Recombinant factor VIIa versus placebo for spontaneous intracerebral haemorrhage within 2 h of symptom onset (FASTEST): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial

*Joseph P Broderick, Andrew M Naidech, Jordan J Elm, Kazunori Toyoda, Dar Dowlatshahi, Andrew M Demchuk, Pooja Khatri, Thorsten Steiner, Philip M Bath, Heinrich J Audebert, Achala Vagal, Sohei Yoshimura, Stephan A Mayer, Lily L Wang, Noor Sabagha, J D Mocco, Carlos Molina, Richard Aviv, Emily Stinson, Syed A Quadri, Janice Carrozzella, Thien Huynh, Anh Phan, Jonathan Beall, Iris Davis, Nobuyuki Sakai, Tsuyoshi Ohta, Michiko Yokosawa, Takayuki Hara, Navdeep Sangha, Kenichi Morita, Ming Yin Dominc Tse, Christopher D Streib, Fumio Miyashita, Yolanda Silva, Yoshinari Nagakane, Tudor Gheorghiu, Chung-Huan Sun, Teruyuki Hirano, Sven Poli, Tsuyoshi Izumo, Mayumi Fukuda-Doi, Masafumi Ihara, Masatoshi Koga, Brian Buck, Kyle B Walsh, Ilana Spokovny, James C Grotta, for the FASTEST Investigators**

Summary

Background Recombinant factor VIIa has been shown to slow bleeding in patients with intracerebral haemorrhage (ICH), but no haemostatic agent has been shown to improve clinical outcomes. We aimed to evaluate the safety, clinical efficacy, and effect on growth of ICH and intraventricular haemorrhage (IVH) of recombinant factor VIIa in patients with acute spontaneous ICH who were most likely to benefit from treatment with this agent.

Methods We conducted a multicentre, prospective, double-blind, randomised, placebo-controlled, adaptive, phase 3 trial (FASTEST) at 93 sites across the USA, Japan, Canada, Spain, Germany, and the UK. Adults aged 18–80 years with a spontaneous ICH of 2–60 mL, IVH in less than two-thirds of one lateral ventricle or in less than a third of both lateral ventricles, a Glasgow Coma Scale score of at least 8, no evidence of recent ischaemic stroke or myocardial infarction, no recent use of anticoagulation medication or other structural cause of ICH, and who had been treated with study medication within 2 h of stroke onset or last known well were eligible for inclusion. Patients were randomly assigned (1:1) by a simple randomisation scheme to either 80 µg/kg recombinant factor VIIa (intervention group) or an identical placebo (placebo group), administered intravenously over 2 min. All investigators and participants were masked to allocated group assignment. The primary outcome was functional outcome at 180 days, measured by modified Rankin Scale (mRS; score 0–2, 3, and 4–6) and analysed by intention to treat in all randomly assigned patients. The primary safety outcome was life-threatening thromboembolic events during the first 4 days, assessed in all randomly assigned participants. The secondary aim was change in ICH volume and ICH plus IVH volume between baseline and 24 h of treatment administration. We performed an ordinal logistic regression, adjusted for age, baseline ICH volume, baseline IVH volume, and pre-stroke mRS. Preplanned interim analyses, including adaptive sample size re-estimation and enrichment to a younger subgroup (aged ≤70 years), were also conducted. This trial is registered with ClinicalTrials.gov (NCT03496883) and is closed to new participants.

Findings Between Dec 3, 2021, and Oct 1, 2025, we screened 3288 patients, of whom 626 participants were randomly assigned and included in the intention-to-treat analyses: 298 (48%) in the placebo group and 328 (52%) in the intervention group. 216 (35%) participants were female and 410 (65%) were male, with a mean age of 61 years (SD 12). Mean time from stroke onset to administration of study drug was 100 min (SD 22). The trial met the prespecified stopping criteria for futility at the second interim analysis. There was no differential effect in the primary clinical outcome measure of mRS at 180 days between the intervention group and placebo group (adjusted common odds ratio 1·09 [95% CI 0·79–1·51]; p=0·61). Life-threatening thromboembolic complications within 4 days occurred in 15 (<5%) participants in the intervention group and in four (1%) in the placebo group (relative risk 3·41 [95% CI 1·14–10·15]; p=0·020). Compared with placebo, recombinant factor VIIa was associated with decreased growth of ICH (–3·7 mL [95% CI –5·4 to –1·9]) and of ICH plus IVH growth (–5·2 mL [–7·6 to –2·8]) between baseline and CT scan at 24 h.

Interpretation Recombinant factor VIIa administered within 2 h of ICH onset slowed haematoma growth, but did not improve functional outcomes and showed a small increased risk of life-threatening thromboembolic complications. Further testing of recombinant factor VIIa in patients with the greatest risk of continued bleeding is ongoing.

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*Members listed in appendix 1 (pp 3–4)

Department of Neurology and Rehabilitation Medicine (J P Broderick MD, N Sabagha PharmD, E Stinson MS, S A Quadri MD, I Davis MS), **Department of Radiology** (A Vagal MD, L L Wang MBBS, J Carrozzella MSN), **and Department of Emergency Medicine** (K B Walsh MD), **University of Cincinnati, Cincinnati, OH, USA; Department of Neurology, Northwestern Medicine, Chicago, IL, USA** (A M Naidech MD MSPH); **Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA** (J J Elm PhD, A Phan MS, J Beall PhD); **Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan** (K Toyoda MD, S Yoshimura MD, M Koga MD PhD); **Division of Neurology, Department of Medicine, University of Ottawa and Ottawa Hospital Research Institute, Ottawa, ON, Canada** (D Dowlatshahi MD PhD); **Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada** (A M Demchuk MD); **Department of Neurology, Yale School of Medicine, New Haven, CT, USA** (P Khatri MD MSc); **Department**

of Neurology, Varisano Klinikum Frankfurt Höchst, Frankfurt, Germany (T Steiner MD); Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany (T Steiner); Stroke Trials Unit, Mental Health & Clinical Neuroscience, Queens Medical Centre, University of Nottingham, Nottingham, UK (P M Bath FMedSci DSc); Department of Neurology and Center for Stroke Research Berlin, Charité–Universitätsmedizin Berlin, Berlin, Germany (H J Audebert MD); New York Medical College, Valhalla, NY, USA (S A Mayer MD); Department of Neurosurgery, Icahn School of Medicine, Mount Sinai Health System, New York, NY, USA (J D Mocco MD); Department of Neurology, Stroke Unit, Vall d'Hebron University Hospital, Universitat Autonoma de Barcelona, Barcelona, Spain (C Molina MD); Department of Radiology, Radiation Oncology and Medical Physics, University of Ottawa, Ottawa, ON, Canada (R Aviv MD); Department of Radiology, Mayo Clinic, Jacksonville, FL, USA (T Huynh MD); Department of Neurosurgery, Kobe City Medical Center General Hospital, Hyogo, Japan (N Sakai MD, T Ohta MD PhD); Department of Neurosurgery, Iwate Prefectural Central Hospital, Morioka, Japan (M Yokosawa MD); Department of Neurosurgery, Toranomon Hospital, Tokyo, Japan (T Hara MD); Department of Neurology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA, USA (N Sangha MD); Department of Cerebrovascular Medicine, Niigata City General Hospital, Niigata, Japan (K Morita MD PhD); University of British Columbia, Vancouver, BC, Canada (M Y Dominc Tse MBChB); Department of Neurology, University of Minnesota, Minneapolis, MN, USA (C D Streib MD); Division of Neurology, Kagoshima City Hospital, Kagoshima, Kagoshima, Japan (F Miyashita MD); Hospital Universitari de Girona, Dr Josep Trueta, IDIBG, Girona, Spain (Y Silva MD); Department of

