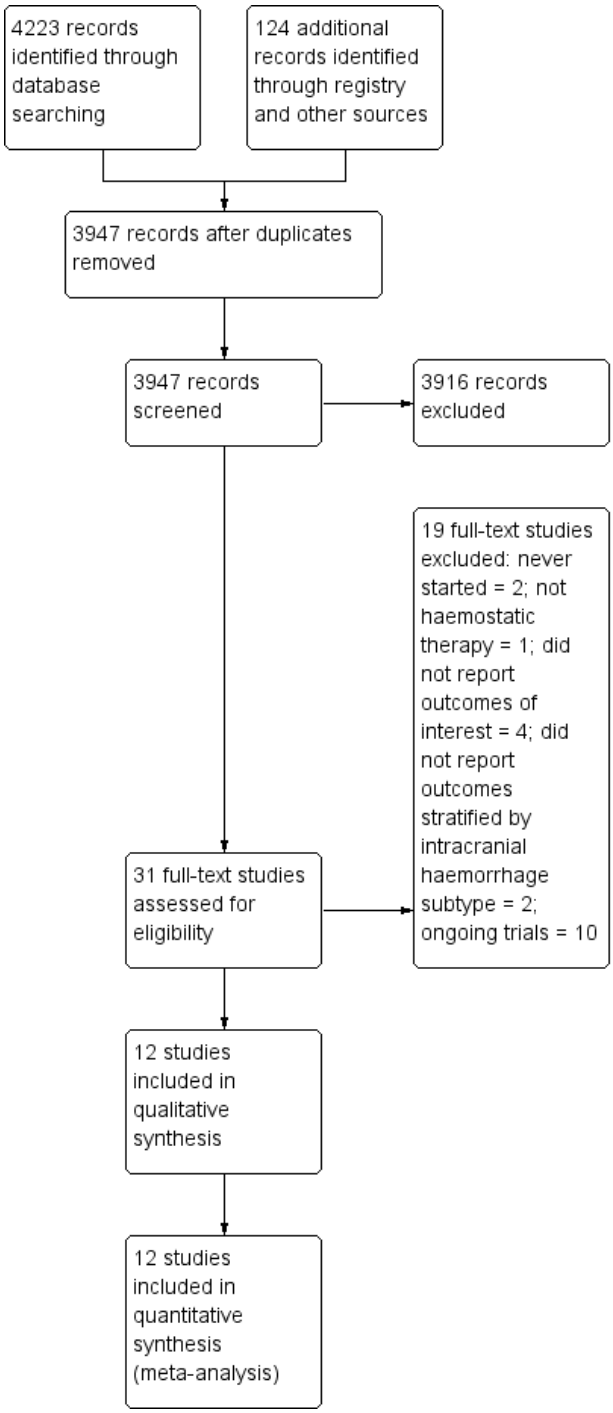
RESULTS

Description of studies

Results of the search

Our searches identified 31 potentially eligible randomised controlled trials (RCT); see Figure 1 for the flowchart describing the searches done for this update. We excluded nine studies because: they never started (Ciccone 2007; NCT02429453), they did not report any of our primary or secondary outcomes (Meng 2003; Zhou 2005), they did not report data and outcomes in the intracerebral haemorrhage population (Kerebel 2013; Steiner 2016 (INCH)), they did not quantify outcomes (Madjdinasab 2008), the study was stopped due to poor enrolment but never reported results (NCT00222625), or the study did not relate to a haemostatic therapy (Li 2016). Ten RCTs were still in the process of recruitment (Liu 2017 (TRAIGE); Meretoja 2014 (STOP-AUST); NCT00699621; NCT02777424; NCT02866838; NCT03044184; NOR-ICH), follow-up (Sprigg 2016 (TICH-2)), or reporting (NCT00810888; NCT01359202) at the time of writing, and will be assessed for inclusion with the next update. This left 12 RCTs that we included in this review, all of which included acute intracerebral haemorrhage (ICH) in adults aged 18 years or older (Arumugam 2015; Baharoglu 2016 (PATCH); Boulis 1999; F7ICH-1602 2007; Imbert 2012 (PRE-SICH); Li 2012; Mayer 2005a; Mayer 2005b; Mayer 2006; Mayer 2008 (FAST); Sprigg 2014 (TICH-1); Zazulia 2001 (ATICH)).

Figure 1. Study flow diagram



We included seven RCTs of blood clotting factors versus placebo or open control involving 1480 participants (F7ICH-1602 2007; Imbert 2012 (PRE-SICH); Li 2012; Mayer 2005a; Mayer 2005b; Mayer 2006; Mayer 2008 (FAST)), three RCTs of antifibrinolytic drugs versus placebo or open control involving 57 participants (Arumugam 2015; Sprigg 2014 (TICH-1); Zazulia 2001 (ATICH)), one RCT of platelet transfusion versus open control involving 190 participants (Baharoglu 2016 (PATCH)), and one RCT of blood clotting factors versus fresh frozen plasma involving five participants (Boulis 1999).

Included studies

We included 12 RCTs. For details, please refer to the 'Characteristics of included studies' table.

Of the seven RCTs of blood clotting factors versus placebo or open control, six examined blood clotting factors in adults with acute spontaneous ICH (F7ICH-1602 2007; Li 2012; Mayer 2005a; Mayer 2005b; Mayer 2006; Mayer 2008 (FAST)), and one in adults with acute spontaneous ICH undergoing craniotomy (Imbert 2012 (PRE-SICH)). Five studies were funded and conducted by Novo Nordisk, and compared the use of various doses of intravenous recombinant activated clotting factor VII (rFVIIa; (973 participants)) against placebo (422 participants), started within four hours of ICH onset in adults (F7ICH-1602 2007; Mayer 2005a; Mayer 2005b; Mayer 2006; Mayer 2008 (FAST)). Novo Nordisk supplied supplementary, unpublished data from three trials (Mayer 2005a; Mayer 2005b; Mayer 2006), but did not respond to several requests to provide further data from two trials (F7ICH-1602 2007; Mayer 2008 (FAST)). The other study of intravenous rFVIIa was performed independently of Novo Nordisk, as a single centre, phase II study, in adults with acute spontaneous ICH within six hours of ICH onset (Li 2012). We had not prespecified the exclusion of RCTs of haemostatic therapies following surgical intervention, so we included Imbert 2012 (PRE-SICH), which was a phase II study of intravenous rFVIIa in adults with acute spontaneous ICH undergoing craniotomy, administered immediately after the evacuation of the haematoma, within 24 hours of ICH onset.

Of the three RCTs of antifibrinolytic drugs versus placebo or open control, Zazulia 2001 (ATICH) was a phase II RCT of intravenous aminocaproic acid compared against supportive treatment alone, started within three hours of ICH onset in adults. Dr Allyson Zazulia provided unpublished data, because the trial was stopped after the enrolment of three participants because recruitment had been slow, and the investigators decided that the rationale for rFVIIa was better (Zazulia 2005). Sprigg 2014 (TICH-1) was a phase II RCT of intravenous tranexamic acid compared against supportive treatment alone, started within 24 hours of ICH onset in adults. Arumugam 2015 was a phase II RCT of intravenous tranexamic acid compared against supportive treatment alone, started within eight hours of ICH onset in adults.

We found one RCT of platelet transfusion versus open control involving 190 participants (Baharoglu 2016 (PATCH)).

We found one RCT of blood clotting factors versus fresh frozen plasma involving five participants with acute spontaneous ICH associated with anticoagulant drug use (Boulis 1999).

Excluded studies

We excluded nine studies. For details, please refer to the 'Characteristics of excluded studies' table. We excluded two eligible RCTs because they presented aggregate data for adults with ICH as well as other types of intracranial haemorrhage, and the study authors could not provide data restricted to the ICH group alone by the time this review was submitted (Kerebel 2013; Steiner 2016 (INCH)). One abstract proposed a RCT of tranexamic acid for ICH, but the corresponding author confirmed that funding had not been obtained (Ciccone 2007). We found two studies of aprotinin, but it was unclear whether they included some participants in both studies, and the outcome measures used were unsuitable for meta-analysis in this review (Meng 2003; Zhou 2005). NCT02429453 was a planned RCT of fresh frozen plasma (FFP) versus prothrombin complex concentrate (PCC), but was terminated before enrolment began. NCT00222625 was a study of coagulation factors, but it was "stopped due to slow recruitment" (Iorio 2012). Dr Iorio has not responded to requests for clarification about whether any data were collected. Madjdinasab 2008 was a study of coagulation factors, but no results were reported, and there was no response from the authors to requests for information for this review. Finally, Li 2016 was excluded as the intervention (TRABC) did not appear to be haemostatic, and had four Traditional Chinese Medicine (TCM) medicinals.

We identified 10 ongoing or recently completed but unreported RCTs. See 'Characteristics of ongoing studies' table for details. Two RCTs examined blood clotting factors versus placebo or open control (NCT00810888; NCT01359202), five examined antifibrinolytic drugs versus placebo or open control in acute spontaneous ICH (Liu 2017 (TRAIGE); Meretoja 2014 (STOP-AUST); NCT03044184; NOR-ICH; Sprigg 2016 (TICH-2)); one RCT examined antifibrinolytic drugs versus placebo or open control in acute spontaneous ICH associated with anticoagulant drug use (NCT02866838); one RCT examined platelet transfusion versus open control (NCT00699621), and one RCT examined blood clotting factors versus fresh frozen plasma in acute spontaneous ICH associated with anticoagulant drug use (NCT02777424).

Risk of bias in included studies

Across all seven domains in the 12 included RCTs, we assessed that the risk of bias, according to the Cochrane 'Risk of bias' tool, and guidance in the *Cochrane Handbook for Systematic Reviews of Interventions,* was unclear in 37 (44%), high in 16 (19%), and low in 31 (37%; (Figure 2; Figure 3; Higgins 2011)). Only one RCT was at low risk of bias in all domains (Sprigg 2014 (TICH-1)).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias criteria for each included study

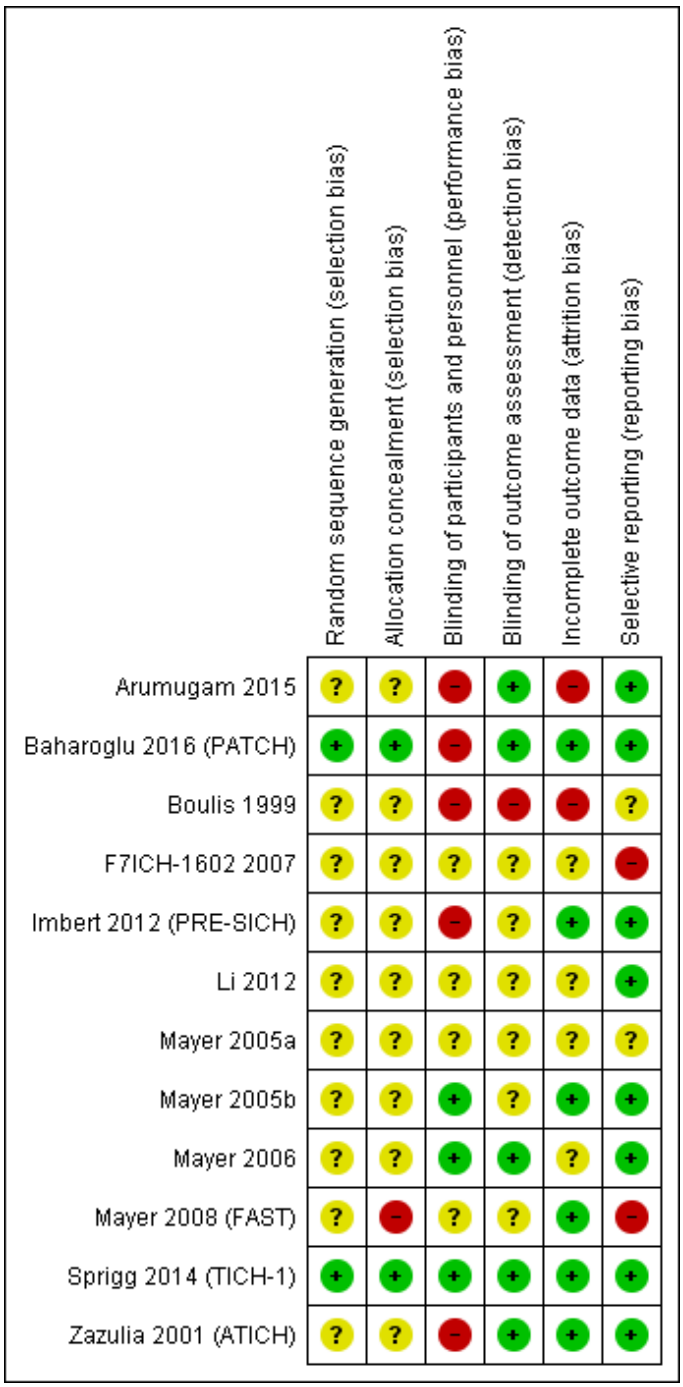
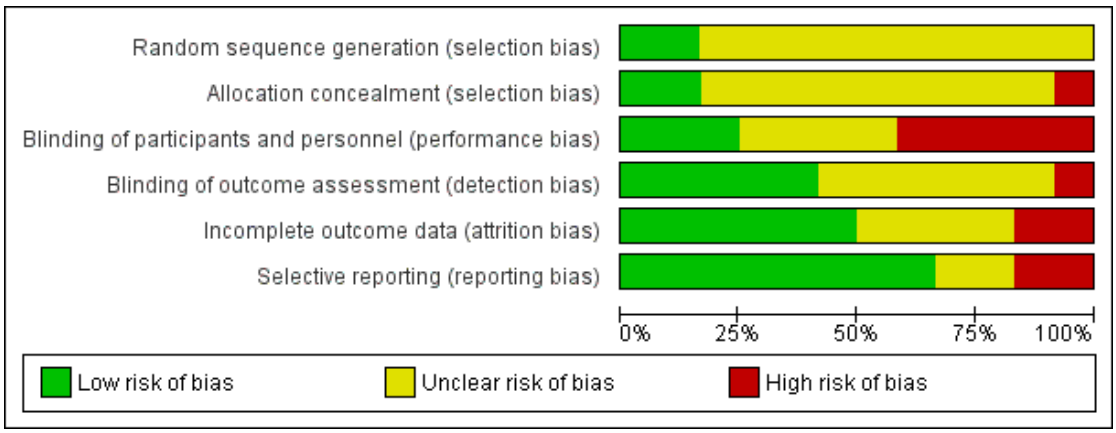


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias criteria presented as percentages across all included studies



Allocation

The risk of bias in random sequence generation was low in two RCTs, unclear in 10 RCTs, and high in none. The risk of bias in allocation concealment was low in two RCTs, unclear in nine RCTs, and high in one.

Only four RCTs clearly described the method of randomization (Baharoglu 2016 (PATCH); Mayer 2005b; Sprigg 2014 (TICH-1); Zazulia 2001 (ATICH)), and one RCT simply mentioned 'block randomization according to site' (Mayer 2008 (FAST)).

Allocation was reported as being concealed in the papers for Baharoglu 2016 (PATCH) and Sprigg 2014 (TICH-1), there was a risk of unblinding in one study (Mayer 2008 (FAST)), and the rest were unclear about allocation concealment.

It became apparent during questioning after the presentation of the Mayer 2008 (FAST) data at the European Stroke Conference in Glasgow, UK, in 2007 (Mayer 2007), that the imbalance in allocation between the three groups in this trial (there were approximately 30 more participants analysed in the 80 mcg/kg dose group than the other two groups) was due to the 80 mcg/kg dose of rFVIIa tending to be packed in the first of the three boxes of study drug for part of the trial (which might have unblinded investigators, in view of the preponderance of thromboembolic adverse events with the higher dose).

Blinding

Five of the 12 RCTs did not blind the intervention and comparator (Arumugam 2015; Baharoglu 2016 (PATCH); Boulis 1999; Imbert 2012 (PRE-SICH); Zazulia 2001 (ATICH)), four did blind intervention and comparator, and the risk of bias was unclear in three RCTs. Whether participants and personnel were blinded to treatment allocation was only explicitly stated in Baharoglu 2016 (PATCH), but correspondence with the study authors verified that this was the case for Mayer 2006; Zazulia 2001 (ATICH), and Sprigg 2014 (TICH-1). The risk of bias in the remaining RCTs was unclear in three RCTs, and high in five RCTs.

Risk of bias from blinding of outcome assessment was low in five RCTs, high in one RCT, and unknown in six RCTs. Assessment of radiological outcome was blinded to treatment allocation in nine included RCTs (Arumugam 2015; Baharoglu 2016 (PATCH); Imbert 2012 (PRE-SICH); Mayer 2005a; Mayer 2005b; Mayer 2006; Mayer 2008 (FAST); Sprigg 2014 (TICH-1); Zazulia 2001 (ATICH)), but information was not provided in others.

Incomplete outcome data

Overall, the risk of bias from incomplete outcome data was low in six RCTs, high in two RCTs, and unclear in the remaining four RCTs. Only Baharoglu 2016 (PATCH); Mayer 2008 (FAST), and Sprigg 2014 (TICH-1) provided data about completeness of clinical follow-up. In Arumugam 2015 and Li 2012, four participants had missing data. Boulis 1999 excluded eight participants after randomization. The last-observation-carried-forward technique was used in Mayer 2005b and Mayer 2008 (FAST), which is likely to be unbiased only if the completeness of follow-up was high.

