

# Haemostatic therapy in spontaneous intracerebral haemorrhage patients with high-risk of haematoma expansion by CT marker: a systematic review and meta-analysis of randomised trials

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## ABSTRACT

**Background and purpose** Current randomised controlled trials (RCTs) showed an uncertain benefit of haemostatic therapy on preventing haematoma expansion and improving the outcome in patients with intracerebral haemorrhage (ICH). This meta-analysis aims to systematically evaluate the effect of haemostatic agents on the prevention of haemorrhage growth in patients with high-risk spontaneous ICH predicted by CT signs in RCTs.

**Methods** A comprehensive search of PubMed, EMBASE and Cochrane library from 1 January 2005 to 30 June 2021 was conducted. RCTs that compared haemostatic agents with placebo for the treatment of spontaneous patients with ICH with high-risk haemorrhage growth were included. The primary endpoint was haematoma expansion at 24 hours. Other major endpoints of interest included 90-day functional outcome and mortality.

**Results** The meta-analysis included four RCTs that randomised 2666 patients with ICH with high-risk haemorrhage growth. Haemostatic therapy reduced the rate of haematoma expansion at a marginally statistically significant level when compared with placebo (OR 0.84; 95% CI 0.70 to 1.00;  $p=0.051$ ). Subgroup analysis for patients with black hole sign on CT revealed a significant reduction of haematoma expansion with haemostatic therapy (OR 0.61; 95% CI 0.39 to 0.94;  $p=0.03$ ). However, both the primary analysis and subgroup analyses showed that haemostatic therapy could not reduce the rate of poor functional outcome (modified Rankin Scale  $>3$ ) or death.

**Conclusions** Haemostatic therapy showed a marginally significant benefit in reducing early haematoma expansion in patients with high-risk spontaneous ICH predicted by markers on CT scan. However, no significant improvement in functional outcome or reduction of mortality was observed.

## INTRODUCTION

Spontaneous intracerebral haemorrhage (ICH) is one of the devastating strokes associated with the highest mortality and disability worldwide.<sup>1</sup> Current surgical or medical treatment showed no clear benefit.<sup>2,3</sup> Clinically,

haematoma expansion is associated with early neurological deterioration and poor clinical outcome and a target of intervention.<sup>4,5</sup> Haemostatic therapy has been shown to prevent haematoma expansion in patients with spontaneous ICH but with very limited evidence.<sup>6</sup> In theory, haemostatic therapy is more suitable for patients with high-risk for ICH growth, such as patients with early CT signs of haematoma expansion.<sup>7</sup> For this reason, high-risk haematoma growth patients with ICH with image markers, such as the spot sign,<sup>8,9</sup> black hole sign<sup>10</sup> and blend sign<sup>11</sup> on CT scan were identified as candidates for haemostatic therapy studied in several randomised trials.<sup>6,12-14</sup> With the recent completion of Tranexamic Acid for Acute ICH Growth prEdicted by Spot Sign (TRAIGE) trial<sup>12</sup> and the results of other trials using haemostatic agents, a possible consistent trend for reducing haematoma expansion was seen. On the other hand, some of these trials showed conflicting results. We, therefore, performed a meta-analysis and systematic review of the available evidence to evaluate the effect of haemostatic agents on the prevention of haemorrhage growth in patients with high-risk spontaneous ICH predicted by positive signs on CT (spot sign, blend sign or black hole sign).

## METHODS

### Search strategy

The Preferred Reporting Items for Systematic reviews and Meta-Analyses statement for reporting systematic reviews and meta-analyses of randomised controlled trials (RCTs) were followed in this meta-analysis.<sup>15</sup> PubMed, EMBASE and Cochrane library were searched for English peer-reviewed

publications that were published from 1 January 2005 (year of publication of the Factor Seven for Acute Hemorrhagic Stroke phase II trials (FAST II)<sup>16</sup>) to 30 June 2021. Randomised trials that compared haemostatic agents with placebo for the patients with ICH with high risk for haematoma expansion predicted by CT signs were identified. The following terms were used for the database search: 'intracranial hemorrhages', 'hemorrhages', 'cerebral brain hemorrhage', 'tranexamic acid', 't-AMCHA', 'AMCA', 'anvitoff', 'cyklokapron', 'spotof', 'transamin', 'mchafibrin', 'exacyl', 'Recombinant activated coagulation factor VII', 'rFVIIa', 'factor vii', 'factor seven', 'coagulation factor', 'aminocaproic acid', '6-Aminohexanoic Acid', 'epsilon-Aminocaproic Acid', '6-Aminocaproic Acid', 'CT', 'computed tomography', 'spot', 'black hole', 'blend'. Related reviews, clinical trial databases and the reference lists of all retrieved articles were also searched manually to identify relevant studies.

### Selection criteria

According to the objective of this analysis, only randomised trials that reported original data on haematoma expansion incidence after any haemostatic agents use in high-risk patients with ICH predicted by positive signs on CT were considered for inclusion in the meta-analysis, and the needed data could be from overall analysis, subgroup analysis or post hoc analyses. All non-RCTs, including observational studies, reviews, editorials, letters and case reports, were excluded. The study subjects were restricted to adult patients with spontaneous ICH. In addition, haematoma expansion should be defined as the presence of any ICH growth at 24 hours (>33% or >6 mL from baseline volume).

### Primary and secondary outcomes

The primary outcome was early haematoma expansion, defined as the presence of ICH growth measured at 24 hours (>33% or >6 mL from baseline volume). The secondary outcomes were poor functional outcome defined by a modified Rankin Scale (mRS) between 4 and 6 at 90±7 days and death at 90 days.

### Data extraction and quality assessment

Two physicians independently extracted data from identified publications based on the inclusion criteria. Disagreements were resolved through the discussion among all authors until a consensus was reached. Methods specified in the Cochrane Handbook of Systematic Reviews were adopted in this study for the objective assessment of the included trials.<sup>17</sup> Data on the total number of patients treated, duration of follow-up and specifics of the intervention and control groups were extracted from publications. The occurrence of the following events was extracted for individual trials and analysed separately for the haemostatic therapy group and the control group: number of patients with haematoma expansion, number of patients with an mRS of 4–6 (indicating reasonably poor functional outcome at 90 days) and number of

deceased patients at 90 days. If the above data were not available, the unadjusted ORs, as the indicators of the efficacy, were extracted, as an alternative. Characteristic data were also retrieved. To assess the reliability of the pooled results, risks of bias for each article and the overall study were assessed and reported according to the recommendations of the Cochrane Handbook for Systematic Reviews of Intervention using Cochrane collaboration's tool.<sup>17</sup>

### Data synthesis and analysis

To combine the data from each study, the common-effect model with an inverse-variance (CE IV) method was used to calculate a summary estimate across all included studies. The OR estimates and associated 95% CIs for each of the endpoints were calculated. If only the subgroup of the trial met the inclusion criteria, analysis with and without the overall population from that trial would be carried out separately, as a part of sensitivity analysis. Subgroup analysis was prespecified based on the CT signs, types of haemostatic agents, following the methods outlined by CE IV for each outcome. Between-study and between-subgroup heterogeneities were evaluated by calculating the  $I^2$  statistic and the Cochrane  $Q$  ( $\chi^2$ ) statistic, with a p value of 0.10 set for significance of the test of heterogeneity. The results of sensitivity analysis were showed graphically, demonstrating the influence of each study on the overall meta-analysis summary estimate. Funnel plots graphically showing the logarithm of the SE and the effect size to evaluate publication bias was also created. All tests were two-tailed with a p value of 0.05 considered significant. All analyses were performed using the Review Manager V.5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, 2020, Copenhagen, Denmark) and Stata V.16.0 (StataCorp LLC, College Station, 2019, Texas, USA) software.

## RESULTS

### Description of study characteristics

The database search identified 2406 publications with one additional report from other sources (online supplemental 1). A total of four randomised trials with 2666 patients were eligible for the meta-analysis.<sup>6 12–14</sup> Of the four trials, one enrolled both supratentorial and infratentorial patients with ICH<sup>6</sup> and three enrolled only supratentorial patients with ICH.<sup>12–14</sup> Two trials included patients with a positive spot sign only<sup>13 14</sup> and one trial selected patients with at least one of the three positive CT signs (positive spot sign, black hole sign or blend sign).<sup>12</sup> In another trial, CT signs were not considered as inclusion criteria,<sup>6</sup> for which, the original data needed for the current analysis were extracted from the subgroup analysis and post hoc analysis.<sup>18</sup> Tranexamic acid was used in three trials<sup>6 12 14</sup> and recombinant activated coagulation factor VII (rFVIIa) in one trial.<sup>13</sup> The control group in all trials received saline as the placebo. The average duration of follow-up was 90 days. The mean duration from