Introduction

Intracerebral haemorrhage (ICH) is the deadliest type of stroke. Despite advances in neurocritical care over the past four decades, ICH has a 30-day mortality of approximately 40% and only 20% of survivors are functionally independent at 6 months.[1] ICH leads to substantial disability and mortality in direct proportion to the volume of bleeding. Therefore, achieving haemostasis is a primary therapeutic objective. The primary challenge for haemostatic therapy in patients with spontaneous ICH is that almost all bleeding expansion occurs within the first 2–3 h after symptom onset.[2–6] For haemostatic therapies to be effective, it is crucial to treat patients who are most likely to have ongoing bleeding. Giving haemostatic therapies to patients with ICH without active bleeding increases the known risk of thromboembolic complications without any potential benefit.

The key consideration in haemostatic trials is the decrease in volume of ICH and intraventricular haemorrhage (IVH) expansion that is needed to improve functional outcomes. A pooled analysis of placebo data from trials investigating recombinant factor VIIa and a prospective population study of ICH in Greater Cincinnati, USA, indicated that 3–4 mL is the minimum volume reduction necessary to improve functional outcomes, as measured by the modified Rankin Scale (mRS).[7] But this estimate does not account for the risks of ischaemia caused by a haemostatic agent, which could negatively impact outcomes. Another study of haemorrhage growth suggests that larger decreases in growth are necessary to change functional outcomes.[8]

Recombinant factor VIIa slows bleeding when administered within 3 h of onset of spontaneous ICH, with its greatest effect on haemorrhage growth within 2 h.[2–4] However, this agent is also associated with a 5% increased risk of life-threatening thromboembolic complications compared with placebo in this patient group.[2–4] The clinical benefit of recombinant factor VIIa seen in a phase 2b trial[2] was not shown in a larger phase 3 trial.[3] Post-hoc analyses of these two studies indicated that recombinant factor VIIa had the greatest potential for benefit when administered within 2 h in patients aged 70 years and younger who did not have a large ICH or a large amount of IVH on baseline CT scan of the head.[4,9]

Research in context

Evidence before this study

Intracerebral haemorrhage (ICH), the second most common type of stroke with the greatest disability and mortality of all stroke subtypes, leads to substantial disability and mortality in direct proportion to the volume of bleeding. We performed a pooled analysis of previous phase 2b and phase 3 trials of recombinant factor VIIa. We also reviewed the treatment trials of ICH summarised in 2025 by the European Stroke Organisation and European Association of Neurosurgical Societies guideline on stroke due to spontaneous ICH in October, 2025. The primary challenge for haemostatic therapy in patients with spontaneous ICH is that almost all bleeding expansion occurs within the first 2–3 h after symptom onset. Recombinant factor VIIa slows bleeding in patients with ICH, but the clinical benefit with this agent observed in a phase 2b trial was not subsequently shown in a larger phase 3 trial. Post-hoc analyses of these two randomised trials indicated that recombinant factor VIIa had its greatest potential for benefit when administered within 2 h in patients aged 70 years and younger who did not have a large ICH or large amount of intraventricular haemorrhage on baseline CT scan of the head. A major unanswered question is the decrease in the volume of bleeding in the brain that is needed to improve functional outcomes in patients with ICH.

Added value of this study

To our knowledge, this multicentre, double-blind, randomised, placebo-controlled, phase 3 trial (FASTEST) is the largest trial to date investigating the hyperacute treatment of patients with ICH. We found that recombinant factor VIIa slowed bleeding but did not improve functional outcomes overall and was associated with a small increase in life-threatening thromboembolic complications. We also show that the agent's haemostatic effects were concentrated in patients with the greatest likelihood of ongoing bleeding: those treated within 90 min or with a spot sign on CT angiography identified within 2 h of onset. This study suggests that the mean volume of decreased haemorrhage growth needed to improve functional outcomes for any haemostatic agent is likely to be at least 6–12 mL. Our findings highlight the importance of CT angiography and rapid treatment in identifying efficacious haemostatic treatments for patients with ICH.

Implications of all the available evidence

Although we report neutral results overall, this trial provides a roadmap for the management of two subgroups of patients with ICH. Additionally, this study provides insight into the amount of haemostasis needed to improve functional outcomes for patients with spontaneous ICH treated with recombinant factor VIIa or other haemostatic agents.

In addition to time from symptom onset, another biological marker of ongoing bleeding in ICH is contrast leakage into the bed of the brain haemorrhage during baseline CT angiogram of the brain, as indicated by a spot sign.[10,11] Nevertheless, the predictive value of this spot sign decreases over time.[12] We aimed to evaluate the safety, clinical efficacy, and effect on growth of ICH and IVH of recombinant factor VIIa in patients with acute spontaneous ICH who were most likely to benefit from treatment with this agent.

Methods

Study design

We conducted a multicentre, prospective, double-blind, randomised, placebo-controlled, adaptive, phase 3 trial (FASTEST) at 93 sites across the USA (54 sites), Japan (14 sites), Canada (nine sites), Spain (six sites), Germany (six sites), and the UK (four sites), including 12 mobile stroke units. A central review board or a site-specific review board approved the trial in each participating country and at each participating global site (Advarra approval number for US central institutional review board: Pro00041014).

Because of the narrow time window to halt ongoing bleeding and the inability to obtain informed consent from many patients with ICH due to severe brain damage, the trial operated under exception from informed consent in the USA and approved emergency consent procedures in all other countries, except for Japan, which does not currently have procedures for emergency consent. Informed consent was obtained from the patient or by a legally authorised representative either before enrolment or after enrolment when emergency consent procedures were used. Although there was no specific patient involvement in the design of the trial, exception from informed consent in the USA requires focus groups and educational activities within participating communities to educate patients about the trial and listen to their input.

An independent data and safety monitoring board (DSMB) appointed by the National Institute of Neurological Diseases and Stroke (NINDS) provided oversight of the trial. This trial is registered with ClinicalTrials.gov (NCT03496883), EudraCT (2019-003722-25), and EU Clinical Trials Register (2024-517383-28-00); its Universal Trial Number is U1111-1201-0087. The trial is closed to new participants.

