Treatment of spontaneous intracerebral haemorrhage with tranexamic acid

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Abstract

Spontaneous intracerebral haemorrhage is a devastating condition with high morbidity and mortality. Haematoma expansion and subsequent secondary brain injuries lead to worse outcomes in intracerebral haemorrhage. Tranexamic acid is a promising haemostatic agent that may prevent haematoma expansion and improve outcomes. The current thesis explores the effects of tranexamic acid in intracerebral haemorrhage from clinical, radiological and biochemical aspects, based on data from the now completed Tranexamic acid in IntraCerebral Haemorrhage-2 (TICH-2) trial.

Two systematic reviews explore available evidence on efficacy and safety of tranexamic acid and other haemostatic therapies in intracerebral haemorrhage. There was insufficient evidence to support the routine use of tranexamic acid or blood clotting factors in treating intracerebral haemorrhage. Platelet transfusion had been found to be harmful and should be avoided in intracerebral haemorrhage.

Predictors of neurological deterioration and seizures and the effects of tranexamic acid on both were explored. Older age, more severe stroke, larger haematoma volume, intraventricular and subarachnoid extension, previous intracerebral haemorrhage and antiplatelet therapy independently predicted neurological deterioration. Tranexamic acid reduced early neurological deterioration occurring within 48 hours from symptom onset through a reduction in haematoma expansion, but had no significant effect on late neurological deterioration (48 hours to 7 days).

Lobar location of haematoma was the strongest predictor of early (≤ 7 days) and late seizures (> 7 days). The risk of seizures in intracerebral haemorrhage was not increased in patients treated with tranexamic acid.

The role of several noncontrast CT signs, namely blend sign, black hole sign, hypodensities and island sign, in predicting haematoma expansion and poor functional outcome was assessed. Blend sign, black hole sign and

hypodensities independently predicted haematoma expansion while black hole sign, hypodensities and island sign predicted poor functional outcome (modified Rankin Scale of 4 to 6). Tranexamic acid reduced haematoma expansion but there was no benefit on functional outcome. There was no significant interaction between the presence of noncontrast CT signs and benefit from tranexamic acid in terms of reduction in haematoma expansion or improvement in functional outcome

From a biochemical aspect, a range of plasma biomarkers involved in fibrinolysis and haemostasis were examined in a single-centre substudy of the TICH-2 trial involving 22 patients and 9 healthy volunteers. Patients with intracerebral haemorrhage had higher D-dimer and plasmin-alpha-2-antiplasmin complex levels compared to healthy controls. Elevated baseline tissue-type plasminogen activator and urokinase-type plasminogen activator, lower baseline plasminogen and elevated day 2 matrix metalloproteinase-9 levels were associated with haematoma progression. Tranexamic acid did not have significant effects on plasma biomarker levels.

In summary, there were clinical and radiological signals that tranexamic acid may be beneficial in patients with spontaneous intracerebral haemorrhage. Plasma biomarker results suggest fibrinolysis may be a pathophysiological mechanism in intracerebral haemorrhage. There is a role for further trials of tranexamic acid in intracerebral haemorrhage.

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Abbreviations

BBB	Blood brain barrier
CAA	Cerebral amyloid angiopathy
CI	Confidence interval
CT	Computed tomography
CTA	Computed tomography angiography
DICOM	Digital Imaging and Communications in Medicine
DNAR	Do not attempt resuscitation
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
EEG	Electroencephalography
END	Early neurological deterioration
ES	Early seizures
EuroQoL-5D-HUS	EuroQoL-5-dimensions Health Utility Status
EuroQoL VAS	EuroQoL Visual Analogue Scale
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
ICH	Intracerebral haemorrhage
IQR	Interquartile range
IMP	Investigational medicinal product
INR	International normalised ratio
IPDMA	Individual patient data meta-analysis
IVH	Intraventricular haemorrhage
LND	Late neurological deterioration
LS	Late seizures
MMP	Matrix Metalloproteinase
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NCCT	Noncontrast computed tomography
ND	Neurological deterioration
NIHSS	National Institute of Health Stroke Scale
OR	Odds ratio
PAP	Plasmin-alpha-2-antiplasmin complex
PE	Pulmonary embolism
PHO	Perihaematomal oedema
RCT	Randomised controlled trial
rFVIIa	Recombinant activated clotting factor VII
SAE	Serious adverse event
SAS	Semi-automated segmentation
TAT	Thrombin-antithrombin Complex
TICH-2	Tranexamic acid for IntraCerebral Haemorrhage-2
TICS-m	Modified Telephone Interview Cognitive Status
TND	Transient neurological deterioration
tPA	Tissue-type plasminogen activator
uPA	Urokinase-type plasminogen activator
VKA	Vitamin-K antagonist
VTE	Venous thromboembolism
ZDS	Zung Depression Self-Rating Scale

Chapter 1 Background and literature review

1.1 Publications contributing to this chapter

1) Zhe Kang Law, Jason P Appleton, Philip M Bath, Nikola Sprigg. Management of acute intracerebral haemorrhage –an update. Clinical Medicine 2017 Vol 17, No 2: 166-72.

2) Zhe Kang Law, Nikola Sprigg. Chapter 10. Intracerebral haemorrhage in older people. In Stroke in older people. Eds Sunil Munshi & Rowan Harwood. Oxford University Press (in-press)

1.2 Epidemiology of intracerebral haemorrhage

Stroke is a common medical emergency affecting 15 million people per year worldwide.[1] Of this figure, approximately 2 million people suffered from spontaneous intracerebral haemorrhage yearly.[2] Spontaneous intracerebral haemorrhage has a median 30-day mortality rate of 40%.[2] In addition, between 70 to 80% of patients with intracerebral haemorrhage are dependent at one year after stroke.[3, 4]

Worldwide incidence of intracerebral haemorrhage varies according to geographical location between 1.9 to 129.6/100,000 person-years.[5, 6] East Asia has a higher incidence of intracerebral haemorrhage compared with Western population. Incidence in White (24.2, 95% confidence interval [CI] 20.9-28.0), Black (22.9, 14.8-35.6), Indian (21.4, 16.6-27.1), Hispanic (19.6, 15.7-24.5) and Maoris (22.2, 15.8-30.3) are similar but twice higher in East Asia and Southeast Asia (51.8, 38.8-69.3).[2] In addition, a higher proportion of stroke subtypes is intracerebral haemorrhage in East Asia. Studies in Hong Kong, China, Taiwan, Japan found that 23% to 52.2% of all strokes are intracerebral haemorrhage [7-11] compared to 9% to 18% in Western population.[12-14] This east-west difference may be caused by lifestyle, diet and environmental factors rather than genetic factors. An epidemiological study in China showed variable incidences in different parts of the same country in

the people of same ethnicity (Han Chinese).[15] East and Southeast Asian immigrants living in Auckland had lower incidence (20.7, 13.5-30.3) than Asian living in China and Japan, and similar incidences to Maoris and white people living in the same area.[16]

1.3 Intracranial haemorrhage and intracerebral haemorrhage

Intracranial haemorrhage refers to any accumulation of blood within the cranial vault [17] and should not be confused with intracerebral haemorrhage. Intracranial haemorrhage comprises of intracerebral haemorrhage, subdural haemorrhage, extradural haemorrhage and subarachnoid haemorrhage.[18, 19] Intracerebral haemorrhage refers to bleeding within brain parenchyma and may occur with or without intraventricular extension.[20] Subdural haemorrhage or haematoma refers to accumulation of blood within subdural space (between dura and arachnoid layer of meninges). Extradural or epidural haemorrhage refers to accumulation of blood in extradural space i.e. between dura mater and skull.[18] Subarachnoid haemorrhage refers to bleeding in the subarachnoid space i.e. between arachnoid and pia mater.[18] Subarachnoid space is where the circle of Willis and major intracranial arteries lie.

Apart from anatomical location, the different types of intracranial haemorrhage differ in terms of aetiologies. Extradural and subdural haemorrhages are commonly caused by trauma, though in subdural haemorrhage the precipitating event may be trivial.[21, 22] Subarachnoid haemorrhage may be traumatic (causing tearing of blood vessels within the subarachnoid space) or non-traumatic.[23] The commonest cause of non-traumatic subarachnoid haemorrhage is rupture of a berry aneurysm involving a major intracranial artery or bleeding from arteriovenous malformation though it sometimes may occur as a result of intracranial arterial dissection, vasculitis or an extension of bleeding from intracerebral haemorrhage.[23] Intracerebral haemorrhage may occur spontaneously (spontaneous intracerebral haemorrhage) or as a result of trauma (traumatic intracerebral haemorrhage). Spontaneous intracerebral haemorrhage and

subarachnoid haemorrhage are considered subtypes of stroke while extradural, subdural and traumatic intracerebral haemorrhage are not considered strokes.

This thesis will focus on spontaneous intracerebral haemorrhage.

1.4 Symptoms and diagnosis of intracerebral haemorrhage

The onset of intracerebral haemorrhage is often gradual with progression over minutes or hours, as oppose to subarachnoid haemorrhage or cardioembolic cerebral infarction, which present with relatively sudden deterioration. The neurological deficits resulting from intracerebral haemorrhage depends on the location of the haematoma. The common locations of haematoma include basal ganglia (40-60%), thalamus (~30%), lobar/cortical (~20%), brainstem or cerebellum (<10%).[24, 25] They are the results of direct damage to the involved region and compression of surrounding tissues. Putaminal haematoma presents as hemiparesis, facial weakness, dysarthria, hemi-sensory loss, gaze palsy and homonymous hemianopia. Thalamic haematoma causes hemi-sensory loss with expansion of haematoma to midbrain inferiorly causes gaze palsy, cranial nerves palsy and reduced level of consciousness. Cortical haematoma causes hemiparesis, hemi-sensory loss, dysarthria, dysphasia, homonymous hemianopia and other cortical signs depending on cortical area involved. Cerebellar haematoma manifests as ataxia, clumsiness and vertigo. Brainstem haematoma often leads to coma rapidly. In addition, quadriparesis, cranial nerves palsy and gaze palsy may occur with brainstem haematoma. Haematoma at any location can leads to reduced conscious level and coma if it causes raised intracranial pressure, hydrocephalus and cerebral oedema or disrupts the reticular activating system, the pathway responsible for consciousness.

Bleeding into the brain parenchyma per se do not cause headache, as brain tissues are devoid of pain receptors. However, headache occurs in half of patients with intracerebral haemorrhage due to stretching of meningeal pain fibres or irritation caused by blood in the cerebrospinal fluid and ventricles.

Vomiting commonly occurs together with headache and may signify raised intracranial pressure. Neck stiffness is uncommon unless there is concurrent subarachnoid haemorrhage or extensive intraventricular haemorrhage. Seizures are more common in lobar/ cortical haemorrhage and occur in 4 to 14% of patients with acute intracerebral haemorrhage.[26-32]

Several scoring systems were design to discern supratentorial intracerebral haemorrhage from ischaemic stroke on clinical basis including the Siriraj stroke score and Guy's hospital score.[33, 34] However, clinical scores are unreliable in the diagnosis of intracerebral haemorrhage.[35] Neuroimaging should be utilised in all cases.

1.5 Neuroimaging for ICH

CT scan and magnetic resonance imaging (MRI) are equally effective in diagnosing ICH.[36, 37] Acute haematoma appears hyperdense (40 to 60 Hounsfield unit) on CT scan before becoming isodense then hypodense.[36] The appearance of haematoma on MRI depends on the timing of imaging and sequence used (Table 1-1).[36]

Table 1-1 Appearance and evolution of haematoma on MRI

Stage	T1	T2	DWI	T2*GRE/ SWI
Hyperacute (<24 hours)	Hypointense	Hyperintense	Hyperintense	Hypointense
Acute (1-3 days)	Isointense/ Hypointense	Hypointense	Hypointense	Hypointense
Early subacute (> 3 days)	Hyperintense	Hypointense	Hypointense	Hypointense
Late Subacute (> 7 days)	Hyperintense	Hyperintense	Hyperintense	Hypointense
Chronic (>14 days)	Isointense/ Hypointense	Hypointense	Hypointense	Hypointense

DWI = diffusion weighted imaging; GRE = Gradient recalled echo; SWI = susceptibility weighted imaging

Apart from diagnosing ICH, the main aims of neuroimaging are to detect complications such as haematoma expansion, intraventricular extension, hydrocephalus, cerebral oedema and mass effect (Figure 1-1, Section 1.7.1.2 Haematoma expansion). In addition, neuroimaging is crucial to

identify the underlying aetiology. Urgent CT angiography (CTA) is often done in a research setting to look for contrast extravasation or positive spot sign, which predicts haematoma expansion.[38] CTA positive spot sign has a sensitivity of 63% and specificity of 90% in predicting haematoma expansion.[38] Predicting haematoma expansion could be useful in stratifying patients for haemostatic therapy.

It was previously thought that investigations for an underlying structural or vascular lesion should be reserved for patients aged <45 years, with normotension and lobar haemorrhage.[39] This assumption is unreliable as angiographic studies showed that up to 20% of patients with spontaneous intracerebral haemorrhage have underlying vascular abnormalities; many of them were elderly, hypertensive with deep-seated haematomas.[40] Hence all patients should be considered for a non-invasive vascular imaging (CT angiography or MR angiography) and a structural imaging (MRI). These should be performed as early as possible to enable early interventions. Invasive digital subtraction angiography (DSA) should be reserved for patients where the suspicion of vascular anomalies remains high despite negative non-invasive imaging.[41]

1.6 Causes of spontaneous intracerebral haemorrhage

About 78 to 88% of spontaneous intracerebral haemorrhage are primary intracerebral haemorrhage, as a result of chronic hypertension or cerebral amyloid angiopathy (CAA).[42]

1.6.1 Hypertensive ICH

Long standing poorly controlled hypertension can result in degenerative changes in the cerebral arterial wall: fibrinoid necrosis, lipohyalinolysis and formation of Charcot-Bouchard microaneuryms.[43] Rupture of penetrating arteries or arterioles affected by hypertensive vascular changes causes ICH in deep-seated locations such as basal ganglia, thalamus, cerebellum and brainstem, though lobar haemorrhage may occur as well.[44] However, hypertension is not the only cause of deep-seated ICH. Only 50% to 70% of

patients with deep-seated ICH were hypertensive.[45-47] On the other hand, acute hypertensive response occurs in approximately 60% of ICH in the first 24 hours and may be a result of raised intracranial pressure, dysregulated autonomic system and stress response.[48] Hence, the finding of elevated blood pressure during acute phase of ICH may not indicate hypertension as the cause of ICH. In summary, most deep-seated ICHs are hypertensive-related though alternative causes should be considered.

1.6.2 Cerebral amyloid angiopathy

Sporadic cerebral amyloid angiopathy (CAA) is characterised by deposition of β-amyloid (Aβ) in the media and adventitia of small and medium blood vessels in the cortex and leptomeninges.[49] Sporadic CAA is predominantly a disease of older people. It affects 33% of people aged 60 to 70 years with increasing prevalence of up to 75% in those more than 90 years old.[50] It rarely affects people below the age of 55 years. In addition APOE ε4 and ε2 alleles are risk factors for development of CAA and CAA-related ICH.[51] CAA-related spontaneous intracerebral haemorrhage typically affects normotensive elderly patients causing large lobar haematomas.[52] Though hypertension is not a risk factor for CAA, elevated blood pressure may increase the risk of CAA-related ICH.[53] A subgroup analysis of the PROGRESS trial showed that lowering BP by 9/4 mmHg with perindopril and indapamide in patients with CAA-related ICH reduced the risk of recurrence by 77%.[54]

Superficial lobar haemorrhage, multiple or recurrent haemorrhage and the presence of convexity subarachnoid haemorrhage are supportive of the diagnosis of CAA. CAA-related ICH most commonly affects occipital and temporal lobes, followed by frontal and parietal lobe. CAA may also cause cerebellar haemorrhage but most brainstem haemorrhages are not CAA-related.[52, 55]

The Boston diagnostic criteria for CAA (Table 1-2)[56] are widely used. In addition, the Edinburgh CT and genetic diagnostic criteria used three criteria:

finger-like projections and subrachnoid haemorrhage on CT and APOE ε4 possession on genetic testing to diagnose CAA in lobar haemorrhage.[57] The presence of at least two of the three criteria indicates a high probability of moderate to severe CAA with a high rule in specificity of 96%.[57]

Table 1-2 Boston criteria for diagnosis of cerebral amyloid angiopathy[56]

Boston criteria for diagnosis of CAA
Definite CAA: Full post-mortem examination reveals lobar, cortical, or cortical/subcortical haemorrhage and pathological evidence of severe cerebral amyloid angiopathy
Probable CAA with supporting pathological evidence: Clinical data and pathological tissue from evacuated haematoma or cortical biopsy demonstrate a ICH in typical location and some degree of vascular amyloid deposition
Probable CAA: Pathological confirmation not required Age ≥ 55 years Appropriate clinical history MRI findings reveal multiple haemorrhages of varying sizes/ages with no other explanation
Possible CAA: Age ≥ 55 years Appropriate clinical history MRI findings reveal a single lobar, cortical, or cortical/subcortical haemorrhage without another cause, multiple ICH with a possible but not a definite cause, or ICH in an atypical location.

1.6.3 Secondary causes of intracerebral haemorrhage

Although secondary causes of spontaneous intracerebral haemorrhage are less common, it is important to identify them, as they may warrant specific treatments. There are certain clinical and radiological clues that aid in the diagnosis of secondary intracerebral haemorrhage. Patients with history of malignancy, in particular melanoma, choriocarcinoma, thyroid carcinoma or renal cell carcinoma should be suspected of having haemorrhagic cerebral metastasis.[58] Cerebral venous thrombosis should be considered in patients with superficial cortical or bilateral symmetrical haemorrhages.[59] Intracranial aneurysm should be suspected in patients with subarachnoid haemorrhage or inter-hemispheric and peri-sylvian haemorrhage. Table 1-3 illustrates the causes of spontaneous intracerebral haemorrhage, investigations and characteristic findings.

Table 1-3 Causes of spontaneous intracerebral haemorrhage, investigations and characteristics

Causes	Investigations	Characteristics
Hypertensive arteriopathy	MRI including T2 GRE or SWI sequence	Presence of deep-seated cerebral microbleeds, leukoaraiosis and lacunar infarctions is supportive.
Cerebral amyloid angiopathy	MRI including T2 GRE or SWI sequence Apolipoprotein E (ε2 and ε4 alleles)	MRI: lobar haemorrhage, microbleeds at cortico-subcortical junctions. Carriers of Apolipoprotein ε2 and ε4 alleles have higher risk of recurrent ICH.
Cavernoma	MRI	MRI: heterogeneous signal intensities on T1 and T2 with a hypointense surrounding rim. Typically described as “popcorn” or “berry” appearance.
Arteriovenous malformation	MRI, MRA, DSA	MRA/DSA: dilated arteries feeding a nidus and multiple draining veins.
Intracranial aneurysm	CTA, MRI, MRA, DSA	Presence of subarachnoid haemorrhage. DSA is the gold standard in detecting aneurysm.
Cerebral venous thrombosis	CTV, MRV	Clinical signs of increased intracranial pressure. Symmetrical haemorrhagic infarctions. Filling defect (flow void) in the venous system.
Dural arteriovenous fistula	CTA, MRA, DSA	Haematoma location near venous sinus and cortical veins.
Brain tumour/metastasis	CECT/MRI	50% of patients with brain metastasis will have multiple lesions that may show contrast enhancement.
Anticoagulant	History/ coagulation profile	Prolongation of coagulation profile. In patients on DOACs, the presence of normal coagulation profile does not indicate absence of coagulopathy.
Thrombolysis agent	History	Diagnosis of prior ischaemic stroke or myocardial infarction requiring thrombolysis is usually evident.
Cocaine and sympathomimetic drugs	History Urine cocaine levels	Elevated urine cocaine levels can be detected within 72 hours of cocaine use.

CECT=contrast-enhanced computed tomography; CTA=computer tomography angiography; CTV= computed tomography venography; DOAC= direct oral anticoagulants; DSA=digital subtraction angiography; GRE=gradient recall echo; MRA=magnetic resonance angiography; MRI=magnetic resonance imaging; MRV=magnetic resonance venography; SWI=susceptibility weighted imaging

1.7 Complications of spontaneous intracerebral haemorrhage

Complications after spontaneous intracerebral haemorrhage are common. Between 24.2 % and 95% of patients with stroke suffer from complications in the acute and subacute phase.[60-65] These complications can be broadly classified into neurological and non-neurological complications. Neurological complications of ICH include haematoma expansion, perihaematomal oedema, hydrocephalus, intraventricular extension of haematoma, raised intracranial pressure and seizure.[66] Examples of non-neurological complications include venous thromboembolic events, acute coronary syndrome, elevated blood pressure, hyperglycaemia, fever and infection.

1.7.1 Neurological complications

1.7.1.1 Neurological deterioration

Neurological complications manifest as early and late neurological deterioration. In addition, non-neurological complications such as infection, electrolyte imbalance, renal failure etc. may also manifest as neurological deterioration. The definition of neurological deterioration is not standardised with different studies using different neurological scales and cut-offs (Table 1-4). Early neurological deterioration occurs in 32 to 37.5% [67-70] of patients with ICH while late neurological deterioration occurs in 20.3 to 28.9%.[70,71] Neurological deterioration is an independent negative prognostic factor. Neurological deterioration is associated higher death and dependency[72-74] in 90% of patients,[67, 75] increasing the risk by 8-fold.[75] Neurological deterioration result in higher in-hospital mortality (44% vs. 10%, OR 12.8, 95%CI 3.8-43.1, $p < 0.001$)[76] and institutionalisation (OR 5.82, 95%CI 1.06-31.87, p=0.042).[76] It is therefore important to identify, prevent and treat neurological complications.

Table 1-4 Definitions of early and late neurological deterioration

Definitions of deterioration
Increase in NIHSS • ≥1 point[77] • ≥2 points[76, 78] • ≥4 points[79, 80] Decrease in SSS • ≥2 points in consciousness or motor power or ≥3 points in speech scores[68, 70] • > 5 points, or decrease in consciousness level by > 3 points[81] Decrease in CSS • ≥1[69, 75, 82] Decrease in GCS • ≥2[80]
Definitions of early and late deterioration
Early: <24 hours[72, 78, 83], 48 hours[69, 75], 72 hours[68] or 5 days.[76] Late: between 24 hours to 7 days.[70]

NIHSS: National Institute of Health Stroke Scale; SSS: Scandinavian Stroke Scale; CSS: Canadian Stroke Scale; GCS: Glasgow Coma Scale

1.7.1.2 Haematoma expansion

Haematoma expansion is an increase in haematoma volume compared to baseline haematoma volume (Figure 1-1). There are several definitions of haematoma expansion. The most commonly used definition is a relative increase of >33% or absolute increase of >12.5 mL or 6 mL as used in the Factor Seven for Acute Haemorrhagic Stroke (FAST) and the Predicting haematoma growth and outcome in intracerebral haemorrhage using contrast bolus CT (PREDICT) trials respectively.[38, 84-86] A relative growth of > 40% or >50% or an absolute growth of > 20 mL were used by several investigators.[87, 88]

Haematoma expansion occurs in up to 38% of patients with ICH within 24 hours.[86] Brott *et al* reported that 26% of haematoma expansion occurred within 4 hours and another 12% occurred between 4 to 20 hours.[86] Similarly, Kazui *et al* found that the risk of haematoma expansion was less after 6 hours (17%) and was rare beyond 24 hours.[88, 89] Haematoma expansion is independently associated with neurological deterioration, mortality and worse functional outcome.[86, 90, 91] With every 10% increase in haematoma volume, mortality increases by 5%. Every mL increase in haematoma volume increases the risk of dependency by 7%.[90] On the other hand, small

haematoma volume is associated with good functional outcome.[92, 93] Hence, haematoma expansion is an important clinical outcome surrogate marker and therapeutic target.

Several factors predict haematoma expansion. An early presentation of ICH within 3 hours is predictive of haematoma expansion.[84, 87, 89, 94] A larger initial haematoma volume is predictive of haematoma expansion. Several studies found that haematoma volume of >25 to 30 mL is associated with haematoma expansion and poor outcome. [88, 95-97] In contrast, only 2.6% of haematoma < 3ml undergo haematoma expansion.[98] Haematoma volume and location are independent and strong predictors of 30-day mortality.[96] Haematoma volume of >60 mL and infratentorial location predicts the highest mortality (Table 1-5).[96]

A positive spot sign on CT angiography (Figure 1-2) or CT perfusion study is indicative of active bleeding and predicts haematoma expansion independently. The spot sign is defined as a spot-like or serpiginous appearance on CT angiography within the margin of a haematoma that is not connected to a blood vessel. The contrast appearance should be at least 1.5 mm in size in at least one dimension, with a density that is at least two times of the background haematoma. This should be no hyperdensity in corresponding area on the noncontrast CT.[38] Between 53 to 77% of patients with positive spot sign have haematoma expansion compared to 4 to 21.6% in patients with negative spot sign.[38, 99, 100] In addition, positive spot sign is associated with larger haematoma expansion (8.6 mL vs 0.4 mL).[38] In fact, patients with positive spot sign are more likely to have larger initial haematoma volume. Patients with positive spot sign had worse functional outcome[99-101] and higher 90-day mortality (43.4% vs 19.6%).[38] Shorter onset to baseline imaging time, larger baseline haematoma volume, prior antiplatelet and anticoagulant therapy were identified as independent predictors of haematoma expansion with C-index of 0.78 (95% CI 0.75-0.82) in a large individual patient data meta-analysis.[102] The predicted probability of haematoma expansion increased with increasing haematoma volume and peaked at approximately 75 mL before declining while the probability of

haematoma expansion is highest in patients with onset to CT time of < 3 hours.[102] CT angiography (CTA) spot sign has a sensitivity of approximately 60% and specificity of 90% in predicting haematoma expansion but the addition of spot sign only increased the C-index by 0.05.[38,102]

Several signs that can be seen on noncontrast CT (NCCT) scans can predict haematoma expansion as well. Heterogeneous density and irregular shape of haematoma are predictive of haematoma expansion.[87, 103-105] The blend sign and black hole signs are predictors of haematoma expansion as well.[106, 107] The blend sign is defined as the blending of a relatively hypodense area with an adjacent hyperdense region with the haematoma (Figure 1-3, left).[106] The black hole sign is a relatively hypoattenuated area (black hole) encapsulated within the hyperattenuating hematoma (Figure 1-3, right) with a difference of at least 28 Hounsfield units between the areas.[107] The blend sign and black hole sign has a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 39.3%, 95.5%, 82.7%, 74.1%; and 31.9%, 94.1%, 73.3%, 73.2% respectively.[106, 107]

The swirl sign is an area of hypo- or iso-density within the hyperdense haematoma. This area could be round, streak-like or irregular.[108] It is similar to the black hole sign except that there is no restriction of difference in Hounsfield unit and it may not be fully encapsulated by the hyperdense area within haematoma. It is associated with larger haematoma volume and worse functional outcome.[108] Boulouis *et al* described 4 different types of intrahaematoma hypodensities: type 1 hypodensity has a brain-like density and distinct margins, type 2 has a brain-like density and indistinct margins, type 3 has an oedematous or cerebrospinal fluid-like density and type 4 has a mixed density with a fluid-fluid level.[109, 110] Hypodensities within the haematoma, regardless of the density or margin, predict haematoma expansion and poor functional outcome.[109] With this regards, black hole and swirl signs are both subsets of intrahaematoma hypodensity.

Island sign is a sign of irregular shape defined as presence of at least three separate small haematomas adjacent to, or 4 small haematomas partially

connected to the main haematoma (Figure 1-4). It was reported to have a sensitivity of 44.7%, specificity of 98.2%, positive predictive value of 92.7% and negative predictive value of 77.7% in predicting haematoma expansion.[111] The island sign was reported to be an independent predictor of poor functional outcome after ICH as well (OR 3.51, 95%CI 1.26-9.81).[111]

Prior antiplatelet or anticoagulant use is associated with haematoma expansion and worse outcome.[102, 112, 113] Prior anticoagulant use increases the risk of haematoma expansion approximately two-fold (56% in patients on warfarin compared to 26% in patients without prior anticoagulant).[113, 114] In warfarin-related ICH, a higher international normalised ratio (INR) is associated with haematoma expansion.[115] To make matters worse, continuing bleeding or rebleeding in anticoagulant-related ICH may be prolonged despite reversal of anticoagulation.[115] APOE ε2 allele increases the risk of haematoma expansion in lobar haemorrhage.[116] Lastly, lower fibrinogen and thrombin activities were found to increase the risk of haematoma expansion in some studies but not others.[87, 117]

Table 1-5 30-day mortality rate according to haematoma volume and location

Haematoma volume	Haematoma location	30-day mortality rate
>60 mL	Supratentorial, lobar	71%
	Supratentorial, deep	93%
30-60 mL	Supratentorial, lobar	60%
	Supratentorial, deep	64%
	Cerebellar	75%
<30 mL	Supratentorial, lobar	7%
	Supratentorial, deep	23%
	Cerebellar	57%
> 5 mL	Pontine	100%

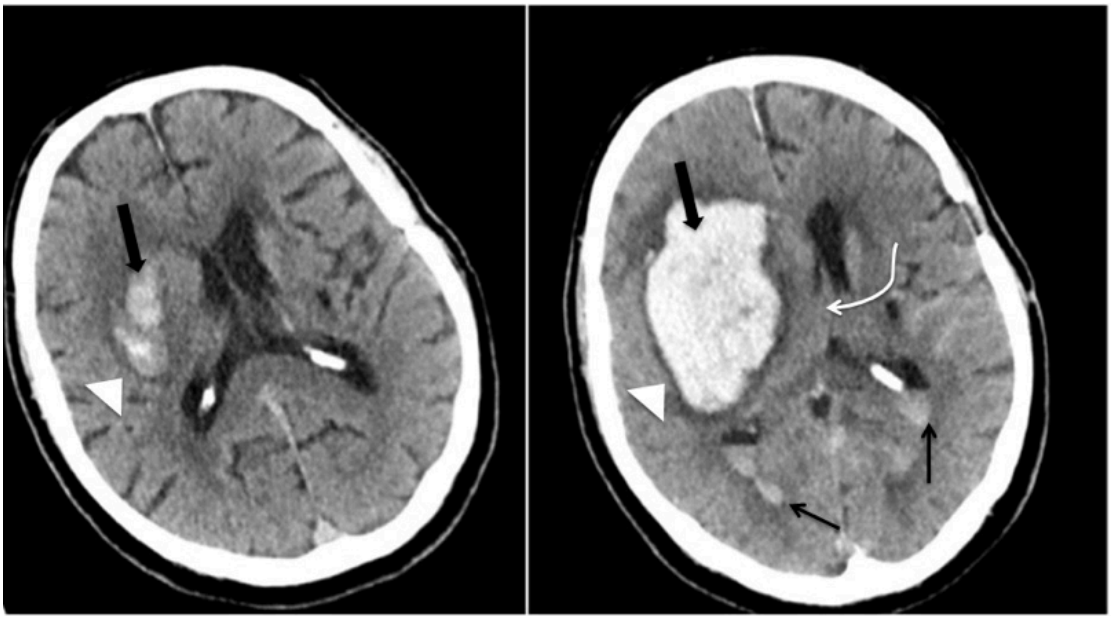


Figure 1-1 Haematoma expansion. Right basal ganglia haematoma (left panel) with haematoma expansion 6 hours later (right panel, thick black straight arrow). It is complicated with perihaematomal oedema (white arrow head), intraventricular haemorrhage (thin black straight arrows) and midline shift (white curved arrow).

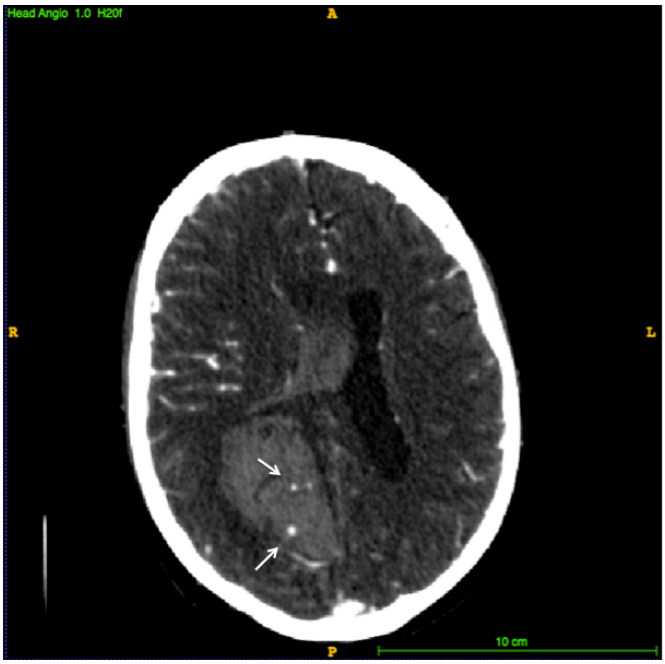


Figure 1-2 CT angiography spot sign (white arrows): extravasation of contrast within the haematoma indicating active bleeding

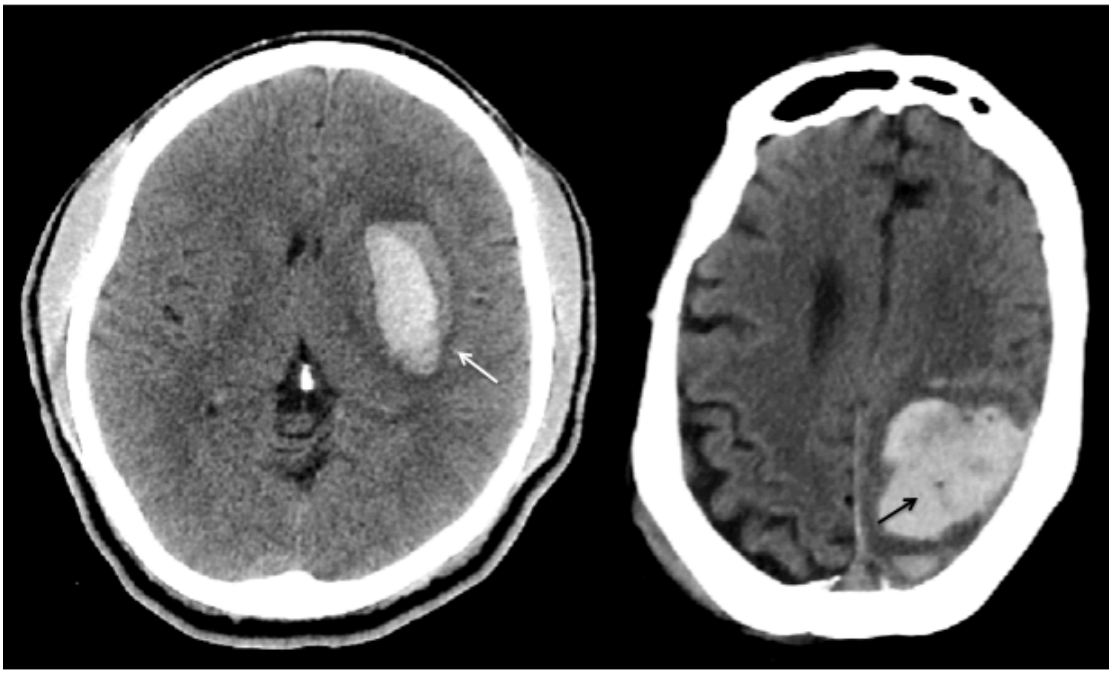


Figure 1-3 Blend sign (left panel, white arrow) and black hole sign (right panel, black arrow)

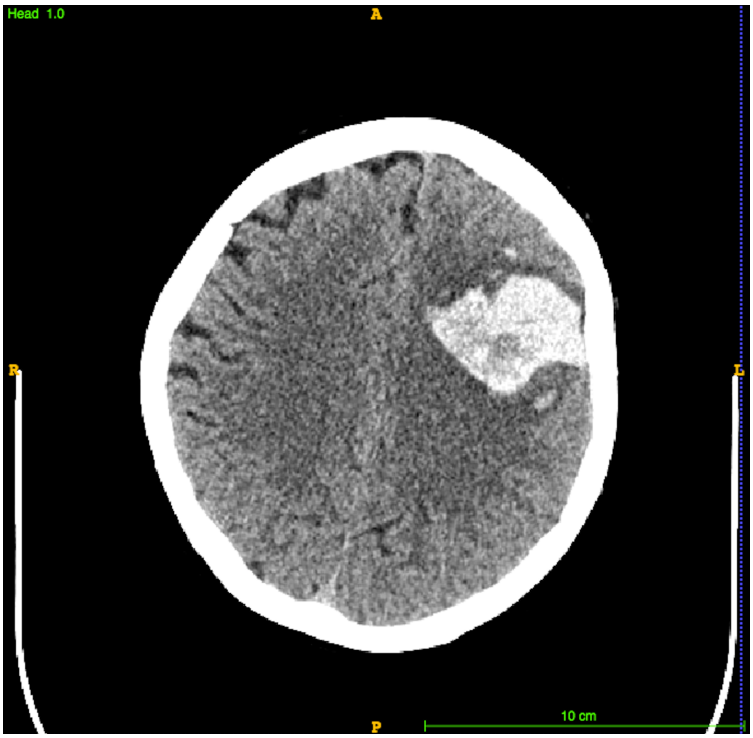


Figure 1-4 Island sign: 3 small haematomas (islands) adjacent to the large haematoma

1.7.1.3 Perihaematomal oedema (PHO)

The development of cerebral oedema in the area surrounding the haematoma is known as perihaematomal oedema (PHO). Perihaematomal oedema is associated with worse functional outcome. An increase in absolute PHO volume of 10cm^3 increases mortality by three times.[118] In addition, the rate of increase in PHO volume is an independent predictor of mortality and poor functional outcomes.[119] Nevertheless, one study showed that increase in PHO volume was only related to poor functional outcomes in basal ganglia and small (<30 mL) ICH.[120] It is uncertain whether diffusion changes of PHO correlated with poor outcome. PHO diffusion restriction was found not associated with worse clinical outcome in on retrospective study.[121] However, another study using functional MRI found that early diffusion changes within PHO is associated with poor outcome.[122] The mechanisms of development of perihaematomal oedema are further discussed in section 1.9 mechanisms of brain injury.

1.7.1.4 Intraventricular extension of haemorrhage & hydrocephalus

Intraventricular extension of haemorrhage occurs in 30 to 50% of patients with ICH.[123] Intraventricular haemorrhage (IVH) is more common in thalamic haematoma, due to its proximity to the third ventricle and the tendency for thalamic haematoma to expand medially.[124] A larger initial haematoma size is predictive of intraventricular extension as well.[123] In addition, elevated mean arterial pressure of >120mm Hg is predictive of IVH growth.[125]

Intraventricular haemorrhage (IVH) is a negative prognostic factor, increasing risk of poor outcome two-fold.[126] Mortality after ICH with IVH had been reported to be around 50 to 80%.[123, 127] A greater volume of IVH, especially if > 20 mL correlated with worse prognosis.[123, 128] Volume of IVH can be measured semi-quantitatively as well with modified Graeb score or Graeb score (Table 1-6).[129, 130] Each unit increase in modified Graeb sore increases poor outcome by 12%.[129] In addition, IVH contributes to the total ICH volume (ICH volume plus IVH volume). A total volume of > 40 mL increases the risk

of poor outcome by 41 times, while a volume of >50 mL result in poor outcome in 100% of patients according to one study.[131]

Table 1-6 The modified Graeb Score[129]

% of blood	R temp tip	R lateral	R post tip	L temp tip	L lateral	L post tip	3rd	4th
None	0	0	0	0	0	0	0	0
≤25%	1	1	1	1	1	1	2	2
>25 to ≤50%	1	2	1	1	2	1	2	2
>50 to ≤75%	2	3	2	2	3	2	4	4
>75 to 100%	2	4	2	2	4	2	4	4
Expanded*	1	1	1	1	1	1	1	1

* An additional +1 score is given if intraventricular blood expands beyond the ventricles. R=right; L= left; temp=temporal; post=posterior.

Hydrocephalus is a life-threatening complication of IVH, particularly if it involves the third or fourth ventricles. Approximately 50% of patients with IVH would develop hydrocephalus.[132] The development of hydrocephalus in IVH worsen the prognosis further, with only 11.5% having favourable outcome.[133] Acute hydrocephalus is more common if IVH volume is greater (modified Graeb score >6) and in thalamic haematoma.[134] Thalamic haematoma lies adjacent to third ventricle, predisposing it to obstruction of cerebrospinal fluid flow.[132]

1.7.1.5 Seizures

Seizures occur in approximately 4 to 14% of patients with acute ICH.[26-32] The incidence of seizure is much higher at approximately 30% when subclinical seizures or non-convulsive seizure are diagnosed by continuous electroencephalogram (EEG).[135, 136] More than 90% of early seizures occur within 48 hours of ICH.[135-137] Early seizures are the results of direct physical disruption caused by haematoma and cerebral oedema.[138] Predictors associated with seizures are haematoma expansion, lobar location, IVH, low GCS and younger age.[26, 30, 136]

Amongst those who survived more than 7 days, 6 to 9.2% developed late onset seizure.[138, 139] The risk factors for late onset seizures include cortical involvement, young age <65 years, haematoma volume >10 mL, early seizure (<7 days), previous lobar ICH, pre-ICH dementia, and white matter disease.[138, 139]

The effects of seizure on functional outcome were controversial. Several studies reported an increased in-patient and 30-day mortality rate of two to three times in patients with seizures compared to those with no seizures.[135, 140, 141] Others found no differences in mortality amongst patients with and without seizures.[30] Paradoxically, several studies found that seizures independently decreased morbidity and mortality in patients with ICH.[142]

1.7.2 Non-neurological complications

1.7.2.1 Dysphagia

Between 37 to 78% of patients with stroke had impaired swallowing depending on assessment that was done to diagnose dysphagia.[143] The incidence was lowest when screening test was used (37 to 45%) and higher when clinical testing (51 to 55%) and instrumental testing (64 to 78%) were used.[143] Dysphagia increases the risk of aspiration and pneumonia as well as malnutrition and dehydration.[143, 144] Patients with dysphagia have three-fold higher risk of pneumonia while those with severe dysphagia and aspiration have 11 times higher risk.[143] Aspiration pneumonia is preventable with proper swallowing assessment before oral feeding is commenced.

1.7.2.2 Pneumonia

Pneumonia is the most common complication of stroke and results in three times higher mortality, significant morbidity and prolongation of hospitalisation.[145, 146] Most stroke-related pneumonia occurs as a result of aspiration of oropharyngeal bacteria. In addition, ventilator associated pneumonia may occur in ventilated patients. Risk factors for pneumonia in stroke include age of >65 years, severe disability, decreased level of consciousness, dysphagia, speech impairment, severe facial weakness,

cognitive impairment, brainstem stroke, mechanical ventilation and tracheostomy.[145, 147, 148] In addition, tube feeding did not offer protection against aspiration. In fact, nasogastric tube increased the risk of pneumonia through colonisation and aspiration of pharyngeal and gastric content.[145, 148]

1.7.2.3 Fever and infection

Fever is common after ICH, affecting up to 40% of patients.[149] This may be a direct sequelae of brain damage and re-setting of thermostat centre in hypothalamus. Fever is more common in ICH affecting the basal ganglia/ thalamus/ right lobar.[149] In addition, fever may be caused by infections such as pneumonia, urinary tract infection and pressure sores which patients with ICH are prone to. Risk factors for fever in ICH include larger haematoma, dysphagia, severe stroke, impaired conscious level and ventilation.[66]

Fever is an independent predictor of poor functional outcome, early neurological deterioration and mortality.[66,149] Fever is associated with higher risk of haematoma expansion and PHO.[150]

1.7.2.4 Venous thromboembolism

Venous thromboembolism (VTE) encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). Approximately 3 to 7% of ICH is complicated with symptomatic VTE: including 1-4% DVT and 1-2% PE while asymptomatic VTE may occur in 17 to 40% of patients.[151-153] VTE commonly occurs in the first week after ICH.[154] PE is the embolic complication of deep vein thrombosis of proximal lower limb and pelvic vein in patients who are immobilised after stroke. However, about 30% of PEs occurs without DVT.[154] Risk factors for VTE include prolonged immobilisation, elderly age, severe stroke, dehydration and prothrombotic state.[154, 155]

Pulmonary embolism is potentially fatal, with 26 to 30% of untreated pulmonary embolism resulting in death.[156] VTE leads to higher mortality, increased length of stay and delay in rehabilitation in patients with ICH.[157] Concurrence of VTE and ICH presents a therapeutic dilemma where

treatment of VTE with anticoagulant may result in worsening of ICH. The management of VTE in ICH is further discussed in section 1.10.5.4.