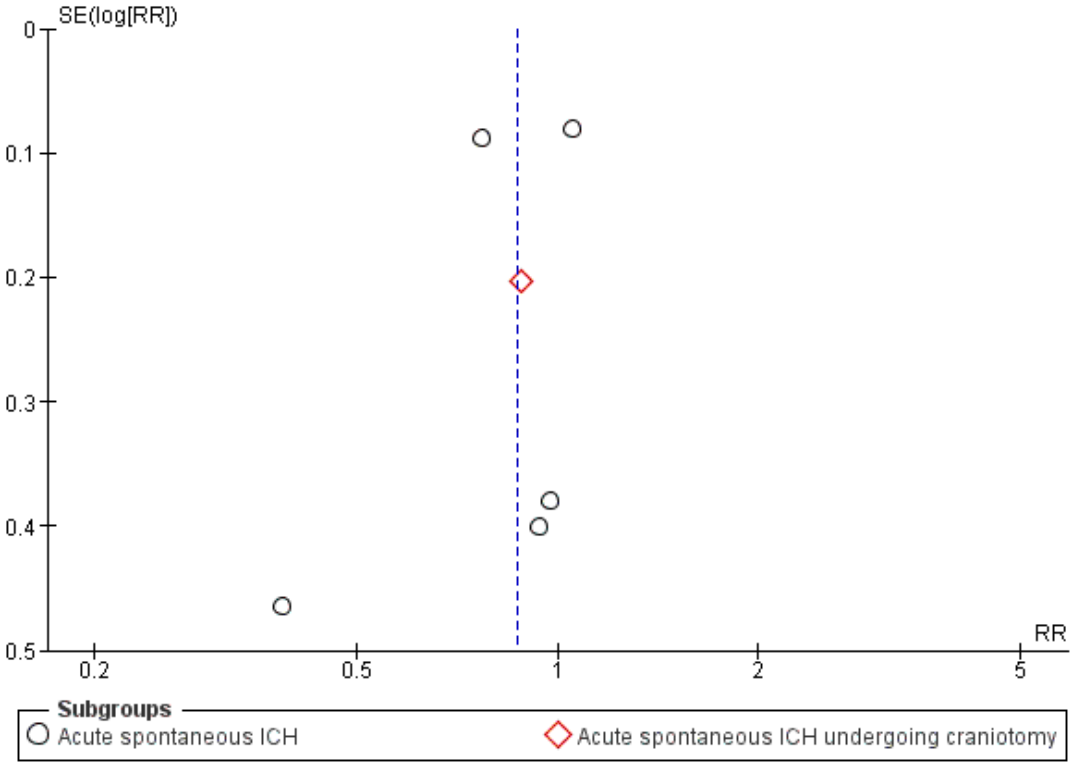
Selective reporting

Bias from selective outcome reporting was low in eight RCTs, appeared to be low in two RCTs, and high in two other RCTs.

Other potential sources of bias

There were differences in baseline characteristics between treatment and control arms in the rFVIIa RCTs, especially in Mayer 2008 (FAST): 90-day case fatality was worse in the placebo group in Mayer 2005b (29%) than in Mayer 2008 (FAST) (19%), which might be one explanation for the difference between the RCTs' findings. There was no visual evidence of funnel plot asymmetry in the largest group of RCTs, which compared blood clotting factors versus placebo or open control for death or dependency (Figure 4).

Figure 4. Funnel plot of comparison: 1 Blood clotting factors vs placebo or open control, outcome: 1.1 Death or dependence (mRS 4 to 6) at day 90



Effects of interventions

See: **Summary of findings for the main comparison** Blood clotting factors versus placebo or open control; **Summary of**

findings 2 Antifibrinolytic drugs versus placebo; **Summary of findings 3** Platelet transfusion versus open control; **Summary of findings 4** Blood clotting factors versus fresh frozen plasma

We analysed data on intervention effects In 12 RCTs involving 1732 participants (1150 allocated to intervention and 582 allocated to control or active comparator), split by type of intervention as follows.

Blood clotting factors versus placebo or open control

In RCTs of blood clotting factors (N = 1018) versus placebo or open control (N = 462) for acute spontaneous ICH with or without surgery, use of blood clotting factors led to non-significant reductions in death or dependence (risk ratio (RR) 0.87, 95% confidence interval (CI) 0.70 to 1.07; six trials, 1390 participants; moderate-quality evidence; Analysis 1.1); in death (RR 0.75, 95% CI 0.51 to 1.09; seven trials, 1480 participants; moderate-quality evidence; Analysis 1.3); in all serious adverse events (RR 0.81, 95% CI 0.30 to 2.22; two trials, 87 participants; moderate-quality evidence; Analysis 1.4); and in ICH growth (RR 0.74, 95% CI 0.36 to 1.48; three trials, 151 participants; moderate-quality evidence; Analysis 1.6). Blood clotting factors resulted in a non-significant increase in all serious thromboembolic serious adverse events (RR 1.24, 95% CI 0.80 to 1.91; five trials, 1398 participants; moderate-quality evidence; Analysis 1.5). In these analyses, the I^2 varied from 0% to 53%. We downgraded the quality of the evidence by one level because of concerns with design and risk of bias.

Antifibrinolytic drugs versus placebo or open control

In RCTs of antifibrinolytic drugs (N = 33) versus placebo or open control (N = 24) for acute spontaneous ICH, use of antifibrinolytic drugs led to non-significant increases in death or dependence (RR 1.25, 95% CI 0.57 to 2.75; one trial, 24 participants; moderate-quality evidence; Analysis 2.1), in death (RR 1.16, 95% CI 0.31 to 4.39; three trials, 57 participants; moderate-quality evidence; Analysis 2.2), in all serious adverse events (RR 1.50, 95% CI 0.39 to 5.83; one trial, 24 participants; moderate-quality evidence; Analysis 2.3), and in thromboembolic serious adverse events (RR 1.59, 95% CI 0.07 to 35.15; one trial, 24 participants; moderate-quality evidence; Analysis 2.4). Antifibrinolytic drugs led to a non-significant reduction in ICH growth (RR 0.76, 95% CI 0.56 to 1.05; three trials, 57 participants; moderate-quality evidence; Analysis 2.7). In these analyses, the I^2 was 0% to 1%. We downgraded the quality of the evidence to moderate because of imprecision.

Platelet transfusion versus open control

In one RCT of platelet transfusion (N = 97) versus open control (N = 93) for acute spontaneous ICH associated with antiplatelet drug use, platelet transfusion led to a significant increase in death or dependence (RR 1.29, 95% CI 1.04 to 1.61; one trial, 190 participants; moderate-quality evidence; Analysis 3.1), and non-significant increases in death (RR 1.42, 95% CI 0.88 to 2.28; one trial, 190 participants; moderate-quality evidence; Analysis 3.2), in all serious adverse events (RR 1.46, 95% CI 0.98 to 2.16; one trial, 190 participants; moderate-quality evidence; Analysis 3.3), in thromboembolic serious adverse events (RR 3.84, 95% CI 0.44 to 33.68; one trial, 190 participants; moderate-quality evidence; Analysis 3.4), and in ICH growth (RR 1.11, 95% CI 0.56 to 2.20; one trial, 190 participants; moderate-quality evidence; Analysis 3.5). We downgraded the quality of the evidence by one level because of imprecision.

Clotting factors versus fresh frozen plasma

No conclusions could be drawn from one small RCT of clotting factors (N = 2) versus fresh frozen plasma (N = 3) for acute spontaneous ICH associated with anticoagulant drug use, which did not report the primary outcome of this review.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Antifibrinolytic drugs compared with placebo for acute spontaneous intracerebral haemorrhage

Patient or population: adults with acute spontaneous intracerebral haemorrhage
Settings: secondary care
Intervention: tranexamic acid
Comparison: placebo

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Death or dependence (mRS 4 to 6) at day 90	**RR 1.25** (0.57 to 2.75)	24 (1)	⊕⊕⊕◯ **moderate**[1]	

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

CI: confidence interval; RR: risk ratio; mRS: modified Rankin Scale

[1]We downgraded the quality of the evidence once because of imprecision.

Platelet transfusion compared with open control for acute spontaneous intracerebral haemorrhage associated with antiplatelet drug use

Patient or population: adults with acute spontaneous intracerebral haemorrhage associated with antiplatelet drug use
Settings: secondary care
Intervention: platelet transfusion
Comparison: open control

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Death or dependence (mRS 4 to 6) at day 90	**RR 1.29** (1.04 to 1.61)	190 (1)	⊕⊕⊕◯ **moderate**[1]	

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

CI: confidence interval; RR: risk ratio; mRS: modified Rankin Scale
[1]We downgraded the quality of the evidence once because of imprecision.

Blood clotting factors compared with fresh frozen plasma for acute spontaneous intracerebral haemorrhage associated with anticoagulant drug use

Patient or population: adults with acute spontaneous intracerebral haemorrhage associated with anticoagulant drug use
Settings: secondary care
Intervention: fresh frozen plasma (intravenous), vitamin K (subcutaneous), and factor IX complex concentrate
Comparison: fresh frozen plasma (intravenous)

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Death or dependence (mRS 4 to 6) at day 90			No evidence	No evidence as mRS not measured

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

CI: confidence interval

DISCUSSION

Summary of main results

There was moderate-quality evidence, based on the findings of one RCT (190 participants), that platelet transfusion appeared hazardous in comparison to standard care for adults with antiplatelet-associated intracerebral haemorrhage (ICH). Based on moderate-quality evidence, we were unable to draw firm conclusions about the efficacy and safety of blood clotting factors versus placebo or open control for acute spontaneous ICH with or without surgery (seven trials, 1480 participants), or antifibrinolytic drugs versus placebo or open control for acute spontaneous ICH (three trials, 57 participants). The one very small trial (five participants) we found on clotting factors versus fresh frozen plasma for acute spontaneous ICH associated with anticoagulant drug use did not measure our primary outcome, and provided limited data on the secondary outcomes.

Overall completeness and applicability of evidence

Alongside the 12 included RCTs, we were unable to include two eligible RCTs (N = 113) comparing clotting factors versus fresh frozen plasma for acute spontaneous ICH associated with anticoagulant drug use because data on participants with intracerebral haemorrhage could not be separated from participants with subdural intracranial haemorrhage (Kerebel 2013; Steiner 2016 (INCH)). This resulted in a shortage of data comparing clotting factors versus fresh frozen plasma for acute spontaneous ICH associated with anticoagulant drug use.

The results of 10 ongoing or recently completed unreported RCTs are awaiting completion and publication (Characteristics of ongoing studies). Two of these were recently completed RCTs (N = 142) investigating clotting factors in participants with radiological criteria associated with increased risk of haematoma expansion, so the RCTs in the review only include all patients with ICH and not the subgroup most at risk of ICH growth, i.e. those with the radiological 'spot sign' (tiny, enhancing foci within haematomas) (NCT00810888; NCT01359202).

There were few data available on antifibrinolytic drugs versus placebo after spontaneous acute ICH, but five ongoing RCTs (N > 2500) are investigating the antifibrinolytic drug tranexamic acid versus placebo in acute spontaneous ICH without anticoagulant use (Liu 2017 (TRAIGE); Meretoja 2014 (STOP-AUST); NCT03044184; NOR-ICH; Sprigg 2016 (TICH-2)), and with anticoagulant drug use (NCT02866838). Publication of the largest RCT is expected in 2018 (Sprigg 2016 (TICH-2)).

It was unclear whether recruitment was complete for one RCT of platelet transfusion (N = 100; NCT00699621). Further RCTs of platelet transfusion seem unlikely, so we await the publication of this RCT to see if the findings of Baharoglu 2016 (PATCH) are externally valid.

Quality of the evidence

We included 12 RCTs with 1732 participants (1150 allocated to intervention, 582 allocated to control or active comparator). One double-blind RCT (Sprigg 2014 (TICH-1)), and one open RCT (Baharoglu 2016 (PATCH)), were at low risk of bias, but the risk of bias of most other RCTs was moderate to high (Figure 2; Figure 3). The RCT finding harm from platelet transfusion has not been replicated in another RCT (Baharoglu 2016 (PATCH)).

The largest quantity of data was from RCTs of recombinant activated clotting factor VII (rFVIIa), which were at moderate risk of bias, and their results were moderately inconsistent, showing non-significant benefits of rFVIIa. These findings have not changed practice (Hemphill 2015 (AHA ICH); RCP 2016; Steiner 2014 (ESO ICH)), and have led to explorations of the use of rFVIIa in ICH sub-groups in as-yet-unpublished RCTs (NCT00810888; NCT01359202).

We rated the overall quality of all of the available evidence as moderate for three comparisons on the grounds of imprecision (Analysis 1.1; Analysis 2.1; Analysis 3.1), and poor for one comparison on the grounds of imprecision and limitations in study design (Analysis 4.1).

Potential biases in the review process

We followed a dual review process: two authors (NS and RA-SS) independently extracted data that reduced identification bias and improved risk of bias assessment in comparison to the previous update of this review.

We were unable to include data from two eligible studies that separately showed benefits of clotting factors versus FFP on intermediate outcomes (speed of international normalised ratio (INR) reduction) after intracranial haemorrhage as data were not available for the ICH population; we hope to include these RCTs in the next update of this review to also examine the effect of clotting factors versus FFP on clinical outcomes (Steiner 2016 (INCH); Kerebel 2013).

Agreements and disagreements with other studies or reviews

This review was completed after the most recent updates of the European and North American ICH guidelines (Hemphill 2015 (AHA ICH); Steiner 2014 (ESO ICH)). These guidelines predated the results of Baharoglu 2016 (PATCH), and simply found that "the usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is uncertain". Guidance on platelet transfusion has changed to reflect the results of Baharoglu 2016

(PATCH), where platelet transfusion was associated with a worse outcome, hence platelet transfusion is not recommended (Dastur 2017). Consistent with our findings, guidelines have not recommended the use of clotting factors, such as rFVIIa for acute spontaneous ICH not associated with anticoagulant use (Hemphill 2015 (AHA ICH); RCP 2016; Steiner 2014 (ESO ICH)). The AHA and ESO guidelines preceded the publication of Steiner 2016 (INCH), but the national stroke guidelines in the UK recommend using prothrombin complex concentrate for anticoagulant-associated ICH, reflecting the findings of Steiner 2016 (INCH) on the intermediate outcome of speed of INR reduction (RCP 2016).

AUTHORS' CONCLUSIONS

Implications for practice

Platelet transfusion appears hazardous in comparison to standard care for adults with antiplatelet-associated ICH (this is based on the findings of one trial). We are unable to draw firm conclusions about the efficacy and safety of blood clotting factors for acute spontaneous ICH (with or without surgery), antifibrinolytic drugs for acute spontaneous ICH, clotting factors or fresh frozen plasma for acute spontaneous ICH associated with anticoagulant drug use.