Participants

Adults aged 18–80 years with a spontaneous ICH of at least 2 mL and below 60 mL, IVH in less than two-thirds of one lateral ventricle or in less than a third of both lateral ventricles, a Glasgow Coma Scale score of at least 8, no evidence of recent ischaemic stroke or myocardial infarction within the previous 90 days, no recent use of anticoagulation medication within the previous 7 days or other structural cause of ICH, and who had been treated with study medication within 2 h of stroke onset were eligible for inclusion. Full inclusion and exclusion criteria are provided in appendix 1 (p 10). Data on participant sex, as well as race and ethnicity, were self-reported.

Randomisation and masking

We randomly assigned (1:1) patients to recombinant factor VIIa (intervention group) or placebo (placebo group). Any patient to receive an injection of either study treatment was enrolled in the trial.[13] Due to the high time sensitivity of the intervention, a simple randomisation scheme was used in which the lowest numbered pre-randomised kit at a site was selected. Investigators responsible for the central labelling of pre-randomised kits had no further involvement with participant enrolment or assessment.

All investigators and participants, including those assessing the outcomes and analysing the data, were masked to allocated group assignment throughout the study. To achieve masking, placebo appeared identical to the intervention agent, by use of the same solvent and process (appendix 2 p 24). The interim analyses were conducted by an unmasked statistician (JJE), in conjunction with the DSMB, who were independent of the conduct of the trial.

Procedures

All participants were assessed at baseline with the National Institutes of Health (NIH) Stroke Scale and a CT scan of the head. CT angiography at baseline was not required, but was collected when performed. All imaging data were collected and read centrally by a single senior neuroradiologist at the imaging core, including ICH and IVH volume and the presence of a spot sign on CT angiography. A baseline electrocardiogram was obtained and patients were screened for clinical signs of myocardial ischaemia before study enrolment. Serum troponin concentrations were obtained but did not need to be reviewed before enrolment.

Participants in both treatment groups received management of acute ICH supported by American Heart Association guidelines.[14] Participants in the intervention group received recombinant factor VIIa intravenously at a dose of 80 µg/kg (maximum dose 10 000 µg or 10 mg) over 2 min. Participants in the placebo group received the same volume of placebo intravenously over 2 min. All study medications were administered by someone licensed to give medication, such as a nurse, physician, or pharmacist.

Acute blood pressure management was required, with a target systolic blood pressure of 140 mm Hg by use of intravenous medications as available within a given country. These medications included intravenous nicardipine, diltiazem, clevidipine, labetalol, urapidil, enalaprilat, nitroglycerin, and nitroprusside. All participants were managed in an intensive care unit or

Neurology, Kyoto Second Red Cross Hospital, Kyoto, Japan (Y Nagakane MD PhD); **Department of Neurology, Royal Victoria Infirmary, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK** (T Gheorghiu MD); **Neuroscience Institute, The Queen's Medical Center, Honolulu, Hawaii** (C-H Sun MD); **Department of Stroke and Cerebrovascular Medicine, Kyorin University School of Medicine, Tokyo, Japan** (T Hirano MD); **Department of Neurology and Stroke and Hertie-Institute for Clinical Brain Research University of Tübingen, Tübingen, Germany** (S Poli MD); **Department of Neurosurgery, Gifu University Graduate School of Medicine, Nagasaki, Japan** (T Izumo MD); **Department of Data Science, National Cerebral and Cardiovascular Center, Osaka, Japan** (M Fukuda-Doi MD); **Department of Neurology, National Cerebral and Cardiovascular Center, Osaka, Japan** (M Ihara MD); **University of Alberta, Edmonton, AB, Canada** (B Buck MD); **Department of Neurology, Sutter Health, Mills Peninsula Medical Center, Burlingame, CA USA** (I Spokovny MD); **Memorial Hermann Hospital-Texas Medical Center, Houston, TX, USA** (J C Grotta MD)

Correspondence to:
Dr Joseph P Broderick, Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, OH 45215, USA
broderjp@ucmail.uc.edu

See **Online** for appendices 1 and 2

stroke unit after treatment. CT imaging of the brain was performed 24 h after enrolment or before surgery, if surgery within 24 h of enrolment was clinically indicated. Serum troponin concentrations were also collected 24 h after treatment administration. The type of testing used to measure troponin (eg, high sensitivity or conventional) was recorded. Study investigators followed up participants on days 30, 90, and 180 after enrolment.

Outcomes

The primary outcome was the ordinal mRS 0–2, 3, and 4–6 at 180 days, measured by the Rankin Focused Assessment Tool.[15] Secondary efficacy outcome measures included the ordinal mRS (0–2, 3, and 4–6) at 90 days; the ordinal mRS (all seven steps) at 180 days; the mRS 0–2 at 180 days; the utility-weighted mRS at 180 days; the EQ-5D health-related quality of life (EQ-5D) questionnaire at days 90 and 180; and change in ICH volume and in ICH plus IVH volume between baseline and 24 h of treatment administration. Other prespecified endpoints are listed in appendix 1 (pp 29–31).

The primary safety measure was life-threatening thromboembolic complications during the first 4 days after completing treatment with the assigned study drug. Life-threatening thromboembolic complications were defined as the development of either acute myocardial infarction, acute cerebral infarction, or acute pulmonary embolism. Secondary safety measures were these same events within 90 days, as well as all-cause mortality at 180 days.