1.7.2.5 Cardiac complications

Cardiac complications including myocardial infarction, arrhythmias, cardiac failure and cardiac death affect 4% of patients with ICH.[158] Ischaemic heart disease and ICH share several risk factors including hypertension, older age and smoking. In addition, ischaemic heart disease is commonly treated with antiplatelet agents, which increase the risk of ICH. Valvular heart disease and atrial fibrillation are commonly treated with oral anticoagulant, which increases the risk of ICH as well. Acute stress response after ICH results in the release of catecholamine and enhanced sympathetic response, which increases myocardial demand.[159] Tachycardia together with elevated blood pressure may precipitate an acute coronary event. In addition, a specific type of stress-induced cardiomyopathy known as Takotsubo cardiomyopathy may rarely complicate ICH.[160] On the other hand, intensive blood pressure reduction had the potential of inducing hypotension, again precipitating a cardiac event. In the INTERACT 2 and ATACH-2 trial, cardiac adverse event was reported in 1 to 2% of the patients.[161, 162] Hypotension was uncommon (0.5%). Reassuringly, cardiac complications were not more common in the intensive blood pressure lowering arm.[161, 162]

1.7.2.6 Acute hypertensive response

Elevated blood pressure above normal or premorbid range is common after stroke. More than 60% of patients with acute stroke had acute hypertensive response within the first 24 hours of stroke.[48, 163, 164] Acute hypertensive response is attributable to dysregulation of cardiovascular response due to temporary or permanent damage of brain region responsible for autonomic regulation. In addition, increased intracranial pressure causing Cushing's reflex, stress response due to headache, urinary retention and release of inflammatory cytokines contribute to increase in blood pressure. In some patients, elevated blood pressure may be a reflection of previously undiagnosed or uncontrolled hypertension. Blood pressure will usually

reduce spontaneously after the first few days indicating the return of normal cerebral autoregulation.

Elevated blood pressure is deleterious in ICH, leading to worse functional outcome, death and haematoma expansion.[165, 166] Elevated blood pressure may elevate the hydrostatic pressure within the haematoma, increasing the extravasation of blood, resulting in haematoma expansion and also perihaematomal oedema.[165]

1.7.2.7 Hyperglycaemia

Hyperglycaemia occurs in approximately 60% of patients with ICH as a result of stress response regardless of whether they are diabetic or non-diabetic.[167, 168] In animal ICH models, hyperglycaemia led to haematoma expansion and worsening perihaematomal oedema.[169, 170] Similarly, the ATACH trial reported that hyperglycaemia led to expansion of haematoma and perihaematomal oedema. In addition, hyperglycaemic emergencies such as hyperglycaemic hyperosmolar state and diabetic ketoacidosis lead to overall high mortality. The INTERACT-2 trial (2839 patients) found that baseline hyperglycaemia (blood glucose >6.5 mmol/L) and diabetes mellitus are independent predictors of poor outcome.[167] The relationship between baseline glucose level and disability and death are continuous: patients with higher blood glucose level had worse outcome.[167]

1.7.2.8 Other complications

Common complications of ICH and their prevalence are listed in Table 1-7.

Table 1-7 Medical complications after stroke

Complications	**Incidence/prevalence (%)**
Respiratory	
Pneumonia/ chest infection	5-22%[61-63, 171]
Pulmonary oedema	1%[63]
Venous thromboembolism	3-7%[62, 63,137,172]
Deep vein thrombosis	1-4%[62, 63,137,172]
Pulmonary embolism	1-2%[62, 63,137,172]
Hypoxia	1%[63]
Cardiovascular	
Myocardial infarction/angina	1-6%[61, 63,172]
Cardiac arrhythmia	2-3.2%[172]
Cardiac failure	3-11%[63]
Cardiac arrest	2%[63]
Hypertensive crisis	60%[48, 163, 164]
Hypotension	~0.5%[161, 162]
Peripheral vascular disease	1%[63]
Gastrointestinal	
Dysphagia	37-78%[143]
Gastrointestinal bleeding	3%[63,172]
Faecal incontinence	30-56%[173, 174]
Renal/urological	
Renal impairment	11-35%[175]
Urinary tract infection	1-30.5%[61-63, 172]
Urinary incontinence	5-36%[63, 174]
Urinary retention	29-56%
Musculoskeletal/cutaneous	
Pressure sore	0.6-21%[61,62,137]
Cellulitis	1%[63]
Shoulder subluxation/pain	9%[62]
Falls	25%[62]
Pain	14.2-25.3%[137,172]
Metabolic	
Hyponatraemia	15.6%[176]
Hyperglycaemia	60%[167, 168]
Dehydration	1%[63]
Systemic	
Fever	1.2-40%[61, 63, 149]
Sepsis	1%[63]
Psychiatric	
Depression	16-25.3%[62,137]
Cognitive impairment/ dementia	14.2-77%[177, 178]
Suicidal thoughts	6.6-11.3%[179]

1.8 Prognostic factors in ICH

Various prognostic factors are associated with poor outcome in ICH. These include: older age, low GCS (≤8), increased blood pressure, prior anticoagulant or antiplatelet agent, infratentorial location, larger haematoma volume, haematoma expansion, presence and volume of IVH, hydrocephalus, perihaematomal oedema, early neurological deterioration, and presence of stroke complications.[96, 180, 181 86, 96, 182] Most of these prognostic factors are complications of ICH explained above.

Based on these, several prognostic scoring had been devised, including the widely used ICH score.[95] The ICH score was based on a retrospective study of 188 patients with ICH and has a sensitivity of 96% and a specificity of 98%.[95]

Table 1-8 ICH score for prognosis after intracerebral haemorrhage[95]

Components	Score points
Glasgow Coma Scale	
3-4	2
5-12	1
13-15	0
ICH Volume (mL)	
≥30	1
<30	0
Infratentorial location	
Yes	1
No	0
Age (Years)	
≥80	1
<80	0

ICH score 0 to 6: 30-day mortality rate for score 0=0%; 1= 13%; 2=26%; 3=72%; 4=97%; 5=100%. No patient in the validation study scored 6 points

1.9 Mechanisms of brain injury after ICH

Brain injury after ICH is a dynamic and complex process consisting of primary brain injury that starts immediately after ICH and secondary mechanisms that may persist for days to weeks after ICH. Understanding the

pathophysiological processes of brain injury after ICH is crucial in determining treatment targets.

1.9.1 Primary brain injury

1.9.1.1 Direct mechanical effect

Primary brain injury occurs at the time of ictus, when the rupture of an abnormal intracranial vessel resulted in extravasation of blood into the extravascular spaces and formation of haematoma. Subsequently the haematoma caused the shearing of surrounding blood vessels with further haematoma expansion.[183, 184] Direct mechanical effects of the haematoma result in physical disruption and cause necrosis and apoptosis of adjacent neurons.[185] Large haematoma causes midline shift and fatal herniation syndromes.[186] In this respect, patients with infratentorial haematoma are more liable to herniation syndrome due to the confined posterior fossa space.[95] In addition, obstructive hydrocephalus may occur due to compression of ventricles by haematoma or intraventricular extension of haematoma.[132] The haematoma may also cause an increased intracranial pressure leading to a reduced cerebral perfusion pressure, especially in the perihaematomal zone.[187] However, it is controversial whether the reduced cerebral blood flow causes cerebral infarction. A positron emission tomography (PET) imaging study found a zone of hypoperfusion without ischaemia in the perihaematomal zone.[187] Similarly, another study utilising diffusion weighted MRI and proton magnetic resonance spectroscopy concluded no perihaematomal ischaemia.[188]

1.9.1.2 Intraventricular haemorrhage

The presence of blood in the ventricles may obstruct the flow of CSF, resulting in acute obstructive hydrocephalus. In addition, IVH may cause damage to the peri-ventricular tissues especially the brainstem, causing herniation. Blood degradation products may also induce inflammation within the ventricles.[134]

1.9.2 Secondary brain injury

1.9.2.1 Thrombin

Thrombin is a serine protease that is produced immediately after ICH. Thrombin asserts haemostatic effects by acting on fibrinogen, converting it to fibrin, an essential component of a blood clot. In addition, thrombin is a potent pro-inflammatory agent. Thrombin stimulates leukocytes infiltration after ICH and subsequent release of reactive oxygen species by leukocytes results in oxidative stress, tissue injury and cerebral oedema.[189] Thrombin activates resident microglia by binding to protease-activated receptor-4 (PAR-4).[190] Activated microglia secrete pro-inflammatory cytokines (interleukin-1β [IL-1β], tumour necrosis factor α [TNFα]). TNFα induces the opening of blood-brain barrier (BBB), resulting in cerebral oedema.[190, 191] Thrombin may also cause perihaematomal oedema by acting on protease-activated receptor-1 (PAR-1) on endothelial cells, resulting in retraction and widening of intraepithelial gaps.[192] Thrombin plays a central role in the development of perihaematomal oedema in the early stage (first few hours) and later (after two days).[191] Administration of a thrombin inhibitor, argatroban inhibits perihaematomal oedema (PHO) in animal ICH models.[193]

On the other hand, thrombin mediates healing after ICH. While thrombin increases PHO, it also mediates the resolution of PHO the later stages. In addition, thrombin enhances neurogenesis by stimulating the secretion of nerve growth factors in glial cells, modulating neurite outgrowth and astrocytes proliferation.[194, 195] Thrombin also promotes angiogenesis via PAR-1 and modulation of vascular endothelial growth factor, hypoxia inducible factor-1, and angiopoietin.[196]

A high level of thrombin is harmful while a very low concentration of thrombin may be protective.[197] Hence, larger haematoma volume is associated with higher thrombin levels contributing to greater brain injury.

1.9.2.2 Inflammation, complements and matrix metalloproteinases

Infiltration of leukocytes, macrophages and plasma protein occurs after ICH with breach of BBB, although resident microglia is likely the first to

respond.[198] Animal models showed that microglia activation occurs as early as one hour after brain injury, peaks at three to seven days and persist for four weeks.[189] Damaged neurons release danger signals including adenosine triphosphate (ATP), neurotransmitters, nucleic acids, heat shock proteins and high mobility group box 1.[199] These signals stimulate resident microglia via Toll-like receptors (TLR), subsequently leading to upregulation of proinflammatory genes via nuclear factor-kB (NF-kB) signalling.[200] Resident microglia may be activated via TLR/ NF-kB pathway by thrombin, fibrin and haem.[201]

Neutrophils infiltration occurs as early as four hours in animal ICH models and peaks at three days.[199] Neutrophils produce reactive oxygen species (ROS), TNFα and pro-inflammatory proteases leading to neuronal death and breach of BBB.[189] In addition, dying neutrophils stimulate pro-inflammatory cytokines secretion by macrophages.

Complement system is usually excluded from the central nervous system by the blood brain barrier. However, with extravasation of blood and breach in BBB, complement system becomes involved in brain injury after ICH. Complement activation results in formation of membrane attack complex (MAC) from complement C5b to C9.[202] The MAC causes lysis of neurons, glial cells, erythrocytes and endothelial cells by forming pores in the cell membrane, leading to neuronal death and breach of BBB.[203] In addition, C3a and C5a are potent chemotactic agents, mobilizing neutrophils and resident microglia.[204] Subsequent release of cytokines, ROS and matrix proteins promotes inflammatory response and neuronal death.[202]

Matrix metalloproteinases, in particular MMP-2, -3 and -9, are activated by thrombin, plasmin and vascular endothelial growth factors following ICH.[205] MMP-9 causes enzymatic degradation of extracellular matrix including collagen type IV, laminin and fibronectin.[206] This causes a breach in tight junctions and basal membrane that surrounds capillaries resulting in BBB leakage.[207] MMP-9 also induces pathologic angiogenesis. Animal studies showed that MMP-9 activation is associated with larger haematoma volume

and perihaematomal oedema.[208] The positive correlation between MMP overexpression with neurological deterioration, haematoma expansion and perihaematomal oedema had been demonstrated in human studies as well.[209]

1.9.2.3 Lysed erythrocytes, haemoglobin degradation products and iron

Erythrocyte lysis occurs after several days in ICH, as a result of intracellular energy depletion and cytolysis by MAC after complement activation, though this may occur within 24 hours of insult.[210] Lysed erythrocytes release haemoglobin and haem. Haem is then broken down by haem oxygenase to iron, carbon monoxide and biliverdin which is converted to bilirubin by biliverdin reductase.[211] These haemoglobin and haemoglobin degradation products induce free radical production, breach of BBB, cytotoxic perihaematomal oedema, neutrophils infiltration and neuronal death.[210] Delayed perihaematomal oedema in the second to third week after ICH is probably attributable to haemoglobin and its degradation products.[212]

1.9.2.4 Perihaematomal oedema

Perihaematomal oedema occurs as early as three hours after ICH and peaks between 10 to 20 days.[213] Perihaematomal oedema at different stages is attributable to different pathophysiological mechanisms. In the first few hours after ICH, thrombin initiates a haemostasis process that halts bleeding from the haematoma. As a result, clot retraction occurs causing extrusion of serum protein from the haematoma to surrounding tissues resulting in cerebral oedema.[213]

The second stage of perihaematomal oedema occurs within the first two days and is attributable to vasogenic oedema caused by inflammation. The third stage of delayed vasogenic perihaematomal oedema occurs after three days and can be attributed to toxic effects of haemoglobin degradation products.[191, 214]

Perihaematomal oedema is the end results of many pathophysiological processes, therefore a surrogate marker of secondary brain injury. Perihaematomal oedema may contribute to mass effects in addition to haematoma, leading to complications including, midline shift, herniation, hydrocephalus and increased neuronal death.[189]

The mechanisms of brain injury in ICH are illustrated in Figure 1-5.

1.9.2.5 Plasmin-mediated pathway

The role of plasminogen and plasmin in brain injury after spontaneous intracerebral haemorrhage is uncertain. Intracerebral haemorrhage occurs in ≈ 5 to 6% of patients given intravenous rtPA for acute ischaemic stroke [215] implicating the possible role of fibrinolytic process and plasminogen activating system.[216] Administration of tranexamic acid in post-thrombolysis haemorrhagic transformation appears to prevent haematoma expansion.[217] In addition, fibrinolysis plays an important role in progressive brain injury after traumatic intracranial haemorrhage, hence the justification of using tranexamic acid in traumatic brain injury in CRASH-3.[218, 219] Plasmin was found to potentiate thrombin toxicity in an animal ICH model.[220] However, in a human study, levels of plasmin-antiplasmin complex were found to be significantly higher than normal healthy volunteers only in patients with ICH with intraventricular extension (IVE) or subarachnoid haemorrhage (SAH) but not those without.[221]

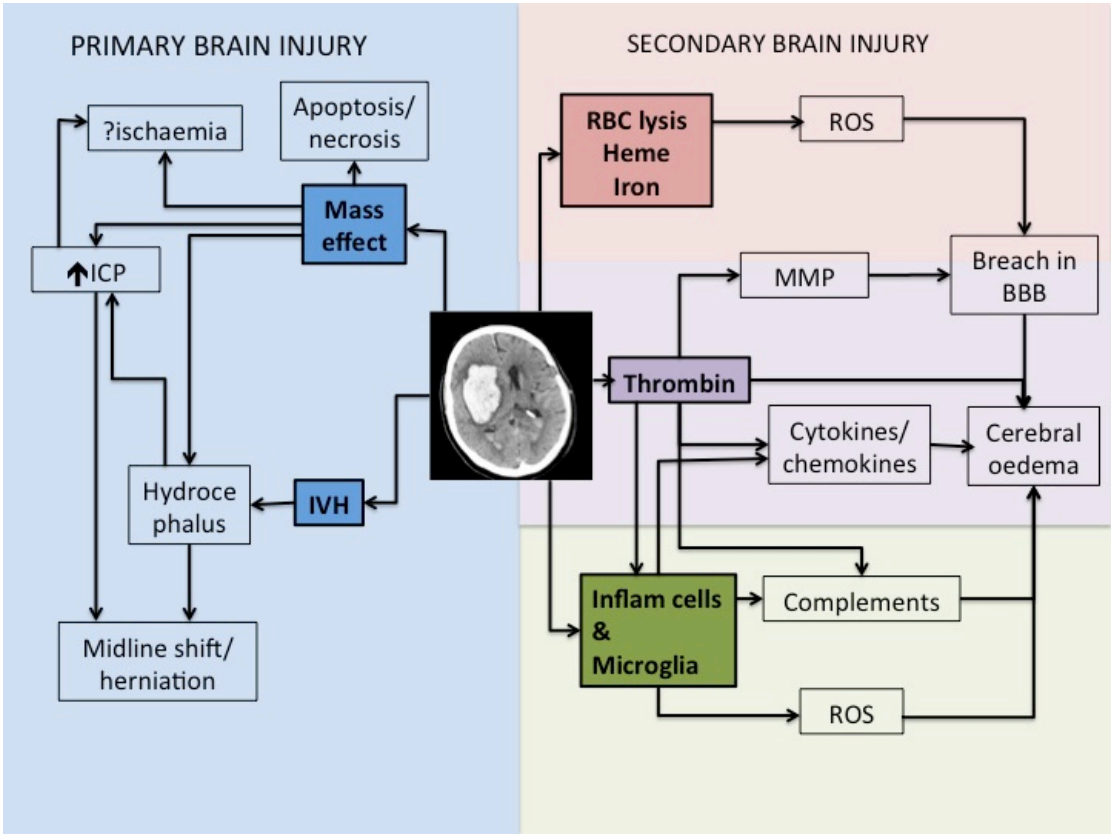


Figure 1-5 Mechanism of brain injury in intracerebral haemorrhage (Abbreviations: BBB= blood brain barrier; ICP= intracranial pressure; IVH= intraventricular haemorrhage; MMP= matrix metalloproteinase; ROS= reactive oxygen species)

Table 1-9 Therapeutic goals, targets and treatments in ICH

Goals	Measureable targets	Potential interventions	Evidence
Reducing haematoma volume	Haematoma expansion (>33%)	BP reduction[161, 162, 222] Haemostatic therapy[223] Surgical evacuation (craniotomy, minimally invasive surgery)[224, 225, 226]	Phase III- neutral
	Positive spot sign		Phase III-neutral
	Haematoma shape		Phase III-neutral
	Haematoma density		
	SBP measurement	BP reduction[162]	Phase III-neutral
	BP variability	BP reduction, antihypertensive with sustained effects[227]	Phase III-neutral
	Coagulation profile,	Haemostatic therapy (PCC, FFP)[228]	Phase III-beneficial
	dTT, ECT, factor Xa activity	Haemostatic therapy (idarucizumab, andexanet)[229, 230, 243]	Phase I/II-beneficial
	D-dimer, fibrinogen (fibrinolysis)	Haemostatic therapy (tranexamic acid)[80, 231]	Phase III-neutral
	Platelet function test	Platelet transfusion[232], Desmopressin[233]	Phase III-negative Phase II- possibly beneficial
	Calcium level	Calcium infusion[234, 235]	-
Clearance of intraventricular haemorrhage	IVH volume	Intraventricular rtPA[236, 272]	Phase III-neutral
	Modified Graeb index		
	Degree of hydrocephalus	Endoscopic surgery[237]	Phase II, Ongoing phase III
Reducing perihaematomal oedema	PHO volume	BP reduction[161, 162, 222] Surgical evacuation[238, 226] Osmotic agents[239, 240] Anti-inflammatory[241-247] Anti-oxidative[243, 245, 248]	Phase III-beneficial
	PHO expansion rate		Phase III-neutral
	PHO to haematoma ratio		Phase I/II-neutral
	PHO diffusion		Phase II-neutral
	Inflammatory markers- CRP, WCC	Anti-inflammatory - Statins[241] - hypothermia[242] - PPARγ[243] - Minocycline[244] - EPO[245] - Fingolimod[246] - Celecoxib[247]	Phase I/II
	Cytokine levels		
	Complement levels		
	MMP levels		
	Thrombin levels	Thrombin inhibitor[249]	Pre-clinical, Phase I
	Brain iron levels	Deferoxamine[250]	Pre-clinical
	Haem products	HO-1 inhibitor[251]	Pre-clinical
	ROS	Anti-oxidative- NXY-059[248], EPO[245]	Pre-clinical

*Abbreviations: BP= blood pressure; CRP=C-reactive protein; dTT=diluted thrombin time; ECT=ecarin clotting time; EPO= erythropoietin; FFP=fresh frozen plasma; HO-1= haem oxygenase-1 IVH= intraventricular haemorrhage; MMP= matrix metalloproteinases; PCC= prothrombin complex concentrate; PHO=perihaematomal oedema; PPARγ= Peroxisome proliferator-activated receptor gamma; ROS= reactive oxygen species; rtPA=recombinant tissue plasminogen activator; WCC= white cell count

1.10 Management of acute ICH

The main goals of management in acute ICH are to attenuate the primary and secondary brain injury caused by haematoma as well as prevention and treatment of complications. There are many therapeutic targets and goals that are being explored for these purposes. A summary of the therapeutic goals, targets and treatment is provided in Table 1-9. The following paragraphs described a few common and important treatments.

1.10.1 Blood pressure reduction

There are several strategies to limit haematoma expansion. Firstly, ameliorating the driving force of haematoma expansion by intensive reduction of systemic blood pressure. Systolic blood pressure is the primary target as it has greater effect on haematoma expansion than diastolic blood pressure. Intensive blood pressure to SBP of <140 mmHg compared to <180 mmHg was reported to reduce haematoma expansion significantly in INTERACT (mean haematoma volume difference of 3.15 mL at 24 hours, p=0.004).[252] Similarly the INTERACT-2, ATACH and ATACH-2 trial reported non-significant reduction in haematoma expansion with intensive blood pressure reduction.[161, 162, 253] However, there were no significant benefits on functional outcome. On the other hand, the trials did establish that intensive blood pressure reduction did not result in significant cerebral ischaemia and is therefore safe. Current guidelines suggest lowering SBP to <140 mmHg within an hour is safe and may be effective.[254, 255]

Fluctuations in blood pressure after ICH are thought to play a role in haematoma expansion. Greater blood pressure variability is associated with worse clinical outcome.[227, 256-258] However, the relation between blood pressure variability and haematoma expansion is controversial, with several studies showing no correlation between the two, despite significant effect of blood pressure variability on functional outcome.[227, 257] These findings suggest that choosing antihypertensive agents with stable and sustained

lowering effects of blood pressure may be as important as treating to specific SBP targets.

1.10.2 Haemostatic agents

The second strategy to limit haematoma expansion involves the use of haemostatic agents. Haemostatic therapy targeting the coagulation cascade, specific coagulation factors and fibrinolytic system are central to the treatment of anticoagulant-related ICH. In vitamin K antagonist-related ICH, intravenous vitamin K, prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP) are effective haemostatic agents. PCC normalises the international normalised ratio (INR) more rapidly than FFP. PCC reverses the INR within 30 minutes in 93% of patients.[228] On the contrary, 17% of the patients given FFP still had elevated INR at 24 hours.[259] Hence PCC is preferred over FFP in vitamin K antagonist-related ICH.[260] ICH secondary to direct oral anticoagulants (DOACs-dabigatran, rivaroxaban, apixaban and edoxaban) may be treated similarly with PCC.[260] In addition, a specific reversal agent, idarucizumab is available for dabigatran.[229] Idarucizumab normalises diluted thrombin time and ecarin thrombin time within minutes in 88 to 100% of patients.[229] Andexanet, a reversal agent for direct and indirect factor Xa inhibitor was found to reverse the anti-Xa activities of rivaroxaban and apixaban within minutes of administration.[261, 262] It was tested in a single-arm study amongst 352 patients who had intracranial and other major bleeding secondary to rivaroxaban, apixaban, edoxaban and enoxaparin. Good or excellent haemostasis was achieved in 82% of the patients within 12 hours. [243] However, 10% (34/352) of the patients had thromboembolic events. Andexanet alfa was approved as an antidote in the United States in May 2018.[263] The role of an antifibrinolytic agent, tranexamic acid in DOAC-related ICH is being examined.[264]

The role of haemostatic therapy in ICH unrelated to anticoagulant is unclear. Dynamic angiography studies suggest that continuing bleed or rebleeding within a haematoma resulting in haematoma expansion. This may be caused by failure of the natural haemostasis process and hence a need to

compensate for it. Several haemostatic agents had been researched for this purpose. Recombinant activated factor VIIa is the most widely researched haemostatic agents. A systematic review including 6 randomised controlled trials (1398 patients) concluded no significant benefits of activated factor VIIa on functional outcome despite reduction in haematoma expansion.[265] The benefits on haematoma expansion may have been negated by increased thromboembolic complications. Several ongoing trials aim to examine the role of tranexamic acid as a haemostatic agent in intracerebral haemorrhage.[80, 266]

Platelet dysfunction and lower platelet count is common in ICH especially in patients on prior antiplatelet therapy but may occur in patients not taking antiplatelet.[267] Normalisation of platelet function in patients with ICH was considered a potential therapeutic target. One possible intervention to improve platelet function was replenishment of platelets. A phase III randomised, open label, controlled trial compared the efficacy and safety of platelet transfusion to standard treatment in ICH associated with antiplatelet therapy (PATCH trial). However, the trial was terminated early as the odds of adverse events, death and dependency were found to be significantly higher in patients receiving platelet transfusion.[232] Desmopressin was found to improve platelet function in a proof-of-concept study but larger trials are needed.[233]

1.10.3 Surgical treatment for ICH

Not all patients with spontaneous ICH benefit from surgery. Several factors should be taken into consideration when deciding on surgery including haematoma location, patient's prognostic factors, timing and type of surgery.

1.10.3.1 Haematoma location

1.10.3.1.1 Supratentorial Haemorrhage

There is inconclusive evidence that routine surgery for all patients with supratentorial haemorrhage is beneficial. The International Surgical Trial in Intracerebral Haemorrhage (STICH) trial was a prospective open-label

blinded endpoint randomised controlled trial that randomised 1033 patients with ICH to early surgical haematoma evacuation and initial conservative treatment. There was no significant difference in outcome between the two groups.[224] However, a subgroup analysis of the trial showed that patients with superficial haematoma (<1cm from surface) benefited from early surgery. The trial also found that patients with poor initial GCS of <8 and intraventricular haemorrhage had poor outcome despite surgery.[224]

The subsequent STICH II trial randomised 601 patients with superficial lobar haematoma, with haematoma volume of 10 to 100 mL and without intraventricular extension to undergo early surgery or initial conservative management. There was an absolute reduction in mortality of 6% and 4% increase in favourable outcome in the early surgery arm though the difference was not statistically significant.[225] One reason that may explain this neutral result is that the trial recruited patients who were conscious or mildly confused that might not benefit from surgery. Patients with poorer GCS of 9 to 12 benefited from early surgery.[225] A meta-analysis including STICH II and 14 other trials (3366 patients) concluded overall benefit for early surgery (OR 0.74; 95% CI 0.64-0.86).[225] However, the meta-analysis should be interpreted discreetly as there was significant heterogeneity in the trials. It is unclear whether surgical intervention benefited certain subgroup of patients. Current European Stroke Organisation (ESO) guideline does not recommend routine surgery for supratentorial haematoma, though early surgery may be considered in patients with GCS of 9 to 12.[255] Similarly the American Heart Association/ American Stroke Association (AHA/ASA) guideline does not recommend routine surgery for supratentorial haematoma except in patients who are deteriorating.[254]

1.10.3.1.2 Cerebellar Haemorrhage

The posterior fossa is a narrow confined space containing the brainstem and cerebellum. Cerebellar haemorrhage may cause compression on the fourth ventricle resulting in obstructive hydrocephalus and on the brainstem causing herniation syndrome. Therefore, posterior decompression should be

performed in patients with cerebellar haematoma of >3cm and that result in hydrocephalus or brainstem compression.[268, 269] Insertion of an intraventricular drain or ventriculostomy without decompression is insufficient and may be harmful.[254]

1.10.3.1.3 Intraventricular haemorrhage

When IVH obstructs the ventricle and cause hydrocephalus, the placement of an external ventricular drain lowers intracranial pressure and may reduce mortality.[270]

Intraventricular thrombolysis had been reported to improve survival in several small studies.[271-273] In one small RCT (n=27), there was significant improvement in 1-year survival rate (p=0.014) in 16 patients treated with external ventricular drainage (EVD) and intraventricular urokinase compared to 11 treated with EVD alone.[273] The Intraventricular Hemorrhage Thrombolysis Trial (CLEAR IVH) reported significantly higher intraventricular clot lysis rate in patients treated with intraventricular low dose rtPA compared to placebo (18%/day vs 8%/day, p <0.001).[236] There was no significant difference in death and disability in this phase II trial.[236, 274] The Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR III) trial was a recently concluded randomised controlled trial comparing intraventricular rtPA to intraventricular normal saline (placebo) for the treatment of IVH. There was no significant improvement in functional outcome (RR 1.06, 95% CI 0.88-1.28; p=0.554) though there was a 50% reduction in odds of death (adjusted OR 0.50, 95% CI 0.31-0.80; p=0.004).[275] A secondary analysis showed that greater efficiency in IVH removal results in significantly better outcome (mRS ≤3; adjusted OR 0.96, 95% CI 0.94-0.97; p<0.0001).[275] Hence, there is a need for improved intraventricular catheter placement for more rapid and effective clot reduction.

Endoscopic surgery is a promising treatment option for intraventricular haemorrhage. A meta-analysis comparing endoscopic surgery plus EVD to EVD plus intraventricular fibrinolysis reported significantly less mortality (4

RCTs, 340 patients; OR 0.29, 95% CI 0.13-0.65) and higher favourable outcomes (3 RCTs, 246 patients; OR 4.47, 95% CI 2.42-8.24) favouring endoscopic surgery.[237] However, there is insufficient evidence comparing endoscopic surgery alone to EVD alone.

In conclusion, the role of intraventricular thrombolysis and endoscopic surgery is uncertain at this point in time.[254]

1.10.3.2 Timing of surgery

Based on a systematic review including 8 randomised controlled trials, surgery performed within 8 hours from onset appeared to be beneficial.[276] However, ultra-early surgery performed within 4 hours from onset was not beneficial and may be harmful.

1.10.3.3 Type of surgery

Craniotomy was the surgery that was performed in a majority of patients in large clinical trials. However, craniectomy may be life saving in patients with coma, large haematoma with midline shift and medically intractable raised intracranial pressure based on case-control studies and case series.[254, 277]

Minimally invasive surgery for clot evacuation was evaluated in Minimally Invasive Surgery and rtPA in ICH Evacuation phase II (MISTIE II). The trial found that minimal invasive surgery, whether alone or with intraclot recombinant tissue-type plasminogen activator (rtPA), result in greater removal of haematoma and significant reduction in perihaematomal oedema.[99] MISTIE III, a phase 3 randomised controlled trial, found that clot removal with intraclot rtPA via image-guided catheter did not improve functional outcome at one year in patients with large intracerebral haemorrhage (>30 mL) despite significant reduction in mortality on secondary analysis.[226] In view of these results, minimally invasive surgery cannot be routine recommended.

In conclusion, the decision to operate on a patient with supratentorial haemorrhage should be individualised with consideration of the following points:

- Patients with superficial lobar haemorrhage <1cm from surface may benefit whereas patients with deep seated hematomas do not.
- Surgery may be life saving for patients with clinical deterioration.
- Patients with poor GCS of <8 or fully alert may not benefit from surgery. Surgery should be considered for patients with intermediate GCS of 9 to 12. Craniotomy is the surgery most commonly undertaken in clinical trials.
- Despite its low level of evidence, decompressive craniectomy may be life saving for patients with coma, large haematoma with midline shift and medically intractable raised intracranial pressure.
- When ICH is complicated with hydrocephalus, the placement of an external ventricular drain lowers intracranial pressure and may reduce mortality.[270] Furthermore, external ventricular drain allows for monitoring of intracranial pressure.

1.10.4 Stroke care unit

Patients with ICH are often managed in different setting including acute stroke unit, intensive care unit and neurosurgical unit. The benefit of stroke unit for stroke patients is established. A systematic review pooling data from 5855 patients concluded that admission to an acute stroke unit improves outcome in terms of death and dependency (OR 0.79, 95% CI 0.68 to 0.90; p=0.0007).[278] Patients with ICH showed similar reduction in death and dependency compared to patients with ischaemic stroke.[278, 279] The benefit of stroke unit may be attributable to prevention and treatment of complications of stroke such as chest infection, pressure sores and other infections.[280] Death attributable to complications of immobility is significantly reduced in patients admitted to stroke unit (OR 0.59; 95% CI 0.41-0.86) due to better care plan including prevention of aspiration, avoidance of urinary catheter, use of oxygen for hypoxia and paracetamol for fever.[280] In addition,

continuous monitoring of physiological parameters blood pressure, heart rate, oxygen saturation, temperature, and electrocardiogram (ECG) carried out in a stroke unit ensure early detection and treatment of complications.[281]

1.10.5 Prevention and treatment of ICH complications

1.10.5.1 Dysphagia and pneumonia

All patients should be kept nil by mouth until a formal swallowing assessment by a trained professional.[282] Dysphagic patients may be fed modified diet, or have a nasogastric tube inserted and/or be given intravenous fluid depending on severity of dysphagia, hydration and nutritional status. This assessment and commencement of a nutritional plan should be initiated within 24 hours.[282] Patients who were unable to tolerate nasogastric tube or those needing tube feeding for more than four weeks should be considered for percutaneous endoscopic gastrostomy (PEG) tube insertion for long term feeding. Behavioural training, acupuncture and pharyngeal stimulation may be effective in regaining swallowing function in selected patients. Oral hygiene and frequent clearing of oral secretions is crucial in prevention of aspiration. Nasogastric tube should be changed every two to six weeks depending on the type of tube used.

1.10.5.2 Fever and infection

Patients with fever (>38^{0}C) should be treated with tepid sponging and paracetamol. While evidence for prophylactic antibiotics is lacking, those suspected to having an infection should be treated with empirical antibiotics.

1.10.5.3 Hyperglycaemia

Although hyperglycaemia is detrimental, there is no strong evidence to suggest that strict glycaemic control leads to better outcome. Maintaining blood glucose levels of 5 to 15 mmol/L is reasonable.[282] Glycaemic control should be achieved using insulin rather than oral antidiabetic.

1.10.5.4 Venous thromboembolism

Intermittent pneumatic compression is the most efficacious and safe method to prevent VTE after ICH. The Clots in Legs Or sTockings after Stroke-3 (CLOTS-3) trial concluded that intermittent pneumatic compression reduced the risk of VTE compared to graduated compression stoking.[283] Graduated compression stoking should be avoided, as it is not effective in preventing VTE compared to control. In addition, graduated compression stoking increases the risk of skin excoriation. There are conflicting evidences of whether heparin/ low molecular weight heparin (LMWH) is effective in preventing VTE after ICH. While there are concerns that heparin/LMWH may increase the risk of haematoma expansion, several studies showed that it is safe to be given after 24 hours.[284]

When ICH is complicated by DVT or pulmonary embolism, an observational approach is not feasible due to high mortality rate in untreated pulmonary embolism. Inferior vena cava filter may be considered as an alternative to anticoagulant as it does not increase the risk of recurrent ICH.[285, 286] Where this is not possible, anticoagulant can be started after the first few days of ICH when there is imaging evidence of haematoma stability.[254] The intricacies of starting anticoagulant in ICH are discussed in section 1.10.6 Restarting antithrombotic after ICH.

1.10.5.5 Seizures

Clinical seizures after ICH should be treated with antiepileptic agents. In addition, subclinical seizures detected by EEG should be treated. Approximately 30% of patients with seizures may develop non-convulsive seizures manifesting as altered consciousness.[135, 136] Treatment of non-convulsive seizures may lead to improvement in consciousness level. While prophylactic antiepileptic agents is previous practised, there is no evidence that routine antiepileptic agents prevent development of seizures or improve outcome.[287]

Table 1-10 General management of patients with intracerebral haemorrhage[288]

Section	Recommendations
General care/ nursing care	All patients should be admitted to an acute stroke unit or intensive care unit. Frequent vital sign checks, neurological assessment and continuous cardiopulmonary monitoring (pulse oximetry, automated BP cuff and ECG telemetry) should be performed.
Airway protection	Ventilation should be considered for patients with impending ventilator failure, at risk of aspiration, signs of raised intracranial pressure or brainstem dysfunction.
ICP monitoring	ICP should be monitored in patients with IVH, hydrocephalus, and signs of transtentorial herniation or GCS ≤ 8 that were presumably caused by haematoma mass effect. Maintenance of ICP of <20 mmHg and CPP of 50 to 70 mmHg is reasonable.
Blood pressure	In patients with acute ICH presenting within 6 hours, blood pressure should be lowered to SBP <140 mmHg within 1 hour
VTE prophylaxis	Intermittent pneumatic compression should be used. Graduated compression stockings should be avoided.
Dysphagia screening	Patients should be kept nil by mouth until a formal swallowing assessment is done.
Fever	High grade fever of >38^{0}C should be treated with paracetamol and/or tepid sponging
Glucose	Hypoglycaemia and hyperglycaemia should be treated. In treating hyperglycaemia, insulin should be used.
Intravenous fluid	Avoid over-hydration. Avoid dextrose containing fluid.
Seizure	Patients with clinical seizure(s) should be treated with antiepileptic agent(s). Patients without seizure should not be prophylactically treated with antiepileptic agent(s). Patients with altered conscious level and epileptic discharges detected on electroencephalography should be treated with antiepileptic agents.
DNAR order	Early DNAR order within the first 24 hours should be avoided as it may limit active medical treatment.

BP=blood pressure; CPP=cerebral perfusion pressure; DNAR=do not attempt resuscitation; ECG=electrocardiography; GCS=Glasgow Coma Scale; ICP=intracranial pressure; IVH=intraventricular haemorrhage; SBP=systolic blood pressure; VTE=venous thromboembolism

1.10.6 Restarting antithrombotic after ICH

In all cases of ICH (except in cerebral venous thrombosis, when anticoagulant is the treatment), antiplatelet therapy and anticoagulants should be withheld in the first 24 hours.[289, 290] The risk of haematoma expansion and mortality is highest at time of presentation and far outweighs a smaller risk of thromboembolism.[290] However, in the longer term, there is a clinical dilemma of whether and when antithrombotic therapy should be restarted. A patient taking VKA for prosthetic heart valves may suffer from a cardioembolic stroke or valve thrombosis if VKA is withheld but may get a recurrent ICH if VKA is continued. Both thromboembolic and bleeding events are disastrous. The decision of restarting antithrombotic therapy should be tailored after carefully considering the benefit of antithrombotic therapy over the risk of recurrent spontaneous ICH.

1.10.6.1 Risk of recurrent ICH

Most rebleeding in ICH occurs in the first 24 hours. Subsequently the annual risk of recurrent ICH is estimated to be 2 to 3%.[291] However, certain factors are associated with higher risk of recurrent ICH. Patients with poorly controlled hypertension have three to four-fold risk of rebleeding.[292] Patients with cerebral amyloid angiopathy also have higher risk of rebleeding (up to 22% per year).[293] Arteriovenous malformation has an 18% annual risk of rebleeding unless operated upon.[294] The risk of recurrence is higher in lobar haemorrhage compared to deep-seated haemorrhage (3 to 14% compared to 2 to 4% in deep-seated haemorrhage).[295] This perhaps reflects the underlying aetiologies where lobar haemorrhages are commonly caused by cerebral amyloid angiopathy with higher risk of recurrence, while deep-seated haemorrhages are caused by hypertensive angiopathy. Patients with cerebral microbleeds on MRI carries eight times higher risk of recurrent ICH.[296] In addition, higher number of cerebral microbleeds is associated with higher risk of intracerebral haemorrhage post-thrombolysis.[297]

The risk of recurrent ICH increases three to five-fold in patients taking a Vitamin-K antagonist (VKA).[298] In addition, VKA is associated with larger

haematoma and worse outcome. DOAC has been considered to have lower risk of recurrent ICH compared to VKA (relative risk of 0.46).[299] As for antiplatelet therapy, there is conflicting evidence to whether they increase the risk of recurrent ICH. Some studies concluded that antiplatelet therapy increased the risk of recurrent ICH while others did not.[293]

1.10.6.2 Risk of thromboembolism and protective effect of antithrombotic therapy

Prosthetic heart valves are highly thrombogenic and carry a 4 to 8% annual risk of thromboembolism if not anticoagulated.[300] VKA reduces the risk of thromboembolism by 75%.[301] DOACs carries a lower risk of bleeding than VKA but cannot be used in prosthetic valves. A trial evaluating the use of dabigatran in prosthetic valves was terminated early due to excessive adverse events.[302]

The annual risk of systemic thromboembolism in patients with atrial fibrillation varies between 1 to 15%.[303] The CHA_2DS_2-VASc score, with a minimum score of 0 and maximum score of 9, aids in stroke risk stratification in patients with atrial fibrillation. The risk is nearly 0 when CHA_2DS_2-VASc score is 0 but nearly 15% when the score is 9 (Table 1-11).[303, 304] Treatment with anticoagulant confers a 64% relative risk reduction for stroke.[305]

Table 1-11 CHA_2DS_2-VASc score and annual risk of stroke

Risk factor	Score
Congestive cardiac failure/ LV dysfunction	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1
Age 65 to 74	1
Sex category- female	1
Total	9

*Annual stroke risk according to score: 0=0%; 1=1.3%; 2=2.2%; 3=3.2%; 4=4.0%; 5=6.7%; 6=9.8%; 7=9.6%; 8=6.7%; 9=15.2%

1.10.6.3 Risk-benefit analysis

There is no established evidence to guide decision in restarting antithrombotic therapy in patients with prior ICH. The REstart or STop

Antithrombotics Randomised Trial (RESTART) recruited 537 patients with ICH who had prior antithrombotic to prevent vaso-occlusive disease. The trial compared whether restarting antiplatelet therapy would be superior to withholding antiplatelet therapy after ICH.[306] The incidence of recurrence ICH was lower in patients who took antiplatelet therapy (12/268, 4% vs 23/268, 9%; adjusted hazard ratio [aHR] 0.51, 95% CI 0.25-1.03; p=0·060).[307] The incidence of major bleeding was lower in the antiplatelet group as well (18/268, 7% vs 25/268, 9%; aHR 0.71, 95% CI 0.39-1.30; p=0·27).[307] This suggests that restarting antiplatelet therapy in patients with ICH was not necessary harmful though clinical equipoise remains, as antiplatelet therapy was not significantly superior to avoidance of antiplatelet therapy. In addition, several trial explore whether starting an anticoagulant would be beneficial in patients with atrial fibrillation after ICH.[308, 309]

The decision to restart or withhold antithrombotics should be tailored individually, taking into account its risk and benefit. A general approach would be avoiding anticoagulant therapy in patients with high risk of recurrent ICH (cerebral amyloid angiopathy, presence of microbleeds, lobar haemorrhage, uncontrolled hypertension) with low risk of thromboembolic events. Conversely, in patients with high risk of thromboembolism (prosthetic heart valves, high risk atrial fibrillation, high risk coronary artery disease, intracardiac thrombus) and low risk of recurrent ICH (deep-seated haemorrhage, well controlled blood pressure) antithrombotic therapy may be considered. One method of coming to a decision was using a Markov decision analysis as employed by Eckman *et al*. Based on this analysis model, anticoagulant should be avoided after lobar haemorrhage regardless of the thromboembolic risk while anticoagulant may be restarted after deep-seated haemorrhage if the thromboembolic risk in non-valvular atrial fibrillation is high (>7%/year).[254, 310] Antiplatelet agents carry a lower risk of recurrent ICH than anticoagulant and should be considered in patients with high risk of recurrent ICH.[254]

The optimal timing to restart antithrombotic therapy is unknown. In the early period after ICH, the risk of recurrent ICH is highest while risk of

thromboembolism increases with time. One retrospective analysis suggest that the optimal timing to restart antithrombotic would be 10 to 30 weeks after ICH when the combined risk of recurrent ICH and thromboembolism reach a nadir.[311] AHA/ASA guideline recommend avoiding warfarin in warfarin-related ICH for at least four weeks while aspirin may be initiated after a few days.[254]

1.10.7 Do not attempt resuscitation (DNAR) order

Early withdrawal of medical care in patients with ICH is an independent factor for poor outcome.[312,313, 314] Whilst do not attempt resuscitation (DNAR) order means that there should be no attempt for cardiopulmonary resuscitation in case of cardiopulmonary arrest, this is often extended to withdrawal of all active medical treatment. An early DNAR order could limit optimal medical care, resulting in poor outcome and thus should be avoided for at least 24 hours up to the first few days.[254]

1.11 Tranexamic acid in intracerebral haemorrhage

1.11.1 Fibrinolysis cascade

The fibrinolysis cascade is the counter-regulatory system of coagulation cascade to prevent excessive clot formation. The final product of the coagulation cascade, stable cross-linked fibrin, is the target of the fibrinolysis cascade. The process of fibrinolysis is initiated by two major plasminogen activators, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) in response to tissue injury. TPA and uPA catalyse the cleavage of plasminogen converting it to active form plasmin.[315] Plasmin is a serine protease that binds to polymerised fibrin, leading to the breakdown of cross-linked fibrin and resolution of clot.[316] Plasmin gives a positive feedback on tPA and uPA, increasing their activities and further enhancing fibrinolysis. On the other hand, counter-mechanisms to this fibrinolytic process involved thrombin-activatable fibrinolysis inhibitor (TAFI)[317], plasminogen activator inhibitors -1 and 2 (PAI-1, 2)[318] and α2-antiplasmin which inhibit plasminogen/plasmin activities.[319, 320] In addition,

exogenous antagonist - aprotinin, epsilon-aminocaproic acid (EACA) and tranexamic acid inhibit the action of plasmin.[321-323]

1.11.2 Non-fibrinolytic functions of plasmin

Plasmin contributes to pro-inflammatory response via several pathways. Plasmin activates monocytes and polymorphonuclear neutrophils (PMNs) as well as inducing cytokine IL-1 release from macrophages.[324, 325] Plasmin induces microglia activation as well.[326] In addition, plasmin upregulates the complement system, further increases inflammatory response by chemotactic actions. Membrane attack complexes (MAC) form from complement activation, leading to lysis and cell death of neurons and glia cells.[327] Plasmin activates MMP-1, -2, -3, -9, and -13, which degrade extracellular matrixes, laminin and basal membrane protein.[328] In brain injury, this can lead to further inflammatory response, breach in blood-brain barrier and cerebral oedema.[329] MMPs also degrade fibronectin, inducing apoptosis leading to cell death. In one animal ICH model, plasminogen augments thrombin cytotoxicity, leading to neuronal death.[220] Figure 1-6 illustrates components of plasmin-mediated pathways.

