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Haemostatic therapies for stroke due to acute, spontaneous intracerebral haemorrhage (Review)

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[Intervention Review]

Haemostatic therapies for stroke due to acute, spontaneous intracerebral haemorrhage

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ABSTRACT

Background

Outcome after acute spontaneous (non-traumatic) intracerebral haemorrhage (ICH) is influenced by haematoma volume. ICH expansion occurs in about 20% of people with acute ICH. Early haemostatic therapy might improve outcome by limiting ICH expansion. This is an update of a Cochrane Review first published in 2006, and last updated in 2018.

Objectives

To examine 1. the effects of individual classes of haemostatic therapies, compared with placebo or open control, in adults with acute spontaneous ICH, and 2. the effects of each class of haemostatic therapy according to the use and type of antithrombotic drug before ICH onset.

Search methods

We searched the Cochrane Stroke Trials Register, CENTRAL (2022, Issue 8), MEDLINE Ovid, and Embase Ovid on 12 September 2022. To identify further published, ongoing, and unpublished randomised controlled trials (RCTs), we scanned bibliographies of relevant articles and searched international registers of RCTs in September 2022.

Selection criteria

We included RCTs of any haemostatic intervention (i.e. procoagulant treatments such as clotting factor concentrates, antifibrinolytic drugs, platelet transfusion, or agents to reverse the action of antithrombotic drugs) for acute spontaneous ICH, compared with placebo, open control, or an active comparator.

Data collection and analysis

We used standard Cochrane methods. Our primary outcome was death/dependence (modified Rankin Scale (mRS) 4 to 6) by day 90. Secondary outcomes were ICH expansion on brain imaging after 24 hours, all serious adverse events, thromboembolic adverse events,

death from any cause, quality of life, mood, cognitive function, Barthel Index score, and death or dependence measured on the Extended Glasgow Outcome Scale by day 90.

Main results

We included 20 RCTs involving 4652 participants: nine RCTs of recombinant activated factor VII (rFVIIa) versus placebo/open control (1549 participants), eight RCTs of antifibrinolytic drugs versus placebo/open control (2866 participants), one RCT of platelet transfusion versus open control (190 participants), and two RCTs of prothrombin complex concentrates (PCC) versus fresh frozen plasma (FFP) (47 participants). Four (20%) RCTs were at low risk of bias in all criteria.

For rFVIIa versus placebo/open control for spontaneous ICH with or without surgery there was little to no difference in death/dependence by day 90 (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.74 to 1.05; 7 RCTs, 1454 participants; low-certainty evidence). We found little to no difference in ICH expansion between groups (RR 0.81, 95% CI 0.56 to 1.16; 4 RCTs, 220 participants; low-certainty evidence). There was little to no difference in all serious adverse events and death from any cause between groups (all serious adverse events: RR 0.81, 95% CI 0.30 to 2.22; 2 RCTs, 87 participants; very low-certainty evidence; death from any cause: RR 0.78, 95% CI 0.56 to 1.08; 8 RCTs, 1544 participants; moderate-certainty evidence).

For antifibrinolytic drugs versus placebo/open control for spontaneous ICH, there was no difference in death/dependence by day 90 (RR 1.00, 95% CI 0.93 to 1.07; 5 RCTs, 2683 participants; high-certainty evidence). We found a slight reduction in ICH expansion with antifibrinolytic drugs for spontaneous ICH compared to placebo/open control (RR 0.86, 95% CI 0.76 to 0.96; 8 RCTs, 2866 participants; high-certainty evidence). There was little to no difference in all serious adverse events and death from any cause between groups (all serious adverse events: RR 1.02, 95% CI 0.75 to 1.39; 4 RCTs, 2599 participants; high-certainty evidence; death from any cause: RR 1.02, 95% CI 0.89 to 1.18; 8 RCTs, 2866 participants; high-certainty evidence). There was little to no difference in quality of life, mood, or cognitive function (quality of life: mean difference (MD) 0, 95% CI -0.03 to 0.03; 2 RCTs, 2349 participants; mood: MD 0.30, 95% CI -1.98 to 2.57; 2 RCTs, 2349 participants; cognitive function: MD -0.37, 95% CI -1.40 to 0.66; 1 RCTs, 2325 participants; all high-certainty evidence).

Platelet transfusion likely increases death/dependence by day 90 compared to open control for antiplatelet-associated ICH (RR 1.29, 95% CI 1.04 to 1.61; 1 RCT, 190 participants; moderate-certainty evidence). We found little to no difference in ICH expansion between groups (RR 1.32, 95% CI 0.91 to 1.92; 1 RCT, 153 participants; moderate-certainty evidence). There was little to no difference in all serious adverse events and death from any cause between groups (all serious adverse events: RR 1.46, 95% CI 0.98 to 2.16; 1 RCT, 190 participants; death from any cause: RR 1.42, 95% CI 0.88 to 2.28; 1 RCT, 190 participants; both moderate-certainty evidence).

For PCC versus FFP for anticoagulant-associated ICH, the evidence was very uncertain about the effect on death/dependence by day 90, ICH expansion, all serious adverse events, and death from any cause between groups (death/dependence by day 90: RR 1.21, 95% CI 0.76 to 1.90; 1 RCT, 37 participants; ICH expansion: RR 0.54, 95% CI 0.23 to 1.22; 1 RCT, 36 participants; all serious adverse events: RR 0.27, 95% CI 0.02 to 3.74; 1 RCT, 5 participants; death from any cause: RR 0.49, 95% CI 0.16 to 1.56; 2 RCTs, 42 participants; all very low-certainty evidence).

Authors' conclusions

In this updated Cochrane Review including 20 RCTs involving 4652 participants, rFVIIa likely results in little to no difference in reducing death or dependence after spontaneous ICH with or without surgery; antifibrinolytic drugs result in little to no difference in reducing death or dependence after spontaneous ICH, but result in a slight reduction in ICH expansion within 24 hours; platelet transfusion likely increases death or dependence after antiplatelet-associated ICH; and the evidence is very uncertain about the effect of PCC compared to FFP on death or dependence after anticoagulant-associated ICH. Thirteen RCTs are ongoing and are likely to increase the certainty of the estimates of treatment effect.

PLAIN LANGUAGE SUMMARY

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

Key messages

Treatments that help blood to clot (known as 'haemostatic therapies') might help people who have a stroke due to bleeding in the brain (known as 'intracerebral haemorrhage').

– Platelet transfusion probably harms people who had intracerebral haemorrhage whilst taking a drug like aspirin.

– All other therapies showed neither harm nor benefit.

– 13 ongoing studies are investigating haemostatic therapies after intracerebral haemorrhage and their results might change our conclusions.

What is an intracerebral haemorrhage?

More than one-tenth of all strokes are caused by intracerebral haemorrhage. The bigger the haemorrhage, the more likely it is to be fatal. Roughly one-fifth of intracerebral haemorrhages enlarge significantly, most during the first three hours after the bleed started.

How could haemostatic therapies improve outcome after intracerebral haemorrhage?

Haemostatic therapies might slow down bleeding and reduce brain damage, leading to better recovery, especially if given soon after the bleeding starts.

However, haemostatic therapies might cause unwanted side effects due to clotting, such as heart attacks, strokes, and clots in lungs.

What did we want to find out?

We wanted to find out if haemostatic therapies such as platelet transfusions, antifibrinolytic medicines (mostly tranexamic acid), clotting factor 7, or prothrombin complex concentrate improve the recovery of people with stroke due to intracerebral haemorrhage.

We also wanted to find out if haemostatic therapies caused any unwanted effects.

What did we do?

We searched for clinical trials involving people with intracerebral haemorrhage that compared haemostatic therapies with standard care, placebo (pretend treatment), or an alternative blood clotting treatment.

We separated the treatments into four groups: clotting factor 7 versus placebo, antifibrinolytic medicines versus placebo, platelet transfusion versus standard care for people already taking an antiplatelet medicine (medications that prevent blood clots from forming such as aspirin), and fresh frozen plasma (a blood product made from the liquid portion of whole blood used to treat people with low blood clotting factors) versus prothrombin complex concentrate (which causes blood clotting) for people already taking warfarin (a medicine commonly used to treat and prevent blood clots).

We compared and summarised the results of the studies and rated our certainty about the evidence, based on factors such as study numbers, methods, and sizes.

What did we find?

We found 20 clinical trials including 4652 people with intracerebral haemorrhage.

Clotting factor 7 likely results in little to no difference in improving recovery, reducing further bleeding, death, or unwanted effects.

Antifibrinolytic medicines result in little to no difference in improving recovery; a slight reduction in further bleeding within 24 hours; and little to no difference in death, unwanted effects, mood, memory, and quality of life.

Platelet transfusion likely worsens recovery for people already taking an antiplatelet medicine, but has little to no effect on further bleeding, death, or unwanted effects.

The evidence is very uncertain about the effect of different clotting factors for people already taking warfarin, and there is little to no difference between them on recovery, further bleeding, death, and unwanted effects.

What are the limitations of the evidence?

Although we found 20 studies including 4652 people, they were spread across four different comparisons of haemostatic therapies. This meant that many of the studies were not precise enough and they could have missed small but important benefits. Two of the comparisons included only one study each. Eight studies used placebo but in the others it is possible that people were aware of which treatment they were getting, which might have biased the results. Some of the studies did not provide data about all the outcomes that we intended to assess. More information will become available from 13 studies that were ongoing at the time of this review.

How up to date is this evidence?

This review updates our previous review in 2018. The evidence is up to date to September 2022.

Summary of findings 1. Summary of findings table - Recombinant activated factor VII compared to placebo/open control for adults with acute spontaneous intracerebral haemorrhage

Recombinant activated factor VII compared to placebo/open control for adults with acute spontaneous intracerebral haemorrhage

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/open control	Risk with recombinant activated factor VII				
Death or dependence (mRS 4–6) assessed with: clinical assessment of the modified Rankin Scale (mRS) score follow-up: 90 days	528 per 1000	**464 per 1000** (391 to 554)	**RR 0.88** (0.74 to 1.05)	1454 (7 RCTs)	⊕⊕⊖⊖ Low[a,b]	Recombinant activated factor VII likely results in little to no difference in death or dependence (mRS 4–6) at day 90.
Intracerebral haemorrhage expansion by 24 hours assessed with: radiological assessment follow-up: 1 day	398 per 1000	**322 per 1000** (223 to 461)	**RR 0.81** (0.56 to 1.16)	220 (4 RCTs)	⊕⊕⊖⊖ Low[a,c]	Recombinant activated factor VII may result in little to no difference in intracerebral haemorrhage growth by 24 hours.
All serious adverse events assessed with: clinical assessment follow-up: range 1 day to 90 days	211 per 1000	**171 per 1000** (63 to 467)	**RR 0.81** (0.30 to 2.22)	87 (2 RCTs)	⊕⊖⊖⊖ Very low[a,d]	Recombinant activated factor VII may result in little to no difference in all serious adverse events.
Death from any cause assessed with: clinical assessment follow-up: 90 days	214 per 1000	**167 per 1000** (120 to 231)	**RR 0.78** (0.56 to 1.08)	1544 (8 RCTs)	⊕⊕⊕⊖ Moderate[a]	Recombinant activated factor VII likely results in little to no difference in death from any cause by day 90.

Quality of life - not reported	-	-	-	-	-	None of the RCTs reported on quality of life.
Mood - not reported	-	-	-	-	-	None of the RCTs reported on mood.
Cognitive function - not reported	-	-	-	-	-	None of the RCTs reported on cognitive function.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_436893648430170226.

[a] Downgraded one level due to several ratings with unclear or high risk of bias in random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, or selective reporting.
[b] Downgraded one level due to moderate heterogeneity.
[c] Downgraded one level due to small total population size.
[d] Downgraded two levels due to very small population size

Summary of findings 2. Summary of findings table - Antifibrinolytic drug(s) compared to placebo/open control for adults with acute spontaneous intracerebral haemorrhage

Antifibrinolytic drug(s) compared to placebo/open control for adults with acute spontaneous intracerebral haemorrhage

Patient or population: adults with acute spontaneous intracerebral haemorrhage
Setting: secondary care
Intervention: antifibrinolytic drug(s)
Comparison: placebo/open control

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with placebo/open control	Risk with antifibrinolytic drug(s)				
Death or dependence (mRS 4–6) assessed with: clinical assessment of the modified Rankin Scale (mRS) score follow-up: 90 days	533 per 1000	**533 per 1000** (495 to 570)	**RR 1.00** (0.93 to 1.07)	2683 (5 RCTs)	⊕⊕⊕⊕ High	Antifibrinolytic results in little to no difference in death or dependence.
Intracerebral haemorrhage expansion by 24 hours assessed with: radiological assessment follow-up: 1 day	284 per 1000	**245 per 1000** (216 to 273)	**RR 0.86** (0.76 to 0.96)	2866 (8 RCTs)	⊕⊕⊕⊕ High	Antifibrinolytic results in a slight reduction in intracerebral haemorrhage growth by 24 hours.[a]
All serious adverse events assessed with: clinical assessment follow-up: range 1 day to 90 days	314 per 1000	**320 per 1000** (236 to 437)	**RR 1.02** (0.75 to 1.39)	2599 (4 RCTs)	⊕⊕⊕⊕ High	Antifibrinolytic results in little to no difference in all serious adverse events.
Death from any cause assessed with: clinical assessment follow-up: 90 days	197 per 1000	**201 per 1000** (175 to 232)	**RR 1.02** (0.89 to 1.18)	2866 (8 RCTs)	⊕⊕⊕⊕ High	Antifibrinolytic results in little to no difference in death.[a]
Quality of life (EuroQoL health utility score) assessed with: questionnaire Scale from: 0 to 1	The mean quality of life ranged from **0.34 to 0.54**	MD **0** (0.03 lower to 0.03 higher)	-	2349 (2 RCTs)	⊕⊕⊕⊕ High	Antifibrinolytics results in no difference in EuroQoL health utility scores.
Mood assessed with: Zung Depression Scale (ZDS) Scale from: 0 to 100	The mean mood ranged from **18.6 to 67.29**	MD **0.3 higher** (1.98 lower to 2.57 higher)	-	2349 (2 RCTs)	⊕⊕⊕⊕ High	Antifibrinolytic results in little to no difference in mood.
Cognitive function assessed with: Modified Telephone Interview for Cognitive Status (TICS-M) Scale from: 0 to 50 follow-up: 90 days	The mean cognitive function was **13.94**	MD **0.37 lower** (1.4 lower to 0.66 higher)	-	2325 (1 RCT)	⊕⊕⊕⊕ High	Antifibrinolytic results in little to no difference in cognitive function.[b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_436916189554228065.

[a] One study investigated aminocaproic acid versus placebo, whereas the remaining seven studies investigated tranexamic acid versus placebo/open control.
[b] We have chosen TICS-M as the assessment scale for cognitive function, since this was the assessment used in the included study with the largest sample size.

Summary of findings 3. Summary of findings table - Platelet transfusion compared to open control for adults with acute spontaneous intracerebral haemorrhage associated with antiplatelet drug use

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

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with open control	Risk with platelet transfusion				
Death or dependence (mRS 4–6) assessed with: clinical assessment of the modified Rankin Scale (mRS) score follow-up: 90 days	559 per 1000	**721 per 1000** (582 to 900)	**RR 1.29** (1.04 to 1.61)	190 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Platelet transfusion likely increases death or dependence (mRS 4–6) at day 90 slightly.
Intracerebral haemorrhage expansion by 24 hours assessed with: radiological assessment follow-up: 1 day	370 per 1000	**488 per 1000** (337 to 710)	**RR 1.32** (0.91 to 1.92)	153 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Platelet transfusion likely results in little to no difference in intracerebral haemorrhage growth by 24 hours.
All serious adverse events assessed with: clinical assessment	290 per 1000	**424 per 1000** (285 to 627)	**RR 1.46** (0.98 to 2.16)	190 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Platelet transfusion likely results in little to no difference in all serious adverse events.

follow-up: range 1 day to 90 days						
Death from any cause assessed with: clinical assessment follow-up: 90 days	226 per 1000	**321 per 1000** (199 to 515)	**RR 1.42** (0.88 to 2.28)	190 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Platelet transfusion likely results in little to no difference in death by day 90.
Quality of life - not reported	-	-	-	-	-	Quality of life was not an outcome of the 1 RCT in this comparison.
Mood - not reported	-	-	-	-	-	Mood was not an outcome of the 1 RCT in this comparison.
Cognitive function - not reported	-	-	-	-	-	Cognitive function was not an outcome of the 1 RCT in this comparison.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_436915418232989547.

[a] Downgraded one level due to only one study and small total population size.

Summary of findings 4. Summary of findings table - Prothrombin complex concentrates compared to fresh frozen plasma for adults with acute spontaneous intracerebral haemorrhage associated with anticoagulant drug use

Prothrombin complex concentrates compared to fresh frozen plasma for adults with acute spontaneous intracerebral haemorrhage associated with anticoagulant drug use

Patient or population: adults with acute spontaneous intracerebral haemorrhage associated with anticoagulant drug use
Setting: secondary care
Intervention: prothrombin complex concentrates
Comparison: fresh frozen plasma

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with fresh frozen plasma	Risk with prothrombin complex concentrates				
Death or dependence (mRS 4–6) assessed with: clinical assessment of the modified Rankin Scale (mRS) score follow-up: 90 days	611 per 1000	**739 per 1000** (464 to 1000)	**RR 1.21** (0.76 to 1.90)	37 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	The evidence is very uncertain about the effect of prothrombin complex concentrates compared to fresh frozen plasma on death or dependence (mRS 4–6) at 90 days.
Intracerebral haemorrhage expansion by 24 hours assessed with: radiological assessment follow-up: 1 day	533 per 1000	**288 per 1000** (123 to 651)	**RR 0.54** (0.23 to 1.22)	36 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	The evidence is very uncertain about the effect of prothrombin complex concentrates compared to fresh frozen plasma on intracerebral haemorrhage growth by 24 hours.[c]
All serious adverse events assessed with: clinical assessment follow-up: range 1 day to 90 days	667 per 1000	**180 per 1000** (13 to 1000)	**RR 0.27** (0.02 to 3.74)	5 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	The evidence is very uncertain about the effect of prothrombin complex concentrates compared to fresh frozen plasma on all serious adverse events.[d]
Death from any cause assessed with: clinical assessment follow-up: 90 days	333 per 1000	**163 per 1000** (53 to 520)	**RR 0.49** (0.16 to 1.56)	42 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b]	The evidence is very uncertain about the effect of prothrombin complex concentrates compared to fresh frozen plasma on death by any cause by day 90.[d]
Quality of life - not reported	-	-	-	-	-	None of the RCTs reported on quality of life.
Mood - not reported	-	-	-	-	-	None of the RCTs reported on mood.
Cognitive function - not reported	-	-	-	-	-	None of the RCTs reported on cognitive function.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __RR:__ risk ratio

__GRADE Working Group grades of evidence__

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a] Downgraded one level due to several ratings with unclear or high risk of bias in random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, or selective reporting.
[b] Downgraded two levels due to very small total population size.
[c] Intracerebral haemorrhage growth defined in this comparison as greater than 6 mL change from baseline.
[d] One trial treated the intervention group with the combination of prothrombin complex concentrates, vitamin K, and fresh frozen plasma (Boulis 1999).

BACKGROUND

This is an update of a previously published review on 'Haemostatic therapies for acute spontaneous intracerebral haemorrhage'. This is the third update. The review was first published in 2006 (You 2006), and updated in 2009 (Al-Shahi Salman 2009a; Al-Shahi Salman 2009b), and 2018 (Al-Shahi Salman 2018).

Description of the condition

Intracerebral haemorrhage (ICH) accounts for 10% to 15% of strokes in European and American countries and 20% to 30% of strokes in Asian countries. ICH globally constituted 3.41 million (95% confidence interval (CI) 2.97 million to 3.91 million), or 28%, of all incident strokes in 2019 (Asch 2010; Global Burden of Disease 2019). ICH caused 44% of all stroke deaths, and approximately 48% (69 millions) of the disability-adjusted life years lost due to stroke in the 2019 Global Burden of Disease study (Global Burden of Disease 2019). The age-specific incidence of ICH rises with age (Feigin 2015), such that two-thirds of people with incident ICH are 75 years or older (Lovelock 2007; Samarasekera 2015). The overall incidence of ICH is increasing due to the ageing population, with ICH-related death and disability set to rise (Feigin 2013; Kleindorfer 2010). Recent improvements in stroke pathways have led to rapid imaging, with early diagnosis providing an opportunity to rapidly administer treatments to improve outcome.

Outcome after stroke due to ICH is poor: one-year survival is 46% (95% 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 (GCS) score, increasing ICH volume, presence of intraventricular haemorrhage, and deep or infratentorial ICH location (Poon 2014). ICH expansion occurs in approximately 20% of people with ICH and the highest risk of expansion occurs within the first three hours (ICH Growth IPDMA Collaborators 2018). ICH expansion is independently associated with death and poor outcome (Davis 2006).

Acute, spontaneous ICH may occur while people are taking antithrombotic (i.e. anticoagulant or antiplatelet) agents for prevention of major adverse cardiovascular events for comorbidities such as atrial fibrillation (AF) or ischaemic heart disease. Vitamin K antagonists were used for oral anticoagulation for AF and venous thromboembolism treatment/prevention until direct oral anticoagulants (DOAC) were shown to be non-inferior, equivalent, or ultimately superior, although vitamin K antagonists continue to be superior for prevention of systemic embolism for people with mechanical heart valves. Consequently, DOAC use has increased and vitamin K antagonist use has declined over time in general, and in association with ICH.

Description of the intervention

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

Vascular smooth muscle cell vasoconstriction constricts damaged vessels in response to injury, which reduces the amount of blood flow through the area and limits blood loss. Collagen is exposed at the site of injury and von Willebrand Factor is released. Primary haemostasis is the formation of a platelet plug. This is initiated when von Willebrand Factor tethers platelets through their GPIb receptors to endothelial collagen. Platelets are then activated leading to secretion of thromboxane A2 and platelet granules, which in turn activate other platelets. Platelet granules contain vasoactive serotonin, which contributes towards vasoconstriction. Activated platelets aggregate through platelet GPIIb/IIIa receptors. Secondary haemostasis is the formation of a fibrin clot. This is triggered by exposure of endothelial tissue factors, which then initiates a cascade of clotting factor activation. The final step in this pathway is the activation of fibrinogen to form fibrin. Clots are then broken down in a process known as fibrinolysis. In fibrinolysis, plasmin lyses fibrin to fibrin degradation products. Plasmin is activated from plasminogen by tissue plasminogen activator.

In acute, spontaneous ICH, clotting factor concentrates and antifibrinolytics are the most common agents that have been investigated. Clotting factor concentrates can consist of either one specific clotting factor such as recombinant activated factor VII (rFVIIa) or combinations of clotting factors such as three-factor or four-factor prothrombin complex concentrates (PCC). rFVIIa directly stimulates the extrinsic pathways of the clotting cascade, leading to the formation of fibrin from fibrinogen. Three- or four-factor PCC are often used for reversing the effects of vitamin K antagonists, such as warfarin, where they lead to direct replacement of factors II, VII, IX, and X. Three- or four-factor PCC are sometimes used in the absence of a measured factor deficiency when they are used to increase available clotting factors. Therapies that inhibit fibrinolysis include tranexamic acid, epsilon aminocaproic acid (EACA), and aprotinin. Tranexamic acid and EACA are synthetic lysine analogues that inhibit the activation of plasminogen to plasmin. Aprotinin is a serine protease inhibitor that attaches to active sites of plasmin thereby reducing the activity of plasmin.

In ICH associated with antiplatelet drugs, patients have inhibition of platelet activation and hence reduced primary haemostasis. Possible treatment targets for primary haemostasis are platelet transfusion or administration of desmopressin. Desmopressin is a synthetic analogue of vasopressin. It stimulates the release of von Willebrand factor and factor VIII from endothelial Weibel-Palade bodies. Increased von Willebrand factor levels may increase platelet adhesion, reducing the effects of antiplatelet drugs. Desmopressin may also have other effects on platelets, such as increasing the formation of active coated platelets (Colucci 2014).

For anticoagulant-associated ICH, specific antidotes for oral anticoagulants are possible therapeutic targets for improved haemostasis. Patients treated with vitamin K antagonists have induced deficiencies in factors II, VII, IX, and X. Vitamin K can normalise these levels in six to eight hours. When more urgent reversal of the effects of vitamin K antagonists are required (such as in ICH), factor concentrates containing factors II, VII, IX, and X are used as these normalise the levels of these clotting factors within minutes. For DOACs (factor Xa or IIa inhibitors), there are reversal agents that may reverse their effects within minutes. Idarucizumab, a monoclonal antibody fragment can be used to reverse the effects of factor IIa inhibitors. Andexanet alfa, a modified factor Xa that binds to factor Xa inhibitors, can be used to reduce the effects of factor Xa inhibitors.

How the intervention might work

Theoretically, early interventions to reduce acute ICH volume might improve outcome. 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 (especially with minimally invasive approaches). However, there was considerable qualitative and quantitative heterogeneity between the included trials and surgical evacuation is not frequently used in clinical practice (Sondag 2020).

Various haemostatic therapies have been investigated in a variety of spontaneous bleeding conditions with little evidence of their effects in some settings (Johansen 2015; Stanworth 2012; Wikkelsø 2013), but clear benefit in others (Ker 2015).

Therefore, medical (non-surgical) interventions to promote haemostasis, limit ICH expansion, and thereby improve outcome have become a focus of acute ICH therapeutic research.

Why it is important to do this review

ICH was identified as a priority research area with interventions to stop bleeding as a treatment target by the Stroke Association's Priority Setting Partnership using the James Lind Alliance process (JLA SPSP 2022). Therefore, we systematically reviewed the literature for randomised controlled trials (RCTs) of all haemostatic therapies to improve outcome after acute, spontaneous ICH.

OBJECTIVES

To examine 1. the effects of individual classes of haemostatic therapies, compared with placebo or open control, in adults with acute spontaneous ICH, and 2. the effects of each class of haemostatic therapy according to the use and type of antithrombotic drug before ICH onset.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs, whether published or unpublished, regardless of the language of publication. We excluded quasi-randomised studies (i.e. one in which participants were allocated to different interventions using a method of allocation that was not truly random).