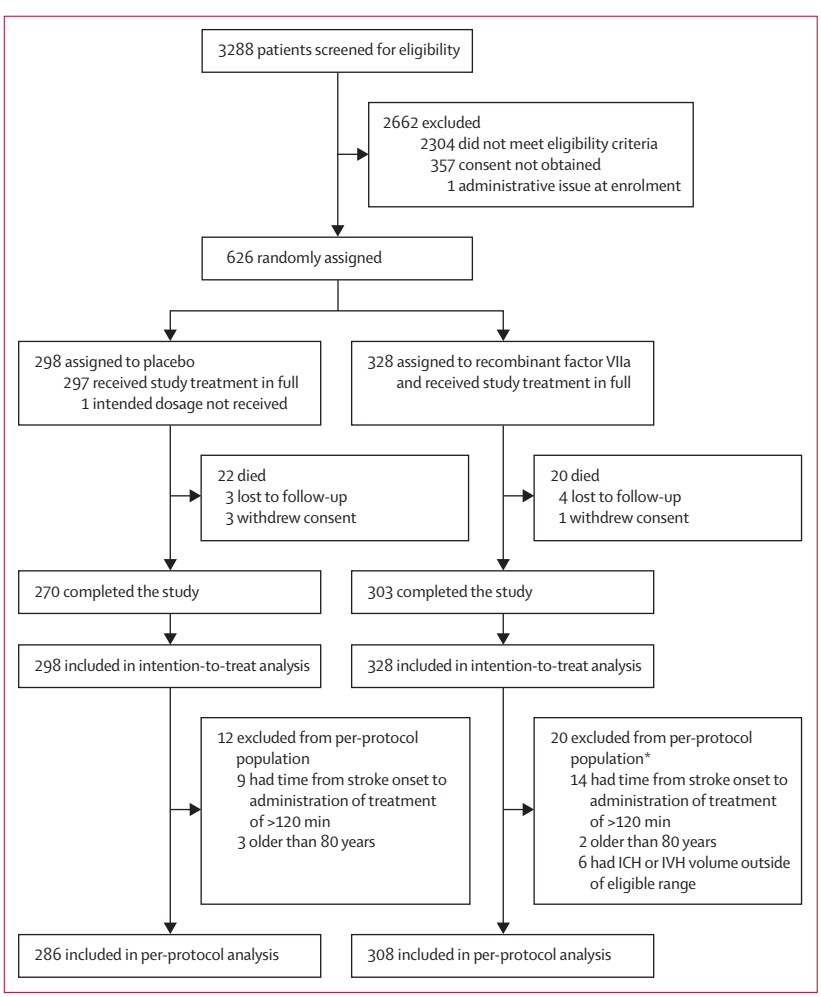

Figure 1: **Trial profile**
ICH=intracerebral haemorrhage. IVH=intraventricular haemorrhage. *Some participants were excluded for multiple reasons.

Statistical analysis

We calculated the sample size using a two-sample test of proportions of mRS 0–2 at 90 days, including the subset of patients from the FAST trial that we planned to enrol (14% absolute difference in proportions between treatment groups).[3] We chose a smaller but still clinically important difference of 10% to calculate the final sample size. With a sample size of 388 participants per group, a χ^2 test provided 80% power to detect a 10% absolute difference in proportions at a two-sided α level of 0·05, assuming a placebo proportion of mRS 0–2 of 40%. The sample size was inflated to a total of 860 participants to account for 10% of participants lost to follow-up or missing data, as well as the interim analysis.

We performed the primary analysis and safety analysis on the intention-to-treat population, which included all randomly assigned patients. We compared the ordinal values of mRS at 180 days by treatment group using an ordinal logistic regression adjusted for age, baseline ICH volume, baseline IVH volume, and pre-stroke mRS. The proportionality assumption was assessed with the score test, with a plan to use a partial proportional odds model if violated. For participants who were missing a primary outcome assessment at 180 days and had not died, we applied a multiple imputation approach to model missing scores using the 90-day mRS, 30-day mRS, assigned treatment, and aforementioned covariates. The per-protocol analysis excluded participants who received less than 1·5 min of infusion of the study medication or who did not meet the key eligibility criteria. These patients included those who did not have a spontaneous ICH, had time from stroke onset of more than 120 min, were older than 80 years, had a baseline ICH or IVH volume outside of the eligible range, or had a baseline Glasgow Coma Scale score of less than 8.

The secondary and subgroup analyses of mRS outcome and EQ-5D at days 90 and 180 are detailed in the statistical analysis plan (appendix 1 pp 29–31). We analysed secondary efficacy outcomes on the intention-to-treat population in a linear, ordinal logistic, or logistic regression adjusted for age, baseline ICH volume, baseline IVH volume, and pre-stroke mRS. We used the Hochberg's step-up procedure to control for multiple comparisons. We assessed safety outcomes with the Fisher's exact test at a two-sided α level of 0·05 unadjusted

	Placebo group (n=298)	Intervention group (n=328)
Age, years	60 (12)	61 (12)
Age group, years		
≤70	232 (78%)	241 (73%)
>70	66 (22%)	87 (27%)
Sex		
Female	105 (35%)	111 (34%)
Male	193 (65%)	217 (66%)
Ethnicity		
Hispanic or Latinx	25 (8%)	32 (10%)
Not Hispanic or Latinx	271 (91%)	296 (90%)
Unknown	2 (1%)	0
Race		
American Indian or Alaska Native	0	1 (<1%)
Asian	169 (57%)	173 (53%)
Black or African American	23 (8%)	30 (9%)
Native Hawaiian or other Pacific Islander	1 (<1%)	1 (<1%)
Unknown or not reported	5 (2%)	5 (2%)
White	100 (34%)	118 (36%)
Pre-stroke modified Rankin Scale score		
0	281 (94%)	303 (92%)
1	10 (3%)	17 (5%)
2	6 (2%)	8 (2%)
3	1 (<1%)	0
Time between stroke onset and administration of study drug, min	99·2 (18·7)	101·2 (23·8)
ICH volume, mL	16·5 (13·3)	16·9 (15·6)
IVH volume, mL	1·4 (4·1)	1·7 (5·9)
NIH Stroke Scale score	13 (8–17)	13 (8–17)
Baseline Glasgow Coma Scale score		
8	5 (2%)	8 (2%)
9	8 (3%)	10 (3%)
10	15 (5%)	14 (4%)
11	21 (7%)	19 (6%)
12	11 (4%)	15 (5%)
13	29 (10%)	24 (7%)
14	69 (23%)	50 (15%)
15	140 (47%)	188 (57%)
	(Table 1 continues in next column)	

	Placebo group (n=298)	Intervention group (n=328)
(Continued from previous column)		
Location of ICH		
Lobar	41 (14%)	35 (11%)
Deep	254 (85%)	287 (88%)
Infratentorial	3 (1%)	6 (2%)
Blood pressure, mm Hg	170/98	173/99
CT angiography performed	254 (85%)	257 (78%)
Spot sign on CT angiography	77 (26%)	71 (22%)
Study medication administered in mobile stroke unit	6 (2%)	11 (3%)
ECG result		
Abnormal, clinically significant	5 (2%)	4 (1%)
Abnormal, not clinically significant	131 (44%)	145 (44%)
ECG not performed	1 (<1%)	3 (1%)
Normal	161 (54%)	176 (54%)
Troponin elevation	50 (17%)	64 (20%)
Ultra-early haematoma growth <10 mL/h	128 (43%)	153 (47%)
Ultra-early haematoma growth, ≥10 mL/h	170 (57%)	175 (53%)

Data are mean (SD), n (%), or median (IQR). ICH=intracerebral haemorrhage. IVH=intraventricular haemorrhage. NIH=National Institutes of Health. ECG=electrocardiogram.

Table 1: **Baseline participant characteristics in the intention-to-treat population**

for multiple comparisons. Additional prespecified subgroup analyses are detailed in the statistical analysis plan (appendix 1 pp 29–31) and study protocol (appendix 2 pp 21–22).

At the beginning of enrolment, the study protocol had a planned analysis for futility and overwhelming efficacy after approximately 430 participants (half of the planned study sample population of 860 participants) had completed their 180-day assessment. An additional interim analysis was subsequently added for futility alone and had two components that had to be met. The first component was clinical functional outcome, as measured by the mRS at 180 days (conditional power <0·20 for the primary outcome). The second component was mean difference in ICH growth between both treatment groups, with the 95% upper confidence bound for the observed difference in ICH growth exceeding that for a mean difference of –2·5 mL less growth in the intervention group than in the control group, as predicted for this subgroup of patients from the FAST trial.[3] This analysis occurred after 200 randomly assigned participants had completed 6 months of follow-up, and the DSMB recommended continuation of the trial.