In cardiopulmonary bypass, platelet surface contact with extracorporeal circuit leads to plasmin-platelet interation.[330] Plasmin selectively release adenosine diphosphate (ADP) granules from platelet, leading to excessive platelet aggregation and platelet depletion in vivo, a contributing factor to blood loss.[330] On the other hand, plasmin has antiplatelet functions in vivo by inducing proteolysis of GpIb and GpIIb/IIIa, essential platelet surface receptors.

Plasmin promotes angiogenesis by activation of TGFβ, FGF-2 and HGF.[331] Angiogenesis is demonstrated as an important process in tumour growth. Its role in ICH is unclear.

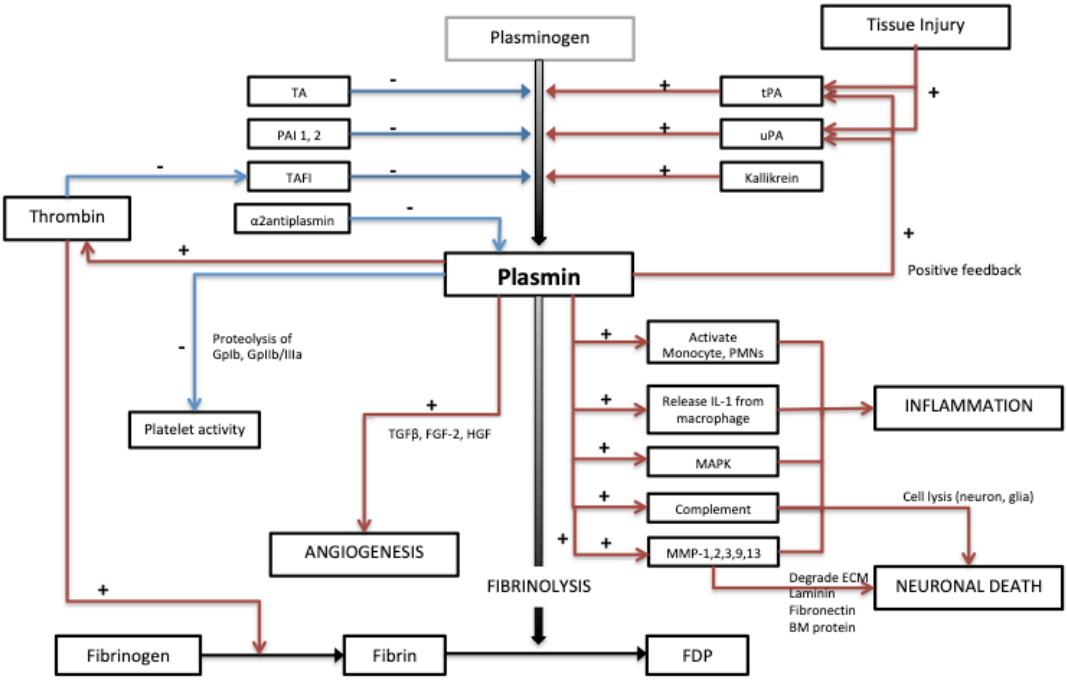


Figure 1-6 Plasmin-mediated pathway

1.11.3 Tranexamic acid

1.11.3.1 Pharmacokinetics

Tranexamic acid can be given via oral route or intravenously. It has a oral bioavailability of 30% and reached peak concentration approximately three hours after oral administration.[323] When given intravenously, the peak concentration is reached within five minutes.[332] Tranexamic acid has a wide intracellular and extracellular distribution into cerebrospinal fluid, joint fluid, aqueous humour, semen, placenta and breast milk.[333] About 90 to 95% of tranexamic acid is excreted unchanged in the urine after 24 hours.[332] Tranexamic acid has a plasma elimination half-life of three hours though due to its wide distribution, antifibrinolytic activities can remain in tissues up to 17 hours with repeated dosing of 4 to 5 times a day.[333]

1.11.3.2 Pharmacodynamics & mechanisms of action

Tranexamic acid has a rapid onset of action within a few minutes of intravenous administration. It is an analogue of amino acid lysine and binds

reversibly to lysine residues on plasminogen and plasmin, thus preventing the binding of plasmin to fibrin.[323] Its anti-fibrinolytic activity is 6 to 10 times greater than EACA, another antifibrinolytic agent.[323] It is postulated that tranexamic acid reduces haematoma expansion as stopping continuing bleed or prevent rebleeding.

In addition to its antifibrinolytic function, by inhibiting plasminogen and plasmin, tranexamic acid also attenuates plasmin-mediated inflammatory response.[334] Tranexamic acid has been shown to have an anti-inflammatory effect based on clinical studies. Jimmenez *et al* conducted a randomised trial recruiting patients undergoing extracorporeal circulation in cardiac surgery to receive tranexamic acid versus placebo. The trial reported significant reduction in inflammatory response in tranexamic acid group as well as a reduction in inflammatory markers including IL-6 and soluble TNF-α receptor antigen[335]. In a second randomised controlled trial, Jimmenez *et al* reported reduced incidence of inflammatory response in patients given higher dose of tranexamic acid (40mg/kg given twice) than those given a lower dose (40mg/kg given once)[336]

Animal studies showed that tranexamic acid may be neuroprotective by inhibiting plasminogen and thrombin-induced neuronal injury[220]. Tranexamic acid may also reduce matrix metalloproteinase-9 (MMP-9) levels thus conferring neuroprotection.[337] However, tranexamic acid may also potentiate the effect of thrombin, which results in cerebral ischaemia as we see in the subarachnoid haemorrhage trials.[338]

1.11.3.3 Clinical indications & evidences

1.11.3.3.1 Major trauma

The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2), a megatrial involving 20211 patients concluded that tranexamic acid reduced mortality in patients with polytrauma (relative risk, RR 0.91, 95% CI 0.85-0.97; p=0.0035).[339] The risk of bleeding associated mortality is significantly reduced [489 patients (4.9%) in the TXA group died compared to

574 patients (5.7%) in the placebo group; RR 0.85; 95% CI 0.76-0.96; p=0.0077].[340] However, the efficacy of tranexamic acid is time-dependent. Only patients receiving treatment within 3 hours of injury had reduced mortality (<1 hour: RR 0.68; 95% CI 0.57-0.82; p< 0.0001 and for 1 to 3 hours: RR 0.79; 95% CI 0.64-0.97; p=0.03). On the contrary, patients receiving tranexamic acid beyond 3 hours of injury had an increased mortality. 144/3272 patients (4.4%) died in the tranexamic group compared to 103/3362 patients (3.1%) in the placebo group (RR 1.44; 95% CI 1.12 to 1.84; p = 0.004).[340] Current guidelines recommend giving intravenous tranexamic acid in patients with major trauma within 3 hours of injury.[341]

1.11.3.3.2 Traumatic intracranial haemorrhage

A subgroup analysis of CRASH-2 (n=270) showed that patients with traumatic ICH had a non-significant reduction in mortality (adjusted OR 0.47, 95% CI 0.21 to 1.04).[342] An ongoing trial, CRASH-3, is examining the efficacy of tranexamic acid in improving outcome after traumatic brain injury.[219] There are some promising reports regarding the use of tranexamic acid in resolving chronic subdural haematoma, which is frequently related to minor trauma.[343] In addition, an ongoing trial is exploring the efficacy of tranexamic acid in chronic subdural haemorrhage.[344] The benefit of tranexamic acid in traumatic intracranial haemorrhage is uncertain at this point.

1.11.3.3.3 Aneurysmal subarachnoid haemorrhage

A systematic review including 10 RCTs (1904 patients) concluded no benefits of tranexamic acid on mortality in aneurysmal subarachnoid haemorrhage (pooled RR 1.00; 95% CI 0.85 to 1.18).[345] This is despite a 35% lower rate of rebleeding in patients given tranexamic acid. Sensitivity analysis showed that the increased risk of cerebral ischaemia (pooled RR 1.41; 95% CI 1.04 to 1.91) offsets the benefits from reduced bleeding.[345] Many of the trials of tranexamic acid in subarachnoid haemorrhage involved giving high doses of up to 6 g per day for a prolonged duration of three to six weeks and this could have accounted for the increased ischaemic events. In view of this, an ongoing trial is examining the efficacy of shorter-term

tranexamic acid in subarachnoid haemorrhage at lower dose, i.e. 1 g given 8-hourly for a maximum of 24 hours.[346] The AHA/ASA guideline recommended short-term (<72 hours) use of tranexamic acid in subarachnoid haemorrhage where risk of bleeding is high and when there is unavoidable delay in obliteration of aneurysm.[347] However, the ESO guideline did not recommend it.[348]

1.11.3.3.4 Cardiac surgery

The use of antifibrinolytic agents aprotinin, tranexamic acid and EACA were established. However, the choice of antifibrinolytic in cardiac surgery had shifted from aprotinin to tranexamic acid since the observational study by Mangano e*t al*. This observational study of 4374 patients found that aprotinin increased the risk of renal failure by two times and a 55% increase in risk of cardiac failure and myocardial infarction post-cardiac surgery.[349] The Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) trial (2331 patients) reported higher 30-day mortality rate in patients given aprotinin compared to tranexamic acid (6.0% vs 3.9%, RR 1.55; 95% CI, 0.99-2.42) and EACA (6.0% vs 4.0%, RR 1.52; 95% CI, 0.98-2.36).[350] Despite a modest reduction in perioperative bleeding rate (9.5% vs 12.1%), cardiac death was significantly increased in patients given aprotinin compared to tranexamic acid (RR 2.47; 95% CI 1.19-5.10).[350] Aprotinin was withdrawn in the United States in 2008 follow these reports. The efficacy and safety of tranexamic acid in cardiac surgery was well established. Tranexamic acid reduces peri-cardiac surgery blood loss by approximately 300 mL and the need for blood transfusion by 32 to 47%.[351-353] The 2011 Society of Thoracic Surgery guideline gave a 1a recommendation for use of tranexamic acid to reduce blood loss in cardiac surgery.[354] A recent RCT of 4631 found reduced risk of death, blood transfusion and need for reoperation without increasing the risk of thromboembolism.[355]

1.11.3.3.5 Orthopaedic surgery

Tranexamic acid reduces peri-operative blood loss in knee arthroplasty, hip arthroplasty and spinal surgery.[334, 356] In a meta-analysis of 14 RCTS,

tranexamic acid use in knee arthroplasty reduces blood loss by 591 mL and need for blood transfusion (RR 3.00; 95% CI 2.51-3.59).[357] In addition, tranexamic acid appears to reduce knee swelling after knee arthroplasty independent of blood loss.[358] In another meta-analysis of 11 RCTs, tranexamic acid reduces risk of bleeding by 289 mL (95% CI -440 to -138, p<0.0002) in hip arthroplasty.[359] In addition, tranexamic acid reduces the blood loss by 389 to 427 mL and need for blood transfusion by 35% in spinal surgery.[360, 361] Although the risk of thromboembolism after orthopaedic surgery raise concerns for its use, the risk is in fact not increased in patients given tranexamic acid.[356, 357, 362]

1.11.3.3.6 Gastrointestinal tract bleeding

A Cochrane systematic review including 8 RCTs (1701 patients) found that tranexamic acid reduced mortality in gastrointestinal bleeding (RR 0.60, 95% CI 0.42-0.87; p=0.007).[363] However, as there were high drop out rate from in some of the trials, the benefits of tranexamic acid could not be ascertained.[363] Haemorrhage ALleviation with Tranexamic acid- IntesTinal system (HALT-IT, NCT01658124) is an ongoing RCT aiming to recruit 8000 patients to determine the effects of tranexamic acid on mortality, morbidity, blood transfusion, surgery and health status of patients with acute gastrointestinal bleed.[364]

1.11.3.3.7 Obstetrics and gynaecological indications

The efficacy of tranexamic acid in reducing heavy menstrual blood loss had been studied since 1970's. [365, 366] Tranexamic acid reduced menstrual blood loss by 26 to 60% compared to non-steroidal anti-inflammatory drugs, oral luteal progesterone and ethamsylate.[367, 368] This results in significant improvement in flooding, leakage, sex life and quality of life as well.[368, 369]

Tranexamic acid is effective in reducing blood loss after vaginal delivery and caesarean section. The World Maternal Antifibrinolytic Trial (WOMAN) was a randomised controlled trial who had recruited 20060 patients and found that tranexamic acid reduced the risk of death due to postpartum haemorrhage

(155 [1.5%] of 10036 patients in tranexamic acid group vs 191 [1.9%] of 9985 in the placebo group, risk ratio [RR] 0.81, 95% CI 0.65-1.00; p=0.045).[370] The benefit is greater when given within 3 hours of giving birth (RR 0.69, 95% CI 0.52-0.91; p=0.008).[370] A Cochrane meta-analysis that included three trials (n=20412) concluded that intravenous tranexamic acid reduced bleeding-related death in primary postpartum haemorrhage regardless of modes of delivery, while at the same time did not increase the risk of venous thromboembolism.[371]

1.11.3.3.8 Other indications

Tranexamic acid had been used to reduce blood loss after tonsillectomy[372], traumatic hyphema,[373] prostatectomy[374], epistaxis[375] and gum bleeding.[376]

1.11.3.4 Spontaneous intracerebral haemorrhage

The use of tranexamic acid in intracerebral haemorrhage is detailed in two systematic reviews in Chapter 2 and 3.

1.11.3.5 Adverse effects

1.11.3.5.1 Thromboembolic events

Venous thromboembolism i.e. deep vein thrombosis and pulmonary embolism are possible adverse effects of tranexamic acid. However, patients receiving tranexamic acid are often immobile due to pre-existing conditions (post operative, trauma and intracranial haemorrhage), which increase the risk of venous thromboembolism as well.

Several large studies had found no significant increase in risk of VTE in patients given tranexamic acid for hip and knee arthroplasty. One large retrospective analysis (n=872416) of tranexamic acid use in hip and knee arthroplasty reported no significant increase in prevalence of venous thromboembolism (0.6% in tranexamic acid vs 0.8% in control).[362] A prospective study of 2532 patients who underwent knee arthroplasty, the incidence of VTE was not increased in patients who received tranexamic acid.[377] One meta-analysis of tranexamic acid in surgical bleeding concluded

that the risk of venous and arterial thromboembolism with tranexamic acid is uncertain.[378] The risk of thromboembolic events was either moderately increased or moderately decreased with tranexamic acid: myocardial infarction (RR 0.68, 95% CI 0.43-1.09; p=0.11), stroke (1.14, 0.65-2.00; p=0.65), deep vein thrombosis (0.86, 0.53-1.39; p=0.54), and pulmonary embolism (0.61, 0.25-1.47; p=0.27).[378] The use of tranexamic acid did not increase the risk of VTE in pregnant patients as well.[371, 379] A nested case-control study found a non-significant increase in VTE amongst patients receiving tranexamic acid, though this is possibly confounded by anaemia and menorrhagia, which may be pro-thrombotic states.[380] The use of tranexamic acid in major trauma did not increase the incidence of venous thromboembolism, stroke or myocardial infarction in the CRASH-2 trial (0.3% in tranexamic acid group vs 0.5% in control group; RR 0.69, 95% CI 0.44-1.07; p=0.096).[381]

1.11.3.5.2 Seizure

Seizure is a known complication of tranexamic acid with an estimated incidence of 2.7%.[382] According to one meta-analysis, it increases the risk of seizure by approximately five times (pooled OR 5.39, 95%CI 3.29-8.85; I^2 = 0%; p<0.001).[382] A recent trial of tranexamic acid in cardiac surgery reported even higher risk of seizure with a relative risk 7.6 (0.7% had seizure in tranexamic acid group compared to 0.1% in placebo).[355]

1.11.3.5.3 Other adverse effects

Reported adverse effects of tranexamic acid include nausea, vomiting, diarrhoea, headache, dizziness, fatigue, flushing, collapse, hypotension tachycardia, hypersensitivity, anaphylaxis and colour visual changes.

Chapter 2 Systematic review: Treatment of intracerebral haemorrhage with tranexamic acid – A review of current evidence and ongoing trials.

2.1 Publication contributing to this chapter

Zhe Kang Law, Atte Meretoja, Stefan T Engelter, Hanne Christensen, Eugenia-Maria Muresan, Solveig B Glad, Liping Liu, Philip M Bath, and Nikola Sprigg. Treatment of intracerebral haemorrhage with tranexamic acid – A review of current evidence and ongoing trials. European Stroke Journal 2017, Vol. 2(1) 13–22. First published on October 25, 2016 as doi:10.1177/2396987316676610

2.2 Abstract

2.2.1 Purpose

Haematoma expansion is a devastating complication of intracerebral haemorrhage (ICH) with no established treatment. Tranexamic acid had been an effective haemostatic agent in reducing post-operative and traumatic bleeding. We review current evidence examining the efficacy of tranexamic acid in improving clinical outcome after ICH.

2.2.2 Method

We searched MEDLINE, EMBASE, CENTRAL and clinical trial registers for studies using search strategies incorporating the terms ‘intracerebral haemorrhage’, ‘tranexamic acid’ and ‘antifibrinolytic’. Authors of ongoing clinical trials were contacted for further details.

2.2.3 Findings

We screened 268 publications and retrieved 17 articles after screening. Unpublished information from three ongoing clinical trials was obtained. We found five completed studies. Of these, two randomised controlled trials

(RCTs) comparing intravenous tranexamic acid to placebo (n=54) reported no significant difference in death or dependency. Three observational studies (n=281) suggested less haematoma growth with rapid tranexamic acid infusion. There are six ongoing RCTs (n=3089) with different clinical exclusions, imaging selection criteria (spot sign and haematoma volume), time window for recruitment and dosing of tranexamic acid.

2.2.4 Discussion

Despite their heterogeneity, the ongoing trials will provide key evidence on the effects of tranexamic acid on ICH. There are uncertainties of whether patients with negative spot sign, large haematoma, intraventricular haemorrhage, or poor Glasgow Coma Scale should be recruited. The time window for optimal effect of haemostatic therapy in ICH is yet to be established.

2.2.5 Conclusion

Tranexamic acid is a promising haemostatic agent for ICH. We await the results of the trials before definite conclusions can be drawn.

2.3 Introduction

Spontaneous intracerebral haemorrhage (ICH) is a devastating condition with a median 30-days mortality rate of 40%.[2] It is also associated with significant morbidity with 60% of patients remaining dependent one year after the event.[2] Haematoma expansion is a major cause of early neurological deterioration and poor outcome, occurring in 38% of ICH patients within the first few hours from onset of symptoms.[86] Nevertheless, patients with small haematoma volume have an excellent prognosis.[92] Therefore, there is an urgent need to direct treatment goal towards limiting haematoma size.

To date, there is no proven treatment to limit haematoma expansion. However, two main non-surgical strategies have been postulated to reduce haematoma expansion: ameliorating the driving force of haematoma

expansion and haemostatic therapy.[383] The former can be achieved through reduction of perfusion pressure by decreasing systemic blood pressure. The INTERACT trial reported reduction in haematoma expansion (mean haematoma volume difference of 3.15 mL at 24 hours, p=0.004) in patients treated with intensive blood pressure reduction (systolic blood pressure, SBP <140 mmHg) as compared to standard blood pressure reduction (SBP<180 mmHg).[222] In addition, The INTERACT 2, ATACH and ATACH-II trials reported non-significant reduction in haematoma expansion. However, these did not translate into significant reduction in death or dependency.[161, 162, 253] At the same time, there were concerns that rapid blood pressure reduction may result in cerebral ischaemia. The INTERACT, INTERACT 2, ATACH and ATACH-II reported no significant cerebral ischaemic events in patients treated with intensive blood pressure reduction.[161, 162, 222, 253] Current guidelines suggest treating blood pressure to a SBP of 140 mmHg is safe and can/may be effective.[254, 255]

Several haemostatic agents have been researched for possible effect in limiting HE. An extensively researched haemostatic agent, recombinant activated factor VIIa, was highly effective in reducing haematoma expansion but failed to significantly improve clinical outcomes in five trials (total patient number =1395), possibly due to a trend towards increased thromboembolic complications.[265]

2.3.1 Tranexamic acid

Tranexamic acid has been used as an effective haemostatic agent in acute gastrointestinal bleeding, menorrhagia, epistaxis, post-cardiac and post-orthopaedic surgery.[363, 384-387] Besides reducing bleeding rate and need for blood transfusion, tranexamic acid also improves healing and reduces inflammation.[335, 388]

Tranexamic acid has been studied in subarachnoid, subdural and traumatic intracranial haemorrhage. In aneurysmal subarachnoid haemorrhage (SAH), tranexamic acid was effective in stopping bleeding when use in conjunction

with endovascular coiling or clipping [389] although an increased risk of cerebral ischaemia offset any benefit.[345] Many of the trials of tranexamic acid in SAH involved giving high doses of up to 6 g per day for a prolonged duration of three to six weeks and this could have accounted for the increased ischaemic events. In view of this, an ongoing trial is examining the efficacy of shorter-term tranexamic acid in SAH at lower dose, i.e. 1 g given 8-hourly for a maximum of 24 hours.[346]

The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2), a megatrial involving 20,211 patients found that tranexamic acid reduced mortality in patients with polytrauma (Odds Ratio, OR 0.91, 95% confidence interval, CI 0.85 to 0.97).[339] A subgroup analysis of CRASH-2 (n=270) showed that patients with traumatic ICH had a non-significant reduction in mortality (adjusted OR 0.47, 95% CI 0.21 to 1.04).[342] An ongoing trial, CRASH-3, is examining the efficacy of tranexamic acid in improving outcome after traumatic brain injury.[219] An additional trial is testing tranexamic acid in the non-surgical treatment of chronic subdural haematoma.[343,344]

Given these promising results from trials of tranexamic acid in various conditions, we examined the efficacy of tranexamic acid in improving clinical outcome in spontaneous ICH.

2.4 Methods

The aim was to assess whether tranexamic acid, as compared to placebo or no additional treatment, improved outcome in patients with intracerebral haemorrhage. Randomised and quasi-randomised controlled clinical trials, and before-after studies, were included and assessed by systematic review and meta-analysis. Trials were included if they involved adult patients with primary non-traumatic intracerebral haemorrhage, i.e. likely to be due to hypertension or cerebral amyloid angiopathy. Trials of patients with secondary ICH due to arteriovenous malformation, intracranial aneurysm, cavernoma, dural arteriovenous fistula, haemorrhagic brain metastasis,

trauma or thrombolysis were excluded. Trials could use tranexamic acid at any dose, route of administration and time window for administration. The main functional outcomes of interest were modified Rankin Scale (mRS), Barthel Index and Glasgow Outcome Scale. Meta-analysis of the primary outcome was performed if at least two RCTs reported relevant data.

Trials were identified in MEDLINE, EMBASE and CENTRAL using search strategies incorporating the terms ‘tranexamic acid’, ‘antifibrinolytic’ and ‘intracerebral haemorrhage’. No language restrictions were imposed in searches. Searches of www.clinicaltrials.gov, the European registry of clinical trials and WHO international clinical trial registries were also performed, which covered both ongoing and unpublished trials. Where relevant, experts in the field were contacted for further information regarding unpublished data or trials. A complete list of search strategies and results is included in the online supplementary material. Two authors (NS, ZL) independently screened the search results for potential studies. The full text of shortlisted articles was then obtained for review.

2.5 Results

2.5.1 Identified studies

Our search identified 268 articles; after deduplication, 163 articles were available for screening. Of these, 146 articles were excluded for various reasons (Figure 2-1). The full text of 17 articles were extracted and reviewed. A search of clinical trial registers revealed nine relevant records of trials, these corresponding to four clinical trials. Some clinical trials were registered in more than one trial register. Unpublished information on three ongoing studies was obtained from authors. These articles and unpublished information described five completed and six ongoing studies that are described in the following text.

The five completed studies including two small randomised controlled trials involving 54 patients (Table 2-1). Since these trials did not report sufficiently

information on clinical outcomes, meta-analysis could not be performed.

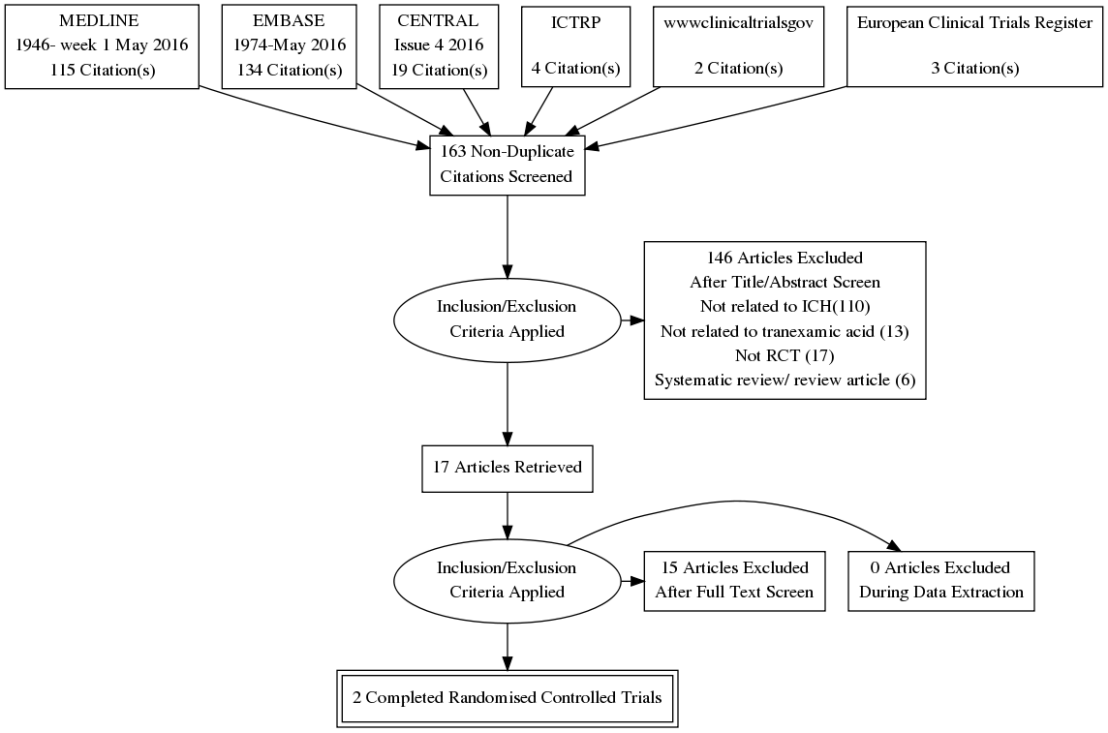


Figure 2-1 PRISMA flow chart of systematic search. ICH: intracerebral haemorrhage; ICTRP: International Clinical Trials Registry Platform; RCT: randomised controlled trial.

2.5.2 Completed observational studies and clinical trials

2.5.2.1 Observational studies

Sorimachi *et al* reported a retrospective observational before-after study comparing the efficacy of rapid infusion of tranexamic acid 2 g over 10 minutes to prolonged infusion of 1 g over 6 hours in patients presenting within 24 hours of ICH. The study recruited 156 patients (>80% presented within 3 hours of onset) and showed that rapid infusion was associated with less haematoma enlargement of >20% than prolonged infusion (17.5% vs. 4.3%, p=0.011).[390] The authors subsequently reported a study of additional 95 patients treated with rapid infusion of tranexamic acid with haematoma expansion occurring in 4.2% of these patients.[391] However, there was no control arm in either study.

Ojacastro *et al* reported an observational study of 30 patients aged 40 to 70 years with hypertensive ICH who received either intravenous tranexamic acid 500 mg for 3 doses or standard care. The study is reported as an abstract

only, with no data other than a general statement of significant haematoma volume reduction with tranexamic acid without effect on length of stay or in-hospital NIHSS.[392] We were unsuccessful in contacting the authors for further information.

Table 2-1 Completed studies and clinical trials of tranexamic acid in intracerebral haemorrhage

	Sorimachi 2005[390]	Sorimachi 2007[391]	Ojacastro 2008[392]	TICH 2014[393]	Arumugam 2015[394]
Design	Retrospective observational	Observational	Observational	RCT	RCT
Number of patients	156	95*	30	24	30
Intervention (intravenous tranexamic acid infusion)	2 g over 10 minutes	2 g over 10 minutes	500 mg 3 times	1 g over 10 minutes followed by 1 g over 8 hours	1 g over 10 minutes followed by 1 g over 8 hours
Control	1 g TA over 6 hours	No control	Usual care	Placebo	Placebo
Baseline to 24 hour haematoma expansion	Less HE of >20% with rapid infusion (17.5% vs. 4.3%, p=0.011)	HE of >20% in 4.2%	Less HE by day 3 with TA (no data provided)	HE of >6 mL (13% placebo vs 19% TA, p=NR)	No ICH volume change with TA (placebo median 14.53 to 17.59 mL, p = 0.001 vs TA 10.06 to 10.08 mL, p=0.313)
Clinical outcome	NR	Earlier of discharge or 30 day mRS 0-2=29%, no control arm	No effect on length of stay or in-hospital NIHSS (p=NR)	Mean mRS (3.4 control vs 3.6 TA p=0.82)	Mean GOS score (3.6 control vs 4.3 TA, p NA)

*Paper additionally includes all rapid infusion patients of the 2005 study, total n=188.
RCT=randomised controlled trial, IV=intravenous, HE=haematoma expansion, TA=tranexamic acid, NR=not reported, NIHSS=National Institutes of Health Stroke Scale, mRS=modified Rankin Scale, GOS=Glasgow Outcome Scale

2.5.2.2 Randomised controlled trials

The Tranexamic acid in IntraCerebral Haemorrhage (TICH) trial recruited 24 patients within 24 hours (mean 12.6 hours) of ICH to receive either 1 g tranexamic acid or placebo over 10 minutes followed by 1 g over 8 hours. There was no 90-day outcome difference (mean mRS 3.6 in treatment arm and 3.4 in control, p=0.82) with non-significantly more haematoma expansion (>6 mL growth) in the treatment arm (19% vs 13%).[393] However, this trial was designed as a feasibility trial and not to demonstrate efficacy.

In addition, Arumugam *et al*[394] conducted a single centre, single blind randomised controlled trial that allocated 30 patients to receive within 8 hours (mean 6 hours) of ICH either intravenous tranexamic acid 1 g over 10 minutes followed by 1 g over 8 hours or placebo. The control group had significant haematoma expansion (median growth from 14.53 to 17.59 mL, p=0.001) while the treatment group did not (10.06 to 10.08 mL, p=0.313).[394] The mean Glasgow Outcome Scale score was 3.6 in the control and 4.4 in the treatment group, but no statistical tests comparing the groups were provided.

2.5.2.3 Ongoing clinical trials (including those in preparation, **Table 2-2***)*

2.5.2.3.1 STOP-AUST

The Spot sign and Tranexamic acid On Preventing ICH growth – AUStralasia Trial (STOP-AUST, NCT01702636) is a phase II multicentre randomised, double blind, placebo-controlled trial exploring the efficacy of tranexamic acid in preventing haematoma expansion in ICH patients, recruiting patients from Australia, Finland, and Taiwan.[266] The trial selects patients with a positive spot sign on CT angiography to receive either placebo or 1 g tranexamic acid over 10 minutes followed by 1 g over 8 hours. The primary outcome measure is haematoma expansion (>33% or >6 mL) by 24 hours, with mRS and thromboembolic complications at 90 days as secondary outcomes. The trial aims to recruit 100 patients and has recruited 39 patients by August 2016.

2.5.2.3.2 TICH-2

Tranexamic acid for Intracerebral Haemorrhage-2 (TICH-2, EudraCT number 2012-004108-37) is a phase III, pragmatic double blind randomised placebo controlled trial aiming to recruit 2000 patients in United Kingdom and internationally. The study commenced in March 2013 and is due to be completed in December 2017. It has recruited 1683 patients as of August 2016. The TICH-2 trial is recruiting ICH patients presenting within 8 hours of onset regardless of whether they had CT angiography to detect positive spot sign, a predictor of haematoma expansion. Of the patients recruited, only 7% (n=103) had CT angiography and of that, 17.5% (n=18) were spot sign positive. The patients are randomised to receive intravenous tranexamic acid 1 g bolus (given within 10 minutes) followed by a 1 g infusion given over 8 hours. The primary outcome assessed is death or dependency using mRS at 90 days. Secondary outcomes include neurological impairment (National Institute of Health Stroke Scale - NIHSS) at day 7 or sooner, functional outcome (Barthel index), quality of life (EuroQol, EQ-5D, and EQ-VAS), cognition (Telephone Interview Cognition Score-Modified), mood (Zung Depression Scale) at days 90 and 365; cost, radiological efficacy and safety outcomes up to day 90. Selected centres are invited to participate in an MRI sub-study looking at diffusion weighted imaging hyperintense lesions (DWIHL), perihaematomal oedema volume and diffusion restriction at 5 days as well as haematoma cavity volume and surrounding gliosis at 90 days.[80]

PATCH-iT is a Danish substudy of TICH-2 aiming to recruit 72 patients with spot sign or post-contrast extravasation. Primary endpoint in analysis of this sub-group is hematoma volume in spot-sign positive patients, secondary endpoints include difference in proportion of neurological deterioration within 24 hours of symptom onset; recruitment is starting in July 2016.

2.5.2.3.3 NOR-ICH

The Norwegian Intracerebral Haemorrhage Trial (NOR-ICH, EudraCT number 2012-005594-30) is a multicentre prospective randomised, open-label, blinded endpoint (PROBE) trial. There are two arms in the study: arm A

treat patients presenting within 2.5 hours from onset and arm B treat patients presenting between 2.5 to 4.5 hours. The trial recruits spot positive and negative patients. The participants are randomised to receive IV tranexamic acid 1 g bolus followed by 1 g at 2 hours, 4 hour and 8 hours from the first dose compared to no treatment. The primary endpoint is haematoma expansion at 24 hours while secondary endpoints include increase in NIHSS score ≥4 within 36 hours, NIHSS at day 7, mRS at 90 days and symptomatic thromboembolic events within 7 days. The investigators originally planned to recruit 540 patients by early 2017. However, the recruitment of patients has been slow, as many participating centres have not started recruiting patients yet.

2.5.2.3.4 TRAIGE

Tranexamic Acid for Acute ICH Growth prEdicted by Spot Sign (TRAIGE, NCT02625948) is a multicentre phase II randomised, double blind, placebo-controlled trial recruiting patients from China who have a positive spot sign on CT angiography and can be treated within 8 hours from onset. The trial compares the efficacy of intravenous tranexamic acid 1 g followed by intravenous tranexamic acid 1 g infusion over 8 hours versus placebo. The primary outcome measure is haematoma expansion (>33% or >6 mL) by 24 hours, with mRS and thromboembolic complications at 90 days as secondary outcomes. The trial aims to recruit 240 patients by December 2018.

2.5.2.3.5 TICH-NOAC

Tranexamic acid for IntraCerebral Haemorrhage secondary to Novel Oral AntiCoagulants (TICH-NOAC, NCT02866838) is an investigator-initiated, multicentre double-blind placebo controlled trial, investigating the safety and efficacy of tranexamic acid in ICH related to non-vitamin K (direct) oral anticoagulants (NOAC).[395] The trial will include patients from Switzerland who had ICH and taken a NOAC (dabigatran, apixaban, rivaroxaban, edoxaban) within the prior 48 hours, or proven NOAC activity by relevant coagulation assays. The time window for recruitment is up to 12 hours after the onset of ICH. Patients are randomised to received tranexamic acid 1 g

bolus followed by 1 g infusion over 8 hours or placebo. All patients receive standard treatment including specific antidote where available. TICH- NOAC aims to demonstrate that treatment with tranexamic acid reduces rate of hematoma expansion as measured at 24 hours compared to best medical treatment. The study implementation process has started. The first patient is expected to be included in fall 2016.

2.5.2.3.6 EsICH

Tranexamic acid and biomarkers in Emergency management of Spontaneous IntraCerebral Hemorrhage (EsICH) is a Romanian multicentre double blind RCT recruiting spot positive and negative ICH patients within 8 hours of onset. Patients will be given a total of 2 g tranexamic acid or placebo (normal saline, 10mL in total) during a course of 8 hours. A series of biomarkers will be tested upon arrival in the emergency department (including point-of-care biomarkers for troponin, D-dimer and C-reactive protein) to evaluate their role in early risk stratification. The primary endpoint is a favourable functional outcome (mRS 0 to 3) at 90 days, assessed by telephone survey. The study is awaiting ethical approval. EsICH aims to recruit 100 patients between January 2017 and December 2018.

Table 2-2 Comparison of ongoing trials of tranexamic acid in intracerebral haemorrhage

	STOP-AUST	TICH-2	NOR-ICH	TRAIGE	TICH-NOAC	EsICH
Start date	Dec 2012	March 2013	June 2014	Sept 2015	November 2016	January 2017
Number recruited/target	39/100	1683/2000	20/540	-/240	0/109	0/100
TA dose (g x no.)	1 x 2	1 x 2	1 x 4	1 x 2	1 x 2	1 x 2
Age, years	≥18	≥18	18-80	≥18	≥18	≥18
Premorbid mRS	N/A	0-3	0-2	0-1	0-4	0-3
GCS	8-15	5-15	9-15	8-15	5-15	8-15
Time, hour	<4.5	<8	Arm A: <2.5 Arm B: 2.5-4.5	<8	<12, NOAC intake <48 h	<8
Haematoma location	Brainstem bleed excluded	N/A	N/A	supratentorial only	N/A	N/A
ICH volume, ml	<70	N/A	<60	<70	N/A	N/A
IVH volume, ml	N/A	N/A	<10	<50% of lateral ventricles	N/A	N/A
Spot sign positive only	Y	N	N	Y	N	N
Planned surgery < 24 hours	exclude	not excluded	exclude	exclude	exclude	exclude
Primary Outcome	HE 24 h*	mRS 90d†	HE 24 h	HE 24 h*	HE 24 h*	mRS 90d†
Secondary Outcome	mRS 90d†		mRS 90d†	mRS 90d†	mRS 90d† mortality 90d; major TE events 90d‡	

BSRG: Bergen Stroke Research Group; ECRI: European Cerebrovascular Research Infrastructure; GCS: Glasgow coma scale; HE: haematoma expansion; ICH: intracerebral haemorrhage; IVH: intraventricular haemorrhage; mRS: modified Rankin Scale; N/A: not available; NHMRC: National Health and Medical Research Council, Australia; NOAC: novel oral anticoagulants; NORSTROKE: Norwegian Stroke Research Registry; TA: tranexamic acid; UMF: University of Medicine & Pharmacy. *Haematoma expansion measured at 24 h post-ictus. †Modified Rankin Scale at 90 days. ‡Myocardial infarction, ischemic stroke, pulmonary embolism.

2.6 Discussion

Tranexamic acid is a promising haemostatic agent given its efficacy in reducing bleeding rates in surgical and trauma patients. However, there is currently insufficient evidence from completed trials to draw conclusion on the effect of tranexamic acid on clinical outcome and haematoma expansion (HE) in ICH. The completed trials recruited only a small number of patients and did not provide sufficient data for meta-analysis.

Apart from recruiting patients with primary ICH while excluding secondary ICH, the six ongoing trials vary in terms of selection criteria, dosing regime and outcome assessments. This raises several questions about the design of clinical trials. The first is whether tranexamic acid should only be given to patients with positive spot sign? Some trials only include patients who had positive spot sign on CT angiography (STOP-AUST, PATCH-It, TRAIGE) while others do not (TICH-2, NOR-ICH, TICH-NOAC, EsICH). A positive spot sign is an indication of ongoing haemorrhage in ICH, with a 61% chance of significant HE (>33% or >6 mL).[38] However approximately 22% of spot sign negative patients also have HE.[38, 396] Therefore, excluding spot negative patients may unnecessarily preclude them from possible benefits.[396] On the other hand targeting haemostatic therapy to patients with ongoing haemorrhage only will reduce the number of patients unnecessarily exposed to potential thromboembolic complications. As CT angiography is not done routinely in ICH in many centres, translation of clinical trial results into practice would be easier if spot sign evaluation were not necessary.

The second clinical question is: what is the optimal time window that tranexamic acid might be beneficial? Whilst there is no doubt that treatment benefit is time-dependent, the exact cut-off time is uncertain. STOP-AUST and NOR-ICH exclude patients presenting later than 4.5 hours, where presumably haematoma expansion would have occurred. However, a few considerations should be taken into account here. In a study based on serial measurements of hematoma volumes by B-mode ultrasound, haematoma expansion was observed up to 7 to 8 hours after symptom onset but most

frequently in the first hours.[397] Brott *et al* reported that 26% of HE occurred by 4 hours and an additional 12% haematoma expansion between 4 and 20 hours.[86] By recruiting patients presenting later than 4 hours means, a larger pool of patients who may suffer subsequent haematoma expansion may be included. In addition, there may be other causes of neurological deterioration besides HE such as perihaematomal oedema and neuroinflammation.[185] Tranexamic acid may potentially reduce perihaematomal oedema and attenuate inflammatory response, a process that starts within the first few hours and last for days to weeks after ICH. On the other hand, the mega-trial CRASH-2 demonstrated in trauma patients a strongly time-dependent treatment effect with tranexamic acid, with reduced mortality when given within 3 hours and strongly increased mortality when given beyond 5 hours, when compared to placebo.[398] A clearer time window in ICH may be established in the future pending results of ongoing studies.