Types of participants

We included people of any sex, aged 16 years or older. We restricted this review to people with radiographically confirmed acute spontaneous ICH (which involved attempting to obtain data restricted to a subgroup with ICH if an RCT included any type of intracranial haemorrhage). Where possible, we grouped RCTs, or participant subgroups, by whether ICH was associated with antiplatelet agent or anticoagulant use, or neither.

Types of interventions

Single or multiple haemostatic therapies (including antifibrinolytic drugs, clotting factor concentrates (i.e. rFVIIa, prothrombin complex concentrate (PPC), fresh frozen plasma (FFP)), reversal agents 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 clinical and radiographic outcomes at 90 days after randomisation (or at the end of scheduled follow-up, if not provided at 90 days).

Primary outcomes

- Death or dependence (measured on a standard rating scale, such as the modified Rankin Scale (mRS)) by day 90.

Secondary outcomes

- Change in volume of ICH on follow-up brain imaging (to assess ICH expansion) within 24 hours of randomisation.
- All serious adverse events from day 1 to day 90.
- Thromboembolic adverse events (arterial and venous thromboembolic events, including deep vein thrombosis, symptomatic pulmonary embolism, arterial embolism, myocardial infarction, ischaemic stroke, and disseminated intravascular coagulation) from day 1 to day 90.
- 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) by day 90.
- Quality of life (measured on a standard rating scale, such as the EuroQol health utility score) at day 90.
- Mood (measured on a standard rating scale, such as the Zung Depression Score) at day 90.
- Cognitive function (measured on a standard rating scale, such as the Modified Telephone Interview for Cognitive Status (TICS-M), Mini-Mental State Examination (MMSE), or Montreal Cognitive Assessment (MoCA)) at day 90.
- Barthel Index score at day 90.
- Death or dependence measured on the GOS-E (1 to 4) at day 90.

Search methods for identification of studies

We searched for trials in all languages, and arranged for the translation of relevant articles when necessary.

Electronic searches

The Cochrane Stroke Group's Information Specialist searched: the Cochrane Stroke Trials Register (last searched 12 September 2022); the Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 8) in the Cochrane Library (searched 12 September 2022; Appendix 1); MEDLINE Ovid (1946 to 12 September 2022;Appendix 2); and Embase Ovid (1974 to 12 September 2022;Appendix 3).

One review author also searched the following international registers of RCTs on 12 September 2022.

- ClinicalTrials.gov (clinicaltrials.gov; search strategy in Appendix 4).
- World Health Organization (WHO) International Clinical Trials Registry Platform (trialsearch.who.int; search strategy in Appendix 5).

Searching other resources

We revised and updated all search strategies since the last version of this review to account for newly identified relevant controlled vocabulary headings and keywords. The Cochrane Stroke Group's Information Specialist developed the MEDLINE search strategy and

linked it to the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format, as referenced in the Box 3.c in the Technical Supplement to Chapter 4: Searching for and selecting studies in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.3 (updated February 2022) (Lefebvre 2022).

In an effort to identify further published, ongoing, and unpublished RCTs, two review authors (HE and CSM) scanned bibliographies of relevant articles.

Data collection and analysis

Selection of studies

Two review authors (HE and CSM) 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), using Covidence software (Covidence 2022). Two review authors (HE and CSM) 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 review authors (HE and CSM) independently read these potentially eligible RCTs in full, and confirmed their inclusion according to the inclusion criteria. All conflicting decisions between the two review authors were arbitrated and re-reviewed by a third, unconflicted co-author.

Data extraction and management

Two review authors (HE and CSM) 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. One study investigating the effects of the antifibrinolytic drug tranexamic acid versus placebo was written in Chinese, so only one review author (CC) fluent in Chinese critically appraised and extracted the data from this study (Ni 2020).

In the current review, in one of the RCTs examining PCC versus FFP, the principal investigator (TS) provided the individual data for participants with ICH alone, having excluded participants with other types of intracranial haemorrhages (i.e. subdural haemorrhage) (Steiner 2016 – INCH). Two RCTs of rFVIIa versus placebo were published together; we attempted to obtain the datasets of each of these RCTs individually in correspondence with the corresponding author, but these data were not provided before submission of this review, so we used the pooled published data (Gladstone 2019 – SPOTLIGHT – STOP-IT).

In one phase II study, we could obtain only limited data from the Novo Nordisk website (F7ICH-1602 2007).

In the previous update of the review, in the one study for which these data were not forthcoming, one review author (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).

Assessment of risk of bias in included studies

Two review authors (HE and CSM) independently assessed the risk of bias of the included RCTs according to the six criteria of the Cochrane RoB 1 tool (Higgins 2011), with oversight by a third review author (ZKL). The six domains included random sequence generation, blinding of participants and personnel, allocation concealment, blinding of outcome assessment, incomplete outcome data, and reporting of selective outcome. The two review authors (HE and CSM) rated the domains as low risk, high risk, or unclear risk. A third, unconflicted review author arbitrated and re-reviewed any conflicting decisions.

Two review authors (HE and CSM) discussed and agreed on the overall certainty of the evidence for each outcome, using the GRADE approach (Higgins 2011) for seven of eight studies that were written in English. One review author (CC) fluent in Chinese assessed a Chinese study for risk of bias and certainty of evidence.

Measures of treatment effect

We calculated risk ratio (RR) for dichotomous data, and mean difference (MD; where studies used the same scales), or standardised mean difference (SMD; where studies used different scales for different measures of the same outcome), for continuous data, with 95% CIs.

Unit of analysis issues

There were no analysis issues identified in the included studies as the participants were randomised at an individual level. None of the included or ongoing RCTs have cluster, cross-over, or multiple-arm designs.

Dealing with missing data

We sought missing data from the corresponding authors of the studies, and used all the data that were available to us in complete case analyses. If we were unsuccessful in collecting missing data, we considered this when grading the certainty of evidence.

Assessment of heterogeneity

We estimated heterogeneity between RCTs using the I^2 statistic, and interpreted it as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and 75% to 100%: considerable heterogeneity. We considered clinical heterogeneity between RCTs according to differences in participants' baseline characteristics (e.g. age, sex, and comorbidities), intervention characteristics (e.g. dosage and duration of treatment), and outcome measures (e.g. length of follow-up).

Assessment of reporting biases

We used funnel plots to assess publication bias where there were sufficient data (i.e. 10 or more studies). If there were fewer than 10 studies, we still created a funnel plot, but interpreted these plots with caution, given their low power.

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% CIs, pooled using 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. FFP or PCC for anticoagulant-associated ICH, platelet transfusion for antiplatelet-associated ICH). However, where interventions were used for ICH, whether ICH was associated with antithrombotic drug use or not (e.g. rFVIIa, antifibrinolytic drugs), and where ICH evacuation using craniotomy was performed, we intended to perform subgroup analyses by pre-ICH antithrombotic drug use (antiplatelet versus anticoagulant versus none) and use of surgery (yes versus no).

Sensitivity analysis

We performed sensitivity analysis in all outcome categories that included more than one RCT and had at least one domain with a high risk of bias rating. To conduct the analysis, we removed any RCT(s) with a domain rated as high risk of bias and performed the sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

All available data for the primary and secondary outcomes are presented in analysis tables. In the summary of finding tables for all four intervention groups, we prioritised seven outcomes at specific timepoints in descending order of priority.

- Death or dependence (measured on a standard rating scale, such as the mRS) by day 90
- Change in volume of ICH on follow-up brain imaging (to assess ICH expansion) within 24 hours of randomisation
- All serious adverse events from day 1 to day 90
- Death from any cause by day 90
- Quality of life (EuroQol health utility score) at day 90
- Mood (Zung Depression Score) at day 90
- Cognitive function (TICS-M) at day 90

Two review authors (HE and CSM) assessed the certainty in the body of evidence (GRADE Handbook 2013) as: high, moderate, low, or very low using GRADEpro GDT software (GRADEpro GDT). These risks were assessed in five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. A third, unconflicted review author arbitrated and re-reviewed conflicting decisions.

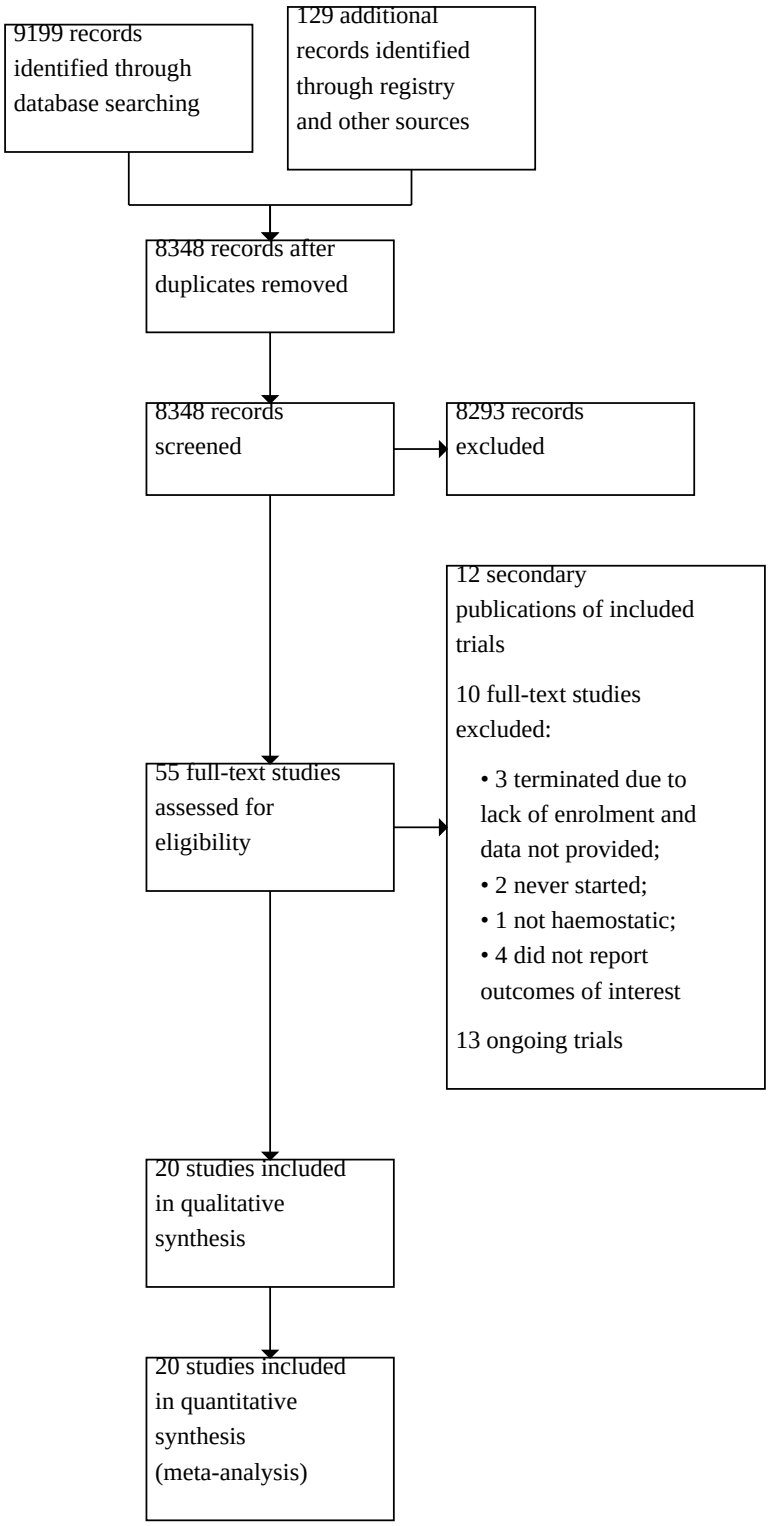
RESULTS

Description of studies

Results of the search

Our updated search found 4981 additional records, of which 580 were duplicates and we excluded 4377 due to irrelevance. We assessed the full text of 24 records, and included eight new RCTs in the systematic review and meta-analysis. We added these to the previous update, totalling 20 eligible RCTs. We have updated the PRISMA chart by adding these numbers to previous searches (Figure 1).

Figure 1. Study flow diagram.



Overall, our searches identified 55 (24 from the current search and 31 from previous searches) potentially eligible RCTs.

We identified 12 studies that were secondary publications of the included RCTs. We excluded 10 studies (Figure 1); two never started recruiting (Ciccone 2007; NCT02429453), two did not report any of our primary or secondary outcomes (Meng 2003; Zhou 2005), one did not report data and outcomes in the ICH population (Kerebel 2013), one did not quantify outcomes (Madjdinasab 2008), three were stopped due to poor enrolment and never reported results (Glad 2012 – NOR-ICH; NCT00222625; NCT03388970), and one did not relate to a haemostatic therapy (Li 2016).

Thirteen RCTs were in the process of recruitment (2018-002620-17 – Annexa-I; IRCT20191014045103N1; Jiang 2020 – THE-ICH; Naidech 2022 – FASTEST; NCT02777424 – CLOT-CRANE; NCT03044184 – TRANSACT; NCT04742205; Pandian 2022 – INTRINSIC; Qi 2021 – TARGET; Sprigg 2022 – TICH-3; Yassi 2022 – STOP-MSU), or reporting (Desborough 2020 – DASH; NCT00699621) at the time of writing, and will be assessed for inclusion with the next update.

We included 20 RCTs in this review, all of which included acute spontaneous ICH in adults aged 18 years or older. One publication reported the results of two included RCTs (Gladstone 2019 – SPOTLIGHT – STOP-IT).

- Nine RCTs compared rFVIIa versus placebo or open control involving 1549 participants (F7ICH-1602 2007; Gladstone 2019 – SPOTLIGHT – STOP-IT (included two RCTs); Imberti 2012 – PRESICH; Li 2012; Mayer 2005a; Mayer 2005b; Mayer 2006; Mayer 2008 – FAST)
- Eight RCTs compared antifibrinolytic drugs versus placebo or open control involving 2866 participants (Arumugam 2015; Liu 2021 – TRAIGE; Meretoja 2020 – STOP-AUST; Ni 2020; Polymeris 2023 – TICH-NOAC; Sprigg 2014 – TICH-1; Sprigg 2018 – TICH-2; Zazulia 2001 – ATICH)
- One RCT compared platelet transfusion versus open control involving 190 participants (Baharoglu 2016 – PATCH)
- Two RCTs compared PCC versus FFP involving 47 participants (Boulis 1999; Steiner 2016 – INCH)

Included studies

For details of the 20 included RCTs, refer to the Characteristics of included studies table. We identified 12 studies that were secondary publications of the included RCTs.

Recombinant activated factor VII versus placebo or open control

All included RCTs investigated rFVIIa.

Of the nine RCTs of rFVIIa versus placebo or open control, eight examined rFVIIa in adults with acute spontaneous ICH (F7ICH-1602 2007; Li 2012; Mayer 2005a; Mayer 2005b; Mayer 2006; Mayer 2008 – FAST; Gladstone 2019 – SPOTLIGHT – STOP-IT (included two RCTs)), and one in adults with acute spontaneous ICH undergoing craniotomy (Imberti 2012 – PRESICH). Novo Nordisk funded and conducted five RCTs, and compared the use of various doses of intravenous 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 RCTs (Mayer 2005a; Mayer 2005b; Mayer 2006), but did not respond to several requests to provide further data from two RCTs (F7ICH-1602 2007; Mayer 2008 – FAST). Li 2012 was performed independently of Novo Nordisk, as a single-centre, phase II RCT, in adults with acute spontaneous ICH within six hours of ICH onset investigating rFVIIa versus placebo. Gladstone 2019 – SPOTLIGHT – STOP-IT was a publication of the pooled results of two RCTs investigating rFVIIa versus placebo; we sought separate results from the separate trials, but did not receive them before the completion of this review, so we included the published pooled results. We had not prespecified the exclusion of RCTs of haemostatic therapies following surgical intervention, so we included Imberti 2012 – PRESICH, which was a phase II RCT 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.

Antifibrinolytic drugs versus placebo or open control

One RCT for this comparison investigated aminocaproic acid. The other seven RCTs investigated tranexamic acid.

Zazulia 2001 – ATICH was a phase II RCT of intravenous aminocaproic acid compared with 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 [pers comm]). Sprigg 2014 – TICH-1 was a phase II RCT of intravenous tranexamic acid compared with supportive treatment alone, started within 24 hours of ICH onset in adults. Arumugam 2015 was a phase II RCT of intravenous tranexamic acid compared with supportive treatment alone, started within eight hours of ICH onset in adults. Meretoja 2020 – STOP-AUST was a phase II RCT of intravenous tranexamic acid compared to placebo, started within 4.5 hours of symptom onset. Liu 2021 – TRAIGE was an RCT of intravenous tranexamic acid compared with placebo, started within eight hours of symptom onset. Sprigg 2018 – TICH-2 was a phase III RCT of intravenous tranexamic acid compared to placebo, started within eight hours of symptom onset. Polymeris 2023 – TICH-NOAC was a phase II RCT of intravenous tranexamic acid compared to placebo in people receiving novel oral anticoagulant medication; although TICH-NOAC (Treatment of Intracerebral Hemorrhage in Patients on Non–Vitamin K Antagonist Oral Anticoagulants With Tranexamic Acid) has not been published, Dr Seiffge kindly provided the unpublished data for this review. Ni 2020 was a non-registered single-centre RCT of intravenous tranexamic acid compared with placebo started within eight hours of symptom onset.

Platelet transfusion versus open control

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

Prothrombin complex concentrates versus fresh frozen plasma

We found two RCTs of PCC versus FFP involving 47 participants with acute spontaneous ICH associated with anticoagulant drug use (Boulis 1999; Steiner 2016 – INCH). Boulis 1999 was an RCT of FFP, vitamin K, and PCC versus FFP alone. Steiner 2016 – INCH was an RCT of intravenous four-factor PCC versus FFP in people with vitamin K-associated intracerebral or subdural haematoma. Professor Steiner provided us with unpublished data on the ICH population of the study for analysis in this review.

Excluded studies

We excluded 10 RCTs. For details, see the Characteristics of excluded studies table. We excluded one eligible RCT because it 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). One abstract proposed an RCT of tranexamic acid for ICH, but the corresponding author confirmed that funding had not been obtained (Ciccone 2007). We found two RCTs 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 FFP versus PCC, but was terminated before enrolment began. NCT00222625 was a study of rFVIIa, but it was "stopped due to slow recruitment" (Iorio 2012 [pers comm]). Dr Lorio has not responded to requests for clarification about whether any data were collected. Glad 2012 – NOR-ICH was a study of tranexamic acid, but it was "stopped due to slow recruitment". Dr Glad has replied that no results are available. NCT03388970 was a study of vitamin K, but it was "stopped due to slow recruitment". Dr Xian-jian has not responded to whether any results are available. Madjdinasab 2008 was an RCT of rFVIIa, 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 (therapeutic regimen of activating blood circulation (TRABC)) did not appear to be haemostatic, and had four traditional Chinese medicine products.

Ongoing studies

We identified 13 ongoing or recently completed but unreported RCTs. See Characteristics of ongoing studies table for details. We found one ongoing RCT investigating rFVIIa versus placebo or open control after acute spontaneous ICH (Naidech 2022 – FASTEST), eight ongoing RCTs examining antifibrinolytic drugs versus placebo or open control after acute spontaneous ICH (IRCT20191014045103N1; Jiang 2020 – THE-ICH; NCT03044184 – TRANSACT; NCT04742205; Pandian 2022 – INTRINSIC; Qi 2021 – TARGET; Sprigg 2022 – TICH-3; Yassi 2022 – STOP-MSU), one RCT examining platelet transfusion versus open control (NCT00699621), one RCT investigating PCC versus FFP in acute spontaneous ICH associated with anticoagulant drug use (NCT02777424 – CLOT-CRANE), one RCT examining desmopressin versus placebo (Desborough 2020 – DASH), and one RCT examining andexanet alfa in factor Xa inhibitor-associated acute intracranial haemorrhage (2018-002620-17 – Annexa-I).

Risk of bias in included studies

We assessed risk of bias using the Cochrane RoB 1 tool, and guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Across all six risk of bias domains in the 20 included RCTs, we assessed that the overall risk of bias was high in 12%, unclear in 37%, and low in 51% (Figure 2; Figure 3; Higgins 2011). Only four of the 20 RCTs were at low risk of bias in all domains (Meretoja 2020 – STOP-AUST; Polymeris 2023 – TICH-NOAC; Sprigg 2014 – TICH-1; Sprigg 2018 – TICH-2).

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

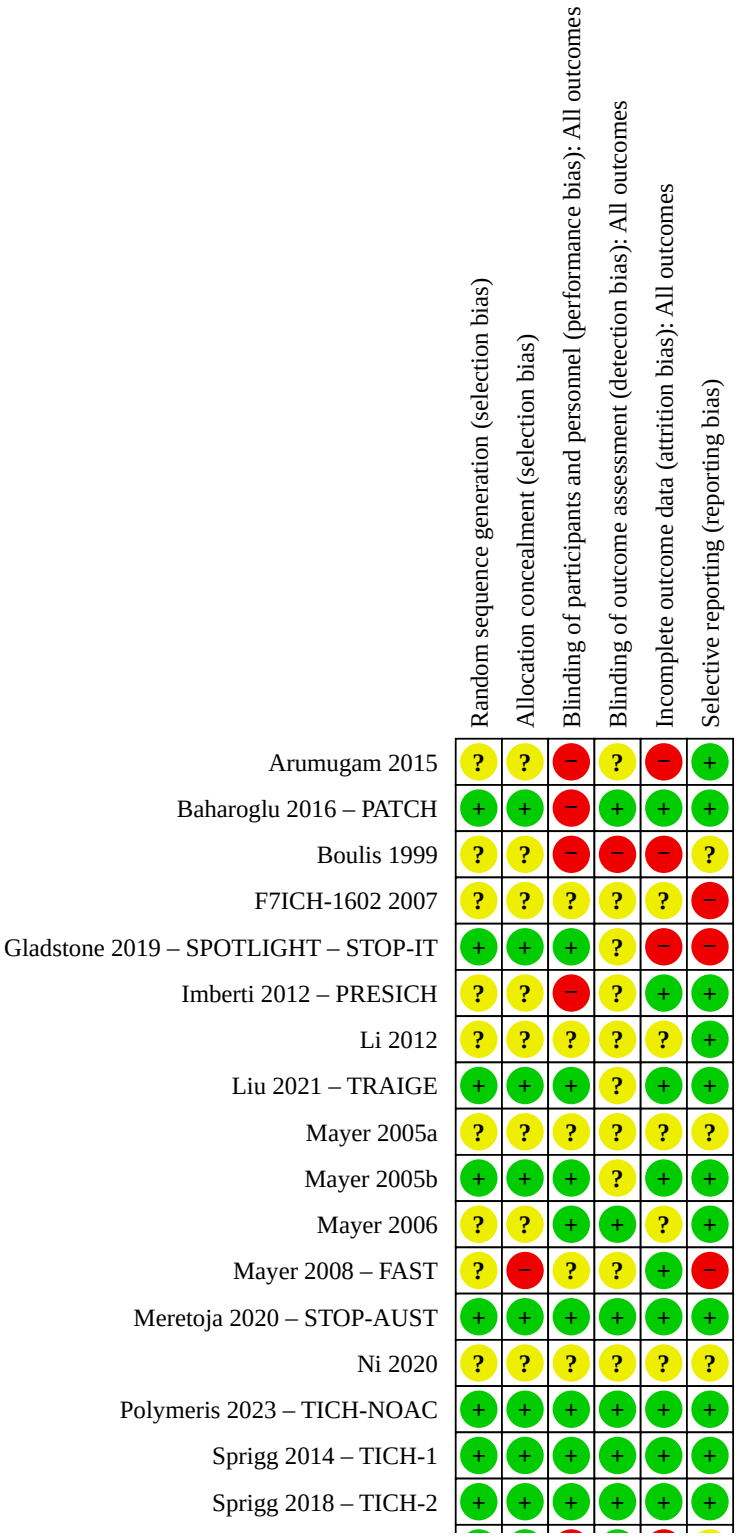


Figure 2. (Continued)

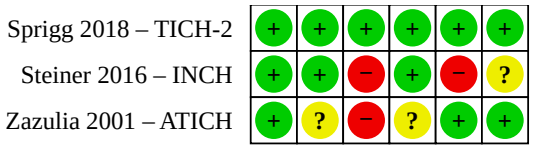
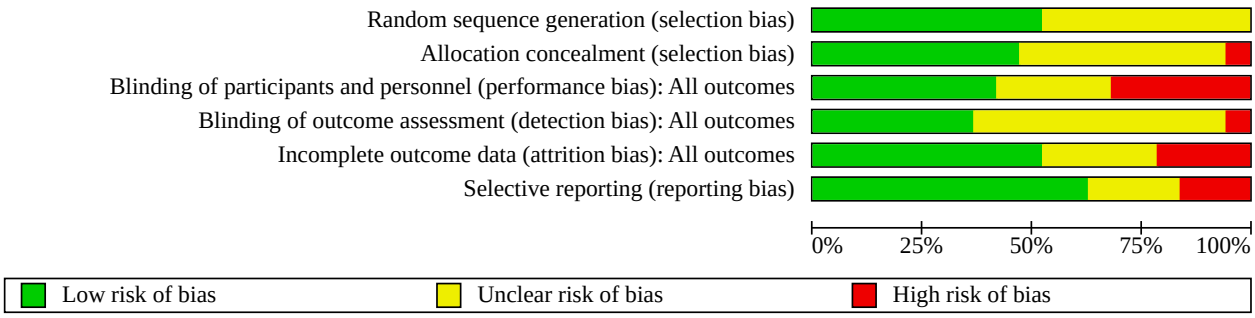


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias criterion presented as the proportion of all included studies.



Allocation

The risk of bias in random sequence generation was low in 11 RCTs, unclear in nine RCTs, and high in none. The risk of bias in allocation concealment was low in nine RCTs, unclear in 10 RCTs, and high in one.