The second planned interim analysis, performed after approximately 430 participants had completed their 180-day assessment, was subsequently expanded. An alpha spending function with O'Brien–Fleming type stopping boundaries (two-sided) was used to stop the trial for overwhelming superiority of either group, while maintaining the two-sided type 1 error rate at 0·05. The trial could also be stopped early for futility if the conditional power was less than 0·20. Additionally, at the second interim analysis, we prespecified the following two adaptations: an adaptive re-estimation of the study population up to a maximum of 1330 patients when the interim results were promising,[16] and an adaptive population enrichment of an age-defined subgroup (aged ≤70 years).[17] Both adaptations were defined with the promising zone approach.[16,17] A simulation report conducted before the first interim

analysis showed that type I and type II errors were controlled.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, except for the scientific programme officer from the NINDS, who was a member of the executive committee of the trial.

Results

On Jan 9, 2025, the NINDS and DSMB recommended that enrolment stop for overall futility based on the interim analysis of 434 participants who had completed the evaluation at 180 days (conditional power <1% under the current trend). Additionally, the prespecified enrichment to the age group 70 years and younger showed no evidence of benefit (conditional power <1%). At this point, we had randomly assigned 626 participants between Dec 3, 2021, and Oct 1, 2025 (figure 1; appendix 1 p 11). After all 626 participants had completed their 180-day evaluation, the database was locked on July 25, 2025. All 626 randomly assigned participants were included in the intention-to-treat analyses (298 [48%] in the placebo group and 328 [52%] in the intervention group); 594 participants were included in the per-protocol analyses (286 [48%] in the placebo group and 308 [52%] in the intervention group; figure 1).

216 (35%) participants were female and 410 (65%) were male, with a mean age of 61 years (SD 12) at baseline. Overall, mean ICH volume was 16·7 mL (SD 14·6) and mean IVH volume was 1·5 mL (SD 5·1), median NIH

	Placebo group	Intervention group	OR (95% CI)*	Two-sided p value
Primary outcome				
mRS at 180 days in the intention-to-treat population				
0–2	134/298 (45%)	151/328 (46%)	1·09 (0·79 to 1·51)	0·61
3	76/298 (26%)	80/328 (24%)	..	..
4–6	88/298 (30%)	97/328 (30%)	..	..
mRS at 180 days in the per-protocol population				
0–2	129/286 (45%)	146/308 (47%)	1·12 (0·80 to 1·56)	0·87
3	75/286 (26%)	79/308 (26%)	..	..
4–6	82/286 (29%)	83/308 (27%)	..	..
Secondary outcomes				
Ordinal distribution of the mRS at 90 days				
0–2	113/298 (38%)	132/328 (40%)	1·13 (0·82 to 1·56)	0·87
3	57/298 (19%)	59/328 (18%)	..	..
4–6	128/298 (43%)	137/328 (42%)	..	..
Ordinal distribution of the mRS at 90 days†	3 (2 to 4)	3 (2 to 4)	1·13 (0·86 to 1·51)	0·87
Ordinal distribution of the mRS at 180 days†	3 (2 to 4)	3 (2 to 4)	1·10 (0·83 to 1·47)	0·87
mRS 0–2 at 90 days	113/298 (38%)	132/328 (40%)	1·15 (0·80 to 1·66)	0·87
mRS 0–2 at 180 days	134/298 (45%)	151/328 (46%)	1·12 (0·77 to 1·61)	0·87
Utility-weighted mRs at 90 days	5·5 (2·9)	5·5 (3·0)	..	..
OR (95% CI)	4·78 (4·20 to 5·35)	4·97 (4·40 to 5·53)	..	0·87
Utility-weighted mRs at 180 days	6·1 (2·9)	6·1 (2·9)	..	..
OR (95% CI)	5·27 (4·71 to 5·8)	5·40 (4·86 to 5·94)	..	0·87
Change in ICH volume from baseline to 24 h, mL	5·5 (13·7)	1·9 (7·0)	..	..
OR (95% CI)	4·76 (2·31 to 7·21)	1·0 (–1·39 to 3·38)	..	0·0011
Change in ICH plus IVH volume from baseline to 24 h, mL	7·4 (19·6)	2·2 (8·4)	..	..
OR (95% CI)	7·41 (4·02 to 10·78)	1·99 (–1·31 to 5·28)	..	0·0011
EQ-5D at 90 days	0·5 (0·4)	0·5 (0·4)	..	0·87
OR (95% CI)	0·40 (0·32 to 0·48)	0·40 (0·33 to 0·48)	..	..
EQ-5D at 180 days	0·5 (0·4)	0·5 (0·5)	..	0·87
OR (95% CI)	0·47 (0·39 to 0·54)	0·47 (0·39 to 0·54)	..	..

Data are n (%), median (IQR), or mean (SD), unless otherwise indicated. The imputed dataset included 626 participants. mRS at day 180 was missing for ten participants; data were imputed using multiple imputation. mRS was missing for seven participants at day 30 and for 15 participants at day 90; data were imputed using hot-deck imputation. OR=odds ratio. mRS=modified Rankin Scale. ICH=intracerebral haemorrhage. IVH=intraventricular haemorrhage. EQ-5D=EQ-5D health-related quality of life. *Adjusted common ORs and 95% CIs from a proportional odds regression model are provided for categorical outcomes; least squared means and 95% CIs from a linear regression model are reported for numerical outcomes. Both regression analyses are adjusted for age, baseline ICH volume, baseline IVH volume, and pre-stroke mRS. p values for secondary outcomes were calculated with Hochberg's step-up procedure to adjust for multiple comparisons. †All seven steps of the mRS.

Table 2: **Efficacy outcomes after missing data imputation**

Stroke Scale was 13 (IQR 8–17), and mean time from stroke onset to administration of study drug was 100 min (SD 22; table 1). The use of emergency consent procedures by country is provided in appendix 1 (p 12). Among the 626 participants, 615 (98%) completed the mRS assessment at 180 days, four (<1%) withdrew consent, and seven (1%) completed either a 30-day or 90-day follow-up visit but were lost to follow-up before the 180-day assessment. Blood pressure control was similar between the two treatment groups (appendix 1 p 13).

There was no differential effect in the primary clinical outcome measure of mRS at 180 days between the intervention group and placebo group (adjusted common odds ratio [OR] 1·09 [95% CI 0·79–1·51]; p=0·61; table 2; appendix 1 p 8). No differential effects were found in the secondary outcome of mRS at 90 days (1·13 [0·82–1·56]; p=0·87; table 2; appendix 1 p 8), nor in patients aged 70 years or younger (1·09 [0·75–1·59]; appendix 1 pp 9, 14–16). Overall, compared with placebo, recombinant factor VIIa was associated with significantly decreased growth of ICH (–3·68 mL [95% CI –5·40 to –1·94; p=0·0011) and of ICH plus IVH (–5·23 [–7·64 to –2·82]; p=0·0011) between baseline and CT scan of the head at 24 h after administration (table 2). Categories of absolute volume of haemorrhage growth for both treatment groups are presented in appendix 1 (p 17).[8]

The primary safety outcome of life-threatening thromboembolic complications within 4 days of treatment administration occurred in 15 (<5%) participants in the intervention group and in four (1%) of those in the placebo group (relative risk 3·41 [95% CI 1·14–10·15]; two-sided Fisher's exact test p=0·020; table 3). The secondary safety outcome of life-threatening thromboembolic complications within 90 days occurred in 21 (6%) participants in the intervention group and in 11 (4%) in the placebo group (1·73 [0·85–3·54]; p=0·15).