**Table 1** Characteristics of the studies included in the systematic review and meta-analysis

Variable	TRAIGE	STOP-AUST	SPOTLIGHT and STOP-IT	TICH-2
Start time, y	2015	2012	2010	2013
Publication time, y	2021	2020	2019	2018
Location	10 centres in China	13 centres in Australia	12 centres in Canada	123 centres in 12 countries
Study type	mRCT	mRCT	mRCT	mRCT
Participant	Supratentorial ICH	Supratentorial ICH	Supratentorial ICH	ICH
CT signs	Spot sign, black hole sign, or blend sign	Spot sign only	Spot sign only	Data on CT sign were unavailable for subjects included in the overall analysis; spot sign in subgroup analysis; black hole sign and blend sign in post hoc analyses
Time (hour)	<6	<4.5	<6.5	<8
Number of patients in treatment group/ total for primary analysis	89/172	50/100	32/69	1161/2325 in main overall analysis; 24/56 in spot sign subgroup; 411 in black hole sign subgroup; 364 in blend sign subgroup*
Age, mean±SD, y	55.9±11.6	71 (IQR 57–79)	70.7±13.7   66.7±12.4†	68.9±13.8
Male, n (%)	124 (72.5)	62 (62.0)	35 (50.7)	1301 (56.0)
Baseline NIHSS, median (IQR)	11.0 (7.0–15.0)	NA	16.0 (11.0–18.5)   16.0 (13.0–20.0)	13.1±7.5   12.9±7.5
Hypertension, n (%)	114 (66.7)	69 (69.0)	49 (71.0)	1421 (61.1)
ICH volume, mean±SD, mL	23.7±18.7	14.6 (IQR 7.9–32.7)	16.3 (9.6–19.2)   20.4 (8.6–32.6)	24.0±27.2
Intraventricular haemorrhage, n (%)	33 (19.3)	22 (22.0)	28 (40.6)	745 (32.0)
Spot sign, n (%)	94 (55.0)	100 (100.0)	69 (100.0)	56 (2.4)
Blend sign, n (%)	47 (27.5)	NA	NA	411 (17.7)
Black hole sign, n (%)	107 (62.6)	NA	NA	364 (15.7)
Onset to treatment, median (IQR), hour	290 (185–370)	150 (118–203)	178 (138–197)	246 (NA)
Randomisation	Randomised 1:1, double-blind, placebo-controlled	Randomised 1:1, double-blind, placebo-controlled	Randomised 1:1, double-blind, placebo-controlled	Randomised 1:1, double-blind, placebo-controlled
Intervention	Tranexamic acid: 1 g in 100 mL 0.9% NaCl over 10 min followed by 1 g in 250 mL 0.9% NaCl infusion over 8 hours	Tranexamic acid: 1 g in 100 mL 0.9% NaCl over 10 min followed by 1 g in 500 mL 0.9% NaCl infusion over 8 hours	rFVIIa: 80 µg/kg bolus	Tranexamic acid: 1 g in 100 mL 0.9% NaCl over 10 min followed by 1 g in 250 mL 0.9% NaCl infusion over 8 hours
Control	Placebo: saline	Placebo: saline	Placebo: saline	Placebo: saline
ITT	Yes	Yes	Yes	Yes
Primary outcome	HE 24 hours	HE 24 hours	HE 24 hours	mRS 90 days
Secondary outcome‡	mRS 90 days, death	mRS 90 days, death	mRS 90 days, death	HE 24 hours, death
Follow-up	90 days	90 days	90 days	90 days

Continued

Table 1 Continued

Variable	TRAIGE	STOP-AUST	SPOTLIGHT and STOP-IT	TICH-2
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Haemostatic therapy for preventing haematoma expansion.

\*Numbers of subjects in the treatment group and the control group in the subgroups of TICH-2 were unavailable.

†a | b indicated data for the treatment group and the control group when data for total population were unavailable.

‡Details of other secondary outcomes of each included trial were listed in online supplemental 2.

HE, haematoma expansion; ICH, intracerebral haemorrhage; ITT, intention-to-treat analysis; mRCT, multicenter randomised controlled trial; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rFVIIa, Recombinant factor VIIa; SPOTLIGHT, The "Spot Sign" Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy; STOP-AUST, the Spot sign and Tranexamic acid On Preventing ICH growth—AUStralasia Trial; STOP-IT, The Spot Sign for Predicting and Treating ICH Growth Study; TICH-2, Tranexamic acid for hyperacute primary intracerebral hemorrhage; TRAIGE, Tranexamic Acid for Acute ICH Growth prEdicted by Spot Sign.

the onset to treatment was 150 to 290 mins and the ICH volume at baseline was 14.6~24.0 mL. The risk of bias assessment for randomised clinical trials is presented in online supplemental 2 and all studies included in this review presented a low risk of bias and high quality. All trials adopted the randomised, double-blind, placebo-controlled design and intention-to-treat analysis for the primary analysis. More details of the design and characteristics of the included trials are provided in table 1 and online supplemental file 3.

Haemostatic therapy reduced the rate of haematoma expansion at a marginally significant level, compared with placebo (27.4 vs 40.0% in the control group; OR 0.84; 95% CI 0.70 to 1.00;  $p=0.051$ ), and the result had similar trends but with less significance when patients from Tranexamic acid for hyperacute primary intracerebral hemorrhage (TICH-2) were excluded<sup>6</sup> (41.5 vs 45.0% in the control group; OR 0.87; 95% CI 0.57 to 1.34;  $p=0.52$ ) (figure 1A). For patients with the spot sign, the rate of haematoma expansion was similar between the haemostatic therapy group and the control group (OR 0.98; 95% CI 0.60 to 1.59;  $p=0.93$ ). For patients with the blend sign, the rate of haematoma expansion was marginally lower in the haemostatic therapy group with no statistical significance (OR 0.75; 95% CI 0.50 to 1.11;  $p=0.15$ ). For patients with the black hole sign, a significant reduction of haematoma expansion was seen in the haemostatic therapy group (OR 0.61; 95% CI 0.39 to 0.94;  $p=0.03$ ). The subgroup analysis on different haemostatic agents revealed no significant difference in the rate of haematoma expansion. Notably, there was no significant heterogeneity across the four studies and subgroups, except for the subgroup with the black hole sign (figure 1B,C).

### Haemostatic therapy and clinical outcome

A total of four studies were included for the analysis of the clinical outcome. There was no significant heterogeneity between the four studies and their subgroups. When all patients were analysed, haemostatic therapy did not reduce the rate of the poor functional outcome when compared with placebo (53.3 vs 53.3% in the control group; OR 1.00; 95% CI 0.86 to 1.17;  $p=0.96$  and 45.8 vs 46.3% in the control group; OR 0.94; 95% CI 0.60 to 1.47;  $p=0.78$ ) whether TICH-2 (figure 2A) was included

or not. The results in all subgroup analyses were generally consistent with the main analysis (figure 2B,C). No benefit was seen in reducing 90-day mortality after haemostatic therapy (figure 3A–C) in the main or subgroup analysis.

### Sensitivity analyses and risk of bias

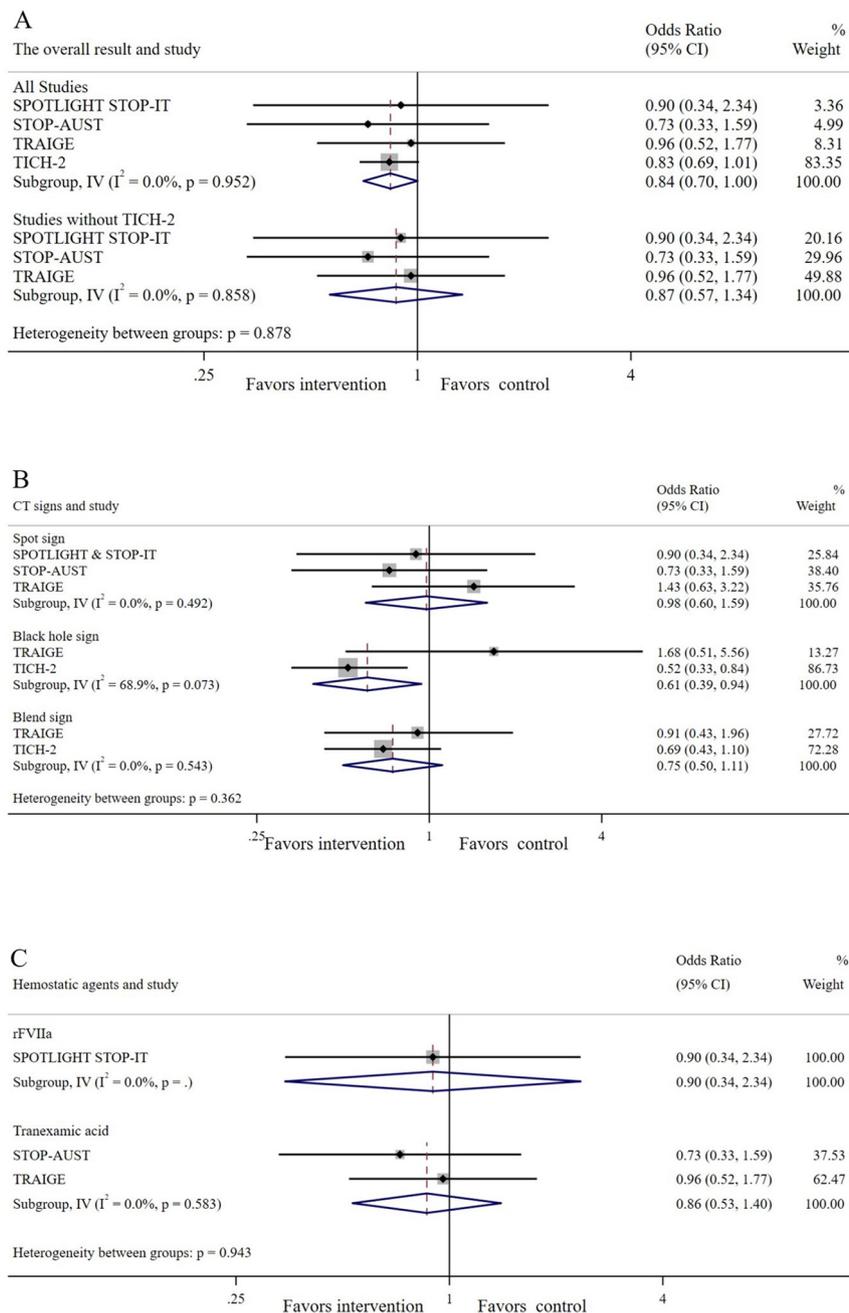
Sensitivity analysis for the rate of each endpoint showed that the overall effect of haemostatic therapy was consistent with the overall estimate from all studies excluding the TICH-2 study. Sensitivity analysis by sequentially dropping individual trials and then evaluating the overall outcomes failed to identify any of the individual trials that influenced the outcomes to any significant extent. Fixed-effects analyses showed a consistent trend for haemostatic therapy in all sensitivity analyses for the rate of haematoma expansion (online supplemental 4). There was also no significant publication bias detected with the examination of funnel plots for the outcome of haematoma expansion or with Egger's regression test (online supplemental 5).