The third question is whether patients with poor prognostic factors should be excluded from trials? Such factors include advanced age, poor pre-morbid mRS, poor GCS, infratentorial haematoma, high haematoma volume (>60ml or 70ml), intraventricular extension and patient undergoing surgery should be excluded from trials? A key point in anti-fibrinolytic therapy is it aims to prevent haematoma expansion but not treat haematoma expansion after it occurred. It would be logical to exclude patients in whom the haematoma expansion have presumably already occurred (high haematoma volume, intraventricular extension) or have resulted or would have resulted in poor clinical outcome (poor GCS, brainstem haematoma, need for surgery). However, the initial haematoma volume in itself is a predictor of haematoma expansion.[223] The risk of haematoma expansion is greater in large haematoma and as there is no definite way to determine whether a rebleeding has stopped, tranexamic acid may still benefit those with poor prognostic factors.[223] As customary, we noted that of the ongoing trials, the Phase III were more inclusive.

The optimal dosing of tranexamic acid needs to be determined as well. After intravenous administration, tranexamic acid reaches peak concentration

almost immediately and has an onset of action within a few minutes. It has a short plasma elimination half-life of 3 hours. The tissue half-life is 17 hours due to low plasma protein binding (3%) and wider distribution in the tissue compartment.[333] Repeated dosing may result in higher concentration and accumulation in the brain. TICH-2, STOP-AUST, TRIAGE, TICH-NOAC and EsICH trials administer intravenous tranexamic acid at the same dose similar as the CRASH-2 trial (1g bolus, 1g infusion over 8 hours), while NOR-ICH involve giving 1 g tranexamic acid boluses 4 times in the first 24 hours. It is not known whether more frequent dosing will result in longer accumulation in the target organ or whether this will result in better outcome or more adverse events.

The effects of tranexamic acid beyond anti-fibrinolysis remain to be explored. Diffusion weighted imaging hyperintense lesions (DWIHL) indicative of acute or subacute ischaemic infarcts are known to co-exist in ICH.[399] Given the potential of tranexamic acid to precipitate ischaemic events, the TICH-2 MRI sub-study explores whether the incidence of DWIHL will be higher in those receiving the drug. Secondly, tranexamic acid may have anti-inflammatory and neuroprotective effects. This may reduce perihaematomal oedema and improve healing process manifesting as a reduction in residual haematoma cavity and surrounding gliosis.

We plan to resolve the uncertainties concerning the use of tranexamic acid by conducting an individual patient data meta-analysis (IPDMA). IPDMA had been shown to improve data quality and reliability of effect estimates of several stroke interventions.[43-45] In addition, a broader meta-analysis of clinical trials encompassing the use of tranexamic acid in polytrauma, traumatic brain injury, subarachnoid haemorrhage, subdural haemorrhage and spontaneous ICH may provide answers regarding the optimal time window and dosage of tranexamic acid. Such a meta-analysis may provide a more accurate estimation of thromboembolic risk with use of tranexamic acid as well.

2.7 Conclusion

In summary, the results of ongoing trials of tranexamic acid for ICH are awaited. Future trials should also examine the effect of tranexamic acid on plasma biomarkers and pathological changes to determine the effects of tranexamic acid. Prospective meta-analysis of individual patient data from these on-going trials will provide the most reliable method of assessing the efficacy and safety of tranexamic acid.

2.8 Acknowledgements/ Funding

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2.9 Conflict of interest

AM has received speaker honoraria and consulting fees from Boehringer Ingelheim, Stryker, Phagenesis, and Nestle, and is the principal investigator of the STOP-AUST trial.

STE has received funding for travel or speaker honoraria from Bayer and Boehringer Ingelheim; he has served on scientific advisory boards for Bayer, Boehringer Ingelheim, BMS/Pfizer, and Covidien and on the editorial board of Stroke. He has received an educational grant from Pfizer and research support from the Science Funds [Wissenschaftsfonds] of the University Hospital Basel, the University Basel, the Swiss Heart Foundation, and the Swiss National Science Foundation and is the Co-Principal Investigator of TICH-NOAC.

PB is Stroke Association Professor of Stroke Medicine. He has received consulting fees from Athersys, Nestle, Phagenesis and ReNeuron; he is an unpaid advisor to Platelet Solutions.

EMM has been granted a 2016 ESO fellowship through the "Department-to-Department Visit" program for a one-week study visit at TICH-2 Coordinating Centre from Nottingham, UK

Chapter 3 Systematic review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

3.1 Publications contributing to chapter

1) Al-Shahi Salman R, **Law ZK**, Bath PM, Steiner T, Sprigg N. Haemostatic therapies for acute spontaneous intracerebral haemorrhage. Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD005951. DOI: 10.1002/14651858.CD005951.pub4.

2) **Zhe Kang Law**, Rustam Al-Shahi Salman, Philip M Bath, Thorsten Steiner, Nikola Sprigg. Cochrane Corner- Hemostatic therapies for acute spontaneous intracerebral hemorrhage. Stroke. 2018;49: e271-e272. DOI: 10.1161/STROKEAHA.118.022071 (Published online first 5th July 2018)

3.2 Abstract

3.2.1 Background

Outcome after spontaneous intracerebral haemorrhage (ICH) is worsened by hematoma growth, which occurs in up to one-third of patients within 24 hours of onset. Early haemostatic therapy might improve outcome by limiting haematoma growth.

3.2.2 Objectives

This updated review aimed to examine the efficacy and safety of individual classes of haemostatic therapies in adults with acute spontaneous ICH, according to the type of antithrombotic drug taken immediately before ICH onset (i.e. anticoagulant, antiplatelet, or none).

3.2.3 Methods

3.2.3.1 Search methods

We searched the Cochrane Stroke Trials Register, MEDLINE, EMBASE, reference list of articles and international trial registers up to November 2017.

3.2.3.2 Selection criteria

We included randomized controlled trials (RCTs) of any haemostatic intervention for acute spontaneous ICH, compared with placebo, open control, or an active comparator, reporting relevant clinical outcomes.

3.2.3.3 Data collection and analysis

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

3.2.4 Main Results

We included 12 RCTs involving 1732 participants. There were seven RCTs of clotting factors versus placebo/control (1480 participants), three RCTs of antifibrinolytic drugs versus placebo/control (57 participants), one RCT of platelet transfusion versus control (190 participants) and one RCT of clotting factors versus fresh frozen plasma (five participants). We could not include two eligible RCTs of clotting factors versus fresh frozen plasma because they presented aggregate data for ICH and other types of intracranial haemorrhage. In one RCT of platelet transfusion versus control for antiplatelet-related ICH, there was a significant increase in death or dependence (modified Rankin Scale score 4 to 6) at day 90 (70/97 versus 52/93; risk ratio [RR] 1.29; 95% confidence interval [CI] 1.04 -1.61). There were no significant differences in death or dependency at day 90 for clotting factors versus placebo/control (RR 0.87; 95% CI 0.70 -1.07) and antifibrinolytic drugs versus placebo/control (RR 1.25; 95% CI 0.57-2.75) for acute spontaneous ICH. There was no significant difference in death at day 90 for clotting factors versus fresh frozen plasma for anticoagulant-related ICH (RR 0.27; 95% CI 0.02-3.74).

3.2.5 Implications for Practice

Platelet transfusion seems harmful in comparison to standard care for adults with antiplatelet-associated ICH. We were unable to draw firm conclusions about the efficacy and safety of clotting factors and antifibrinolytic drugs for acute spontaneous ICH, or clotting factors versus fresh frozen plasma for anticoagulant-related ICH.

3.2.6 Implications for Research

Although recombinant factor VIIa does not appear beneficial based on existing evidence, RCTs of its use in patients with ICH and a spot sign on CT angiography are awaited (NCT00810888; NCT01359202).[400,401] There are six ongoing RCTs of antifibrinolytic drugs in ICH. The superiority of clotting factors compared to fresh frozen plasma in improving clinical outcome needs to be established despite superiority in normalization of coagulation in the RCTs that we could not include. There is a need to distinguish between ICH and other intracranial haemorrhage while recruiting and reporting results in future trials of haemostatic therapies.

3.3 Background

3.3.1 Description of the condition

The burden of haemorrhagic stroke is out of proportion to its frequency as a subtype of stroke. Although haemorrhagic stroke causes 11% to 22% of all new strokes,[1] it caused 50% of all stroke deaths, and approximately 42% (47 million) of the disability-adjusted life years lost due to stroke in the 2013 Global Burden of Disease study.[402] Spontaneous (nontraumatic) intracerbral haemorrhage (ICH) accounts for two-thirds of haemorrhagic stroke, amounting to more than two million strokes per year.[19] ICH is due to cerebral small vessel disease, and may be associated with the use of antithrombotic (i.e. anticoagulant or antiplatelet) drugs. The age-specific incidence of ICH - like the age-specific incidence of ischaemic stroke and myocardial infarction - rises with age.[402] Two-thirds of people who have an ICH are 75 years or older.[403, 404] Given that the number of people aged 75 years and older is projected to rise in many parts of the world, the burden due to ICH incidence,

recurrence, and prevalence will rise.

Outcome after stroke due to ICH is poor: one-year survival is 46% (95% confidence interval (CI) 43% to 49%), five-year survival is 29% (95% CI 26% to 33%), and predictors most consistently associated with death are increasing age, decreasing Glasgow Coma Scale score, increasing ICH volume, presence of intraventricular haemorrhage, and deep or infratentorial ICH location.[295] Approximately one-third of acute ICHs (i.e. less than 24 hours after symptom onset or time last seen well) enlarge from three to 24 hours after onset;[86] ICH growth is independently associated with death and poor outcome.[90]

3.3.2 Description of the intervention

The three main components of haemostasis (the process that stops bleeding) are vasoconstriction, platelet plug formation, and coagulation. Vascular smooth muscle cell vasoconstriction is a blood vessel's first response to injury. They constrict the damaged vessels, which reduces the amount of blood flow through the area and limits the amount of blood loss. Collagen is exposed at the site of injury, which causes platelets to adhere to the injury site.

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

Secondary haemostasis starts once a platelet plug has been formed.

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

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

3.3.3 How the intervention might work

Theoretically, early interventions to reduce acute ICH volume might improve outcomes. Although surgical craniotomy to evacuate spontaneous supratentorial ICH and reduce ICH volume was found to reduce the odds of dying or becoming dependent compared with medical management alone, the result was not very robust, and surgical evacuation is not frequently used.[405] Therefore, medical (non-surgical) interventions to promote haemostasis, and limit haematoma growth, have become the main focus of acute ICH therapeutic research.

3.3.4 Why it is important to do this review

Various haemostatic therapies have been investigated in a variety of spontaneous bleeding conditions with little evidence for their effectiveness in some settings,[406-408] but clear benefit in others.[409] It is unclear whether they are effective for acute ICH. Therefore, we systematically reviewed the literature for randomised controlled trials (RCTs) of all potential haemostatic therapies for the treatment of acute spontaneous ICH.

3.4 Objectives

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

3.5 Methods

3.5.1 Criteria for considering studies for this review

3.5.1.1 Types of studies

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

3.5.1.2 Types of participants

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

3.5.1.3 Types of interventions

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

3.5.1.4 Types of outcome measures

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

3.5.1.4.1 Primary outcomes

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

3.5.1.4.2 Secondary outcomes

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

3.5.2 Search methods for identification of studies

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

3.5.2.1 Electronic searches

The Cochrane Stroke Group Information Specialist searched the Cochrane Stroke Group Trials Register (last searched 27 November 2017), the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 11) in the Cochrane Library (searched 27 November 2017; Appendix 4); MEDLINE Ovid (1946 to 27 November 2017; Appendix 5); and EMBASE Ovid (1974 to 27 November 2017; Appendix 6).

One review author (ZL) also searched the following international registers of RCTs on 27 November 2017.
• US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov) using the search strategy in Appendix 7;

• World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch) using the search strategy in Appendix 8.

3.5.2.2 Searching other resources

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

3.5.3 Data collection and analysis

3.5.3.1 Selection of studies

Two authors independently checked the titles and abstracts of studies identified by the search strategy for RCTs meeting the selection criteria for the first version of this review.[410] Two authors (ZL or RA-SS) independently screened the results of the updated searches for potentially eligible studies for this updated review, and obtained the full published articles or trial registry entries for studies likely to be relevant RCTs. Two authors (NS and RA-SS) independently read these potentially eligible RCTs in full, and confirmed their inclusion according to the inclusion criteria.

3.5.3.2 Data extraction and management

Two authors (NS and RA-SS) used a standard data collection form to independently extract data on risk of bias, other RCT characteristics, participants, methods, interventions, outcomes, and results. If necessary, we sought additional data from the principal investigators of RCTs that met, or potentially met the inclusion criteria. We sought unpublished data that were not quantified in the original publications, or not presented as stratified by intracranial haemorrhage type, from the principal investigators and pharmaceutical companies. In the one study for which these data were not forthcoming, RA-SS measured the numbers in the relevant groups in the stacked bar charts, using Adobe Acrobat Professional measuring tools on the PDF of the published study.[223] In one phase II study, we could obtain only limited data from the Novo Nordisk website.[411]

3.5.3.3 Assessment of risk of bias in included studies

Two authors (NS and RA-SS) independently assessed included RCTs' risk of bias, according to the seven criteria of the Cochrane 'Risk of bias' tool.[412] The same two authors discussed and agreed on the overall quality of the evidence for each outcome, using the GRADE approach.[412]

3.5.3.4 Measures of treatment effect

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

3.5.3.5 Dealing with missing data

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

3.5.3.6 Assessment of heterogeneity

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

3.5.3.7 Assessment of reporting biases

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

3.5.3.8 Data synthesis

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

3.5.3.9 Subgroup analysis and investigation of heterogeneity

We expected to find that the choice of intervention and comparator would be largely determined by the use and type of antithrombotic drug taken prior to a spontaneous acute ICH (e.g. fresh frozen plasma (FFP), or prothrombin

complex concentrate (PCC) for anticoagulant-associated ICH, platelet transfusion for antiplatelet-associated ICH). However, where interventions were used for ICH, whether it was associated with antithrombotic drug use or not (e.g. the clotting factor recombinant activated factor VII, antifibrinolytic drugs), and where ICH evacuation using craniotomy was performed, we stratified our analyses by pre-ICH antithrombotic drug use and use of surgery.

3.6 Results

3.6.1 Description of studies

3.6.1.1 Results of the search

Our searches identified 31 potentially eligible randomised controlled trials (RCT); see Figure 3-1 for the flowchart describing the searches done for this update. We excluded nine studies because: they never started (Ciccone 2007; NCT02429453),[413, 414] they did not report any of our primary or secondary outcomes (Meng 2003; Zhou 2005),[415, 416] they did not report data and outcomes in the intracerebral haemorrhage population (Kerebel 2013; Steiner 2016 (INCH)),[417, 418] they did not quantify outcomes (Madjdinasab 2008),[419] the study was stopped due to poor enrolment but never reported results (NCT00222625),[420] or the study did not relate to a haemostatic therapy (Li 2016).[421] Ten RCTs were still in the process of recruitment (Liu 2017 (TRAIGE)[422]; Meretoja 2014 (STOP-AUST)[266]; NCT00699621[423];NCT02777424[424]; NCT02866838[425]; NCT03044184[426]; NOR-ICH[427]), follow-up (Sprigg 2016 (TICH-2)[80]), or reporting (NCT00810888[400]; NCT01359202[401]) at the time of writing, and will be assessed for inclusion with the next update. This left 12 RCTs that we included in this review, all of which included acute intracerebral haemorrhage (ICH) in adults aged 18 years or older (Arumugam 2015[394]; Baharoglu 2016 (PATCH)[232]; Boulis 1999[428]; F7ICH-1602 2007[411]; Imbert 2012 (PRE-SICH)[429]; Li 2012[430]; Mayer 2005a[431]; Mayer 2005b[24]; Mayer 2006[432];Mayer 2008 (FAST)[223]; Sprigg 2014 (TICH-1)[393]; Zazulia 2001 (ATICH)[433]).

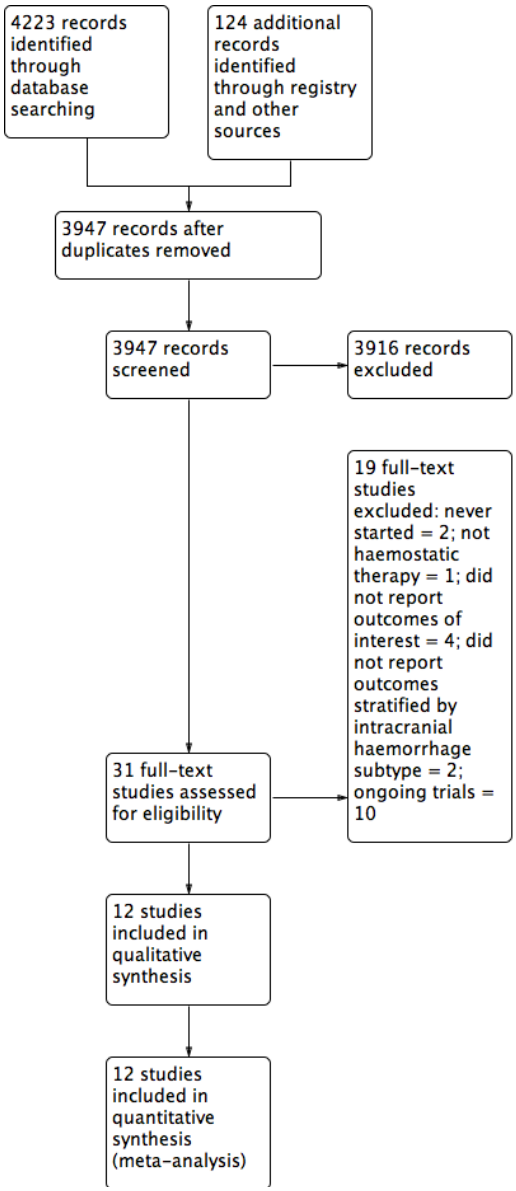


Figure 3-1 Study flow diagram

We included seven RCTs of blood clotting factors versus placebo or open control involving 1480 participants (F7ICH-1602 2007[411]; Imbert 2012 (PRE-SICH)[429]; Li 2012[430];Mayer 2005a[431];Mayer 2005b[24]; Mayer 2006[432]; Mayer 2008 (FAST)[223]), three RCTs of antifibrinolytic drugs versus placebo or open control involving 57 participants (Arumugam 2015[394]; Sprigg 2014 (TICH-1)[393]; Zazulia 2001 (ATICH)[433]), one RCT of platelet transfusion versus open control involving 190 participants (Baharoglu 2016 (PATCH) [232]), and one RCT of blood clotting factors versus fresh frozen plasma involving five participants (Boulis 1999)[428].

3.6.2 Included studies

We included 12 RCTs. For details, please refer to the 'Characteristics of included studies' section. Of the seven RCTs of blood clotting factors versus placebo or open control, six examined blood clotting factors in adults with acute spontaneous ICH (F7ICH-1602 2007[411]; Li 2012[430]; Mayer 2005a[431]; Mayer 2005b[24]; Mayer 2006[432]; Mayer 2008 (FAST)[223]) and one in adults with acute spontaneous ICH undergoing craniotomy (Imbert 2012 (PRE-SICH)[429]). Five studies were funded and conducted by Novo Nordisk, and compared the use of various doses of intravenous recombinant activated clotting factor VII (rFVIIa; (973 participants)) against placebo (422 participants), started within four hours of ICH onset in adults (F7ICH-1602 2007[411];Mayer 2005a[431]; Mayer 2005b[24]; Mayer 2006[432]; Mayer 2008 (FAST)[223]). Novo Nordisk supplied supplementary, unpublished data from three trials (Mayer 2005a[431];Mayer 2005b[24];Mayer 2006[432]), but did not respond to several requests to provide further data from two trials (F7ICH-1602 2007[411];Mayer 2008 (FAST)[223]). The other study of intravenous rFVIIa was performed independently of Novo Nordisk, as a single centre, phase II study, in adults with acute spontaneous ICH within six hours of ICH onset (Li 2012[430]). We had not prespecified the exclusion of RCTs of haemostatic therapies following surgical intervention, so we included Imbert 2012 (PRE-SICH)[429], which was a phase II study of intravenous rFVIIa in adults with acute spontaneous ICH undergoing craniotomy, administered immediately after the evacuation of the haematoma, within 24 hours of ICH onset.

Of the three RCTs of antifibrinolytic drugs versus placebo or open control, Zazulia 2001 (ATICH)[433] was a phase II RCT of intravenous aminocaproic acid compared against supportive treatment alone, started within three hours of ICH onset in adults. Dr Allyson Zazulia provided unpublished data, because the trial was stopped after the enrolment of three participants because recruitment had been slow, and the investigators decided that the rationale for rFVIIa was better (Zazulia 2005)[434]. Sprigg 2014 (TICH-1)[393] was a phase II RCT of intravenous tranexamic acid compared against supportive treatment alone, started within 24 hours of ICH onset in adults. Arumugam 2015[394] was a phase II RCT of intravenous tranexamic acid

compared against supportive treatment alone, started within eight hours of ICH onset in adults.

We found one RCT of platelet transfusion versus open control involving 190 participants (Baharoglu 2016 (PATCH)[232]). We found one RCT of blood clotting factors versus fresh frozen plasma involving five participants with acute spontaneous ICH associated with anticoagulant drug use (Boulis 1999)[428].

3.6.2.1 Characteristics of included studies [ordered by study ID]

Table 3-1 Characteristics of included studies-Arumugam 2015

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

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

Table 3-2 Characteristics of included studies-Baharoglu 2016 (PATCH)

Methods	Multicentre, open-label, masked-endpoint, randomized trial, using a secure web-based system that concealed allocation and used biased coin randomization (1:1 stratified by hospital and type of antiplatelet therapy)
Participants	Inclusion criteria • Participants aged 18 years or older • Non-traumatic supratentorial intracerebral haemorrhage confirmed by brain imaging • GCS score of 8 to15 • In whom platelet transfusion could be initiated within 6 h of symptom onset (or last seen well) and within 90 minutes of brain imaging • Who had been on antiplatelet therapy with a cyclo-oxygenase (COX) inhibitor (aspirin or carbasalate calcium), adenosine diphosphate (ADP) receptor inhibitor (clopidogrel), or an adenosine reuptake inhibitor (dipyridamole) for at least 7 days preceding intracerebral haemorrhage • Pre-intracerebral haemorrhage mRS score of 0 (no symptoms) or 1 (no significant disability despite symptoms; able to carry out all usual duties and activities) Exclusion criteria • Blood on brain imaging suggestive of epidural or subdural haematoma, or an underlying aneurysm or arteriovenous malformation • Planned surgical evacuation of intracerebral haemorrhage within 24 h of admission • Intraventricular blood more than sedimentation in the posterior horns of the lateral ventricles • Previous adverse reaction to platelet transfusion • Known use of vitamin K antagonist (unless INR ≤ 1.3) or history of coagulopathy • Known thrombocytopenia (lower than 100 cells x 10 /L) • Lacking mental capacity by national legal standards before intracerebral haemorrhage • Death appeared imminent
Interventions	Intervention: standard care with platelet transfusion within 90 minutes of diagnostic brain imaging Comparator: standard care
Outcomes	The primary outcome was shift towards death or dependence rated on the mRS at 3 months, and analysed by ordinal logistic regression, adjusted for stratification. Variables and the Intracerebral Haemorrhage Score Secondary clinical outcomes at 3 months were: survival (mRS score of 1 to 5), poor outcome defined as an mRS score of 4 to 6, and poor outcome defined as an mRS score of 3 to 6. The secondary explanatory outcome was median absolute intracerebral haemorrhage growth in mL after 24 h on brain imaging Safety outcomes were defined as

	complications of platelet transfusion (transfusion reactions, thrombotic complications)	
Notes	NTR1303	
Risk of bias		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Quote "Randomisation was done by investigators via a secure, web-based, computerised randomization system (TENALEA, Clinical Trial Data Management system; NKIAVL, Amsterdam, The Netherlands) that stratified assignment by study hospital and type of pre-intracerebral haemorrhage antiplatelet therapy (COX inhibitor alone, ADP receptor inhibitor alone, COX inhibitor with an adenosine-reuptake inhibitor, or COX inhibitor with an ADP receptor inhibitor). A biased coin randomization was used, with coin bias factor of 3 and coin bias threshold of 2"
Allocation concealment (selection bias)	Low risk	Allocation was concealed from investigators by the web-based randomization system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and local investigators giving interventions were not masked to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treatment allocation was concealed to out- come assessors and investigators analysing data
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up for the primary outcome was complete
Selective reporting (reporting bias)	Low risk	All outcomes were reported

Table 3-3 Characteristics of included studies-Boulis 1999

Methods	RCT	
Participants	Inclusion criteria • CT-proven intracranial haemorrhage • Documented history of warfarin use • Prothrombin time > 17 seconds Exclusion criteria • Clinical evidence of brainstem herniation	
Interventions	Intervention: fresh frozen plasma Comparator: fresh frozen plasma (intravenous), vitamin K (subcutaneous) and factor IX complex concentrate (Konyne; Bayer, Elkhart, IN: containing high concentrations of activated vitamin K-dependent clotting factors II, VII, IX, and X; dosage according to body weight; intravenous infusion at 100 IU/min)	
Outcomes	Time to INR correction, rate of INR correction, change in GCS	
Notes	-	
Risk of bias		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not described
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Post-randomisation exclusion of 8 participants
Selective reporting (reporting bias)	Unclear risk	Outcomes not pre-specified

Table 3-4 Characteristics of included studies- F7ICH-1602 2007

Methods	Randomised, double-blind, Japanese multicentre, placebo-controlled, phase II dose- escalation trial with 3 dose tiers	
Participants	Inclusion criteria • Age ≥ 20 years • Spontaneous ICH (not in brainstem) • Within 3 h of onset	
Interventions	Intervention: recombinant activated factor VII (NovoSeven) at doses of 40 mcg/kg (N = 15), 80 mcg/kg (N = 15), or 120 mcg/kg (N = 15), within 1 h of baseline CT Comparator: placebo (N = 45), within 1 h of baseline CT	
Outcomes	Preliminary efficacy evaluations were performed as follows • mRS, the BI scores at 15 days post-dose and 90 days post-dose • Absolute and percent change in ICH volume, total haemorrhage volume (ICH + IVH), and total lesion volumes (ICH + IVH + oedema) as measured by head CT scans from baseline to 24 h, 48 h, and 72 h post-dose • Change in the GCS and the NIHSS scores from baseline to 1 h post-dose, 24 h post-dose, 48 h post-dose, 72 h post-dose, 15 days post-dose, and 90 days post-dose • Mortality at 90 days post-dose	
Notes	ClinicalTrials.gov number NCT00266006. This unpublished trial was funded by Novo Nordisk, which did not respond to requests to provide data beyond what was on their website	
Risk of bias		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel said to be blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The assessment of outcomes was not explicitly stated to be
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	High risk	Data not provided for most major outcomes

Table 3-5 Characteristics of included studies- Imbert 2012 (PRE-SICH)

Methods	Randomised (2:1), open-label, single-blinded parallel group phase 2 pilot trial involving 21 participants with spontaneous supratentorial ICH diagnosed by CT	
Participants	Inclusion criteria • People 18 to 75 years of age with spontaneous supratentorial ICH documented by CT scan • Surgery was expected within 24 h from the onset of symptoms Exclusion criteria • MI or the placement of coronary or carotid stents in the 6 months prior to the study • Solid organ transplantation • Pregnancy	
Interventions	All participants were intubated, ventilated, and underwent craniotomy with the intention of complete haematoma removal. The haematoma cavity was lined with Surgicel (Johnson & Johnson, New Brunswick, NJ, USA). Blood pressure was measured continuously, and data were collected every 1 to 2 h. Efforts were made to maintain the mean arterial blood pressure between 90 mmHg and 130 mmHg, PaCO within the range of 35 mmHg to 40 mmHg, sodium levels of between 137 and 147 mmol/L and to obtain normoglycaemia (80 mg/dL to 110 mg/dL) Intervention: 100 mcg/kg of rFVIIa (NovoSeven, Novo Nordisk, Denmark) by intra- venous infusion in 5 to 10 minutes immediately after evacuation of the haematoma, at the beginning of the closure of the dura Comparator: saline solution by intravenous infusion in 5 to 10 minutes immediately after evacuation of the haematoma, at the beginning of the closure of the dura	
Outcomes	Haematoma volume was assessed by CT scan immediately, 18 h to 30 h, and 5 days to 7 days after evacuation of the haematoma. The primary endpoint was haematoma volume at 18 h to 30 h after surgery. Outcome was evaluated at 6 months using the mRS; poor outcome was defined as death or an mRS score of 4 to 5, and good outcome was defined as an mRS score of 0 to 3	
Notes	NCT00128050	
Risk of bias		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Blinding of participants and personnel (performance bias) All outcomes	High risk	They stated the trial was both open label and placebo controlled in the methods, but that 'saline' was the comparator. This seemed like an open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Haematoma volume assessment blinded, but unsure about clinical outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seemed complete for all outcomes. Unable to extract data on haematoma growth, all SAEs, and all thromboembolic adverse events (although they were reported separately)
Selective reporting (reporting bias)	Low risk	All outcomes specified in the methods appeared to have been reported.

Table 3-6 Characteristics of included studies- Li 2012

Methods	Single-centre
Participants	Inclusion criteria • Intracerebral haemorrhage • Within 6 h of onset • Age ≥ 18 years • Able to perform CT scan 24 h post-treatment Exclusion criteria • Secondary haemorrhage, i.e. tumour, AVM, anticoagulant-associated • Surgery within 24 h • Admission GCS 3 to 5 • Hereditary or acquired coagulation dysfunction • Previous ICH in which haematoma had not been fully resolved • Serious comorbidities or end-stage diseases (unspecified) • Known renal impairment or thyroid dysfunction (unspecified)
Interventions	Interventions: intravenous rFVIIa (NovoSeven) 40 μg/kg, concentration at 0.6 g/L, within 6 h of ICH onset, injected over 2 to 5 minutes Comparator: routine or best medical treatment All participants received Piracetam 8 g iv 4 times/day
Outcomes	ICH growth, GCS at 24 h, NIHSS at 24 h, mRS at 90 days, adverse events
Notes	Data extracted by Dr Michael Poon (www.researchgate.net/profile/Michael_Poon3) from full text record available from en.cnki.com.cn/Article en/CJFDTotal-ZXYZ201202009.htm

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

Table 3-7 Characteristics of included studies-Mayer 2005a

Methods	Parallel group, randomised, placebo-controlled, phase II: a dose-escalation safety and efficacy study
Participants	Inclusion criteria: • Age 18 years or older • Spontaneous ICH within 3 h of onset with no obvious secondary cause Exclusion criteria: • GCS 3 to 5 • Surgical ICH evacuation planned within 24 h • mRS > 2 pre-ICH • Allergy to trial product • Participation in another RCT
Interventions	Intervention: recombinant activated factor VII (NovoSeven) at doses of 10 mcg/kg, 20 mcg/kg, 40 mcg/kg, 80 mcg/kg, 120 mcg/kg, or 160 mcg/kg, within 1 h of baseline CT Comparator: placebo, within 1 h of baseline CT
Outcomes	Adverse events at days 1 to 5, 15 (or hospital discharge), and 90; change in ICH ± IVH volume on CT between baseline and 24 h; ICH growth (> 33% or 12.5 mL); drop of > 1 GCS point or increase of > 3 NIHSS points on days 0 to 5; dead versus alive with little disability (BI 95 to 100, GOS-E 8, mRS 0 to 2), versus alive and functionally independent (BI 60 to 100, GOS-E 5 to 8, mRS 0 to 3) at day 90

Notes	There was imbalance in the baseline ICH volumes between placebo and treatment groups (increasing with higher recombinant factor VIIa doses), although the authors stated that this was not statistically significant. The trial drug was given to 2 of 47 participants more than 4 h after ICH onset. This trial was funded by Novo Nordisk.	
Risk of bias		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not specified
Allocation concealment (selection bias)	Unclear risk	Not described. Quote: "A randomization schedule was generated."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Providers were said to be blinded to treatment allocation (but treatment dose escalation may have been apparent)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The assessment of outcomes was not explicitly stated to be blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Selective reporting (reporting bias)	Unclear risk	Unclear

Table 3-8 Characteristics of included studies-Mayer 2005b

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

Allocation concealment (selection bias)	Unclear risk	Quote: "A randomization schedule was generated and as patients were recruited, they were allocated to the next available randomization number within the dose tier, which indicated whether the patient was to receive placebo or rFVIIa."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	4/block, sequentially numbered, identical-appearing containers
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Radiological outcomes blinded. Clinical and lab outcomes - unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appeared complete
Selective reporting (reporting bias)	Low risk	Appeared complete

Table 3-9 Characteristics of included studies-Mayer 2006

Methods	Parallel group, randomised, double-blind, placebo-controlled, phase II: a dose escalation safety study	
Participants	Inclusion criteria • Age 18 years or older • Spontaneous ICH within 3 h of onset Exclusion criteria • GCS 3 to 5 • Surgical ICH evacuation planned within 24 h • Known underlying cause of ICH • On oral anticoagulants • Known thrombocytopaenia • Coagulopathy, disseminated intravascular coagulation, sepsis, or crush injury • Pregnant • mRS > 2 pre-ICH • Any history or acute evidence of thrombotic, hypercoagulable, or vaso-occlusive disease • Known or suspected allergy to trial product • Participation in another trial	
Interventions	Intervention: recombinant activated factor VII (NovoSeven) at doses of 5 mcg/kg, 20 mcg/kg, 40 mcg/kg, or 80 mcg/kg, within 4 h of ICH onset Comparator: placebo, within 4 h of ICH onset	
Outcomes	Serious adverse events; coagulation parameters; perihaematomal oedema; ICH volume ratio on CT; change in ICH volume from baseline on CT; change in neurological scores	
Notes	This trial was funded by Novo Nordisk	
Risk of bias		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described.
Allocation concealment (selection bias)	Unclear risk	The method of allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant clinically deteriorated prior to dosing and underwent emergency haematoma evacuation, so dropped out after randomization. Otherwise, completeness of follow-up was not mentioned.
Selective reporting (reporting bias)	Low risk	All stated outcomes were reported.

Table 3-10 Characteristics of included studies-Mayer 2008 (FAST)

Methods	Parallel group, randomised, placebo-controlled, phase III trial
Participants	Inclusion criteria • Spontaneous ICH (including bleeding in brainstem and cerebellum) diagnosed by a CT scan within 3 h of symptom onset • Men or women, aged 18 years or over (20 or over in Taiwan) • Informed consent Exclusion criteria • Time of ICH onset is unknown, or more than 3 h • People with secondary ICH • Surgical haematoma evacuation planned within 24 h of symptom onset • GCS 3 to 5 • Known oral anticoagulant use (unless the INR is documented below 1.4) • Known thrombocytopenia (unless current platelets documented above 50,000/mL) • Pre-existing disability (mRS 3 to 5) • Any known history of haemophilia or other coagulopathy • Known acute myocardial ischaemia, unresolved unstable angina, acute septicaemia, acute crush injury, acute disseminated intravascular coagulation, or acute thrombotic stroke • Pregnancy • Known or suspected allergy to trial product or related products • Previous participation in this trial • Known participation in any investigational drug or device trial within 30 days of entry into this trial • People known or suspected of not being able to comply with this trial protocol (e.g. due to alcoholism, drug dependency, or psychological disorder)
Interventions	Intervention: Recombinant activated factor VII (NovoSeven) at doses of 20 mcg/kg or 80 mcg/kg, within 1 h of baseline CT and no later than 4 h after ICH onset Comparator: Placebo

Outcomes	Primary efficacy endpoint was poor outcome, defined as death or severe disability (scores of 5 to 6 on the mRS) at day 90. Analysis claimed to be intention-to-treat, but it did not appear to be. Secondary efficacy endpoints: BI, GOS-E, NIHSS, the EuroQol scale, and the Revised Hamilton Rating Scale for Depression at day 90; absolute and percent change in ICH volume as measured by CT from prior to dosing to 24 h after the baseline scan; good outcome (mRS 0 to 1) at day 90; absolute and percent change in total lesion volumes (ICH + IVH + oedema) from baseline to 72 h; BI at day 90; case fatality. Safety endpoints: the occurrence of adverse events until hospital discharge, or until day 90, whichever came first, and serious adverse events until the 'End of trial' form was completed	
Notes	This trial was funded by Novo Nordisk, which did not respond to repeated requests to provide further data from this trial	
Risk of bias		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Quote: "Block randomization according to site..."
Allocation concealment (selection bias)	High risk	It became apparent during questioning after the presentation of this trial's data at the European Stroke Conference (Glasgow 2007), that the imbalance in allocation between the 3 groups in this trial (there were approximately 30 more participants analysed in the 80 mcg/kg dose group than the other 2 groups) was due to the fact that the 80 mcg/kg dose of rFVIIa tended to be packed in the first of the 3 boxes of study drug for part of the trial (which might have unblinded investigators, in view of the preponderance of thromboembolic adverse events with the higher

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

Table 3-11 Characteristics of included studies-Sprigg 2014 (TICH-1)

Methods	Single-centre, prospective, randomised (2:1), double-blind, placebo-controlled blinded endpoint trial of tranexamic acid (intravenous 1 g bolus, 1 g infusion/8 h) in acute (< 24 h) spontaneous ICH
Participants	Adults with acute (< 24 h after ictus) spontaneous ICH were identified and enrolled from the stroke service at Nottingham University Hospital NHS Trust. The principal exclusion criteria included secondary ICH (anticoagulation, known vascular malformations), previous venous thromboembolic disease, recent (< 12 months) ischaemic events (ischaemic stroke, MI, PAD), renal impairment (estimated glomerular filtration rate < 50 mmol), and pregnancy or breast feeding
Interventions	Intervention: intravenous tranexamic acid (Cyklokapron; Phamacia Limited, Kent, UK) administered as a 1 g loading dose infusion for 10 minutes followed by a 1 g

	infusion for a period of 8 h Comparator: matching placebo (0.9% saline) administered by identical regime	
Outcomes	The primary outcome was trial feasibility (surrogate for trial acceptability: number of participants screened who were eligible for enrolment and who gave informed consent). Secondary outcomes included tolerability (adverse events occurring during or after administration of tranexamic acid) and safety (clinical information on ischaemic events, i.e. ischaemic stroke, TIA, acute coronary syndrome, PAD, and VTE were also recorded). The Data Safety Monitoring Committee reviewed unblinded safety data after 6, 12, and 18 participants had been recruited and followed for 7 days	
Notes	Dr N Sprigg provided information for assessment of risk of bias	
Risk of bias		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Details not given in paper, but confirmed by author as computer-generated.
Allocation concealment (selection bias)	Low risk	Details not given in paper, but confirmed by author as concealment until end of trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Details not given in paper, but confirmed by author as participants and trial staff all blinded to allocation for duration of trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not presented in paper, but author confirmed all assessments (clinical and radiological) were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data presented
Selective reporting (reporting bias)	Low risk	No selective reporting

Table 3-12 Characteristics of included studies Zazulia 2001 (ATICH)

Methods	Parallel group, RCT
Participants	Inclusion criteria: • Spontaneous non-traumatic supratentorial ICH (on brain CT), • Age 18 years or older, • Treatment begun within 3 h of ICH onset Exclusion criteria: • Clinical suspicion of ICH due to aneurysm, tumour, bleeding diathesis, • SAH Fisher grade > 3, • Plans for immediate surgery, • On Coumadin, • Prothrombin time > 14, • Pregnant, • Platelet count < 100,000, • Undergoing haemodialysis, • Treated with thrombolytic therapy in the last 48 h, • Known DVT, MI, or PE within the last 3 months, • Acute MI on ECG, • GCS < 5
Interventions	Intervention: aminocaproic acid (Amicar) intravenous bolus of 10 g over 5 to 10 minutes, followed by a continuous intravenous infusion of 50 g diluted in 478 mL 0.9% NaCl and infused at 30 cc/h over 24 h Comparator: routine treatment
Outcomes	• Antifibrinolytic activity levels, • ICH enlargement on CT by > 33% from baseline to 24 h, • In-hospital death, • 90-day case fatality, • FIM and mRS, • Aminocaproic acid plasma levels, • Development of ischaemic stroke (defined as a new lucency in a vascular distribution not in the area of the initial haemorrhage on the 7-day CT, or a new focal neurological deficit reflecting a vascular territory separate from the initial haemorrhage and that cannot be explained by other cause), • Symptomatic DVT confirmed by venous duplex ultrasonography, • Symptomatic PE confirmed by ventilation-perfusion lung scan, pulmonary angiogram, or autopsy, • Change in hydrocephalus score, • Laboratory evidence of disseminated intravascular coagulation, evidence of haemodynamic compromise during drug infusion (hypotension > 15% of baseline mean arterial pressure ± bradycardia or arrhythmia)
Notes	Studied terminated prematurely after 3 participants enrolled

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

3.6.3 Excluded studies

We excluded nine studies. For details, please refer to Table 3-13 'Characteristics of excluded studies'. We excluded two eligible RCTs because they presented aggregate data for adults with ICH as well as other types of intracranial haemorrhage, and the study authors could not provide data restricted to the ICH group alone by the time this review was submitted (Kerebel 2013; Steiner 2016 (INCH)).[417, 418] One abstract proposed a RCT of tranexamic acid for ICH, but the corresponding author confirmed that funding had not been obtained (Ciccone 2007).[366] We found two studies of aprotinin, but it was unclear whether they included some participants in both studies, and the outcome measures used were unsuitable for meta-analysis in this review (Meng 2003; Zhou 2005).[415, 416] NCT02429453 was a planned RCT of fresh frozen plasma (FFP) versus prothrombin complex concentrate (PCC), but was terminated before enrolment began.[367] NCT00222625 was a study of coagulation factors, but it was "stopped due to slow recruitment"(Iorio 2012)[420]. Dr Iorio has not responded to requests for clarification about whether any data were collected. Madjdinasab 2008 was a study of coagulation factors, but no results were reported, and there was no response from the authors to requests for information for this review. Finally, Li 2016 was excluded as the intervention (TRABC) did not appear to be haemostatic,

and had four Traditional Chinese Medicine (TCM) medicinals.[421]

Table 3-13 Characteristics of excluded studies

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

We identified 10 ongoing or recently completed but unreported RCTs. See 'Characteristics of ongoing studies' section for details.

Two RCTs examined blood clotting factors versus placebo or open control (NCT00810888; NCT01359202)[400,401], five examined antifibrinolytic drugs versus placebo or open control in acute spontaneous ICH (Liu 2017 (TRAIGE)[422]; Meretoja 2014 (STOP-AUST)[266];NCT03044184[426]; NOR-ICH[427]; Sprigg 2016 (TICH-2)[80]); one RCT examined antifibrinolytic drugs

versus placebo or open control in acute spontaneous ICH associated with anticoagulant drug use (NCT02866838)[425]; one RCT examined platelet transfusion versus open control (NCT00699621)[423], and one RCT examined blood clotting factors versus fresh frozen plasma in acute spontaneous ICH associated with anticoagulant drug use (NCT02777424).