Implications for research

Although rFVIIa does not appear beneficial on the basis of existing evidence, RCTs of its use in specific subgroups have been undertaken and their results are awaited (NCT00810888; NCT01359202). Clotting factors appear superior to fresh frozen plasma for normalising coagulation in the RCTs that we could not include because they were not restricted to ICH (Kerebel 2013; Steiner 2016 (INCH)), but their superiority for improving clinical outcome needs to be established. The effect of antifibrinolytic drugs for acute ICH is uncertain, but in view of their effects in other conditions (Ker 2015), the results of several ongoing RCTs are keenly awaited (Liu 2017 (TRAIGE); Meretoja 2014 (STOP-AUST); NCT02866838; NCT03044184; Sprigg 2016 (TICH-2)).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arumugam 2015

Methods	Single-blinded, randomised placebo-controlled trial of tranexamic acid (intravenous 1 g bolus, followed by infusion 1 g/h for 8 h) in acute (< 8 h) primary ICH. Strict blood pressure control (target SBP 140 mmHg to 160 mmHg) A repeat brain CT was done after 24 h to reassess haematoma growth. The primary objective was to test the effect of tranexamic acid on haematoma growth. Other objectives were to test the feasibility, tolerability, and adverse events of tranexamic acid in primary ICH
Participants	Inclusion criteria • Patients aged ≥ 18 years (either sex), • Non-surgically managed patients who were evaluated by the on-call neurosurgeon and, were deemed inappropriate for surgical intervention, • Event within 8 h of onset, • Hypertensive intracerebral bleed, and • Supratentorial lesion. Exclusion criteria • Patients on anticoagulant therapy, • Brainstem bleed, • Intraventricular bleed on the first brain CT brain, including participants who developed an intraventricular bleed during the study, • Malignant hypertension, • Subarachnoid haemorrhage suggestive of a ruptured aneurysm, • Trauma, • Blood disorder (e.g. haemophilia and idiopathic thrombocytopenic purpura), • Infection (e.g. dengue haemorrhagic fever), • Hepatic or renal impairment, • Previous venous thrombosis or embolic disease, • Recent ischaemic event (within 12 months), such as ischaemic stroke, MI, or peripheral artery disease, and • Pregnant or breast-feeding women (pregnancy was evaluated in women of child-bearing age using a urine pregnancy test).
Interventions	Intervention: tranexamic acid (1 g diluted in 100 mL of 0.9% saline) over a period of 10 minutes. The initial dose was followed by a maintenance dose of 1 g/h for 8 h. Labetalol infusion 2 mg/min to achieve SBP 140 mmHg to 160 mmHg Comparator: placebo mentioned, but not described. Labetalol infusion 2 mg/min to achieve SBP 140 mmHg to 160 mmHg
Outcomes	Repeat CT brain scan was performed after 24 h, and a blinded radiologist evaluated the size and volume of the haematoma. Adverse events due to tranexamic acid that occurred within 24 h of the treatment were documented by the investigator or pharmacist
Notes	-

Arumugam 2015 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Each envelope represented either the drug or control group, which was assigned using a random sequence programmer."
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients or their family members randomly chose one envelope from a box containing 30 closed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded radiologist for primary outcome. High risk for other outcomes (not stated as blinded)
Incomplete outcome data (attrition bias) All outcomes	High risk	4 participants had missing data
Selective reporting (reporting bias)	Low risk	All outcomes in the paper were reported. No protocol

Baharoglu 2016 (PATCH)

Methods	Multicentre, open-label, masked-endpoint, randomized trial, using a secure web-based system that concealed allocation and used biased coin randomization (1:1 stratified by hospital and type of antiplatelet therapy)
Participants	Inclusion criteria • Participants aged 18 years or older • Non-traumatic supratentorial intracerebral haemorrhage confirmed by brain imaging • GCS score of 8 to 15 • In whom platelet transfusion could be initiated within 6 h of symptom onset (or last seen well) and within 90 minutes of brain imaging • Who had been on antiplatelet therapy with a cyclo-oxygenase (COX) inhibitor (aspirin or carbasalate calcium), adenosine diphosphate (ADP) receptor inhibitor (clopidogrel), or an adenosine reuptake inhibitor (dipyridamole) for at least 7 days preceding intracerebral haemorrhage • Pre-intracerebral haemorrhage mRS score of 0 (no symptoms) or 1 (no significant disability despite symptoms; able to carry out all usual duties and activities) Exclusion criteria • Blood on brain imaging suggestive of epidural or subdural haematoma, or an

	underlying aneurysm or arteriovenous malformation • Planned surgical evacuation of intracerebral haemorrhage within 24 h of admission • Intraventricular blood more than sedimentation in the posterior horns of the lateral ventricles • Previous adverse reaction to platelet transfusion • Known use of vitamin K antagonist (unless INR $\leq$ 1.3) or history of coagulopathy • Known thrombocytopenia (lower than 100 cells x 10^9 /L) • Lacking mental capacity by national legal standards before intracerebral haemorrhage • Death appeared imminent
Interventions	Intervention: standard care with platelet transfusion within 90 minutes of diagnostic brain imaging Comparator: standard care
Outcomes	The primary outcome was shift towards death or dependence rated on the mRS at 3 months, and analysed by ordinal logistic regression, adjusted for stratification. Variables and the Intracerebral Haemorrhage Score Secondary clinical outcomes at 3 months were: survival (mRS score of 1 to 5), poor outcome defined as an mRS score of 4 to 6, and poor outcome defined as an mRS score of 3 to 6 The secondary explanatory outcome was median absolute intracerebral haemorrhage growth in mL after 24 h on brain imaging Safety outcomes were defined as complications of platelet transfusion (transfusion reactions, thrombotic complications)
Notes	NTR1303

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done by investigators via a secure, web-based, computerised randomization system (TENALEA, Clinical Trial Data Management system; NKIAVL, Amsterdam, The Netherlands) that stratified assignment by study hospital and type of pre-intracerebral haemorrhage antiplatelet therapy (COX inhibitor alone, ADP receptor inhibitor alone, COX inhibitor with an adenosine-reuptake inhibitor, or COX inhibitor with an ADP receptor inhibitor). A biased coin randomization was used, with coin bias factor of 3 and coin bias threshold of 2"

Baharoglu 2016 (PATCH) (*Continued*)

Allocation concealment (selection bias)	Low risk	Allocation was concealed from investigators by the web-based randomization system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and local investigators giving interventions were not masked to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treatment allocation was concealed to outcome assessors and investigators analysing data
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for the primary outcome was complete
Selective reporting (reporting bias)	Low risk	All outcomes were reported

Boulis 1999

Methods	RCT
Participants	Inclusion criteria • CT-proven intracranial haemorrhage • Documented history of warfarin use • Prothrombin time > 17 seconds Exclusion criteria • Clinical evidence of brainstem herniation
Interventions	Intervention: fresh frozen plasma Comparator: fresh frozen plasma (intravenous), vitamin K (subcutaneous) and factor IX complex concentrate (Konyne; Bayer, Elkhart, IN: containing high concentrations of activated vitamin K-dependent clotting factors II, VII, IX, and X; dosage according to body weight; intravenous infusion at 100 IU/min)
Outcomes	Time to INR correction, rate of INR correction, change in GCS
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Boulis 1999 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not described
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Post-randomisation exclusion of 8 participants
Selective reporting (reporting bias)	Unclear risk	Outcomes not pre-specified

F7ICH-1602 2007

Methods	Randomised, double-blind, Japanese multicentre, placebo-controlled, phase II dose-escalation trial with 3 dose tiers
Participants	Inclusion criteria • Age ≥ 20 years • Spontaneous ICH (not in brainstem) • Within 3 h of onset
Interventions	Intervention: recombinant activated factor VII (NovoSeven) at doses of 40 mcg/kg (N = 15), 80 mcg/kg (N = 15), or 120 mcg/kg (N = 15), within 1 h of baseline CT Comparator: placebo (N = 45), within 1 h of baseline CT
Outcomes	Preliminary efficacy evaluations were performed as follows • mRS, the BI scores at 15 days post-dose and 90 days post-dose • Absolute and percent change in ICH volume, total haemorrhage volume (ICH + IVH), and total lesion volumes (ICH + IVH + oedema) as measured by head CT scans from baseline to 24 h, 48 h, and 72 h post-dose • Change in the GCS and the NIHSS scores from baseline to 1 h post-dose, 24 h post-dose, 48 h post-dose, 72 h post-dose, 15 days post-dose, and 90 days post-dose • Mortality at 90 days post-dose Criteria for evaluation: safety • Occurrence of thromboembolic serious adverse events until the 'End of trial' form was completed • Changes in laboratory coagulation parameters (D-dimer, Fragment 1+2, Fibrinogen, Platelets, PT-INR, and APTT) from prior to dosing to 1 h post-dose, 24 h post-dose, 48 h post-dose, and 72 h post-dose • Exacerbation of brain oedema (oedema/ICH volume ratio > 2.5) assessed using head CT scan at 24 h post-dose, 48 h post-dose, and 72 h post-dose • Occurrence of adverse events until discharge or 90 days post-dose, whichever came first, and serious adverse events until the 'End of trial' form was completed
Notes	ClinicalTrials.gov number NCT00266006. This unpublished trial was funded by Novo Nordisk, which did not respond to requests to provide data beyond what was on their

F7ICH-1602 2007 (*Continued*)

	website

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel said to be blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The assessment of outcomes was not explicitly stated to be blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	High risk	Data not provided for most major outcomes

Imbert 2012 (PRE-SICH)

Methods	Randomised (2:1), open-label, single-blinded parallel group phase 2 pilot trial involving 21 participants with spontaneous supratentorial ICH diagnosed by CT
Participants	Inclusion criteria • People 18 to 75 years of age with spontaneous supratentorial ICH documented by CT scan • Surgery was expected within 24 h from the onset of symptoms Exclusion criteria • MI or the placement of coronary or carotid stents in the 6 months prior to the study • Solid organ transplantation • Pregnancy
Interventions	All participants were intubated, ventilated, and underwent craniotomy with the intention of complete haematoma removal. The haematoma cavity was lined with Surgicel (Johnson & Johnson, New Brunswick, NJ, USA). Blood pressure was measured continuously, and data were collected every 1 to 2 h. Efforts were made to maintain the mean arterial blood pressure between 90 mmHg and 130 mmHg, $PaCO_2$ within the range of 35 mmHg to 40 mmHg, natraemia between 137 and 147 mmol/L and to obtain normoglycaemia (80 mg/dL to 110 mg/dL) Intervention: 100 mcg/kg of rFVIIa (NovoSeven, Novo Nordisk, Denmark) by intravenous infusion in 5 to 10 minutes immediately after evacuation of the haematoma, at

Imbert 2012 (PRE-SICH) (*Continued*)

	the beginning of the closure of the dura Comparator: saline solution by intravenous infusion in 5 to 10 minutes immediately after evacuation of the haematoma, at the beginning of the closure of the dura
Outcomes	Haematoma volume was assessed by CT scan immediately, 18 h to 30 h, and 5 days to 7 days after evacuation of the haematoma. The primary endpoint was haematoma volume at 18 h to 30 h after surgery. Outcome was evaluated at 6 months using the mRS; poor outcome was defined as death or an mRS score of 4 to 5, and good outcome was defined as an mRS score of 0 to 3
Notes	NCT00128050

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	They stated the trial was both open label and placebo controlled in the methods, but that 'saline' was the comparator. This seemed like an open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Haematoma volume assessment blinded, but unsure about clinical outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seemed complete for all outcomes. Unable to extract data on haematoma growth, all SAEs, and all thromboembolic adverse events (although they were reported separately)
Selective reporting (reporting bias)	Low risk	All outcomes specified in the methods appeared to have been reported

Li 2012

Methods	Single-centre RCT
Participants	Inclusion criteria • Intracerebral haemorrhage • Within 6 h of onset • Age ≥ 18 years • Able to perform CT scan 24 h post-treatment

Li 2012 (*Continued*)

	Exclusion criteria • Secondary haemorrhage, i.e. tumour, AVM, anticoagulant-associated • Surgery within 24 h • Admission GCS 3 to 5 • Hereditary or acquired coagulation dysfunction • Previous ICH in which haematoma had not been fully resolved • Serious comorbidities or end-stage diseases (unspecified) • Known renal impairment or thyroid dysfunction (unspecified)
Interventions	Intervention: intravenous rFVIIa (NovoSeven) 40 μg/kg, concentration at 0.6 g/L, within 6 h of ICH onset, injected over 2 to 5 minutes Comparator: routine or best medical treatment All participants received Piracetam 8 g iv 4 times/day
Outcomes	ICH growth, GCS at 24 h, NIHSS at 24 h, mRS at 90 days, adverse events
Notes	Data extracted by Dr Michael Poon (www.researchgate.net/profile/Michael_Poon3) from full text record available from en.cnki.com.cn/Article_en/CJFDTotal-ZXYZ201202009.htm

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes appeared to be reported

Mayer 2005a

Methods	Parallel group, randomised, placebo-controlled, phase II: a dose-escalation safety and efficacy study
Participants	Inclusion criteria: • Age 18 years or older • Spontaneous ICH within 3 h of onset with no obvious secondary cause Exclusion criteria: • GCS 3 to 5 • Surgical ICH evacuation planned within 24 h • mRS > 2 pre-ICH • Allergy to trial product • Participation in another RCT
Interventions	Intervention: recombinant activated factor VII (NovoSeven) at doses of 10 mcg/kg, 20 mcg/kg, 40 mcg/kg, 80 mcg/kg, 120 mcg/kg, or 160 mcg/kg, within 1 h of baseline CT Comparator: placebo, within 1 h of baseline CT
Outcomes	Adverse events at days 1 to 5, 15 (or hospital discharge), and 90; change in ICH ± IVH volume on CT between baseline and 24 h; ICH growth (> 33% or 12.5 mL); drop of > 1 GCS point or increase of > 3 NIHSS points on days 0 to 5; dead versus alive with little disability (BI 95 to 100, GOS-E 8, mRS 0 to 2), versus alive and functionally independent (BI 60 to 100, GOS-E 5 to 8, mRS 0 to 3) at day 90
Notes	There was imbalance in the baseline ICH volumes between placebo and treatment groups (increasing with higher recombinant factor VIIa doses), although the authors stated that this was not statistically significant. The trial drug was given to 2 of 47 participants more than 4 h after ICH onset. This trial was funded by Novo Nordisk

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not specified
Allocation concealment (selection bias)	Unclear risk	Not described. Quote: "A randomization schedule was generated."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Providers were said to be blinded to treatment allocation (but treatment dose escalation may have been apparent)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The assessment of outcomes was not explicitly stated to be blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear

Mayer 2005a (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Unclear

Mayer 2005b

Methods	Parallel group, randomised, placebo-controlled, phase IIB, dose-ranging, proof-of-concept study
Participants	Inclusion criteria: • Age 18 years or older • Spontaneous ICH • Within 3 h of onset Exclusion criteria: • GCS 3 to 5 • Surgical ICH evacuation planned within 24 h • Known underlying cause of ICH • On oral anticoagulants • Known thrombocytopaenia • Coagulopathy, disseminated intravascular coagulation, sepsis, or crush injury • Pregnant • mRS > 2 pre-ICH • Symptomatic thrombotic or vaso-occlusive disease within 30 days before ICH (mid-way through the trial this was amended to exclude patients with any history of thrombotic or vaso-occlusive disease)
Interventions	Intervention: recombinant activated factor VII (NovoSeven) at doses of 40 mcg/kg, 80 mcg/kg, or 160 mcg/kg, within 1 h of baseline CT and no later than 4 h after ICH onset Comparator: placebo, within 1 h of baseline CT and no later than 4 h after ICH onset
Outcomes	Percentage change in ICH volume on CT from baseline to 24 h; mRS 4 to 6, or GOS-E 1 to 4 at 90 days; adverse events in hospital, and serious adverse events until day 90
Notes	One important exclusion criterion was changed mid-way through the RCT. This trial was funded by Novo Nordisk, which did not respond to repeated requests to provide further data from this trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Quote: "A randomization schedule was generated and as patients were recruited, they were allocated to the next available randomization number within the dose tier, which indicated whether the patient was to receive placebo or rFVIIa."

Mayer 2005b (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	4/block, sequentially numbered, identical-appearing containers
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Radiological outcomes blinded. Clinical and lab outcomes - unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appeared complete
Selective reporting (reporting bias)	Low risk	Appeared complete

Mayer 2006

Methods	Parallel group, randomised, double-blind, placebo-controlled, phase II: a dose escalation safety study
Participants	Inclusion criteria • Age 18 years or older • Spontaneous ICH within 3 h of onset Exclusion criteria • GCS 3 to 5 • Surgical ICH evacuation planned within 24 h • Known underlying cause of ICH • On oral anticoagulants • Known thrombocytopaenia • Coagulopathy, disseminated intravascular coagulation, sepsis, or crush injury • Pregnant • mRS > 2 pre-ICH • Any history or acute evidence of thrombotic, hypercoagulable, or vaso-occlusive disease • Known or suspected allergy to trial product • Participation in another trial
Interventions	Intervention: recombinant activated factor VII (NovoSeven) at doses of 5 mcg/kg, 20 mcg/kg, 40 mcg/kg, or 80 mcg/kg, within 4 h of ICH onset Comparator: placebo, within 4 h of ICH onset
Outcomes	Serious adverse events; coagulation parameters; perihaematomal oedema; ICH volume ratio on CT; change in ICH volume from baseline on CT; change in neurological scores
Notes	This trial was funded by Novo Nordisk

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Mayer 2006 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant clinically deteriorated prior to dosing and underwent emergency haematoma evacuation, so dropped out after randomization. Otherwise, completeness of follow-up was not mentioned
Selective reporting (reporting bias)	Low risk	All stated outcomes were reported

Mayer 2008 (FAST)

Methods	Parallel group, randomised, placebo-controlled, phase III trial
Participants	Inclusion criteria • Spontaneous ICH (including bleeding in brainstem and cerebellum) diagnosed by a CT scan within 3 h of symptom onset • Men or women, aged 18 years or over (20 or over in Taiwan) • Informed consent Exclusion criteria • Time of ICH onset is unknown, or more than 3 h • People with secondary ICH • Surgical haematoma evacuation planned within 24 h of symptom onset • GCS 3 to 5 • Known oral anticoagulant use (unless the INR is documented below 1.4) • Known thrombocytopenia (unless current platelets documented above 50,000/mL) • Pre-existing disability (mRS 3 to 5) • Any known history of haemophilia or other coagulopathy • Known acute myocardial ischaemia, unresolved unstable angina, acute septicaemia, acute crush injury, acute disseminated intravascular coagulation, or acute thrombotic stroke • Pregnancy • Known or suspected allergy to trial product or related products • Previous participation in this trial • Known participation in any investigational drug or device trial within 30 days of