### DISCUSSION

Our meta-analysis of meticulously performed RCTs that compared haemostatic therapy with placebo in patients with spontaneous ICH predicted by CT signs showed a potential nonstatistically significant benefit of reducing early haematoma expansion with haemostatic therapy. Haemostatic therapy did not lower the 90-day risk of poor functional outcome and all-cause mortality. However, in patients with the black hole sign, there was a statistically significant reduction of haematoma expansion with haemostatic therapy, a benefit not seen in subgroups with other CT signs. This is the first meta-analysis of published trials of high-quality and low bias risk that evaluates the effectiveness of haemostatic therapy for spontaneous ICH predicted by CT signs.

### Haemostatic therapy for spontaneous ICH without CT signs

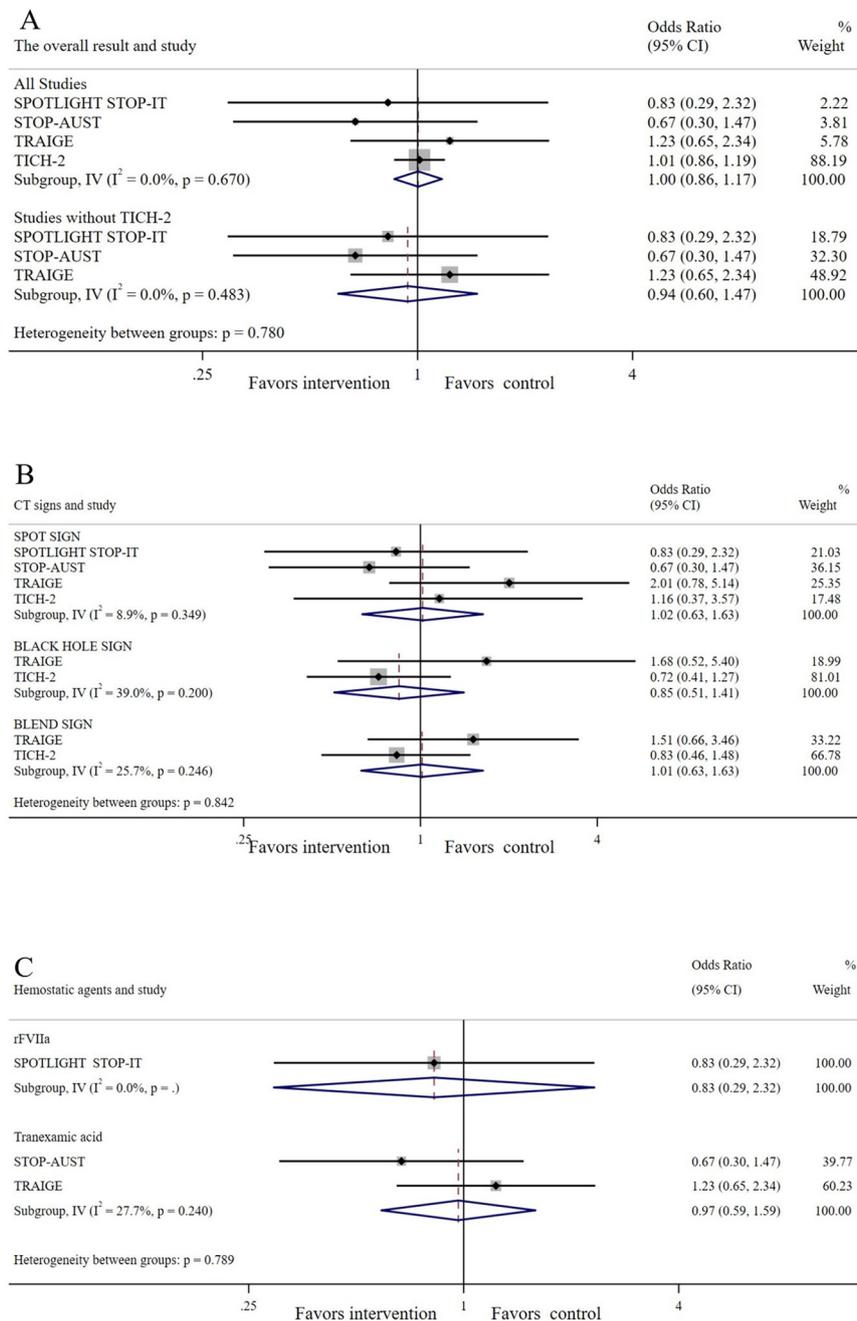
The rFVIIa was a rapid procoagulant developed for haemophilia-related haemorrhage. In previous trials (FAST-2,<sup>16</sup> FAST-3<sup>19</sup>), FVIIa reduced ICH expansion by about 50% compared with placebo but did not improve clinical outcomes.<sup>19</sup> Tranexamic acid for patients with



**Figure 1** Haematoma expansion for haemostatic therapy and placebo. (A) Analysis of all trials with and without TICH-2. (B) Subgroup analysis of CT signs. (C) Subgroup analysis of haemostatic agents. rFVIIa, recombinant activated coagulation factor VII; STOP-AUST, the Spot sign and Tranexamic acid On Preventing ICH growth—AUstralasia Trial; SPOTLIGHT, The “Spot Sign” Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy; STOP-IT, The Spot Sign for Predicting and Treating ICH Growth Study; TICH-2, Tranexamic acid for hyperacute primary intracerebral hemorrhage; TRAIGE, Tranexamic Acid for Acute ICH Growth prEdicted by Spot Sign.

ICH was first tested in Malaysian trial ( $n=30$ )<sup>20</sup> and TICH trial ( $n=24$ ),<sup>21</sup> which revealed a reduction of ICH expansion. Following that, a pragmatic phase III prospective double-blind randomised placebo-controlled trial, TICH-2<sup>6</sup> enrolled 2325 patients with ICH who received either tranexamic acid or placebo within 8 hours of onset. In the TICH-2 trial, tranexamic acid did not show any benefit in 90-day functional outcome when compared with placebo (adjusted OR 0.88; 95% CI 0.76 to 1.03;  $p=0.11$ ), despite a reduction in early deaths and serious adverse events.

However, a potential benefit of reducing haematoma expansion was seen in a smaller proportion of patients treated with the tranexamic acid (265 (25%)/1054 vs placebo 304 (29%)/1058) with an OR of 0.80 (95% CI 0.66 to 0.98;  $p=0.03$ ). The absolute effect on reducing haematoma growth was modest (1 mL). Overall, haemostatic therapy had a slight benefit in reducing haematoma growth but did not significantly improve the functional outcome in patients with ICH without any CT signs.