Eleven RCTs clearly described the method of randomisation (low risk; Baharoglu 2016 – PATCH; Gladstone 2019 – SPOTLIGHT – STOP-IT (included two RCTs); Liu 2021 – TRAIGE; Mayer 2005b; Meretoja 2020 – STOP-AUST; Polymeris 2023 – TICH-NOAC; Sprigg 2014 – TICH-1; Sprigg 2018 – TICH-2; Steiner 2016 – INCH; Zazulia 2001 – ATICH), one RCT simply mentioned "block randomisation according to site" (unclear risk; Mayer 2008 – FAST), and one RCT mentioned "patients were randomised by random number table" (unclear risk; Ni 2020). The risk of bias in random sequence generation was unclear in the remaining studies.

Nine RCTs reported allocation as being concealed (low risk; Baharoglu 2016 – PATCH; Gladstone 2019 – SPOTLIGHT – STOP-IT (included two RCTs); Liu 2021 – TRAIGE; Meretoja 2020 – STOP-AUST; Polymeris 2023 – TICH-NOAC; Sprigg 2014 – TICH-1; Sprigg 2018 – TICH-2; Steiner 2016 – INCH). There was a risk of unblinding in one study (high risk; 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 µg/kg dose group than the other two groups) was due to the 80 µg/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

Six RCTs did not blind the intervention and comparator (high risk; Arumugam 2015; Baharoglu 2016 – PATCH; Boulis 1999; Imberti 2012 – PRESICH; Steiner 2016 – INCH; Zazulia 2001 – ATICH), nine did blind intervention and comparator (low risk; Gladstone 2019 – SPOTLIGHT – STOP-IT (included two RCTs); Liu 2021 – TRAIGE; Mayer 2005b; Mayer 2006; Meretoja 2020 – STOP-AUST; Polymeris 2023 – TICH-NOAC; Sprigg 2014 – TICH-1; Sprigg 2018 – TICH-2), and the risk of bias was unclear in five RCTs (F7ICH-1602 2007; Li 2012; Mayer 2005a; Mayer 2008 – FAST; Ni 2020). Whether participants and personnel were blinded to treatment allocation were explicitly stated in Baharoglu 2016 – PATCH; Gladstone 2019 – SPOTLIGHT – STOP-IT; Meretoja 2020 – STOP-AUST; Polymeris 2023 – TICH-NOAC; Sprigg 2018 – TICH-2. Correspondence with the study authors verified that this was the case also for Mayer 2006 and Sprigg 2014 – TICH-1. The risk of bias was assessed as low in the clearly stated blinded RCTs. In the six RCTs that did not blind the intervention and comparator, it was assessed as high. The remaining five RCTs where blinding of intervention and comparator was not stated, were assessed as unclear.

Risk of bias from blinding of outcome assessment was high in one RCT (Boulis 1999), low in seven RCTs (Baharoglu 2016 – PATCH; Mayer 2006; Meretoja 2020 – STOP-AUST; Polymeris 2023 – TICH-NOAC; Sprigg 2014 – TICH-1; Sprigg 2018 – TICH-2; Steiner 2016 – INCH), and unclear in 12 RCTs (Arumugam 2015; Gladstone 2019 – SPOTLIGHT – STOP-IT (included two RCTs); Imberti 2012 – PRESICH; Li 2012; Liu 2021 – TRAIGE; Mayer 2005a; Mayer 2005b; Mayer 2008 – FAST; Ni 2020; Zazulia 2001 – ATICH).

Seven RCTs report blinding of all outcomes (Baharoglu 2016 – PATCH; Mayer 2006; Meretoja 2020 – STOP-AUST; Polymeris 2023 – TICH-NOAC; Sprigg 2014 – TICH-1; Sprigg 2018 – TICH-2; Steiner 2016 – INCH). Six RCTs report that assessment of radiological

outcome was blinded to treatment, but do not provide information of other outcome assessments (Arumugam 2015; Gladstone 2019 – SPOTLIGHT – STOP-IT (included two RCTs); Imberti 2012 – PRESICH; Mayer 2005b; Zazulia 2001 – ATICH). Seven RCTs do not provide information on blinding of outcomes (Boulis 1999; F7ICH-1602 2007; Li 2012; Liu 2021 – TRAIGE; Mayer 2005b; Mayer 2008 – FAST; Ni 2020).

Incomplete outcome data

Overall, the risk of bias from incomplete outcome data was low in 10 RCTs, high in five RCTs, and unclear in the remaining five RCTs.

Seven RCTs provided data about completeness of clinical follow-up (low risk; Baharoglu 2016 – PATCH; Imberti 2012 – PRESICH; Mayer 2005b; Meretoja 2020 – STOP-AUST; Polymeris 2023 – TICH-NOAC; Sprigg 2014 – TICH-1; Zazulia 2001 – ATICH). Three RCTs had very few missing data and the missing data were balanced between groups (Liu 2021 – TRAIGE; Mayer 2008 – FAST; Sprigg 2018 – TICH-2). Five RCTs were at high risk of bias due to the proportion of missing data (Arumugam 2015; Boulis 1999; Gladstone 2019 – SPOTLIGHT – STOP-IT (included two RCTs); Steiner 2016 – INCH).

Mayer 2005b and Mayer 2008 – FAST used the last-observation-carried-forward technique, 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 12 RCTs, unclear in four RCTs, and high in four RCTs.

For the four RCTs assessed as high risk of bias for selective reporting, one RCT did not provide data for major outcomes (F7ICH-1602 2007), one RCT did not report on two clinical outcomes (Mayer 2008 – FAST), and two RCTs primarily reported radiological and safety outcomes in the publication, but reported some of the prespecified clinical outcomes in the supplementary appendix (Gladstone 2019 – SPOTLIGHT – STOP-IT (included two RCTs)). Steiner 2016 – INCH reported all prespecified outcomes in the primary publication, but we do not have data on serious adverse events, thromboembolic events, and quality of life for the acute, spontaneous ICH subpopulation of the trial.

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. We found no clear evidence of publication bias when performing funnel plot analysis of the largest group of RCTs (Figure 4; Figure 5), but as there were few studies included in the plots it should be interpreted with caution.

Figure 4. Recombinant factor VIIa versus placebo/open control for people with acute spontaneous intracerebral haemorrhage.

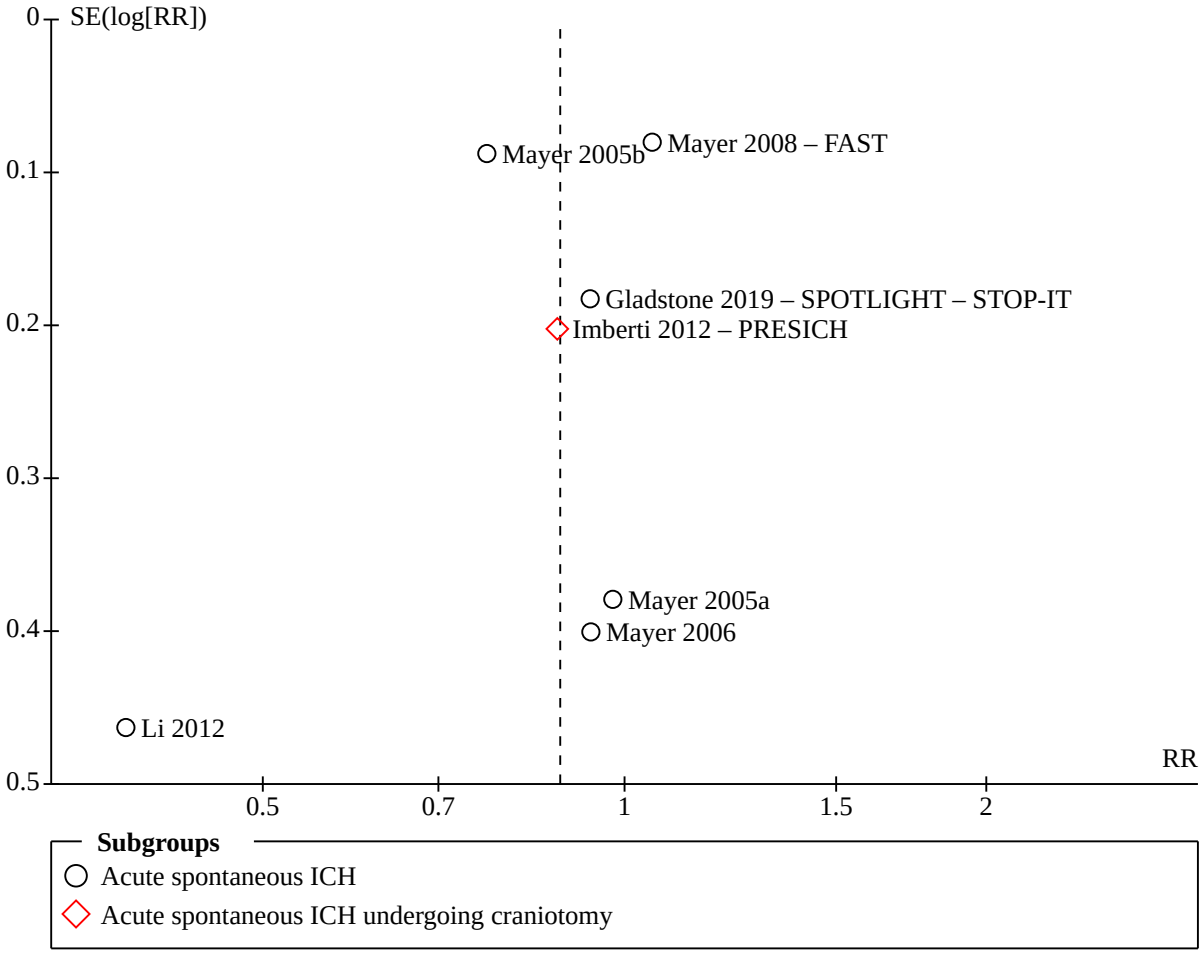
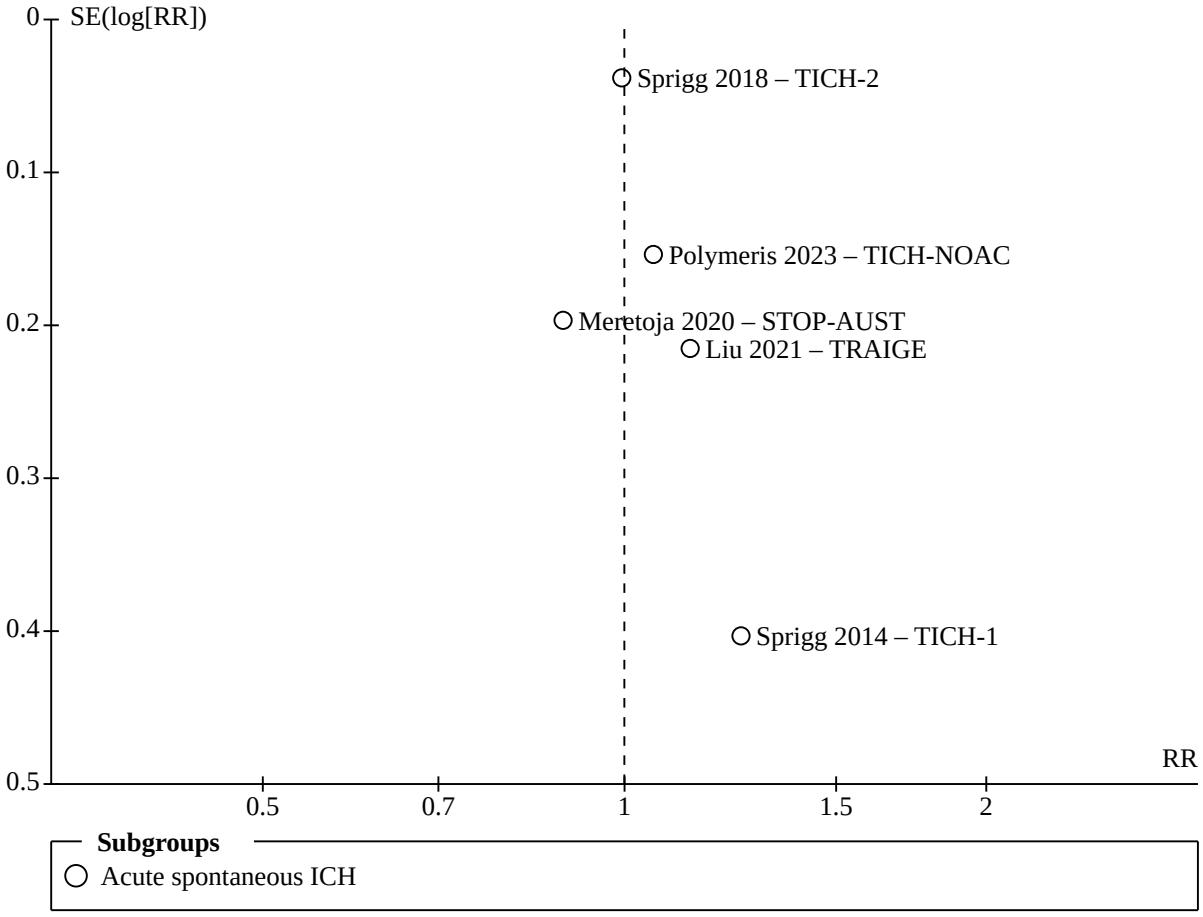


Figure 5. Antifibrinolytic treatment versus placebo/open control for people with acute spontaneous intracerebral haemorrhage.



We assessed studies for data dredging bias. We found one RCT that reported four additional subgroups that were not prespecified (Polymeris 2023 – TICH-NOAC). We could not determine if the authors made conclusions of the study based on those analyses and we assessed the risk of bias as low.

We assessed two intervention groups for publication bias for our primary outcome of death or dependence, rFVIIa versus placebo/open control and antifibrinolytics versus placebo/open control (Figure 4; Figure 5). The antifibrinolytics group appeared to have skewed data to suggest negative resulting trials have not been published. However, given that we had fewer than 10 trials, we cannot confidently conclude that there was publication bias.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Recombinant activated factor VII compared to placebo/open control for adults with acute spontaneous intracerebral haemorrhage; **Summary of findings 2** Summary of findings table - Antifibrinolytic drug(s) compared to placebo/open control for adults with acute spontaneous intracerebral haemorrhage; **Summary of findings 3** Summary of findings table - Platelet transfusion compared to open control for adults with acute spontaneous intracerebral haemorrhage associated with antiplatelet drug use; **Summary of findings 4** Summary of findings table - Prothrombin complex concentrates compared to fresh frozen plasma for adults with acute spontaneous intracerebral haemorrhage associated with anticoagulant drug use

We analysed data on intervention effects in 20 RCTs (one study reference included two RCTs) involving 4652 participants (2608 allocated to intervention and 2044 allocated to control or active comparator), split by type of intervention as follows.

Recombinant activated factor VII versus placebo or open control

In RCTs of rFVIIa (1050 participants) versus placebo or open control (499 participants) for acute spontaneous ICH with or without surgery, use of rFVIIa resulted in little to no difference in death or dependence (using the mRS) (RR 0.88, 95% CI 0.74 to 1.05; 7 RCTs, 1454 participants; low-certainty evidence; Analysis 1.1), in ICH expansion (RR 0.81, 95% CI 0.56 to 1.16; 4 RCTs, 220 participants; low-certainty evidence; Analysis 1.2), in all serious adverse events (RR 0.81, 95% CI 0.30 to 2.22; 2 RCTs, 87 participants; very low-certainty evidence; Analysis 1.3), in thromboembolic adverse events (RR 1.18, 95% CI 0.78 to 1.79; 6 RCTs, 1467 participants; low-certainty evidence; Analysis 1.4), and death from any cause (RR 0.78, 95% CI 0.56 to 1.08; 8 RCTs, 1544 participants; moderate-

certainty evidence; Analysis 1.5). For acute spontaneous ICH, use of rFVIIa resulted in little to no difference in death or dependence using the GOS-E score (RR 0.90, 95% CI 0.81 to 1.01; 3 RCTs, 486 participants; Analysis 1.6). In these analyses, the I^2 varied from 0% to 44%. None of the RCTs reported on quality of life, mood, or cognitive function.

We performed sensitivity analyses on all outcomes by removing three trials in this group with high risk of bias in at least one domain (Gladstone 2019 – SPOTLIGHT – STOP-IT (included two RCTs); Mayer 2008 – FAST). This changed the result on death or dependence (mRS 4 to 6) at 90 days in favour of rFVIIa compared to placebo/open control (RR 0.77, 95% CI 0.66 to 0.90) and death from any cause at 90 days in favour of rFVIIa versus placebo/open control (RR 0.57, 95% CI 0.34 to 0.93).

Antifibrinolytic drugs versus placebo or open control

In RCTs of antifibrinolytic drugs (1438 participants) versus placebo or open control (1428 participants) for acute spontaneous ICH, use of antifibrinolytic drugs resulted in little to no difference in death or dependence (RR 1.00, 95% CI 0.93 to 1.07; 5 RCTs, 2683 participants; high-certainty evidence; Analysis 2.1). Antifibrinolytic drugs led to a slight reduction in ICH expansion (RR 0.86, 95% CI 0.76 to 0.96; 8 RCTs, 2866 participants; high-certainty evidence; Analysis 2.2). Antifibrinolytic drugs led to little or no difference in all serious adverse events (RR 1.02, 95% CI 0.75 to 1.39; 4 RCTs, 2599 participants; high-certainty evidence; Analysis 2.3), thromboembolic adverse events (RR 1.23, 95% CI 0.88 to 1.71; 6 RCTs, 2833 participants; Analysis 2.4), death by any cause at 90 days (RR 1.02, 95% CI 0.89 to 1.18; 8 RCTs, 2866 participants; high-certainty evidence; Analysis 2.5), death by any cause by seven days (RR 0.82, 95% CI 0.64 to 1.06; 1 RCT, 2325 participants; high-certainty evidence; Analysis 2.6), quality of life (MD 0, 95% CI −0.03 to 0.03; 2 RCTs, 2349 participants; high-certainty evidence; Analysis 2.7), mood (MD 0.30, 95% CI −1.98 to 2.57; 2 RCTs, 2349 participants; high-certainty evidence; Analysis 2.8), cognitive function assessed with TICS-M (MD −0.37, 95% CI −1.40 to 0.66; 1 RCT, 2325 participants; high-certainty evidence; Analysis 2.9), cognitive function assessed with MMSE (MD 2.70, 95% CI −0.10 to 5.50; 1 RCT, 24 participants; Analysis 2.10), or the Barthel Index score (MD −8.33, 95% CI −29.24 to 12.58; 2 RCT, 2349 participants; Analysis 2.11). There was a moderate amount of heterogeneity between the four trials evaluating all serious adverse events (I^2 = 38%) and considerable heterogeneity between the two trials analysing the Barthel Index score (I^2 = 71%), but in all other analyses, the I^2 statistic was 0%.

We performed sensitivity analysis, which did not change our conclusions.

Platelet transfusion versus open control

In one RCT of platelet transfusion (97 participants) versus open control (93 participants) for acute spontaneous ICH associated with antiplatelet drug use, platelet transfusion led to a slight increase in death or dependence at day 90 (RR 1.29, 95% CI 1.04 to 1.61; 1 RCT, 190 participants; moderate-certainty evidence; Analysis 3.1), and little to no difference in ICH expansion (RR 1.32, 95% CI 0.91 to 1.92; 1 trial, 153 participants; moderate-certainty evidence; Analysis 3.2), all serious adverse events (RR 1.46, 95% CI 0.98 to 2.16; 1 RCT, 190 participants; moderate-certainty evidence; Analysis 3.3), thromboembolic adverse events (RR 3.84, 95% CI 0.44 to 33.68; 1 RCT, 190 participants; moderate-certainty evidence; Analysis 3.4), and death by any cause (RR 1.42, 95% CI 0.88 to 2.28; 1 RCT, 190 participants; moderate-certainty evidence; Analysis 3.5). The trial did not report on quality of life, mood, or cognitive function.

Sensitivity analysis was not performed to any of these outcomes as there was only one RCT.

Prothrombin complex concentrates versus fresh frozen plasma

In two RCTs of PCC (23 participants) versus FFP (24 participants) for acute spontaneous ICH associated with anticoagulant drug use, the evidence was very uncertain about the effect on death and dependence at 90 days (RR 1.21, 95% CI 0.76 to 1.90; 1 RCT, 37 participants; very low-certainty evidence; Analysis 4.1), ICH expansion (RR 0.54, 95% CI 0.23 to 1.22; 1 RCT, 36 participants; very low-certainty evidence; Analysis 4.2), all serious adverse events (RR 0.27, 95% CI 0.02 to 3.74; 1 RCT, 5 participants; very low-certainty evidence; Analysis 4.3), and death by any cause (RR 0.49, 95% CI 0.16 to 1.56; 2 RCTs, 42 participants; very low-certainty evidence; Analysis 4.4). For the one outcome where both RCTs reported results, the I^2 statistic was 0%.

In the primary publication, the INCH trial did report on thromboembolic events and quality of life; however, we did not receive the data on these outcomes for the specific ICH subpopulation (Steiner 2016 – INCH). Boulis 1999 did not report on thromboembolic events, quality of life, mood, or cognitive function.

Sensitivity analysis was performed on the secondary outcome death by any cause by day 90; removing Boulis 1999 due to an element with high risk of bias did not change the direction of the result.

DISCUSSION

Summary of main results

This updated Cochrane Review included 20 RCTs involving 4652 participants. In nine RCTs involving 1549 participants, rFVIIa likely results in little to no difference in reducing death or dependence after spontaneous ICH with or without surgery (Summary of findings 1). In eight RCTs involving 2866 participants, antifibrinolytic drugs result in little to no difference in reducing death or dependence after spontaneous ICH, but result in a slight reduction in ICH expansion within 24 hours (Summary of findings 2). In one RCT involving 190 participants, platelet transfusion likely increases death or dependence after antiplatelet-associated ICH (Summary of findings 3). In two RCTs involving 47 participants, the evidence is very uncertain about the effect of PCC compared to FFP on death or dependence after anticoagulant-associated ICH (Summary of findings 4). Thirteen RCTs are ongoing and are likely to increase the certainty about some of these estimates of treatment effect.

Overall completeness and applicability of evidence

Two RCTs on rFVIIa versus placebo/open control have been published since the last update of the review (Gladstone 2019 – SPOTLIGHT – STOP-IT (included two RCTs)). These RCTs were small and did not change the overall results or level of evidence.

When performing sensitivity analysis by removing RCTs with high risk of bias (Gladstone 2019 – SPOTLIGHT – STOP-IT; Mayer 2008 – FAST), we found that rFVIIa might be superior to placebo/open control for people with spontaneous ICH in reducing death or dependence at 90 days and reducing death from any cause at 90 days.

For the comparison of antifibrinolytic drugs versus placebo/open control, five new RCTs have been published (Liu 2021 – TRAIGE; Meretoja 2020 – STOP-AUST; Ni 2020; Polymeris 2023 – TICH-NOAC; Sprigg 2018 – TICH-2). These RCTs have raised the overall completeness and level of evidence, but the evidence of effect on antifibrinolytic treatment in people with anticoagulant-associated ICH is still uncertain since only one small RCT has investigated this (Polymeris 2023 – TICH-NOAC).

In the one RCT that reported death by seven days (Sprigg 2018 – TICH-2), we found little to no effect on this outcome; however, in the primary publication, treatment with tranexamic acid seemed superior to standard care (odds ratio 0.73, 95% CI 0.53 to 0.99). The difference is likely due to unadjusted analysis of the results in this review compared to the primary publication where the analysis was adjusted according to the minimisation criteria (Flaherty 2017 – TICH-2 SAP).

One RCT of platelet transfusion is ongoing (NCT00699621). We await the publication of this RCT to see if it is consistent with the findings of Baharoglu 2016 – PATCH.

The results of 13 ongoing or recently completed unreported RCTs are awaiting completion and publication (see Characteristics of ongoing studies table). Many of these are investigating antifibrinolytic treatment versus placebo/open control, where the level of evidence is the highest. One of these RCTs is comparing desmopressin to placebo in people with antiplatelet-associated ICH, which have not been investigated in an RCT previously (Desborough 2020 – DASH).

One limitation of this review is that the timing of intervention varied between studies, from three to 24 hours after symptom onset. Studies have found that the risk of ICH expansion is largest before three hours, so haemostatic interventions might be more effective in this earlier time window. We await the results of the ongoing RCTs, most of which have a shorter time frame from symptom onset to randomisation. Future updates of this review should investigate differences of effect in relation to timing of intervention.

Certainty of the evidence

Four double-blind RCTs (Meretoja 2020 – STOP-AUST; Polymeris 2023 – TICH-NOAC; Sprigg 2014 – TICH-1; Sprigg 2018 – TICH-2), 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 largest quantity of data was from RCTs of antifibrinolytic drugs, which overall had low risk of bias. Their results were consistent in showing little to no benefit of antifibrinolytic drug for the primary outcome of death or dependence by day 90. Clinical and statistical heterogeneity amongst all eight trials were low. Therefore, we graded the level of evidence as high for all outcomes.

The results from the RCTs of rFVIIa were at moderate risk of bias. Clinical heterogeneity amongst the trials of rFVIIa was substantial given baseline characteristic differences and treatment group differences. The studies showed moderately inconsistent results of little to no benefit of rFVIIa. These findings have not changed practice (Christensen 2019 – ESO reversal OAC ICH; Greenberg 2022 – AHA/ASA ICH; NICE guideline 2019; RCP 2016; Steiner 2014 – ESO ICH). Therefore, we downgraded the certainty of the evidence to low.

For platelet transfusion versus placebo/open control, the evidence was rated as moderate. We downgraded the certainty of the evidence one level because of imprecision as the results were based on one study with small sample size. The RCT finding harm from platelet transfusion has not been replicated in another RCT (Baharoglu 2016 – PATCH).

For PCC versus FFP, the evidence was rated as very low certainty. We downgraded the certainty of evidence three levels because of risk of bias in several domains, imprecision due to very small sample size, and due to indirectness in the study question.

Potential biases in the review process

For the English language papers we followed a dual review process: two review authors (HE and CSM) independently extracted data that reduced identification bias and improved risk of bias assessment. All conflicts were arbitrated by an unconflicted third review author in the identification of studies, risk of bias decisions, and GRADE criteria decisions; all decisions were made by consensus and were not subjective. For the Chinese language paper (Ni 2020), this was not possible, and one review author (CC) performed data extraction and risk of bias assessment.