3.6.3.1 Characteristics of ongoing studies

Table 3-14 Characteristics of ongoing studies-Liu 2017 (TRAIGE)

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

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

Table 3-15 Characteristics of ongoing studies-Meretoja 2014 (STOP-AUST)

Study name	STOP-AUST: The Spot Sign and Tranexamic Acid On Preventing ICH Growth - AUStralasia Trial (STOP-AUST)
Methods	The aim of the study is to test if ICH patients who have contrast extravasation on CTA, the 'spot sign', have lower rates of haematoma growth when treated with tranexamic acid within 4.5 h of stroke onset, compared with placebo
Participants	Inclusion criteria • People presenting with an acute ICH • Contrast extravasation within the haemorrhage, 'spot sign', evaluated from the CTA according to 3 criteria, all of which must be present: Serpiginous or spot-like appearance within the margin of a parenchymal haematoma without connection to an outside vessel; the density (in Hounsfield units) should be greater than that of the background haematoma (site investigators are not required to document the density); and no hyperdensity at the corresponding location on noncontrast CT • Age ≥ 18 years • Treatment can commence within 1 h of initial CT and within 4.5 h of symptom onset (or in people with unknown time of symptom onset, the time the person was last known to be well)

	• Informed consent has been received in accordance to local ethics committee requirements Exclusion criteria • GCS total score < 8 • Brainstem ICH • ICH volume > 70 mL as measured by the ABC/2 method • ICH known or suspected by study investigator to be secondary to trauma, aneurysm, vascular malformation, haemorrhagic transformation of ischaemic stroke, cerebral venous thrombosis, thrombolytic therapy, tumour, or infection • Contrast already administered within 24 h prior to initial CT or contraindication to imaging with CT contrast agents (e.g. known or suspected iodine allergy or significant renal failure) • Any history or current evidence suggestive of venous or arterial thrombotic events within the previous 12 months, including clinical, ECG, laboratory, or imaging findings. Clinically silent chance findings of old ischaemia are not considered exclusion criteria. • Hereditary or acquired haemorrhagic diathesis or coagulation factor deficiency • Use of heparin, low-molecular weight heparin, GPIIb/IIIa antagonist, or oral anticoagulation (e.g. warfarin, factor Xa inhibitor, thrombin inhibitor) within the previous 14 days, irrespective of laboratory values • Pregnancy (women of childbearing potential must be tested) • Planned surgery for ICH within 24 h • Concurrent or planned treatment with haemostatic agents (e.g. PCC, vitamin K, fresh frozen plasma, or platelet transfusion) • Participation in any investigational study in the last 30 days • Known terminal illness, or planned withdrawal of care or comfort care measures • Any condition that in the judgment of the investigator could impose hazards to the patient if study therapy is initiated, or affect the participation of the patient in the study
Interventions	Intervention: intravenous tranexamic acid 1000 mg in 100 mL 0.9% normal saline over 10 minutes followed by 1000 mg in 500 mL 0.9% normal saline infusion over 8 h Comparator: intravenous placebo in 100 mL 0.9% normal saline over 10 minutes followed by 500 mL 0.9% normal saline infusion over 8 h
Outcomes	Primary outcome measures • ICH growth by 24 ± 3 h as defined by either 33% or 6 mL increase from baseline, adjusted for baseline ICH volume. Secondary outcome measures

	• Major thromboembolic events (MI, ischaemic stroke, PE), measured within 90 ± 7 days) • Absolute ICH growth volume by 24 ± 3 h, adjusted for baseline ICH volume • Absolute IVH growth volume by 24 ± 3 h, adjusted for baseline IVH volume • mRS score of 0 to 4 at 3 months • mRS score of 0 to 3 at 3 months • Categorical shift in mRS at 3 months, subject to the validity of proportional odds assumption • Death due to any cause by 3 months
Starting date	December 2012
Contact information	Atte Meretoja, The Florey Institute of Neuroscience and Mental Health
Notes	NCT01702636

Table 3-16 Characteristics of ongoing studies NCT00699621

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

	24 h) Secondary outcome measures • GOS (time frame: 90 days) • Cardiovascular death occurring within the treatment period (time frame: 90 days) • Death due to any cause occurring within the treatment period (time frame: 90 days) • Acute MI (time frame: 90 days) • VTE (time frame: 90 days)
Starting date	January 2009
Contact information	Matti E Hillbom, Oulu University Central Hospital, Department of Neurology
Notes	NCT00699621

Table 3-17 Characteristics of ongoing studies-NCT00810888

Study name	The Spot Sign for Predicting and Treating ICH Growth study (STOP-IT)
Methods	The purpose of this study is to determine if computed tomography angiography can predict which individuals with ICH will experience significant growth in the size of the haemorrhage. For individuals who are at high risk for haemorrhage growth, the study will compare the drug recombinant activated factor VII (rFVIIa) to placebo to determine the effect of rFVIIa on ICH growth
Participants	Inclusion criteria • Acute, spontaneous ICH (including bleeding in cerebellum) diagnosed by non-enhanced CT scan within 5 h of symptom onset. (Time of onset is defined as the last time the patient was witnessed to be at baseline, i.e. people who have stroke symptoms upon awakening will be considered to have their onset at beginning of sleep) • Age ≥ 18 years through 80 years (candidates must have had their 18th birthday, but not had their 81st birthday) • For spot positive patients, dosing of study drug within 90 minutes of enrolling CT scan Exclusion criteria • Time of symptom onset of ICH is unknown or more than 5 h prior to baseline CT scan • ICH secondary to known or suspected trauma, aneurysm, vascular malformation, haemorrhagic conversion of ischaemic stroke, venous sinus thrombosis, thrombolytic treatment of any condition (e.g. MI, cerebral infarction, etc.), CNS tumour or CNS infection • Brainstem location of haemorrhage (people with cerebellar haemorrhage may be enrolled) • Serum creatinine > 1.4 mg/dL (123 μmol/L). Sites that currently perform CTA as standard of care for ICH will follow their standard procedures regarding renal insufficiency • Known allergy to iodinated contrast media

	• Intravenous or intra-arterial administration of iodinated contrast media within the previous 24 h of baseline CT scan • Known hereditary (e.g. haemophilia) or acquired haemorrhagic diathesis, coagulation factor deficiency, or anticoagulant therapy with INR > 1.2 • Known or suspected thrombocytopenia (unless current platelet count documented above 50,000/μL) • Unfractionated heparin use with abnormal PTT • Low-molecular weight heparin use within the previous 24 h • GPIIb/IIIa antagonist use in the previous 2 weeks • GCS score < 8 at time of proposed enrolment • Pre-admission mRS score > 2 • Baseline ICH volume of < 0.5 cc (haematoma volume will be estimated by local investigators from the baseline CT using the ABC/2 method) • Baseline ICH volume > 90 cc • Planned surgical evacuation of ICH within 24 h of symptom onset (placement of intraventricular catheter is not a contraindication to study enrolment) • Evidence of acute or subacute ischaemic stroke on baseline qualifying CT scan • Clinical history of thromboembolism or ischaemic vascular disease, including MI, coronary artery bypass surgery, cardiac angina, TIA, ischaemic stroke, peripheral artery disease (vascular claudication), cerebral bypass surgery, carotid endarterectomy, deep venous thrombosis, pulmonary embolism, or coronary or cerebrovascular angioplasty or stenting. (Clinically silent evidence of old ischaemia on EKG (Q waves) or CT scan (silent old infarct) will not be considered reasons for exclusion) • Baseline electrocardiogram shows evidence of acute cardiac ischaemia (ST elevation in 2 contiguous leads, new LBBB, or ST depression) • Clinical history suggestive of acute cardiac ischaemia (e.g. chest pain) • Abnormal baseline troponin • Females of childbearing potential who are known to be pregnant, lactating, or who have positive pregnancy tests on admission • Advanced or terminal illness or any other condition the investigator feels would pose a significant hazard to the patient if rFVIIa were administered • Recent (within 30 days) participation in any investigational drug or device trial or earlier participation in any investigational drug or device trial for which the duration of effect is expected to persist until the time of STOP-IT enrolment • Planned withdrawal of care or comfort care measures • Person known or suspected of not being able to comply with trial protocol (e.g. due to alcoholism, drug dependency or psychological disorder) • Informed consent cannot be obtained from the

	patient or legally authorised representative
Interventions	Intervention: recombinant activated factor VII. Participants will receive rFVIIa at 80 mcg/kg (maximum dose volume 21.3 mL, equivalent to maximum weight of 160 kg) Comparator: placebo. An inactive substance (maximum dose volume 21.3 mL, equivalent to maximum weight of 160 kg)
Outcomes	Primary outcome measures: life-threatening thromboembolic complications defined as development of 1) acute myocardial ischaemia, 2) acute cerebral ischaemia, and 3) acute pulmonary embolism (time frame: through day 4 after completion of study drug). The rate of haematoma growth among spot sign positive participants at 24 h, comparing participants treated with rFVIIa to those treated with placebo. Haematoma growth will be defined as a > 33% or > 6 cc increase in volume (time frame: at 24 h). The sensitivity and specificity of the spot sign for predicting haematoma growth (time frame: baseline head CT scan within 5 h, followed by a CT angiogram. Haematoma growth determined by comparison with a head CT scan performed at 24 h). Secondary outcome measures: incidence of other potentially study drug-related thromboembolic complications, such as deep venous thrombosis and elevations in troponin not associated with ECG changes (time frame: through day 4 after completion of study drug). 90-day outcomes among spot positive people, dichotomised as mRS score of 0 to 4 verses 5 to 6, comparing participants treated with rFVIIa to those treated with placebo (time frame: 90 days (± 7 days) from time of study enrolment). The positive and negative predictive values of the spot sign and the accuracy of the site investigators for correct identification of the spot sign as compared to a blinded study neuroradiologist (time frame: baseline head CT scan within 5 h, followed by a CT angiogram. Haematoma growth determined by comparison with a head CT scan performed at 24 h. Rate of total haemorrhage volume growth (haematoma + IVH) among spot-positive participants (time frame: 24 h (± 3 h) from baseline CT scan)
Starting date	November 2010
Contact information	Matthew Flaherty, Associate Professor, University of Cincinnati
Notes	NCT00810888

Table 3-18 Characteristics of ongoing studies - NCT01359202

Study name	'Spot Sign' Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT)
Methods	This clinical trial will enrol 110 participants from approximately 15 Canadian stroke centres. People coming to the emergency department with bleeding in the brain not due to trauma or other known causes who can be treated within 6 h of onset will undergo CT angiography using standard CT scanners ('CAT scan'). Those with a 'spot sign', a type of marker on the CT scan that shows the brain is still bleeding, will be randomly assigned to a single injection of 'factor 7' (a blood clotting drug used in haemophilia) or placebo (inactive saline); people without a spot sign will not be treated. The researchers will look at how much bleeding happens after the treatments are administered, as well as clinical outcomes such as death and disability. The researchers think that factor 7 will cause the bleeding to stop faster and possibly decrease death and disability.
Participants	Inclusion criteria • Acute spontaneous primary supratentorial ICH diagnosed by CT scan • Presence of a spot sign within the haematoma on CTA source images • Baseline ICH volume 3 mL to 90 mL • Age 18 or older • Investigator is able to randomise and administer study drug as soon as possible within a target of 60 minutes after CT angiogram and no later than 6 h after stroke symptom onset (using the 'last seen normal' principle) • Plan to provide full medical care for at least 24 h • Assent-consent from participant or LAR prior to enrolment, or a waiver of consent (where REB approved) if patient or LAR assent-consent is not possible prior to enrolment Exclusion criteria • Brainstem or cerebellar haemorrhage • ICH secondary to known or suspected trauma, aneurysm, vascular malformation, haemorrhagic conversion of ischaemic stroke, venous sinus thrombosis, thrombolytic treatment, tumour, or infection; or an in-hospital ICH or ICH as a result of any in-hospital procedure or illness • Baseline brain imaging shows evidence of acute or subacute ischaemic stroke (chronic infarcts are not an exclusion) • Contrast administration within the previous 24 h • Evidence of thromboembolic risk factors, defined as any of the following: known history within the past 6 months of any of the following: 1) MI, 2) coronary artery bypass surgery, 3) angina, 4) ischaemic stroke, 5) TIA, 6) carotid endarterectomy, 7) cerebral bypass surgery, 8) deep venous thrombosis, 9) pulmonary embolism, 10) any vascular angioplasty, stenting (coronary, peripheral

	vascular, or cerebrovascular) or filter (e.g. vena cava filter); 11) prosthetic cardiac valve, and, or 12) known history of a high-risk thrombophilia (e.g. antithrombin III deficiency, antiphospholipid antibody syndrome, protein C deficiency, etc.) • Known hereditary (e.g. haemophilia) or acquired haemorrhagic diathesis or coagulation factor deficiency • Any known condition that the investigator feels would pose a significant hazard if rFVIIa were administered • Planned surgery for ICH within 24 h (placement of intraventricular catheter is not an exclusion) • Planned withdrawal of care before 24 h post-ICH onset • Known participation in another therapeutic trial • Known allergy or other contraindication to iodinated contrast dye • Known or suspected hypersensitivity to the trial product • Known unfractionated heparin use - must check PTT and exclude if elevated above upper limit of local lab's reference range • Known low-molecular weight heparin, heparinoid, factor X inhibitor, or direct thrombin inhibitor use within previous 7 days • Known GPIIb/IIIa antagonist use in previous 2 weeks • Known warfarin (or other anticoagulant) therapy with INR > 1.40. Note: if the patient is suspected to have cirrhosis, study staff are to wait for the INR value prior to dosing, and ensure they do not enrol the patient if the INR value is > 1.40. Otherwise, the physician should use their discretion if they believe the patient is not at risk for elevated INR • Concurrent or planned treatment with prothrombin complex concentrate, vitamin K, fresh frozen plasma, or platelet transfusion • Pregnancy or lactation. Women of childbearing potential must have a negative pregnancy test prior to randomization. • Current clinical symptoms suggestive of acute coronary ischaemia (e.g. chest pain). • Baseline ECG evidence of acute coronary ischaemia (e.g. ST elevation in 2 contiguous leads, new LBBB, ST depression) • Baseline platelet count < 50,000, INR > 1.40, or elevated PTT
Interventions	Intrevention: rFVIIa 80 ug/kg IV bolus Comparator: placebo standard saline solution
Outcomes	Primary outcome measures • ICH size: difference between groups in ICH size on CT scan at 24 h post-dose, adjusted for baseline ICH size Secondary outcome measures: • Feasibility (time frame: 0): percentage of sites that can meet recruitment targets of 2 patients per site per year; % of patients who meet the target time of < 45 minutes

	from emergency department arrival to the start of the scan; % of patients who meet the target time of < 60 minutes from the end of the CT angiogram to administration of study drug; local site spot sign interpretation accuracy as judged by central adjudicator; protocol violations; waiver of consent process, evaluation, and effectiveness (time frame: 4.90 days); waiver of consent use, acceptability, and effect on treatment times. Questionnaire will be administered to subject or LAR at 4 days and 90 days • Acute blood pressure control (time frame: 1 h): % of participants in whom blood pressure control was achieved, defined as achieving systolic BP < 180 mmHg within 1 h post-randomisation • Thromboembolic events : incidence of MI and ischaemic stroke within 4 days; any other arterial or venous thromboembolic SAEs within 4 days • Mortality : 90-day mortality rate • Unstable angina: unstable angina within 4 days of treatment • Troponin increase : troponin rise above upper limit of normal within 4 days (without clinical symptoms or ECG evidence of acute coronary syndrome) • DVT: deep venous thrombosis (DVT) within 4 days • Pulmonary embolism: PE within 30 days • Cognition: Montreal Cognitive Assessment (MoCA) and Stroke Impact Scale at 90 days and 1 year • Disability: proportion of participants with mRS score 5 to 6 (death or severe disability) at 90 days and 1 year
Starting date	May 2011
Contact information	Dr David Gladstone, Sunnybrook Health Sciences Centre
Notes	NCT01359202

Table 3-19 Characteristics of ongoing studies-NCT02777424

Study name	Prothrombin complex concentrate versus fresh frozen plasma to correct coagulation disorders in adult neurosurgical patients (CLOT-CRANE)
Methods	This prospective, randomized, multicentre study is performed to determine whether prothrombin complex concentrates confers any benefits over fresh frozen plasma in adult neurological patients with coagulation disorders (PT value less than 60%)
Participants	Inclusion criteria • People with spontaneous ICH, traumatic ICH, or people requiring neurological surgery • Coagulation disorder defined by PT < 60% Exclusion criteria • Concomitant use of oral anticoagulant drugs • Acquired deficiency of coagulation factors whose treatment is established • Hypersensitivity to a PCC

	• History of thrombocytopenia induced by heparin • Disseminated intravascular coagulation • Extracranial active bleeding • Hypersensitivity to vitamin K
Interventions	Intervention: PCC. Administration of a single dose of PCC (25 U/kg equivalent factor IX) Comparator: fresh frozen plasma. Administration of a single dose of fresh frozen plasma of 15 mL/kg
Outcomes	Primary outcome measures Proportion of participants with correction of prothrombin time (PT < 60% at end of treatment administration - an average of 1 h)
Starting date	January 2016
Contact information	Laurence Salomon, Fondation Ophtalmologique Adolphe de Rothschild
Notes	NCT02777424

Table 3-20 Characteristics of ongoing studies NCT02866838

Study name	Treatment of intracerebral hemorrhage in patients on non-vitamin K antagonist (TICH-NOAC)
Methods	NOACs target selected players in the coagulation cascade as the direct thrombin inhibitor dabigatran and the factor Xa-inhibitors apixaban and rivaroxaban. ICH is the most feared complication of NOAC treatment (NOAC-ICH) Outcome of NOAC-ICH can be devastating and is a major cause of death and disability. There is no proven treatment for NOAC-ICH. Haematoma expansion (HE) is associated with unfavourable outcome. Tranexamic acid (TA) is an anti-fibrinolytic drug that is used in a number of bleeding conditions other than ICH
Participants	Inclusion criteria • Acute ICH (symptom onset < 12 h) • Prior treatment with a novel direct oral anticoagulant (apixaban, dabigatran, edoxaban, or rivaroxaban; last intake < 48 h or proven NOAC activity by relevant coagulation assays) • Age > 18 years, no upper age limit • Informed consent has been received in accordance to local ethics committee requirements Exclusion criteria • Severe pre-morbid disability (mRS > 4) • Anticoagulation with vitamin K antagonists (VKA; recent intake) • Secondary ICH (e.g. AVM, tumour, trauma). Note: it is not necessary for investigators to exclude underlying structural abnormality prior to enrolment, but where an underlying structural abnormality is already known, these people should not be recruited. • GCS < 5 • Pregnancy

	• Planned neurosurgical haematoma evacuation within 24 h (before follow-up imaging) • PE or DVT within the last 2 weeks
Interventions	Intervention: intravenous tranexamic acid: 1 g loading dose given as 100 mL infusion over 10 minutes, followed by another 1 g in 250 mL infused over 8 h Comparator: placebo: saline 0.9% given in identical dosage as experimental drug
Outcomes	Primary outcome measures • Haematoma expansion (time frame: up to 27 h): change in ICH-volume between baseline CT and follow-up CT at 24 ± 3 h of 33% relative or 6 mL absolute increase Secondary outcome measures: • mRS 0 to 4 at month 3 • mRS 0 to 3 at month 3 • Categorical shift in mRS at month 3 • Mortality due to any cause at month 3 • In-hospital mortality (time frame: baseline until discharge from hospital - hospital stays last, on average, 10 days) • Absolute ICH growth volume by 24 ± 3 h, adjusted for baseline ICH volume • Symptomatic HE defined as HE plus a neurological deterioration of NIHSS > 4 points or GCS > 2 points • Number of major thromboembolic events (MI, ischaemic stroke, PE - safety endpoints; 3 months) • Number of neurosurgical interventions (including craniectomy, external ventricular drain, haematoma evacuation; 3 months)
Starting date	December 2016
Contact information	Philippe Lyrer, Stroke Centre and Neurology, University Hospital Basel
Notes	NCT02866838

Table 3-21 Characteristics of ongoing studies NCT03044184

Study name	Tranexamic acid for spontaneous acute cerebral hemorrhage trial (TRANSACT)
Methods	This study aims to explore the effectiveness of tranexamic acid (also known as transamine or TXA) in reducing haematoma expansion in people with haemorrhagic stroke when given in the acute phase
Participants	Inclusion criteria • People with CT evidence of supratentorial ICH • Initiation of trial medication within 3 h from the time of symptoms onset • Ethnic Chinese • Reasonable expectation of completion of outcome measures at follow-up • Written informed consent from either the patient, next-of-kin, or legal guardian Exclusion criteria • Patients not expected to survive 24 h after admission • Patients with brainstem herniation syndrome on admission • Patients who need immediate neurosurgical intervention • GCS of 5 or less on admission i.e. a GCS score of 2 according to the Hemphil ICH score • Previous antiplatelet and anticoagulant medication use • Known thrombocytopenia or coagulopathy • Disseminated intravascular coagulation on admission • Acute sepsis on admission • ICH secondary to intracranial vascular lesion: aneurysm, AVM, neoplasm, or dural venous sinus thrombosis • Previous venous thromboembolic disease: DVT • History of ischaemic stroke or TIA within 12 months • History of ischaemic heart disease or MI • History of peripheral vascular disease • Patients with previous disability (pre-stroke mRS score > 2) • Pregnancy or breast feeding • History of allergy to tranexamic acid
Interventions	Intervention: standard management for people with spontaneous ICH according to 2015 AHA/ASA Guidelines for the Management of Intracerebral Hemorrhage. Participants will have 1 g of tranexamic acid (diluted in 100 mL of normal saline 0.9%) intravenously infused over 10 minutes, within 3 h of symptom presentation, and another 1 g of tranexamic acid (diluted in 100 mL of normal saline 0.9%) infused over 8 h Comparator: standard management for participants with spontaneous ICH according to 2015 AHA/ASA Guidelines for the Management of Intracerebral Hemorrhage. Participants will have 100 mL of normal saline 0.9% intravenously infused over 10 minutes within 3 h of symptom presentation, and another 100 mL of normal saline 0.9% infused over 8 h

Outcomes	Primary outcome measures • ICH volume (by CT brain scan) at 6 h: intracerebral haematoma volume (mL) as assessed by CT brain scan • ICH volume (by CT brain scan) at 24 h: intracerebral haematoma volume (mL) as assessed by CT brain scan • ICH volume (by CT brain scan) at 1 week: intracerebral haematoma volume (mL) as assessed by CT brain scan Secondary outcome measures • GOS (at 3 months and 6 months after stroke) • mRS (at 3 months and 6 months after stroke) • Stroke-specific quality of life scale (at 3 months and 6 months after stroke) • 30-day mortality: all-cause mortality within 30 days of admission • Vascular occlusive events (at 30 days after admission): ischaemic stroke, MI, PE, DVT • Rate of seizures: rate of seizures within 30 days of stroke • Tranexamic acid-associated adverse effects (at 30 days after admission): intolerable gastrointestinal symptoms, such as dyspepsia, diarrhoea, vomiting. Allergic reaction to tranexamic acid • Need for neurosurgical intervention (at 30 days after admission): need for operative management of the haemorrhagic stroke
Starting date	1 April 2017
Contact information	Peter YM Woo, Neurosurgery, Kwong Wah Hospital
Notes	NCT03044184

Table 3-22 Characteristics of ongoing studies NOR-ICH

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

	sjekt?p_document_id=324797

Table 3-23 Characteristics of ongoing studies-Sprigg 2016 (TICH-2)

Study name	Tranexamic acid for IntraCerebral Haemorrhage (TICH-2)
Methods	A pragmatic phase III prospective double-blind randomised placebo-controlled trial
Participants	Inclusion criteria • Adults with acute spontaneous ICH • Within 8 h of stroke symptom onset or time last seen well Exclusion criteria • People with ICH secondary to anticoagulation, thrombolysis or known underlying structural abnormality such as AVM, aneurysm, tumour, or venous thrombosis. An underlying structural abnormality does not need to be excluded before enrolment, but where known, patients should not be recruited • Contraindication to tranexamic acid • 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 • Pre-stroke life expectancy Target sample size 2000
Interventions	Intervention: intravenous tranexamic acid: 1 g loading dose given as 100 mL infusion over 10 minutes, followed by another 1 g in 250 mL infused over 8 h Comparator: matching placebo (normal saline 0.9%) administered by identical regimen
Outcomes	Primary outcome measure: to assess whether tranexamic acid is safe and reduces death or dependency after primary ICH. Death or dependency (ordinal shift on mRS) at day 90 will be analysed by intention-to-treat using ordinal logistic regression (OLR), with adjustment for minimisation factors. The assumption of proportional odds will be tested using the likelihood ratio test. Comparison of tranexamic acid versus control Secondary outcome measures • At day 7 (or discharge if sooner), neurological impairment (NIHSS) • At day 90, disability (BI), Quality of Life (EuroQoL), cognition, cognition and mood (TICS and ZDS) • Safety: death, serious adverse events, thromboembolic events, seizures • Costs: length of hospital stay, re-admission, institutionalisation Radiological efficacy and safety (CT scan): change in haematoma volume from baseline to 24 h, haematoma location, and new infarction

Starting date	1 March 2013
Contact information	Prof Nikola Sprigg, University of Nottingham
Notes	ISRCTN93732214

3.6.4 Risk of bias in included studies

Across all seven domains in the 12 included RCTs, we assessed that the risk of bias, according to the Cochrane 'Risk of bias' tool, and guidance in the Cochrane Handbook for Systematic Reviews of Interventions, was unclear in 37 (44%), high in 16 (19%), and low in 31 (37%; (Figure 3-2; Figure 3-3)[412] Only one RCT was at low risk of bias in all domains (Sprigg 2014 (TICH-1))[393].

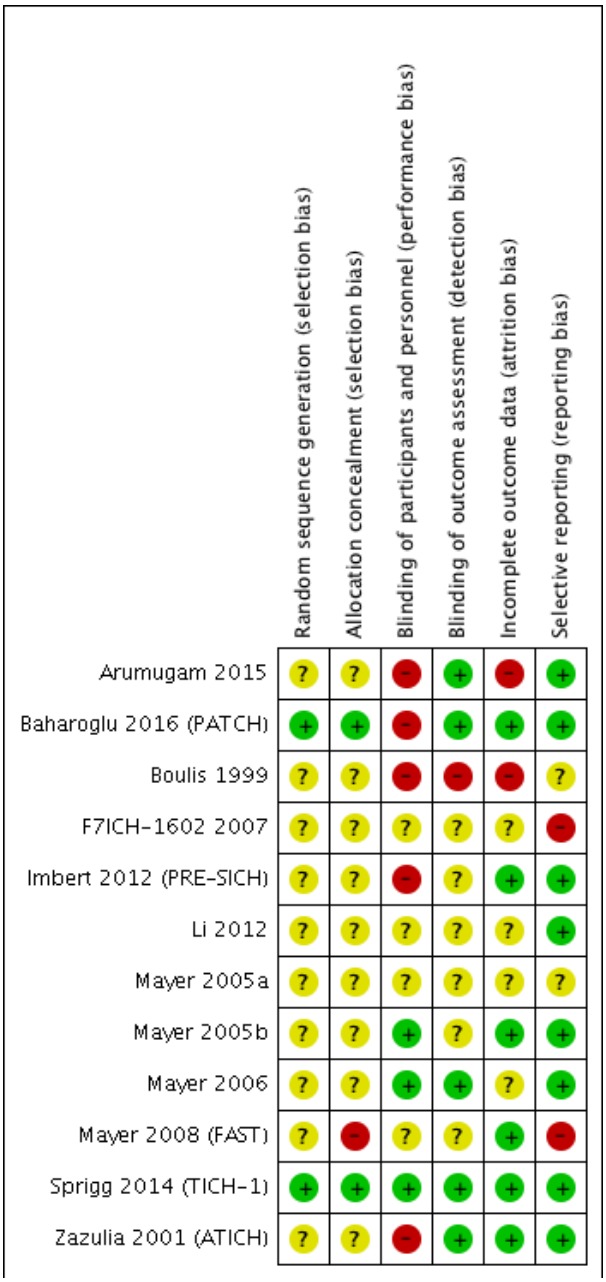


Figure 3-2 'Risk of bias' summary: review authors' judgments about each risk of bias criteria for each included study

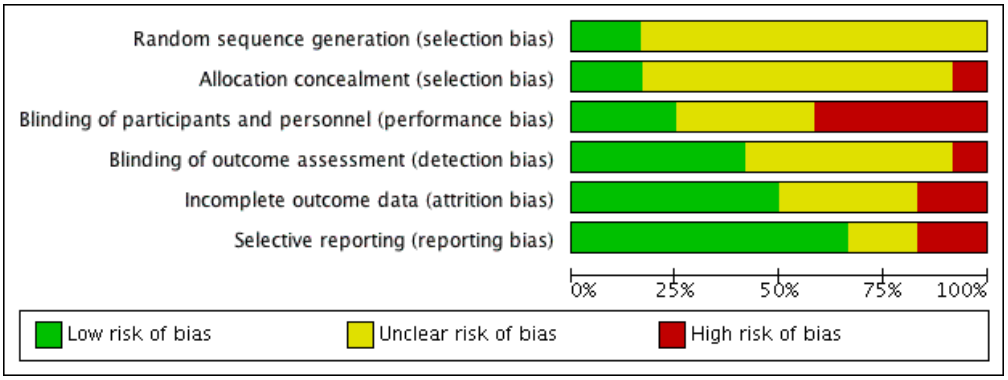


Figure 3-3 Risk of bias graph: review authors' judgments about each risk of bias criteria presented as percentages across all included studies

3.6.4.1 Allocation

The risk of bias in random sequence generation was low in two RCTs, unclear in 10 RCTs, and high in none. The risk of bias in allocation concealment was low in two RCTs, unclear in nine RCTs, and high in one. Only four RCTs clearly described the method of randomization (Baharoglu 2016 (PATCH) [232]; Mayer 2005b[24]; Sprigg 2014 (TICH-1)[393]; Zazulia 2001 (ATICH))[433], and one RCT simply mentioned 'block randomization according to site' (Mayer 2008 (FAST)).[223]

Allocation was reported as being concealed in the papers for Baharoglu 2016 (PATCH)[232] and Sprigg 2014 (TICH-1)[393], there was a risk of unblinding in one study (Mayer 2008 (FAST))[223], and the rest were unclear about allocation concealment.

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

3.6.4.2 Blinding

Five of the 12 RCTs did not blind the intervention and comparator (Arumugam 2015[394]; Baharoglu 2016 (PATCH)[232]; Boulis 1999[428]; Imbert 2012 (PRE-SICH)[429]; Zazulia 2001 (ATICH))[433], four did blind intervention and comparator, and the risk of bias was unclear in three RCTs. Whether participants and personnel were blinded to treatment allocation was only explicitly stated in Baharoglu 2016 (PATCH)[232], but correspondence with the study authors verified that this was the case for Mayer 2006[432]; Zazulia 2001 (ATICH)[433], and Sprigg 2014 (TICH-1).[393] The risk of bias in the remaining RCTs was unclear in three RCTs, and high in five RCTs.

Risk of bias from blinding of outcome assessment was low in five RCTs, high in one RCT, and unknown in six RCTs. Assessment of radiological outcome was blinded to treatment allocation in nine included RCTs (Arumugam 2015[394]; Baharoglu 2016 (PATCH) [232]; Imbert 2012 (PRE-SICH)[429]; Mayer 2005a; Mayer 2005b[24]; Mayer 2006[432];Mayer 2008 (FAST)[223]; Sprigg 2014 (TICH-1)[393]; Zazulia 2001 (ATICH))[433], but information was not provided in others.

3.6.4.3 Incomplete outcome data

Overall, the risk of bias from incomplete outcome data was low in six RCTs, high in two RCTs, and unclear in the remaining four RCTs. Only Baharoglu 2016 (PATCH)[232];Mayer 2008 (FAST)[223], and Sprigg 2014 (TICH-1)[393] provided data about completeness of clinical follow-up. In Arumugam 2015[394] and Li 2012, four participants had missing data. Boulis 1999 excluded eight participants after randomization.[428] The last-observation-carried-forward technique was used in Mayer 2005b[24] and Mayer 2008 (FAST)[223], which is likely to be unbiased only if the completeness of follow-up was high.

3.6.4.4 Selective reporting

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

3.6.4.5 Other potential sources of bias

There were differences in baseline characteristics between treatment and control arms in the rFVIIa RCTs, especially in Mayer 2008 (FAST): 90-day case fatality was worse in the placebo group in Mayer 2005b (29%) than in Mayer 2008 (FAST) (19%), which might be one explanation for the difference between the RCTs' findings. [24,223] There was no visual evidence of funnel plot asymmetry in the largest group of RCTs, which compared blood clotting factors versus placebo or open control for death or dependency (Figure 3-4).

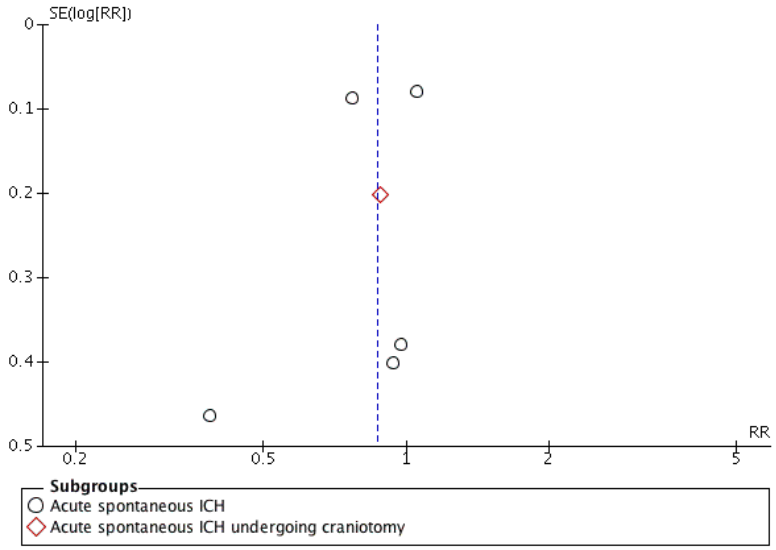


Figure 3-4 Funnel plot of comparison: 1 Blood clotting factors vs placebo or open control, outcome: Death or dependence (mRS 4 to 6) at day 90

3.6.5 Effects of interventions

Summary of findings for the main comparison Blood clotting factors versus placebo or open control

Table 3-24 Summary of findings: Blood clotting factors vs placebo/controls

Blood clotting factors compared with placebo or open control for acute spontaneous intracerebral haemorrhage				
Patient or population: adults with acute spontaneous intracerebral haemorrhage **Settings:** secondary care **Intervention:** recombinant activated factor VII **Comparison:** placebo or open control				
Outcomes	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Death or dependence (mRS 4 to 6) at day 90	**RR 0.87** (0.70 to 1.07)	1390 (6)	⊕⊕⊕○ **moderate**[1]	
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.				

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

Table 3-25 Summary of findings: Antifibrinolytic drugs versus placebo

Antifibrinolytic drugs compared with placebo for acute spontaneous intracerebral haemorrhage				
Patient or population: adults with acute spontaneous intracerebral haemorrhage **Settings:** secondary care **Intervention:** tranexamic acid **Comparison:** placebo				
Outcomes	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Death or dependence (mRS 4 to 6) at day 90	**RR 1.25** (0.57 to 2.75)	24 (1)	⊕⊕⊕◯ **moderate**[1]	
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.				

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

Table 3-26 Summary of findings: Platelet transfusion versus open control

Platelet transfusion compared with open control for acute spontaneous intracerebral haemorrhage associated with antiplatelet drug use				
Patient or population: adults with acute spontaneous intracerebral haemorrhage associated with antiplatelet drug use **Settings:** secondary care **Intervention:** platelet transfusion **Comparison:** open control				
Outcomes	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Death or dependence (mRS 4 to 6) at day 90	**RR 1.29** (1.04 to 1.61)	190 (1)	⊕⊕⊕◯ **moderate**[1]	
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.				

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

Table 3-27 Summary of findings: Blood clotting factors versus fresh frozen plasma

Blood clotting factors compared with fresh frozen plasma for acute spontaneous intracerebral haemorrhage associated with anticoagulant drug use				
Patient or population: adults with acute spontaneous intracerebral haemorrhage associated with anticoagulant drug use **Settings:** secondary care **Intervention:** fresh frozen plasma (intravenous), vitamin K (subcutaneous), and factor IX complex concentrate **Comparison:** fresh frozen plasma (intravenous)				
Outcomes	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Death or dependence (mRS 4 to 6) at day 90			No evidence	No evidence as mRS not measured
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.				

CI: confidence interval

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

3.6.5.1 Blood clotting factors versus placebo or open control

In RCTs of blood clotting factors (N = 1018) versus placebo or open control (N = 462) for acute spontaneous ICH with or without surgery, use of blood clotting factors led to non-significant reductions in death or dependence (risk ratio (RR) 0.87, 95% confidence interval (CI) 0.70 to 1.07; six trials, 1390 participants; moderate-quality evidence; Figure 3-5); in death (RR 0.75, 95% CI 0.51 to 1.09; seven trials, 1480 participants; moderate-quality evidence; Figure 3-7); in all serious adverse events (RR 0.81, 95% CI 0.30 to 2.22; two trials, 87 participants; moderate-quality evidence; Figure 3-8); and in ICH growth (RR 0.74, 95% CI 0.36 to 1.48; three trials, 151 participants; moderate-quality evidence; Figure 3-10). Blood clotting factors resulted in a non-significant increase in all serious thromboembolic serious adverse events (RR 1.24, 95% CI 0.80 to 1.91; five trials, 1398 participants; moderate-quality evidence; Figure 3-9). In these analyses, the I^2 varied from 0% to 53%. We downgraded the quality of the evidence by one level because of concerns with design and risk of bias.

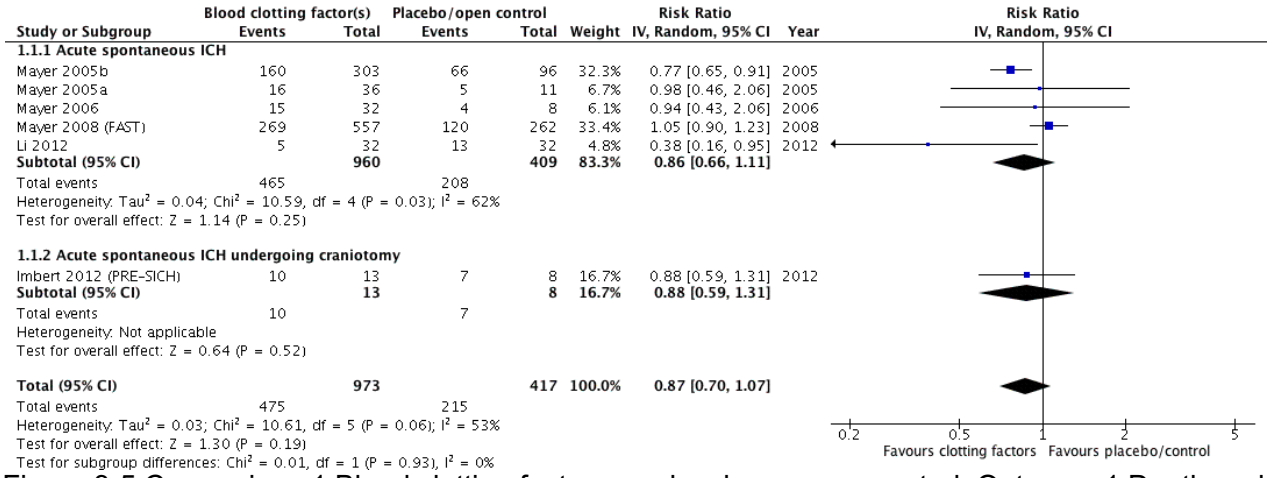


Figure 3-5 Comparison 1 Blood clotting factors vs placebo or open control, Outcome 1 Death or dependence (mRS 4 to 6) at day 90.

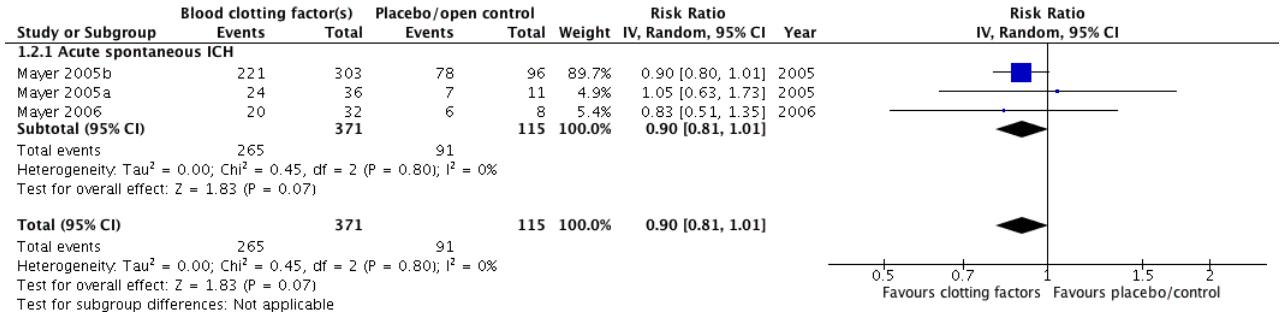


Figure 3-6 Comparison 1 Blood clotting factors vs placebo or open control, Outcome 2 Death or dependence (GOS-E 1 to 4) at day 90

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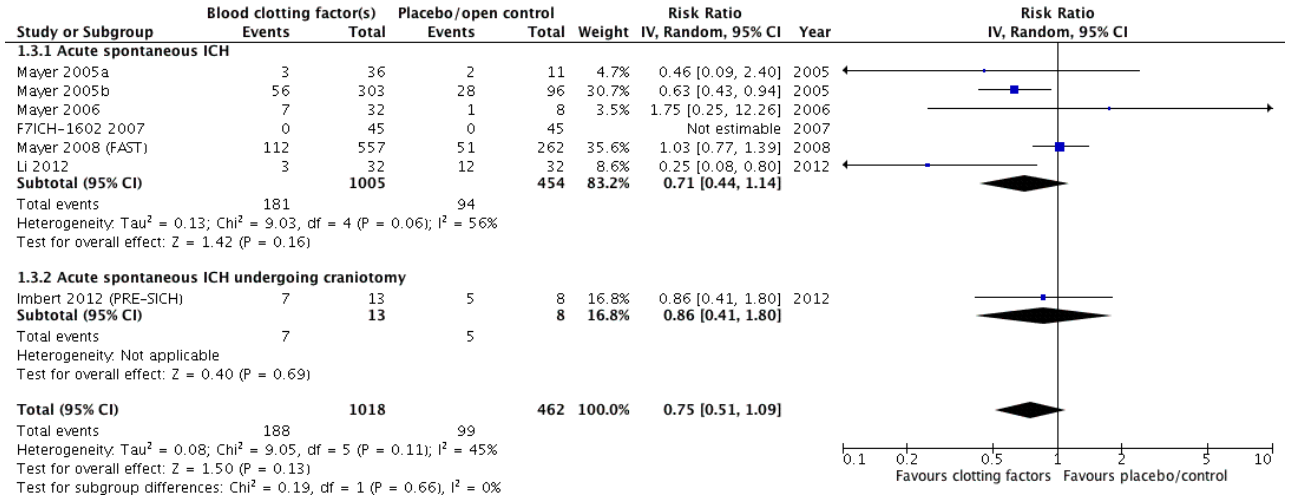


Figure 3-7 Comparison 1 Blood clotting factors vs placebo or open control, Outcome 3 Death by day 90.

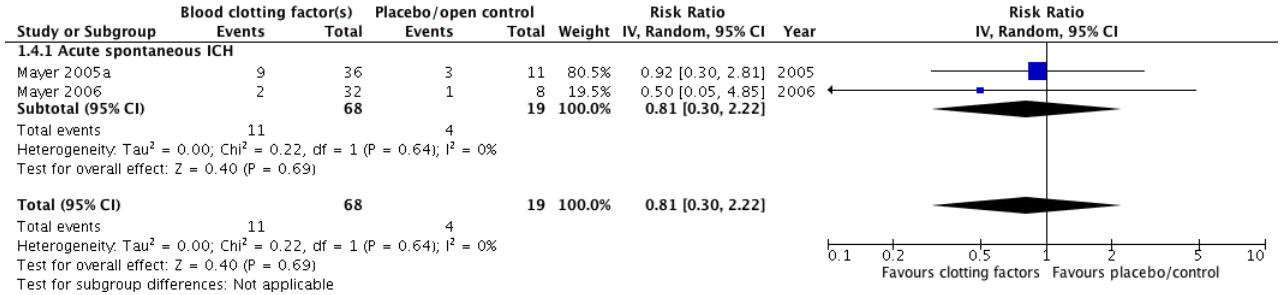


Figure 3-8 Comparison 1 Blood clotting factors vs placebo or open control, Outcome 4 All serious adverse events.