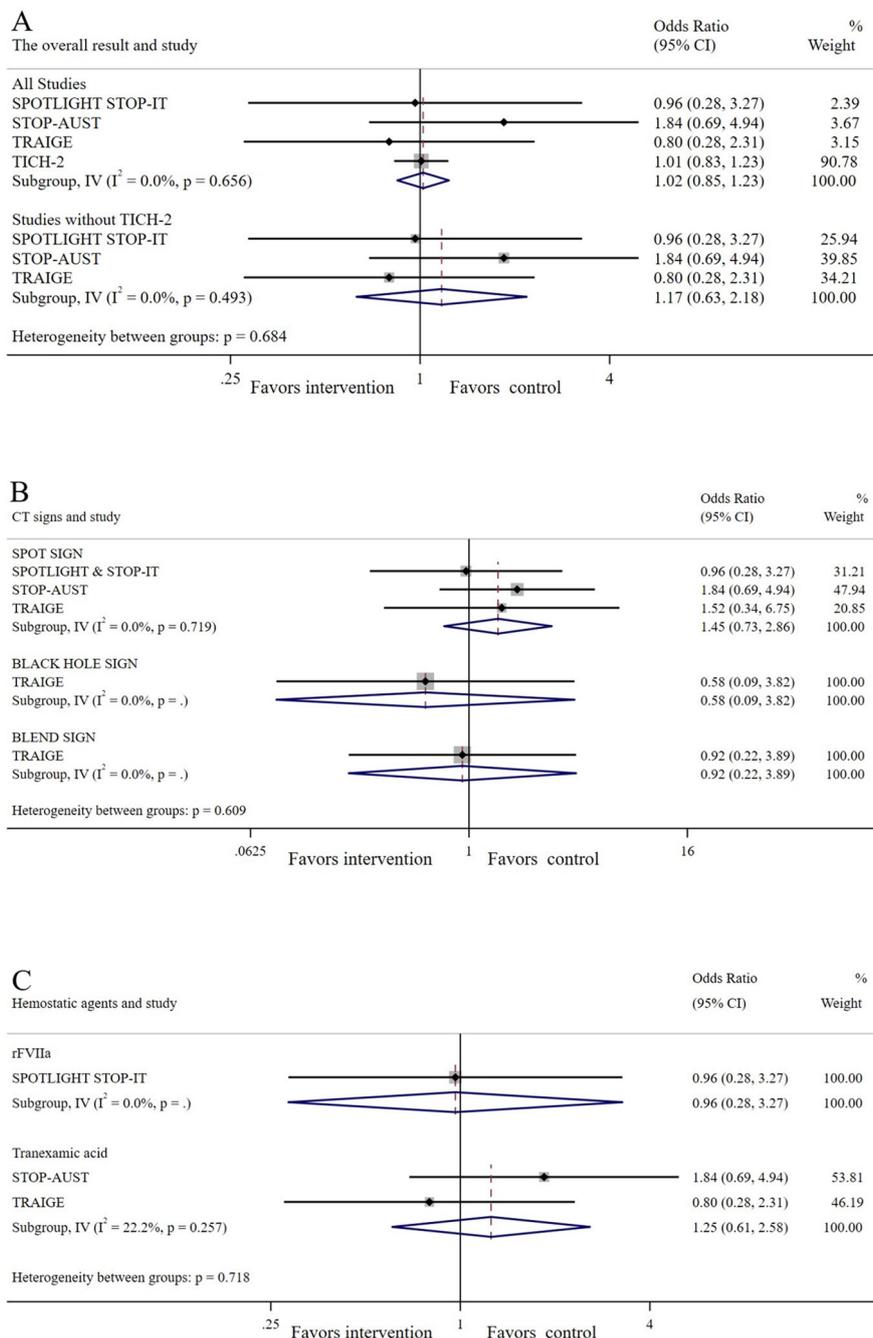


**Figure 2** Poor functional outcome (mRS>3) for haemostatic therapy and placebo. (A) Analysis of all trials with and without TICH-2. (B) Subgroup analysis of CT signs. (C) Subgroup analysis of haemostatic agents. rFVIIa, recombinant activated coagulation factor VII; STOP-AUST, the Spot sign and Tranexamic acid On Preventing ICH growth—AUstralasia Trial; SPOTLIGHT, The “Spot Sign” Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy; STOP-IT, The Spot Sign for Predicting and Treating ICH Growth Study; TICH-2, Tranexamic acid for hyperacute primary intracerebral hemorrhage; TRAIGE, Tranexamic Acid for Acute ICH Growth predicted by Spot Sign.

### Haemostatic therapy for spontaneous ICH with CT signs

Some researchers believe that haemostatic therapy is more appropriate for patients at high risk for ICH growth, such as patients presented early and with early CT signs predicting haematoma growth. For this reason, high-risk patients with ICH with image biomarkers, such as the spot, black hole and blend signs on CT, were identified as candidates for haemostatic therapy in recent randomised trials.

The Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT) and the “Spot Sign” Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT), published in 2019, were phase 2 trials using the spot sign as a selection criterion.<sup>13</sup> These trials recruited 69 patients with ICH over 6 years to receive either rFVIIa or placebo, with a median time from CT scan to treatment of 79 min (IQR 61–99) in the rFVIIa group. Both trials did not show any significant



**Figure 3** All-cause mortality for haemostatic therapy and placebo. (A) Analysis of all trials with and without TICH-2. (B) Subgroup analysis of CT signs. (C) Subgroup analysis of haemostatic agents. rFVIIa, recombinant activated coagulation factor VII; STOP-AUST, the Spot sign and Tranexamic acid On Preventing ICH growth—AUStrolasia Trial; SPOTLIGHT, The “Spot Sign” Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy; STOP-IT, The Spot Sign for Predicting and Treating ICH Growth Study; TICH-2, Tranexamic acid for hyperacute primary intracerebral hemorrhage; TRAIGE, Tranexamic Acid for Acute ICH Growth Predicted by Spot Sign.

reductions of haematoma growth with rFVIIa (13 (41%)/vs 16 (43%)/37;  $p=0.83$ ) or severe disability (9 (30%)/30 vs 13 (38%)/34;  $p=0.60$ ).

The Spot sign and Tranexamic acid On Preventing ICH growth—AUStrolasia Trial (STOP-AUST), published in 2020, was a phase 2 trial with 100 patients with ICH with the spot sign randomised to receive tranexamic acid (50) or placebo (50).<sup>14</sup> The study did not show any benefit of tranexamic acid in reducing haematoma growth (OR

0.72; 95% CI 0.32 to 1.59;  $p=0.41$ ), although the treatment is proven to be safe.

TRAIGE was a phase 2 trial that compared tranexamic acid with placebo in patients with ICH with the spot, blend or black hole signs.<sup>12</sup> All qualified patients had a noncontrast computed tomography (NCCT) or contrast-enhanced CT within 6 hours from the onset. This latest study found no benefit of tranexamic acid on reducing haematoma growth (OR 0.96; 95% CI 0.52 to 1.77;  $p=0.89$ )

or improving clinical outcomes with a generalised OR of 1.11 (95% CI 0.65 to 1.90;  $p=0.70$ ), which is consistent with the previous studies.

Furthermore, in 249 patients enrolled in the TICH-2 trial, 56 patients with a positive spot sign were randomised to receive tranexamic acid (24) or placebo (32). The trial found a poor treatment effect of tranexamic acid in the subgroup analysis. In the post hoc analysis in the same study<sup>18</sup> for the purpose of defining the role of the NCCT signs as predictors of haematoma expansion and poor functional outcome, blend sign, black hole sign and hypodensities were found to be predictive of haematoma expansion. Black hole sign, hypodensities and island signs predicted a poor functional outcome. The study did not show any significant correlation between the presence of signs and the benefit of tranexamic acid in reducing haematoma expansion. NCCT signs do not indicate a better response to tranexamic acid regarding the clinical outcome. In summary, studies on patients susceptible to haemorrhage expansion predicted by CT signs, especially the spot sign, showed that haemostatic therapy did not significantly prevent the haematoma growth or improve the outcome.

#### Future direction

This meta-analysis showed that haemostatic therapy might have the benefit of reducing early haematoma expansion in selected patients with ICH. It has been reported by a prior systematic review<sup>22</sup> that haemostatic therapy does not increase the occurrence of thrombotic events. However, no significant improvement in prognosis or reduction in mortality was observed with haemostatic therapy in patients with ICH with or without CT signs. There are several possible explanations. First, modest absolute volume reduction in haematoma may not be sufficient to show clinical benefit.<sup>6,14</sup> Second, the previous studies<sup>6</sup> showed some other uncertainties that might impact the outcome. Haemostatic therapy could modestly reduce haematoma expansion but not enough to alter the pathophysiological process. For example, haemostatic therapy could not change perihematoma brain oedema<sup>23</sup> and other complications, similar to the limitations of surgical intervention for ICH.<sup>24,25</sup> However, these unresolved clinical problems may have a bigger impact on the final prognosis of patients with ICH.<sup>23</sup> Predictive CT signs used in these studies were proved to be valuable in predicting haematoma expansion and poor prognosis,<sup>26</sup> but the underlying pathological mechanisms remain unclear. It appears that different CT signs may have different predictive roles in evaluating the therapeutic effects of the haemostatic therapy. It is time to evaluate different predictive CT signs in those subgroups that showed potentially improved outcome. In the post hoc analysis of Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-2),<sup>27</sup> ultraearly blood pressure (BP) reduction  $\leq 2$  hours could reduce haematoma growth and further

improve functional outcome. Subgroup analyses from the TICH-2, STOP-AUST and TRAIGE all found that earlier treatment (within 2–3 hours) seemed to show more benefit. The proposed time window could also be used for haemostatic therapy in future research. More trials using tranexamic acid to treat ICH in the early time window are already ongoing (EudraCT 2012-005594-30 and ClinicalTrials.gov NCT03385928). There was speculation that haemostatic therapy might be similar to intravenous thrombolysis for ischaemic stroke, namely, earlier cessation of haematoma expansion might stop the trend of a cascade of deterioration.<sup>28</sup>

Even though the results of these studies do not support the haemostatic therapy at present, further studies on better-defined subgroups of ICH patients are warranted. Tranexamic acid has certain advantages for this role. It is low-cost, widely used, safe and suitable for promotion on a global scale. However, recruitment of patients with high-risk ICH is difficult because of the strict selection criteria and difficulty of obtaining emergency CT angiography routinely. Global collaboration may be the solution to the re-evaluation of tranexamic acid with a trial in a highly selective ICH population.