Agreements and disagreements with other studies or reviews

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 (Christensen 2019 – ESO reversal OAC ICH; Greenberg 2022 – AHA/ASA ICH; Steiner 2014 – ESO ICH). The American Heart Association/American Stroke Association (AHA/ASA) guideline calls for further evidence about the effect of rFVIIa. One ongoing RCT is examining the effect of rFVIIa when given within two hours of ICH onset (Naidech 2022 – FASTEST).

The updated AHA/ASA guideline states that the effect of tranexamic acid on functional outcome is not well established (Greenberg 2022 – AHA/ASA ICH). We found a high level of evidence supporting no to little effect of tranexamic acid on functional outcome. Our finding is consistent with results of other published systematic reviews and meta-analyses of the effect of tranexamic acid (Guo 2021; Wang 2021; Yu 2023). Several studies on the effect of tranexamic acid are still ongoing, some especially examining the effect of tranexamic acid on mortality when given earlier after ICH onset.

The PATCH trial found that platelet transfusion in people with antiplatelet-associated spontaneous ICH can be harmful (Baharoglu 2016 – PATCH). This is incorporated in AHA/ASA guidelines (Greenberg 2022 – AHA/ASA ICH).

We found two RCTs investigating PCC versus FFP in people with vitamin K-associated ICH (Boulis 1999; Steiner 2016 – INCH). We investigated the subgroup of participants with ICH in the INCH trial and found no clear difference in functional outcome between the

group receiving PCC and FFP. The number of participants was small and the RCT was stopped prematurely by official authorities due a larger proportion of ICH expansion in the group that received FFP compared to those treated with PCC. The RCT found that PCC was superior to FFP in the normalisation of international normalised ratio (INR). This study is the main reference in the updated AHA/ASA recommendation of PCC being preferred to FFP in people with vitamin K antagonist-associated spontaneous ICH and INR of 2.0 or greater (Greenberg 2022 – AHA/ASA ICH).

We found no completed RCTs investigating the effect and safety of idarucizumab for reversal of factor IIa-inhibitor or andexanet alfa for the reversal of factor Xa inhibitors. We are awaiting the results of the Annexa-I RCT investigating the effect and safety of andexanet alfa in factor Xa-associated ICH (2018-002620-17 – Annexa-I). We have found no ongoing RCTs on idarucizumab.

AUTHORS' CONCLUSIONS

Implications for practice

Recombinant activated factor VII (rFVIIa) may result in little to no difference compared to placebo for reducing death or dependence 90 days after acute spontaneous intracerebral haemorrhage (ICH) with or without surgery. This finding is based on randomised controlled trials (RCTs) with varying degrees of risk of bias; when removing RCTs with high risk of bias in a sensitivity analysis, we found that rFVIIa might be superior to placebo for reducing death or dependency. The ongoing Naidech 2022 – FASTEST RCT will help to determine the effects of rFVIIa for reducing death or dependency early after acute spontaneous ICH.

Antifibrinolytic drugs (such as tranexamic acid) result in little to no difference for reducing death or dependence 90 days after acute spontaneous ICH, but they seem superior in reducing ICH expansion within 24 hours. Several ongoing RCTs will help to determine the effects of tranexamic acid for reducing early death and death or dependency after acute spontaneous ICH overall, and in subgroups.

Platelet transfusion likely increases death or dependence 90 days after acute antiplatelet-associated ICH. This finding is based on one RCT and the ongoing NCT00699621 study may help confirm these results.

Prothrombin complex concentrates (PCC) may have little to no effect compared to fresh frozen plasma (FFP) for reducing death or dependence 90 days after acute anticoagulant-associated ICH, but the evidence is very uncertain (and PCC is superior for the intermediate outcome of speed of international normalised ratio reversal compared to FFP after vitamin K antagonist-associated ICH).

Implications for research

rFVIIa does not appear beneficial on the basis of existing evidence in clinical or radiographic outcomes. RCTs in the future need to be undertaken with larger study populations and look specifically at subgroups such as earlier time windows after onset. We await the results of the FASTEST trial treating people within two hours after symptom onset (Naidech 2022 – FASTEST).

Tranexamic acid is likely superior to standard care in reducing ICH expansion, but has little to no effect on death or dependence after 90 days. Future RCTs will report on death or dependence and early death alone (which was reported only by Sprigg 2018 – TICH-2 of the included RCTs). Several ongoing RCTs of antifibrinolytic drugs for acute spontaneous ICH may add to this evidence (IRCT20191014045103N1; Jiang 2020 – THE-ICH; NCT03044184 – TRANSACT; NCT04742205; Pandian 2022 – INTRINSIC; Qi 2021 – TARGET; Sprigg 2022 – TICH-3; Yassi 2022 – STOP-MSU). One RCT investigated the use of tranexamic acid in direct oral anticoagulant (DOAC)-associated ICH (Polymeris 2023 – TICH-NOAC), but sample size was small, making it difficult to draw conclusions. We await the results of Sprigg 2022 – TICH-3, which is investigating antifibrinolytic drugs for DOAC-associated ICH as a subgroup within its large main phase RCT.

Given the unfavourable clinical outcome of platelet transfusion in antiplatelet-associated ICH shown in the PATCH trial (Baharoglu 2016 – PATCH), and that these results have changed practice and guidelines, it is unlikely future RCTs investigating this will be performed. However, one platelet transfusion study is yet to publish their results (NCT00699621). We await the results of the DASH trial investigating the effect of desmopressin after antiplatelet-associated ICH, although given this was a feasibility study, larger RCTs are likely to be needed (Desborough 2020 – DASH).

PCC is likely superior to FFP for normalising coagulation after vitamin K antagonist-associated ICH in the INCH trial (Steiner 2016 – INCH), but the superiority of PCC for improving clinical outcomes is uncertain. Steiner 2016 – INCH has changed practice and clinical guidelines, so future RCTs investigating this seem unlikely to be done. The use of vitamin K antagonists is decreasing and the use of DOACs is increasing, so adequate recruitment to Annexa-I is a high priority (2018-002620-17 – Annexa-I).

The timing of the intervention varied between studies. Some studies included participants up to 24 hours after symptom onset. Most of the ongoing studies are investigating the effect of earlier treatment (Jiang 2020 – THE-ICH; Naidech 2022 – FASTEST; NCT03044184 – TRANSACT; Pandian 2022 – INTRINSIC; Qi 2021 – TARGET; Sprigg 2022 – TICH-3; Yassi 2022 – STOP-MSU). Future updates of this review could investigate differences of effect in relation to timing of intervention.

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The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Amanda Barugh, Department of Geriatric Medicine, University of Edinburgh
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Luisa M Fernandez Mauleffinch, Cochrane Central Editorial Service
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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Arumugam 2015

Study characteristics	
Methods	Single-blind, 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 140–160 mmHg). A repeat brain CT was done after 24 h to reassess HE. The primary objective was to test the effect of tranexamic acid on HE. Other objectives were to test the feasibility, tolerability, and adverse events of tranexamic acid in primary ICH.
Participants	Inclusion criteria • 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 • Supratentorial lesion Exclusion criteria • Patients on anticoagulant therapy • Brainstem bleed • Intraventricular bleed on the first brain CT scan, including participants who developed an intraventricular bleed during the study • Malignant hypertension • SAH 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 • Pregnant or breastfeeding 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% sodium chloride) over 10 min. Initial dose followed by a maintenance dose of 1 g/h for 8 h. Labetalol infusion 2 mg/min to achieve SBP 140–160 mmHg

Arumugam 2015 *(Continued)*

	Comparator: placebo mentioned, but not described. Labetalol infusion 2 mg/min to achieve SBP 140–160 mmHg
Outcomes	Repeat CT brain scan 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	

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	Unclear risk	Blinded radiologist for primary outcome. Not stated as blinded for other outcomes.
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

Study characteristics

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

Baharoglu 2016 – PATCH *(Continued)*

	Exclusion criteria • Blood on brain imaging suggestive of epidural or subdural haematoma, or an underlying aneurysm or AVM • Planned surgical evacuation of ICH 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 VKA (unless INR ≤ 1.3) or history of coagulopathy • Known thrombocytopenia (< 100 cells × 10^9/L) • Lacking mental capacity by national legal standards before ICH • Death appeared imminent
Interventions	Intervention: standard care with platelet transfusion within 90 min of diagnostic brain imaging Comparator: standard care
Outcomes	Primary outcome: 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 1–5), poor outcome defined as an mRS score 4–6, and poor outcome defined as an mRS score 3–6. Secondary explanatory outcome: median absolute ICH expansion in mL after 24 h on brain imaging. Safety outcomes: 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 [cyclo-oxygenase] 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."
Allocation concealment (selection bias)	Low risk	Allocation was concealed from investigators by the web-based randomisation system.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and local investigators giving interventions were not blinded 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.

Baharoglu 2016 – PATCH *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Boulis 1999

Study characteristics	
Methods	RCT
Participants	Inclusion criteria • CT-confirmed ICH • Documented history of warfarin use • Prothrombin time > 17 seconds Exclusion criteria • Clinical evidence of brainstem herniation
Interventions	Intervention: FFP Comparator: FFP (intravenous), vitamin K (subcutaneous) and factor IX complex concentrate – PCC (Konyne; Bayer, Elkhart, IN: containing high concentrations of activated vitamin K-dependent clotting factors II, VII, IX, and X; dosage according to bodyweight; 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.
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 prespecified.

F7ICH-1602 2007

Study characteristics	
Methods	Randomised, double-blind, Japanese multicentre, placebo-controlled, phase II dose-escalation trial with 3 dose tiers
Participants	Inclusion criteria • Aged ≥ 20 years • Spontaneous ICH (not in brainstem) • Within 3 h of onset
Interventions	Intervention: rFVIIa (NovoSeven) at 40 µg/kg (n = 15), 80 µg/kg (n = 15), or 120 µg/kg (n = 15), within 1 h of baseline CT Comparator: placebo (n = 45), within 1 h of baseline CT
Outcomes	Preliminary evaluations were performed as follows • mRS, the BI scores at 15 days postdose and 90 days postdose • 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 postdose • Change in the GCS and the NIHSS scores from baseline to 1 h postdose, 24 h postdose, 48 h postdose, 72 h postdose, 15 days postdose, and 90 days postdose • Mortality at 90 days postdose Criteria for evaluation: safety • Occurrence of thromboembolic SAEs 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 postdose, 24 h postdose, 48 h postdose, and 72 h postdose • Exacerbation of brain oedema (oedema/ICH volume ratio > 2.5) assessed using head CT scan at 24 h postdose, 48 h postdose, and 72 h postdose • Occurrence of adverse events until discharge or 90 days postdose, whichever came first, and SAEs 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 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 reported to be blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessment of outcomes was not explicitly stated to be blinded.

F7ICH-1602 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified.
Selective reporting (reporting bias)	High risk	Data not provided for most major outcomes.

Gladstone 2019 – SPOTLIGHT – STOP-IT

Study characteristics	
Methods	Parallel, double-blind RCTs Consisted of 2 RCTs reported in 1 publication with individual trial registrations (SPOTLIGHT and STOP-IT)
Participants	Inclusion criteria for SPOTLIGHT • Acute spontaneous primary supratentorial ICH diagnosed by CT scan • Presence of a spot sign within the haematoma on CTA source images • Baseline ICH volume 3–90 mL • Aged ≥ 18 years • Investigator able to randomise and administer study drug as soon as possible within 60 min after CTA and no later than 6 h after stroke symptom onset (using the 'last seen normal' principle) • Plan to provide full medical care for ≥ 24 h • Assent-consent from participant or LAR prior to enrolment, or a waiver of consent (where REB approved) if participant or LAR assent-consent was not possible prior to enrolment Exclusion criteria for SPOTLIGHT • Brainstem or cerebellar haemorrhage • ICH secondary to known or suspected trauma, aneurysm, vascular malformation, haemorrhagic 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 were not an exclusion) • Contrast administration within previous 24 h • Evidence of thromboembolic risk factors, defined as any of the following: known history within past 6 months of any of the following: MI; coronary artery bypass surgery; angina; ischaemic stroke; TIA; carotid endarterectomy; cerebral bypass surgery; DVT; PE; any vascular angioplasty; stenting (coronary, peripheral vascular, or cerebrovascular) or filter (e.g. vena cava filter); prosthetic cardiac valve; 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 considered 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 have checked PTT and excluded if elevated above upper limit of local laboratory's reference range

Gladstone 2019 – SPOTLIGHT – STOP-IT *(Continued)*

- 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 was suspected to have cirrhosis, study staff were to wait for the INR value prior to dosing, and ensure they did not enrol the patient if the INR value was > 1.40. Otherwise, the physician used their discretion if they believed the patient was not at risk for elevated INR
- Concurrent or planned treatment with PCC, VKA, FFP, or platelet transfusion
- Pregnancy or lactation. Women of childbearing potential must have had a negative pregnancy test prior to randomisation
- 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 left bundle branch block, ST depression)
- Baseline platelet count < 50,000/µL, INR > 1.40, or elevated PTT

Inclusion criteria for STOP-IT

- Acute, spontaneous ICH (including bleeding in cerebellum) diagnosed by non-enhanced CT scan within 5 h of symptom onset (time of onset defined as the last time the patient was witnessed to be at baseline, i.e. people who had stroke symptoms upon awakening were considered to have their onset at beginning of sleep)
- Age ≥ 18 years to 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 min of enroling CT scan

Exclusion criteria for STOP-IT

- Time of symptom onset of ICH was unknown or > 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 enroled)
- 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 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 < 0.5 mL (haematoma volume estimated by local investigators from the baseline CT using the ABC/2 method)
- Baseline ICH volume > 90 mL
- 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, DVT, PE, or coronary or cerebrovascular angioplasty or stenting. (Clinically silent evidence of old ischaemia on ECG (Q waves) or CT scan (silent old infarct) was not considered reasons for exclusion)

Gladstone 2019 – SPOTLIGHT – STOP-IT *(Continued)*

	• Baseline ECG showed 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 • Women 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 LAR
Interventions	Intervention for SPOTLIGHT: single intravenous bolus rFVIIa 80 µg/kg Comparator for SPOTLIGHT: standard sodium chloride solution Intervention for STOP-IT: rFVIIa 80 µg/kg (maximum dose volume 21.3 mL, equivalent to maximum weight of 160 kg) Comparator for STOP-IT: placebo. An inactive substance (maximum dose volume 21.3 mL, equivalent to maximum weight of 160 kg)
Outcomes	Primary outcome measures for SPOTLIGHT • ICH size: difference between groups in ICH size on CT scan at 24 h postdose, adjusted for baseline ICH size Secondary outcome measures for SPOTLIGHT • Feasibility (time frame: 0): percentage of sites that can meet recruitment targets of 2 participants per site per year; % of participants who met the target time < 45 min from emergency department arrival to the start of the scan; % of participants who met the target time < 60 min from the end of the CTA to administration of study drug; local site spot sign interpretation accuracy as judged by central adjudicator; protocol violations; waiver of consent process, evaluation, and effects (time frame: 90 days); waiver of consent use, acceptability, and effect on treatment times. Questionnaire will be administered to participant 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 within 4 days of treatment • Troponin increase above upper limit of normal within 4 days (without clinical symptoms or ECG evidence of acute coronary syndrome) • DVT within 4 days • PE within 30 days • Cognition: Montreal Cognitive Assessment and Stroke Impact Scale at 90 days and 1 year • Disability: proportion of participants with mRS score 5–6 (death or severe disability) at 90 days and 1 year Primary outcome measures for STOP-IT • Life-threatening thromboembolic complications defined as development of acute myocardial ischaemia, acute cerebral ischaemia, and acute PE (time frame: to day 4 after completion of study drug)

Gladstone 2019 – SPOTLIGHT – STOP-IT *(Continued)*

- Rate of HE amongst spot sign-positive participants at 24 h, comparing participants treated with rFVIIa to those treated with placebo. HE defined as > 33% or > 6 mL increase in volume
- Sensitivity and specificity of the spot sign for predicting HE (time frame: baseline head CT scan within 5 h, followed by a CTA. HE determined by comparison with a head CT scan performed at 24 h)

Secondary outcome measures for STOP-IT

- Incidence of other potentially study drug-related thromboembolic complications, such as DVT and elevations in troponin not associated with ECG changes (time frame: to day 4 after completion of study drug).
- 90-day outcomes amongst spot-positive people, dichotomised as mRS score 0–4 versus 5–6, comparing participants treated with rFVIIa to those treated with placebo (at 90 days (± 7 days) from time of study enrolment).
- 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 CTA)
- HE determined by comparison with a head CT scan performed at 24 h
- Rate of total haemorrhage volume expansion (haematoma + IVH) amongst spot-positive participants (time frame: 24 h (± 3 h) from baseline CT scan)

Notes	SPOTLIGHT: NCT01359202 STOP-IT: NCT00810888 SPOTLIGHT: sample size estimation of 110 participants (55 in each group) according to the protocol. 51 participants were enroled. STOP-IT: 19 participants out of an estimated sample size of 84 were enroled. SPOTLIGHT and STOP-IT were assessed as 2 separate trials in evaluating risk of bias. The risk of bias was assessed to be equal in both studies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	SPOTLIGHT: "A computer-generated randomization schedule will be created for the trial by the study statistician such that there will be an equal number of patients assigned to each treatment." STOP-IT: "Assignment to a treatment group will be done centrally. The local study investigator enrolling a patient will access a web-based program to determine the randomization number."
Allocation concealment (selection bias)	Low risk	SPOTLIGHT: "[The] dispensing team will assign the patient a randomization number based on the next sequential randomization number on the site randomization list." STOP-IT: "The randomization will be performed with equal allocation between treatment arms. Neither the treating physicians nor the patients will know to which treatment arm the patient is randomized."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	SPOTLIGHT: "The unblinded dispensing team will prepare the corresponding product (NiaStase RT or saline) in a blinded syringe ready for dosing (out of sight of the patient, investigator, and any other members of the blinded study team)." STOP-IT: "At each site, a designated unblinded individual (pharmacist, blood bank technician, or nurse not involved in patient enrollment or follow-up) prepared the study drug in a blinded syringe ready for injection (out of sight of the patient, investigators, and members of the blinded study team). Both saline

Gladstone 2019 – SPOTLIGHT – STOP-IT *(Continued)*

		and reconstituted rFVIIa are clear, colorless solutions identical in appearance and texture."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	SPOTLIGHT: we were unable to find a specification as to how the outcome assessment was blinded. STOP-IT: stated that the assessment of radiographic outcomes were blinded, but we could not find a specification on this was achieved.
Incomplete outcome data (attrition bias) All outcomes	High risk	SPOTLIGHT and STOP-IT: 64/70 participants had outcomes reported.
Selective reporting (reporting bias)	High risk	SPOTLIGHT: many outcomes were listed in the protocol. In the publication, mainly the primary radiographic and thromboembolic outcomes were listed. Some clinical outcomes were listed in the supplementary appendix. STOP-IT: in the publication, mainly the primary radiographic and thromboembolic outcomes were listed. Some clinical outcomes were listed in the supplementary appendix.

Imberti 2012 – PRESICH

Study characteristics	
Methods	Randomised (2:1), open-label, single-blind parallel group phase II pilot trial involving 21 participants with spontaneous supratentorial ICH diagnosed by CT
Participants	Inclusion criteria • Aged 18–75 years 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, New Jersey, USA). Blood pressure was measured continuously, and data were collected every 1–2 h. Attempted to maintain the mean arterial blood pressure at 90–130 mmHg, $PaCO_2$ within 35–40 mmHg, natraemia 137–147 mmol/L, and to obtain normoglycaemia (80–110 mg/dL) Intervention: rFVIIa 100 µg/kg (NovoSeven, Novo Nordisk, Denmark) by intravenous infusion in 5–10 min immediately after evacuation of haematoma, at beginning of closure of the dura Comparator: sodium chloride solution by intravenous infusion in 5–10 min immediately after evacuation of the haematoma, at beginning of closure of the dura
Outcomes	• Haematoma volume assessed by CT scan immediately, 18–30 h, and 5–7 days after evacuation of haematoma. Evaluated at 6 months using mRS; poor outcome defined as death or mRS score 4–5, and good outcome defined as mRS score 0–3
Notes	NCT00128050 PRE-SICH trial

Imberti 2012 – PRESICH *(Continued)*

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	Stated trial was both open label and placebo controlled in the methods, but that 'saline' was the comparator. Appeared to be 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 HE, 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

Study characteristics	
Methods	Single-centre RCT
Participants	Inclusion criteria • ICH • Within 6 h of onset • Age ≥ 18 years • Able to perform CT scan 24 h post-treatment Exclusion criteria • Secondary haemorrhage, i.e. tumour, AVM, anticoagulant-associated • Surgery within 24 h • Admission GCS 3–5 • 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 0.6 g/L, within 6 h of ICH onset, injected over 2–5 min Comparator: routine or best medical treatment All participants received piracetam 8 g intravenously 4 times/day

Li 2012 *(Continued)*

Outcomes	• ICH expansion • 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.

Liu 2021 – TRAIGE

Study characteristics

Methods	Randomised, double-blind, placebo-controlled study
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 • Aged 18–79 years • Randomisation can be finished and treatment can commence within 8 h of symptom onset • Informed consent 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

Liu 2021 – TRAIGE *(Continued)*

- GCS total score < 8
- ICH volume > 70 mL
- Parenchymal haemorrhage with ventricle involved, blood completely fills 1 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)
- History or current evidence suggestive of venous or arterial thrombotic events within 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 > 2

Interventions	Interventions: tranexamic acid 1 g in 100 mL 0.9% sodium chloride over 10 min followed by 1 g in 250 mL 0.9% sodium chloride infusion over 8 h Comparator: 100 mL 0.9% sodium chloride over 10 min, followed by 250 mL 0.9% sodium chloride infusion over 8 h
Outcomes	Primary outcomes • Haemorrhage expansion (time frame: 24 ± 2 h) either > 33%, or > 6 mL increase from baseline, adjusted for baseline ICH volume Secondary outcome • Major thromboembolic events (time frame: 30 ± 4 days; acute MI, acute cerebral ischaemia, acute PE) • Poor clinical outcome (time frame: 90 ± 7 days): number of participants who died or had major disability (mRS 4–6) • Short-term outcome: the number of participants with mRS 0–2 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 participants who died due to any cause by 90 ± 7 days
Notes	NCT02625948 Original sample size estimation of 240 participants. The sample size was readjusted (protocol amendment) to 188 participants. Unclear why the sample size was readjusted. The final included number of participants was 171.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to receive either placebo (0.9% NaCl) or tranexamic acid (1:1) using a computer generated procedure with randomly permuted blocks of varying size."
Allocation concealment (selection bias)	Low risk	Quote: "The treatment number was allocated using a centralised treatment allocation system at the baseline visit."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Treatment allocation was concealed from all patients and investigators involved in the trial."

Liu 2021 – TRAIGE *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear report how they blinded the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	171/171 CT scans for primary outcome. Few participants were lost to follow-up: 3 in tranexamic acid group and 2 in placebo group out of 171 (3%). Loss to follow-up was balanced between groups.
Selective reporting (reporting bias)	Low risk	They reported the outcome measured specified in the methods section and in the protocol article.

Mayer 2005a

Study characteristics	
Methods	Parallel group, randomised, placebo-controlled, phase II dose-escalation study
Participants	Inclusion criteria • Aged ≥ 18 years • Spontaneous ICH within 3 h of onset with no obvious secondary cause Exclusion criteria • GCS 3–5 • Surgical ICH evacuation planned within 24 h • mRS > 2 pre-ICH • Allergy to trial product • Participation in another RCT
Interventions	Intervention: rFVIIa (NovoSeven) at doses of 10 µg/kg, 20 µg/kg, 40 µg/kg, 80 µg/kg, 120 µg/kg, or 160 µg/kg, within 1 h of baseline CT Comparator: placebo, within 1 h of baseline CT
Outcomes	• Adverse events at days 1–5, 15 (or hospital discharge), and 90 • Change in ICH ± IVH volume on CT between baseline and 24 h • ICH expansion (> 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 95–100, GOS-E 8, mRS 0–2), versus alive and functionally independent (BI 60–100, GOS-E 5–8, mRS 0–3) at day 90
Notes	There was imbalance in the baseline ICH volumes between placebo and treatment groups (increasing with higher rFVIIa doses), although the authors stated that this was not statistically significant. The trial drug was given to 2/47 participants > 4 h after ICH onset. Trial was funded by Novo Nordisk.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified.

Mayer 2005a *(Continued)*

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	Assessment of outcomes was not explicitly stated to be blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear.
Selective reporting (reporting bias)	Unclear risk	Unclear.

Mayer 2005b

Study characteristics	
Methods	Parallel group, randomised, placebo-controlled, phase IIB, dose-ranging, proof-of-concept study
Participants	Inclusion criteria • Aged ≥ 18 years • Spontaneous ICH • Within 3 h of onset Exclusion criteria • GCS 3–5 • Surgical ICH evacuation planned within 24 h • Known underlying cause of ICH • On oral anticoagulants • Known thrombocytopenia • 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: rFVIIa (NovoSeven) at doses of 40 µg/kg, 80 µg/kg, or 160 µg/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 4–6, or GOS-E 1–4 at 90 days • Adverse events in hospital • SAEs until day 90

Mayer 2005b *(Continued)*

Notes	1 important exclusion criterion was changed mid-way through the RCT. 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)	Low risk	Randomisation performed in blocks of 4 participants by means of sequentially numbered, identical-appearing containers.
Allocation concealment (selection bias)	Low risk	Randomisation performed in blocks of 4 participants by means of sequentially numbered, identical-appearing containers.
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 laboratory outcomes blinding unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appeared complete.
Selective reporting (reporting bias)	Low risk	Appeared complete.