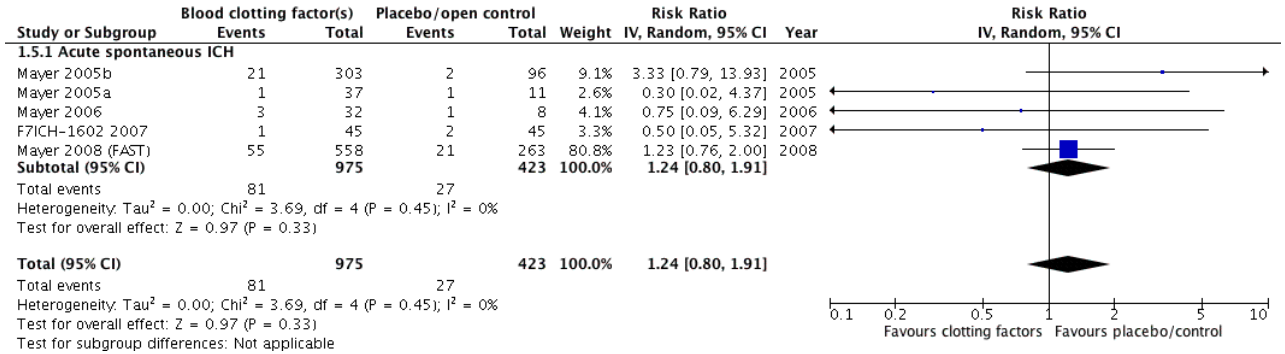


Figure 3-9 Comparison 1 Blood clotting factors vs placebo or open control, Outcome 5 Thromboembolic serious adverse events.

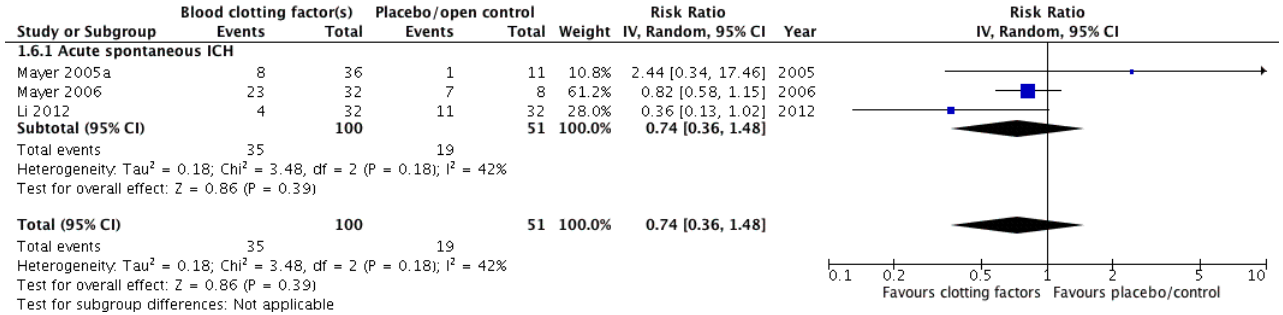


Figure 3-10 Comparison 1 Blood clotting factors vs placebo or open control, Outcome 6 Intracerebral haemorrhage growth by 24 hours

3.6.5.2 Antifibrinolytic drugs versus placebo or open control

In RCTs of antifibrinolytic drugs (N = 33) versus placebo or open control (N = 24) for acute spontaneous ICH, use of antifibrinolytic drugs led to non-significant increases in death or dependence (RR 1.25, 95% CI 0.57 to 2.75; one trial, 24 participants; moderate-quality evidence; Figure 3-11), in death (RR 1.16, 95% CI 0.31 to 4.39; three trials, 57 participants; moderate-quality evidence; Figure 3-12), in all serious adverse events (RR 1.50, 95% CI 0.39 to 5.83; one trial, 24 participants; moderate-quality evidence; Figure 3-13), and in thromboembolic serious adverse events (RR 1.59, 95%CI 0.07 to 35.15; one trial, 24 participants; moderate-quality evidence; Figure 3-14). Antifibrinolytic drugs led to a non-significant reduction in ICH growth (RR 0.76, 95% CI 0.56 to 1.05; three trials, 57 participants; moderate-quality evidence; Figure 3-17). In these analyses, the I^2 was 0% to 1%. We downgraded the quality of the evidence to moderate because of imprecision.

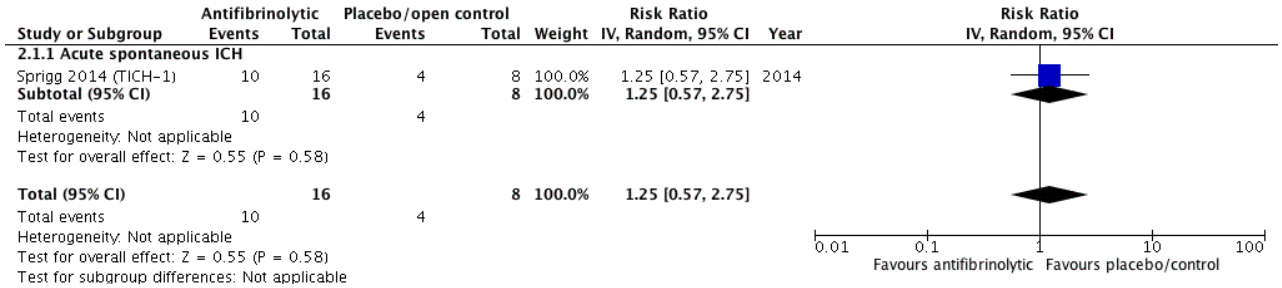


Figure 3-11 Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 1 Death or dependence (mRS 4 to 6) at day 90.

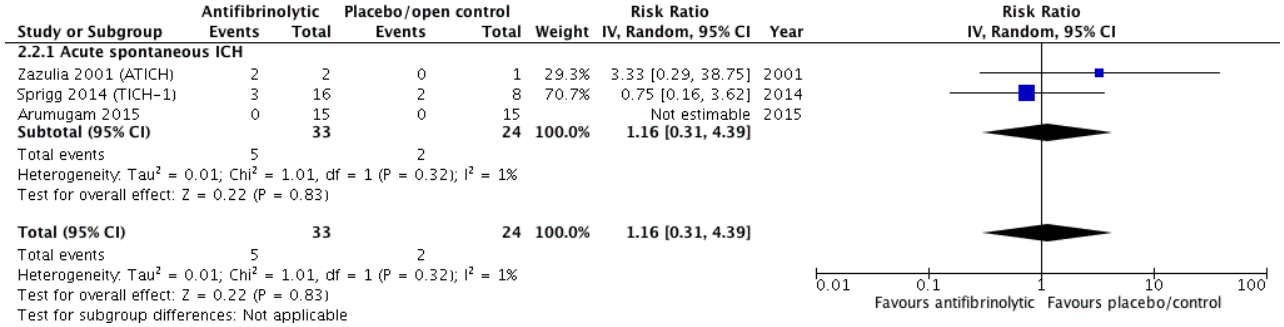


Figure 3-12 Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 2 Death by day 90.

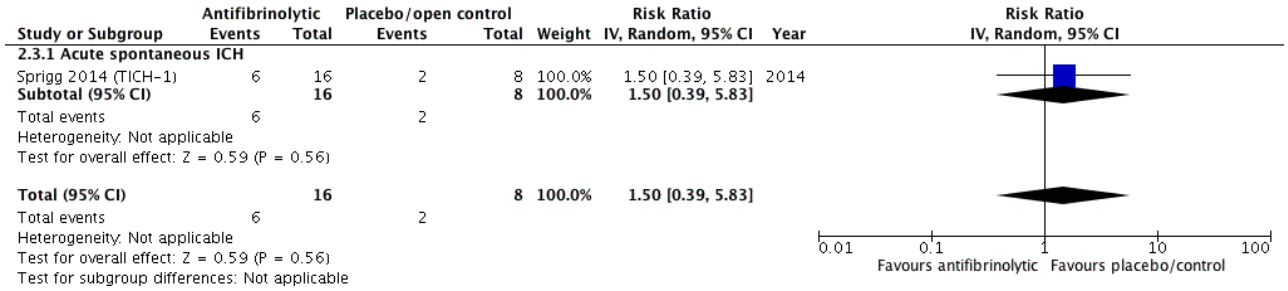


Figure 3-13 Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 3 All serious adverse events.

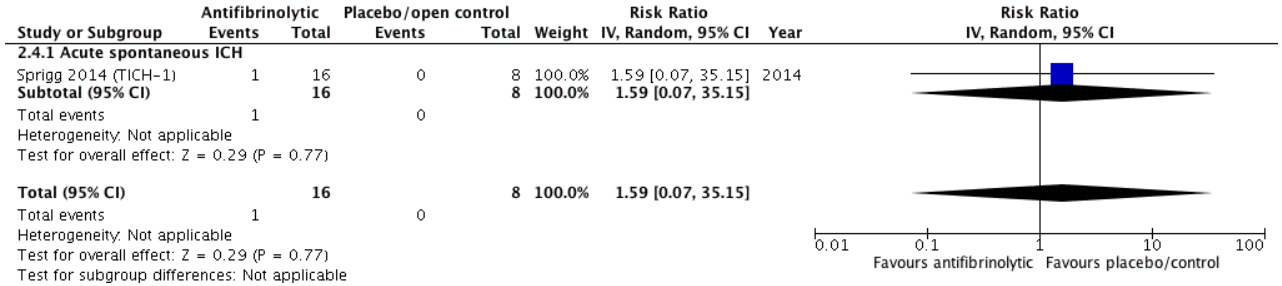


Figure 3-14 Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 4 Thromboembolic serious adverse events.

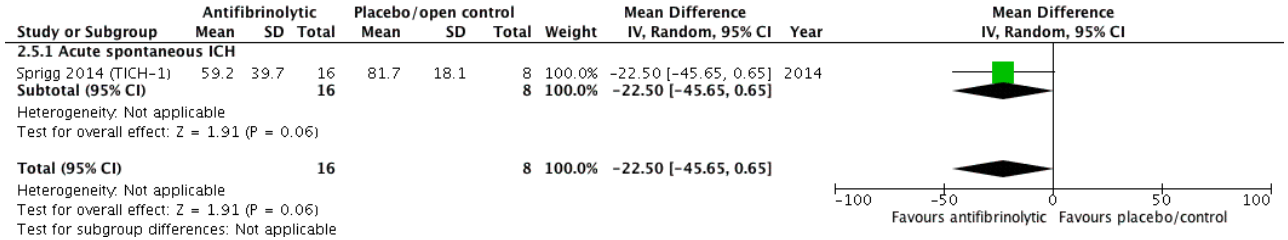


Figure 3-15 Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 5 Barthel Index.

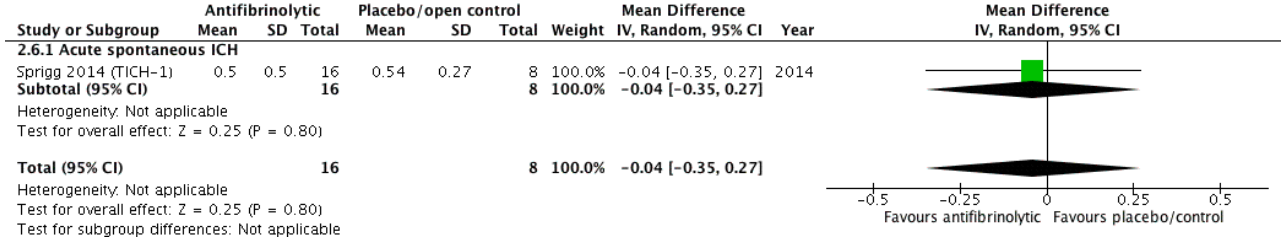


Figure 3-16 Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 6 EuroQoL health utility score.

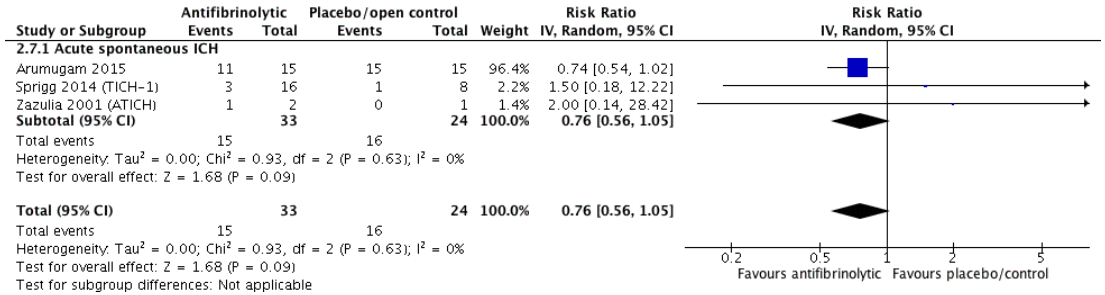


Figure 3-17 Comparison 2 Antifibrinolytic drugs vs placebo or open control, Outcome 7 Intracerebral haemorrhage growth by 24 hours.

3.6.5.3 Platelet transfusion versus open control

In one RCT of platelet transfusion (N = 97) versus open control (N = 93) for acute spontaneous ICH associated with antiplatelet drug use, platelet transfusion led to a significant increase in death or dependence (RR 1.29, 95% CI 1.04 to 1.61; one trial, 190 participants; moderate-quality evidence; Figure 3-18), and non-significant increases in death (RR 1.42, 95% CI 0.88 to 2.28; one trial, 190 participants; moderate-quality evidence; Figure 3-19), in all serious adverse events (RR 1.46, 95% CI 0.98 to 2.16; one trial, 190 participants; moderate-quality evidence; Figure 3-20), in thromboembolic serious adverse events (RR 3.84, 95%CI 0.44 to 33.68; one trial, 190 participants; moderate-quality evidence; Figure 3-21), and in ICH growth (RR 1.11, 95%CI 0.56 to 2.20; one trial, 190 participants; moderate-quality evidence; Figure 3-22). We downgraded the quality of the evidence by one level because of imprecision.

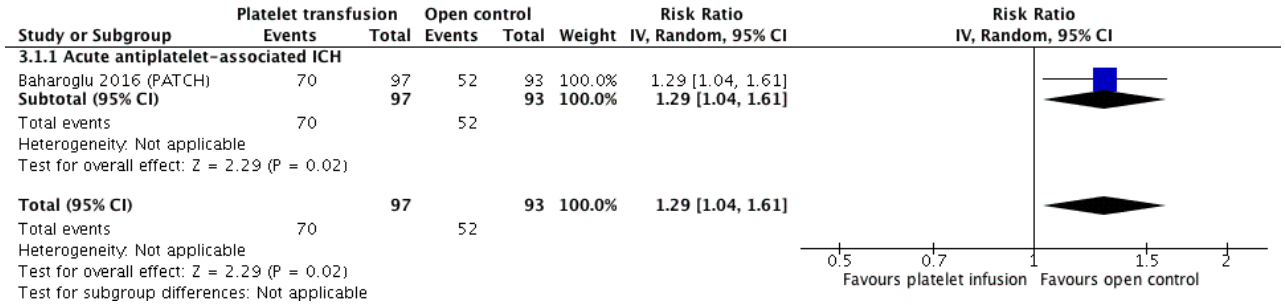


Figure 3-18 Comparison 3 Platelet transfusion vs open control, Outcome 1 Death or dependence (mRS 4 to 6) at day 90.

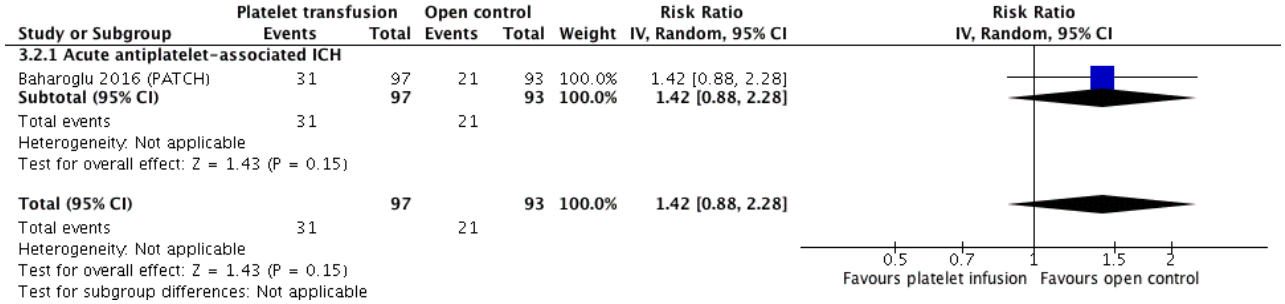


Figure 3-19 Comparison 3 Platelet transfusion vs open control, Outcome 2 Death by day 90.

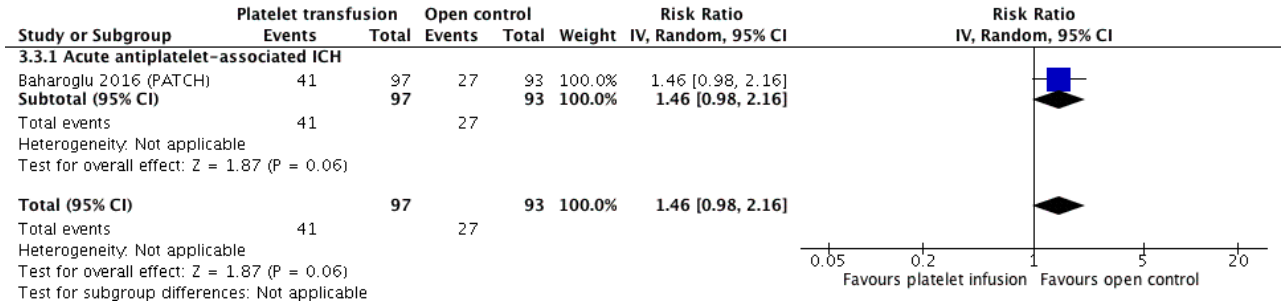


Figure 3-20 Comparison 3 Platelet transfusion vs open control, Outcome 3 All serious adverse events.

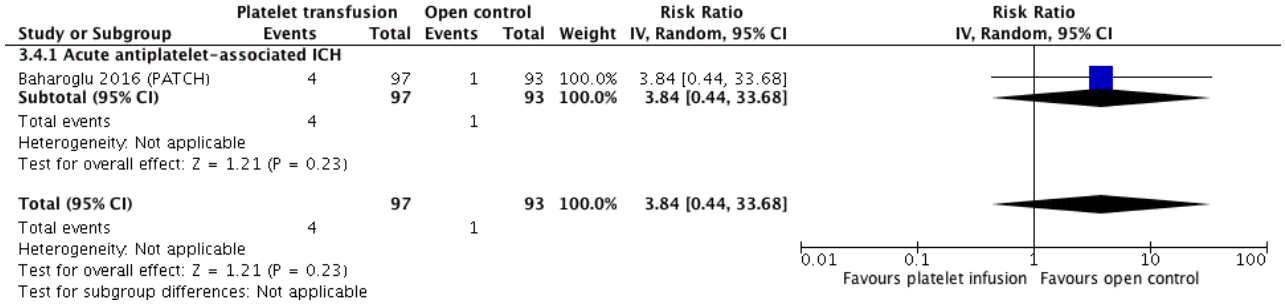


Figure 3-21 Comparison 3 Platelet transfusion vs open control, Outcome 4 Thromboembolic serious adverse events.

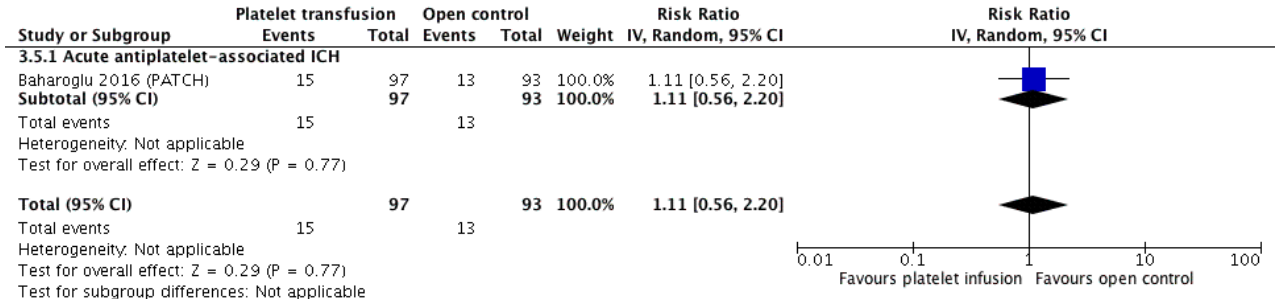


Figure 3-22 Comparison 3 Platelet transfusion vs open control, Outcome 5 Intracerebral haemorrhage growth by 24 hours.

3.6.5.4 Clotting factors versus fresh frozen plasma

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

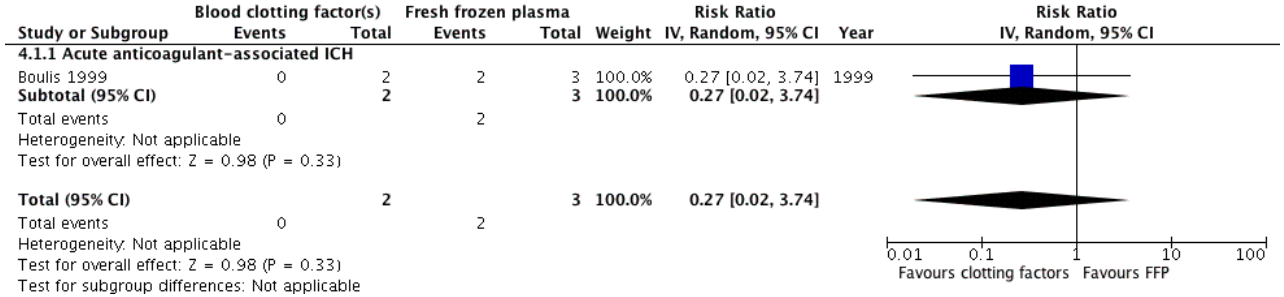


Figure 3-23 Comparison 4 Blood clotting factors vs fresh frozen plasma, Outcome 1 Death by day 90.

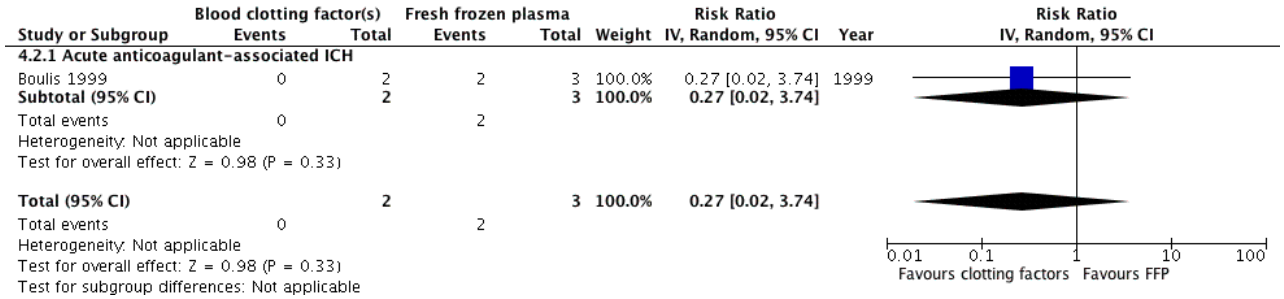


Figure 3-24 Comparison 4 Blood clotting factors vs fresh frozen plasma, Outcome 2 All serious adverse events

3.7 Discussion

3.7.1 Summary of main results

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

3.7.2 Overall completeness and applicability of evidence

Alongside the 12 included RCTs, we were unable to include two eligible RCTs (N = 113) comparing clotting factors versus fresh frozen plasma for acute spontaneous ICH associated with anticoagulant drug use because data on participants with intracerebral haemorrhage could not be separated from participants with subdural intracranial haemorrhage (Kerebel 2013; Steiner 2016 (INCH)).[417, 418] This resulted in a shortage of data comparing clotting factors versus fresh frozen plasma for acute spontaneous ICH associated with anticoagulant drug use.

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

(NCT00810888; NCT01359202).[400,401]

There were few data available on antifibrinolytic drugs versus placebo after spontaneous acute ICH, but five ongoing RCTs (N > 2500) are investigating the antifibrinolytic drug tranexamic acid versus placebo in acute spontaneous ICH without anticoagulant use (Liu 2017 (TRAIGE)[422]; Meretoja 2014 (STOP-AUST)[266]; NCT03044184[426]; NOR-ICH[427]; Sprigg 2016 (TICH-2)[80]), and with anticoagulant drug use (NCT02866838)[425]. Publication of the largest RCT is expected in 2018 (Sprigg 2016 (TICH-2)[80]). It was unclear whether recruitment was complete for one RCT of platelet transfusion (N=100; NCT00699621).[423] Further RCTs of platelet transfusion seem unlikely, so we await the publication of this RCT to see if the findings of Baharoglu 2016 (PATCH)[232] are externally valid.

3.7.3 Quality of the evidence

We included 12 RCTs with 1732 participants (1150 allocated to intervention, 582 allocated to control or active comparator). One double-blind RCT (Sprigg 2014 (TICH-1))[393], and one open RCT (Baharoglu 2016 (PATCH)[232]), were at low risk of bias, but the risk of bias of most other RCTs was moderate to high (Figure 3-2; Figure 3-3). The RCT finding harm from platelet transfusion has not been replicated in another RCT (Baharoglu 2016 (PATCH)[232]).

The largest quantity of data was from RCTs of recombinant activated clotting factor VII (rFVIIa), which were at moderate risk of bias, and their results were moderately inconsistent, showing nonsignificant benefits of rFVIIa. These findings have not changed practice (Hemphill 2015 (AHA ICH)[234]; RCP 2016[282]; Steiner 2014 (ESO ICH)[255]), and have led to explorations of the use of rFVIIa in ICH sub-groups in as-yet-unpublished RCTs (NCT00810888; NCT01359202).[400,401]

We rated the overall quality of all of the available evidence as moderate for three comparisons on the grounds of imprecision (Figure 3-5; Figure 3-11; Figure 3-18), and poor for one comparison on the grounds of imprecision and

limitations in study design (Figure 3-23).

3.7.4 Potential biases in the review process

We followed a dual review process: two authors (NS and RA-SS) independently extracted data that reduced identification bias and improved risk of bias assessment in comparison to the previous update of this review. We were unable to include data from two eligible studies that separately showed benefits of clotting factors versus FFP on intermediate outcomes (speed of international normalised ratio (INR) reduction) after intracranial haemorrhage as data were not available for the ICH population; we hope to include these RCTs in the next update of this review to also examine the effect of clotting factors versus FFP on clinical outcomes (Steiner 2016 (INCH); Kerebel 2013).[417, 418]

3.7.5 Agreements and disagreements with other studies or reviews

This review was completed after the most recent updates of the European and North American ICH guidelines (Hemphill 2015 (AHA ICH)[234]; Steiner 2014 (ESO ICH)[255]). These guidelines predated the results of Baharoglu 2016 (PATCH)[232], and simply found that "the usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is uncertain". Guidance on platelet transfusion has changed to reflect the results of Baharoglu 2016 (PATCH)[232], where platelet transfusion was associated with a worse outcome, hence platelet transfusion is not recommended.[435] Consistent with our findings, guidelines have not recommended the use of clotting factors, such as rFVIIa for acute spontaneous ICH not associated with anticoagulant use (Hemphill 2015 (AHA ICH)[234]; RCP 2016[282]; Steiner 2014 (ESO ICH)[255]). The AHA and ESO guidelines preceded the publication of Steiner 2016 (INCH), but the national stroke guidelines in the UK recommend using prothrombin complex concentrate for anticoagulant-associated ICH, reflecting the findings of Steiner 2016 (INCH) on the intermediate outcome of speed of INR reduction (RCP 2016).[417, 418]

3.8 Authors' conclusions

3.8.1 Implications for practice

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

3.8.2 Implications for research

Although rFVIIa does not appear beneficial on the basis of existing evidence, RCTs of its use in specific subgroups have been undertaken and their results are awaited (NCT00810888; NCT01359202).[400,401] Clotting factors appear superior to fresh frozen plasma for normalising coagulation in the RCTs that we could not include because they were not restricted to ICH (Kerebel 2013; Steiner 2016 (INCH)), but their superiority for improving clinical outcome needs to be established.[417, 418] The effect of antifibrinolytic drugs for acute ICH is uncertain, but in view of their effects in other conditions[409], the results of several ongoing RCTs are keenly awaited (Liu 2017 (TRAIGE)[422]; Meretoja 2014 (STOP-AUST)[266]; NCT02866838[425]; NCT03044184[426]; Sprigg 2016 (TICH-2)[80]).

Chapter 4 Clinical assessments used in the Tranexamic acid in Intracerebral Haemorrhage-2 (TICH-2) trial

4.1 Publications contributing to chapter:

1. Nikola Sprigg, Katie Robson, Philip Bath, Robert Dineen, Ian Roberts, Tom Robinson, Christine Roffe, David Werring, Rustam Al-Shahi Salman, Stuart Pocock, Lelia Duley,Tim England, David Whynes, Alfonso Ciccone, Ann Charlotte Laska, Hanne Christensen, Serefnur Ozturk, Ronan Collins, Daniel Bereczki, Juan Jose Egea-Guerrero, **Zhe Kang Law**, Anna Czlonkowska, David Seiffge and Maia Beredzie; on behalf of TICH-2 Investigators. Intravenous tranexamic acid for hyperacute primary intracerebral hemorrhage: Protocol for a randomized, placebo-controlled trial. Int J Stroke. 2016 Aug;11(6):683-94. doi:10.1177/1747493016641960. Epub 2016 Apr 5.

2. Katie Flaherty, Philip M. Bath, Robert Dineen, **Zhe Law**, Polly Scutt, Stuart Pocock and Nikola Sprigg on behalf of the TICH-2 investigators. Statistical analysis plan for the 'Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage' (TICH-2) trial. Trials 2017; 18:607. DOI 10.1186/s13063-017-2341-5

4.2 Introduction

The results in this thesis were based on data from the Tranexamic acid in IntraCerebral Haemorrhage-2 (TICH-2) randomised controlled trial. This chapter describes the clinical assessments used in the TICH-2 trial. Specific methods related to the sub-studies/ sub-group analyses are described in the respective chapters (Chapter 5, 6 and 7). The protocols and statistical analysis plan of TICH-2 trial including were previously published[80, 231, 436] and not discussed in details in this section.

4.3 Objectives/rationale

Tranexamic acid is an effective haemostatic agent in several bleeding conditions including polytrauma and postpartum haemorrhage. However, there is insufficient evidence up till the time of the trial for its use in spontaneous intracerebral haemorrhage. Therefore, the TICH-2 trial aims to explore the efficacy and safety of tranexamic acid in ICH.

4.4 Methods

4.4.1 Trial overview

The TICH-2 was an international multicentre phase III randomised double-blind placebo controlled clinical trial, involving 124 centres from 12 countries (United Kingdom, Denmark, Georgia, Hungary, Italy, Malaysia, Poland, Republic or Ireland, Spain, Sweden, Switzerland and Turkey). The trial included adult patients with spontaneous intracerebral haemorrhage presenting within 8 hours of onset, while secondary intracerebral haemorrhages were excluded. Ethical approvals were obtained from each country's ethic committee prior to commencement of trial. The TICH-2 was registered as ISRCTN93732214 and EudraCT Number 2012-004108-37. Consents were obtained from the patient, or a personal or legal representative prior to enrolment. Patients were randomised 1:1 to receive 2g intravenous tranexamic acid or matching placebo.

There were three optional sub-studies: the day 365 follow-up (United Kingdom only), MRI (selected sites internationally) and plasma biomarkers (single-centre at Nottingham University Hospitals NHS Trust). This thesis discusses the plasma biomarker sub-study in Chapter 7 but not the other two sub-studies.

4.5 Clinical assessments and outcomes

4.5.1 In-patient assessments

At baseline, investigators recorded demographics, onset to randomisation time, medical history, blood pressure, haematoma location, presence of

intraventricular haemorrhage and spot sign, premorbid modified Rankin Scale (mRS), National Institute of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS). The patients were reassessed face-to-face at day 2, 7 and at discharge for stroke severity (NIHSS and GCS), management (blood pressure, neurosurgery, do not attempt resuscitation [DNAR] status, intensive care) by site investigators. CT scan was performed at 24 hours from onset.

The National Institute of Health Stroke Scale (NIHSS) is a widely utilised assessment of neurological deficits after stroke.[392] It consist of 11 items with a score ranging from 0 to 42, where 0 is the mildest and 42 the most severe deficit. It has a good inter-rater reliability. Full details of NIHSS are shown in Appendix 9.

4.5.2 Day 90 telephone follow-up

Central telephone follow-up were performed at day 90 by trial coordinators from the University of Nottingham, for patients from United Kingdom and assessors from the respective countries' national coordinating centre, for international sites. The assigned assessors were blinded to patients' clinical data and must not have randomised, treated or be in contact with the patients or family prior to follow-up. The assessors first contacted the patients' general practitioner or obtained information through the Medical Research Information Service, to find out the patients vital status (if they were dead or alive). Permission to contact their general practitioners was obtained at the time of initial consent. For patients who were alive, the assessors performed telephone follow-up with the patients, or their carer if the patients were not able to answer the questionnaires. Assessors were trained to perform telephone follow-up using scripted forms containing structured questions. However, measurement of inter-rater agreement amongst the assessors was not performed as this was already validated in previous studies. The assessments performed included modified Rankin Scale which was the primary outcome; quality of life (EuroQoL-5D Health Utility Status [EQ-5D HUS] and EuroQoL-Visual Analogue Scale [EQ-VAS]),

disability (Barthel index), cognition (modified Telephone Interview Cognitive Status, TICS-m) and depression (Zung depression scale) at day 90 which were all secondary outcomes.[391] When the carer completed the follow-up on behalf of the patient, cognitive and depression questionnaires were omitted. The patients or their carers were also enquired about the occurrence of safety outcomes including venous thromboembolism and vascular events (stroke, transient ischaemic attack, ischaemic heart disease, peripheral artery disease) and seizures up till day 90. When the patients or their carer were not contactable by telephone, postal questionnaires were mailed to the addresses that were provided by the patients or their relatives at the time of initial contact. The postal questionnaires did not contain the cognitive test.

When the patients or their carer were not contactable by phone and had not responded to postal questionnaire, attempts to obtain the patients' outcome and contact information were made by contacting the hospital where they were admitted to, their general practitioners or next of kin. When these attempted failed, the recruiting centres were asked to visit the patient's last known address and ask the neighbours if they knew where the patient was. These measures were taken to minimise the number of patients lost to follow-up. The following section describes the clinical assessments performed at day 90.

4.5.3 Modified Rankin Scale

Modified Rankin Scale is a seven-tier scale of death and dependency ranging from 0 to 6[391]:

0 No symptoms at all

1 No significant disability despite symptoms; able to carry out all usual duties and activities

2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 Moderate disability; requiring some help, but able to walk without assistance

4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 Dead

The primary outcome analysis was a shift in modified Rankin Scale on ordinal analysis. In addition, a dichotomised modified Rankin Scale of 0 to 3 was considered a favourable outcome.

4.5.4 Telephone interview for cognition status-modified version (TICS-m)

The TICS-m is a 13-item cognitive test that may be administered in person or via telephone interview. This test was used to assess cognitive function at day 90 as it can be performed within 5 to 10 minutes via telephone by trial coordinators. It correlates highly with Mini Mental State Examination (MMSE, r=0.57) and Cambridge Cognitive Examination (CAMCOG, r=0.62).[396] The TICS-m is shown in Appendix 10.

4.5.5 Barthel index

The Barthel index is a 10-item ordinal scale that is used to assess ability to perform activities of daily living.[397,437] The score ranges from 0-fully dependent to 100-fully independent. The items assessed in this scale are help needed with grooming, dressing, bathing, toilet use, feeding, transfer chair to bed, walking, climbing stairs as well as presence or absence of faecal and urinary incontinence. Barthel index is shown in Appendix 11.

4.5.6 EuroQoL-5 Dimensions Health Utility Status and EuroQoL Visual Analogue Scale

EuroQol-5 Dimensions Health Utility State (EQ-5D HUS) is a measure of health state using five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (Appendix 12).[393] Each of these dimensions has three levels on which the patient can score themselves; level

one means they have no problems, level two means some problems and level three means they have severe problems.[393,438] All five of the questions must be answered for a total to be calculated, using the following algorithm.[394,395]

Table 4-1 EuroQoL 5D Health Utility Status

	Weight
Full health	1
At least one 2 or 3	-0.081
At least one 3	-0.269
Mobility	
- Score 2	-0.069
- Score 3	-0.314
Self-care	
- Score 2	-0.104
- Score 3	-0.214
Usual activities	
- Score 2	-0.036
- Score 3	-0.094
Pain/discomfort	
- Score 2	-0.123
- Score 3	-0.386
Anxiety/depression	
- Score 2	-0.071
- Score 3	-0.236

Euro-QoL VAS (visual analogue scale) records the patient's self-rated health on an analogue scale, with score ranging between 0 (worst imagined) and 100 (best imagined).[393]

4.5.7 Zung Depression scale

The Zung depression scale (ZDS) is a self-rating depression questionnaire designed by William Zung in 1965.[398] It has 20 questions to be answered by the trial participants. It is a well-validated test for depression. The original ZDS score range from 20 to 80. The Zung Depression scale used in the trial is a short version of the original ZDS (Appendix 13).[437, 439] Only 10 questions were answered by the participants, giving a score of between 10 to 40. This score is then converted to 100 by multiplying with a factor of 2.5. Depression is considered to be present with a score of ≥ 70.

4.6 Discussion

The TICH-2 trial explored whether tranexamic acid benefit patients with spontaneous intracerebral haemorrhage by looking at several clinical outcomes at day 90. This section discusses the strength and limitations of these assessments. Firstly, assessments were performed mainly via telephone follow-up, which was a pragmatic and cost-effective method of data collection. This allowed a large number of patients to be followed up by a relatively small number of trial coordinators, with very low drop out rate. In this trial, modified Rankin Scale was obtained in 99.2% (2307/2325) of the patients enrolled.[231] However, telephone follow-up was often perceived as less ideal than face-to-face interview. One study reported an agreement of only 43% in mRS between telephone interview and face-to-face interview.[440] Modified Rankin Scale had moderate to good inter-rater agreement with a weighted kappa of between 0.45 to 0.95 whether performed in face-to-face or telephone interview.[441-444] The reliability of mRS may be improved by using structured interview or a simplified questionnaire.[440,445] Postal questionnaires of modified Rankin Scale had moderate agreement (kappa 0.47 to 0.55; 57% to 64% agreement) with telephone interview with a response rate of 66% in one study.[446] Nevertheless, this was a feasible alternative when the patients could not be contacted by telephone. Telephone follow-up for quality of life, depression, cognition and disability scores used in this trial were also previously validated.[396,437] Measurement of inter-rater agreement of mRS and other assessments in the TICH-2 trial was not performed and could not be compared to previous studies.

Modified Rankin Scale at day 90 or later was recommended by the European Stroke Organisation Outcomes Working Group to be the preferred outcome measures for acute stroke trials.[447] The timing of assessment was intended to demonstrate durable clinical benefits. The first 3 months after stroke is the period of greatest motor recovery.[448] However, motor functions of people with stroke continue to improve up to 12 months albeit to a lesser degree.[449, 450] Language and cognitive function may continue to improve up to two years after stroke.[451] In addition, stroke complications are common with approximately 46% of the trial patients experiencing serious adverse events

in the first 90 days, thus impairing the recovery process.[231] The natural history of recovery in intracerebral haemorrhage is less well studied compared to ischaemic stroke but studies had shown that recovery might occur up to 6 months after intracerebral haemorrhage.[452,453] Functional outcome assessment at day 90 was possibly too early. Several clinical trials of intracerebral haemorrhage assessed their primary outcome at 6 months to allow longer period for potential recovery.[224, 275] The day 365 sub-study was designed to study delayed recovery but the results are not discussed in this thesis.

The primary analysis of the TICH-2 was the ordinal shift analysis of modified Rankin Scale, which was more sensitive than dichotomised modified Rankin Scale.[454] In addition, a dichotomised mRS of 4 to 6 was considered unfavourable in the secondary analysis. The rationale for using a higher cut-off point for mRS than the one used in many ischaemic stroke trials (where mRS of 2 or 3 to 6 indicate poor outcome)[455, 456] was that intracerebral haemorrhage was in general a more severe type of stroke. This mRS cut-off was also used in several large ICH trial including CLEAR III and STICH.[224, 275]

In conclusion, the day 90 outcomes used in the TICH-2 trial were outcomes that were commonly used in stroke trials. Early neurological outcome as assessed by the presence of neurological deterioration was an important outcome as well, although longer-term death and dependency was most relevant to patients.[457] Neurological deterioration was discussed in greater detail in the next chapter (Chapter 5).

Chapter 5 Clinical effects of tranexamic acid on neurological deterioration and seizures

The Tranexamic acid in primary IntraCerebral Haemorrhage-2 (TICH-2) trial was completed and published. Tranexamic acid did not improve the primary outcome of shift in modified Rankin Scale at day 90 in patients with spontaneous intracerebral haemorrhage.[231] This chapter describes secondary analyses based on data from the TICH-2 trial and consists of 2 sections looking at 2 outcomes of interest: neurological deterioration within 7 days and seizures within 90 days.

5.1 Predictors of neurological deterioration in spontaneous intracerebral haemorrhage and the effects of tranexamic acid

5.1.1 Publication contributing to this chapter

Z Kang Law, K Flaherty, P Scutt, JP Appleton, PM Bath and N Sprigg. Predictors of neurological deterioration in intracerebral haemorrhage: results of interim data from the TICH-2 trial (AS20-013-oral abstract), 3rd European Stroke Organisation Conference, 2017. European Stroke Journal 2017, Vol. 2(IS) 3–97. DOI: 10.1177/2396987317705236

5.1.2 Abstract

5.1.2.1 Background

Neurological deterioration leads to poor outcome after intracerebral haemorrhage. We aim to identify the predictors of neurological deterioration and whether tranexamic acid reduced the risk of neurological deterioration.

5.1.2.2 Methods

Data from the Tranexamic acid in primary IntraCerebral Haemorrhage-2 (TICH-2) randomised controlled trial were analysed. Neurological deterioration (ND) was defined as an increase in National Institute of Health Stroke Scale (NIHSS) of ≥4 points or a fall in Glasgow Coma Scale (GCS) of

≥2 points from baseline or day 2 assessments. Early neurological deterioration (END) was defined as within 48 hours of stroke onset and late neurological deterioration (LND) if occurred between 48 hours up to 7 days. Logistic regression was used to identify predictors of ND, the effect of ND on outcomes and the effect of tranexamic acid on ND.

5.1.2.3 Results

From 2325 patients recruited, 735 (31.7%) had neurological deterioration: 590 (80.3%) occurred within 48 hours and 145 (19.7%) between 48 hours and 7 days from onset. Predictors of neurological deterioration included older age, previous intracerebral haemorrhage, higher systolic blood pressure, higher NIHSS, larger baseline haematoma volume, intraventricular haemorrhage and antiplatelet therapy. Tranexamic acid reduced the risk of neurological deterioration ≤ 7 days (adjusted odds ratio [aOR] 0.75, 95% confidence interval [CI] 0.60-0.94; p=0.013) and END (aOR 0.75, 0.59-0.96; p=0.022) but not LND deterioration (aOR 0.73, 0.49-1.08; p=0.12). Tranexamic acid significantly reduced the risk of haematoma expansion (aOR 0.77, 0.63-0.94;p=0.011). Neurological deterioration was independently associated with higher 90-day mortality (aOR 7.69, 5.75-10.29; p<0.001) and poor functional outcome (modified Rankin Scale of 4 to 6; aOR 4.78, 3.55-6.44; p<0.001).