#### Limitation

The analysis on the overall population and subgroup population of TICH-2 were included in the current analysis, where the overall population also included patients without CT signs. To reduce the effect of bias of population differences, analysis with and without the overall population of TICH-2 was carried out separately as part of sensitivity analysis. However, the CI of primary analysis when patients from TICH-2 were excluded was significantly wider ( $p=0.52$ ) than with TICH-2 included ( $p=0.051$ ). Perhaps the sample size of the TICH-2 study is the main reason that TICH-2 may be driving much of the potential significance for reducing rate of haematoma expansion. The Factor VII phase IIb and phase III trials (FAST III) were representative researches on the evaluation of the effect of Factor VII on the prevention of haemorrhage growth in all ICH patients and the original data from FAST III on a subgroup of high-risk patients with ICH predicted by positive signs on CT could not be extracted from published reports, therefore, we could not get the original data. For these reasons, we excluded FAST III from the current analysis. Furthermore, subgroup analysis for each CT sign was performed to determine the difference in efficacy for patients with different CT signs. Since the inclusion of the RCT subgroup would lead to the decline of the overall study quality, the quality of subgroup analysis based on CT signs in this study was only equivalent to the level of a meta-analysis of cohort study. In addition, there were some differences in the protocols across the studies. For instance, the onset-to-randomisation time limits ranged from 4.5 to 8 hours, and different

haemostatic agents were used. These differences may lead to differences in the results. Sensitivity analysis was carried out to test the interstudy bias, but no positive interstudy bias that affected the results was found. Moreover, there were obvious differences in the sample size across studies. The sample size of the TICH-2 study was significantly larger than that of other studies. However, there was no significant publication bias found.

## CONCLUSIONS

Haemostatic therapy may reduce haematoma expansion at a marginally significant level but could not lower the risk of 90-day poor functional outcome and all-cause mortality in high-risk patients with ICH with predictive CT signs. Although the data did not support the wide use of haemostatic therapy clinically, it may have provided directions in future research of treating patients with ICH.

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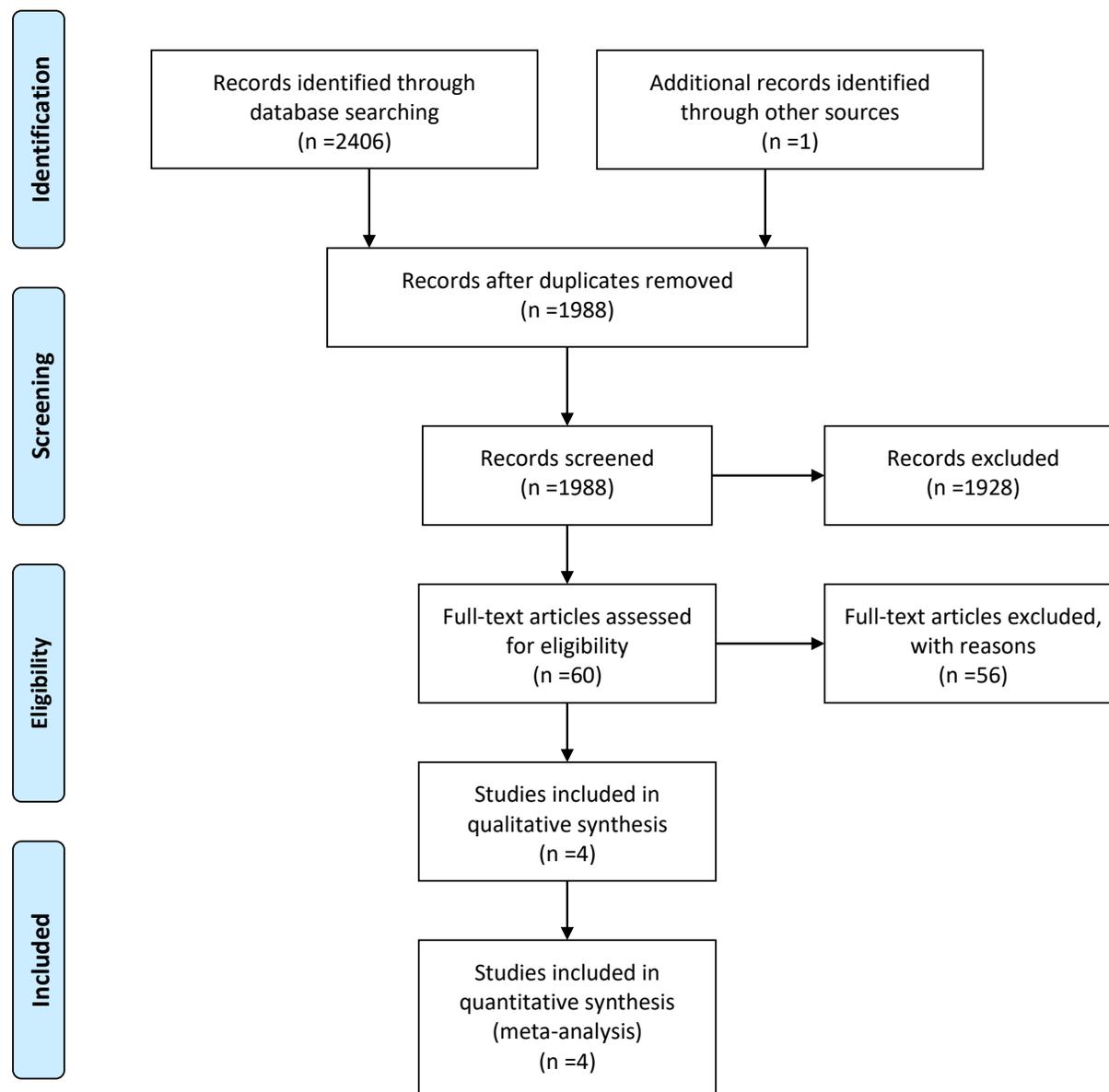
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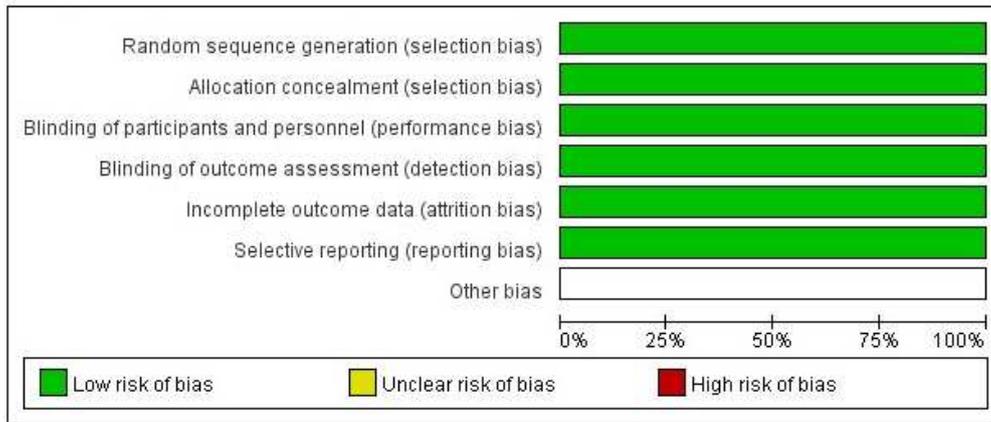
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For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

**Risk of bias in individual studies**



**A** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
SPOTLIGHT STOP-IT 2019	+	+	+	+	+	+	
STOP-AUST 2020	+	+	+	+	+	+	
TICH-2 2018	+	+	+	+	+	+	
TRAIGE 2021	+	+	+	+	+	+	

**B** Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

[Intervention] for [health problem]

26-Jan-2021

## Characteristics of studies

### Characteristics of included studies

#### SPOTLIGHT STOP-IT 2019

<p><b>Methods</b></p>	<p><b>SPOTLIGHT:</b> This clinical trial will enrol 110 participants from approximately 15 Canadian stroke centres. People coming to the emergency department with bleeding in the brain not due to trauma or other known causes who can be treated within 6 h of onset will undergo CT angiography using standard CT scanners ('CAT scan'). Those with a 'spot sign', a type of marker on the CT scan that shows the brain is still bleeding, will be randomly assigned to a single injection of 'factor 7' (a blood clotting drug used in haemophilia) or placebo (inactive saline); people without a spot sign will not be treated. The researchers will look at how much bleeding happens after the treatments are administered, as well as clinical outcomes such as death and disability. The researchers think that factor 7 will cause the bleeding to stop faster and possibly decrease death and disability</p> <p><b>STOP-IT:</b> The purpose of this study is to determine if computed tomography angiography can predict which individuals with ICH will experience significant growth in the size of the haemorrhage. For individuals who are at high risk for haemorrhage growth, the study will compare the drug recombinant activated factor VII (rFVIIa) to placebo to determine the effect of rFVIIa on ICH growth</p>
<p><b>Participants</b></p>	<p><b>SPOTLIGHT:</b> Inclusion criteria</p> <ul style="list-style-type: none"> <li>• Acute spontaneous primary supratentorial ICH diagnosed by CT scan</li> <li>• Presence of a spot sign within the haematoma on CTA source images</li> <li>• Baseline ICH volume 3 mL to 90 mL</li> <li>• Age 18 or older</li> <li>• Investigator is able to randomise and administer study drug as soon as possible within a target of 60 minutes after CT angiogram and no later than 6 h after stroke symptom onset (using the 'last seen normal' principle)</li> <li>• Plan to provide full medical care for at least 24 h</li> <li>• Assent-consent from participant or LAR prior to enrolment, or a waiver of consent (where REB approved) if patient or LAR assent-consent is not possible prior to enrolment</li> </ul> <p>Exclusion criteria</p> <ul style="list-style-type: none"> <li>• Brainstem or cerebellar haemorrhage</li> <li>• ICH secondary to known or suspected trauma, aneurysm, vascular malformation, hemorrhagic conversion of ischaemic stroke, venous sinus thrombosis, thrombolytic treatment, tumour, or infection; or an in-hospital ICH or ICH as a result of any in-hospital procedure or illness</li> <li>• Baseline brain imaging shows evidence of acute or subacute ischaemic stroke (chronic infarcts are not an exclusion)</li> <li>• Contrast administration within the previous 24 h</li> <li>• Evidence of thromboembolic risk factors, defined as any of the following:</li> </ul>