Mayer 2008 (FAST) (*Continued*)

	entry into this trial • People known or suspected of not being able to comply with this trial protocol (e. g. due to alcoholism, drug dependency, or psychological disorder)
Interventions	Intervention: Recombinant activated factor VII (NovoSeven) at doses of 20 mcg/kg or 80 mcg/kg, within 1 h of baseline CT and no later than 4 h after ICH onset Comparator: Placebo
Outcomes	Primary efficacy endpoint was poor outcome, defined as death or severe disability (scores of 5 to 6 on the mRS) at day 90. Analysis claimed to be intention-to-treat, but it did not appear to be Secondary efficacy endpoints: BI, GOS-E, NIHSS, the EuroQol scale, and the Revised Hamilton Rating Scale for Depression at day 90; absolute and percent change in ICH volume as measured by CT from prior to dosing to 24 h after the baseline scan; good outcome (mRS 0 to 1) at day 90; absolute and percent change in total lesion volumes (ICH + IVH + oedema) from baseline to 72 h; BI at day 90; case fatality Safety endpoints: the occurrence of adverse events until hospital discharge, or until day 90, whichever came first, and serious adverse events until the 'End of trial' form was completed
Notes	This trial was funded by Novo Nordisk, which did not respond to repeated requests to provide further data from this trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Block randomization according to site..."
Allocation concealment (selection bias)	High risk	It became apparent during questioning after the presentation of this trial's data at the European Stroke Conference (Glasgow 2007), that the imbalance in allocation between the 3 groups in this trial (there were approximately 30 more participants analysed in the 80 mcg/kg dose group than the other 2 groups) was due to the fact that the 80 mcg/kg dose of rFVIIa tended to be packed in the first of the 3 boxes of study drug for part of the trial (which might have unblinded investigators, in view of the preponderance of thromboembolic adverse events with the higher dose)

Mayer 2008 (FAST) (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Classified as 'double-blind', but not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Classified as 'double-blind', but not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Outcome scores at day 15 were used according to the principle of the last observation carried forward for 9 patients receiving placebo, 9 patients receiving 20 μg of rFVIIa per kilogram, and 13 patients receiving 80 μg of rFVIIa per kilogram (3.7% of patients overall), for whom scores at day 90 were missing. Modified Rankin scale scores were not available for one patient receiving placebo and one patient receiving 20 μg of rFVIIa per kilogram."
Selective reporting (reporting bias)	High risk	EuroQuol and Hamilton depression score not reported

Sprigg 2014 (TICH-1)

Methods	Single-centre, prospective, randomised (2:1), double-blind, placebo-controlled blinded endpoint trial of tranexamic acid (intravenous 1 g bolus, 1 g infusion/8 h) in acute (< 24 h) spontaneous ICH
Participants	Adults with acute (< 24 h after ictus) spontaneous ICH were identified and enrolled from the stroke service at Nottingham University Hospital NHS Trust. The principal exclusion criteria included secondary ICH (anticoagulation, known vascular malformations), previous venous thromboembolic disease, recent (< 12 months) ischaemic events (ischaemic stroke, MI, PAD), renal impairment (estimated glomerular filtration rate < 50 mmol), and pregnancy or breast feeding
Interventions	Intervention: intravenous tranexamic acid (Cyklokapron; Phamacia Limited, Kent, UK) administered as a 1 g loading dose infusion for 10 minutes followed by a 1 g infusion for a period of 8 h Comparator: matching placebo (0.9% saline) administered by identical regime
Outcomes	The primary outcome was trial feasibility (surrogate for trial acceptability: number of participants screened who were eligible for enrolment and who gave informed consent) Secondary outcomes included tolerability (adverse events occurring during or after administration of tranexamic acid) and safety (clinical information on ischaemic events, i.e. ischaemic stroke, TIA, acute coronary syndrome, PAD, and VTE were also recorded) . The Data Safety Monitoring Committee reviewed unblinded safety data after 6, 12, and 18 participants had been recruited and followed for 7 days

Sprigg 2014 (TICH-1) (*Continued*)

Notes	Dr N Sprigg provided information for assessment of risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Details not given in paper, but confirmed by author as computer-generated
Allocation concealment (selection bias)	Low risk	Details not given in paper, but confirmed by author as concealment until end of trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Details not given in paper, but confirmed by author as participants and trial staff all blinded to allocation for duration of trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not presented in paper, but author confirmed all assessments (clinical and radiological) were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data presented
Selective reporting (reporting bias)	Low risk	No selective reporting

Zazulia 2001 (ATICH)

Methods	Parallel group, RCT
Participants	Inclusion criteria: • spontaneous non-traumatic supratentorial ICH (on brain CT), • age 18 years or older, • treatment begun within 3 h of ICH onset Exclusion criteria: • clinical suspicion of ICH due to aneurysm, tumour, bleeding diathesis, • SAH Fisher grade > 3, • plans for immediate surgery, • on coumadin, • prothrombin time > 14, • pregnant, • platelet count < 100,000, • undergoing haemodialysis, • treated with thrombolytic therapy in the last 48 h, • known DVT, MI, or PE within the last 3 months, • acute MI on ECG, • GCS < 5

Zazulia 2001 (ATICH) (*Continued*)

Interventions	Intervention: aminocaproic acid (Amicar) intravenous bolus of 10 g over 5 to 10 minutes, followed by a continuous intravenous infusion of 50 g diluted in 478 mL 0.9% NaCl and infused at 30 cc/h over 24 h Comparator: routine treatment
Outcomes	• Antifibrinolytic activity levels, • ICH enlargement on CT by > 33% from baseline to 24 h, • in-hospital death, • 90-day case fatality, • FIM and mRS, • aminocaproic acid plasma levels, • development of ischaemic stroke (defined as a new lucency in a vascular distribution not in the area of the initial haemorrhage on the 7-day CT, or a new focal neurological deficit reflecting a vascular territory separate from the initial haemorrhage and that cannot be explained by other cause), • symptomatic DVT confirmed by venous duplex ultrasonography, • symptomatic PE confirmed by ventilation-perfusion lung scan, pulmonary angiogram, or autopsy, • change in hydrocephalus score, • laboratory evidence of disseminated intravascular coagulation, • evidence of haemodynamic compromise during drug infusion (hypotension > 15% of baseline mean arterial pressure ± bradycardia or arrhythmia)
Notes	Studied terminated prematurely after 3 participants enrolled

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	10/block
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Radiological outcomes blinded. Clinical outcomes unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data presented
Selective reporting (reporting bias)	Low risk	No selective reporting

APTT: activated partial thromboplastin time

AVM: arteriovenous malformation
BI: Barthel Index
CT: computed tomography
DVT: deep vein thrombosis
ECG: electrocardiogram
FIM: Functional Independence Measure
GCS: Glasgow Coma Score
GOS-E: Extended Glasgow Outcome Scale
ICH: intracerebral haemorrhage
INR: international normalised ratio
IVH: intraventricular haemorrhage
MI: myocardial infarction
mRS: modified Rankin Scale
NaCl: sodium chloride
NIHSS: National Institutes of Health Stroke Scale
PE: pulmonary embolism
RCT: randomised controlled trial
SAE: serious adverse event
SAH: subarachnoid haemorrhage
SBP: systolic blood pressure
TIA: transient ischaemic attack

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

Study	Reason for exclusion
Ciccone 2007	This was a proposal for a study, but was not initiated due to 'lack of funding', according to Dr Ciccone
Kerebel 2013	This trial combined participants with either intracerebral haemorrhage or subdural haemorrhage, but did not report outcomes by intracranial haemorrhage subtype. We requested data restricted to the group with ICH, but did not receive these data before submission of this review; we hope to include them in the next update
Li 2016	The intervention (TRABC) did not appear to be haemostatic, according to a Traditional Chinese Medicine expert (sarah-price.co.uk/): Xing Nao Jing has 4 TCM medicinals (She Xiang, Yu Jin, Zhi Zi and Bing Pian) , traditionally used to revive the unconscious patient
Madjdinasab 2008	No quantifiable outcome results were reported.
Meng 2003	It was unclear whether the participants in this study were included in Zhou 2005. The outcome measures used were unsuitable for meta-analysis in this review. none of the pre-specified primary or secondary outcomes were collected
NCT00222625	This study was 'stopped due to slow recruitment', according to Dr Iorio, who has not yet responded to requests for clarification about whether any data were collected
NCT02429453	This study was 'withdrawn before enrolment', according to the Clinical Trial Registry

(*Continued*)

Steiner 2016 (INCH)	This trial combined participants with either intracerebral haemorrhage or subdural haemorrhage, but did not report outcomes by intracranial haemorrhage subtype. We requested data restricted to the group with ICH, but did not receive these data before submission of this review; we hope to include them in the next update
Zhou 2005	It was unclear whether this study included the participants in Meng 2003. The outcome measures used were unsuitable for meta-analysis in this review, none of the pre-specified primary or secondary outcomes were collected

ICH: intracerebral haemorrhage

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

Liu 2017 (TRAIGE)

Trial name or title	Tranexamic Acid for Acute ICH Growth prEdicted by Spot Sign (TRAIGE)
Methods	The purpose of this study is to determine if CTA can predict which individuals with ICH will experience significant growth in the size of the haemorrhage. For individuals who are at high risk for haemorrhage growth, the study will compare the drug tranexamic acid to placebo to determine the effect and safety on ICH
Participants	Inclusion criteria People presenting with an acute spontaneous hypertensive ICH • CTA evaluation can be accomplished within 6 h of symptom onset, with 'spot sign' positive in CTA original image • Age range from 18 to 79 years • Randomisation can be finished and treatment can commence within 8 h of symptom onset • Informed consent has been received in accordance with local ethics committee requirements Exclusion Criteria: • ICH known or suspected to be secondary to tumour, vascular malformation, aneurysm, or trauma • Infratentorial ICH • GCS total score < 8 • ICH volume > 70 mL • Parenchymal haemorrhage with ventricle involved, blood completely fills one lateral ventricle or more than half of both lateral ventricles • Contraindication of CTA imaging (e.g. known or suspected iodine allergy or significant renal failure) • Any history or current evidence suggestive of venous or arterial thrombotic events within the previous 6 months, including clinical, ECG, laboratory, or imaging findings. Clinically silent chance findings of old ischaemia are not considered exclusion criteria. • Planned surgery for ICH • Pregnancy, within 30 days after delivery, or during lactation • Use of heparin, low-molecular weight heparin, or oral anticoagulation within the previous 1 week, with abnormal laboratory values • Known allergy to tranexamic acid • Prestroke modified mRS score of > 2

Liu 2017 (TRAIGE) (*Continued*)

Interventions	Intervention: tranexamic acid Comparator: 0.9% normal saline placebo
Outcomes	Primary outcome measures • haemorrhage growth (time frame: 24 ± 2 h) either > 33%, or > 6 mL increase from baseline, adjusted for baseline ICH volume Secondary outcome measures • Major thromboembolic events (time frame: 30 ± 4 days; acute MI, acute cerebral ischaemia, acute PE) • Poor clinical outcome (time frame: 90 ± 7 days): the number of participants who died or have major disability (mRS 4 to 6) • Short-term outcome: the number of participants with mRS 0 to 2 at 30 ± 4 days • Other thromboembolic events (time frame: 90 ± 7 days): other thromboembolic events, such as venous thrombosis and other peripheral arterial embolism • Death due to any cause: number of patients that died due to any cause by 90 ± 7 days
Starting date	September 2015
Contact information	Liping Liu, Professor of Neurology and Stroke Center, Beijing Tiantan Hospital, Capital Medical University, Ministry of Science and Technology of the People's Republic of China
Notes	NCT02625948

Meretoja 2014 (STOP-AUST)

Trial name or title	STOP-AUST: The Spot Sign and Tranexamic Acid On Preventing ICH Growth - AUStralasia Trial (STOP-AUST)
Methods	The aim of the study is to test if ICH patients who have contrast extravasation on CTA, the 'spot sign', have lower rates of haematoma growth when treated with tranexamic acid within 4.5 h of stroke onset, compared with placebo
Participants	Inclusion criteria • People presenting with an acute ICH • Contrast extravasation within the haemorrhage, 'spot sign', evaluated from the CTA according to 3 criteria, all of which must be present: Serpiginous or spot-like appearance within the margin of a parenchymal haematoma without connection to an outside vessel; the density (in Hounsfield units) should be greater than that of the background haematoma (site investigators are not required to document the density); and no hyperdensity at the corresponding location on non-contrast CT • Age ≥ 18 years • Treatment can commence within 1 h of initial CT and within 4.5 h of symptom onset (or in people with unknown time of symptom onset, the time the person was last known to be well) • Informed consent has been received in accordance to local ethics committee requirements Exclusion criteria • GCS total score < 8 • Brainstem ICH • ICH volume > 70 mL as measured by the ABC/2 method • ICH known or suspected by study investigator to be secondary to trauma, aneurysm, vascular

	malformation, haemorrhagic transformation of ischaemic stroke, cerebral venous thrombosis, thrombolytic therapy, tumour, or infection • Contrast already administered within 24 h prior to initial CT or contraindication to imaging with CT contrast agents (e.g. known or suspected iodine allergy or significant renal failure) • Any history or current evidence suggestive of venous or arterial thrombotic events within the previous 12 months, including clinical, ECG, laboratory, or imaging findings. Clinically silent chance findings of old ischaemia are not considered exclusion criteria. • Hereditary or acquired haemorrhagic diathesis or coagulation factor deficiency • Use of heparin, low-molecular weight heparin, GPIIb/IIIa antagonist, or oral anticoagulation (e.g. warfarin, factor Xa inhibitor, thrombin inhibitor) within the previous 14 days, irrespective of laboratory values • Pregnancy (women of childbearing potential must be tested) • Planned surgery for ICH within 24 h • Concurrent or planned treatment with haemostatic agents (e.g. PCC, vitamin K, fresh frozen plasma, or platelet transfusion) • Participation in any investigational study in the last 30 days • Known terminal illness, or planned withdrawal of care or comfort care measures • Any condition that in the judgment of the investigator could impose hazards to the patient if study therapy is initiated, or affect the participation of the patient in the study
Interventions	Intervention: intravenous tranexamic acid 1000 mg in 100 mL 0.9% normal saline over 10 minutes followed by 1000 mg in 500 mL 0.9% normal saline infusion over 8 h Comparator: intravenous placebo in 100 mL 0.9% normal saline over 10 minutes followed by 500 mL 0.9% normal saline infusion over 8 h
Outcomes	Primary outcome measures • ICH growth by 24 ± 3 h as defined by either 33% or 6 mL increase from baseline, adjusted for baseline ICH volume. Secondary outcome measures • Major thromboembolic events (MI, ischaemic stroke, PE), measured within 90 ± 7 days) • Absolute ICH growth volume by 24 ± 3 h, adjusted for baseline ICH volume • Absolute IVH growth volume by 24 ± 3 h, adjusted for baseline IVH volume • mRS score of 0 to 4 at 3 months • mRS score of 0 to 3 at 3 months • Categorical shift in mRS at 3 months, subject to the validity of proportional odds assumption • Death due to any cause by 3 months
Starting date	December 2012
Contact information	Atte Meretoja, The Florey Institute of Neuroscience and Mental Health
Notes	NCT01702636

NCT00699621

Trial name or title	Platelet transfusion in acute intracerebral haemorrhage
Methods	• To explore whether use of antiplatelet agents leads to a rapid enlargement of haematoma after onset of acute ICH • To explore the efficacy and safety of platelet transfusion for prevention of haematoma growth in people who experienced acute ICH while on antiplatelet medication
Participants	Inclusion criteria • Taking either aspirin, clopidogrel, or a combination of aspirin and dipyridamole • Acute primary ICH • > 17 years • Admitted within 6 h after onset of ICH • ICH score < 4 Exclusion criteria • Type of ICH other than acute primary ICH • People who need neurosurgery • Life expectancy < 3 months due to comorbid disorders • Confirmed malignant disease (cancer) • Confirmed acute MI • Hepatitis, liver cirrhosis, or both • Renal failure • Infectious disease (HIV, endocarditis, etc) • Current or previous haematologic disease • Women of childbearing age, if pregnant • Participation in another study within the preceding 30 days
Interventions	Intervention: 4 units of fresh platelets will be infused immediately Comparator: no platelet transfusion (open control)
Outcomes	Primary outcome measures • Haematoma growth within 24 h measured as increase in haematoma volume observed by head CT (time frame: 24 h) Secondary outcome measures • GOS (time frame: 90 days) • Cardiovascular death occurring within the treatment period (time frame: 90 days) • Death due to any cause occurring within the treatment period (time frame: 90 days) • Acute MI (time frame: 90 days) • VTE (time frame: 90 days)
Starting date	January 2009
Contact information	Matti E Hillbom, Oulu University Central Hospital, Department of Neurology
Notes	NCT00699621

