Characteristics of studies

Characteristics of included studies

SPOTLIGHT STOP-IT 2019

Methods	SPOTLIGHT: 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 STOP-IT: The purpose of this study is to determine if computed tomography angiography can predict which individuals with ICH will experience significant growth in the size of the haemorrhage. For individuals who are at high risk for haemorrhage growth, the study will compare the drug recombinant activated factor VII (rFVIIa) to placebo to determine the effect of rFVIIa on ICH growth
Participants	SPOTLIGHT: Inclusion criteria • Acute spontaneous primary supratentorial ICH diagnosed by CT scan • Presence of a spot sign within the haematoma on CTA source images • Baseline ICH volume 3 mL to 90 mL • Age 18 or older • Investigator is able to randomise and administer study drug as soon as possible within a target of 60 minutes after CT angiogram and no later than 6 h after stroke symptom onset (using the ’last seen normal’ principle) • Plan to provide full medical care for at least 24 h • Assent-consent from participant or LAR prior to enrolment, or a waiver of consent (where REB approved) if patient or LAR assent-consent is not possible prior to enrolment Exclusion criteria • Brainstem or cerebellar haemorrhage • ICH secondary to known or suspected trauma, aneurysm, vascular malformation, hemorrhagic conversion of ischaemic stroke, venous sinus thrombosis, thrombolytic treatment, tumour, or infection; or an in-hospital ICH or ICH as a result of any in-hospital procedure or illness • Baseline brain imaging shows evidence of acute or subacute ischaemic stroke (chronic infarcts are not an exclusion) • Contrast administration within the previous 24 h • Evidence of thromboembolic risk factors, defined as any of the following:

	known history within the past 6 months of any of the following: 1) MI, 2) coronary artery bypass surgery, 3) angina, 4) ischaemic stroke, 5) TIA, 6) carotid endarterectomy, 7) cerebral bypass surgery, 8) deep venous thrombosis, 9) pulmonary embolism, 10) any vascular angioplasty, stenting (coronary, peripheral vascular, or cerebrovascular) or filter (e.g. vena cava filter); 11) prosthetic cardiac valve, and, or 12) known history of a high-risk thrombophilia (e.g. antithrombin III deficiency, antiphospholipid antibody syndrome, protein C deficiency, etc) • Known hereditary (e.g. haemophilia) or acquired haemorrhagic diathesis or coagulation factor deficiency • Any known condition that the investigator feels would pose a significant hazard if rFVIIa were administered • Planned surgery for ICH within 24 h (placement of intraventricular catheter is not an exclusion) • Planned withdrawal of care before 24 h post-ICH onset • Known participation in another therapeutic trial • Known allergy or other contraindication to iodinated contrast dye • Known or suspected hypersensitivity to the trial product • Known unfractionated heparin use - must check PTT and exclude if elevated above upper limit of local lab's reference range • Known low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use within previous 7 days • Known GPIIb/IIIa antagonist use in previous 2 weeks • Known warfarin (or other anticoagulant) therapy with INR > 1.40. Note: if the patient is suspected to have cirrhosis, study staff are to wait for the INR value prior to dosing, and ensure they do not enrol the patient if the INR value is > 1.40. Otherwise, the physician should use their discretion if they believe the patient is not at risk for elevated INR • Concurrent or planned treatment with prothrombin complex concentrate, vitamin K, fresh frozen plasma, or platelet transfusion • Pregnancy or lactation. Women of childbearing potential must have a negative pregnancy test prior to randomization. • Current clinical symptoms suggestive of acute coronary ischaemia (e.g. chest pain). • Baseline ECG evidence of acute coronary ischaemia (e.g. ST elevation in 2 contiguous leads, new LBBB, ST depression) Baseline platelet count 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 ⩾ 18 years through 80 years (candidates must have had their 18th birthday, but not had their 81st birthday) • For spot positive patients, dosing of study drug within 90 minutes of enrolling CT scan

	Exclusion criteria • Time of symptom onset of ICH is unknown or more than 5 h prior to baseline CT scan • ICH secondary to known or suspected trauma, aneurysm, vascular malformation, haemorrhagic conversion of ischaemic stroke, venous sinus thrombosis, thrombolytic treatment of any condition (e.g. MI, cerebral infarction, etc), CNS tumour or CNS infection • Brainstem location of haemorrhage (people with cerebellar haemorrhage may be enrolled) • Serum creatinine > 1.4 mg/dL (123 μmol/L). Sites that currently perform CTA as standard of care for ICH will follow their standard procedures regarding renal insufficiency • Known allergy to iodinated contrast media • Intravenous or intra-arterial administration of iodinated contrast media within the previous 24 h of baseline CT scan • Known hereditary (e.g. haemophilia) or acquired haemorrhagic diathesis, coagulation factor deficiency, or anticoagulant therapy with INR > 1.2 • Known or suspected thrombocytopenia (unless current platelet count documented above 50,000/μL) • Unfractionated heparin use with abnormal PTT • Low-molecular weight heparin use within the previous 24 h • GPIIb/IIIa antagonist use in the previous 2 weeks • GCS score 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)