[Intervention] for [health problem]

26-Jan-2021

known history within the past 6 months of any of the following: 1) MI, 2) coronary artery bypass surgery, 3) angina, 4) ischaemic stroke, 5) TIA, 6) carotid endarterectomy, 7) cerebral bypass surgery, 8) deep venous thrombosis, 9) pulmonary embolism, 10) any vascular angioplasty, stenting (coronary, peripheral vascular, or cerebrovascular) or filter (e.g. vena cava filter); 11) prosthetic cardiac valve, and, or 12) known history of a high-risk thrombophilia (e.g. antithrombin III deficiency, antiphospholipid antibody syndrome, protein C deficiency, etc)

- Known hereditary (e.g. haemophilia) or acquired haemorrhagic diathesis or coagulation factor deficiency
- Any known condition that the investigator feels would pose a significant hazard if rFVIIa were administered
- Planned surgery for ICH within 24 h (placement of intraventricular catheter is not an exclusion)
- Planned withdrawal of care before 24 h post-ICH onset
- Known participation in another therapeutic trial
- Known allergy or other contraindication to iodinated contrast dye
- Known or suspected hypersensitivity to the trial product
- Known unfractionated heparin use - must check PTT and exclude if elevated above upper limit of local lab's reference range
- Known low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use within previous 7 days
- Known GPIIb/IIIa antagonist use in previous 2 weeks
- Known warfarin (or other anticoagulant) therapy with INR > 1.40. Note: if the patient is suspected to have cirrhosis, study staff are to wait for the INR value prior to dosing, and ensure they do not enrol the patient if the INR value is > 1.40. Otherwise, the physician should use their discretion if they believe the patient is not at risk for elevated INR
- Concurrent or planned treatment with prothrombin complex concentrate, vitamin K, fresh frozen plasma, or platelet transfusion
- Pregnancy or lactation. Women of childbearing potential must have a negative pregnancy test prior to randomization.
- Current clinical symptoms suggestive of acute coronary ischaemia (e.g. chest pain).
- Baseline ECG evidence of acute coronary ischaemia (e.g. ST elevation in 2 contiguous leads, new LBBB, ST depression)

Baseline platelet count 1.40, or elevated PTT

STOP-IT:

Inclusion criteria

- Acute, spontaneous ICH (including bleeding in cerebellum) diagnosed by non-enhanced CT scan within 5 h of symptom onset. (Time of onset is defined as the last time the patient was witnessed to be at baseline, i.e. people who have stroke symptoms upon awakening will be considered to have their onset at beginning of sleep)
- Age  $\geq$  18 years through 80 years (candidates must have had their 18th birthday, but not had their 81st birthday)
- For spot positive patients, dosing of study drug within 90 minutes of enrolling CT scan

[Intervention] for [health problem]

26-Jan-2021

## Exclusion criteria

- Time of symptom onset of ICH is unknown or more than 5 h prior to baseline CT scan
- ICH secondary to known or suspected trauma, aneurysm, vascular malformation, haemorrhagic conversion of ischaemic stroke, venous sinus thrombosis, thrombolytic treatment of any condition (e.g. MI, cerebral infarction, etc), CNS tumour or CNS infection
- Brainstem location of haemorrhage (people with cerebellar haemorrhage may be enrolled)
- Serum creatinine > 1.4 mg/dL (123 µmol/L). Sites that currently perform CTA as standard of care for ICH will follow their standard procedures regarding renal insufficiency
- Known allergy to iodinated contrast media
- Intravenous or intra-arterial administration of iodinated contrast media within the previous 24 h of baseline CT scan
- Known hereditary (e.g. haemophilia) or acquired haemorrhagic diathesis, coagulation factor deficiency, or anticoagulant therapy with INR > 1.2
- Known or suspected thrombocytopenia (unless current platelet count documented above 50,000/µL)
- Unfractionated heparin use with abnormal PTT
- Low-molecular weight heparin use within the previous 24 h
- GPIIb/IIIa antagonist use in the previous 2 weeks
- GCS score 2
- Baseline ICH volume of 90 cc
- Planned surgical evacuation of ICH within 24 h of symptom onset (placement of intraventricular catheter is not a contraindication to study enrolment)
- Evidence of acute or subacute ischaemic stroke on baseline qualifying CT scan
- Clinical history of thromboembolism or ischaemic vascular disease, including MI, coronary artery bypass surgery, cardiac angina, TIA, ischaemic stroke, peripheral artery disease (vascular claudication), cerebral bypass surgery, carotid endarterectomy, deep venous thrombosis, pulmonary embolism, or coronary or cerebrovascular angioplasty or stenting. (Clinically silent evidence of old ischaemia on EKG (Q waves) or CT scan (silent old infarct) will not be considered reasons for exclusion)
- Baseline electrocardiogram shows evidence of acute cardiac ischaemia (ST elevation in 2 contiguous leads, new LBBB, or ST depression)
- Clinical history suggestive of acute cardiac ischaemia (e.g. chest pain)
- Abnormal baseline troponin
- Females of childbearing potential who are known to be pregnant, lactating, or who have positive pregnancy tests on admission
- Advanced or terminal illness or any other condition the investigator feels would pose a significant hazard to the patient if rFVIIa were administered
- Recent (within 30 days) participation in any investigational drug or device trial or earlier participation in any investigational drug or device trial for which the duration of effect is expected to persist until the time of STOP-IT enrolment
- Planned withdrawal of care or comfort care measures
- Person known or suspected of not being able to comply with trial protocol (e.g. due to alcoholism, drug dependency or psychological disorder)

[Intervention] for [health problem]

26-Jan-2021

	<ul style="list-style-type: none"> <li>• Informed consent cannot be obtained from the patient or legally authorised representative</li> </ul>
<b>Interventions</b>	<p><b>SPOTLIGHT:</b>  Intervention: rFVIIa 80 ug/kg IV bolus  Comparator: placebo standard saline solution</p> <p><b>STOP-IT:</b>  Intervention: recombinant activated factor VII. Participants will receive rFVIIa at 80 mcg/kg (maximum dose volume 21.3 mL, equivalent to maximum weight of 160 kg)  Comparator: placebo. An inactive substance (maximum dose volume 21.3 mL, equivalent to maximum weight of 160 kg)</p>
<b>Outcomes</b>	<p><b>SPOTLIGHT:</b>  Primary outcome measures</p> <ul style="list-style-type: none"> <li>• ICH size: difference between groups in ICH size on CT scan at 24 h post-dose, adjusted for baseline ICH size</li> </ul> <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> <li>• Feasibility (time frame: 0): percentage of sites that can meet recruitment targets of 2 patients per site per year; % of patients who meet the target time of &lt;45 minutes from emergency department arrival to the start of the scan; % of patients who meet the target time of &lt;60 minutes from the end of the CT angiogram to administration of study drug; local site spot sign interpretation accuracy as judged by central adjudicator; protocol violations; waiver of consent process, evaluation, and effectiveness (time frame: 4.90 days); waiver of consent use, acceptability, and effect on treatment times. Questionnaire will be administered to subject or LAR at 4 days and 90 days</li> <li>• Acute blood pressure control (time frame: 1 h): % of participants in whom blood pressure control was achieved, defined as achieving systolic BP &lt; 180 mmHg within 1 h post-randomisation</li> <li>• Thromboembolic events : incidence of MI and ischaemic stroke within 4 days; any other arterial or venous thromboembolic SAEs within 4 days</li> <li>• Mortality : 90-day mortality rate</li> <li>• Unstable angina: unstable angina within 4 days of treatment</li> <li>• Troponin increase : troponin rise above upper limit of normal within 4 days (without clinical symptoms or ECG evidence of acute coronary syndrome)</li> <li>• DVT : deep venous thrombosis (DVT) within 4 days</li> <li>• Pulmonary embolism : PE within 30 days</li> <li>• Cognition : Montreal Cognitive Assessment (MoCA) and Stroke Impact Scale at 90 days and 1 year</li> <li>• Disability : proportion of participants with mRS score 5 to 6 (death or severe disability) at 90 days and 1 year</li> </ul> <p><b>STOP-IT:</b>  Primary outcome measures: life-threatening thromboembolic complications defined as development of 1) acute myocardial ischaemia, 2) acute cerebral ischaemia, and 3) acute pulmonary embolism (time frame: through day 4 after completion of study drug). The rate of haematoma growth among spot sign positive participants at 24 h, comparing participants treated with rFVIIa to those treated with placebo. Haematoma growth will be defined as a &gt; 33% or &gt; 6 cc</p>

[Intervention] for [health problem]