Mayer 2006

Study characteristics

Methods	Parallel group, randomised, double-blind, placebo-controlled, phase II: a dose escalation safety study
Participants	Inclusion criteria • Aged ≥ 18 years • Spontaneous ICH within 3 h of onset Exclusion criteria • GCS 3–5 • 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

Mayer 2006 *(Continued)*

Interventions	Intervention: rFVIIa (NovoSeven) at doses of 5 µg/kg, 20 µg/kg, 40 µg/kg, or 80 µg/kg, within 4 h of ICH onset Comparator: placebo, within 4 h of ICH onset
Outcomes	• SAEs • Coagulation parameters • Perihaematomal oedema • ICH volume ratio on CT • Change in ICH volume from baseline on CT • Change in neurological scores
Notes	Trial was funded by Novo Nordisk.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment 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 randomisation. Otherwise, completeness of follow-up was not mentioned.
Selective reporting (reporting bias)	Low risk	All stated outcomes were reported.

Mayer 2008 – FAST

Study characteristics

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 (≥ 20 years in Taiwan) • Informed consent Exclusion criteria • Time of ICH onset unknown, or > 3 h

Mayer 2008 – FAST *(Continued)*

- People with secondary ICH
- Surgical haematoma evacuation planned within 24 h of symptom onset
- GCS 3–5
- Known oral anticoagulant use (unless INR was documented < 1.4)
- Known thrombocytopenia (unless current platelets documented > 50,000/mL)
- Pre-existing disability (mRS 3–5)
- 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 entry into this trial
- People known or suspected of not being able to comply with trial protocol (e.g. due to alcoholism, drug dependency, or psychological disorder)

Interventions	Intervention: rFVIIa (NovoSeven) at doses of 20 µg/kg or 80 µg/kg, within 1 h of baseline CT and no later than 4 h after ICH onset Comparator: placebo
Outcomes	Primary endpoint • Poor outcome, defined as death or severe disability (mRS score 5–6) at day 90. Analysis claimed to be intention-to-treat, but it did not appear to be Secondary 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 0–1) 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 • Occurrence of adverse events until hospital discharge, or until day 90, whichever came first • SAEs until the 'End of trial' form was completed
Notes	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 µg/kg dose group than the other 2 groups) was due to the fact that the 80 µg/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

Mayer 2008 – FAST *(Continued)*

		have unblinded investigators, in view of the preponderance of thromboembolic adverse events with the higher dose).
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	EuroQol and Hamilton depression score not reported.

Meretoja 2020 – STOP-AUST

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled trial
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 • Aged ≥ 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 with 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) • 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

Meretoja 2020 – STOP-AUST *(Continued)*

- 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, FFP, 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 judgement 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 sodium chloride over 10 min followed by 1000 mg in 500 mL 0.9% normal sodium chloride infusion over 8 h Comparator: intravenous placebo in 100 mL 0.9% normal sodium chloride over 10 min followed by 500 mL 0.9% normal sodium chloride infusion over 8 h
Outcomes	Primary outcome measures • ICH expansion 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 expansion volume by 24 ± 3 h, adjusted for baseline ICH volume • Absolute IVH expansion volume by 24 ± 3 h, adjusted for baseline IVH volume • mRS score 0–4 at 3 months • mRS score 0–3 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
Notes	NCT01702636 Sample size estimation of 100 participants was reached.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to receive either placebo or tranexamic acid (1:1) using a centralised web-based procedure with randomly permuted blocks of varying size."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned to receive either placebo or tranexamic acid (1:1) using a centralised web-based procedure with randomly permuted blocks of varying size."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients and all those involved in patient management or clinical or imaging assessment of adverse events or outcomes were masked to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients and all those involved in patient management or clinical or imaging assessment of adverse events or outcomes were masked to treatment allocation."

Meretoja 2020 – STOP-AUST *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported primary outcome in all participants and had the reasons for death for all participants.
Selective reporting (reporting bias)	Low risk	The outcome measures reported were the ones mentioned as outcomes in the methods section and in the protocol article.

Ni 2020

Study characteristics	
Methods	Randomised, placebo-controlled study
Participants	Inclusion criteria • Time from onset within 8 h • Aged 40–75 years • ICH confirmed by CT or MRI • GCS ≥ 5, midline shift ≤ 1 cm, haematoma volume 10–30 mL Exclusion criteria • Cerebral haemorrhage due to anticoagulant, thrombolysis, injury, tumour, infection, or other potential structural anomalies • Evidence of thrombosis event within 12 months • Hereditary or acquired blood diseases • Using heparin, low-molecular weight heparin, tirofiban, or other anticoagulant within 2 weeks • Pregnancy • Expected having surgery within 24 h • Using or plan to use haemostatic agent, including prothrombin complex, vitamin K, plasma, platelet, etc. • Contraindication to tranexamic acid • Severe liver or kidney disease • Life expectancy < 3 months
Interventions	Interventions: tranexamic acid 1 g injection, dissolved in 100 mL normal sodium chloride, intravenous injection for 10 min; then tranexamic acid 1 g, dissolved in 250 mL normal sodium chloride, intravenous drip for 8 h Comparator: same dose of sodium chloride
Outcomes	Primary outcome • mRS at 90 day (0–2 = good outcome) Secondary outcome • Haematoma enlargement (24 h baseline > 6 mL or enlarge by 33%) • NIHSS at day 7 and 30 Secondary safety outcomes • Platelets and fibrinogen 4 h after end of intervention • Other SAEs, e.g. death, VTE, ischaemic event (cerebral infarction, TIA, MI, acute coronary syndrome, peripheral artery disease) and seizure

Ni 2020 *(Continued)*

Notes	Trial was not reported in detail, did not follow CONSORT guideline point by point. It is single-centre, non-registered, without providing protocol or SAP before publication. In the discussion, it is written that the study might be underpowered due to small sample size. However, no sample size calculation, no statistical analysis plan, no protocol was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described. Quote: "Patients were randomised by random number table." Just 1 sentence for the randomisation method.
Allocation concealment (selection bias)	Unclear risk	Not described. Quote: "Patients were randomised by random number table." Just 1 sentence for the randomisation method.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described for most of the outcomes. Only total number included in the analysis for death at 90 days, good outcome at 90 days, and haematoma enlargement at 24 h can be calculated by numbers of outcomes and their proportion.
Selective reporting (reporting bias)	Unclear risk	Not described, because this trial was not registered and protocol was not provided.

Polymeris 2023 – TICH-NOAC

Study characteristics

Methods	Randomised, double-blind, placebo-controlled study
Participants	Inclusion criteria • Acute ICH (symptom onset < 12 h) • Prior treatment with a novel DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban; last intake < 48 h or confirmed NOAC activity by relevant coagulation assays) • Age > 18 years, no upper age limit • Informed consent received in accordance with local ethics committee requirements Exclusion criteria • Severe premorbid disability (mRS > 4) • Anticoagulation with VKAs (recent intake)

Polymeris 2023 – TICH-NOAC *(Continued)*

	• 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 was already known, these people should not have been recruited. • GCS < 5 • Pregnancy • Planned neurosurgical haematoma evacuation within 24 h (before follow-up imaging) • PE or DVT within last 2 weeks
Interventions	Intervention: intravenous tranexamic acid 1 g loading dose given as 100 mL infusion over 10 min, followed by another 1 g in 250 mL infused over 8 h Comparator: placebo: 0.9% sodium chloride given in identical dosage regimen
Outcomes	Primary outcome • HE 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 outcomes • mRS 0–4 at month 3 • mRS 0–3 at month 3 • Categorical shift in mRS at month 3 • Mortality due to any cause at month 3 • In-hospital mortality from baseline to discharge from hospital – hospital stays lasted, on average, 10 days • Absolute ICH expansion 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)
Notes	NCT02866838 Unpublished manuscript provided by Dr Seiffge Sample size estimation was 109 participants. 63 participants were randomised and analysed. The trial was stopped early due to lack of funding. Trial reported 4 additional subgroups that were not prespecified: SBP (≤ 170 mmHg vs > 170 mmHg), treatment with 4fPCC (yes vs no), small vessel disease burden score (0–1 vs 2–3) and ANNEXa-I eligibility (ineligible vs eligible). The authors have not made a conclusion of the study based on that significant finding. All participants who were randomised to this trial were also given PCC as standard of care in treatment of DOAC-associated ICH

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly allocated to receive either tranexamic acid or matching placebo in a 1:1 ratio via a centralised, web-based, secure procedure, with minimisation for key prognostic factors."
Allocation concealment (selection bias)	Low risk	Quote: "To avoid predictable alternation of treatment allocation, and thus potential loss of allocation concealment, participants were allocated with a probability of 80% to the treatment group that would minimise be-

Polymeris 2023 – TICH-NOAC *(Continued)*

		tween-group imbalances of the minimisation factors. The randomisation sequence was generated by the Clinical Trial Unit Basel."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants, investigators involved in study assessments and independent physicians involved in patient management were all masked to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants, investigators involved in study assessments and independent physicians involved in patient management were all masked to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All participants had complete 90-day follow-up and allocation masking was not broken in any participant."
Selective reporting (reporting bias)	Low risk	All the prespecified outcomes are reported.

Sprigg 2014 – TICH-1

Study characteristics	
Methods	Single-centre, prospective, randomised (2:1), double-blind, placebo-controlled endpoint trial
Participants	Adults with acute (< 24 h after ictus) spontaneous ICH were identified and enroled from the stroke service at Nottingham University Hospital NHS Trust (UK) Principal exclusion criteria • Secondary ICH (anticoagulation, known vascular malformations) • Previous venous thromboembolic disease • Recent (< 12 months) ischaemic events (ischaemic stroke, MI, peripheral arterial disease) • Renal impairment (estimated glomerular filtration rate < 50 mmol) • Pregnancy or breastfeeding
Interventions	Intervention: intravenous tranexamic acid (Cyklokapron; Pharmacia Limited, Kent, UK) 1 g loading dose infusion for 10 min followed by a 1 g infusion for 8 h Comparator: matching placebo (0.9% sodium chloride) administered by identical regimen
Outcomes	Primary outcome • Trial feasibility (surrogate for trial acceptability: number of participants screened who were eligible for enrolment and who gave informed consent) Secondary outcomes • 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, peripheral arterial disease, 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
Notes	Dr N Sprigg provided information for assessment of risk of bias.
Risk of bias	

Sprigg 2014 – TICH-1 *(Continued)*

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 that participants and trial staff were 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.

Sprigg 2018 – TICH-2

Study characteristics	
Methods	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 did not need to be excluded before enrolment, but where known, patients should not have been recruited • Contraindication to tranexamic acid • Premorbid dependency (mRS > 4) • Concurrent participation in another drug or device trial. Participants enroled in TICH-2 may be enroled 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 min, followed by another 1 g in 250 mL infused over 8 h Comparator: matching placebo (normal sodium chloride 0.9%) administered by identical regimen
Outcomes	Primary outcome

Sprigg 2018 – TICH-2 *(Continued)*

- Death or dependency (ordinal shift on mRS) at day 90 analysed by intention-to-treat using ordinal logistic regression, with adjustment for minimisation factors. Assumption of proportional odds tested using the likelihood ratio test

Secondary outcomes

- 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, SAEs, thromboembolic events, seizures
- Costs: length of hospital stay, re-admission, institutionalisation
- Radiology (CT scan): change in haematoma volume from baseline to 24 h, haematoma location, and new infarction

Notes	ISRCTN93732214

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done centrally in real time. A secure website was used to randomly assign all participants eligible for inclusion to receive tranexamic acid or matching placebo, with 1:1 allocation. The random allocation sequence was generated by the trial programmer."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation system allocated each participant a unique number corresponding to a treatment pack containing either tranexamic acid or placebo. Treatment allocation was concealed from all staff and patients involved in the trial."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Treatment allocation was concealed from all staff and patients involved in the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Central assessors, who were trained and certified in administration of the mRS and masked to treatment allocation, did the final follow-up at 90 days by telephone from the coordinating centre in each country. Central independent expert assessors, who were masked to treatment assignment, assessed CT scans for the location of the intracerebral haemorrhage using a web-based adjudication system."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The primary outcome of mRS at day 90 was assessed in 2307 (99%) of 2325 participants; nine (<1%) were lost to follow-up and nine (<1%) withdrew from their day 90 follow-up."
Selective reporting (reporting bias)	Low risk	The outcomes described in protocol were consistent with outcomes reported.

Steiner 2016 – INCH

Study characteristics

Methods	Parallel group, open label RCT. Randomisation 1:1
Participants	Inclusion criteria

Steiner 2016 – INCH *(Continued)*

- Aged ≥ 18 years with ICH (i.e. intracerebral or subdural) diagnosed by cerebral CT scanning within 12 h of the onset of symptoms or after they were last seen well
- Receiving VKA treatment
- INR at admission ≥ 2.0

Exclusion criteria

- Traumatic or secondary ICH (e.g. due to vascular malformations, transformation of cerebral infarction, cerebral venous thrombosis, tumour, haemophilia, or other coagulopathies)
- GCS ≤ 5
- Concurrent acute ischaemic events
- Congestive heart failure (to prevent cardiac decompensation by fluid overload in the FFP group)
- Thrombotic events within the past 30 days
- Liver failure (Child-Pugh score C)
- Moderate-to-severe premorbid disability (i.e. mRS score > 2)

Interventions	Interventions: intravenous FFP 20 mL/kg (after blood group typing or by using AB group plasma supplied by local transfusion units) Comparator: intravenous 4-factor PCC 30 IU/kg (Octaplex, Octapharma, Lachen, Switzerland) All participants received intravenous vitamin K 10 mg
Outcomes	Primary outcome • Anticoagulation reversal, measured as the proportion of participants with INR ≤ 1.2 at 3 h after start of treatment Secondary outcomes • Death and HE by day 90 after start of treatment • mRS score • NIHSS on day 15 (or discharge if earlier) • Day 90 mRS, BI, and EGOS-E by telephone interview • Quality of life at day 90, assessed using EQ-5D self-report questionnaire • Time until INR ≤ 1.2 • In an exploratory analysis, feasibility of application of the 2 reversal strategy treatments by measurement of time from onset to baseline cerebral CT, time from baseline cerebral CT to start of treatment, and duration of infusion • Adjusted difference in absolute change in haematoma volume and relative HE defined as ≥ 15% changes, at 3 h and 24 h • Relative HE of ≥ 33% with respect to baseline was also analysed because previous trials on spontaneous ICH had used this threshold. • Planimetric measuring procedures predefined in a specific imaging protocol and related to all subtypes of bleeding • Adverse events and SAEs recorded and assessed by investigators throughout trial until day 90 • Thromboembolic events of special interest (MI, ischaemic stroke, PE, and DVT) prespecified according to international recommendations
Notes	Trial funded by Octapharma. Original sample size estimation was 64 participants. Due to dropout rate, sample size was recalculated to 74 participants. 54 participants were randomised, of whom 42 had ICH. Sample size was powered to compare the effect on acute haemostasis and not designed for clinical endpoints. Trial stopped prematurely by competent authority due to a higher proportion of HE in the FFP group compared to the PCC group.

Steiner 2016 – INCH *(Continued)*

Supplementary data of participants with ICH was provided by Prof Steiner.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation sequence was implemented with a randomisation list computer generated at the Coordination Centre for Clinical Trials at Heidelberg University Hospital (Heidelberg, Germany)."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation list linked sequential numbers to treatment codes allocated at random in site-stratified blocks of varying length (four, six, eight, and ten, with a probability 0.25 each) using a customised R program. The person responsible for generation of the randomisation list was independent of all other trial procedures."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Masking of treatment was not possible because of the different appearance of the two products and study drug preparation at bedside."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The trial was observer masked for all laboratory data, including the primary endpoint, and for neuroradiological and clinical outcome assessments."
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% missing outcome data for death and dependency at 90 days.
Selective reporting (reporting bias)	Unclear risk	All mentioned outcomes were reported in the primary publication, but we were missing some of the outcomes for the ICH subpopulation.

Zazulia 2001 – ATICH

Study characteristics

Methods	Parallel group RCT
Participants	Inclusion criteria • Spontaneous non-traumatic supratentorial ICH (on brain CT) • Aged ≥ 18 years • Treatment started 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/μL • Undergoing haemodialysis • Treated with thrombolytic therapy in last 48 h • Known DVT, MI, or PE within the last 3 months

Zazulia 2001 – ATICH *(Continued)*

	• Acute MI on ECG • GCS < 5
Interventions	Intervention: aminocaproic acid intravenous bolus of 10 g over 5–10 min, followed by a continuous intravenous infusion of 50 g diluted in 478 mL 0.9% sodium chloride and infused at 30 mL/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 enroled.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low 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	Unclear 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; CNS: central nervous system; CT: computed tomography; CTA: computed tomography angiography; DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; ECG: electrocardiogram; FFP: fresh frozen plasma; GCS: Glasgow Coma Scale; OS-E: Extended Glasgow Outcome Scale; h: hour; HE: haematoma expansion; ICH: intracerebral haemorrhage; INR: international normalised ratio; IU: international units; IVH: intraventricular haemorrhage;

LAR: legally authorised representative; MI: myocardial infarction; min: minute; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NOAC: non-vitamin K antagonist oral anticoagulants; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PCC: prothrombin complex concentrate; PE: pulmonary embolism; PT-INR: prothrombin time-international normalised ratio; RCT: randomised controlled trial; REB: Research Ethics Board; rFVIIa: recombinant activated factor VII; SAE: serious adverse event; SAH: subarachnoid haemorrhage; SBP: systolic blood pressure; TICS (-M): (modified) Telephone Interview for Cognitive Status; TIA: transient ischaemic attack; VKA: vitamin K antagonist; VTE: venous thromboembolism; ZDS: Zung Depression Scale.

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.
Glad 2012 – NOR-ICH	The study was stopped due to lack of enrolment. According to Dr Glad, very few patients were included, and no results are available.
Kerebel 2013	This trial combined participants with either ICH or subdural haemorrhage, but did not report outcomes by ICH subtype. We requested data restricted to the group with ICH again for this review update, but did not receive them before review submission; we hope to include them in the next update.
Li 2016	The intervention (therapeutic regimen of activating blood circulation (TRABC)) did not appear to be haemostatic, according to a traditional Chinese medicine expert (sarah-price.co.uk/): Xing Nao Jing has 4 traditional Chinese medicinals (She Xiang, Yu Jin, Zhi Zi, and Bing Pian), traditionally used to revive unconscious patients.
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 prespecified 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.
NCT03388970	This study was excluded due to lack of enrolment, according to Dr Xian-jian, who has not yet indicated if any data were collected.
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 prespecified primary or secondary outcomes were collected.

ICH: intracerebral haemorrhage.

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

2018-002620-17 – Annexa-I

Study name	Annexa-I – a randomized clinical trial of andexanet alfa in acute intracranial hemorrhage in patients receiving an oral factor Xa inhibitor
Methods	RCT
Participants	Inclusion criteria

2018-002620-17 – Annexa-I *(Continued)*

- Written informed consent. Either the patient or his or her legally acceptable representative if permissible by local or regional laws and regulations has been adequately informed of the nature and risks of the study and has given written informed consent prior to screening
- Age ≥ 18 years at time of consent
- Acute intracranial bleeding episode, defined as an estimated blood volume of 0.5–60 mL acutely observed radiographically within the cerebrum. Patients may have extracerebral (e.g. subdural, subarachnoid, epidural) or extracranial (e.g. gastrointestinal, intraspinal) bleeding additionally, but the ICH must be considered the most clinically significant bleed at the time of enrolment
- Performance of a head CT or MRI scan demonstrating the intracranial bleeding within 2 h prior to randomisation (baseline scan maybe repeated only once to meet this criterion)
- Treatment with an oral fXa inhibitor (apixaban (last dose ≥ 2.5 mg), rivaroxaban (last dose ≥ 10 mg), edoxaban (last dose ≥ 30 mg), or enoxaparin (last dose ≥ 1 mg/kg)): ≤ 15 h prior to randomisation or > 15 h prior to randomisation or unknown time of last dose, only if
  - the local anti-fXa activity > 100 ng/mL (for direct fXa inhibitors (apixaban, rivaroxaban, or edoxaban) or > 0.5 IU/mL for enoxaparin), and
  - the local anti-fXa activity level is obtained within 2 h prior to consent
- Women of childbearing potential and men with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy for 30 days after the last dose of study drug
- Have a negative pregnancy test documented prior to enrolment (for women of childbearing potential)
- NIHSS score ≤ 35 at the time of consent

Exclusion criteria

- Planned surgery, including burr holes for haematoma drainage, within 12 h after randomisation. Minimally invasive surgery/procedures not directly related to the treatment of intracranial bleeding and that are not expected to significantly affect haematoma volume are allowed
- GCS < 7 at time of consent. If a patient is intubated or sedated (or both) at time of consent, they may be enroled if it can be documented that they were intubated/sedated for non-neurological reasons within 2 h prior to consent
- Anticipation that the baseline and follow-up brain scans will not be able to use the same imaging modalities (i.e. patients with a baseline CT scan should have a CT scan in follow-up; similarly for MRI)
- Expected survival < 1 month (not related to intracranial bleed)
- Recent history (within 2 weeks) of a diagnosed thromboembolism or clinically relevant symptoms of the following: VTE (e.g. DVT, PE, cerebral venous thrombosis), MI, disseminated intravascular coagulation, cerebral vascular accident, TIA, acute coronary syndrome, or arterial systemic embolism
- Acute decompensated heart failure or cardiogenic shock at time of randomisation
- Severe sepsis or septic shock at time of randomisation
- Pregnant or lactating
- Receipt of any of the following drugs or blood products within 7 days prior to consent
  - VKA (e.g. warfarin)
  - Dabigatran
  - PCC (e.g. Kcentra) or rfVIIa (e.g. NovoSeven), or anti-inhibitor coagulant complex (e.g. FEIBA), FFP, and whole blood
- Past use of andexanet (or planned use of commercial andexanet)
- Treatment with an investigational drug < 30 days prior to consent
- Any tumor-related bleeding
- Known hypersensitivity to any component of andexanet
- NIHSS score > 35 at time of consent

Interventions	Intervention: andexanet alfa 200 mg intravenously Comparator: usual care

2018-002620-17 – Annexa-I *(Continued)*

Outcomes	Primary outcomes • Effective haemostasis at 12 h postrandomisation as determined by the blinded endpoint adjudication committee, based on prespecified criteria • Anti-fXa activity at 12 h Secondary outcome • % change from baseline to nadir in anti-fXa activity during first 2 h postrandomisation.
Starting date	11 August 2020 (date of competent authority decision)
Contact information	European Clinical Trial Information, Alexion Europe SAS Clinicaltrials.eu@alexion.com
Notes	EUDRACT: 2018-002620-17 Registered as ongoing according to the clinicaltrialsregister.eu

Desborough 2020 – DASH

Study name	Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage (DASH)
Methods	Placebo-controlled, RCT
Participants	Inclusion criteria • Adults (≥ 18 years) • Confirmed ICH on imaging • < 24 h from onset of symptoms (or from when last seen free of stroke symptoms) • Prescribed and thought to be taking a daily oral antiplatelet drug in the preceding 7 days (cyclo-oxygenase inhibitors, phosphodiesterase inhibitors, or P2Y12 inhibitors) • Signed consent (or waiver of consent) Exclusion criteria • Aneurysmal SAH known at time of enrolment • Haemorrhage suspected to be due to transformation of ischaemic stroke • Haemorrhage known to be due to thrombolytic drug • Haemorrhage known to be due to venous thrombosis • Risk of fluid retention associated with desmopressin judged clinically significant by the attending physician (e.g. patients with pulmonary oedema or cardiac failure, or both) • Significant hypotension (SBP < 90 mmHg) • Known drug-eluting coronary artery stent in previous 3 months • Allergy to desmopressin • Pregnant or breastfeeding • Life expectancy < 4 h, or planned for palliative care only • GCS < 5, mRS > 4
Interventions	Intervention: desmopressin injection single dose 20 µg in 50 mL normal sodium chloride as intravenous injection infused over 20 min Comparator: normal sodium chloride single dose 50 mL as intravenous injection infused over 20 min

Desborough 2020 – DASH *(Continued)*

Outcomes	Primary outcomes • Number of eligible participants who received allocated treatment • Rate of eligible participants randomised • Proportion of eligible participants and randomised • Proportion of participants followed up at 90 days • Proportion of participants with full outcome data available, and reasons for non-availability • Proportion of eligible participants approached • Adherence to intervention Secondary outcomes • Death or dependency at 90 days • Number of participants dead or with SAE • Change in ICH volume at 24 h • Disability – BI • Quality of life – EuroQol • Cognition – telephone MMSE • Length of hospital stay • Discharge destination • Health Economic assessment (EQ-5D) • SAEs (including thromboembolic events) • Change in factor VIII, von Willebrand Factor antigen, and von Willebrand Factor activity
Starting date	1 April 2019
Contact information	Diane Havard: +44 1158231775; diane.havard@nottingham.ac.uk Nikola Sprigg: +44 1158231778; nikola.sprigg@nottingham.ac.uk
Notes	NCT03696121 The recruitment of participants has finished, but no results are yet available.

IRCT20191014045103N1

Study name	Effect of tranexamic acid on mortality and morbidity in spontaneously ICH patients
Methods	Double-blind, placebo-controlled RCT
Participants	Inclusion criteria • People with spontaneous ICH referred to emergency department of Arak Amiralmomenin Hospital in Arak • Both genders • No age limit Exclusion criteria • Patient is a candidate for surgery • History of documented cerebral venous thrombosis and venous thrombosis
Interventions	Interventions: tranexamic acid 1 g bolus in first 10 min and 1 g intravenous infusion in first 8 h

IRCT20191014045103N1 *(Continued)*

	Comparator: normal sodium chloride 1 g bolus in first 10 min and 1 g intravenous infusion in the first 8 h
Outcomes	Primary outcomes • Duration of hospitalisation • Evaluation of patient's clinical condition Secondary outcomes: not reported
Starting date	6 December 2019
Contact information	Omid Ezati: i.am.khodam.dg@gmail.com
Notes	IRCT20191014045103N1

Jiang 2020 – THE-ICH

Study name	Randomized, double-blind trial evaluating the effects of tranexamic acid on hematoma expansion and peri-hematomal edema in patients with spontaneous intracerebral hemorrhage within 4.5 h after symptom onset: the THE-ICH trial
Methods	Placebo-controlled RCT
Participants	Inclusion criteria • Aged > 18 years • ICH was documented by CT scanning within 4.5 h after symptom onset • GCS > 7 • No planned surgery Exclusion criteria • No identified secondary cause of ICH, including anticoagulation, thrombolysis, or known underlying structural abnormality such as AVM, aneurysm, tumour, or venous thrombosis. Patients with known structural abnormality should not be recruited. Otherwise, patients with an unknown structural abnormality should not be excluded before enrolment • Malignant tumour, participation in another interventional trial • Contraindication to tranexamic acid. No planned surgery • Premorbid dependency (mRS > 4) • Life expectancy < 3 months
Interventions	Intervention: intravenous tranexamic 1 g 10 min bolus followed by 1 g 8 h infusion within 4.5 h after symptom onset Comparator: intravenous sodium chloride 0.9% at the same time points as participants in the tranexamic acid group
Outcomes	Primary outcome • HE and PHE expansion rate at 24 h ± 3 h and 72 h ± 3 h after spontaneous ICH Secondary outcomes • Mortality and NIHSS on day 7 • Mortality and mRS on day 90 after spontaneous ICH

Jiang 2020 – THE-ICH *(Continued)*

Starting date	30 October 2019
Contact information	Jiang Chao: email chaojzzu@126.com zhangjiewen9900@126.com
Notes	ChiCTR1900027065 According to correspondence with Dr Chau the study is still recruiting.