5.1.2.4 Discussion and conclusion

Tranexamic acid reduced the risk of early neurological deterioration probably through reduction of haematoma expansion. Neurological deterioration, even if transient, was associated with poor functional outcome.

5.1.3 Background

Neurological deterioration affects approximately one-third of patients with spontaneous intracerebral haemorrhage (ICH) and leads to death and dependency.[71, 75, 79] While neurological deterioration refers to a worsening of neurological symptoms and signs measured by an objective scoring scale, there is no standardised definition. Various definitions of neurological deterioration were described in Table 1-4, section 1.7.1.1.[75-77, 79] Older age, prior use of anticoagulant, larger baseline haematoma, CT angiography spot sign, haematoma expansion, perihaematomal oedema, intraventricular haemorrhage, subarachnoid extension, hydrocephalus and leukoaraiosis increase the risk of neurological deterioration after ICH.[75, 79, 86, 458] A more detailed description of predictors of neurological deterioration in intracerebral haemorrhage is described in Table 5-1.

Tranexamic acid is an antifibrinolytic agent that was effective in preventing death due to bleeding in major trauma and postpartum haemorrhage.[339, 370] In the Tranexamic acid in Intracerebral Haemorrhage-2 (TICH-2) trial, there was no significant difference in primary outcome of death and dependency at day 90 between the tranexamic acid and placebo arm.[231] However, there was a significant reduction in the rates of haematoma expansion, early death and serious adverse events.[231]

Table 5-1 Predictors of neurological deterioration in intracerebral haemorrhage

Predictors of early neurological deterioration in ICH
• CTA spot sign positive (OR 10.7, 95% CI 4.79-24.3)[459] • Extensive IVH (OR 8.73, 95% CI 2.87-26.5)[459] • Intraventricular haemorrhage (OR 2.6, 95% CI 1.4-5.0)[75] • Haematoma expansion (OR 6.1, 95% CI 2.2-17.3)[459], (OR 4.3, 95% CI 1.3-14.5)[75]; (OR 3.6, 95% CI 1.7-7.6)[79] • Expansion of IVH (OR 1.7, 95% CI 1.2- 2.3 per point increase)[459] • Hydrocephalus[459] • Perihaematomal oedema: initial PHO volume was not a predictor[460], increased relative oedema volume within the first 3 hours after symptom onset as a strong predictor of better functional outcome in ICH presumably due to successful haematoma clotting and clot retraction.[460] PHO volume or expansion that occurs days or weeks later contribute to ND[75, 461-463] • Cerebral herniation[75] • Anticoagulant[459] • SBP (by 10-unit increase; OR 1.17, 95% CI 1.02-1.32)[75] • Serum fibrinogen levels of >523 mg/dL (OR 5.6, 95% CI 1.9-16.2)[75] • Fever >37.5^{0}C (OR 24.5, 95% CI 4.8-125)[75] • Higher leukocyte count (by 1,000-unit increase; OR 2.1, 95% CI 1.6–2.6)[75] • Inflammatory markers- causes endothelial injury and subsequent haematoma expansion.[461] • Glutamate level[461] • MMP-9[464] • Fibronectin[464] • Troponin[79] • Infection • Cardiac failure[75]
Predictors of late neurological deterioration in ICH
• GCS[464] • Haematoma volume[71] • Extent of IVH[459] • Expansion of IVH (OR 2.3, 95% CI 1.3–4.2 per 25 point increase)[465] • Fever[79] • Cerebral oedema[71, 79] • White cell count[462] • Troponin[79] • Serum glucose[71]

CI= confidence interval; CTA=computed tomography angiography; GCS=Glasgow Coma Scale; ICH=intracerebral haemorrhage; IVH=intraventricular haemorrhage; MMP-9=matrix metalloproteinase-9; OR=odds ratio; PHO=perihaematomal oedema; SBP=systolic blood pressure

5.1.4 Methods

5.1.4.1 Aim

We aimed to examine the incidence and predictors of neurological deterioration and the effects of tranexamic acid on neurological deterioration in the first 7 days after ICH.

5.1.4.2 Definition of neurological deterioration

Neurological deterioration was defined arbitrary as an increase in NIHSS of ≥4 points or a decline in GCS of ≥2 points.[436] This definition was used as a cut-off of ≥4 points in NIHSS has a relatively high sensitivity and specificity for mortality (0.909 and 0.907) compared to lower NIHSS cut-off of ≥2 points (0.955, 0.685).[466] Early neurological deterioration was present if the decline first occurred within the first 48 hours, and late neurological deterioration was present if deterioration first occurred between 48 hours and 7 days. In addition, neurological deterioration was also reported by investigators on the day 7 electronic case report form (eCRF), although this may not necessarily be reflected in the change in NIHSS/GCS. This is because the change may be recorded outside the timepoint of day 2 and day 7 assessment, or because of missing NIHSS/GCS assessment. The deterioration may be transient or the patient may have recovered after treatment (e.g neurosurgical intervention). It is important to capture transient neurological deterioration as it was reported to increase the risk of death and dependency in ischaemic stroke.[467] The significance of transient neurological deficit in ICH has not been reported. As exploratory analysis, we looked at the subsequent neurological status of patients who had early neurological deterioration. We defined transient neurological deterioration as patients with early neurological deterioration who had subsequent neurological improvement (increase in GCS to baseline score or higher or decline in NIHSS to baseline score or lower). Other classification included further neurological deterioration (a further increase in NIHSS of ≥4 points or a decline in GCS of ≥2 points), stable (no changes in NIHSS/GCS or changes of lesser degree than deterioration or improvement) or no further assessment.

5.1.4.3 Imaging analysis

Measurements of haematoma, intraventricular haemorrhage and perihaematomal oedema (PHO) volumes were performed by three independent raters blinded to clinical data using semi-automated segmentation tools of ITK-SNAP software version 3.6.0.[468] Arbitrarily, a threshold of 5 to 33 Hounsfield unit was used to determine areas constituting perihaematoma oedema.[469] The intraclass correlations (ICC) was 0.94 (0.86–0.97) for haematoma volume measurement and 0.88 (0.75-0.95) for PHO volume measurements. Radiological adjudication including location of haematoma and presence of IVH were performed by a separate group of neuroradiologist. Haematoma expansion was defined as increase in intraparenchymal haematoma volume on follow-up scan of >33% or > 6 mL from baseline haematoma.

5.1.4.4 Serious adverse events reporting and adjudication

Serious adverse events (SAE) are any events that are life-threatening, resulted in death, disability, hospitalisation or prolongation of existing hospitalization and a congenital anomaly in the offspring of a participant, or considered medically important. All SAEs including neurological deterioration were adjudicated by expert assessors who were consultant stroke physicians, based on clinical and diagnostic information (laboratory and radiological report) provided by site investigators.

5.1.4.5 Statistical analysis

The baseline characteristics of patients with early or late neurological deterioration was compared with those without neurological deterioration. Multivariable logistic regression analyses were performed to determine the predictors of early, late and any neurological deterioration and their effect on outcomes. Additional multivariable logistic regression analyses were performed to determine the effect of tranexamic acid on neurological deterioration, adjusting for significant predictors of neurological deterioration. Data are mean (standard deviation), median [interquartile range] or number (%). P of <0.05 was considered statistically significant. Analyses were

performed using Statistical Package for the Social Sciences (SPSS) version 24, IBM, Armonk, NY.

5.1.5 Results

Of the 2325 patients recruited into the trial, status of neurological deterioration was available in 2317 (99.7%). 735 patients (31.7%) had neurological deterioration within 7 days from onset of ICH. Early and late neurological deterioration occurred in 590 (25.5%) and 145 (6.3%) respectively. Patients with early and late neurological deterioration were likely to have older age, previous ischaemic stroke, intracerebral haemorrhage, ischaemic heart disease, history of antiplatelet therapy, more severe stroke at onset (higher NIHSS, lower GCS), raised white cell count and blood glucose (Table 5-2). Both early and late neurological deterioration were associated with the presence of intraventricular haemorrhage, subarachnoid extension, positive CT angiography spot sign, lobar location, larger baseline haematoma and oedema volume, more midline shift and leukoaraiosis (Table 5-3). Patients with early and late neurological deterioration had significantly more haematoma expansion, extension into intraventricular space and greater oedema growth (Table 5-3).

Table 5-2 Baseline characteristics of patient with early, late and no neurological deterioration

Characteristics	Any neurological deterioration			First deterioration vs no deterioration			
	Yes (n=735)	No (n=1582)	P	Early (n=590)	P	Late (n=145)	P
Age (years)	72.5 (13.2)	67.3 (13.7)	<0.001	72.4 (13.4)	<0.001	72.9 (12.2)	<0.001
Sex (male)	392 (53.3)	904 (57.1)	0.086	300 (50.8)	0.009	92 (63.4)	0.14
Premorbid mRS (/5)	0 [0, 1]	0 [0, 0]	<0.001	0 [0, 1]	<0.001	0 [0, 1]	0.097
SBP (mmHg)	175.9 (30.3)	174.4 (29.6)	0.27	176.8 (30.9)	0.098	172.1 (27.5)	0.37
GCS (/15)	14 [11, 15]	15 [13, 15]	<0.001	13 [11, 15]	<0.001	14 [11, 15]	<0.001
NIHSS (/42)	17 [11, 20]	10 [5, 16]	<0.001	18 [11, 22]	<0.001	17 [11.5, 20]	<0.001
Previous antiplatelet therapy	266 (36.2)	343 (21.7)	<0.001	216 (36.7)	<0.001	50 (34.5)	<0.001
Previous ischaemic stroke/TIA	134 (18.7)	196 (12.4)	<0.001	105 (18.1)	0.001	29 (20.9)	0.005
Previous ICH	64 (8.8)	61 (3.9)	<0.001	52 (8.9)	<0.001	12 (8.3)	0.011
Ischaemic heart disease	85 (11.9)	118 (7.5)	0.001	68 (11.8)	0.002	17 (12.2)	0.047
Hypertension	451 (62.4)	965 (61.1)	0.56	361 (62.3)	0.60	90 (62.5)	0.75
Diabetes mellitus	106 (14.5)	204 (12.9)	0.28	80 (13.7)	0.63	26 (18.1)	0.082
Atrial fibrillation	24 (3.3)	47 (3.0)	0.66	16 (2.8)	0.79	8 (5.6)	0.081
Onset-CT time (hours)	2.2 (1.2)	2.3 (1.4)	0.006	2.1 (1.1)	0.001	2.4 (1.2)	0.52
Treated with tranexamic acid	349 (47.5)	807 (51.0)	0.11	283 (48.0)	0.21	66 (45.5)	0.20
Raised white cell count	169 (23.6)	250 (16.1)	<0.001	131 (22.9)	<0.001	38 (26.6)	0.001
Glucose (mmol/L)	7.5 (2.7)	7.1 (2.8)	0.003	7.5 (2.7)	0.012	7.6 (2.7)	0.050

Data are number (%), median [interquartile range] or mean (standard deviation). Statistics are t-Student, Mann-Whitney U and Chi-squared test. White cell count of >11.0 $X10^9$/L was considered to be raised. CT=Computed tomography; NIHSS=National Institute of Health Stroke Scale; TIA=transient ischaemic attack

Table 5-3 Baseline and 24-hour CT findings of patients with early, late and no neurological deterioration

Radiological findings	Any neurological deterioration			First deterioration vs no deterioration			
	Yes (n=735)	No (n=1582)	P	Early (n=590)	P	Late (n=145)	P
Baseline CT							
CT available	715 (97.3)	1550 (98.0)		576 (97.6)		139 (95.9)	
Lobar haematoma	315 (43.4)	368 (23.7)	<0.001	260 (44.6)	<0.001	55 (38.5)	<0.001
IVH	339 (46.4)	367 (23.6)	<0.001	272 (46.3)	<0.001	67 (46.9)	<0.001
Haematoma volume (mL)	41.9 (33.7)	15.7 (18.5)	<0.001	42.8 (34.1)	<0.001	38.3 (31.6)	<0.001
IVH volume (mL)	5.5 (11.3)	2.1 (6.3)	<0.001	5.2 (11.2)	<0.001	6.7 (11.7)	<0.001
Subarachnoid extension	175 (24.0)	123 (7.9)	<0.001	150 (25.6)	<0.001	25 (17.5)	<0.001
PHO volume (mL)	21.1 (20.1)	9.1 (10.8)	<0.001	21.8 (20.7)	<0.001	18.7 (17.2)	<0.001
Midline shift ≥5 mm	246 (34.4)	124 (8.0)	<0.001	206 (35.8)	<0.001	40 (28.8)	<0.001
Spot sign positive*	22 (29.7)	33 (19.0)	0.062	18 (32.7)	0.033	4 (21.1)	0.83
Leukoaraiosis	400 (54.9)	654 (41.9)	<0.001	325 (55.5)	<0.001	75 (52.4)	0.015
Old vascular lesion	439 (60.2)	951 (61.0)	0.74	346 (59.0)	0.42	93 (65.0)	0.34
Cerebral atrophy	665 (91.2)	1428 (91.5)	0.80	530 (90.4)	0.42	135 (94.4)	0.23
24-hour CT							
CT available (baseline and 24h)	591 (82.7)	1483 (93.7)		457 (77.5)		134 (92.4)	
Haematoma expansion	308 (52.1)	260 (17.5)	<0.001	269 (58.9)	<0.001	39 (29.1)	0.001
New IVH†	99 (15.5)	80 (5.3)	<0.001	81 (16.2)	<0.001	18 (13.0)	0.001
Change in haematoma volume (mL)	13.3 (24.6)	1.5 (5.9)	<0.001	15.9 (26.8)	<0.001	4.3 (10.8)	0.004
Change in midline shift (mm)	1.9 (4.4)	0.3 (2.7)	<0.001	2.3 (4.6)	<0.001	0.6 (2.9)	0.30
Change in PHO volume (mL)	12.2 (17.9)	4.3 (7.8)	<0.001	13.4 (18.8)	<0.001	7.9 (13.2)	<0.001

Data are number (%) or mean (standard deviation). Statistics are t-Student and Chi-squared test. *Spot sign was based on investigator report; 193 patients had baseline advanced imaging. †Findings of intraventricular haemorrhage on 24-hour CT when the baseline CT did not show any intraventricular haemorrhage. IVH=intraventricular haemorrhage; PHO=perihaematomal oedema

Table 5-4 Multivariable logistic regression analysis for predictors of early and late neurological deterioration

Variables	Any neurological deterioration ≤7 days		Early neurological deterioration		Late neurological deterioration	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Age (years)	1.011 (1.000-1.022)	0.041	1.007 (0.995-1.020)	0.23	1.024 (1.005-1.044)	0.012
Sex (male)	1.07 (0.83-1.37)	0.60	0.97 (0.74-1.27)	0.81	1.47 (0.95-2.28)	0.084
Premorbid modified Rankin Scale (/5)	1.06 (0.94-1.19)	0.38	1.04 (0.91-1.19)	0.54	1.01 (0.82-1.23)	0.96
Systolic blood pressure (mmHg)	1.006 (1.002-1.010)	0.004	1.007 (1.003-1.012)	0.002	1.004 (0.996-1.011)	0.32
NIHSS (/42)	1.04 (1.02-1.06)	<0.001	1.04 (1.02-1.06)	0.001	1.04 (1.00-1.08)	0.027
Onset to CT time (hours)	0.87 (0.79-0.96)	0.007	0.81 (0.72-0.91)	0.001	1.00 (0.85-1.18)	0.99
Previous antiplatelet therapy	1.45 (1.11-1.91)	0.007	1.54 (1.14-2.08)	0.005	1.13 (0.70-1.82)	0.61
Previous intracerebral haemorrhage	2.36 (1.46-3.84)	<0.001	2.49 (1.47-4.22)	0.001	2.73 (1.23-6.04)	0.013
Intraventricular haemorrhage	1.61 (1.24-2.08)	<0.001	1.63 (1.22-2.18)	0.001	1.39 (0.90-2.15)	0.14
Subarachnoid extension	2.04 (1.26-3.29)	0.004	2.39 (1.45-3.95)	0.001	1.41 (0.61-3.24)	0.42
Lobar location	1.35 (0.97-1.87)	0.075	1.55 (1.09-2.21)	0.015	0.86 (0.48-1.55)	0.62
Haematoma volume (per 10 mL increase)	1.26 (1.16-1.37)	<0.001	1.23 (1.13-1.34)	<0.001	1.24 (1.10-1.41)	0.001
PHO volume (per 10 mL increase)	1.09 (0.97-1.23)	0.15	1.12 (0.99-1.27)	0.076	1.07 (0.90-1.28)	0.47
Midline shift ≥5mm	1.59 (1.12-2.25)	0.010	1.62 (1.11-2.37)	0.013	1.32 (0.74-2.36)	0.34
Leukoaraiosis	1.25 (0.96-1.62)	0.096	1.37 (1.03-1.83)	0.031	0.93 (0.60-1.46)	0.77
Raised white cell count (>11.0 $X10^9$/L)	1.00 (0.73-1.37)	0.99	0.97 (0.68-1.37)	0.84	1.05 (0.63-1.76)	0.84
Glucose (mmol/L)	1.03 (1.00-1.08)	0.087	1.03 (0.99-1.07)	0.19	1.04 (0.98-1.11)	0.20

All variables which were significant on univariate analysis were entered into the models.
NIHSS=National Institute of Health Stroke Scale; PHO=perihaematomal oedema.

Multivariable logistic regression analysis showed that age, systolic blood pressure, NIHSS, previous antiplatelet therapy, previous ICH, onset to CT time, baseline haematoma volume, midline shift, intraventricular haemorrhage and subarachnoid extension independently predicted neurological deterioration within the first 7 days (Table 5-4). The strongest predictor of neurological deterioration was previous ICH with an adjusted odds ratio (aOR) of 2.36 (95%CI [confidence interval] 1.46-3.84; p<0.001). An increase in 10 mL of baseline haematoma volume increased the aOR by 1.26. The predictors of early neurological deterioration (<48 hours) were similar to those of any neurological deterioration within 7 days with the exception of age, which was not significant; and lobar location and leukoaraiosis, which were significant predictors of early neurological deterioration (Table 5-4). The predictors of late neurological deterioration were older age, previous intracerebral haemorrhage, higher NIHSS and larger baseline haematoma volume (Table 5-4). CT angiography spot sign was not included in the analysis as only 193 (8.3%) of enrolled patients had CTA.

Neurological deterioration events were reported as serious adverse events in 660 (89.8%) with 75 (10.2%) unreported. A full list of SAEs that resulted in neurological deterioration is given in Table 5-5. In the first 48 hours, the majority of the neurological deterioration (499, 84.6%) was thought to be caused by a cerebral event, where haematoma expansion (256, 43.4%) was the most common cause. Only 6.6 % (n=39) of early neurological deterioration was attributed to non-cerebral events. A majority of neurological deterioration between 48 hours up to 7 days were attributed to a cerebral event (79, 54.5%), but of these only 11.7% were haematoma expansion. More than one-fifth (33, 22.8%) of late neurological deterioration was attributed to medical complications. The commonest medical complication was pneumonia, accounting for 51 (6.9%) of neurological deterioration. In 166 (22.6%) patients with neurological deterioration, the cause was non-specific, classified as neurological deterioration and complication of initial stroke in 152 (20.7%) and 14 (1.9%) respectively (Table 5-5).

Table 5-5 Serious adverse event classification of early and late neurological deterioration

Serious adverse event classification	**END (n=590)**	**LND (n=145)**	**TND (n=119)**	**Total (n=735)**
Not reported	47 (8.0)	28 (19.3)	19 (16.0)	75 (10.2)
Not serious adverse event	5 (0.8)	4 (2.8)	2 (1.7)	9 (1.2)
Not relevant, > 7days	-	1 (0.7)	-	1 (0.1)
Cerebral events	499 (84.6)	79 (54.5)	88 (73.9)	578 (78.6)
Expansion of haemorrhagic stroke	256 (43.4)	17 (11.7)	45 (37.8)	273 (37.1)
Neurological deterioration (Cause not specified)	127 (21.5)	25 (17.2)	18 (15.1)	152 (20.7)
Cerebral oedema	41(6.9)	16 (11.0)	10 (8.4)	57 (7.8)
Hydrocephalus	29 (4.9)	6 (4.1)	8 (6.7)	35 (4.8)
Seizure	20 (3.4)	8 (5.8)	2 (1.7)	28 (3.8)
Complication of initial stroke (Cause not specified)	11 (1.9)	3 (2.1)	1 (0.8)	14 (1.9)
Sedation	6 (1.1)	1 (0.7)	2 (1.7)	7 (1.0)
Recurrent intracerebral haemorrhage	4 (0.7)	-	1 (0.8)	4 (0.5)
Ischaemic stroke	3 (0.5)	2 (1.4)	1 (0.8)	5 (0.7)
Transient ischaemic attack	-	1 (0.7)	-	1 (0.1)
Stroke undetermined	1 (0.2)	-	-	1 (0.1)
Loss of consciousness	1 (0.2)	-	-	1 (0.1)
Non-cerebral events	39 (6.6)	33 (22.8)	10 (8.4)	72 (9.8)
Pneumonia/chest infection/LRTI	29 (4.9)	22 (15.1)	6 (5.0)	51 (6.9)
STEMI/NSTEMI	2 (0.4)	-	-	2 (0.3)
Pulmonary embolism	1 (0.2)	1 (0.7)	-	2 (0.3)
Infection (not otherwise specified)	1 (0.2)	1 (0.7)	1 (0.8)	2 (0.3)
Urinary tract infection	1 (0.2)	2 (1.4)	1 (0.8)	3 (0.4)
Exacerbation of COPD	1 (0.2)	-	-	1 (0.1)
Fall	1 (0.2)	-	-	1 (0.1)
Fatigue	1 (0.2)	-	1 (0.8)	1 (0.1)
Hypotension	1 (0.2)	-	1 (0.8)	1 (0.1)
Alcohol withdrawal	1 (0.2)	1 (0.7)	-	2 (0.3)
Malignancy	-	2 (1.4)	-	2 (0.3)
Cardiac failure/pulmonary oedema	-	2 (1.4)	-	2 (0.3)
Electrolyte imbalance	-	1 (0.7)	-	1 (0.1)
Anaemia	-	1 (0.7)	-	1 (0.1)

COPD=chronic obstructive pulmonary disease; END= early neurological deterioration; LND= late neurological deterioration; LRTI=lower respiratory tract infection; STEMI/NSTEMI=ST elevation myocardial infarction/Non-ST elevation myocardial infarction

Tranexamic acid significantly reduced the risk of neurological deterioration ≤ 7 days (aOR 0.75, 0.60-0.94; p=0.013) and early neurological deterioration (aOR 0.75, 0.59-0.96; p=0.022) but not late neurological deterioration (Table 5-6). Tranexamic acid reduced the risk of haematoma expansion (aOR 0.77, 0.63-0.94; p=0.011) but not oedema growth. There was no significant difference in reported cerebral and non-cerebral events between the treatment groups (Table 5-6).

Table 5-6 Effect of tranexamic acid on haematoma and oedema growth and neurological deterioration

	Tranexamic acid	Placebo	MD/OR 95%CI	P
Neurological deterioration[*]				
All ≤7 days	338 (29.1)	366 (31.4)	0.75 (0.60, 0.94)	0.013
Early (<48 hours)	275 (23.7)	291 (25.0)	0.75 (0.59, 0.96)	0.022
Late (48 hours to 7 days)	63 (7.1)	75 (8.6)	0.73 (0.49, 1.09)	0.13
SAE with neurological deterioration ≤7 days[†]				
Cerebral events	274 (23.6)	304 (26.1)	0.87 (0.72, 1.06)	0.16
Non-cerebral events	33 (2.8)	39 (3.4)	0.84 (0.53, 1.35)	0.48
Radiological outcomes[‡]				
Haematoma expansion	265 (25.5)	305 (29.3)	0.77 (0.63, 0.94)	0.011
PHO growth (mL)	6.8 (11.8)	6.6 (12.7)	-0.12 (-1.10, 0.87)	0.82

Haematoma expansion was defined as an increase in haematoma volume of >33% or >6mL on follow-up scan compared to baseline. Perihaematomal oedema (PHO) growth is the absolute difference in PHO volume between follow-up and baseline scans. [*]Adjusted for age, sex, premorbid modified Rankin Scale, systolic blood pressure, previous antiplatelet therapy, previous ICH, National Institute of Health Stroke Scale, onset to CT time, intraventricular haemorrhage, lobar location, baseline haematoma and oedema volumes. [†]Unadjusted analysis [‡]Adjusted for all variables in neurological deterioration[*] with exception of previous intracerebral haemorrhage and baseline perihaematomal oedema volume. MD=mean difference; OR=odds ratio; SAE=serious adverse event

There were significant differences in the management of patients with neurological deterioration and no neurological deterioration. Patients who had neurological deterioration were more likely to be issued do not attempt resuscitation (DNAR) order, intubated, undergo neurosurgical procedures and intensive care unit admission (Table 5-7). 24.5% of patients with neurological deterioration were not receiving any antihypertensive agents at day 7 compared to 13.5% in patients with no neurological deterioration ($p<0.001$).

Table 5-7 Management of patients with neurological deterioration vs no neurological deterioration

Management	Neurological deterioration	No neurological deterioration	P
No antihypertensive agent, day 7	178 (24.5)	213 (13.5)	<0.001
DNAR, day 2	282 (38.4)	110 (6.9)	<0.001
DNAR, day 7	609 (50.2)	140 (8.8)	<0.001
Neurosurgery, day 7	97 (13.2)	24 (1.5)	<0.001
ICU admission, day 7	165 (22.4)	67 (4.2)	<0.001
Intubation, day 7	141 (19.2)	25 (1.6)	<0.001

Analyses are Chi-squared test. CT=computed tomography; DNAR=do not attempt resuscitation; ICU= intensive care unit

Neurological deterioration increased the risk of early death by 33 times and death at day 90 by 7.7 times and death or dependency by 4.8 times (Table 5-8). Early and late neurological deteriorations were similarly associated with higher risk of death at day 7 and day 90 and death or dependency at day 90 (Table 5-9 and 5-10). Neurological deterioration, whether early or late, resulted in worse Barthel Index, cognition, depression and quality of life scores compared to patients with no neurological deterioration (Table 5-8, 5-9 and 5-10).

Table 5-8 Effect of neurological deterioration on day 90 outcome

Outcomes	Neurological deterioration	No neurological deterioration	OR/MD 95% CI*	P
Day 7, death	214 (29.1)	9 (0.6)	33.74 (16.82, 67.69)	<0.001
Day 90				
Death	380 (52.0)	117 (7.5)	7.69 (5.75, 10.29)	<0.001
mRS>3	636 (87.0)	618 (39.4)	4.78 (3.55, 6.44)	<0.001
Barthel Index	17.5 (34.7)	69.9 (37.2)	-28.8 (-31.7, -26.0)	<0.001
EQ5D HUS	0.09 (0.27)	0.46 (0.39)	-0.19 (-0.23, -0.16)	<0.001
TICS	2.1 (8.0)	20.1 (10.0)	-9.8 (-10.8, -8.7)	<0.001
ZDS	93.6 (21.7)	53.6 (23.5)	21.3 (18.6, 24.1)	<0.001

*Adjusted for age, sex, premorbid modified Rankin Scale, previous antiplatelet therapy, National Institute of Health Stroke Scale, systolic blood pressure, onset to CT time, baseline haematoma volume, intraventricular haemorrhage and lobar location. EQ5D HUS=EuroQoL-5D Health Utility Scores; MD=mean difference; mRS=modified Rankin Scale; OR= odds ratio; TICS=Telephone Interview Cognitive Status; ZDS= Zung Depression Scale

Table 5-9 Effect of early neurological deterioration on day 90 outcome

Outcomes	Early Neurological deterioration	No neurological deterioration	OR/MD 95% CI*	P
Day 7, death	196 (33.2)	9 (0.6)	41.69 (20.68, 84.05)	<0.001
Day 90				
Death	315 (53.8)	117 (7.5)	8.21 (6.01, 11.20)	<0.001
mRS>3	513 (87.5)	618 (39.4)	4.93 (3.54, 6.85)	<0.001
Barthel Index	16.5 (34.0)	69.9 (37.2)	-28.9 (-32.0, -25.9)	<0.001
EQ5D HUS	0.08 (0.27)	0.46 (0.39)	-0.19 (-0.23, -0.16)	<0.001
TICS	1.9 (7.8)	20.1 (10.0)	-9.7 (-10.8, -8.5)	<0.001
ZDS	94.1 (21.0)	53.6 (23.5)	21.4 (18.4, 24.3)	<0.001

*Adjusted for age, sex, premorbid modified Rankin Scale, previous antiplatelet therapy, National Institute of Health Stroke Scale, systolic blood pressure, onset to CT time, baseline haematoma volume, intraventricular haemorrhage and lobar location. EQ5D HUS=EuroQoL-5D Health Utility Scores; MD=mean difference; mRS=modified Rankin Scale; OR= odds ratio; TICS=Telephone Interview Cognitive Status; ZDS= Zung Depression Scale

Table 5-10 Effect of late neurological deterioration on day 90 outcome

Outcomes	Late neurological deterioration	No neurological deterioration	OR/MD 95% CI*	P
Day 7, death	18 (12.4)	9 (0.6)	11.00 (4.34, 27.81)	<0.001
Day 90				
Death	65 (44.8)	117 (7.5)	6.12 (3.85, 9.72)	<0.001
mRS>3	123 (84.8)	618 (39.4)	3.95 (2.27, 6.88)	<0.001
Barthel Index	21.8 (37.4)	69.9 (37.2)	-24.4 (-29.4, -19.5)	<0.001
EQ5D HUS	0.12 (0.29)	0.46 (0.39)	-0.14 (-0.20, -0.08)	<0.001
TICS	2.9 (8.8)	20.1 (10.0)	-8.2 (-10.1, -6.3)	<0.001
ZDS	91.0 (24.6)	53.6 (23.5)	18.5 (13.6, 23.4)	<0.001

*Adjusted for age, sex, premorbid modified Rankin Scale, previous antiplatelet therapy, National Institute of Health Stroke Scale, systolic blood pressure, onset to CT time, baseline haematoma volume, intraventricular haemorrhage and lobar location. EQ5D HUS=EuroQoL-5D Health Utility Scores; MD=mean difference; mRS=modified Rankin Scale; OR= odds ratio; TICS=Telephone Interview Cognitive Status; ZDS= Zung Depression Scale

Of the 590 patients with early neurological deterioration, 119 (20.2%) had transient neurological deterioration, 102 (17.3%) had further neurological deterioration, 179 (30.3%) neurologically stable and 190 (32.2%) did not have a repeat assessment. 157 (82.6%) of patients who did not have a repeat assessment had died in the first 7 days. Table 5-11 describes the baseline characteristics, outcomes and management in patients with early neurological deterioration according to subsequent neurological status. Patients who had further deterioration after an early neurological deterioration, were older, had more severe stroke with larger haematoma volume. At 24-hour, there was greater absolute haematoma growth, haematoma expansion rate and oedema growth in patients who had further deterioration compared to those who were stable or improving. There was a higher proportion of death at day 7 and DNAR order in patients who did not have a repeat assessment. There was no significant difference in treatment with neurosurgical procedure or tranexamic acid between transient neurological deterioration compared to those with stable and deteriorating neurological status. The most common cause of transient neurological deterioration was haematoma expansion (n=45, 37.8%). 74% of transient neurological deteriorations were attributed to a cerebral event (Table 5-5). We performed multivariable logistic regression with adjustment of key prognostic factor (as used in Table 5-8, 5-9 and 5-10) exploring the effect of transient neurological deterioration on day 90 outcome compared to those

with no neurological deterioration. Patients who underwent neurosurgery were excluded from this analysis. Transient neurological deterioration increased the risk of poor functional outcome (aOR 2.37, 1.31-4.27; p=0.004) but not death (aOR 1.31, 0.67-2.56; p=0.43) at day 90 compared to patients with no neurological deterioration.

Table 5-11 Baseline characteristics, outcomes and management in patients with early neurological deterioration according to subsequent neurological status

Characteristics	Stable (n=179, 30.3%)	Deterioration (n=102, 17.3%)	TND (n=119, 20.2%)	Not assessed (n=190, 32.2%)	P
Age	72.0 (13.4)	73.3 (12.9)	69.8 (14.7)	74.0 (12.6)	0.053
Sex	92 (51.4)	57 (55.9)	60 (50.4)	91 (47.9)	0.63
mRS	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 2]	0.052
NIHSS	15 [9, 20]	18 [11, 22]	17 [11, 21]	20 [15, 23.25]	<0.001
GCS	14 [12,15]	14 [10.75, 15]	13 [11,15]	10 [12, 14]	0.001
Haematoma volume	34.9 (27.4)	48.1 (34.3)	30.6 (27.3)	54.9 (38.9)	<0.001
PHO volume	18.0 (15.4)	24.9 (22.8)	17.2 (19.2)	26.7 (23.4)	<0.001
Lobar location	85 (47.8)	50 (49.5)	39 (33.6)	86 (45.7)	0.059
IVH	73 (40.8)	42 (41.2)	41 (43.6)	106 (56.1)	0.012
Outcomes					
Absolute haematoma growth (mL)	12.9 (20.9)	16.3 (26.4)	6.4 (12.1)	28.1 (37.3)	<0.001
Haematoma expansion	87 (56.1)	52 (59.1)	49 (49.0)	81 (71.1)	0.009
Absolute PHO growth (mL)	12.8 (17.4)	16.1 (20.6)	7.8 (14.5)	17.2 (21.4)	0.001
Day 7 death	11 (6.1)	28 (27.5)	0 (0)	157 (82.6)	<0.001
Management					
Tranexamic acid	90 (50.3)	46 (45.1)	58 (48.7)	89 (46.8)	0.84
No antihypertensive agent, day 7	38 (21.2)	29 (28.4)	16 (13.4)	71 (38.8)	<0.001
DNAR, day 2	51 (28.5)	33 (32.4)	25 (21.0)	142 (74.7)	<0.001
DNAR, day 7	68 (38.0)	58 (56.9)	36 (30.3)	154 (81.1)	<0.001
Neurosurgery, day 7	28 (15.6)	15 (14.7)	21 (17.6)	19 (10.1)	0.25
ICU admission, day 7	43 (24.0)	26 (25.5)	26 (21.8)	35 (18.6)	0.50
Intubation, day 7	33 (18.4)	24 (23.5)	24 (20.2)	33 (17.7)	0.66

Data are mean (standard deviation), median [interquartile range] or number (%). Statistics are Chi-Squared, Kruskal Wallis and one-way ANOVA tests. DNAR=do not attempt resuscitation; GCS=Glasgow Coma Scale; ICU=intensive care unit; IVH=intraventricular haemorrhage; mRS= modified Rankin Scale; NIHSS=National Institute of Health Stroke Scale; PHO=perihaematomal oedema; TND=transient neurological deterioration

5.1.6 Discussion

Significant predictors of early neurological deterioration were higher SBP, higher NIHSS, previous ICH, antiplatelet therapy, shorter onset to CT time, intraventricular haemorrhage, subarachnoid extension, lobar location, larger haematoma volume, midline shift and leukoaraiosis. Older age, higher NIHSS, previous ICH larger haematoma volume predicted late neurological deterioration. This is in agreement with previous findings, where patients with more severe stroke and larger haematoma were more likely to suffer from neurological deterioration.[71, 75, 79,458, 470]

Several predictors of neurological deterioration, i.e. baseline haematoma volume, antiplatelet therapy and shorter onset to CT time were also known predictors of haematoma expansion.[102] In addition, haematoma expansion was more than 3 times more common in patients with early neurological deterioration compared to those with no neurological deterioration (58.9% vs 17.5%). Patients with no neurological deterioration had minimal change in haematoma volume (1.5 mL) at 24 hours while the absolute increase in haematoma volume was significantly greater in patients with neurological deterioration (13 mL). We did not include haematoma expansion in the logistic regression model for predictor for neurological deterioration, as it was not a baseline variable. Several studies found haematoma expansion to be significantly associated with neurological deterioration.[75, 79, 86] On the other hand, one meta-analysis concluded that haematoma expansion was not a significant predictor of neurological deterioration.[458] However, there was significant heterogeneity in the two studies included in the meta-analysis. Both studies were relatively small and showed wide confidence interval in estimate for haematoma expansion as a risk for neurological deterioration.[86, 471] In fact, both studies reported significant association between haematoma expansion and neurological deterioration.

Intraventricular and subarachnoid haemorrhages may be associated with complications of hydrocephalus or inflammation, contributing to neurological deterioration.[472, 473] In addition, leukoaraiosis may be linked to endothelial

dysfunction and lacunar infarction, leading to worsening neurological status.[474, 475] Association of subarachnoid extension and leukoaraiosis with early neurological deterioration was similarly described in the INTERACT-2 trial.[470]

Elevated D-dimer levels were reported to be associated with neurological deterioration.[458, 476, 477] D-dimer is a fibrin degradation product and this indirectly suggests that fibrinolysis may play a role in haematoma expansion and neurological deterioration. In the current study, tranexamic acid, an antifibrinolytic agent, had a modest effect in reducing haematoma expansion at 24 hour and early but not late neurological deterioration. Tranexamic acid did not have any significant effect on early oedema growth within the first 24 hours. PHO continues to grow up to the 2nd or 3rd week[478] after ICH but this was not studied in our cohort as we only performed follow-up CT scans at 24 hours.

Approximately one-fifth of neurological deterioration was assigned as non-specific classification of “neurological deterioration” or “complication of initial stroke” due to uncertainties in diagnosis. These cerebral events could be caused by haematoma expansion, hydrocephalus, intraventricular haemorrhage or even cerebral oedema. The uncertainties in diagnosis is perhaps unsurprising as 17% of patients with neurological deterioration did not have a follow-up CT scan. Most previous studies on neurological deterioration aimed at identifying baseline predictors of neurological deterioration rather than finding a definitive cause.[71, 75, 79] This highlight the needs for research to better understand the events leading to neurological deterioration.

One other important observation is that a significant proportion of neurological deterioration was caused by medical complications such as pneumonia. Despite prevention strategies such as dysphagia screening, pneumonia is still a significant problem after stroke and ICH.

Both early and late neurological deteriorations were associated with significantly higher risk of early death and death at day 90. The risk of death and dependency, disability, quality of life, cognitive and depression scores were all significantly worse in patients with early and late neurological deterioration. Interestingly, neurological deterioration was transient in about one-fifth of patients with early neurological deterioration. Lower haematoma expansion rate, absolute haematoma volume growth and oedema growth could have contributed to improvement. However, higher haematoma expansion rate in patients who deteriorated further could also be explained by a larger baseline haematoma volume, which is a risk factor for haematoma expansion. There was no significant difference in processes of care in patients with transient neurological deterioration compared to those with stable or worsening neurological status. Similar to ischaemic stroke[467], early neurological deterioration, even when transient, was associated with poor functional outcome. However, the risk of death at day 90 in patients with transient neurological deterioration was not increased compared to those with no neurological deterioration.

The strength of our study is a large sample size. Using an inclusive definition, we were able to determine if neurological deterioration occurred in almost all patients. We attempted to describe the causes of neurological deterioration using the SAE reports. However, we were limited by loss of data in one-tenth of neurological deterioration where an SAE was not reported. There were difficulties in attributing a cause in one-fifth of neurological deterioration. Although the overall availability of CT scans was good, in patients who suffered from early neurological deterioration, nearly one quarter did not have a follow-up scan. We also did not have routine neuroimaging beyond 24 hours, making the assessment of late neurological deterioration suboptimal. We attempted to describe subsequent neurological status after early neurological deterioration though this was limited by one-third of the patients not having further assessment as a large proportion of them had died.

In conclusion, tranexamic acid reduced the risk of early neurological deterioration, probably through reduction of haematoma expansion. Better

prevention and management of medical complication may also reduce the risk of neurological deterioration. More studies are needed to understand the mechanisms leading to neurological deterioration.

5.2 Incidence and predictors of early and late seizures in intracerebral haemorrhage

5.2.1 Publication contributing to this chapter

Law ZK, Flaherty K, Appleton JP, Scutt P, England T, Bath PB, Sprigg N. Incidence, risk factors and outcomes of seizures in intracerebral haemorrhage: interim analysis from the TICH-2 trial. UK Stroke Forum Abstracts. International Journal of Stroke 2017, Vol. 12(5S) 7–59. DOI: 10.1177/1747493017732216

5.2.2 Abstract

5.2.2.1 Background

Early seizures (ES, ≤7 days) and late seizures (LS, >7 days) after intracerebral haemorrhage may have different risk factors and effects on outcome. We explored the risk factors and outcomes of ES and LS after intracerebral haemorrhage in ongoing the Tranexamic acid for IntraCerebral Haemorrhage-2 (TICH-2) trial. In addition, we explored if tranexamic acid increased the risk of seizures.

5.2.2.2 Methods

Seizures were reported prospectively up to day 90 as a safety outcome in the TICH-2 trial. Chi-squared (categorical), t-Student and Mann Whitney U tests (continuous) were used to compare baseline characteristics. Outcomes of patients with and without seizures were compared using logistic regression adjusting for age, premorbid modified Rankin Scale (mRS), Glasgow Coma Scale (GCS) and National Institute of Health Stroke Scale (NIHSS).

5.2.2.3 Results

Of 2325 patients recruited, 193 (8.3%) had seizures. Early seizures comprised 84.5% (n=163) of seizures, including 66 (34.2%) within 24 hours, median onset-to-seizure time was 31.5 [IQR 9.25, 91.75] hours. Younger age (adjusted odds ratio [aOR] 0.98 per year increase, 95% confidence interval [CI] 0.96-0.99; p=0.006), lobar haematoma (aOR 6.76, 95%CI 4.01-11.38;

p<0.001) higher NIHSS (aOR 1.033, 95%CI 1.005-1.060; p=0.018) and prior stroke (aOR 1.71, 95%CI 1.11-2.63; p=0.015) predicts early seizures while premorbid mRS (aOR 1.56, 95%CI 1.14-2.13; p=0.006) and lobar haematoma (aOR 2.63, 95%CI 1.02-6.84; p=0.047) predicts late seizures. Early seizures were associated with worse mRS (aOR 1.89, 95%CI 1.19-3.01, p=0.007) and increased deaths (aOR 2.66, 95%CI 1.70- 4.14; p<0.001) at day 90. LS were not associated with worse functional outcome.

5.2.2.4 Conclusion

Lobar haematoma predicts both early and late seizures. Early seizures resulted in worse functional outcome and death. Tranexamic acid did not increase the risk of early or late seizures.

5.2.3 Background

Seizures occur in approximately 4 to 14% of patients with acute intracerebral haemorrhage (ICH).[26-32] The incidence of seizure is approximately 30% when subclinical seizures or non-convulsive seizure are diagnosed by continuous electroencephalogram (EEG).[135, 136] The pathophysiological mechanisms of early seizures were thought to be related to the irritative effect of haemosiderin and thrombin as well as excitotoxicity caused by increased glutamate and decreased GABA.[479, 480] The pathophysiological mechanisms of late-onset seizures are not well understood. In line with mechanisms underlying post-ischaemic stroke epilepsy, reorganisation of neural network, white matter and vascular endothelium may play a role.[481] Studies revealed that cerebral small vessel disease increased the risk of late onset seizures, which support the hypothesis that progressive neuronal and white matter damage due to small vessel disease may have amplified epileptogenic processes in ICH.[138] On the other hand, cerebral small vessel disease increases in the risk of seizure in people without ICH and therefore may be a confounder.[482]

Younger age, lobar haematoma, stroke severity and haematoma expansion had been identified as risk factors for early seizures after intracerebral

haemorrhage.[26, 30, 136] In patients with early seizures, larger haematoma and intraventricular haemorrhage volume, lobar location and lower GCS increased the risk of recurrent seizures beyond 7 days.[124] Similarly cortical involvement, younger age and larger haematoma volume increased the risk of late-onset seizures.[138, 139] In addition, previous lobar ICH, pre-ICH dementia, presence of white matter disease on neuroimaging and APOE ε4, which suggest underlying cerebral small vessel disease and/or cerebral amyloid angiopathy are known risk factors as well.[138, 139]

In non-ICH patients, seizure is a known complication of tranexamic acid with an estimated incidence of 2.7%.[382] It increases the risk of seizure by approximately five times (pooled OR 5.39, 95% CI 3.29-8.85; $I^2 = 0\%$; $p< 0.001$).[382] A recent trial of tranexamic acid in cardiac surgery reported even higher risk of seizures with a relative risk 7.6 (0.7% had seizure in tranexamic acid group compared to 0.1% in placebo).[355] Tranexamic acid acts directly to increase the excitability of the neural network by inhibiting Aminobutyric acid type A ($GABA_A$) and glycine receptors, both major mediators of inhibition in the central nervous system (CNS).[483, 484] However, as most studies reporting seizures in people treated with tranexamic acid involved patients who underwent cardiac surgery, it is unclear whether tranexamic acid increases the risk of seizures in patients with ICH.