Among all 626 participants, 511 (82%) had a baseline CT angiography either before or after study drug administration, of whom 148 (29%) had a spot sign. Prespecified subgroup analyses of the primary outcome favoured recombinant factor VIIa over placebo for patients with a spot sign (adjusted common OR 1·86 [95% CI 0·94–3·68]) and for those treated within 90 min (1·82 [0·94–3·68]), although these effects were not significant (figure 2). In tertiary and exploratory analyses, the positive signals in mRS were more apparent at 90 days among both patients with a spot sign (2·52 [1·20–5·28]) and those treated within 90 min (2·66 [1·43–4·96]). Logistic regression interaction modelling in the exploratory analyses suggested that the greatest potential benefit of recombinant factor VIIa was in patients who had both a spot sign on CT angiography and treatment within 90 min (appendix 1 pp 15–16).

Compared with placebo, recombinant factor VIIa was associated with decreased growth of ICH (–3·7 mL [95% CI –5·4 to –1·9]) and of ICH plus IVH growth (–5·2 mL [–7·6 to –2·8]) between baseline and follow-up CT scan at 24 h after treatment administration. Furthermore, recombinant factor VIIa was associated with a substantial decrease in ICH growth (–9·4 mL) and in ICH plus IVH growth (–14·1 mL) in participants with a spot sign, compared with a small decrease in those without a spot sign on CT angiography (ICH growth –2·1 mL and ICH plus IVH growth –2·7 mL; appendix 1 p 17). Treatment with recombinant factor VIIa within 90 min was also associated with a greater decrease in ICH plus IVH growth (–7·5 mL [95% CI –11·9 to –3·3]) than was placebo. Decreases in the absolute growth of ICH associated with recombinant factor VIIa in patients with a spot sign and those treated within 90 min were considered either moderate (6·1–12·5 mL) or major (>12·5 mL; appendix 1 pp 18–19).

Discussion

This multicentre, double-blind, randomised, placebo-controlled, adaptive phase 3 trial showed that recombinant factor VIIa administered within 2 h of

	Placebo group (n=298)	Intervention group (n=328)	Relative risk (95% CI)
Life-threatening thromboembolic complications within 4 days*	4 (1%)	15 (<5%)	3·41 (1·14–10·15)
Life-threatening thromboembolic complications within 90 days*†	11 (4%)	21 (6%)	1·73 (0·85–3·54)
Unstable angina	0	0	..
Deep venous thrombosis (not leading to pulmonary embolism)	4 (1%)	7 (2%)	1·59 (0·47–5·38)
Mortality within 180 days	22 (7%)	20 (6%)	0·83 (0·46–1·48)
mRS 5–6 at 180 days	31 (10%)	37 (11%)	1·08 (0·69–1·70)
Myocardial injury without acute coronary syndrome	30 (10%)	49 (15%)	1·48 (0·97–2·27)
Acute myocardial infarction‡	4 (1%)	3 (1%)	0·68 (0·15–3·02)
Acute cerebral infarction‡	11 (4%)	18 (5%)	1·49 (0·71–3·10)
Acute pulmonary embolism‡	3 (1%)	5 (2%)	1·51 (0·37–6·28)

mRS=modified Rankin Scale. *Defined as a serious adverse event of acute myocardial infarction, acute cerebral infarction, or acute pulmonary embolism. †One life-threatening thromboembolic complication event occurred 97 days after randomisation in the placebo group and was excluded from the secondary safety outcome of life-threatening thromboembolic complications within 90 days. ‡Serious and non-serious adverse events, including small diffusion-positive lesions without any clinical change.