NCT00810888

Trial name or title	The Spot Sign for Predicting and Treating ICH Growth study (STOP-IT)
Methods	The purpose of this study is to determine if computed tomography angiography can predict which individuals with ICH will experience significant growth in the size of the haemorrhage. For individuals who are at high risk for haemorrhage growth, the study will compare the drug recombinant activated factor VII (rFVIIa) to placebo to determine the effect of rFVIIa on ICH growth
Participants	Inclusion criteria • Acute, spontaneous ICH (including bleeding in cerebellum) diagnosed by non-enhanced CT scan within 5 h of symptom onset. (Time of onset is defined as the last time the patient was witnessed to be at baseline, i.e. people who have stroke symptoms upon awakening will be considered to have their onset at beginning of sleep) • Age ≥ 18 years through 80 years (candidates must have had their 18th birthday, but not had their 81st birthday) • For spot positive patients, dosing of study drug within 90 minutes of enrolling CT scan Exclusion criteria • Time of symptom onset of ICH is unknown or more than 5 h prior to baseline CT scan • ICH secondary to known or suspected trauma, aneurysm, vascular malformation, haemorrhagic conversion of ischaemic stroke, venous sinus thrombosis, thrombolytic treatment of any condition (e.g. MI, cerebral infarction, etc), CNS tumour or CNS infection • Brainstem location of haemorrhage (people with cerebellar haemorrhage may be enrolled) • Serum creatinine > 1.4 mg/dL (123 μmol/L). Sites that currently perform CTA as standard of care for ICH will follow their standard procedures regarding renal insufficiency • Known allergy to iodinated contrast media • Intravenous or intra-arterial administration of iodinated contrast media within the previous 24 h of baseline CT scan • Known hereditary (e.g. haemophilia) or acquired haemorrhagic diathesis, coagulation factor deficiency, or anticoagulant therapy with INR > 1.2 • Known or suspected thrombocytopenia (unless current platelet count documented above 50,000/μL) • Unfractionated heparin use with abnormal PTT • Low-molecular weight heparin use within the previous 24 h • GPIIb/IIIa antagonist use in the previous 2 weeks • GCS score < 8 at time of proposed enrolment • Pre-admission mRS score > 2 • Baseline ICH volume of < 0.5 cc (haematoma volume will be estimated by local investigators from the baseline CT using the ABC/2 method) • Baseline ICH volume > 90 cc • Planned surgical evacuation of ICH within 24 h of symptom onset (placement of intraventricular catheter is not a contraindication to study enrolment) • Evidence of acute or subacute ischaemic stroke on baseline qualifying CT scan • Clinical history of thromboembolism or ischaemic vascular disease, including MI, coronary artery bypass surgery, cardiac angina, TIA, ischaemic stroke, peripheral artery disease (vascular claudication), cerebral bypass surgery, carotid endarterectomy, deep venous thrombosis, pulmonary embolism, or coronary or cerebrovascular angioplasty or stenting. (Clinically silent evidence of old ischaemia on EKG (Q waves) or CT scan (silent old infarct) will not be considered reasons for exclusion) • Baseline electrocardiogram shows evidence of acute cardiac ischaemia (ST elevation in 2 contiguous leads, new LBBB, or ST depression) • Clinical history suggestive of acute cardiac ischaemia (e.g. chest pain) • Abnormal baseline troponin

NCT00810888 (*Continued*)

	• Females of childbearing potential who are known to be pregnant, lactating, or who have positive pregnancy tests on admission • Advanced or terminal illness or any other condition the investigator feels would pose a significant hazard to the patient if rFVIIa were administered • Recent (within 30 days) participation in any investigational drug or device trial or earlier participation in any investigational drug or device trial for which the duration of effect is expected to persist until the time of STOP-IT enrolment • Planned withdrawal of care or comfort care measures • Person known or suspected of not being able to comply with trial protocol (e.g. due to alcoholism, drug dependency or psychological disorder) • Informed consent cannot be obtained from the patient or legally authorised representative
Interventions	Intervention: recombinant activated factor VII. Participants will receive rFVIIa at 80 mcg/kg (maximum dose volume 21.3 mL, equivalent to maximum weight of 160 kg) Comparator: placebo. An inactive substance (maximum dose volume 21.3 mL, equivalent to maximum weight of 160 kg)
Outcomes	Primary outcome measures: life-threatening thromboembolic complications defined as development of 1) acute myocardial ischaemia, 2) acute cerebral ischaemia, and 3) acute pulmonary embolism (time frame: through day 4 after completion of study drug). The rate of haematoma growth among spot sign positive participants at 24 h, comparing participants treated with rFVIIa to those treated with placebo. Haematoma growth will be defined as a > 33% or > 6 cc increase in volume (time frame: at 24 h). The sensitivity and specificity of the spot sign for predicting haematoma growth (time frame: baseline head CT scan within 5 h, followed by a CT angiogram. Haematoma growth determined by comparison with a head CT scan performed at 24 h) Secondary outcome measures: incidence of other potentially study drug-related thromboembolic complications, such as deep venous thrombosis and elevations in troponin not associated with ECG changes (time frame: through day 4 after completion of study drug) 90-day outcomes among spot positive people, dichotomised as mRS score of 0 to 4 verses 5 to 6, comparing participants treated with rFVIIa to those treated with placebo (time frame: 90 days (± 7 days) from time of study enrolment). The positive and negative predictive values of the spot sign and the accuracy of the site investigators for correct identification of the spot sign as compared to a blinded study neuroradiologist (time frame: baseline head CT scan within 5 h, followed by a CT angiogram. Haematoma growth determined by comparison with a head CT scan performed at 24 h. Rate of total haemorrhage volume growth (haematoma + IVH) among spot-positive participants (time frame: 24 h (± 3 h) from baseline CT scan)
Starting date	November 2010
Contact information	Matthew Flaherty, Associate Professor, University of Cincinnati
Notes	NCT00810888

NCT01359202

Trial name or title	'Spot Sign' Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT)
Methods	This clinical trial will enrol 110 participants from approximately 15 Canadian stroke centres. People coming to the emergency department with bleeding in the brain not due to trauma or other known causes who can be treated within 6 h of onset will undergo CT angiography using standard CT scanners ('CAT scan'). Those with a 'spot sign', a type of marker on the CT scan that shows the brain is still bleeding, will be randomly assigned to a single injection of 'factor 7' (a blood clotting drug used in haemophilia) or placebo (inactive saline); people without a spot sign will not be treated. The researchers will look at how much bleeding happens after the treatments are administered, as well as clinical outcomes such as death and disability. The researchers think that factor 7 will cause the bleeding to stop faster and possibly decrease death and disability
Participants	Inclusion criteria • Acute spontaneous primary supratentorial ICH diagnosed by CT scan • Presence of a spot sign within the haematoma on CTA source images • Baseline ICH volume 3 mL to 90 mL • Age 18 or older • Investigator is able to randomise and administer study drug as soon as possible within a target of 60 minutes after CT angiogram and no later than 6 h after stroke symptom onset (using the 'last seen normal' principle) • Plan to provide full medical care for at least 24 h • Assent-consent from participant or LAR prior to enrolment, or a waiver of consent (where REB approved) if patient or LAR assent-consent is not possible prior to enrolment Exclusion criteria • Brainstem or cerebellar haemorrhage • ICH secondary to known or suspected trauma, aneurysm, vascular malformation, hemorrhagic conversion of ischaemic stroke, venous sinus thrombosis, thrombolytic treatment, tumour, or infection; or an in-hospital ICH or ICH as a result of any in-hospital procedure or illness • Baseline brain imaging shows evidence of acute or subacute ischaemic stroke (chronic infarcts are not an exclusion) • Contrast administration within the previous 24 h • Evidence of thromboembolic risk factors, defined as any of the following: known history within the past 6 months of any of the following: 1) MI, 2) coronary artery bypass surgery, 3) angina, 4) ischaemic stroke, 5) TIA, 6) carotid endarterectomy, 7) cerebral bypass surgery, 8) deep venous thrombosis, 9) pulmonary embolism, 10) any vascular angioplasty, stenting (coronary, peripheral vascular, or cerebrovascular) or filter (e.g. vena cava filter); 11) prosthetic cardiac valve, and, or 12) known history of a high-risk thrombophilia (e.g. antithrombin III deficiency, antiphospholipid antibody syndrome, protein C deficiency, etc) • Known hereditary (e.g. haemophilia) or acquired haemorrhagic diathesis or coagulation factor deficiency • Any known condition that the investigator feels would pose a significant hazard if rFVIIa were administered • Planned surgery for ICH within 24 h (placement of intraventricular catheter is not an exclusion) • Planned withdrawal of care before 24 h post-ICH onset • Known participation in another therapeutic trial • Known allergy or other contraindication to iodinated contrast dye • Known or suspected hypersensitivity to the trial product • Known unfractionated heparin use - must check PTT and exclude if elevated above upper limit of local lab's reference range • Known low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use

	within previous 7 days • Known GPIIb/IIIa antagonist use in previous 2 weeks • Known warfarin (or other anticoagulant) therapy with INR > 1.40. Note: if the patient is suspected to have cirrhosis, study staff are to wait for the INR value prior to dosing, and ensure they do not enrol the patient if the INR value is > 1.40. Otherwise, the physician should use their discretion if they believe the patient is not at risk for elevated INR • Concurrent or planned treatment with prothrombin complex concentrate, vitamin K, fresh frozen plasma, or platelet transfusion • Pregnancy or lactation. Women of childbearing potential must have a negative pregnancy test prior to randomization. • Current clinical symptoms suggestive of acute coronary ischaemia (e.g. chest pain). • Baseline ECG evidence of acute coronary ischaemia (e.g. ST elevation in 2 contiguous leads, new LBBB, ST depression) • Baseline platelet count < 50,000, INR > 1.40, or elevated PTT
Interventions	Intrevention: rfVIIa 80 ug/kg IV bolus Comparator: placebo standard saline solution
Outcomes	Primary outcome measures • ICH size: difference between groups in ICH size on CT scan at 24 h post-dose, adjusted for baseline ICH size Secondary outcome measures: • Feasibility (time frame: 0): percentage of sites that can meet recruitment targets of 2 patients per site per year; % of patients who meet the target time of < 45 minutes from emergency department arrival to the start of the scan; % of patients who meet the target time of < 60 minutes from the end of the CT angiogram to administration of study drug; local site spot sign interpretation accuracy as judged by central adjudicator; protocol violations; waiver of consent process, evaluation, and effectiveness (time frame: 4.90 days); waiver of consent use, acceptability, and effect on treatment times. Questionnaire will be administered to subject or LAR at 4 days and 90 days • Acute blood pressure control (time frame: 1 h): % of participants in whom blood pressure control was achieved, defined as achieving systolic BP < 180 mmHg within 1 h post-randomisation • Thromboembolic events : incidence of MI and ischaemic stroke within 4 days; any other arterial or venous thromboembolic SAEs within 4 days • Mortality : 90-day mortality rate • Unstable angina: unstable angina within 4 days of treatment • Troponin increase : troponin rise above upper limit of normal within 4 days (without clinical symptoms or ECG evidence of acute coronary syndrome) • DVT : deep venous thrombosis (DVT) within 4 days • Pulmonary embolism : PE within 30 days • Cognition : Montreal Cognitive Assessment (MoCA) and Stroke Impact Scale at 90 days and 1 year • Disability : proportion of participants with mRS score 5 to 6 (death or severe disability) at 90 days and 1 year
Starting date	May 2011
Contact information	Dr David Gladstone, Sunnybrook Health Sciences Centre
Notes	NCT01359202

NCT02777424

Trial name or title	Prothrombin complex concentrate versus fresh frozen plasma to correct coagulation disorders in adult neurosurgical patients (CLOT-CRANE)
Methods	This prospective, randomized, multicentre study is performed to determine whether prothrombin complex concentrates confers any benefits over fresh frozen plasma in adult neurological patients with coagulation disorders (PT value less than 60%)
Participants	Inclusion criteria • People with spontaneous ICH, traumatic ICH, or people requiring neurological surgery • Coagulation disorder defined by PT < 60% Exclusion criteria • Concomitant use of oral anticoagulant drugs • Acquired deficiency of coagulation factors whose treatment is established • Hypersensitivity to a PCC • History of thrombocytopenia induced by heparin • Disseminated intravascular coagulation • Extracranial active bleeding • Hypersensitivity to vitamin K
Interventions	Intervention: PCC. Administration of a single dose of PCC (25 U/kg equivalent factor IX) Comparator: fresh frozen plasma. Administration of a single dose of fresh frozen plasma of 15 mL/kg
Outcomes	Primary outcome measures • Proportion of participants with correction of prothrombin time (PT < 60% at end of treatment administration - an average of 1 h)
Starting date	January 2016
Contact information	Laurence Salomon, Fondation Ophtalmologique Adolphe de Rothschild
Notes	NCT02777424

NCT02866838

Trial name or title	Treatment of intracerebral hemorrhage in patients on non-vitamin K antagonist (TICH-NOAC)
Methods	NOACs target selected players in the coagulation cascade as the direct thrombin inhibitor dabigatran and the factor Xa-inhibitors apixaban and rivaroxaban. ICH is the most feared complication of NOAC treatment (NOAC-ICH) Outcome of NOAC-ICH can be devastating and is a major cause of death and disability. There is no proven treatment for NOAC-ICH. Haematoma expansion (HE) is associated with unfavourable outcome. Tranexamic acid (TA) is an anti-fibrinolytic drug that is used in a number of bleeding conditions other than ICH
Participants	Inclusion criteria • Acute ICH (symptom onset < 12 h) • Prior treatment with a novel direct oral anticoagulant (apixaban, dabigatran, edoxaban, or rivaroxaban; last intake < 48 h or proven NOAC activity by relevant coagulation assays) • Age > 18 years, no upper age limit

NCT02866838 (*Continued*)

	• Informed consent has been received in accordance to local ethics committee requirements Exclusion criteria • Severe pre-morbid disability (mRS > 4) • Anticoagulation with vitamin K antagonists (VKA; recent intake) • Secondary ICH (e.g. AVM, tumour, trauma). Note: it is not necessary for investigators to exclude underlying structural abnormality prior to enrolment, but where an underlying structural abnormality is already known, these people should not be recruited. • GCS < 5 • Pregnancy • Planned neurosurgical haematoma evacuation within 24 h (before follow-up imaging) • PE or DVT within the last 2 weeks
Interventions	Intervention: intravenous tranexamic acid: 1 g loading dose given as 100 mL infusion over 10 minutes, followed by another 1 g in 250 mL infused over 8 h Comparator: placebo: saline 0.9% given in identical dosage as experimental drug
Outcomes	Primary outcome measures • Haematoma expansion (time frame: up to 27 h): change in ICH-volume between baseline CT and follow-up CT at 24 ± 3 h of 33% relative or 6 mL absolute increase Secondary outcome measures: • mRS 0 to 4 at month 3 • mRS 0 to 3 at month 3 • Categorical shift in mRS at month 3 • Mortality due to any cause at month 3 • In-hospital mortality (time frame: baseline until discharge from hospital - hospital stays last, on average, 10 days) • Absolute ICH growth volume by 24 ± 3 h, adjusted for baseline ICH volume • Symptomatic HE defined as HE plus a neurological deterioration of NIHSS > 4 points or GCS > 2 points • Number of major thromboembolic events (MI, ischaemic stroke, PE - safety endpoints; 3 months) • Number of neurosurgical interventions (including craniectomy, external ventricular drain, haematoma evacuation; 3 months)
Starting date	December 2016
Contact information	Philippe Lyrer, Stroke Center and Neurology, University Hospital Basel
Notes	NCT02866838

NCT03044184

Trial name or title	Tranexamic acid for spontaneous acute cerebral hemorrhage trial (TRANSACT)
Methods	This study aims to explore the effectiveness of tranexamic acid (also known as transamine or TXA) in reducing haematoma expansion in people with haemorrhagic stroke when given in the acute phase
Participants	Inclusion criteria • People with CT evidence of supratentorial ICH

NCT03044184 (*Continued*)

	• Initiation of trial medication within 3 h from the time of symptoms onset • Ethnic Chinese • Reasonable expectation of completion of outcome measures at follow-up • Written informed consent from either the patient, next-of-kin, or legal guardian Exclusion criteria • Patients not expected to survive 24 h after admission • Patients with brainstem herniation syndrome on admission • Patients who need immediate neurosurgical intervention • GCS of 5 or less on admission i.e. a GCS score of 2 according to the Hemphil ICH score • Previous antiplatelet and anticoagulant medication use • Known thrombocytopenia or coagulopathy • Disseminated intravascular coagulation on admission • Acute sepsis on admission • ICH secondary to intracranial vascular lesion: aneurysm, AVM, neoplasm, or dural venous sinus thrombosis • Previous venous thromboembolic disease: DVT • History of ischaemic stroke or TIA within 12 months • History of ischaemic heart disease or MI • History of peripheral vascular disease • Patients with previous disability (prestroke mRS score > 2) • Pregnancy or breast feeding • History of allergy to tranexamic acid
Interventions	Intervention: standard management for people with spontaneous ICH according to 2015 AHA/ASA Guidelines for the Management of Intracerebral Hemorrhage. Participants will have 1 g of tranexamic acid (diluted in 100 mL of normal saline 0.9%) intravenously infused over 10 minutes, within 3 h of symptom presentation, and another 1 g of tranexamic acid (diluted in 100 mL of normal saline 0.9%) infused over 8 h Comparator: standard management for participants with spontaneous ICH according to 2015 AHA/ASA Guidelines for the Management of Intracerebral Hemorrhage. Participants will have 100 mL of normal saline 0.9% intravenously infused over 10 minutes within 3 h of symptom presentation, and another 100 mL of normal saline 0.9% infused over 8 h
Outcomes	Primary outcome measures • ICH volume (by CT brain scan) at 6 h: intracerebral haematoma volume (mL) as assessed by CT brain scan • ICH volume (by CT brain scan) at 24 h: intracerebral haematoma volume (mL) as assessed by CT brain scan • ICH volume (by CT brain scan) at 1 week: intracerebral haematoma volume (mL) as assessed by CT brain scan Secondary outcome measures • GOS (at 3 months and 6 months after stroke) • mRS (at 3 months and 6 months after stroke) • Stroke-specific quality of life scale (at 3 months and 6 months after stroke) • 30-day mortality : all-cause mortality within 30 days of admission • Vascular occlusive events (at 30 days after admission): ischaemic stroke, MI, PE, DVT • Rate of seizures: rate of seizures within 30 days of stroke • Tranexamic acid-associated adverse effects (at 30 days after admission): intolerable gastrointestinal symptoms, such as dyspepsia, diarrhoea, vomiting. Allergic reaction to tranexamic acid • Need for neurosurgical intervention (at 30 days after admission): need for operative management of