Naidech 2022 – FASTEST

Study name	Recombinant factor VIIa (rFVIIa) for hemorrhagic stroke trial (FASTEST)
Methods	Randomised, placebo-controlled, double-blind, parallel group trial
Participants	Inclusion criteria • Adults aged 18–80 years • Spontaneous ICH confirmed on brain imaging (haematoma volume ≥ 2 mL and ≤ 60 mL, and intraventricular haematoma volume score ≤ 7) • Treatment within 2 h of symptom onset Exclusion criteria • GCS 3–7 • Secondary ICH related to known causes (e.g. trauma, aneurysm, AVM, oral anticoagulant use (VKA or novel oral anticoagulants) within the past 7 days, coagulopathy, etc.) • ICH volume < 2 mL or ≥ 60 mL • IVH score > 7 • Pre-existing disability (mRS > 2) • Symptomatic thrombotic or vaso-occlusive disease in past 90 days (e.g. cerebral infarction, MI, PE, DVT, or unstable angina) • Clinical or ECG evidence of ST elevation consistent with acute myocardial ischaemia • Brainstem location of haemorrhage (people with cerebellar haemorrhage may be enroled) • Refusal to participate in study by patient, legal representative, or family member • Known or suspected thrombocytopenia (unless current platelet count documented above 50,000/µL) • Unfractionated heparin use with abnormal partial thromboplastin time • Low-molecular weight heparin use within the previous 24 h • Recent (within 90 days) carotid endarterectomy or coronary or cerebrovascular angioplasty or stenting • 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 to the time of FASTEST enrolment • Planned withdrawal of care or comfort care measures • Patient known or suspected of not being able to comply with trial protocol (e.g. due to alcoholism, drug dependency, or psychological disorder) • Known or suspected allergy to trial medication(s), excipients, or related products • Contraindications to study medication • Previous participation in this trial (previously randomised)

Naidech 2022 – FASTEST *(Continued)*

	• Women of childbearing potential who are known to be pregnant or within 12 weeks' postpartum or lactating (or both) at time of enrolment
Interventions	Intervention: rFVIIa 80 µg/kg, maximum 10,000 µg administered intravenously over 2 min within 120 min of stroke onset Comparator: 0.9% sodium chloride given as intravenous injection over 2 min within 120 min of stroke onset
Outcomes	Primary outcome • mRS at 180 days, in ordinal distribution with the following steps: 0–2, 3, 4–6 Primary safety outcome • Rate of life-threatening thromboembolic complications within 4 days (acute MI, cerebral infarction, or PE) and mortality at 90 days Secondary outcomes • mRS at 180 days, utility-weighted • mRS at 180 days, score 0–2 • EQ-5D (quality of life scale) at 180 days • Change in the volume of ICH and ICH + IVH between baseline CT and 24-h CT • mRS at 90 days, in ordinal distribution • EQ-5D (quality of life scale) at 90 days • mRS at 90 days, in ordinal distribution
Starting date	3 December 2021
Contact information	Joseph Broderick: joseph.broderick@uc.edu Emily Stinson: stinsoey@ucmail.uc.edu
Notes	NCT03496883 Correspondence with Dr Broderick confirms that the study is ongoing and recruiting.

NCT00699621

Study name	Platelet transfusion in acute intracerebral haemorrhage
Methods	Randomised, placebo-controlled, open-label study
Participants	Inclusion criteria • Taking aspirin, clopidogrel, or a combination of aspirin and dipyridamole • Acute primary ICH • Age > 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

NCT00699621 *(Continued)*

	• 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 • HE within 24 h measured as increase in haematoma volume observed by head CT (time frame: 24 h) Secondary outcomes • 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 According to correspondence with Dr Huhtakangas, the database includes 140 participants. The analysis is in process, but final data are not available.

NCT02777424 – CLOT-CRANE

Study name	Prothrombin complex concentrate versus fresh frozen plasma to correct coagulation disorders in adult neurosurgical patients (CLOT-CRANE)
Methods	Prospective, randomised, multicentre study
Participants	Inclusion criteria • People with spontaneous ICH, traumatic ICH, or people requiring neurological surgery • Coagulation disorder defined by prothrombin time < 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

NCT02777424 – CLOT-CRANE *(Continued)*

	• Hypersensitivity to vitamin K
Interventions	Intervention: PCC single dose of PCC (25 U/kg equivalent factor IX) Comparator: FFP single dose of 15 mL/kg
Outcomes	Primary outcome • Proportion of participants with correction of prothrombin time (< 60% at end of treatment administration – a mean of 1 h)
Starting date	January 2016
Contact information	Laurence Salomon: Fondation Ophtalmologique Adolphe de Rothschild
Notes	NCT02777424 The study is listed as recruiting on ClinicalTrials.gov. We have tried to contact the study investigators, but have not yet received a reply on how many patients are recruited.

NCT03044184 – TRANSACT

Study name	Tranexamic acid for spontaneous acute cerebral hemorrhage trial (TRANSACT)
Methods	Randomised, double-blind, placebo-controlled trial
Participants	Inclusion criteria • People with CT evidence of supratentorial ICH • 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 ≤ 5 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 breastfeeding • History of allergy to tranexamic acid

NCT03044184 – TRANSACT *(Continued)*

Interventions	Intervention: standard management for people with spontaneous ICH according to 2015 AHA/ASA *Guidelines for the Management of Intracerebral Hemorrhage*. Tranexamic acid 1 g (diluted in 100 mL of normal sodium chloride 0.9%) intravenously infused over 10 min, within 3 h of symptom presentation, and tranexamic acid 1 g (diluted in 100 mL of normal sodium chloride 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*. 100 mL normal sodium chloride 0.9% intravenously infused over 10 min within 3 h of symptom presentation, and another 100 mL of normal sodium chloride 0.9% infused over 8 h
Outcomes	Primary outcome • ICH volume (by CT brain scan) at 6 h • ICH volume (by CT brain scan) at 24 h • ICH volume (by CT brain scan) at 1 week Secondary outcome • GOS-E (at 3 and 6 months after stroke) • mRS (at 3 and 6 months after stroke) • Stroke-specific quality of life scale (at 3 and 6 months after stroke) • 30-day 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 the haemorrhagic stroke
Starting date	1 April 2017
Contact information	Peter YM Woo: Neurosurgery, Kwong Wah Hospital
Notes	NCT03044184 According to principal investigator Dr Woo, the study is still recruiting patients, but the recruitment has been slow due to COVID-19.

NCT04742205

Study name	Effectiveness of intravenous tranexamic acid in primary cerebral hemorrhage for prevention of hematoma progression: protocol for a randomized, double blind placebo-controlled trial
Methods	Placebo-controlled RCT
Participants	Inclusion criteria • People presenting to the emergency department with symptoms of haemorrhagic stroke within 24 h from onset of symptoms or last seen well • People who had a follow-up Exclusion criteria • GCS < 9 after resuscitation (as this can lead to biasness; requires surgery) • Contraindication to tranexamic acid • Haemorrhagic stroke secondary to trauma

NCT04742205 *(Continued)*

	• Haemorrhage was caused by coagulopathy
Interventions	Intervention: tranexamic acid loading dose of trial (1 g of tranexamic acid in 10 mL) mixed in 100 mL sodium chloride 0.9% and given over 10 min. Maintenance dose of trial mixed in 500 mL sodium chloride 0.9% is given over 8 h Comparator: placebo (sodium chloride 0.9%)
Outcomes	Primary outcome • Radiological improvement (CT scan) from baseline to 48-h post-treatment scan Secondary outcomes • NIHSS at day 7 • BI at day 10, 90, and 180 • mRS at day 10, 90, and 180 • Modified Telephone Interview for Cognitive Status at day 10, 90, and 180 • Zung Depression Scale at days 10, 90, and 180
Starting date	February 2021
Contact information	Bibesh Pokhrel, MS: +9779849671672; bibeshpokharel@yahoo.com
Notes	NCT04742205 The study is ongoing and recruiting patients according to Dr Pokhrel. 50 participants have been included by 20 October 2022.

Pandian 2022 – INTRINSIC

Study name	Indian trial of tranexamic acid in spontaneous intracerebral haemorrhage – INTRINSIC
Methods	Multicentre, randomised, open-label, clinical trial
Participants	Inclusion criteria • Adults aged > 18 years presenting with non-traumatic ICH within 4.5 h of symptom onset or when 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 or due to known hereditary coagulation disorders. An underlying structural abnormality does not need to be excluded before enrolment, but where known, patients should not be recruited. • Known allergies to tranexamic acid • mRS score > 4 at time of enrolment • Concurrent participation in another drug or prestroke • Prestroke life expectancy < 3 months (e.g. advanced metastatic cancer) • GCS < 7 • ICH secondary to trauma • Pregnant or breastfeeding at randomisation • Geographical or other factors that prohibit follow-up at 90 days, e.g. no fixed address or telephone contact number, or overseas visitor • Planned surgery for ICH within 24 h

Pandian 2022 – INTRINSIC *(Continued)*

Interventions	Intervention: tranexamic acid 2 g intravenously in 100 mL of normal sodium chloride over 45 min Comparator: standard of care management as per the institutional practice.
Outcomes	Primary outcome • Death at day 7 Secondary outcomes • Radiological (CT scan): change in haematoma volume from baseline to 24 h scan, haematoma location, and new infarction • Neurological impairment (NIHSS) at day 7 (or discharge if sooner) • Dependency using the 7-level mRS at day 90 • Quality of life (EQ-5D) at days 90
Starting date	31 August 2022
Contact information	Dr Jeyaraj Pandian: jeyaraj.pandian@cmcludhiana.in Dr Deepti Arora: instructnetwork@gmail.com
Notes	According to Dr Arora study recruitment started on 31 August 2022 and, by 29 September 2022, 18 participants had been recruited.

Qi 2021 – TARGET

Study name	Effects of tranexamic acid for hyperacute intracerebral hemorrhage treatment: a multi-center randomized controlled trial – TARGET Trial
Methods	Placebo-controlled RCT
Participants	Inclusion criteria • Aged 18–75 years • Treatment can commence within 3 h of symptom onset in people with ICH • Baseline haematoma volume 5–30 mL • Hypertensive ICH and haematoma located in basal ganglia or thalamus • Rate of HE in acute stage (haematoma volume/time to first CT) > 5 mL/h; or any of the following signs: blend sign, black hole sign, CT hypodensity, island sign • If there is IVH, IVH volume < 1/2 of 1 lateral ventricle • Tranexamic acid can be used within 3 h after symptom onset and within 1 h following baseline CT scan • Written informed consent signed by the patient or their legal representative before study began Exclusion criteria • GCS score < 9 • Patients who have undergone or intend to undergo surgery within 24 h • ICH secondary to haemorrhagic transformation of ischaemic stroke, cerebral venous thrombosis, aneurysm, AVM, tumour, or anticoagulation therapy • Score of mRS before disease ≥ 2 • Life expectancy < 3 months • Contraindications to tranexamic acid use • Wake up stroke or stroke with unknown onset time

Qi 2021 – TARGET *(Continued)*

	• Pregnant or lactating women, or planning to become pregnant • Participation in any interventional study within 3 months or is participating in other clinical trials prior to the date of informed consent • Inability to understand or comply with study procedures or follow-up due to mental illness, cognitive, or emotional disorders • Patients considered unsuitable for this clinical trial by the investigator
Interventions	Intervention: loading dose of intravenous tranexamic acid 1 g in 100 mL 0.9% sodium chloride over 10 min, followed by infusion of 1 g in 250 mL 0.9% sodium chloride infusion over 8 h Comparator: placebo (0.9% sodium chloride) Participants in both arms will receive best standard therapy as per published American Heart Association Guidelines for ICH
Outcomes	Primary outcome • HE by 24 h as defined by either 33% or 6 mL increase from baseline, adjusted for baseline ICH volume Secondary outcomes • Absolute HE volume by 24 h, adjusted for baseline haematoma volume • IVH expansion by 24 h, adjusted for baseline IVH volume • mRS score at 3 months • Recurrence rate of stroke within 3 months • Death due to any cause by 3 months • mRS score at 6 months
Starting date	3 April 2021
Contact information	Qi Li, MD, PhD: +86 18523381983; qili_md@126.com
Notes	ChiCTR2100045022 According to Dr Qi Li, principal investigator, the trial is still recruiting. They have recruited 50 patients of a target of 200 per October 2022.

Sprigg 2022 – TICH-3

Study name	Tranexamic acid for very early bleeds in the brain – TICH 3
Methods	Placebo-controlled RCT
Participants	Inclusion criteria • Adults with ICH confirmed on brain imaging within 4.5 h of symptom onset Exclusion criteria • Indication for tranexamic acid • Patient known to be taking anticoagulation • GCS < 54 • Estimated haematoma volume > 60 mL • Palliative care

Sprigg 2022 – TICH-3 *(Continued)*

Interventions	Intervention: tranexamic acid loading dose of intravenous tranexamic acid 1 g in 100 mL 0.9% sodium chloride over 10 min, followed by infusion of 1 g in 250 mL 0.9% sodium chloride infusion over 8 h Comparator: 0.9% sodium chloride
Outcomes	Primary outcomes • Death at 7 days, measured by number of participants who have died by Day 7 Secondary outcomes • Disability measured by mRS at day 180 • VTE/ischaemic events/seizures measured by review of medical notes at day 7 • Quality of life measured by EQ-5D visual analogue score at day 180 • Cognition measured by AD-8 at day 180 • Health economics (use of antihypertensive medication, Do Not Resuscitate orders, admission to intensive care, neurosurgical intervention, hospital length of stay, and discharge disposition) measured by review of medical notes at day 180
Starting date	23 March 2022
Contact information	Dr Tiffany Hamilton: tiffany.hamilton@nottingham.ac.uk
Notes	According to correspondence with investigators, the study is ongoing and recruiting patients.

Yassi 2022 – STOP-MSU

Study name	STOP-MSU: stopping haemorrhage with tranexamic acid for hyperacute onset presentation including mobile stroke units
Methods	Prospective phase II randomised, double-blind, placebo-controlled investigator-driven trial. 2 arms with 1:1 randomisation to either intravenous tranexamic acid or placebo
Participants	Inclusion criteria • People presenting with an acute ICH • Age ≥ 18 years • Treatment can commence within 2 h of symptom onset (or in patients with unknown time of symptom onset, the time patient was last known to be well) • Consent can be obtained from participant or person responsible. When emergency treatment procedures have been followed the participant or person responsible will be asked for consent to continue in the study 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 • 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 • Hereditary or acquired haemorrhagic diathesis or coagulation factor deficiency

Yassi 2022 – STOP-MSU *(Continued)*

	• Use of heparin, low-molecular weight heparin, GPIIb/IIIa antagonist, or oral anticoagulation (e.g. warfarin, factor Xa inhibitor, thrombin inhibitor) within the previous 72 h • 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, FFP, 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 judgement 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: tranexamic acid intravenous 1000 mg in 100 mL 0.9% sodium chloride (or in 50 mL syringe with 0.9% sodium chloride) over 10 min followed by 1000 mg in 500 mL 0.9% sodium chloride infusion over 8 h Comparator: normal sodium chloride (0.9%) 100 mL (or in 50 mL syringe) intravenous 0.9% sodium chloride over 10 min followed by 500 mL intravenous 0.9% sodium chloride infusion over 8 h
Outcomes	Primary outcomes • HE by 24 ± 6 h as defined by either ≥ 33% or ≥ 6 mL increase from baseline ICH volume • Relative ICH HE Secondary outcomes • HE by 24 ± 6 h defined by ≥ 33% or ≥ 6 mL increase from baseline in intracerebral haematoma volume, or any increase intraventricular haematoma volume • ICH or IVH expansion at 24 ± 6 h from baseline • Absolute HE by 24 ± 6 h • ICH expansion as defined by either ≥ 33% or ≥ 6 mL increase from baseline, adjusted for baseline ICH volume • Relative haematoma expansion by 24 ± 6 h • Relative ICH expansion volume, adjusted for baseline ICH volume • Absolute IVH expansion by 24 ± 6 h • IVH expansion at 24 ± 6 h from baseline • Absolute intracerebral plus intraventricular haematoma expansion by 24 ± 6 h • ICH plus IVH expansion from baseline • Number of participants with mRS 0–3 or back to prestroke level at 3 months • mRS 0–3 or back to prestroke level at 3 months • Number of participants with mRS 0–4 or back to prestroke level at 3 months • mRS 0–4 or back to prestroke level at 3 months • Categorical shift in mRS at 3 months • mRS 0–4 or back to prestroke level, or mRS 0–3 or back to prestroke level • Major thromboembolic events (MI, ischaemic stroke, or PE) within 3 months • Death within 3 months • Death within 7 days
Starting date	19 March 2018
Contact information	Henry Zhao: +61 3 9342 7000 henry.zhao@mh.org.au Michele Sallaberger: 0438 471423; michele.sallaberger@florey.edu.au
Notes	NCT03385928 The study is ongoing and recruiting patients according to correspondence with study investigators.

AD-8: Eight-item Informant Interview to Differentiate Aging and Dementia; APTT: activated partial thromboplastin time; AVM: arteriovenous malformation; BI: Barthel Index; CT: computed tomography; CTA: computed tomography angiography; DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; ECG: electrocardiogram; FFP: fresh frozen plasma; GCS: Glasgow Coma Scale; GOS-E: Extended Glasgow Outcome Scale; h: hour; HE: haematoma expansion; ICH: intracerebral haemorrhage; INR: international normalised ratio; IVH: intraventricular haemorrhage; MI: myocardial infarction; MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NOAC: non-vitamin K antagonist oral anticoagulant; PCC: prothrombin complex concentrate; PE: pulmonary embolism; RCT: randomised controlled trial; rFVIIa: recombinant activated factor VII; SAE: serious adverse event; SAH: subarachnoid haemorrhage; SBP: systolic blood pressure; TIA: transient ischaemic attack; VKA: vitamin K antagonist; VTE: venous thromboembolism.

DATA AND ANALYSES

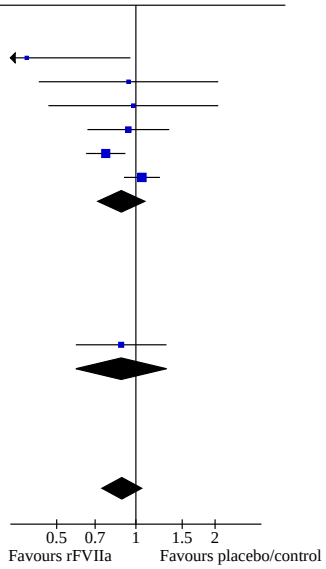
Comparison 1. Recombinant factor VIIa versus placebo or open control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death or dependence (mRS 4–6) at day 90	7	1454	Risk Ratio (IV, Random, 95% CI)	0.88 [0.74, 1.05]
1.1.1 Acute spontaneous ICH	6	1433	Risk Ratio (IV, Random, 95% CI)	0.88 [0.72, 1.08]
1.1.2 Acute spontaneous ICH undergoing craniotomy	1	21	Risk Ratio (IV, Random, 95% CI)	0.88 [0.59, 1.31]
1.2 Intracerebral haemorrhage expansion by 24 hours	4	220	Risk Ratio (IV, Random, 95% CI)	0.81 [0.56, 1.16]
1.2.1 Acute spontaneous ICH	4	220	Risk Ratio (IV, Random, 95% CI)	0.81 [0.56, 1.16]
1.3 All serious adverse events	2	87	Risk Ratio (IV, Random, 95% CI)	0.81 [0.30, 2.22]
1.3.1 Acute spontaneous ICH	2	87	Risk Ratio (IV, Random, 95% CI)	0.81 [0.30, 2.22]
1.4 Thromboembolic adverse events	6	1467	Risk Ratio (IV, Random, 95% CI)	1.18 [0.78, 1.79]
1.4.1 Acute spontaneous ICH	6	1467	Risk Ratio (IV, Random, 95% CI)	1.18 [0.78, 1.79]
1.5 Death from any cause by day 90	8	1544	Risk Ratio (IV, Random, 95% CI)	0.78 [0.56, 1.08]
1.5.1 Acute spontaneous ICH	7	1523	Risk Ratio (IV, Random, 95% CI)	0.75 [0.50, 1.12]
1.5.2 Acute spontaneous ICH undergoing craniotomy	1	21	Risk Ratio (IV, Random, 95% CI)	0.86 [0.41, 1.80]
1.6 Death or dependence (Extended Glasgow Outcome Scale (GOS-E) 1–4) at day 90	3	486	Risk Ratio (IV, Random, 95% CI)	0.90 [0.81, 1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6.1 Acute spontaneous ICH	3	486	Risk Ratio (IV, Random, 95% CI)	0.90 [0.81, 1.01]

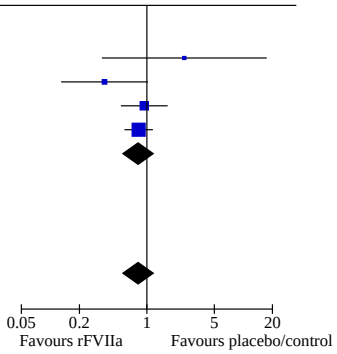
Analysis 1.1. Comparison 1: Recombinant factor VIIa versus placebo or open control, Outcome 1: Death or dependence (mRS 4–6) at day 90

Study or Subgroup	rFVIIa Events	rFVIIa Total	Placebo/open control Events	Placebo/open control Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Acute spontaneous ICH						
Li 2012	5	32	13	32	3.4%	0.38 [0.16 , 0.95]
Mayer 2006	15	32	4	8	4.4%	0.94 [0.43 , 2.06]
Mayer 2005a	16	36	5	11	4.8%	0.98 [0.46 , 2.06]
Gladstone 2019 – SPOTLIGHT – STOP-IT	19	30	23	34	14.9%	0.94 [0.65 , 1.34]
Mayer 2005b	160	303	66	96	29.0%	0.77 [0.65 , 0.91]
Mayer 2008 – FAST	269	557	120	262	30.4%	1.05 [0.90 , 1.23]
Subtotal (95% CI)		**990**		**443**	**86.9%**	**0.88 [0.72 , 1.08]**
Total events:	484		231			
Heterogeneity: Tau² = 0.03; Chi² = 10.63, df = 5 (P = 0.06); I² = 53%						
Test for overall effect: Z = 1.21 (P = 0.23)						
1.1.2 Acute spontaneous ICH undergoing craniotomy						
Imberti 2012 – PRESICH	10	13	7	8	13.1%	0.88 [0.59 , 1.31]
Subtotal (95% CI)		**13**		**8**	**13.1%**	**0.88 [0.59 , 1.31]**
Total events:	10		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**1003**		**451**	**100.0%**	**0.88 [0.74 , 1.05]**
Total events:	494		238			
Heterogeneity: Tau² = 0.02; Chi² = 10.65, df = 6 (P = 0.10); I² = 44%						
Test for overall effect: Z = 1.39 (P = 0.17)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



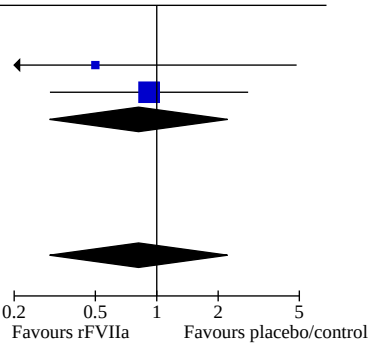
Analysis 1.2. Comparison 1: Recombinant factor VIIa versus placebo or open control, Outcome 2: Intracerebral haemorrhage expansion by 24 hours

Study or Subgroup	rFVIIa Events	rFVIIa Total	Placebo/open control Events	Placebo/open control Total	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 Acute spontaneous ICH						
Mayer 2005a	8	36	1	11	3.3%	2.44 [0.34 , 17.46]
Li 2012	4	32	11	32	11.0%	0.36 [0.13 , 1.02]
Gladstone 2019 – SPOTLIGHT – STOP-IT	13	32	16	37	30.3%	0.94 [0.54 , 1.64]
Mayer 2006	23	32	7	8	55.3%	0.82 [0.58 , 1.15]
Subtotal (95% CI)		**132**		**88**	**100.0%**	**0.81 [0.56 , 1.16]**
Total events:	48		35			
Heterogeneity: Tau² = 0.03; Chi² = 3.79, df = 3 (P = 0.29); I² = 21%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Total (95% CI)		**132**		**88**	**100.0%**	**0.81 [0.56 , 1.16]**
Total events:	48		35			
Heterogeneity: Tau² = 0.03; Chi² = 3.79, df = 3 (P = 0.29); I² = 21%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Not applicable						



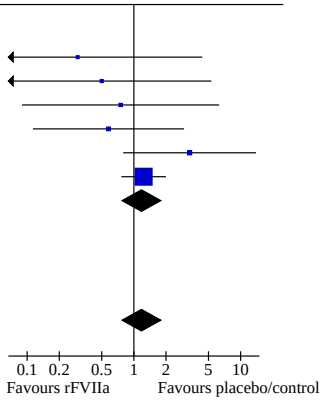
Analysis 1.3. Comparison 1: Recombinant factor VIIa versus placebo or open control, Outcome 3: All serious adverse events