	• Informed consent cannot be obtained from the patient or legally authorised representative
Interventions	SPOTLIGHT: Intrevention: rfVIIa 80 ug/kg IV bolus Comparator: placebo standard saline solution STOP-IT: Intervention: recombinant activated factor VII. Participants will receive rFVIIa at 80 mcg/kg (maximum dose volume 21.3 mL, equivalent to maximum weight of 160 kg) Comparator: placebo. An inactive substance (maximum dose volume 21.3 mL, equivalent to maximum weight of 160 kg)
Outcomes	SPOTLIGHT: Primary outcome measures • ICH size: difference between groups in ICH size on CT scan at 24 h post-dose, adjusted for baseline ICH size Secondary outcome measures: • Feasibility (time frame: 0): percentage of sites that can meet recruitment targets of 2 patients per site per year; % of patients who meet the target time of <45 minutes from emergency department arrival to the start of the scan; % of patients who meet the target time of <60 minutes from the end of the CT angiogram to administration of study drug; local site spot sign interpretation accuracy as judged by central adjudicator; protocol violations; waiver of consent process, evaluation, and effectiveness (time frame: 4.90 days); waiver of consent use, acceptability, and effect on treatment times. Questionnaire will be administered to subject or LAR at 4 days and 90 days • Acute blood pressure control (time frame: 1 h): % of participants in whom blood pressure control was achieved, defined as achieving systolic BP < 180 mmHg within 1 h post-randomisation • Thromboembolic events : incidence of MI and ischaemic stroke within 4 days; any other arterial or venous thromboembolic SAEs within 4 days • Mortality : 90-day mortality rate • Unstable angina: unstable angina within 4 days of treatment • Troponin increase : troponin rise above upper limit of normal within 4 days (without clinical symptoms or ECG evidence of acute coronary syndrome) • DVT : deep venous thrombosis (DVT) within 4 days • Pulmonary embolism : PE within 30 days • Cognition : Montreal Cognitive Assessment (MoCA) and Stroke Impact Scale at 90 days and 1 year • Disability : proportion of participants with mRS score 5 to 6 (death or severe disability) at 90 days and 1 year STOP-IT: Primary outcome measures: life-threatening thromboembolic complications defined as development of 1) acute myocardial ischaemia, 2) acute cerebral ischaemia, and 3) acute pulmonary embolism (time frame: through day 4 after completion of study drug). The rate of haematoma growth among spot sign positive participants at 24 h, comparing participants treated with rFVIIa to those treated with placebo. Haematoma growth will be defined as a > 33% or > 6 cc

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

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

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

Methods	The aim of the study is to test if ICH patients who have contrast extravasation on CTA, the 'spot sign', have lower rates of haematoma growth when treated with tranexamic acid within 4.5 h of stroke onset, compared with placebo
Participants	Inclusion criteria • People presenting with an acute ICH • Contrast extravasation within the haemorrhage, 'spot sign', evaluated from the CTA according to 3 criteria, all of which must be present: Serpiginous or spot-like appearance within the margin of a parenchymal haematoma without connection to an outside vessel; the density (in Hounsfield units) should be greater than that of the background haematoma (site investigators are not required to document the density); and no hyperdensity at the corresponding location on non-contrast CT • Age ⩾ 18 years • Treatment can commence within 1 h of initial CT and within 4.5 h of symptom onset (or in people with unknown time of symptom onset, the time the person was last known to be well) • Informed consent has been received in accordance to local ethics committee requirements Exclusion criteria • GCS total score 70 mL as measured by the ABC/2 method • ICH known or suspected by study investigator to be secondary to trauma, aneurysm, vascular
Interventions	Intervention: intravenous tranexamic acid 1000 mg in 100 mL 0.9% normal saline over 10 minutes followed by 1000 mg in 500 mL 0.9% normal saline infusion over 8 h Comparator: intravenous placebo in 100 mL 0.9% normal saline over 10 minutes followed by 500 mL 0.9% normal saline infusion over 8 h
Outcomes	Primary outcome measures • ICH growth by 24 ± 3 h as defined by either 33% or 6 mL increase from baseline, adjusted for baseline ICH volume. Secondary outcome measures • Major thromboembolic events (MI, ischaemic stroke, PE), measured within 90 ± 7 days) • Absolute ICH growth volume by 24 ± 3 h, adjusted for baseline ICH volume • Absolute IVH growth volume by 24 ± 3 h, adjusted for baseline IVH volume • mRS score of 0 to 4 at 3 months