NCT03044184 (*Continued*)

	the haemorrhagic stroke
Starting date	1 April 2017
Contact information	Peter YM Woo, Neurosurgery, Kwong Wah Hospital
Notes	NCT03044184

NOR-ICH

Trial name or title	The Norwegian Intracerebral Haemorrhage trial (NOR-ICH)
Methods	Multicentre prospective randomized, open-label, blinded endpoint (PROBE) trial. There are 2 arms in the study: arm A treats participants presenting within 2.5 h from onset, and arm B treats participants presenting between 2.5 and 4.5 h
Participants	The trial aims to recruit 500 participants, aged 18 years to 80 years, over 4 years
Interventions	Intervention: intravenous tranexamic acid 1 g bolus followed by 1 g at 2 h, 4 h, and 8 h from the first dose, lasting for 28 h in total Comparator: open control
Outcomes	Primary outcome: haematoma expansion at 24 h Secondary outcomes: increase in NIHSS score within 36 h, NIHSS at day 7, mRS at day 90, and symptomatic thromboembolic events within 7 days
Starting date	2012
Contact information	
Notes	This information is based on a record we found at helseforskning.etikkom.no/prosjekterirek/prosjektregister/prosjekt?p_document_id=324797

Sprigg 2016 (TICH-2)

Trial name or title	Tranexamic acid for IntraCerebral Haemorrhage (TICH-2)
Methods	A pragmatic phase III prospective double-blind randomised placebo-controlled trial
Participants	Inclusion criteria • Adults with acute spontaneous ICH • Within 8 h of stroke symptom onset or time last seen well Exclusion criteria • People with ICH secondary to anticoagulation, thrombolysis or known underlying structural abnormality such as AVM, aneurysm, tumour, or venous thrombosis. An underlying structural abnormality does not need to be excluded before enrolment, but where known, patients should not be recruited • Contraindication to tranexamic acid

Sprigg 2016 (TICH-2) (*Continued*)

	• Premorbid dependency (mRS > 4) • Concurrent participation in another drug or device trial. Participants enrolled in TICH-2 may be enrolled into the RESTART trial after 21 days • Prestroke life expectancy Target sample size 2000
Interventions	Intervention: intravenous tranexamic acid: 1 g loading dose given as 100 mL infusion over 10 minutes, followed by another 1 g in 250 mL infused over 8 h Comparator: matching placebo (normal saline 0.9%) administered by identical regimen
Outcomes	Primary outcome measure: to assess whether tranexamic acid is safe and reduces death or dependency after primary ICH. Death or dependency (ordinal shift on mRS) at day 90 will be analysed by intention-to-treat using ordinal logistic regression (OLR), with adjustment for minimisation factors. The assumption of proportional odds will be tested using the likelihood ratio test. Comparison of tranexamic acid versus control Secondary outcome measures • At day 7 (or discharge if sooner), neurological impairment (NIHSS) • At day 90, disability (BI), Quality of Life (EuroQoL), cognition, cognition and mood (TICS and ZDS) • Safety: death, serious adverse events, thromboembolic events, seizures • Costs: length of hospital stay, re-admission, institutionalisation • Radiological efficacy and safety (CT scan): change in haematoma volume from baseline to 24 h, haematoma location, and new infarction
Starting date	1 March 2013
Contact information	Prof Nikola Sprigg, University of Nottingham
Notes	ISRCTN93732214

AVM: arteriovenous malformation
BI: Barthel Index
CT: computed tomography
CTA: computed tomography angiography
DVT: deep vein thrombosis
ECG: electrocardiogram
GCS: Glasgow Coma Score
GOS: Glasgow Outcome Scale
h: hour(s)
ICH: intracerebral haemorrhage
INR: international normalised ratio
IVH: intraventricular haemorrhage
MI: myocardial infarction
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
NOAC: non-vitamin K antagonist oral anticoagulants
PCC: prothrombin complex concentrate
PE: pulmonary embolism
RCT: randomised controlled trial
SAE: serious adverse event

SAH: subarachnoid haemorrhage
SBP: systolic blood pressure
TIA: transient ischaemic attack
VTE: venous thromboembolism

DATA AND ANALYSES

Comparison 1. Blood clotting factors vs placebo or open control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependence (mRS 4 to 6) at day 90	6	1390	Risk Ratio (IV, Random, 95% CI)	0.87 [0.70, 1.07]
1.1 Acute spontaneous ICH	5	1369	Risk Ratio (IV, Random, 95% CI)	0.86 [0.66, 1.11]
1.2 Acute spontaneous ICH undergoing craniotomy	1	21	Risk Ratio (IV, Random, 95% CI)	0.88 [0.59, 1.31]
2 Death or dependence (GOS-E 1 to 4) at day 90	3	486	Risk Ratio (IV, Random, 95% CI)	0.90 [0.81, 1.01]
2.1 Acute spontaneous ICH	3	486	Risk Ratio (IV, Random, 95% CI)	0.90 [0.81, 1.01]
3 Death by day 90	7	1480	Risk Ratio (IV, Random, 95% CI)	0.75 [0.51, 1.09]
3.1 Acute spontaneous ICH	6	1459	Risk Ratio (IV, Random, 95% CI)	0.71 [0.44, 1.14]
3.2 Acute spontaneous ICH undergoing craniotomy	1	21	Risk Ratio (IV, Random, 95% CI)	0.86 [0.41, 1.80]
4 All serious adverse events	2	87	Risk Ratio (IV, Random, 95% CI)	0.81 [0.30, 2.22]
4.1 Acute spontaneous ICH	2	87	Risk Ratio (IV, Random, 95% CI)	0.81 [0.30, 2.22]
5 Thromboembolic serious adverse events	5	1398	Risk Ratio (IV, Random, 95% CI)	1.24 [0.80, 1.91]
5.1 Acute spontaneous ICH	5	1398	Risk Ratio (IV, Random, 95% CI)	1.24 [0.80, 1.91]
6 Intracerebral haemorrhage growth by 24 hours	3	151	Risk Ratio (IV, Random, 95% CI)	0.74 [0.36, 1.48]
6.1 Acute spontaneous ICH	3	151	Risk Ratio (IV, Random, 95% CI)	0.74 [0.36, 1.48]

Comparison 2. Antifibrinolytic drugs vs placebo or open control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependence (mRS 4 to 6) at day 90	1	24	Risk Ratio (IV, Random, 95% CI)	1.25 [0.57, 2.75]
1.1 Acute spontaneous ICH	1	24	Risk Ratio (IV, Random, 95% CI)	1.25 [0.57, 2.75]
2 Death by day 90	3	57	Risk Ratio (IV, Random, 95% CI)	1.16 [0.31, 4.39]
2.1 Acute spontaneous ICH	3	57	Risk Ratio (IV, Random, 95% CI)	1.16 [0.31, 4.39]
3 All serious adverse events	1	24	Risk Ratio (IV, Random, 95% CI)	1.5 [0.39, 5.83]
3.1 Acute spontaneous ICH	1	24	Risk Ratio (IV, Random, 95% CI)	1.5 [0.39, 5.83]
4 Thromboembolic serious adverse events	1	24	Risk Ratio (IV, Random, 95% CI)	1.59 [0.07, 35.15]
4.1 Acute spontaneous ICH	1	24	Risk Ratio (IV, Random, 95% CI)	1.59 [0.07, 35.15]
5 Barthel Index	1	24	Mean Difference (IV, Random, 95% CI)	-22.50 [-45.65, 0.65]
5.1 Acute spontaneous ICH	1	24	Mean Difference (IV, Random, 95% CI)	-22.50 [-45.65, 0.65]

6 EuroQoL health utility score	1	24	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.35, 0.27]
6.1 Acute spontaneous ICH	1	24	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.35, 0.27]
7 Intracerebral haemorrhage growth by 24 hours	3	57	Risk Ratio (IV, Random, 95% CI)	0.76 [0.56, 1.05]
7.1 Acute spontaneous ICH	3	57	Risk Ratio (IV, Random, 95% CI)	0.76 [0.56, 1.05]

Comparison 3. Platelet transfusion vs open control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependence (mRS 4 to 6) at day 90	1	190	Risk Ratio (IV, Random, 95% CI)	1.29 [1.04, 1.61]
1.1 Acute antiplatelet-associated ICH	1	190	Risk Ratio (IV, Random, 95% CI)	1.29 [1.04, 1.61]
2 Death by day 90	1	190	Risk Ratio (IV, Random, 95% CI)	1.42 [0.88, 2.28]
2.1 Acute antiplatelet-associated ICH	1	190	Risk Ratio (IV, Random, 95% CI)	1.42 [0.88, 2.28]
3 All serious adverse events	1	190	Risk Ratio (IV, Random, 95% CI)	1.46 [0.98, 2.16]
3.1 Acute antiplatelet-associated ICH	1	190	Risk Ratio (IV, Random, 95% CI)	1.46 [0.98, 2.16]
4 Thromboembolic serious adverse events	1	190	Risk Ratio (IV, Random, 95% CI)	3.84 [0.44, 33.68]
4.1 Acute antiplatelet-associated ICH	1	190	Risk Ratio (IV, Random, 95% CI)	3.84 [0.44, 33.68]
5 Intracerebral haemorrhage growth by 24 hours	1	190	Risk Ratio (IV, Random, 95% CI)	1.11 [0.56, 2.20]
5.1 Acute antiplatelet-associated ICH	1	190	Risk Ratio (IV, Random, 95% CI)	1.11 [0.56, 2.20]

Comparison 4. Blood clotting factors vs fresh frozen plasma

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death by day 90	1	5	Risk Ratio (IV, Random, 95% CI)	0.27 [0.02, 3.74]
1.1 Acute anticoagulant-associated ICH	1	5	Risk Ratio (IV, Random, 95% CI)	0.27 [0.02, 3.74]
2 All serious adverse events	1	5	Risk Ratio (IV, Random, 95% CI)	0.27 [0.02, 3.74]
2.1 Acute anticoagulant-associated ICH	1	5	Risk Ratio (IV, Random, 95% CI)	0.27 [0.02, 3.74]

Analysis 1.1. Comparison 1 Blood clotting factors vs placebo or open control, Outcome 1 Death or dependence (mRS 4 to 6) at day 90.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 1 Blood clotting factors vs placebo or open control

Outcome: 1 Death or dependence (mRS 4 to 6) at day 90

Study or subgroup	Blood clotting factor(s) n/N	Placebo/open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute spontaneous ICH					
Mayer 2005b	160/303	66/96		32.3 %	0.77 [0.65, 0.91]
Mayer 2005a	16/36	5/11		6.7 %	0.98 [0.46, 2.06]
Mayer 2006	15/32	4/8		6.1 %	0.94 [0.43, 2.06]
Mayer 2008 (FAST)	269/557	120/262		33.4 %	1.05 [0.90, 1.23]
Li 2012	5/32	13/32		4.8 %	0.38 [0.16, 0.95]
Subtotal (95% CI)	**960**	**409**		**83.3 %**	**0.86 [0.66, 1.11]**
Total events: 465 (Blood clotting factor(s)), 208 (Placebo/open control)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 10.59, df = 4 (P = 0.03); I^2 =62%					
Test for overall effect: Z = 1.14 (P = 0.25)					
2 Acute spontaneous ICH undergoing craniotomy					
Imbert 2012 (PRE-SICH)	10/13	7/8		16.7 %	0.88 [0.59, 1.31]
Subtotal (95% CI)	**13**	**8**		**16.7 %**	**0.88 [0.59, 1.31]**
Total events: 10 (Blood clotting factor(s)), 7 (Placebo/open control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
Total (95% CI)	**973**	**417**		**100.0 %**	**0.87 [0.70, 1.07]**
Total events: 475 (Blood clotting factor(s)), 215 (Placebo/open control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 10.61, df = 5 (P = 0.06); I^2 =53%					
Test for overall effect: Z = 1.30 (P = 0.19)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.93), I^2 =0.0%					

Analysis 1.2. Comparison 1 Blood clotting factors vs placebo or open control, Outcome 2 Death or dependence (GOS-E 1 to 4) at day 90.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 1 Blood clotting factors vs placebo or open control

Outcome: 2 Death or dependence (GOS-E 1 to 4) at day 90

Study or subgroup	Blood clotting factor(s) n/N	Placebo/open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute spontaneous ICH					
Mayer 2005a	24/36	7/11		4.9 %	1.05 [0.63, 1.73]
Mayer 2005b	221/303	78/96		89.7 %	0.90 [0.80, 1.01]
Mayer 2006	20/32	6/8		5.4 %	0.83 [0.51, 1.35]
Total (95% CI)	**371**	**115**		**100.0 %**	**0.90 [0.81, 1.01]**

Total events: 265 (Blood clotting factor(s)), 91 (Placebo/open control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.45$, df = 2 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 1.83 (P = 0.067)

Test for subgroup differences: Not applicable

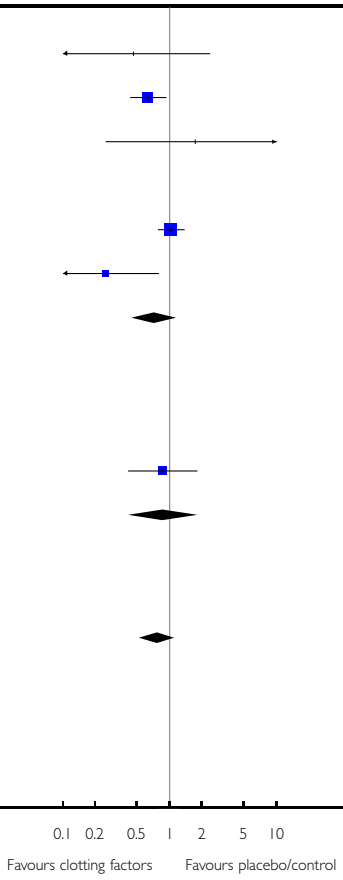
Analysis 1.3. Comparison 1 Blood clotting factors vs placebo or open control, Outcome 3 Death by day 90.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 1 Blood clotting factors vs placebo or open control

Outcome: 3 Death by day 90

Study or subgroup	Blood clotting factor(s) n/N	Placebo/open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute spontaneous ICH					
Mayer 2005a	3/36	2/11		4.7 %	0.46 [0.09, 2.40]
Mayer 2005b	56/303	28/96		30.7 %	0.63 [0.43, 0.94]
Mayer 2006	7/32	1/8		3.5 %	1.75 [0.25, 12.26]
F7ICH-1602 2007	0/45	0/45			Not estimable
Mayer 2008 (FAST)	112/557	51/262		35.6 %	1.03 [0.77, 1.39]
Li 2012	3/32	12/32		8.6 %	0.25 [0.08, 0.80]
Subtotal (95% CI)	**1005**	**454**		**83.2 %**	**0.71 [0.44, 1.14]**
Total events: 181 (Blood clotting factor(s)), 94 (Placebo/open control)					
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 9.03$, df = 4 (P = 0.06); $I^2 = 56\%$					
Test for overall effect: Z = 1.42 (P = 0.16)					
2 Acute spontaneous ICH undergoing craniotomy					
Imbert 2012 (PRE-SICH)	7/13	5/8		16.8 %	0.86 [0.41, 1.80]
Subtotal (95% CI)	**13**	**8**		**16.8 %**	**0.86 [0.41, 1.80]**
Total events: 7 (Blood clotting factor(s)), 5 (Placebo/open control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.40 (P = 0.69)					
Total (95% CI)	**1018**	**462**		**100.0 %**	**0.75 [0.51, 1.09]**
Total events: 188 (Blood clotting factor(s)), 99 (Placebo/open control)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 9.05$, df = 5 (P = 0.11); $I^2 = 45\%$					
Test for overall effect: Z = 1.50 (P = 0.13)					
Test for subgroup differences: $Chi^2 = 0.19$, df = 1 (P = 0.66), $I^2 = 0.0\%$					



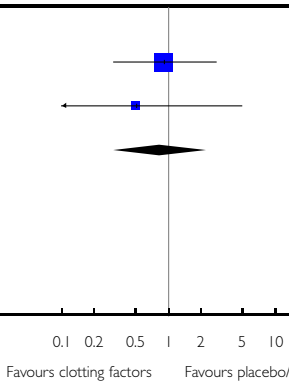
Analysis 1.4. Comparison 1 Blood clotting factors vs placebo or open control, Outcome 4 All serious adverse events.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 1 Blood clotting factors vs placebo or open control

Outcome: 4 All serious adverse events

Study or subgroup	Blood clotting factor(s) n/N	Placebo/open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute spontaneous ICH					
Mayer 2005a	9/36	3/11		80.5 %	0.92 [0.30, 2.81]
Mayer 2006	2/32	1/8		19.5 %	0.50 [0.05, 4.85]
Total (95% CI)	**68**	**19**		**100.0 %**	**0.81 [0.30, 2.22]**
Total events: 11 (Blood clotting factor(s)), 4 (Placebo/open control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.22$, df = 1 (P = 0.64); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.40 (P = 0.69)					
Test for subgroup differences: Not applicable					



Analysis 1.5. Comparison 1 Blood clotting factors vs placebo or open control, Outcome 5 Thromboembolic serious adverse events.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 1 Blood clotting factors vs placebo or open control