Table 3: **Safety outcomes in the intention-to-treat population**

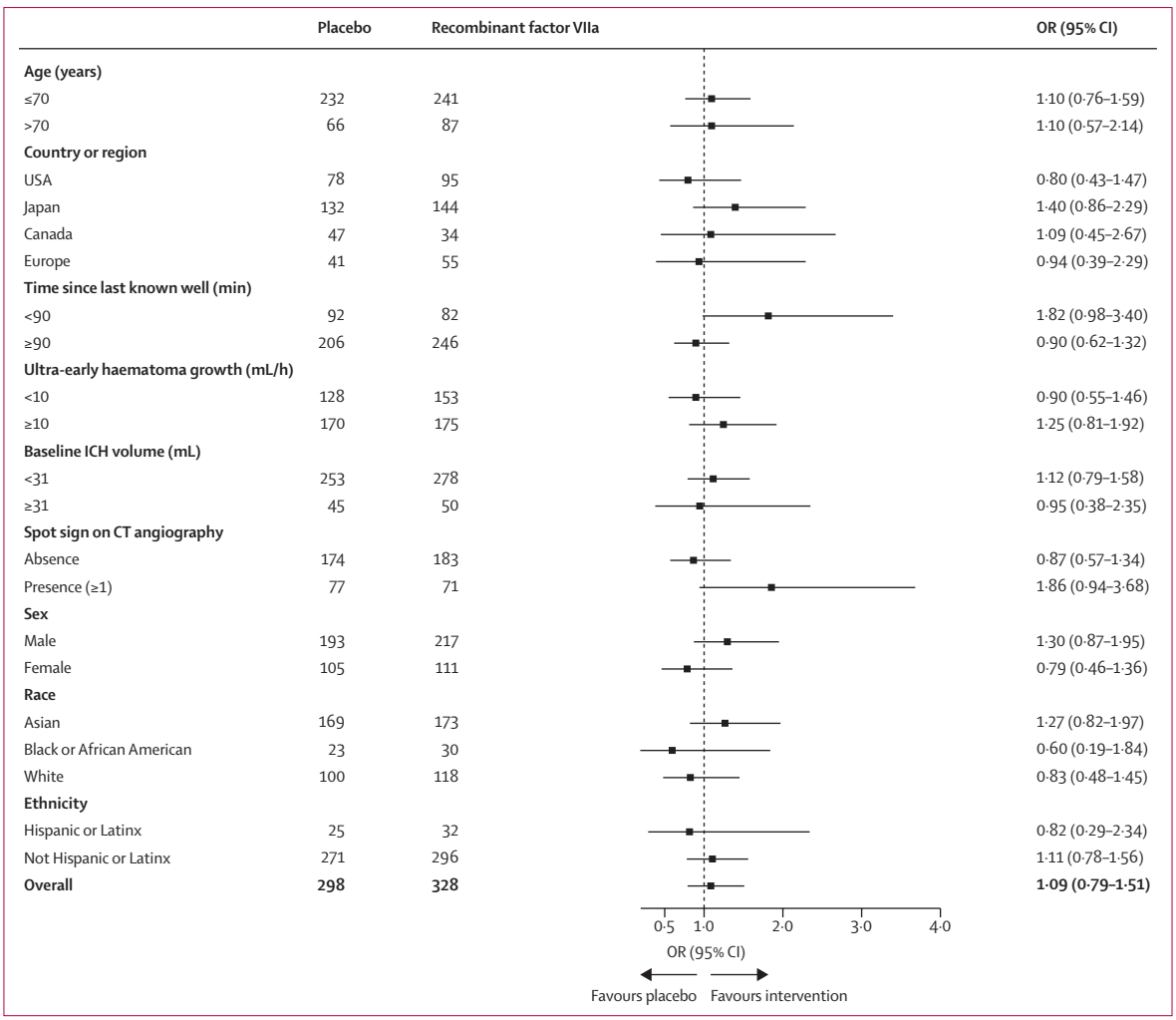

Figure 2: **Prespecified subgroup analyses of mRS at 180 days**
mRS=modified Rankin Scale. OR=odds ratio. ICH=intracerebral haemorrhage.

symptom onset did not improve functional outcomes in patients with spontaneous ICH compared with placebo. Additionally, this agent was associated with a small but significantly increased risk of life-threatening thromboembolic complications. This risk was found even though recombinant factor VIIa decreased the volume of haemorrhage expansion by a mean 3·5 mL overall, which is consistent with previous trials of this agent and is a greater decrease than other reported haemostatic trials for patients with ICH. The FASTEST trial shows that the greatest decrease in ICH growth occurred in participants with a spot sign and in those who were treated within 90 min. Additionally, this study suggests that the mean volume of decreased haemorrhage growth that is necessary to improve functional outcomes is likely not 3–4 mL, but at least 6–12 mL. Larger volumes of haematoma expansion have been linked to an increased likelihood of poor outcomes.[8] To our knowledge, the reduction in haematoma growth observed in participants with a spot sign and in those who were treated within 90 min is the largest observed with any medical therapy for spontaneous ICH to date.

Medical and surgical trials for ICH have shown potential benefit for some subsets of patients, but illustrate remaining challenges.[18] These challenges include selecting subgroups most likely to benefit from treatment, minimising time to treatment, and reducing a sufficient volume of ICH to improve functional outcomes. The ENRICH trial of minimally invasive surgery within 24 h of onset showed improved outcomes for patients with lobar ICH, but not basal ganglia ICH.[19] The study's findings were not substantiated by the MIND trial, which had a treatment window of 72 h.[20] Three trials of early blood pressure control to a target of 140 mm Hg systolic suggested mild to modest improvements in functional outcomes.[21–23] However, none of these studies clearly slowed intracranial bleeding, except for the Chinese INTERACT4 trial, in which patients with potential stroke

and a blood pressure of at least 150 mm Hg in the ambulance were randomly assigned to either intravenous urapidil or standard care before brain imaging.[23] The trial showed neutral results overall, with worse clinical outcomes in patients with ischaemic stroke but significantly improved outcomes in those with ICH. Several haemostatic trials reported a slowing of bleeding with reversal of anticoagulation in patients with ICH while on vitamin K antagonists or factor Xa or thrombin inhibitors; however, none of these trials showed significant improvements in clinical outcomes.[24,25] Previous prospective studies exploring the relationship between decreased haemorrhage expansion in patients with ICH and improved clinical outcomes on the mRS suggest that a mean decrease in the volume of ICH of 3–4 mL due to a haemostatic agent is likely the minimum volume needed to detect a clinical benefit in a trial.[7,8] Nevertheless, the clinical benefit from this amount of haemostasis must outweigh the increase in life-threatening thromboembolic complications associated with haemostatic agents, which can also affect clinical outcomes.[1]

CT angiography as a standard diagnostic test for the evaluation of acute stroke accelerated after the demonstrated efficacy of endovascular therapy for patients with ischaemic stroke in 2015 and the subsequent importance of identifying vascular occlusions and minimising time to treatment.[26] This clinical development led to the routine assessment of more patients with ICH, because CT angiography has become part of the normal workflow for the assessment of patients with potential stroke in high-income countries, generating additional evidence that a spot sign represents a marker of ongoing bleeding. However, the predictive value of the spot sign of clinically significant haematoma growth in patients with ICH substantially diminishes with time. In a pooled patient-level data analysis of 12 studies exploring the relationship between the presence of a spot sign and ICH growth in 1038 patients, Dowlatshahi and colleagues[12] reported a significant decrease in haematoma expansion as time between symptom onset and CT angiography increased in patients with a spot sign (p=0·004), with positive predictive values decreasing from 53% to 33%.

Two small pilot randomised trials of recombinant factor VIIa in patients with ICH and a spot sign treated only four participants within 2 h of onset, and had substantial delays between baseline CT angiography and administration of the intervention.[27] These trials did not show any clear slowing of bleeding with recombinant factor VIIa. In one of these spot sign studies, an immediate post-dose CT was performed to evaluate what proportion of bleeding might have occurred before the study drug could be administered. This analysis revealed that 90% of all haematoma expansion had occurred between baseline CT and post-dose CT, suggesting that much faster study drug administration is needed.[28] These results and our data suggest that the usefulness of CT angiography as a biological marker of substantial ongoing bleeding is strongly related to the timing of CT angiography and how quickly recombinant factor VIIa or other haemostatic agents need to be administered after identification of a spot sign. This finding is supported by the results of other haemostatic trials of tranexamic acid for patients with spontaneous ICH, which showed that the only signal for slowing of intracranial bleeding was in participants who had a spot sign on CT angiography and were treated within 2 h.[29,30]

Exception from informed consent and emergency consent procedures, the use of mobile stroke units, and emphasising time to treatment in the standard workflow of patients with stroke all had a role in the rapid administration of study treatment in the FASTEST trial, even with the requirement of brain imaging.[9] FASTEST is the largest trial treating patients with stroke within 2 h of onset that requires brain imaging before treatment, including trials of ischaemic stroke, which is more than two times more common globally[31] and approximately eight times more common in the USA.[32] FASTEST also reflects the importance of global trials to enrol a sufficient study population of a less common type of stroke, one that is more common in Asian countries.[33] Given that only about 45% of participants in FASTEST received treatment within 90 min or had a spot sign identified within 2 h, the ongoing extension of this trial (FASTEST part 2; NCT07227246) is recruiting from additional sites; therefore, recruitment will be correspondingly slower.

The step-forward randomisation process in the FASTEST trial, identical to that in the NINDS rt-PA Stroke Trial,[34,35] allowed for rapid participant enrolment and minimisation of time to treatment. This process was crucial in FASTEST, but cannot adjust for the potential imbalances in the number of participants in each treatment group nor minimisation of key baseline variables that are known to be related to outcomes after ICH. Adjustment for imbalances in these key variables can only occur at the time of analysis, which was planned for in our statistical approach.