Study or Subgroup	rFVIIa Events	rFVIIa Total	Placebo/open control Events	Placebo/open control Total	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 Acute spontaneous ICH						
Mayer 2006	2	32	1	8	19.5%	0.50 [0.05 , 4.85]
Mayer 2005a	9	36	3	11	80.5%	0.92 [0.30 , 2.81]
Subtotal (95% CI)		**68**		**19**	**100.0%**	**0.81 [0.30 , 2.22]**
Total events:	11		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.40 (P = 0.69)						
Total (95% CI)		**68**		**19**	**100.0%**	**0.81 [0.30 , 2.22]**
Total events:	11		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Not applicable						

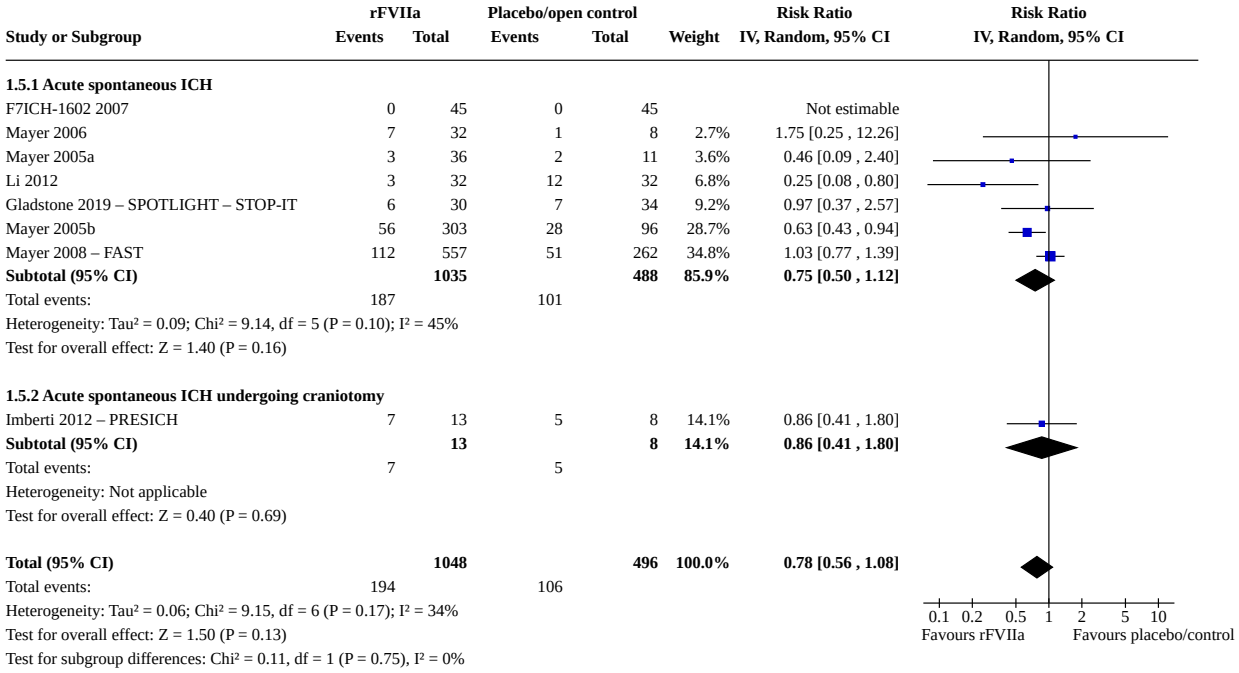


Analysis 1.4. Comparison 1: Recombinant factor VIIa versus placebo or open control, Outcome 4: Thromboembolic adverse events

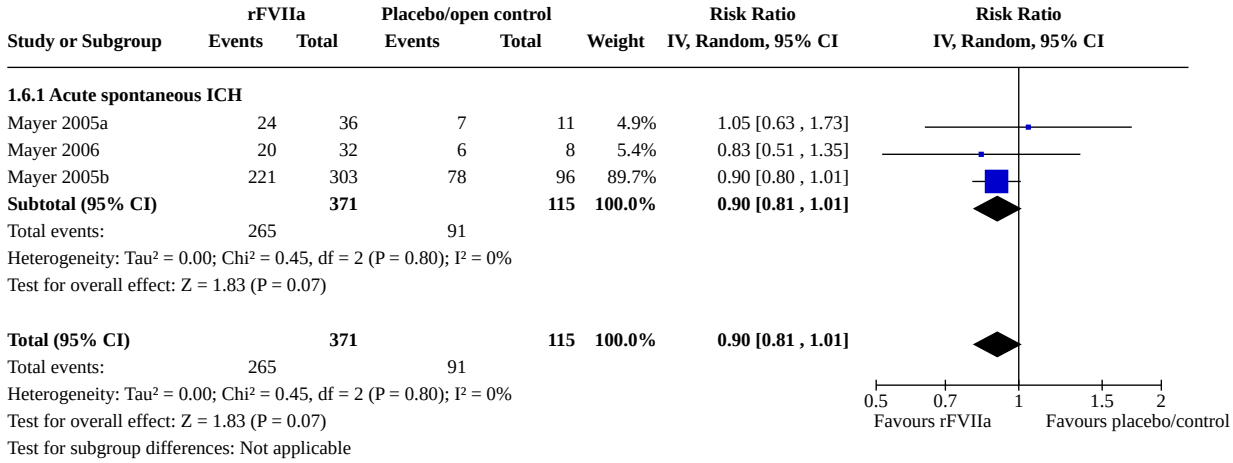
Study or Subgroup	rFVIIa Events	rFVIIa Total	Placebo/open control Events	Placebo/open control Total	Weight	Risk Ratio IV, Random, 95% CI
1.4.1 Acute spontaneous ICH						
Mayer 2005a	1	37	1	11	2.4%	0.30 [0.02 , 4.37]
F7ICH-1602 2007	1	45	2	45	3.1%	0.50 [0.05 , 5.32]
Mayer 2006	3	32	1	8	3.9%	0.75 [0.09 , 6.29]
Gladstone 2019 – SPOTLIGHT – STOP-IT	2	32	4	37	6.6%	0.58 [0.11 , 2.95]
Mayer 2005b	21	303	2	96	8.5%	3.33 [0.79 , 13.93]
Mayer 2008 – FAST	55	558	21	263	75.5%	1.23 [0.76 , 2.00]
Subtotal (95% CI)		**1007**		**460**	**100.0%**	**1.18 [0.78 , 1.79]**
Total events:	83		31			
Heterogeneity: Tau² = 0.00; Chi² = 4.47, df = 5 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Total (95% CI)		**1007**		**460**	**100.0%**	**1.18 [0.78 , 1.79]**
Total events:	83		31			
Heterogeneity: Tau² = 0.00; Chi² = 4.47, df = 5 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Test for subgroup differences: Not applicable						



Analysis 1.5. Comparison 1: Recombinant factor VIIa versus placebo or open control, Outcome 5: Death from any cause by day 90



Analysis 1.6. Comparison 1: Recombinant factor VIIa versus placebo or open control, Outcome 6: Death or dependence (Extended Glasgow Outcome Scale (GOS-E) 1–4) at day 90



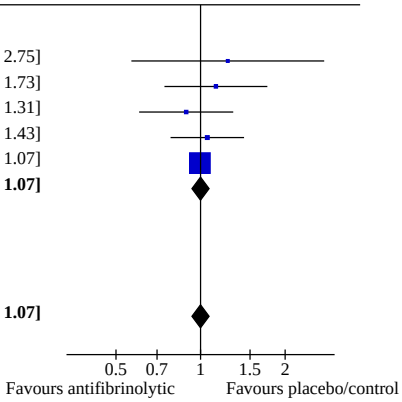
Comparison 2. Antifibrinolytic drugs versus placebo or open control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Death or dependence (mRS 4–6) at day 90	5	2683	Risk Ratio (IV, Random, 95% CI)	1.00 [0.93, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.1 Acute spontaneous ICH	5	2683	Risk Ratio (IV, Random, 95% CI)	1.00 [0.93, 1.07]
2.2 Intracerebral haemorrhage expansion by 24 hours	8	2866	Risk Ratio (IV, Random, 95% CI)	0.86 [0.76, 0.96]
2.2.1 Acute spontaneous ICH	8	2866	Risk Ratio (IV, Random, 95% CI)	0.86 [0.76, 0.96]
2.3 All serious adverse events	4	2599	Risk Ratio (IV, Random, 95% CI)	1.02 [0.75, 1.39]
2.3.1 Acute spontaneous ICH	4	2599	Risk Ratio (IV, Random, 95% CI)	1.02 [0.75, 1.39]
2.4 Thromboembolic adverse events	6	2833	Risk Ratio (IV, Random, 95% CI)	1.23 [0.88, 1.71]
2.4.1 Acute spontaneous ICH	6	2833	Risk Ratio (IV, Random, 95% CI)	1.23 [0.88, 1.71]
2.5 Death by day 90	8	2866	Risk Ratio (IV, Random, 95% CI)	1.02 [0.89, 1.18]
2.5.1 Acute spontaneous ICH	8	2866	Risk Ratio (IV, Random, 95% CI)	1.02 [0.89, 1.18]
2.6 Death by day 7	1	2325	Risk Ratio (IV, Random, 95% CI)	0.82 [0.64, 1.06]
2.7 Quality of life (EuroQoL health utility score)	2	2349	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.03, 0.03]
2.7.1 Acute spontaneous ICH	2	2349	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.03, 0.03]
2.8 Mood (Zung Depression Scale)	2	2349	Mean Difference (IV, Random, 95% CI)	0.30 [-1.98, 2.57]
2.9 Cognitive function (Modified Telephone Interview for Cognitive Status (TICS-M))	1	2325	Mean Difference (IV, Random, 95% CI)	-0.37 [-1.40, 0.66]
2.10 Cognitive function (Mini-Mental State Examination (MMSE))	1	24	Mean Difference (IV, Random, 95% CI)	2.70 [-0.10, 5.50]
2.11 Barthel Index	2	2349	Mean Difference (IV, Random, 95% CI)	-8.33 [-29.24, 12.58]
2.11.1 Acute spontaneous ICH	2	2349	Mean Difference (IV, Random, 95% CI)	-8.33 [-29.24, 12.58]

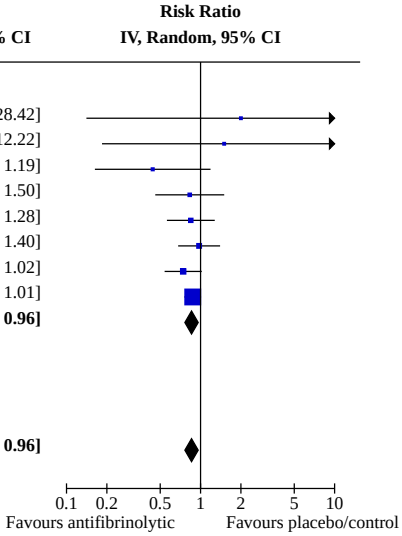
Analysis 2.1. Comparison 2: Antifibrinolytic drugs versus placebo or open control, Outcome 1: Death or dependence (mRS 4–6) at day 90

Study or Subgroup	Antifibrinolytic Events	Antifibrinolytic Total	Placebo/open control Events	Placebo/open control Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Acute spontaneous ICH						
Sprigg 2014 – TICH-1	10	16	4	8	0.8%	1.25 [0.57 , 2.75]
Liu 2021 – TRAIGE	32	89	26	82	2.8%	1.13 [0.74 , 1.73]
Meretoja 2020 – STOP-AUST	24	50	27	50	3.3%	0.89 [0.60 , 1.31]
Polymeris 2023 – TICH-NOAC	24	32	22	31	5.4%	1.06 [0.78 , 1.43]
Sprigg 2018 – TICH-2	627	1161	632	1164	87.7%	0.99 [0.92 , 1.07]
Subtotal (95% CI)		**1348**		**1335**	**100.0%**	**1.00 [0.93 , 1.07]**
Total events:	717		711			
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 4 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**1348**		**1335**	**100.0%**	**1.00 [0.93 , 1.07]**
Total events:	717		711			
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 4 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Test for subgroup differences: Not applicable						



Analysis 2.2. Comparison 2: Antifibrinolytic drugs versus placebo or open control, Outcome 2: Intracerebral haemorrhage expansion by 24 hours

Study or Subgroup	Antifibrinolytic Events	Antifibrinolytic Total	Placebo/open control Events	Placebo/open control Total	Weight	Risk Ratio IV, Random, 95% CI
2.2.1 Acute spontaneous ICH						
Zazulia 2001 – ATICH (1)	1	2	0	1	0.2%	2.00 [0.14 , 28.42]
Sprigg 2014 – TICH-1	3	16	1	8	0.3%	1.50 [0.18 , 12.22]
Ni 2020	5	73	12	77	1.3%	0.44 [0.16 , 1.19]
Polymeris 2023 – TICH-NOAC	12	32	14	31	3.7%	0.83 [0.46 , 1.50]
Meretoja 2020 – STOP-AUST	22	50	26	50	7.8%	0.85 [0.56 , 1.28]
Liu 2021 – TRAIGE	36	89	34	82	10.1%	0.98 [0.68 , 1.40]
Arumugam 2015	11	15	15	15	12.9%	0.74 [0.54 , 1.02]
Sprigg 2018 – TICH-2	265	1161	304	1164	63.7%	0.87 [0.76 , 1.01]
Subtotal (95% CI)		**1438**		**1428**	**100.0%**	**0.86 [0.76 , 0.96]**
Total events:	355		406			
Heterogeneity: Tau² = 0.00; Chi² = 3.77, df = 7 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.66 (P = 0.008)						
Total (95% CI)		**1438**		**1428**	**100.0%**	**0.86 [0.76 , 0.96]**
Total events:	355		406			
Heterogeneity: Tau² = 0.00; Chi² = 3.77, df = 7 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.66 (P = 0.008)						
Test for subgroup differences: Not applicable						

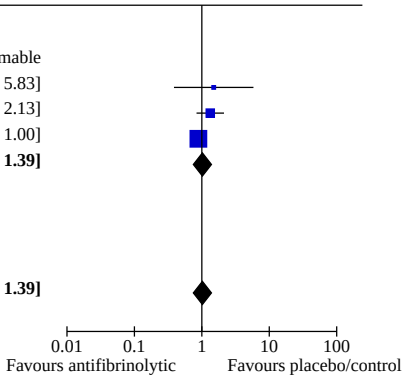


Footnotes

(1) Zazulia 2001 investigated aminocaproic acid, whereas all other RCTs in this analysis investigated tranexamic acid

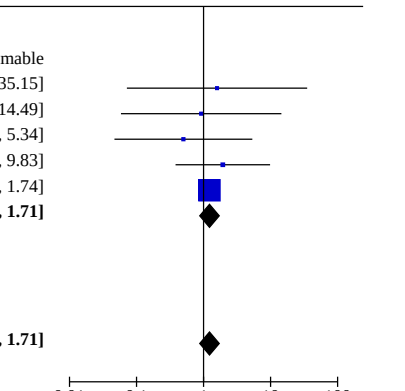
Analysis 2.3. Comparison 2: Antifibrinolytic drugs versus placebo or open control, Outcome 3: All serious adverse events

Study or Subgroup	Antifibrinolytic Events	Antifibrinolytic Total	Placebo/open control Events	Placebo/open control Total	Weight	Risk Ratio IV, Random, 95% CI
2.3.1 Acute spontaneous ICH						
Ni 2020	0	73	0	77		Not estimable
Sprigg 2014 – TICH-1	6	16	2	8	4.8%	1.50 [0.39 , 5.83]
Meretoja 2020 – STOP-AUST	24	50	18	50	27.5%	1.33 [0.83 , 2.13]
Sprigg 2018 – TICH-2	344	1161	388	1164	67.6%	0.89 [0.79 , 1.00]
Subtotal (95% CI)		**1300**		**1299**	**100.0%**	**1.02 [0.75 , 1.39]**
Total events:	374		408			
Heterogeneity: Tau² = 0.03; Chi² = 3.21, df = 2 (P = 0.20); I² = 38%						
Test for overall effect: Z = 0.12 (P = 0.90)						
Total (95% CI)		**1300**		**1299**	**100.0%**	**1.02 [0.75 , 1.39]**
Total events:	374		408			
Heterogeneity: Tau² = 0.03; Chi² = 3.21, df = 2 (P = 0.20); I² = 38%						
Test for overall effect: Z = 0.12 (P = 0.90)						
Test for subgroup differences: Not applicable						



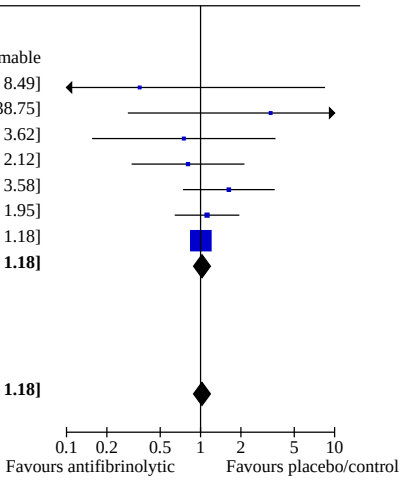
Analysis 2.4. Comparison 2: Antifibrinolytic drugs versus placebo or open control, Outcome 4: Thromboembolic adverse events

Study or Subgroup	Antifibrinolytic Events	Antifibrinolytic Total	Placebo/open control Events	Placebo/open control Total	Weight	Risk Ratio IV, Random, 95% CI
2.4.1 Acute spontaneous ICH						
Ni 2020	0	73	0	77		Not estimable
Sprigg 2014 – TICH-1	1	16	0	8	1.2%	1.59 [0.07 , 35.15]
Liu 2021 – TRAIGE	1	89	1	82	1.5%	0.92 [0.06 , 14.49]
Meretoja 2020 – STOP-AUST	1	50	2	50	2.0%	0.50 [0.05 , 5.34]
Polymeris 2023 – TICH-NOAC	4	32	2	31	4.2%	1.94 [0.38 , 9.83]
Sprigg 2018 – TICH-2	66	1161	54	1164	91.1%	1.23 [0.86 , 1.74]
Subtotal (95% CI)		**1421**		**1412**	**100.0%**	**1.23 [0.88 , 1.71]**
Total events:	73		59			
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 4 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.19 (P = 0.23)						
Total (95% CI)		**1421**		**1412**	**100.0%**	**1.23 [0.88 , 1.71]**
Total events:	73		59			
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 4 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.19 (P = 0.23)						
Test for subgroup differences: Not applicable						



Analysis 2.5. Comparison 2: Antifibrinolytic drugs versus placebo or open control, Outcome 5: Death by day 90

Study or Subgroup	Antifibrinolytic Events	Total	Placebo/open control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.5.1 Acute spontaneous ICH						
Arumugam 2015	0	15	0	15		Not estimable
Ni 2020	0	73	1	77	0.2%	0.35 [0.01 , 8.49]
Zazulia 2001 – ATICH (1)	2	2	0	1	0.3%	3.33 [0.29 , 38.75]
Sprigg 2014 – TICH-1	3	16	2	8	0.8%	0.75 [0.16 , 3.62]
Liu 2021 – TRAIGE	7	89	8	82	2.2%	0.81 [0.31 , 2.12]
Meretoja 2020 – STOP-AUST	13	50	8	50	3.4%	1.63 [0.74 , 3.58]
Polymeris 2023 – TICH-NOAC	15	32	13	31	6.8%	1.12 [0.64 , 1.95]
Sprigg 2018 – TICH-2	250	1161	249	1164	86.3%	1.01 [0.86 , 1.18]
Subtotal (95% CI)		**1438**		**1428**	**100.0%**	**1.02 [0.89 , 1.18]**
Total events:	290		281			
Heterogeneity: Tau² = 0.00; Chi² = 3.17, df = 6 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)		**1438**		**1428**	**100.0%**	**1.02 [0.89 , 1.18]**
Total events:	290		281			
Heterogeneity: Tau² = 0.00; Chi² = 3.17, df = 6 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Not applicable						

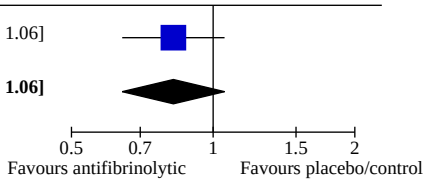


Footnotes

(1) Zazulia 2001 investigated aminocaproic acid, whereas all other RCTs in this analysis investigated tranexamic acid

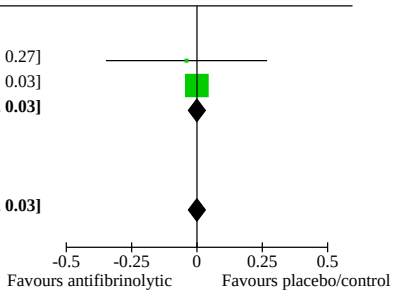
Analysis 2.6. Comparison 2: Antifibrinolytic drugs versus placebo or open control, Outcome 6: Death by day 7

Study or Subgroup	Antifibrinolytic Events	Total	Placebo/open control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Sprigg 2018 – TICH-2	101	1161	123	1164	100.0%	0.82 [0.64 , 1.06]
Total (95% CI)		**1161**		**1164**	**100.0%**	**0.82 [0.64 , 1.06]**
Total events:	101		123			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.52 (P = 0.13)						
Test for subgroup differences: Not applicable						



Analysis 2.7. Comparison 2: Antifibrinolytic drugs versus placebo or open control, Outcome 7: Quality of life (EuroQoL health utility score)

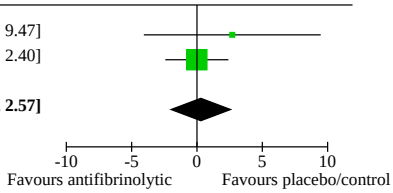
Study or Subgroup	Antifibrinolytic Mean	SD	Total	Placebo/open control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.7.1 Acute spontaneous ICH								
Sprigg 2014 – TICH-1	0.5	0.5	16	0.54	0.27	8	1.1%	-0.04 [-0.35 , 0.27]
Sprigg 2018 – TICH-2	0.34	0.4	1161	0.34	0.4	1164	98.9%	0.00 [-0.03 , 0.03]
Subtotal (95% CI)			**1177**			**1172**	**100.0%**	**-0.00 [-0.03 , 0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%								
Test for overall effect: Z = 0.03 (P = 0.98)								
Total (95% CI)			**1177**			**1172**	**100.0%**	**-0.00 [-0.03 , 0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%								
Test for overall effect: Z = 0.03 (P = 0.98)								
Test for subgroup differences: Not applicable								



Analysis 2.8. Comparison 2: Antifibrinolytic drugs versus placebo or open control, Outcome 8: Mood (Zung Depression Scale)

Study or Subgroup	Antifibrinolytic Mean	SD	Total	Placebo/open control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sprigg 2014 – TICH-1	21.3	12.6	16	18.6	4	8	11.3%	2.70 [-4.07 , 9.47]
Sprigg 2018 – TICH-2	67.28	29.5	1161	67.29	29.9	1164	88.7%	-0.01 [-2.42 , 2.40]
Total (95% CI)			**1177**			**1172**	**100.0%**	**0.30 [-1.98 , 2.57]**

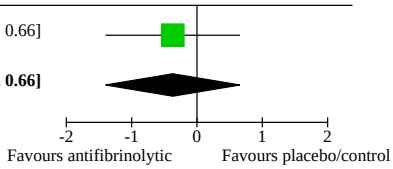
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)
Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2: Antifibrinolytic drugs versus placebo or open control, Outcome 9: Cognitive function (Modified Telephone Interview for Cognitive Status (TICS-M))

Study or Subgroup	Antifibrinolytic Mean	SD	Total	Placebo/open control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sprigg 2018 – TICH-2	13.57	12.5	1161	13.94	12.8	1164	100.0%	-0.37 [-1.40 , 0.66]
Total (95% CI)			**1161**			**1164**	**100.0%**	**-0.37 [-1.40 , 0.66]**

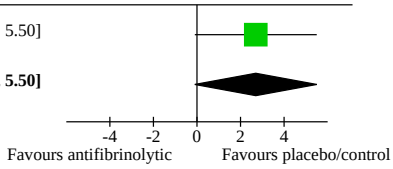
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 2.10. Comparison 2: Antifibrinolytic drugs versus placebo or open control, Outcome 10: Cognitive function (Mini-Mental State Examination (MMSE))

Study or Subgroup	Antifibrinolytic Mean	SD	Total	Placebo/open control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sprigg 2014 – TICH-1	21.3	0.8	16	18.6	4	8	100.0%	2.70 [-0.10 , 5.50]
Total (95% CI)			**16**			**8**	**100.0%**	**2.70 [-0.10 , 5.50]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable



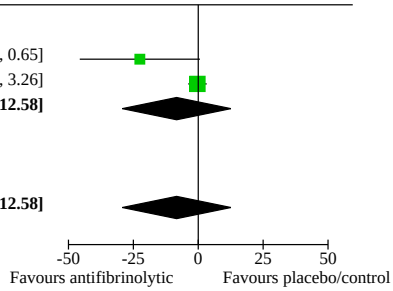
Analysis 2.11. Comparison 2: Antifibrinolytic drugs versus placebo or open control, Outcome 11: Barthel Index

Study or Subgroup	Antifibrinolytic Mean	SD	Total	Placebo/open control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.11.1 Acute spontaneous ICH								
Sprigg 2014 – TICH-1	59.2	39.7	16	81.7	18.1	8	36.2%	-22.50 [-45.65 , 0.65]
Sprigg 2018 – TICH-2	52.9	44	1161	53.2	43.7	1164	63.8%	-0.30 [-3.86 , 3.26]
Subtotal (95% CI)			**1177**			**1172**	**100.0%**	**-8.33 [-29.24 , 12.58]**

Heterogeneity: Tau² = 175.04; Chi² = 3.45, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 0.78 (P = 0.43)