Outcome: 5 Thromboembolic serious adverse events

Study or subgroup	Blood clotting factor(s) n/N	Placebo/open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute spontaneous ICH					
Mayer 2005b	21/303	2/96		9.1 %	3.33 [0.79, 13.93]
Mayer 2005a	1/37	1/11		2.6 %	0.30 [0.02, 4.37]
Mayer 2006	3/32	1/8		4.1 %	0.75 [0.09, 6.29]
F7ICH-1602 2007	1/45	2/45		3.3 %	0.50 [0.05, 5.32]
Mayer 2008 (FAST)	55/558	21/263		80.8 %	1.23 [0.76, 2.00]
Total (95% CI)	**975**	**423**		**100.0 %**	**1.24 [0.80, 1.91]**
Total events: 81 (Blood clotting factor(s)), 27 (Placebo/open control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.69, df = 4 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 0.97 (P = 0.33)					
Test for subgroup differences: Not applicable					

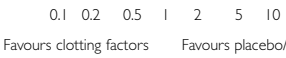
Analysis 1.6. Comparison 1 Blood clotting factors vs placebo or open control, Outcome 6 Intracerebral haemorrhage growth by 24 hours.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 1 Blood clotting factors vs placebo or open control

Outcome: 6 Intracerebral haemorrhage growth by 24 hours

Study or subgroup	Blood clotting factor(s) n/N	Placebo/open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute spontaneous ICH					
Mayer 2005a	8/36	1/11		10.8 %	2.44 [0.34, 17.46]
Mayer 2006	23/32	7/8		61.2 %	0.82 [0.58, 1.15]
Li 2012	4/32	11/32		28.0 %	0.36 [0.13, 1.02]
Total (95% CI)	**100**	**51**		**100.0 %**	**0.74 [0.36, 1.48]**
Total events: 35 (Blood clotting factor(s)), 19 (Placebo/open control)					
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 3.48$, df = 2 (P = 0.18); $I^2 = 42\%$					
Test for overall effect: Z = 0.86 (P = 0.39)					
Test for subgroup differences: Not applicable					

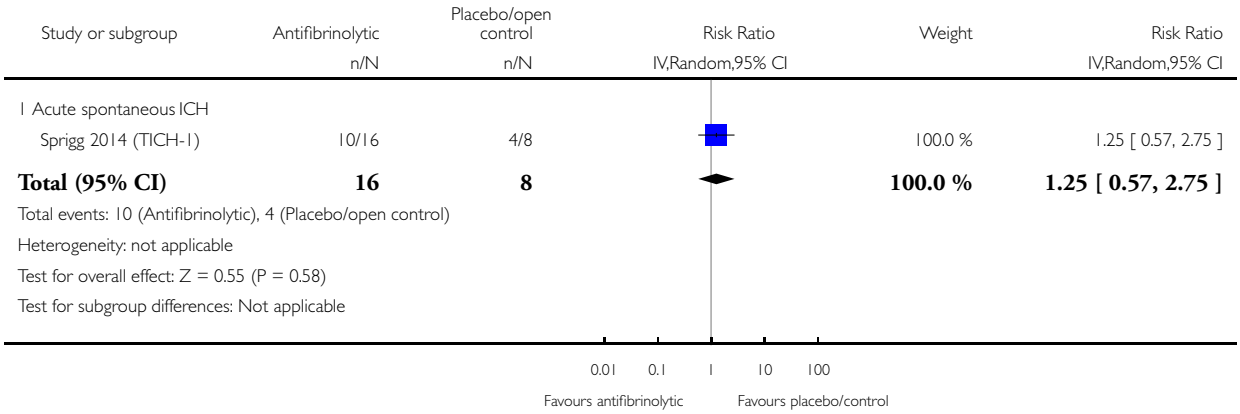


Analysis 2.1. Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 1 Death or dependence (mRS 4 to 6) at day 90.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 2 Antifibrinolytic drugs vs placebo or open control

Outcome: 1 Death or dependence (mRS 4 to 6) at day 90



Analysis 2.2. Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 2 Death by day 90.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 2 Antifibrinolytic drugs vs placebo or open control

Outcome: 2 Death by day 90

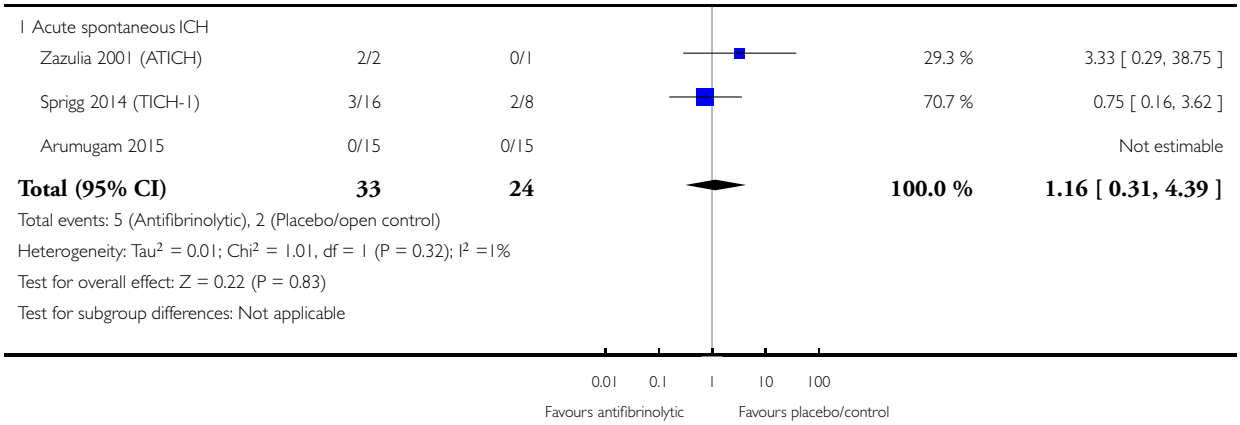
Study or subgroup	Antifibrinolytic n/N	Placebo/open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute spontaneous ICH					
Zazulia 2001 (ATICH)	2/2	0/1		29.3 %	3.33 [0.29, 38.75]
Sprigg 2014 (TICH-1)	3/16	2/8		70.7 %	0.75 [0.16, 3.62]
Arumugam 2015	0/15	0/15			Not estimable
Total (95% CI)	**33**	**24**		**100.0 %**	**1.16 [0.31, 4.39]**

Total events: 5 (Antifibrinolytic), 2 (Placebo/open control)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.01$, df = 1 (P = 0.32); $I^2 = 1\%$

Test for overall effect: Z = 0.22 (P = 0.83)

Test for subgroup differences: Not applicable

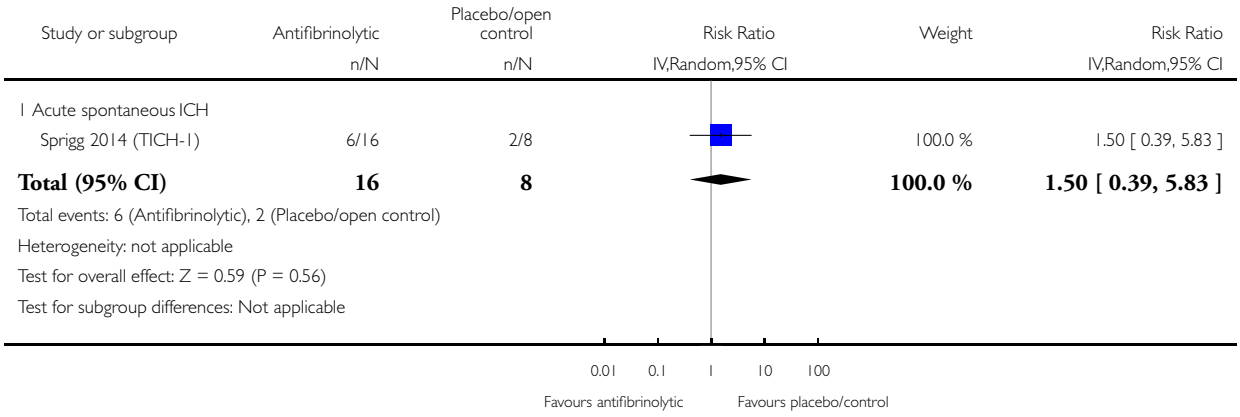


Analysis 2.3. Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 3 All serious adverse events.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 2 Antifibrinolytic drugs vs placebo or open control

Outcome: 3 All serious adverse events

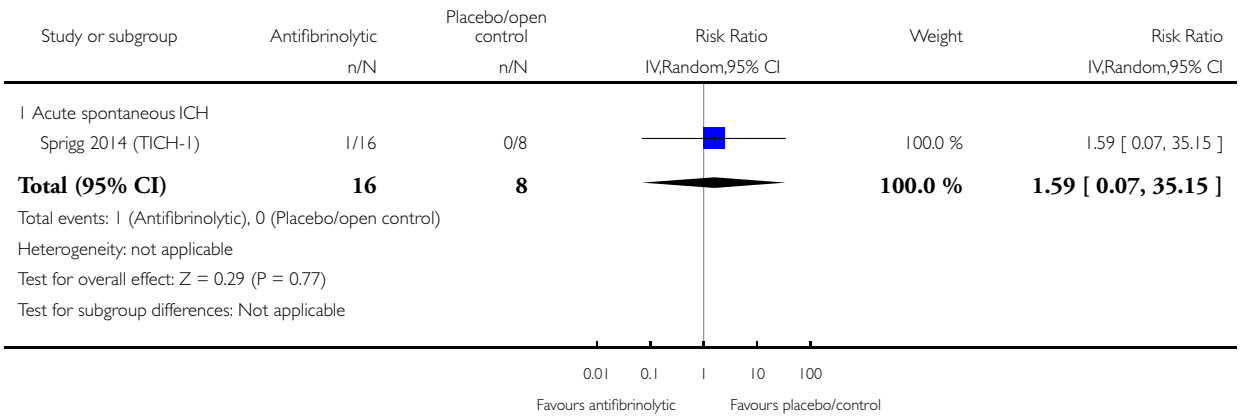


Analysis 2.4. Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 4 Thromboembolic serious adverse events.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 2 Antifibrinolytic drugs vs placebo or open control

Outcome: 4 Thromboembolic serious adverse events



Analysis 2.5. Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 5 Barthel Index.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 2 Antifibrinolytic drugs vs placebo or open control

Outcome: 5 Barthel Index

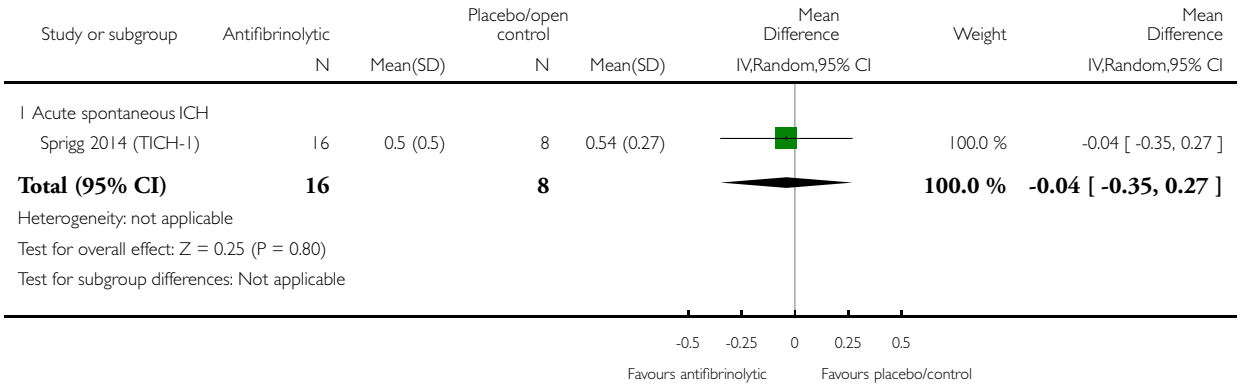
Study or subgroup	Antifibrinolytic N	Mean(SD)	Placebo/open control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Acute spontaneous ICH							
Sprigg 2014 (TICH-1)	16	59.2 (39.7)	8	81.7 (18.1)		100.0 %	-22.50 [-45.65, 0.65]
Total (95% CI)	**16**		**8**			**100.0 %**	**-22.50 [-45.65, 0.65]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.91 (P = 0.057)							
Test for subgroup differences: Not applicable							

Analysis 2.6. Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 6 EuroQoL health utility score.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 2 Antifibrinolytic drugs vs placebo or open control

Outcome: 6 EuroQoL health utility score



Analysis 2.7. Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 7 Intracerebral haemorrhage growth by 24 hours.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 2 Antifibrinolytic drugs vs placebo or open control

Outcome: 7 Intracerebral haemorrhage growth by 24 hours

Study or subgroup	Antifibrinolytic n/N	Placebo/open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute spontaneous ICH					
Arumugam 2015	11/15	15/15		96.4 %	0.74 [0.54, 1.02]
Sprigg 2014 (TICH-1)	3/16	1/8		2.2 %	1.50 [0.18, 12.22]
Zazulia 2001 (ATICH)	1/2	0/1		1.4 %	2.00 [0.14, 28.42]
Total (95% CI)	**33**	**24**		**100.0 %**	**0.76 [0.56, 1.05]**
Total events: 15 (Antifibrinolytic), 16 (Placebo/open control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.93$, df = 2 (P = 0.63); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.68 (P = 0.092)					
Test for subgroup differences: Not applicable					

Analysis 3.1. Comparison 3 Platelet transfusion vs open control, Outcome 1 Death or dependence (mRS 4 to 6) at day 90.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 3 Platelet transfusion vs open control

Outcome: 1 Death or dependence (mRS 4 to 6) at day 90

Study or subgroup	Platelet transfusion n/N	Open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute antiplatelet-associated ICH					
Baharoglu 2016 (PATCH)	70/97	52/93		100.0 %	1.29 [1.04, 1.61]
Total (95% CI)	**97**	**93**		**100.0 %**	**1.29 [1.04, 1.61]**
Total events: 70 (Platelet transfusion), 52 (Open control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.29 (P = 0.022)					
Test for subgroup differences: Not applicable					

Analysis 3.2. Comparison 3 Platelet transfusion vs open control, Outcome 2 Death by day 90.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 3 Platelet transfusion vs open control

Outcome: 2 Death by day 90

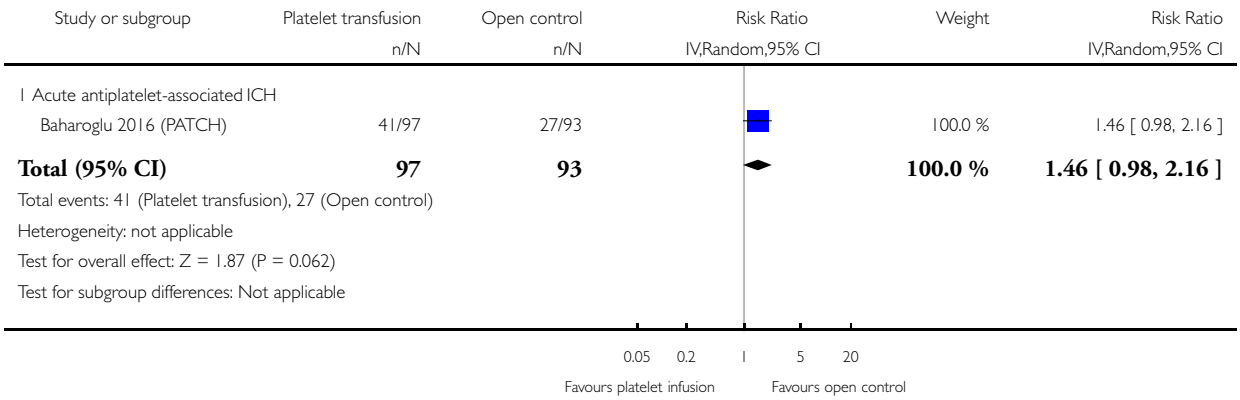
Study or subgroup	Platelet transfusion n/N	Open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute antiplatelet-associated ICH					
Baharoglu 2016 (PATCH)	31/97	21/93		100.0 %	1.42 [0.88, 2.28]
Total (95% CI)	**97**	**93**		**100.0 %**	**1.42 [0.88, 2.28]**
Total events: 31 (Platelet transfusion), 21 (Open control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.43 (P = 0.15)					
Test for subgroup differences: Not applicable					

Analysis 3.3. Comparison 3 Platelet transfusion vs open control, Outcome 3 All serious adverse events.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 3 Platelet transfusion vs open control

Outcome: 3 All serious adverse events



Analysis 3.4. Comparison 3 Platelet transfusion vs open control, Outcome 4 Thromboembolic serious adverse events.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 3 Platelet transfusion vs open control

Outcome: 4 Thromboembolic serious adverse events

Study or subgroup	Platelet transfusion n/N	Open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute antiplatelet-associated ICH					
Baharoglu 2016 (PATCH)	4/97	1/93		100.0 %	3.84 [0.44, 33.68]
Total (95% CI)	**97**	**93**		**100.0 %**	**3.84 [0.44, 33.68]**
Total events: 4 (Platelet transfusion), 1 (Open control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.21 (P = 0.23)					
Test for subgroup differences: Not applicable					