	• mRS score of 0 to 3 at 3 months • Categorical shift in mRS at 3 months, subject to the validity of proportional odds assumption • Death due to any cause by 3 months
Notes	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

Methods	A pragmatic phase III prospective double-blind randomised placebo-controlled trial
Participants	Inclusion criteria • Adults with acute spontaneous ICH • Within 8 h of stroke symptom onset or time last seen well Exclusion criteria • People with ICH secondary to anticoagulation, thrombolysis or known underlying structural abnormality such as AVM, aneurysm, tumour, or venous thrombosis. An underlying structural abnormality does not need to be excluded before enrolment, but where known, patients should not be recruited • Contraindication to tranexamic acid • Premorbid dependency (mRS > 4) • Concurrent participation in another drug or device trial. Participants enrolled in

	TICH-2 may be enrolled into the RESTART trial after 21 days • Prestroke life expectancy
Interventions	Intervention: intravenous tranexamic acid: 1 g loading dose given as 100 mL infusion over 10 minutes, followed by another 1 g in 250 mL infused over 8 h Comparator: matching placebo (normal saline 0.9%) administered by identical regimen
Outcomes	Primary outcome measure: to assess whether tranexamic acid is safe and reduces death or dependency after primary ICH. Death or dependency (ordinal shift on mRS) at day 90 will be analysed by intention-totreat 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
Notes	ISRCTN93732214

Risk of bias table

Bias	Authors' judgement	Support for judgement
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.

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

Methods	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
Participants	Inclusion criteria People presenting with an acute spontaneous hypertensive ICH • CTA evaluation can be accomplished within 6 h of symptom onset, with 'spot sign' positive in CTA original image OR CT evaluation accomplished within 6 h of symptom onset, with "blend sign" or "black hole sign" positive • Age range from 18 to 79 years • Randomisation can be finished and treatment can commence within 8 h of symptom onset • Informed consent has been received in accordance with local ethics committee requirements Exclusion Criteria: • ICH known or suspected to be secondary to tumour, vascular malformation, aneurysm, or trauma • Infratentorial ICH • GCS total score 70 mL • Parenchymal haemorrhage with ventricle involved, blood completely fills one lateral ventricle or more than half of both lateral ventricles • Contraindication of CTA imaging (e.g. known or suspected iodine allergy or significant renal failure) • Any history or current evidence suggestive of venous or arterial thrombotic events within the previous 6 months, including clinical, ECG, laboratory, or imaging findings. Clinically silent chance findings of old ischaemia are not considered exclusion criteria. • Planned surgery for ICH • Pregnancy, within 30 days after delivery, or during lactation • Use of heparin, low-molecular weight heparin, or oral anticoagulation within the previous 1 week, with abnormal laboratory values • Known allergy to tranexamic acid • Prestroke modified mRS score of > 2
Interventions	Intervention: intravenous tranexamic acid 1000 mg in 100 mL 0.9% normal saline over 10 minutes followed by 1000 mg in 500 mL 0.9% normal saline infusion over 8 h Comparator: intravenous placebo in 100 mL 0.9% normal saline over 10 minutes followed by 500 mL 0.9% normal saline infusion over 8 h

Outcomes	Primary outcome measures • haemorrhage growth (time frame: 24 ± 2 h) either > 33%, or > 6 mL increase from baseline, adjusted for baseline ICH volume Secondary outcome measures • Major thromboembolic events (time frame: 30 ± 4 days; acute MI, acute cerebral ischaemia, acute PE) • Poor clinical outcome (time frame: 90 ± 7 days): the number of participants who died or have major disability (mRS 4 to 6) • Short-term outcome: the number of participants with mRS 0 to 2 at 30 ± 4 days • Other thromboembolic events (time frame: 90 ± 7 days): other thromboembolic events, such as venous thrombosis and other peripheral arterial embolism • Death due to any cause: number of patients that died due to any cause by 90 ± 7 days
Notes	NCT02625948

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 (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