Total (95% CI)			**1177**			**1172**	**100.0%**	**-8.33 [-29.24 , 12.58]**

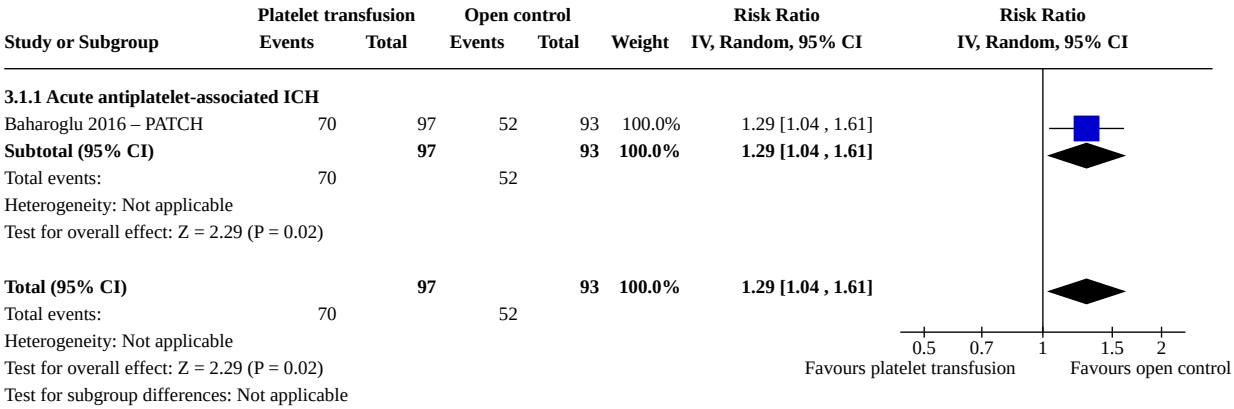
Heterogeneity: Tau² = 175.04; Chi² = 3.45, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 0.78 (P = 0.43)
Test for subgroup differences: Not applicable



Comparison 3. Platelet transfusion versus open control

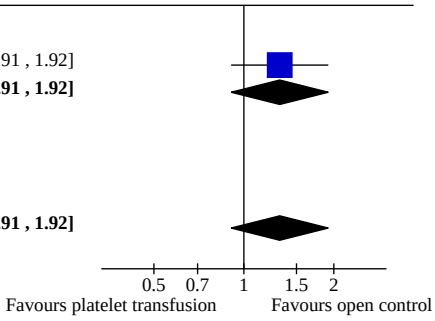
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Death or dependence (mRS 4–6) at day 90	1	190	Risk Ratio (IV, Random, 95% CI)	1.29 [1.04, 1.61]
3.1.1 Acute antiplatelet-associated ICH	1	190	Risk Ratio (IV, Random, 95% CI)	1.29 [1.04, 1.61]
3.2 Intracerebral haemorrhage expansion by 24 hours	1	153	Risk Ratio (IV, Random, 95% CI)	1.32 [0.91, 1.92]
3.2.1 Acute antiplatelet-associated ICH	1	153	Risk Ratio (IV, Random, 95% CI)	1.32 [0.91, 1.92]
3.3 All serious adverse events	1	190	Risk Ratio (IV, Random, 95% CI)	1.46 [0.98, 2.16]
3.3.1 Acute antiplatelet-associated ICH	1	190	Risk Ratio (IV, Random, 95% CI)	1.46 [0.98, 2.16]
3.4 Thromboembolic adverse events	1	190	Risk Ratio (IV, Random, 95% CI)	3.84 [0.44, 33.68]
3.4.1 Acute antiplatelet-associated ICH	1	190	Risk Ratio (IV, Random, 95% CI)	3.84 [0.44, 33.68]
3.5 Death by day 90	1	190	Risk Ratio (IV, Random, 95% CI)	1.42 [0.88, 2.28]
3.5.1 Acute antiplatelet-associated ICH	1	190	Risk Ratio (IV, Random, 95% CI)	1.42 [0.88, 2.28]

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



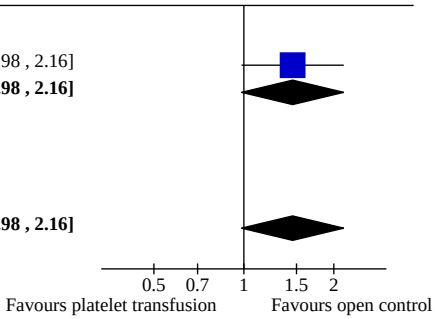
Analysis 3.2. Comparison 3: Platelet transfusion versus open control, Outcome 2: Intracerebral haemorrhage expansion by 24 hours

Study or Subgroup	Platelet transfusion Events	Total	Open control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.2.1 Acute antiplatelet-associated ICH						
Baharoglu 2016 – PATCH	39	80	27	73	100.0%	1.32 [0.91 , 1.92]
Subtotal (95% CI)		**80**		**73**	**100.0%**	**1.32 [0.91 , 1.92]**
Total events:	39		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
Total (95% CI)		**80**		**73**	**100.0%**	**1.32 [0.91 , 1.92]**
Total events:	39		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
Test for subgroup differences: Not applicable						



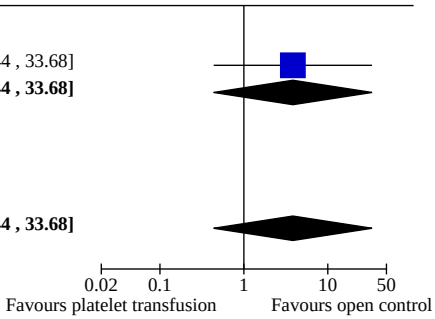
Analysis 3.3. Comparison 3: Platelet transfusion versus open control, Outcome 3: All serious adverse events

Study or Subgroup	Platelet transfusion Events	Total	Open control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.3.1 Acute antiplatelet-associated ICH						
Baharoglu 2016 – PATCH	41	97	27	93	100.0%	1.46 [0.98 , 2.16]
Subtotal (95% CI)		**97**		**93**	**100.0%**	**1.46 [0.98 , 2.16]**
Total events:	41		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.87 (P = 0.06)						
Total (95% CI)		**97**		**93**	**100.0%**	**1.46 [0.98 , 2.16]**
Total events:	41		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.87 (P = 0.06)						
Test for subgroup differences: Not applicable						



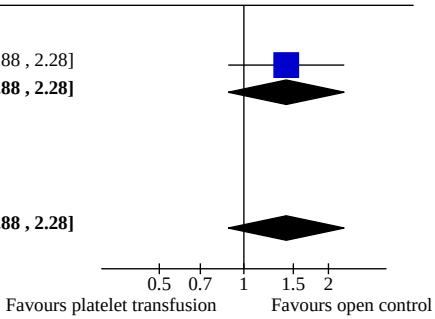
Analysis 3.4. Comparison 3: Platelet transfusion versus open control, Outcome 4: Thromboembolic adverse events

Study or Subgroup	Platelet transfusion Events	Total	Open control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.4.1 Acute antiplatelet-associated ICH						
Baharoglu 2016 – PATCH	4	97	1	93	100.0%	3.84 [0.44 , 33.68]
Subtotal (95% CI)		**97**		**93**	**100.0%**	**3.84 [0.44 , 33.68]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
Total (95% CI)		**97**		**93**	**100.0%**	**3.84 [0.44 , 33.68]**
Total events:	4		1			
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 versus open control, Outcome 5: Death by day 90

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

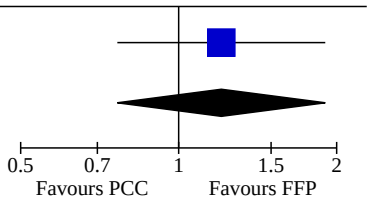


Comparison 4. Prothrombin complex concentrates versus fresh frozen plasma

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Death or dependence (mRS 4–6) at 90 days	1	37	Risk Ratio (IV, Random, 95% CI)	1.21 [0.76, 1.90]
4.2 Intracerebral haemorrhage expansion by 24 hours	1	36	Risk Ratio (IV, Random, 95% CI)	0.54 [0.23, 1.22]
4.3 All serious adverse events	1	5	Risk Ratio (IV, Random, 95% CI)	0.27 [0.02, 3.74]
4.3.1 Acute anticoagulant-associated ICH	1	5	Risk Ratio (IV, Random, 95% CI)	0.27 [0.02, 3.74]
4.4 Death by day 90	2	42	Risk Ratio (IV, Random, 95% CI)	0.49 [0.16, 1.56]
4.4.1 Acute anticoagulant-associated ICH	2	42	Risk Ratio (IV, Random, 95% CI)	0.49 [0.16, 1.56]

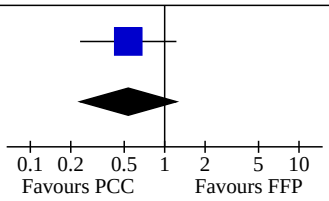
Analysis 4.1. Comparison 4: Prothrombin complex concentrates versus fresh frozen plasma, Outcome 1: Death or dependence (mRS 4–6) at 90 days

Study or Subgroup	PCC Events	Total	FFP Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Steiner 2016 – INCH	14	19	11	18	100.0%	1.21 [0.76 , 1.90]
Total (95% CI)		**19**		**18**	**100.0%**	**1.21 [0.76 , 1.90]**
Total events:	14		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
Test for subgroup differences: Not applicable						



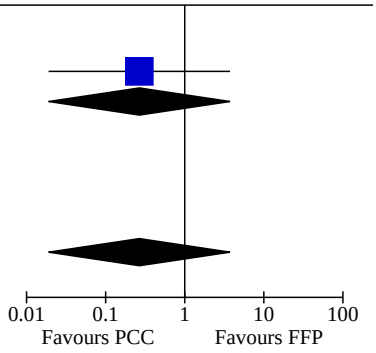
Analysis 4.2. Comparison 4: Prothrombin complex concentrates versus fresh frozen plasma, Outcome 2: Intracerebral haemorrhage expansion by 24 hours

Study or Subgroup	PCC Events	PCC Total	FFP Events	FFP Total	Weight	Risk Ratio IV, Random, 95% CI
Steiner 2016 – INCH	6	21	8	15	100.0%	0.54 [0.23 , 1.22]
Total (95% CI)		**21**		**15**	**100.0%**	**0.54 [0.23 , 1.22]**
Total events:	6		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Not applicable						



Analysis 4.3. Comparison 4: Prothrombin complex concentrates versus fresh frozen plasma, Outcome 3: All serious adverse events

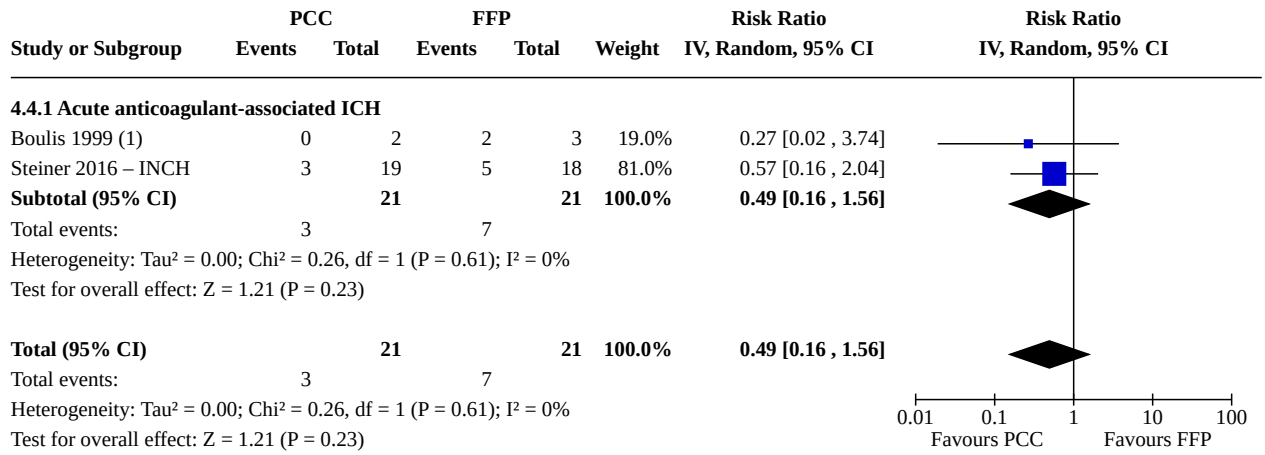
Study or Subgroup	PCC Events	PCC Total	FFP Events	FFP Total	Weight	Risk Ratio IV, Random, 95% CI
4.3.1 Acute anticoagulant-associated ICH						
Boulis 1999 (1)	0	2	2	3	100.0%	0.27 [0.02 , 3.74]
Subtotal (95% CI)		**2**		**3**	**100.0%**	**0.27 [0.02 , 3.74]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
Total (95% CI)		**2**		**3**	**100.0%**	**0.27 [0.02 , 3.74]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
Test for subgroup differences: Not applicable						



Footnotes

(1) The patients in the intervention group recieved PCC, FFP and vitamin K

Analysis 4.4. Comparison 4: Prothrombin complex concentrates versus fresh frozen plasma, Outcome 4: Death by day 90



Footnotes

(1) Patients in the intervention group received PCC, FFP and vitamin K

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 8) in the Cochrane Library (searched 12 September 2022)

ID Search Hits
#1 MeSH descriptor: [Hemostatics] explode all trees 1881
#2 MeSH descriptor: [Blood Coagulation Factors] explode all trees 10446
#3 MeSH descriptor: [Hemostasis] this term only and with qualifier(s): [drug effects - DE] 452
#4 MeSH descriptor: [Blood Coagulation] this term only and with qualifier(s): [drug effects - DE] 1247
#5 MeSH descriptor: [Fibrinolysis] this term only and with qualifier(s): [drug effects - DE] 636
#6 MeSH descriptor: [Platelet Activation] explode all trees and with qualifier(s): [drug effects - DE] 1883
#7 MeSH descriptor: [Antithrombins] explode all trees 1006
#8 MeSH descriptor: [Thrombin] this term only and with qualifier(s): [antagonists & inhibitors - AI] 96
#9 MeSH descriptor: [Receptors, Thrombin] explode all trees 179
#10 MeSH descriptor: [Antifibrinolytic Agents] this term only 904
#11 MeSH descriptor: [Factor Xa] explode all trees and with qualifier(s): [drug effects - DE] 5
#12 ((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag*) NEAR/5 (drug* or agent* or treat* or therap*)):ti,ab,kw 2590
#13 (antifibrinolytic* or ((coagulat* or clot*) NEAR/2 factor*) or aminocaproic acid or tranexamic acid or aprotinin or factor VII* or factor 7 or factor 7a or NovoSeven):ti,ab,kw 41666
#14 ((aminomethylbenzoic NEAR/2 acid) or phylloquinone or (proteinase NEAR/2 inhibit*) or aprotinin or alfa1 antitrypsin or camostat or ulinastatin or phytomenadione or menadione or etamsylate or carbazochrome or emicizumab):ti,ab,kw 2425
#15 MeSH descriptor: [Deamino Arginine Vasopressin] this term only 402
#16 (DDAVP or desmopressin*):ti,ab,kw 924
#17 MeSH descriptor: [Vitamin K] explode all trees and with qualifier(s): [antagonists & inhibitors - AI] 154
#18 MeSH descriptor: [Prothrombin] this term only 389
#19 MeSH descriptor: [Protamines] this term only 192
#20 (prothrombin* or (reversal NEAR/2 agent*) or (fresh NEAR/2 frozen NEAR/2 plasma) or idarucizumab or protamine or darucizumab or protamine or andexanet alfa or ciraparantag or bentracimab):ti,ab,kw 5908
#21 MeSH descriptor: [Platelet Transfusion] this term only 336
#22 MeSH descriptor: [Plasma] this term only 566
#23 {OR #1-#22} 61088
#24 MeSH descriptor: [Intracranial Hemorrhages] this term only 315
#25 MeSH descriptor: [Cerebral Hemorrhage] this term only 1064
#26 MeSH descriptor: [Basal Ganglia Hemorrhage] explode all trees 19

#27 MeSH descriptor: [Cerebral Intraventricular Hemorrhage] this term only 22
#28 MeSH descriptor: [Intracranial Hemorrhage, Hypertensive] this term only 49
#29 MeSH descriptor: [Hemorrhagic Stroke] this term only 19
#30 ((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*) NEAR/5 (h?emorrhag* or h?ematoma* or bleed*)):ti,ab,kw 14279
#31 (ICH or ICHs):ti,ab,kw 3055
#32 {OR #24-#31} 15883
#33 #23 and #32 2075

Appendix 2. MEDLINE Ovid (1946 to 12 September 2022)

The search consists of haemostatic drug therapies and acute spontaneous intracerebral haemorrhage subject searches (lines 1-13 and 14-16) which have been linked to the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (lines 17-27) in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format, as referenced in the Box 3.c in the Technical Supplement to Chapter 4: Searching for and selecting studies in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.3 (updated February 2022) (Lefebvre 2022).

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 or exp receptors, thrombin/ or antifibrinolytic agents/ or factor Xa/de
4. ((haemosta$ or hemosta$ or antihaemorrhag$ or antihemorrhag$) adj5 (drug$ or agent$ or treat$ or therap$)).tw.
5. (antifibrinolytic$ or ((coagulat$ or clot$) adj factor$) or aminocaproic acid or tranexamic acid or aprotinin or factor VII$ or factor 7 or factor 7a or NovoSeven).tw,kf.
6. ((aminomethylbenzoic adj2 acid) or phylloquinone or (proteinase adj2 inhibit$) or aprotinin or alfa1 antitrypsin or camostat or ulinastatin or phytomenadione or menadione or etamsylate or carbazochrome or emicizumab).tw,kf.
7. deamino arginine vasopressin/
8. (DDAVP or desmopressin$).tw,kf.
9. exp vitamin k/ai
10. prothrombin/ or protamines/
11. (prothrombin$ or (reversal adj3 agent$) or (fresh adj2 frozen adj2 plasma) or idarucizumab or protamine or darucizumab or protamine or andexanet alfa or ciraparantag or bentracimab).tw,kf.
12. platelet transfusion/ or plasma/
13. or/1-12
14. intracranial hemorrhages/ or cerebral hemorrhage/ or exp basal ganglia hemorrhage/ or cerebral intraventricular hemorrhage/ or intracranial hemorrhage, hypertensive/ or hemorrhagic stroke/
15. ((brain$ 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.
16. 14 or 15 or (ICH or ICHs).tw.
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. randomized.ab.
20. placebo.ab.
21. drug therapy.fs.
22. randomly.ab.
23. trial.ab.
24. groups.ab.
25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. exp animals/ not humans.sh.
27. 25 not 26
28. 13 and 16 and 27

Appendix 3. Embase Ovid (1974 to 12 September 2022)

1. exp hemostatic agent/
2. exp blood clotting factor/
3. hemostasis/ or blood clotting/ or blood clot/ or fibrin formation/ or exp fibrinolysis/ or plasminogen activation/ or exp thrombin inhibitor/ or thrombin/ or hemostatic agent/ or thrombin receptor/
4. ((haemosta$ or hemosta$ or antihaemorrhag$ or antihemorrhag$) adj5 (drug$ or agent$ or treat$ or therap$)).tw.
5. (antifibrinolytic$ or ((coagulat$ or clot$) adj factor$) or aminocaproic acid or tranexamic acid or aprotinin or factor VII$ or factor 7 or factor 7a or NovoSeven or (thrombin adj2 inhib$) or argatroban).tw.

6. or/1-5
7. brain hemorrhage/ or brain ventricle hemorrhage/ or cerebellum hemorrhage/ or massive intracerebral hemorrhage/
8. ((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$)).tw.
9. 7 or 8 or (ICH or ICHs).tw.
10. randomized controlled trial/ or "randomized controlled trial (topic)"/
11. randomization/
12. controlled study/ or controlled clinical trial/ or "controlled clinical trial (topic)"/
13. control group/
14. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
15. crossover procedure/
16. single blind procedure/ or double blind procedure/ or triple blind procedure/
17. placebo/ or placebo effect/
18. (random$ or rct or rcts).tw.
19. (controlled adj5 (trial$ or stud$)).tw.
20. (clinical$ adj5 trial$).tw.
21. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
22. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
23. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
24. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
25. (cross-over or cross over or crossover).tw.
26. (placebo$ or sham).tw.
27. trial.ti.
28. (assign$ or allocat$).tw.
29. controls.tw.
30. or/10-29
31. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
32. human/ or normal human/ or human cell/
33. 31 not 32
34. 30 not 33
35. 6 and 9 and 34

Appendix 4. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)

Interventional Studies | Intracerebral Haemorrhage OR Haemorragic Stroke

Appendix 5. World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/en/)

Basic search: intracerebral haemorrhage OR intracerebral hemorrhage OR ICH
Phases are: ALL

WHAT'S NEW

Date	Event	Description
23 October 2023	New citation required and conclusions have changed	Our new conclusion is, "In this updated Cochrane Review including 20 RCTs involving 4652 participants, rFVIIa likely results in little to no difference in reducing death or dependence after spontaneous ICH with or without surgery; antifibrinolytic drugs result in little to no difference in reducing death or dependence after spontaneous ICH, but result in a slight reduction in ICH expansion within 24 hours; platelet transfusion likely increases death or dependence after antiplatelet-associated ICH; and the evidence is very uncertain about the effect of PCC compared to FFP on death or dependence after anticoagulant-associated ICH. Thirteen RCTs are ongoing and are likely to increase the certainty of the estimates of treatment effect."

Date	Event	Description
23 October 2023	New search has been performed	• Literature and trial register search strategies updated to September 2022. • The search was updated to also include reversal agents for DOACs. • We added eight new RCTs and data from a further 2922 participants, for a total of 20 RCTs and 4652 participants. • We included RCTs that investigated haemostatic therapies for people taking DOACs prior to ICH. • We have graded the evidence using GRADE, and downgraded some of the previously included studies due to risk of bias, imprecision, indirectness, or inconsistency. • Title modified. • Co-authors added: Helle Eilertsen, Chaamanti Sivakumar Menon, Chen Chen, Michael JR Desborough, and Else Charlotte Sandset.

HISTORY

Protocol first published: Issue 2, 2006
Review first published: Issue 3, 2006

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. • 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.
24 June 2013	Amended	Co-authors added.
29 June 2009	New search has been performed	Updated with the addition of 841 people randomised in the FAST trial.
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.

Date	Event	Description
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. HE and CSM screened the title and abstracts of potentially eligible studies.

HE and CSM reviewed potentially eligible studies in full, appraised their risk of bias, extracted data from them, and obtained further data from study authors.

HE and CSM updated the review.

ZKL arbitrated risk of bias.

CC translated one Chinese study and helped with risk of bias assessment of this study.

ECS reviewed the GRADE assessment.

RA-SS, NS, PB, TS, ZKL, ECS and MJRD edited and provided comments on the review.

RA-SS is responsible for the final version and is the guarantor.

DECLARATIONS OF INTEREST

HE: has received lecture honoraria from Bristol Myers Squibb. She undertook the eligibility decisions about, extracted data from, carried out the risk of bias assessment for, and performed GRADE assessments of all studies. She is not affiliated to any of the included studies.

CSM: none known. CSM undertook the eligibility decisions about, extracted data from, carried out the risk of bias assessment for, and performed GRADE assessments of all studies. She is not affiliated to any of the included studies.

ZKL: was involved with Sprigg 2018 – TICH-2. ZKL played a role in arbitration of risk of bias, but Sprigg 2018 – TICH-2 did not require any decision to be arbitrated.

CC: none known. CC carried out the risk of bias assessment and performed the GRADE assessments of one study. She is not affiliated to any of the included studies.

PMB: has received lecture honoraria and consulting fees from Phagenesis, F Hoffmann-La Roche AG, and DiaMedica. He holds stock options with CoMind. PMB was involved in Sprigg 2014 – TICH-1, Sprigg 2018 – TICH-2, and Sprigg 2022 – TICH-3. PMB had no role in study selection, assessment, and data extraction with regard to these studies. PMB currently holds NIHR and British Heart Foundation grants that are paid to the University of Nottingham, UK.

TS: has received lecture honoraria and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and AstraZeneca, and a travel grant from AstraZeneca. TS has received payment for participation in an adjudication committee from IQVIA. TS has been chair of the European Stroke Organisation guideline board. 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.

MJRD: has received lecture honoraria from Sanofi, Amgen, Portola Pharmaceuticals, Takeda California, and Pfizer. He has received a travel grant from Janssen Biotech. MJRD is involved with the ongoing Desborough 2020 – DASH trial.

ECS: has received honoraria from Boston Scientific, Portola Pharmaceuticals, and Daiichi-Sankyo. ECS is on the Trial Steering Committees for the 2018-002620-17 – Annexa-I trial (funded by AstraZeneca), the Sprigg 2022 – TICH-3 trial (unpaid), AXIOMATIC-SSP trial (funded by Bristol-Myers Squibb), and OCEANIC trial (funded by Bayer). ECS is a member of the working group on ESO ICH guidelines.

NS: has received research funding grants for clinical trials (Sprigg 2018 – TICH-2, Desborough 2020 – DASH, and Sprigg 2022 – TICH-3). NS was involved with Sprigg 2014 – TICH-1 and Sprigg 2018 – TICH-2, and the ongoing Desborough 2020 – DASH and Sprigg 2022 – TICH-3. NS had no role in study selection, assessment, and data extraction with regard to these studies.

RA-SS: was involved with Baharoglu 2016 – PATCH and Sprigg 2018 – TICH-2, and the ongoing Sprigg 2022 – TICH-3. RA-SS was involved in the grant applications for the TICH trials. RA-SS currently holds two NIHR grants paid to the University of Edinburgh. He is the past-

president of the British and Irish Association of Stroke Physicians. RA-SS had no role in study selection, assessment, and data extraction with regard to these studies. RA-SS was a member of the Cochrane Stroke Editorial Team, but he was not involved in the editorial process.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied, Other

  No sources of support supplied

External sources

- No sources of support supplied, Other

  No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Title modified.
- Inclusion criteria clarified to include participants with stroke due to intracerebral haemorrhage accompanied by any type of antithrombotic drug use.
- Inclusion criteria changed from any age group apart from neonates to aged 16 years or older.
- Inclusion criteria clarified to allow placebo, open control, or active comparators.
- Literature and trial register search strategies updated. Some of the names of the databases have been changed, some databases have been superseded, 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 (less than seven days) and late (between seven days and the end of follow-up) if possible), quality of life, mood, cognitive function.
- We stipulated the number of studies required to assess publication bias for funnel plots.
- Stratification of analyses by antithrombotic use and intended surgery.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Humans