Analysis 3.5. Comparison 3 Platelet transfusion vs open control, Outcome 5 Intracerebral haemorrhage growth by 24 hours.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 3 Platelet transfusion vs open control

Outcome: 5 Intracerebral haemorrhage growth by 24 hours

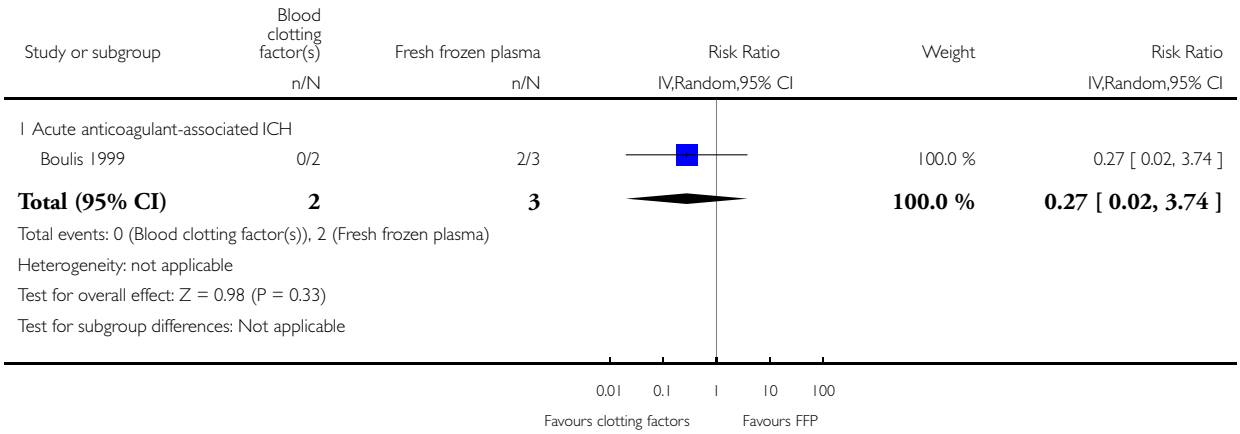
Study or subgroup	Platelet transfusion n/N	Open control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Acute antiplatelet-associated ICH					
Baharoglu 2016 (PATCH)	15/97	13/93		100.0 %	1.11 [0.56, 2.20]
Total (95% CI)	**97**	**93**		**100.0 %**	**1.11 [0.56, 2.20]**
Total events: 15 (Platelet transfusion), 13 (Open control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.29 (P = 0.77)					
Test for subgroup differences: Not applicable					

Analysis 4.1. Comparison 4 Blood clotting factors vs fresh frozen plasma, Outcome 1 Death by day 90.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 4 Blood clotting factors vs fresh frozen plasma

Outcome: 1 Death by day 90

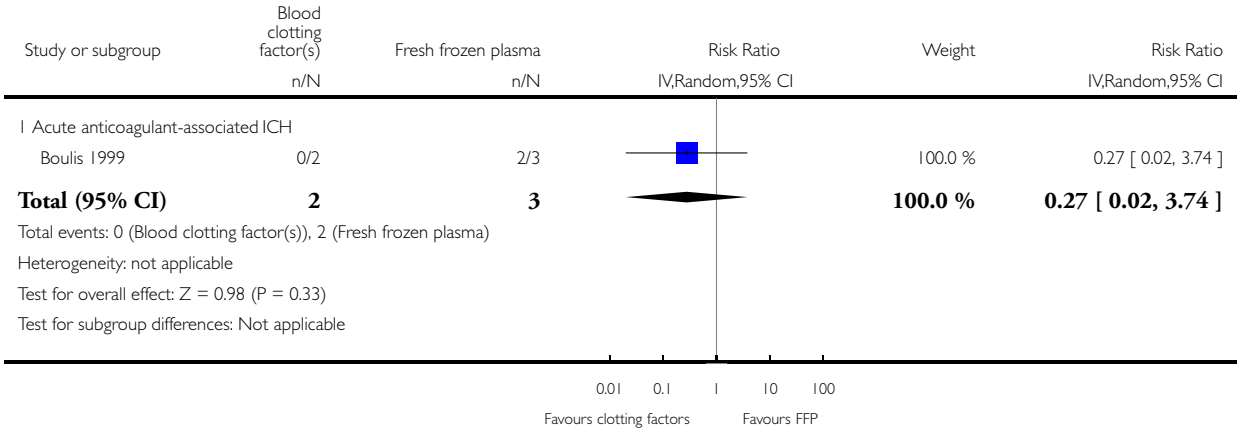


Analysis 4.2. Comparison 4 Blood clotting factors vs fresh frozen plasma, Outcome 2 All serious adverse events.

Review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

Comparison: 4 Blood clotting factors vs fresh frozen plasma

Outcome: 2 All serious adverse events



APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 11) in the Cochrane Library (searched 27 November 2017)

#1 [mh hemostatics]
#2 [mh "Blood Coagulation Factors"]
#3 [mh ^hemostasis/DE] or [mh ^"blood coagulation"/DE] or [mh ^fibrinolysis/DE] or [mh "platelet activation"/DE] or [mh antithrombins] or [mh ^thrombin/AI]
#4 ((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag*) near/5 (drug* or agent* or treat* or therap*)):ti,ab
#5 (antifibrinolytic* or coagulat* next factor* or clotting next factor* or aminocaproic next acid or 6-aminocaproic next acid or "tranexamic acid" or aprotinin or factor next VII* or "factor 7" or "factor 7a" or NovoSeven or thrombin next inhib* or argatroban):ti,ab
#6 [mh ^"platelet transfusion"] or [mh ^"blood component transfusion"]
#7 [mh ^"blood platelets"]
#8 (infus* or transfus*):ti,ab
#9 #7 and #8
#10 ((platelet* or thrombocyte* or blood component*) near/5 (transfus* or infus*)):ti,ab
#11 #1 or #2 or #3 or #4 or #5 or #6 or #9 or #10
#12 [mh "basal ganglia haemorrhage"] or [mh ^"intracranial hemorrhages"] or [mh ^"cerebral haemorrhage"] or [mh ^"intracranial hemorrhage, hypertensive"]

#13 ((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal next gangli* or putaminal or putamen or posterior next fossa or hemispher* or stroke or apoplex*) near/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)):ti,ab
#14 (ICH or ICHs):ti,ab
#15 #12 or #13 or #14
#16 #11 and #15

Appendix 2. MEDLINE Ovid (1946 to 27 November 2017)

1. exp hemostatics/
2. exp Blood Coagulation Factors/
3. hemostasis/de or blood coagulation/de or fibrinolysis/de or exp platelet activation/de or exp antithrombins/ or thrombin/ai
4. ((haemosta$ or hemosta$ or antihaemorrhag$ or antihemorrhag$) adj5 (drug$ or agent$ or treat$ or therap$)).tw.
5. (antifibrinolytic$ or coagulat$ factor$ or clotting factor$ or aminocaproic acid or 6- aminocaproic acid or tranexamic acid or aprotinin or factor VII$ or factor 7 or factor 7a or NovoSeven or thrombin inhib$ or argatroban).tw,nm.
6. platelet transfusion/
7. blood component transfusion/
8. blood platelets/ and (infus$ or transfus$).tw.
9. ((platelet$ or thrombocyte$ or blood component$) adj5 (transfus$ or infus$)).tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp basal ganglia hemorrhage/ or intracranial hemorrhages/ or cerebral hemorrhage/ or intracranial hemorrhage, hypertensive/
12. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or stroke or apoplex$) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.
13. 11 or 12 or (ICH or ICHs).tw.
14. 10 and 13
15. Randomized Controlled Trials as Topic/
16. random allocation/
17. Controlled Clinical Trials as Topic/
18. control groups/
19. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
20. double-blind method/
21. single-blind method/
22. Placebos/
23. placebo effect/
24. Drug Evaluation/
25. Research Design/
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. clinical trial.pt.
29. random$.tw.
30. (controlled adj5 (trial$ or stud$)).tw.
31. (clinical$ adj5 trial$).tw.
32. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
33. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
34. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
35. placebo$.tw.
36. controls.tw.
37. or/15-36
38. 14 and 37
39. exp animals/ not humans.sh.

40. 38 not 39

Appendix 3. Embase Ovid (1974 to 27 November 2017)

1. exp hemostatic agent/ or exp antifibrinolytic agent/ or exp blood clotting factor/ or exp thrombin inhibitor/
2. hemostasis/
3. exp blood clotting/
4. thrombocyte activation/
5. 2 or 3 or 4
6. drug effect/ or dt.fs.
7. 5 and 6
8. ((haemosta$ or hemosta$ or antihaemorrhag$ or antihemorrhag$) adj5 (drug$ or agent$ or treat$ or therap$)).tw.
9. (antifibrinolytic$ or coagulat$ factor$ or clotting factor$ or aminocaproic acid or 6- aminocaproic acid or tranexamic acid or aprotinin or factor VII$ or factor 7 or factor 7a or NovoSeven or thrombin inhib$ or argatroban).tw.
10. thrombocyte transfusion/
11. blood component therapy/
12. exp thrombocyte/ and (infus$ or transfus$).tw.
13. ((platelet$ or thrombocyte$ or blood component$) adj5 (transfus$ or infus$)).tw.
14. 1 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. basal ganglion hemorrhage/ or brain hemorrhage/ or brain ventricle hemorrhage/ or cerebellum hemorrhage/
16. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or stroke or apoplex$) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.
17. 15 or 16 or (ICH or ICHs).tw.
18. 14 and 17
19. randomized controlled trial/
20. "randomized controlled trial (topic)"/
21. Randomization/
22. Controlled Study/
23. control group/
24. exp clinical trial/
25. Double Blind Procedure/
26. Single Blind Procedure/ or triple blind procedure/
27. placebo/
28. drug dose comparison/
29. drug comparison/
30. "types of study"/
31. random$.tw.
32. (controlled adj5 (trial$ or stud$)).tw.
33. (clinical$ adj5 trial$).tw.
34. ((control or treatment or experiment$ or interventionl) adj5 (group$ or subject$ or patient$)).tw.
35. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
36. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
37. placebo$.tw.
38. controls.tw.
39. or/19-38
40. 18 and 39
41. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
42. 40 not 41

Appendix 4. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov

Study Type: Intervention
Study results: All studies
Recruitment: All studies
Age group: Adults & seniors
Condition: (cerebral haemorrhage OR intracerebral haemorrhage OR intracranial haemorrhage OR intraparenchymal haemorrhage OR parenchymal haemorrhage OR intraventricular haemorrhage OR haemorrhagic stroke OR ICH OR intracerebral bleed)
Intervention (performed as four separate searches, and then de-duplicated, due to the word limit for search criteria): haemostatics OR haemostasis OR haemostatic agents OR haemostatic therapy OR haemostatic treatment OR antihaemorrhagic agent OR antihaemorrhagic therapy OR antihaemorrhagic treatment OR antihaemorrhage agent OR antihaemorrhage therapy OR blood clotting OR blood coagulation factors OR blood coagulation OR coagulation factors OR thrombin OR platelet activation OR thrombocyte activation OR platelet transfusion OR blood component transfusion OR thrombocyte transfusion OR antifibrinolytic agents OR antifibrinolysis OR tranexamic acid OR aminocaproic acid OR 6-aminocaproic acid OR aprotinin OR factor VIIa OR factor VII OR Factor 7a OR factor 7 or NovoSeven Or argatroban OR thrombin inhibitor OR desmopressin OR fresh frozen plasma OR FFP OR prothrombin complex concentrates OR PCC

Appendix 5. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)

Condition: brain haemorrhage OR cerebral haemorrhage OR intracerebral haemorrhage OR intracranial haemorrhage OR intraparenchymal haemorrhage OR intraventricular haemorrhage OR cerebellar haemorrhage OR parenchymal haemorrhage OR infratentorial haemorrhage OR supratentorial haemorrhage OR basal ganglia haemorrhage OR basal ganglion haemorrhage OR thalamic haemorrhage OR putaminal haemorrhage OR posterior fossa haemorrhage OR hemispheric haemorrhage OR haemorrhagic stroke OR haemorrhagic apoplexy brain haematoma OR cerebral haematoma OR intracerebral haematoma OR intracranial haematoma OR intraparenchymal haematoma OR intraventricular haematoma OR cerebellar haematoma OR parenchymal haematoma OR infratentorial haematoma OR supratentorial haematoma OR basal ganglia haematoma OR basal ganglion haematoma OR thalamic haematoma OR putaminal haematoma OR posterior fossa haematoma OR hemispheric haematoma OR brain bleed OR cerebral bleed OR intracerebral bleed OR intracranial bleed OR intraparenchymal bleed OR parenchymal bleed OR intraventricular bleed OR cerebellar bleed OR infratentorial bleed OR supratentorial bleed OR basal ganglia bleed OR putaminal bleed OR posterior fossa bleed OR hemispheric bleed OR ICH OR ICHs
Intervention: haemostatics OR haemostasis OR haemostatic agents OR haemostatic therapy OR haemostatic treatment OR antihaemorrhagic agent OR antihaemorrhagic therapy OR antihaemorrhagic treatment OR antihaemorrhage agent OR antihaemorrhage therapy OR antihaemorrhage treatment OR blood clotting OR blood coagulation factors OR blood coagulation OR coagulation factors OR thrombin OR platelet activation OR thrombocyte activation OR platelet transfusion OR blood component transfusion OR thrombocyte transfusion OR antifibrinolytic agents OR antifibrinolysis OR tranexamic acid OR aminocaproic acid OR 6-aminocaproic acid OR aprotinin OR factor VIIa OR factor VII OR Factor 7a OR factor 7 or NovoSeven Or argatroban OR thrombin inhibitor OR desmopressin OR fresh frozen plasma OR FFP OR prothrombin complex concentrates OR PCC

WHAT'S NEW

Last assessed as up-to-date: 27 November 2017.

Date	Event	Description
10 December 2017	New search has been performed	• Title modified. • Inclusion criteria clarified to include participants with stroke due to intracerebral haemorrhage accompanied by any sort of antithrombotic drug use.

(*Continued*)

		• Inclusion criteria clarified to allow placebo, open control, or active comparators. • Literature and trial register search strategies updated to November 2017. • Stratification of analyses by antithrombotic use. • We added six new trials and data from a further 334 participants, for a total of 12 trials and 1732 participants.
10 December 2017	New citation required and conclusions have changed	• Our new conclusion is that platelet transfusion seems hazardous in comparison to standard care for adults with antiplatelet-associated acute spontaneous intracerebral haemorrhage. • We remain unable to draw firm conclusions about the efficacy and safety of blood clotting factors and antifibrinolytic drugs for acute spontaneous intracerebral haemorrhage.

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 3, 2006

Date	Event	Description
24 June 2013	Amended	Co-authors added
29 June 2009	New citation required and conclusions have changed	In comparison to the previous version of this review, haemostatic drugs no longer significantly reduced death or dependence after acute spontaneous intracerebral haemorrhage
29 June 2009	New search has been performed	Updated with the addition of 841 people randomised in the FAST trial
8 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

RA-SS registered the title, developed the original protocol, and wrote the first two versions of the review. All authors revised the protocol. RA-SS and ZKL screened the title and abstracts of potentially eligible studies. RA-SS and NS reviewed potentially eligible studies in full, appraised their risk of bias, extracted data from them, and obtained further data from study authors. RA-SS and NS updated the review. PB and TS edited and provided comments on the review. RA-SS is responsible for the final version and is the guarantor.

DECLARATIONS OF INTEREST

RA-SS: none known.

ZKL: none known.

PB: none known.

TS declared intellectual competing interests due to his involvement with some included RCTs (Mayer 2005a; Mayer 2005b; Mayer 2006; Mayer 2008 (FAST); Steiner 2016 (INCH)). TS had no role in study selection, assessment and data extraction with regard to these studies.

NS: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Title modified.
- Inclusion criteria clarified to include participants with stroke due to intracerebral haemorrhage accompanied by any sort of antithrombotic drug use.
- Inclusion criteria clarified to allow placebo, open control, or active comparators.
- Literature and trial register search strategies updated (see Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5). Some of the names of the databases have been changed, some databases have been superceded, and we abandoned searches of other databases: CenterWatch Clinical Trials Listing Service (www.centerwatch.com); Computer Retrieval of Information on Scientific Projects (crisp.cit.nih.gov); NIH Clinical Research Studies Database (clinicalstudies.info.nih.gov); Stroke Trials Directory (www.strokecenter.org/trials); and Trials Central (www.trialscentral.org/ClinicalTrials.asp) were not searched; pharmaceutical companies were not contacted.
- Introduction of new secondary outcomes: death from any cause (categorised into early (< 7 days) and late (between 7 days and the end of follow-up) if possible), quality of life, mood, cognitive function.
- Stratification of analyses by antithrombotic use and intended surgery.
- New and ongoing trials added.

INDEX TERMS

Medical Subject Headings (MeSH)

Aminocaproic Acid [*therapeutic use]; Antifibrinolytic Agents [adverse effects; *therapeutic use]; Cerebral Hemorrhage [*drug therapy; mortality]; Factor VIIa [adverse effects; *therapeutic use]; Hemostasis; Hemostatics [*therapeutic use]; Randomized Controlled Trials as Topic; Recombinant Proteins [adverse effects; therapeutic use]

MeSH check words

Adult; Humans