26-Jan-2021

	<p>increase in volume (time frame: at 24 h).</p> <p>The sensitivity and specificity of the spot sign for predicting haematoma growth (time frame: baseline head CT scan within 5 h, followed by a CT angiogram. Haematoma growth determined by comparison with a head CT scan performed at 24 h)</p> <p>Secondary outcome measures: incidence of other potentially study drug-related thromboembolic complications, such as deep venous thrombosis and elevations in troponin not associated with ECG changes (time frame: through day 4 after completion of study drug)</p> <p>90-day outcomes among spot positive people, dichotomised as mRS score of 0 to 4 verses 5 to 6, comparing participants treated with rFVIIa to those treated with placebo (time frame: 90 days (<math>\pm</math> 7 days) from time of study enrolment). The positive and negative predictive values of the spot sign and the accuracy of the site investigators for correct identification of the spot sign as compared to a blinded study neuroradiologist (time frame: baseline head CT scan within 5 h, followed by a CT angiogram. Haematoma growth determined by comparison with a head CT scan performed at 24 h. Rate of total haemorrhage volume growth (haematoma + IVH) among spot-positive participants (time frame: 24 h (<math>\pm</math> 3 h) from baseline CT scan)</p>
<b>Notes</b>	<p>SPOTLIGHT: NCT01359202</p> <p>STOP-IT: NCT00810888</p>

## Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The SPOTLIGHT trial used a computer-generated randomization schedule created by an independent statistician; randomization was stratified by site using a variable block randomization scheme. The STOP-IT trial used web-based randomization with an adaptive randomization scheme to improve balance in variables known to influence ICH expansion.
Allocation concealment (selection bias)	Low risk	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 and reconstituted rFVIIa are clear, colorless solutions identical in appearance and texture.
Blinding of participants and personnel (performance bias)	Low risk	double-blinded

[Intervention] for [health problem]

26-Jan-2021

Blinding of outcome assessment (detection bias)	Low risk	Blinded radiologist for primary outcome.High risk for other outcomes (not stated as blinded)
Incomplete outcome data (attrition bias)	Low risk	Analysis for the primary outcome was complete in ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes in the paper were reported.
Other bias	Unclear risk	

**STOP-AUST 2020**

<b>Methods</b>	The aim of the study is to test if ICH patients who have contrast extravasation on CTA, the 'spot sign', have lower rates of haematoma growth when treated with tranexamic acid within 4.5 h of stroke onset, compared with placebo
<b>Participants</b>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>• People presenting with an acute ICH</li> <li>• 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</li> <li>• Age <math>\geq</math> 18 years</li> <li>• 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)</li> <li>• Informed consent has been received in accordance to local ethics committee requirements</li> </ul> <p>Exclusion criteria</p> <ul style="list-style-type: none"> <li>• GCS total score <math>\leq</math> 7 mL as measured by the ABC/2 method</li> <li>• ICH known or suspected by study investigator to be secondary to trauma, aneurysm, vascular</li> </ul>
<b>Interventions</b>	<p>Intervention: intravenous tranexamic acid 1000 mg in 100 mL 0.9% normal saline over 10 minutes followed by 1000 mg in 500 mL 0.9% normal saline infusion over 8 h</p> <p>Comparator: intravenous placebo in 100 mL 0.9% normal saline over 10 minutes followed by 500 mL 0.9% normal saline infusion over 8 h</p>
<b>Outcomes</b>	<p>Primary outcome measures</p> <ul style="list-style-type: none"> <li>• ICH growth by 24 <math>\pm</math> 3 h as defined by either 33% or 6 mL increase from baseline, adjusted for baseline ICH volume.</li> </ul> <p>Secondary outcome measures</p> <ul style="list-style-type: none"> <li>• Major thromboembolic events (MI, ischaemic stroke, PE), measured within 90 <math>\pm</math> 7 days)</li> <li>• Absolute ICH growth volume by 24 <math>\pm</math> 3 h, adjusted for baseline ICH volume</li> <li>• Absolute IVH growth volume by 24 <math>\pm</math> 3 h, adjusted for baseline IVH volume</li> <li>• mRS score of 0 to 4 at 3 months</li> </ul>

Review Manager 5.4.1

6

[Intervention] for [health problem]

26-Jan-2021

	<ul style="list-style-type: none"> <li>• mRS score of 0 to 3 at 3 months</li> <li>• Categorical shift in mRS at 3 months, subject to the validity of proportional odds assumption</li> <li>• Death due to any cause by 3 months</li> </ul>
<b>Notes</b>	NCT01702636

## Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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	The investigational product was distributed to participating centres in externally indistinguishable sealed treatment kits containing either tranexamic acid or placebo
Blinding of participants and personnel (performance bias)	Low risk	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)	Low risk	Patients and all those involved in patient management or clinical or imaging assessment of adverse events or outcomes were masked to treatment allocation.
Incomplete outcome data (attrition bias)	Low risk	Analysis for the primary outcome was complete in ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes in the paper were reported.
Other bias	Unclear risk	

## TICH-2 2018

<b>Methods</b>	A pragmatic phase III prospective double-blind randomised placebo-controlled trial
<b>Participants</b>	<p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>• Adults with acute spontaneous ICH</li> <li>• Within 8 h of stroke symptom onset or time last seen well</li> </ul> <p>Exclusion criteria</p> <ul style="list-style-type: none"> <li>• People with ICH secondary to anticoagulation, thrombolysis or known underlying structural abnormality such as AVM, aneurysm, tumour, or venous thrombosis. An underlying structural abnormality does not need to be excluded before enrolment, but where known, patients should not be recruited</li> <li>• Contraindication to tranexamic acid</li> <li>• Premorbid dependency (mRS &gt; 4)</li> <li>• Concurrent participation in another drug or device trial. Participants enrolled in</li> </ul>

[Intervention] for [health problem]

26-Jan-2021

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

## Risk of bias table

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	A secure website was used to randomly assign all participants eligible for inclusion to receive tranexamic acid or matching placebo, with 1:1 allocation.
Allocation concealment (selection bias)	Low risk	The random allocation sequence was generated by the trial programmer. Sharp Clinical Services (Crickhowell, UK) prepared individual masked treatment packs containing four 5 mL glass ampoules of tranexamic acid 500 mg or sodium chloride 0.9%, which were made identical in appearance by the addition of a heat shrink sleeve. Ampoules and the treatment pack were labelled with a unique pack number. Sharp Clinical Services stored the treatment packs and distributed them to pharmacies within trial sites using a web-based system of control.
Blinding of participants and personnel (performance bias)	Low risk	Treatment allocation was concealed from all staff and patients involved in the trial.
Blinding of outcome assessment (detection bias)	Low risk	Treatment allocation was concealed from all staff and patients involved in the trial.

[Intervention] for [health problem]

26-Jan-2021

Incomplete outcome data (attrition bias)	Low risk	The primary outcome of mRS at day 90 was assessed in 2307 (99%) of 2325 participants
Selective reporting (reporting bias)	Low risk	All outcomes in the paper were reported
Other bias	Unclear risk	

**TRAIGE 2021**

<b>Methods</b>	The purpose of this study is to determine if spot sign, black hole sign, and blend sign can predict which individuals with ICH will experience significant growth in the size of the haemorrhage. For individuals who are at high risk for haemorrhage growth, the study will compare the drug tranexamic acid to placebo to determine the effect and safety on ICH
<b>Participants</b>	<p>Inclusion criteria</p> <p>People presenting with an acute spontaneous hypertensive ICH</p> <ul style="list-style-type: none"> <li>• CTA evaluation can be accomplished within 6 h of symptom onset, with 'spot sign' positive in CTA original image OR CT evaluation accomplished within 6 h of symptom onset, with "blend sign" or "black hole sign" positive</li> <li>• Age range from 18 to 79 years</li> <li>• Randomisation can be finished and treatment can commence within 8 h of symptom onset</li> <li>• Informed consent has been received in accordance with local ethics committee requirements</li> </ul> <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> <li>• ICH known or suspected to be secondary to tumour, vascular malformation, aneurysm, or trauma</li> <li>• Infratentorial ICH</li> <li>• GCS total score 70 mL</li> <li>• Parenchymal haemorrhage with ventricle involved, blood completely fills one lateral ventricle or more than half of both lateral ventricles</li> <li>• Contraindication of CTA imaging (e.g. known or suspected iodine allergy or significant renal failure)</li> <li>• Any history or current evidence suggestive of venous or arterial thrombotic events within the previous 6 months, including clinical, ECG, laboratory, or imaging findings. Clinically silent chance findings of old ischaemia are not considered exclusion criteria.</li> <li>• Planned surgery for ICH</li> <li>• Pregnancy, within 30 days after delivery, or during lactation</li> <li>• Use of heparin, low-molecular weight heparin, or oral anticoagulation within the previous 1 week, with abnormal laboratory values</li> <li>• Known allergy to tranexamic acid</li> <li>• Prestroke modified mRS score of &gt; 2</li> </ul>
<b>Interventions</b>	Intervention: intravenous tranexamic acid 1000 mg in 100 mL 0.9% normal saline over 10 minutes followed by 1000 mg in 500 mL 0.9% normal saline infusion over 8 h Comparator: intravenous placebo in 100 mL 0.9% normal saline over 10 minutes followed by 500 mL 0.9% normal saline infusion over 8 h

[Intervention] for [health problem]