At the time that the DSMB recommended halting the trial for futility in its current iteration, the board also recommended consideration to continue the trial within the subgroup of patients with a spot sign. We subsequently added treatment within 90 min to this subgroup when the full FASTEST database was available for analysis. However, a limitation of our results is that the proportion of patients with ICH worldwide who might benefit from recombinant factor VIIa would be small if treatment is effective only for these subgroups. We estimate that approximately 5% of the 1840 500 patients with ICH globally would qualify for recombinant factor VIIa treatment with a spot sign within 2 h or treatment within 90 min without a spot sign.[36] This trial's focus on rapid treatment by minimising time to evaluation and treatment and emergency consent procedures can be replicated in sites with CT angiography

and processes that minimise time to imaging and treatment. Demonstrating effective haemostatic treatment for ICH, even in a smaller proportion of patients, is likely to expand the number of eligible patients in the future with advances in imaging and recognition, as also occurred with access to thrombolysis treatment for ischaemic stroke. Only 1% of patients with ischaemic stroke were treated with thrombolytics in the years immediately following its approval by the US Food and Drug Administration in 1995, which increased to 7% in the USA by 2014[37] and to 21% in Norway in 2021.[38]

Subgroup analyses, even when prespecified as in the current trial, have limitations of a smaller sample size, limited power, and multiple statistical testing, and are more subject to findings due to chance alone. The linkage between much larger decreases in haemorrhage expansion in the two subgroups with signals of clinical efficacy provides a good biological rationale that these observations were not due to chance; however, this requires further testing in the ongoing FASTEST 2 trial (NCT07227246).

In conclusion, recombinant factor VIIa administered within 2 h of ICH onset slowed haematoma growth, but did not improve functional outcomes at 180 days in patients with spontaneous ICH. Additionally, this agent was associated with a small increased risk of life-threatening thromboembolic complications. Further testing of recombinant factor VIIa in patients with the greatest risk of continued bleeding is ongoing.

Contributors

JPB, JCG, and AMN conceived and designed the study and provided overall scientific oversight. The trial's executive committee, including KT, DD, TS, CM, PMB, AMD, PK, HJA, AV, SY, SAM, LLW, JDM, RA, and ID, contributed to trial governance and supervised study conduct across participating sites. SAM served as the independent medical safety monitor for the study. JJE developed the statistical analysis plan and led the statistical analyses, with analytical support from JB and AP and input from the study investigators. Imaging data were centrally reviewed and adjudicated by the FASTEST Imaging Core Laboratory (LLW, AV, and JCG). ThH and RA developed and maintained imaging training and the certification platform for participating sites. ES, SAQ, and JPB led trial operations, project administration, data curation, validation, and regulatory and site coordination in the USA, and oversaw global efforts in other countries. KT, SY, MK, and MF-D oversaw trial operations in Japan. DD oversaw trial operations in Canada. TS, PMB, and CM oversaw trial operations in Germany, Spain, and the UK. NooS oversaw investigational product supply, international drug shipment, and pharmacy coordination. Site investigators NobS, TO, MY, TaH, NaS, KM, MYDT, CDS, FM, YS, YN, TG, C-HS, TeH, SP, TI, MI, BB, KBW, and IS, together with the FASTEST Investigators, enrolled participants and conducted study procedures at their respective sites. All authors contributed to interpretation of the data, critically reviewed and edited the manuscript, approved the final version, and agreed to be accountable for the work. JJE, AP, and JPB verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JPB reports funding from NINDS as the primary funder of the trial to the University of Cincinnati; and receipt of study medication and financial support from Novo Nordisk for temperature monitoring of study medication and support for investigator efforts outside business hours. JPB also reports consulting fees related to a Roche paediatric stroke trial and consultation for Basking Bioscience, outside of the submitted work. JCG reports consulting fees from Frazer, outside of the submitted work. AMN reports institutional support from the NIH related to the manuscript; royalties from Cambridge University Press for a handbook on neurocritical care; and honoraria for educational activities from the Society of Critical Care Medicine, outside of the submitted work. KT reports research support from the Japan Agency for Medical Research and Development (JP19lk0201094 and JP23lk0221171); grants and contracts from SoftBank Group; consulting fees from Janssen Pharmaceuticals; and honoraria for lectures from Otsuka Pharmaceutical, outside of the submitted work. DD reports funding from the Canadian Institutes of Health Research for the ICATCHER trial. DD also holds a patent for an algorithm for the automatic recognition of contrast extravasation, outside of the submitted work. AMD reports consulting fees from AstraZeneca; honoraria for continuing medical education events from Novo Nordisk and AstraZeneca; participation on a DSMB for the TRUST study (Philips); leadership roles as Chair of the Board of Directors of the Canadian Stroke Consortium; and stock ownership in Circle CVI, outside of the submitted work. SP reports grants or contracts from BMS–Pfizer (ATTICUS trial), Boehringer Ingelheim (non-financial support for the REVISION trial), Daiichi Sankyo, the German Federal Joint Committee Innovation Fund, the German Federal Ministry of Education and Research, Helena Laboratories, Werfen, and the European Union Horizon 2020 programme; consulting fees from Alexion, AstraZeneca, Daiichi Sankyo, and Werfen; honoraria from Alexion, Bayer, Boehringer Ingelheim, BMS–Pfizer, and Portola; and participation on a DSMB for the OPENS-2 trial, outside of the submitted work. HJA reports grants from the German Federal Ministry of Education and Research, the German Research Foundation, and German Innovation Funds; consulting fees from Eli Lilly and Boehringer Ingelheim; honoraria from Boehringer Ingelheim, Pfizer, BMS, Novartis, Ever Neuropharma, and Bayer Healthcare; and participation on an advisory board and DSMB for Novo Nordisk, outside of the submitted work. PMB reports grants from the NIHR Health Technology Assessment programme (PhEAST trial) and the Alzheimer's Society (CVD-Cog trial); consulting roles with CoMind and DiaMedica; chairing the AVERT-DOSE DSMB; leadership roles with the World Stroke Organisation; stock or advisory interests in CoMind and DiaMedica; and receipt of equipment and training from Phagenesis, outside of the submitted work. TO reports honoraria for lectures or participation in speakers bureaus from Daiichi Sankyo, Otsuka Pharmaceutical, Takeda, AstraZeneca, Kowa, Takeda Pharmaceutical Company, and Nestlé Japan, outside of the submitted work. MF-D reports institutional grant support from the Japan Agency for Medical Research and Development (JP22oa0310011 and JP25oa0439003) and JSPS KAKENHI (21K17241), outside of the submitted work. All other authors declare no competing interests.

Data sharing

Upon completion of the trial and the dissemination of primary results, de-identified patient-level data (analysis data files) will be made available to the wider scientific community via the NINDS data repository.

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