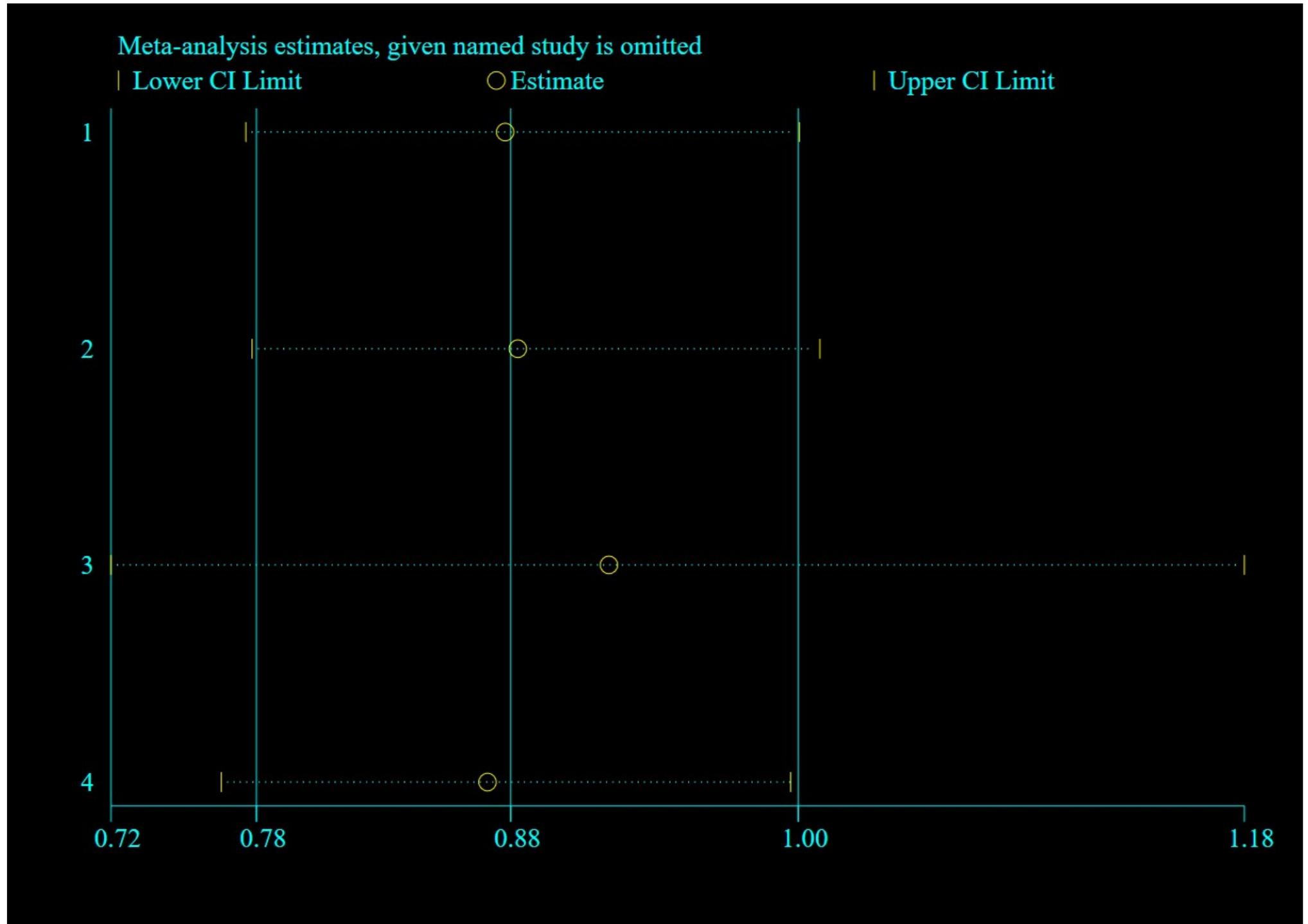
26-Jan-2021

<b>Outcomes</b>	<p>Primary outcome measures</p> <ul style="list-style-type: none"> <li>• haemorrhage growth (time frame: 24 ± 2 h) either &gt; 33%, or &gt; 6 mL increase from baseline, adjusted for baseline ICH volume</li> </ul> <p>Secondary outcome measures</p> <ul style="list-style-type: none"> <li>• Major thromboembolic events (time frame: 30 ± 4 days; acute MI, acute cerebral ischaemia, acute PE)</li> <li>• Poor clinical outcome (time frame: 90 ± 7 days): the number of participants who died or have major disability (mRS 4 to 6)</li> <li>• Short-term outcome: the number of participants with mRS 0 to 2 at 30 ± 4 days</li> <li>• Other thromboembolic events (time frame: 90 ± 7 days): other thromboembolic events, such as venous thrombosis and other peripheral arterial embolism</li> <li>• Death due to any cause: number of patients that died due to any cause by 90 ± 7 days</li> </ul>
<b>Notes</b>	NCT02625948

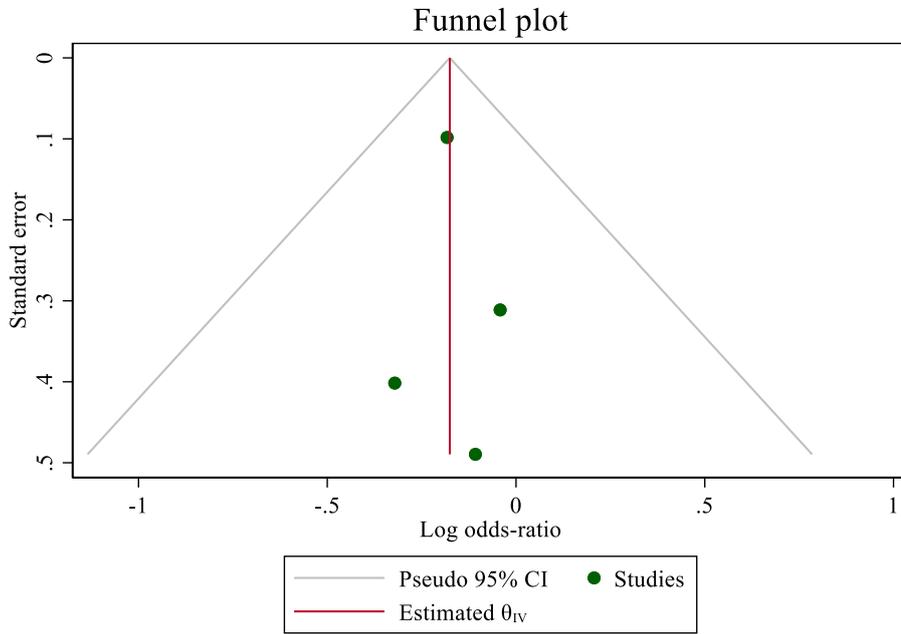
## Risk of bias table

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	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	The investigational product was distributed to participating centers in externally indistinguishable sealed treatment kits containing either tranexamic acid or placebo in identical standard off-the-shelf ampoules.
Blinding of participants and personnel (performance bias)	Low risk	Treatment allocation was concealed from all patients and investors involved in the trial.
Blinding of outcome assessment (detection bias)	Low risk	Treatment allocation was concealed from all patients and investors involved in the trial.
Incomplete outcome data (attrition bias)	Low risk	Analysis for the primary outcome was complete in ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes in the paper were reported
Other bias	Unclear risk	

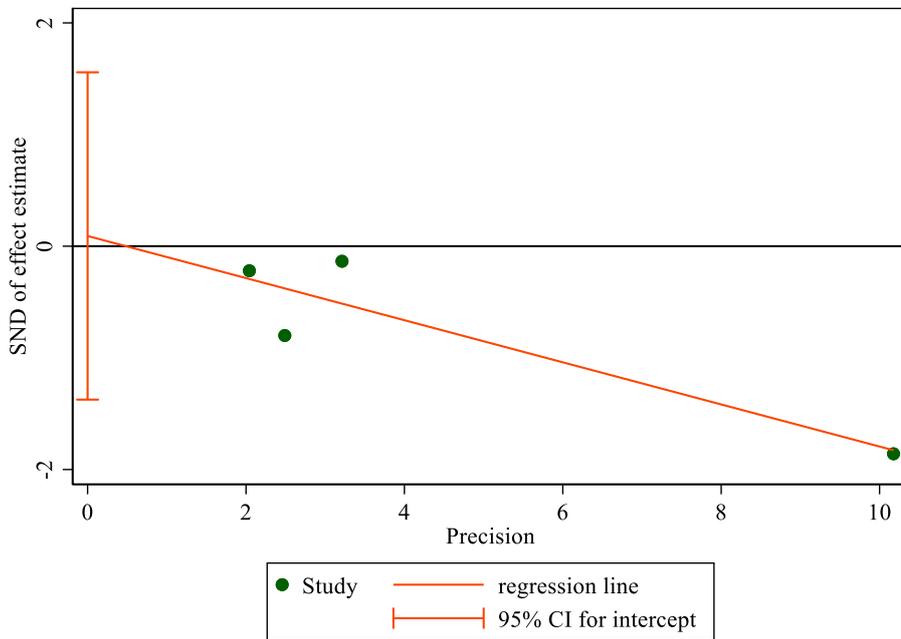
## Footnotes



**Risk of publication bias**



**A Funnel plot for the outcome of HE**



**B Egger's test for small-study effects**