The impact of seizures on outcomes in ICH is debatable as well. Several studies reported an increased in-patient and 30-day mortality rate of two to three times in patients with seizures compared to those with no seizures.[135, 140, 141] Others found no differences in mortality amongst patients with and without seizures.[30] Paradoxically, several studies found that seizures independently decreased morbidity and mortality in patients with ICH.[142, 485] Bruning *et al* and Mehta *et al* both found patients with early seizures to have less severe neurological deterioration and less altered consciousness level at presentation, hence the lower mortality rates.[142, 485] EEG was not routinely performed in both studies and it is possible that patients who had severe ICH had subclinical or non-motor seizures but were not diagnosed to have seizures.[142, 485]

5.2.4 Methods

Given the uncertainties with regards to post-ICH seizures highlighted above, we aimed to explore the risk factors for early and late seizures after ICH and whether administration of tranexamic acid increased the risk of seizure. Secondly, we aim to examine the effect of post-ICH seizure on functional outcomes.

5.2.4.1 Definitions

Early seizure (ES) was defined as occurrence of seizure(s) within 7 days from the onset of ICH. [486] Late seizure was defined as an occurrence of seizure(s) after 7 days from the onset of ICH.[486] Recurrence of early seizures refers to seizures that first occurred within the first seven days of ICH but recurred after seven days. As seizure is a pre-specified safety outcome, reporting of seizure(s) by site investigators as an SAE is mandatory up to 90 days from the onset. The SAE reports were adjudicated by independent assessors blinded to treatment allocation, based on clinical and diagnostic information provided by site investigators

5.2.4.2 Statistical analysis

Descriptive analysis was performed to describe the baseline characteristics of patients who had early seizure, late seizure and no seizure using Mann-Whitney U, Chi-squared and t-Student test where appropriate. Multivariable logistic regression was performed to identify predictors of early and late seizure in our cohort, including treatment allocation as a variable. Multivariable logistic regression analysis was also used to explore the effect of seizure(s) on outcomes, including death, dependency, length of stay, neurological deterioration, quality of life, disability, cognition and depression.

5.2.5 Results

Of 2325 patients recruited, 193 (8.3%) had seizures. Early seizures comprised 84.5% (n=163) of seizures, including 79 (41.1%) within 24 hours and 31 (16.1%) within 6 hours of onset. Late seizures comprised 15.5% (n=30) of all seizures. Median onset-to-seizure time was 31.5 hours [IQR

9.25, 91.75]. 85 (44.0%) had a single episode of seizure, 79 (40.9%) had multiple episodes of seizures and in 29 (15%) patients data on number of seizure episodes were not available. Investigators reported seizure semiology included generalised tonic-clonic (n=34, 17.6%), complex partial (52, 26.9%), simple partial (20, 10.4%), absence (3, 1.6%), status epilepticus (5, 2.6%) and non-specific description (76, 39.4%). Examples of non-specific descriptions include patient had a “fit”, “seizure”, “twitching” or “jerky movement” without specifying body parts involved. In 3 (1.6%), investigators were unsure if seizure occurred or if there was an alternative diagnosis. Electroencephalography (EEG) were reportedly performed in 10 (5.2%) but findings were available only in 7 (3.6%) where 6 EEG showed electrographic evidence of seizure and one did not show any epileptiform activities. It was not known if the other patients have had EEG done.

Patients with early seizures were more likely to have worse premorbid modified Rankin Scale, previous ischaemic stroke and intracerebral haemorrhage as well as more severe impairment (higher NIHSS and lower GCS). Late seizures were associated with female sex, worse modified Rankin scale and previous ICH (Table 5-12).

Patients with any seizure, early seizures and late seizures were more likely to have larger, lobar haematoma and midline shift (Table 5-13). Periventricular leukoaraiosis was more common in patients with any seizures compared to those with no seizures. On 24-hour CT scans, patients with any seizures and early seizures had more haematoma expansion, intraventricular extension and oedema growth, while these were not more common in patients with late seizure compared to those with no seizures (Table 5-13).

On logistic regression analysis, lobar location was the strongest predictor of any seizure with adjusted odds ratio [aOR] of 5.54 (95% CI [confidence interval] 3.42-9.00; $p<0.001$). Other significant predictors include younger age, higher NIHSS and previous ischaemic stroke (Table 5-14). Larger haematoma volume was not a significant predictor. Predictors of early seizures were similar with lobar location as the strongest predictor (aOR

6.76, 4.01-11.38; p<0.001) and younger age, higher NIHSS and previous ischaemic stroke as significant predictors (Table 5-15). As for late seizures, only lobar location 2.63 (1.02-6.84), p=0.047 and worse premorbid Rankin Scale were significant predictors (Table 5-16).

Table 5-12 Clinical characteristics of patients with and without seizures

Characteristics	Any seizure			First seizure vs no seizure			
	Yes (n=193, 8.3%)	No (n=2132, 91.7%)	P	Early seizure (n=163, 7.0%)	P	Late seizure (n=30, 1.3%)	P
Age, years	69.3 (13.3)	68.9 (13.9)	0.68	69.0 (13.3)	0.90	70.8 (13.4)	0.44
Sex, male	96 (49.7)	1205 (56.5)	0.069	85 (52.1)	0.28	11 (36.7)	0.030
Premorbid mRS	0 [0, 1]	0 [0, 1]	0.001	0 [0, 1]	0.011	0 [0, 3]	0.003
Systolic blood pressure	172.8 (30.8)	175.0 (29.7)	0.34	173.7 (31.0)	0.60	167.9 (30.0)	0.20
Glasgow Coma Scale	14 [11, 15]	15 [12, 15]	0.001	14 [11, 15]	0.004	14 [11, 15]	0.12
NIHSS	15 [8.5, 20]	12 [6, 18]	0.001	16 [8, 20]	0.001	13 [8.75, 20]	0.21
Prior antiplatelet	58 (30.1)	553 (26.0)	0.22	51 (31.3)	0.14	7 (23.3)	0.75
Prior stroke/TIA	42 (22.0)	288 (13.6)	0.002	35 (21.6)	0.005	7 (24.1)	0.10
Prior ICH	19 (9.9)	107 (5.0)	0.005	15 (9.3)	0.021	4 (13.3)	0.041
Prior IHD	22 (10.8)	181 (8.6)	0.17	18 (11.1)	0.27	4 (13.8)	0.32
Hypertension	111 (58.1)	1310 (61.8)	0.31	97 (59.9)	0.62	14 (48.3)	0.14
Diabetes mellitus	26 (13.5)	286 (13.4)	0.97	20 (12.3)	0.69	6 (20.0)	0.30
Atrial fibrillation	6 (3.1)	65 (3.1)	0.95	6 (3.7)	0.64	0 (0)	0.33
Onset-CT time (hours)	2.4 (1.3)	2.3 (1.3)	0.15	122 (74.8)	0.38	19 (63.3)	0.10
Tranexamic acid	91 (47.2)	1070 (50.2)	0.42	76 (46.6)	0.38	15 (50.0)	0.98

Data are number (%), mean (standard deviation) or median [interquartile range]. Statistics are Chi-squared, t-Student and Mann-Whitney U tests. ICH=intracerebral haemorrhage; IHD=ischaemic heart disease; mRS= modified Rankin Scale; NIHSS=National Institute of Health Stroke Scale; TIA=transient ischaemic attack

Table 5-13 Baseline and 24-hour CT findings in patients with and without seizures

Characteristics	Any seizure			First seizure vs no seizure			
	Yes (n=193, 8.3%)	No (n=2132, 91.7%)	P	Early seizure(n=163, 7.0%)	P	Late seizure (n=30, 1.3%)	P
Baseline CT							
Haematoma location							
Lobar	106 (55.8)	582 (27.8)	<0.001	90 (55.6)	<0.001	16 (57.1)	0.001
Deep	78 (41.1)	1373 (65.6)	<0.001	68 (42.0)	<0.001	10 (35.7)	0.001
Infratentorial	6 (3.2)	139 (6.6)	0.060	4 (2.5)	0.036	2 (7.1)	0.92
Intraventricular haemorrhage	66 (34.7)	641 (30.5)	0.22	55 (34.0)	0.35	11 (39.3)	0.31
Haematoma volume (mL)	33.2 (31.4)	23.1 (26.6)	<0.001	32.5 (31.7)	<0.001	36.8 (30.2)	0.028
Perihaematomal oedema volume (mL)	15.8 (15.3)	12.7 (15.5)	0.011	15.3 (14.5)	0.048	18.8 (19.5)	0.12
Midline shift (mm)	5.9 (2.5)	5.9 (2.8)	0.78	2.3 (3.2)	0.88	3.4 (3.8)	0.31
Midline shift ≥5 mm	44 (23.5)	327 (15.7)	0.005	35 (21.9)	0.040	9 (33.3)	0.007
Old infarct(s)	114 (60.0)	1279 (60.7)	0.85	93 (57.4)	0.41	21 (75.0)	0.12
Cerebral atrophy	178 (93.7)	1921 (91.2)	0.24	151 (93.2)	0.38	27 (96.4)	0.33
Periventricular leukoaraiosis	101 (52.3)	957 (44.9)	0.040	84 (51.9)	0.11	17 (60.7)	0.11
24- hour CT							
Haematoma expansion	55 (34.8)	513 (26.4)	0.031	47 (35.1)	0.038	8 (32.0)	0.48
Absolute haematoma growth (mL)	7.6 (18.2)	4.7 (14.7)	0.052	8.4 (19.2)	0.036	3.8 (10.1)	0.76
Absolute oedema growth (mL)	9.7 (16.6)	6.4 (11.8)	0.014	10.6 (16.9)	0.005	5.1 (14.9)	0.59
Intraventricular haemorrhage extension*	26 (15.1)	154 (7.8)	0.003	21 (14.5)	0.013	5 (18.5)	0.095
Change in midline shift (mm)	0.8 (4.2)	1.2 (3.7)	0.48	1.0 (4.3)	0.79	0.0 (3.6)	0.26

Data are number (%) or mean (standard deviation). Statistics are Chi-squared and t-Student tests. *Intraventricular haemorrhage extension was present if intraventricular haemorrhage was present on 24-hour CT but not on baseline CT.

Table 5-14 Unadjusted and adjusted binary logistic regression analysis of predictors of any seizure

Variables	Unadjusted OR (95%CI)	P	Adjusted OR (95%CI)*	P
Age (years)	1.00 (0.99-1.01)	0.68	0.98 (0.96-0.99)	0.002
Sex (male)	0.76 (0.57-1.02)	0.070	0.95 (0.68-1.32)	0.76
Premorbid mRS	1.22 (1.08-1.38)	0.002	1.16 (0.99-1.35)	0.060
NIHSS	1.03 (1.01-1.05)	0.001	1.03 (1.00-1.05)	0.041
Prior stroke/TIA	1.78 (1.24-2.57)	0.002	1.72 (1.15-2.56)	0.008
Prior intracerebral haemorrhage	2.07 (1.24-3.45)	0.005	1.11 (0.61-2.00)	0.73
Lobar location	3.28 (2.42-4.43)	<0.001	5.54 (3.42-9.00)	<0.001
Baseline haematoma volume (per 10 mL)	1.12 (1.06-1.17)	<0.001	1.05 (0.96-1.15)	0.30
PHO volume (per 10 mL)	1.12 (1.02-1.21)	0.012	1.06 (0.83-1.33)	0.64
Midline shift ≥5mm	1.66 (1.16-2.37)	0.006	1.30 (0.81-2.07)	0.28
Periventricular leukoaraiosis	1.36 (1.01-1.84)	0.041	1.40 (0.98-2.02)	0.068
Tranexamic acid	0.89 (0.66-1.19)	0.42	0.90 (0.65-1.23)	0.49

*Binary logistic regression adjusted for all variables on univariate analysis.
NIHSS=National Institute of Health Stroke Scale; PHO=perihaematomal oedema; TIA=transient ischaemic attack

Table 5-15 Unadjusted and adjusted binary logistic regression analysis of predictors of early seizures

Variables	Unadjusted OR (95%CI)	P	Adjusted OR (95%CI)*	P
Age (years)	1.00 (0.99-1.01)	0.90	0.98 (0.96-0.99)	0.006
Sex (male)	0.84 (0.61-1.15)	0.28	1.01 (0.71-1.44)	0.95
Premorbid mRS	1.15 (1.00-1.32)	0.058	1.08 (0.91-1.27)	0.40
NIHSS	1.03 (1.01-1.06)	0.002	1.03 (1.01-1.06)	0.018
Prior stroke/TIA	1.74 (1.18-2.59)	0.006	1.71 (1.11-2.63)	0.015
Prior intracerebral haemorrhage	1.92 (1.09-3.38)	0.024	1.22 (0.65-2.28)	0.54
Lobar location	3.25 (2.35-4.49)	<0.001	6.76 (4.01-11.38)	<0.001
Baseline haematoma volume (per 10 mL)	1.10 (1.05-1.16)	<0.001	1.06 (0.96-1.17)	0.27
PHO volume (per 10 mL)	1.09 (1.00-1.20)	0.050	1.10 (0.87-1.41)	0.41
Midline shift ≥5mm	1.51 (1.02-2.23)	0.041	1.12 (0.67-1.86)	0.67
Periventricular leukoaraiosis	1.29 (0.94-1.78)	0.11	1.34 (0.91-1.98)	0.14
Tranexamic acid	0.87 (0.63-1.19)	0.38	0.86 (0.61-1.21)	0.39

*Binary logistic regression adjusted for all variables on univariate analysis.
NIHSS=National Institute of Health Stroke Scale; PHO=perihaematomal oedema; TIA=transient ischaemic attack

Table 5-16 Unadjusted and adjusted binary logistic regression analysis of predictors of late seizures

Variables	Unadjusted OR (95%CI)	P	Adjusted OR (95%CI)*	P
Age (years)	1.01 (0.98-1.04)	0.44	0.97 (0.94-1.01)	0.12
Sex (male)	0.45 (0.21-0.94)	0.034	0.69 (0.30-1.59)	0.38
Premorbid modified Rankin Scale	1.59 (1.23-2.05)	<0.001	1.56 (1.14-2.13)	0.006
NIHSS	1.02 (0.98-1.07)	0.31	-	-
Prior stroke/TIA	2.01 (0.85-4.76)	0.11	1.84 (0.73-4.65)	0.20
Prior intracerebral haemorrhage	2.90 (0.99-8.45)	0.051	0.72 (0.16-3.23)	0.66
Lobar location	3.46 (2.63-7.37)	0.001	2.63 (1.02-6.84)	0.047
Baseline haematoma volume (per 10 mL)	1.14 (1.03-1.27)	0.010	1.02 (0.82-1.27)	0.88
PHO volume (per 10 mL)	1.18 (1.00-1.38)	0.050	0.91 (0.66-1.27)	0.56
Midline shift ≥5mm	2.69 (1.20-6.04)	0.017	2.56 (0.87-7.56)	0.088
Periventricular leukoaraiosis	1.86 (0.87-3.98)	0.11	1.91 (0.75-4.88)	0.18
Tranexamic acid	0.99 (0.48-2.04)	0.98	1.11 (0.50-2.44)	0.80

*Binary logistic regression adjusted for all variables on univariate analysis except NIHSS. NIHSS=National Institute of Health Stroke Scale; PHO=perihaematomal oedema; TIA=transient ischaemic attack

Tranexamic acid did not increase the risk of any seizure (aOR 0.90, 95%CI 0.65-1.23; p=0.49), early seizures (aOR 0.86, 95%CI 0.61-1.21; p=0.39) or late seizures (aOR 1.11, 95%CI 0.50-2.44; p=0.80; Table 5-14, 5-15 and 5-16). Further exploratory analysis showed that the incidence of seizures did not differ between the treatment groups whether a full dose (2g) or less than full dose was given; or by degree of renal impairment (Table 5-17).

Any seizures and early seizures were associated with worse day 7 and day 90 outcomes. Neurological deterioration, neurosurgery, invasive ventilation and intensive care unit admission were significantly increased in any seizure and early seizures (Table 5-18 & Table 5-19). Day 90 death, dependency, disability, mood, cognition and quality of life were all significantly worse in patients with any seizure and early seizure (Table 5-18 & Table 5-19). On the other hand, late seizures did not have any significant effect on day 90 outcomes apart from longer length of hospitalisation (Table 5-20).

Table 5-17 Incidence of seizures by treatment groups according to subgroups of treatment completion and estimated glomerular filtration rate

Subgroups	N	Any seizures ≤90 days		
		Tranexamic acid	Placebo	P
Treatment completion*				
Full dose	2207	80 (7.3)	89 (8.0)	0.49
Less than full dose	100	8 (16.7)	13 (24.5)	0.33
eGFR (mL/min/1.73m2)†				
≥60	1857	73 (7.8)	83 (9.0)	0.34
30-59	280	10 (7.5)	13 (8.8)	0.69
<30	38	3 (13.6)	1 (6.3)	0.46

Data are number (%) and statistics are Chi-Squared test. * Treatment not given at all in 15 patient; completion status was uncertain in 3 patients. †Estimated glomerular filtration rate (eGFR) not available in 150 patients.

Table 5-18 Effects of seizures on day 7 and day 90 outcomes

Outcomes	Seizures	No seizure	OR/MD 95%CI*	P
Day 7				
Death	24 (14.7)	200 (9.4)	0.97 (0.57, 1.65)	0.90
Neurological deterioration	117 (60.9)	618 (29.1)	3.74 (2.60, 5.37)	<0.001
Neurosurgery	26 (13.5)	95 (4.5)	2.71 (1.60, 4.58)	<0.001
Invasive ventilation	33 (17.1)	133 (6.2)	2.77 (1.73, 4.44)	<0.001
ICU admission	42 (21.8)	190 (8.9)	2.73 (1.78, 4.18)	<0.001
Day 90				
Death	67 (35.3)	432 (20.4)	1.97 (1.30, 2.97)	0.001
mRS>3	134 (70.5)	1125 (53.1)	1.79 (1.16, 2.76)	0.008
Barthel Index	35.2 (43.2)	54.7 (43.6)	-10.9 (-15.4, -6.3)	<0.001
EuroQoL-5D HUS	0.21 (0.38)	0.36 (0.40)	-0.08 (-0.13, -0.03)	0.001
TICS-m	7.8 (12.1)	14.3 (12.6)	-3.0 (-4.6, -1.4)	<0.001
ZDS	79.3 (30.1)	66.2 (29.4)	5.8 (1.8, 9.9)	0.005
Length of stay (days)	26.6 (30.9)	19.7 (25.1)	5.4 (2.8, 22.0)	0.011

*Binary logistic regression and multiple linear regression adjusted for age, sex, premorbid modified Rankin Scale, prior antiplatelet therapy, National Institute of Health Stroke Scale, systolic blood pressure, onset to CT <3 hours, baseline haematoma volume, intraventricular haemorrhage and lobar location. EuroQoL-5D HUS=EuroQoL-5 Dimensions Health Utility Status; ICU=intensive care unit; mRS= modified Rankin Scale; TICS-m=modified Telephone Interview Cognitive Status; ZDS=Zung Depression Scale

Table 5-19 Effects of early seizures on day 7 and day 90 outcomes

Outcomes	Early seizure	No early seizure	OR/MD 95%CI*	P
Day 7				
Death	24 (14.7)	200 (9.4)	1.20 (0.70, 2.07)	0.52
Neurological deterioration	102 (63.0)	618 (29.1)	4.23 (2.85, 6.26)	<0.001
Neurosurgery	22 (13.5)	95 (4.5)	2.58 (1.47, 4.52)	0.001
Invasive ventilation	28 (17.2)	133 (6.2)	2.60 (1.57, 4.31)	<0.001
ICU admission	37 (22.7)	190 (8.9)	2.71 (1.72, 4.26)	<0.001
Day 90				
Death	62 (38.8)	437 (20.4)	2.66 (1.70, 4.14)	<0.001
mRS>3	112 (70.0)	1147 (53.4)	1.89 (1.19, 3.01)	0.007
Barthel Index	35.3 (43.9)	54.4 (43.6)	-11.7 (-16.6, -6.8)	<0.001
EuroQoL-5D HUS	0.22 (0.38)	0.35 (0.40)	-0.08 (-0.13, -0.03)	0.002
TICS-m	7.7 (12.1)	14.3 (12.6)	-3.0 (-4.7, -1.3)	<0.001
ZDS	80.3 (30.1)	66.2 (29.4)	6.5 (2.3, 10.8)	0.002
Length of stay (days)	24.9 (31.1)	19.7 (25.1)	3.6 (-0.5, 7.7)	0.083

*Binary logistic regression and multiple linear regression adjusted for age, sex, premorbid modified Rankin Scale, prior antiplatelet therapy, National Institute of Health Stroke Scale, systolic blood pressure, onset to CT <3 hours, baseline haematoma volume, intraventricular haemorrhage and lobar location. EuroQoL-5D HUS=EuroQoL-5 Dimensions Health Utility Status; ICU=intensive care unit; mRS= modified Rankin Scale; TICS-m=modified Telephone Interview Cognitive Status; ZDS=Zung Depression Scale

Table 5-20 Effects of late seizures on outcomes

Outcomes	Late seizure	No late seizure	OR/MD 95%CI*	P
Day 90				
Death	5 (16.7)	494 (21.7)	0.30 (0.09, 1.04)	0.058
mRS>3	22 (73.3)	1237 (54.3)	1.28 (0.44, 3.77)	0.65
Barthel Index	35.0 (40.3)	53.3 (43.9)	-5.2 (-16.5, 6.0)	0.36
EuroQoL-5D HUS	0.20 (0.34)	0.35 (0.40)	-0.06 (-0.18, 0.07)	0.38
TICS-m	8.7 (12.1)	13.8 (12.7)	-2.0 (-7.3, 3.3)	0.46
ZDS	71.0 (30.2)	67.3 (29.7)	-1.3 (-13.3,10.7)	0.84
Length of stay (days)	35.8 (29.0)	19.7 (25.1)	15.8 (6.4, 25.2)	0.001

*Binary logistic regression and multiple linear regression adjusted for age, sex, premorbid modified Rankin Scale, prior antiplatelet, National Institute of Health Stroke Scale, systolic blood pressure, onset to CT <3 hours, baseline haematoma volume, intraventricular haemorrhage and lobar location. EuroQoL-5D HUS=EuroQoL-5 Dimensions Health Utility Status; ICU=intensive care unit; mRS= modified Rankin Scale; TICS-m=modified Telephone Interview Cognitive Status; ZDS=Zung Depression Scale

5.2.6 Discussion

Lobar location of haematoma was the only consistent independent predictor of seizure within 90 days from ICH, including both early and late seizures. In

addition, ICH severity as indicated by worse NIHSS and previous stroke/TIA were independent predictors of early seizure. Although baseline haematoma volume, perihaematomal oedema volume and midline shift were significant predictors on univariate analysis, their significance disappeared after adjusting for lobar location. The pathophysiology of early seizures after intracerebral haemorrhage is unclear but was hypothesized to be related to physical disruption of cortical network by haematoma or irritation by blood products.[30, 138] Our findings did not support haematoma or oedema size or mass effect as an independent risk factor for post-ICH seizures. This is consistent with previous studies, which had consistently reported lobar location as a risk factor for early seizure with an odds ratio of 2 to 16.[26, 30, 32, 487] Haematoma expansion was reported as a risk factor in one study.[136] Haematoma size was a significant risk factor for early seizures in Alberti *et al* but this study involved combined analysis of intracerebral haemorrhage and ischaemic stroke.[488] On the other hand, many other studies found that haematoma volume was not a significant factor for early seizures.[26, 30, 32, 487] In fact, one study found the risk of early seizures to be lower with larger haematoma.[29]

Younger age was a predictor for early seizure in our study in agreement with de Herdt *et al*[32] and Woo *et al*[26], though other studies found no significant association between age and occurrence of early seizures.[29, 30]

Lobar location and worse premorbid mRS were predictive of late seizures. Periventricular leukoaraiosis, a marker of cerebral small vessel disease did not significantly predict late seizure in our cohort of ICH patients, although it was a predictor for any seizure in the first 90 days. The analysis was perhaps limited by the small number of patients with late onset seizure. Only 30 of 2325 patients (1.3%) had late seizures.

Tranexamic acid did not increase the risk of any seizure within 90 days, early or late seizures in all multivariable logistic regression analyses. This would hopefully allay some concerns of using tranexamic acid in CNS disorders. The risk of seizure with tranexamic acid was highlighted in a systematic

review by Zhang *et al* which reported a pooled odds ratio of 5.39.[382] However, the population studied were mostly patients who underwent cardiac surgery. Myles *et al* reported even higher risk of seizures with a relative risk 7.6 (0.7% had seizure in tranexamic acid group compared to 0.1% in placebo) in patients undergoing coronary artery surgery.[355] The overall incidence of seizure with tranexamic acid was lower than incidence of seizures after intracerebral haemorrhage (2.7% vs 4 -14%). Higher doses of tranexamic acid were associated with higher incidence of seizures. The incidence of seizures with low, middle and high doses of tranexamic acid is 1.4%, 2.4% and 5.3% respectively according to one meta-analysis.[382] This meta-analysis classified doses of 24–50 mg/kg as low; 59 mg/kg, 4 g plus 0.5 g/h, and 32 mg/kg plus 16 mg/kg/h as middle; and 30 mg/kg (loading dose) plus 15 mg/kg h (continuous infusion during operation) and 80–109 mg/kg as high.[382] The dose used in the TICH-2 trial of 2g (approximately 28mg/kg total dose or 14mg/kg loading and 1.8 mg/kg/hour for 8 hours, assuming an average adult weight of 70kg) falls into the low dose category.

There were also concerns that adverse events may be increased in patients with renal impairment as tranexamic acid is mainly excreted through kidneys. The product summary of product characteristics (SmPC) recommended dose reduction in renal impairment based on creatinine levels.[489] Table 5-21 describes the recommendation based on creatinine levels and estimated glomerular filtration rate (eGFR, calculated based abbreviated MDRD equation with age of 69 years, non-Black ethnicity and for male and female; the age was based on mean age and ethnicity was mostly non-Black in TICH-2).

Table 5-21 Tranexamic acid dose reduction in renal impairment

Creatinine (µmol/L)	eGFR (mL/min.1.73m2), male	eGFR (mL/min.1.73m2), female	Recommended dose
120-250	24-55	18-41	10 mg/kg twice daily
250-500	11-24	8-18	10 mg/kg once daily
>500	<11	<8	5 mg/kg once daily

Estimated glomerular filtration rate (eGFR) was calculated based abbreviated MDRD equation with age of 69 years and non-Black ethnicity)

A pharmacokinetic study of tranexamic acid in patients who underwent cardiac surgery reported elevated plasma levels of tranexamic acid and high incidence of seizures (8%) in patients with advanced kidney disease.[490] The authors also proposed a new tranexamic acid regime: loading dose of 25-30 mg/kg for patients with eGFR <60 mL/min/1.73m^2; maintenance dose of 5-10 mg/kg/hr for eGFR 30-59 mL/min/1.73m^2 and 3-5 mg/kg/hr for eGFR <30 mL/min/1.73m^2.[490] The dosing regime used in TICH-2 was lower compared this new proposed regime. In our cohort, 318 (13.7%) patients had an eGFR of < 60 mL/min/1.73m2. EGFR were often not available in the acute setting and hence not required prior to randomisation in the interest of time. The protocol also did not require renal dose adjustment. Nevertheless, the incidence of seizures was not increased in patients with renal impairment who were treated with tranexamic acid compared to placebo.

Within the first week, early seizures increased the risk of neurological deterioration and were associated with more aggressive management including neurosurgery, invasive ventilation and intensive care unit admission. Early seizures lead to worse day 90 outcomes in terms of higher death, dependency, disability, cognition, depression and quality of life. This is despite accounting for other known prognostic factors such as age, baseline haematoma volume, IVH and lobar location. This is perhaps indicative that early excitotoxicity after ICH being detrimental and the need for a preventive or treatment strategies. Current guidelines found little evidence in recommending primary seizure prophylaxis for ICH.[491] One small randomised controlled trial found that valproic acid did not reduce the risk of seizures at one year post-ICH although the incidence of early seizures was reduced.[492]

Future clinical trials of primary post-ICH seizure prophylaxis should perhaps focus on patients with lobar haematoma due to the significant risk of seizures associated with it.

On the other hand, late seizure did not have significant effect on any day 90 outcomes. However, this has to be interpreted with caution in view of the small number of patients with late seizure and that the effect of late seizures may be delayed, i.e. seen beyond day 90 follow-up.

The strength of the current analysis is that it was a prospective multicentre trial with large sample size, involving patients from 12 countries. Seizure was a pre-specified safety outcome and hence reporting was mandatory, which may have increased the capture rate. All serious adverse event (SAE) reports were adjudicated by independent expert assessors, further improve the validity of the data. One limitation of the study is a relatively small number of patients with late seizures despite following up the patients up to day 90 for seizures. This is an inherent problem faced when studying rare events and perhaps best studied by longer-term registry-based research. Some data were not available, namely seizure semiology in large proportion of patients, seizure classification, previous history of epilepsy and treatment of seizures. The diagnoses of seizure were mainly made by clinical observation. As EEG was not a routinely performed as part of the study, some subclinical or non-convulsive seizures may be missed, especially in people with depressed conscious level.[135, 136] These limitations occurred, as the primary research design was not to study post-ICH seizures but rather to ensure the safety of tranexamic acid with regards to seizures. Nevertheless, this represents a pragmatic real-world scenario where neurology review and EEG is not always available to patients with seizure.

In conclusion, tranexamic acid did not increase the risk of seizures in spontaneous ICH. Lobar haematoma was the most consistent risk factor for seizures after ICH, while haematoma volume as a risk factor needs to be further studied. Early seizure leads to worse outcome. More research is needed to address the prevention and treatment of early seizure after ICH.

Chapter 6 Noncontrast CT signs as predictors of haematoma expansion, functional outcome and response to tranexamic acid in acute spontaneous intracerebral haemorrhage

6.1 Publications contributing this chapter

1) Z.K. Law, A. Ali, K. Krishnan, A. Bischoff, J. Appleton, P. Scutt, L. Woodhouse, S. Pszczolkowski, R. Dineen, P.M. Bath and N. Sprigg. Noncontrast CT signs as predictors of haematoma expansion, functional outcome and response to tranexamic acid in acute spontaneous intracerebral haemorrhage. AS10-026 (oral presentation at 5th European Stroke Organisation Conference, 22-24 May 2019, Milan, Italy). European Stroke Journal 2019, Vol. 4(1S) 25-26

2) Zhe Kang Law, Azlinawati Ali, Kailash Krishnan, Adam Bischoff, Jason P Appleton, Polly Scutt, Lisa Woodhouse, Stefan Pszczolkowski, Lesley Cala, Rob Dineen, Philip M Bath, Nikola Sprigg on behalf of TICH-2 investigators. Noncontrast CT signs as predictors of hematoma expansion, clinical outcome and response to tranexamic acid in acute intracerebral haemorrhage (in submission to Stroke)

6.2 Abstract

6.2.1 Background

Blend, black hole and island signs and hypodensities were reported to predict hematoma expansion in acute intracerebral hemorrhage (ICH). We explored the value of these noncontrast CT (NCCT) signs in predicting hematoma expansion and functional outcome in our cohort of ICH.

6.2.2 Methods

The Tranexamic acid for IntraCerebral Hemorrhage-2 (TICH-2) was a prospective randomised controlled trial exploring the efficacy and safety of tranexamic acid in acute ICH. Baseline and 24-hour CT scans of patients recruited into the trial were analysed. Hematoma expansion was defined as

an increase in hematoma volume of >33% or > 6 mL on 24-hours CT. Poor functional outcome was defined as modified Rankin Scale of 4 to 6 at day 90. Multivariable logistic regression was performed to identify predictors of hematoma expansion and poor functional outcome.

6.2.3 Results

Of 2325 patients recruited, 2077 (89.3%) had valid baseline and 24-hour scans. 570 patients (27.4%) had hematoma expansion while 1259 patients (54.6%) had poor functional outcome. The prevalence of NCCT signs was: blend sign-366 (16.1%); black hole sign-414 (18.2%); island sign-200 (8.8%); and hypodensities-701 (30.2%). Blend sign (adjusted odds ratio [aOR] 1.53, 95% CI 1.16-2.03; *P*=0.003), black hole (aOR 2.03, 1.34-3.08; *P*=0.001) and hypodensities (aOR 2.06, 1.48-2.89; *P*<0.001) were independent predictors of hematoma expansion on multivariable analysis with adjustment for covariates. Black hole sign (aOR 1.52, 1.10-2.11; *P*=0.012), hypodensities (aOR 1.37, 1.05-1.78; *P*=0.019) and island sign (aOR 2.59, 1.21-5.55; *P*=0.014) were significant predictors of poor functional outcome. Tranexamic acid reduced the risk of hematoma expansion (aOR 0.77, 0.63-0.94; *P*=0.010) but there was no significant interaction between the presence of NCCT signs and benefit of tranexamic acid on hematoma expansion and functional outcome (*P* interaction all >0.05).

6.2.4 Conclusion

Blend sign, black hole sign and hypodensities predict hematoma expansion while black hole sign, hypodensities and island signs predict poor functional outcome. NCCT signs did not predict a better response to tranexamic acid.

6.3 Background

Haematoma expansion complicates up to 38% of patients with acute intracerebral haemorrhage (ICH) within the first few hours of onset and leads to higher mortality and worse functional outcome.[86] However, given that most patients with ICH do not have haematoma expansion, identifying patients at

risk of haematoma expansion is may be important for clinical trials testing haemostatic therapies so that patients who are most likely to benefit can be selectively targeted.

Shorter onset to baseline imaging time, larger baseline haematoma volume, prior antiplatelet and anticoagulant therapy were identified as independent predictors of haematoma expansion with C-index of 0.78 (95% CI 0.75-0.82) in a large patient level meta-analysis of data from cohort studies and randomised trials.[102] The predicted probability of haematoma expansion increased with larger bleeds and peaked at approximately 75 mL before declining while the probability of haematoma expansion was highest in patients with onset to CT time of < 3 hours.[102] CT angiography (CTA) spot sign had a sensitivity of approximately 60% and specificity of 90% in predicting haematoma expansion but the addition of spot sign only increased the C-index by 0.05.[38,102] Furthermore, CT angiography are not routinely performed in patients with ICH. In the Tranexamic acid for IntraCerebral Haemorrhage-2 (TICH-2) trial, only 10% of patients had a baseline CTA.[231]

Several noncontrast CT (NCCT) markers of heterogeneous density and irregular shape have been identified as predictors of haematoma expansion in intracerebral haemorrhage. These include the blend sign, black hole sign, swirl sign, fluid level and intrahaematoma hypodensities, all signs of heterogeneous density; another, the island sign reflects irregular shape.[106-109, 111, 493] The universal availability of noncontrast CT in patients with ICH and the reportedly excellent inter-rater reliability amongst trained assessors (κ of 0.806 to 0.957) makes these signs an attractive alternative to CTA spot sign.[106, 107, 109, 111] These signs have a sensitivity of 31.9% to 44.7% and specificity of 94.7% to 98.2% for prediction of haematoma expansion.[106, 107, 109, 111] However, many source studies were single centre studies with small sample size.[106, 107, 109, 111] One exception was the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2), a multicentre randomised controlled trial, which found NCCT signs to be useful predictors of haematoma expansion.[494] Several meta-analyses have found substantial

heterogeneity between the studies.[495, 496] Therefore further studies are needed to evaluate the value of NCCT signs.

In the TICH-2 trial, there was no significant difference in functional outcome between patients who received tranexamic acid and those who received placebo despite a significant reduction in risk of haematoma expansion.[231] Tranexamic acid reduced the absolute haematoma volume expansion by only 1.4 mL, which may not be sufficient to result in clinical significant benefit.[231] In the current analysis, we explored the role of some of the NCCT signs as predictors of haematoma expansion and poor functional outcome, and if a subgroup of patients with one or more of these signs benefited from tranexamic acid.

6.4 Objectives

The objective of the current chapter is to explore the role of NCCT signs as predictors of haematoma expansion and poor functional outcome. A second objective is to explore if a subgroup of patients with one or more of these signs benefited from tranexamic acid.

6.5 Methods

6.5.1 Acquisition of CT images

A noncontrast CT scan (NCCT) was required for the diagnosis of spontaneous intracerebral haemorrhage prior to recruitment and randomisation in TICH-2. All CT brain scans were performed as per local protocol. CT scans obtained from any scanner of any manufacturer; any slice thickness with a minimum of an axial view was accepted. CT scans with incomplete or missing slices were excluded. Baseline scans were performed before randomisation. Follow-up CT scans were performed at 24 ± 12 hours after the baseline scans.[80] When multiple scans were available, the scan closest to 24 hours after randomisation was used as the follow-up scan to determine haematoma expansion. The exception was if the 24 hour CT was performed after neurosurgery, when a pre-operative CT scan would be used

instead. A patient would be excluded from analysis for haematoma expansion if no follow-up scan or only post-op scans were available. Soft copy files of scans in Digital Imaging and Communications in Medicine (DICOM) format were uploaded into a web-based data submission platform. Alternatively, encrypted DICOM files were copied onto CDs and mailed to the coordinating centre and were then uploaded by the image coordinators.

6.5.2 Haematoma volume measurements

Three independent raters blinded to clinical data (ZKL, neurologist; AA, CT radiographer; KK, stroke physician) performed volumetric measurements using the ITK-SNAP software version 3.6.0.[468] Intraparenchymal and intraventricular haematoma volumes were computed independently using an Active Contour semi-automated segmentation (SAS) algorithm[468], followed by manual editing if necessary.

Evaluation of intra- and interrater reliability of hematoma volume measurement was performed. Each rater performed two measurements on the same CT scan after an interval of at least one day. In addition, to assess intraclass correlation, measurements were performed on 50 CT scans by all three raters blinded to each other's measurements.

6.5.3 Assessment of noncontrast CT signs

Four independent assessors assessed the baseline CT scans for the presence of blend, black hole and island signs and hypodensities (ZKL, KK, AA and AB). Inter-rater agreement (Fleiss kappa) was assessed using a subset of 70 CT scans, with raters blinded to each other's ratings of signs Swirl sign and fluid level were not assessed. The definitions of the assessed signs are described in the following sections.

6.5.3.1 Blend sign

The blend sign (Figure 1-3) was defined as an area of hypodensity with adjacent hyperdensity within a haematoma. The margin between the hypodense and hyperdense should be well defined with a difference of at

least 18 Hounsfield units between the two areas. In addition, the hypodense area should not be entirely encapsulated by the hyperdense area.[106]

6.5.3.2 Black hole sign

The black hole sign (Figure 1-3) was defined as an area of hypodensity (black hole) that is completely encapsulated by an adjacent hyperdense area within a haematoma. The difference between the 2 areas should be at least 28 Hounsfield units. The black hole may be oval, round or rod shape but should not be connected the adjacent brain parenchyma.[107]

6.5.3.3 Hypodensities

Hypodensities was defined as a hypoattenuated area within the haematoma, which is completely encapsulated by hyperdense area. The hypodense area can has distinct or blurred margin and be of any Hounsfield Unit. By definition, black hole sign is a subset of hypodensities.[109]

6.5.3.4 Island sign

The island sign (Figure 1-4) is a sign on noncontrast CT scan that illustrates irregular shape of haematoma. It was defined as the presence of at least three separate small haematomas adjacent to the main haematoma. Alternatively, the presence of at least 4 small haematomas that are partially connected to the main haematoma is considered as a positive island sign as well, provided these haematomas are bubble or sprout-like and not lobulated. It was first described by Li Q *et al* in a cohort of 252 patients. It was reported to have a sensitivity of 44.7%, specificity of 98.2%, positive predictive value of 92.7% and negative predictive value of 77.7% in predicting haematoma expansion.[111] The island sign was reported to be a strong predictor of poor functional outcome after ICH as well (OR 3.51, 95%CI 1.26-9.81).[111]

6.5.4 Radiological outcomes

For this analysis, the outcomes was based on the TICH-2 CT angiography statistical analysis plan[497] as below:

6.5.5 Haematoma expansion

Haematoma expansion was defined as increase in intraparenchymal haematoma volume on follow-up scan of >33% or > 6 mL from baseline haematoma.

6.5.6 Total ICH expansion

Total ICH expansion is defined as expansion of combined intraparenchymal and intraventricular haematoma volume of >33% or > 6 mL. This was analysed as an outcome as it is possible that haematoma may have extended into intraventricular haemorrhage but intraparenchymal haematoma volume was preserved.

6.5.7 Haematoma progression

Haematoma progression was defined as intraparenchymal haematoma expansion or delayed intraventricular or subarachnoid extension or an absolute intraventricular haematoma expansion of ≥ 2 mL. When follow-up scans were not available, early neurological deterioration (≥4 points increase in NIHSS or drop in GCS of ≥ 2) or death before day-2 clinical assessment was considered haematoma progression. The rationale of including neurological deterioration or death is to avoid excluding patients who were not fit enough to have a per-protocol follow-up scan.

6.5.8 Clinical outcome

Unfavourable functional outcome, defined as a dichotomised modified Rankin Scale of 4 to 6, was the clinical outcome of interest.

6.5.9 Statistical analysis

Intraclass correlation and Fleiss kappa were used to measure inter-rater agreement for haematoma volume and the NCCT signs respectively. We interpret kappa as follows: <0 less than chance agreement; 0.01-0.20 slight agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 substantial agreement and 0.81-0.99 excellent agreement.[498] The

sensitivity, specificity, positive and negative predictive value of each NCCT signs were analysed individually. In addition, the baseline characteristics of patients with and without haematoma expansion were compared using student t-test, Mann-Whitney U test and Chi square test as appropriate. Univariate analysis and multivariable logistic regression was used to identify significant predictors of haematoma expansion. The multivariable model included minimisation factors as a priori variables and variables that were significant confounders on univariate analysis (resulting in change of OR ≥ 0.1 when included). We also performed sensitivity analyses using haematoma progression and total ICH expansion as outcomes (for reasons elucidated above). To explore the diagnostic yield of NCCT signs in addition to known predictors, we performed receiver operating characteristics analysis for known predictors (prior antiplatelet, baseline haematoma volume and onset to CT time) and known predictors plus NCCT signs.

Multivariable logistic regression was used to identify predictors of unfavourable functional outcome. In addition, to explore the effect of tranexamic acid in patients with NCCT signs, a logistic regression model was constructed stratified by status of NCCT signs. P values of <0.05 were considered statistically significant and all analysis were performed using Statistical Package for the Social Sciences (SPSS) version 24, IBM, Armonk. NY.

6.6 Results

6.6.1 Completeness of data

2325 patients were recruited into the TICH-2 trials from 124 centres in 12 countries. Baseline scans were available in 2273 patients (97.8%). Of these, 2077 (89.3%) patients also had follow-up CT scans and were included in the analysis of haematoma expansion (Figure 6-1). In addition, 236 patients without follow-up scans had available neurological deterioration or death status at 48 hours and 2313 patients (99.5%) were included in analysis of haematoma progression. Day 90 modified Rankin Scale data were available in 2307 patients (99.2%).

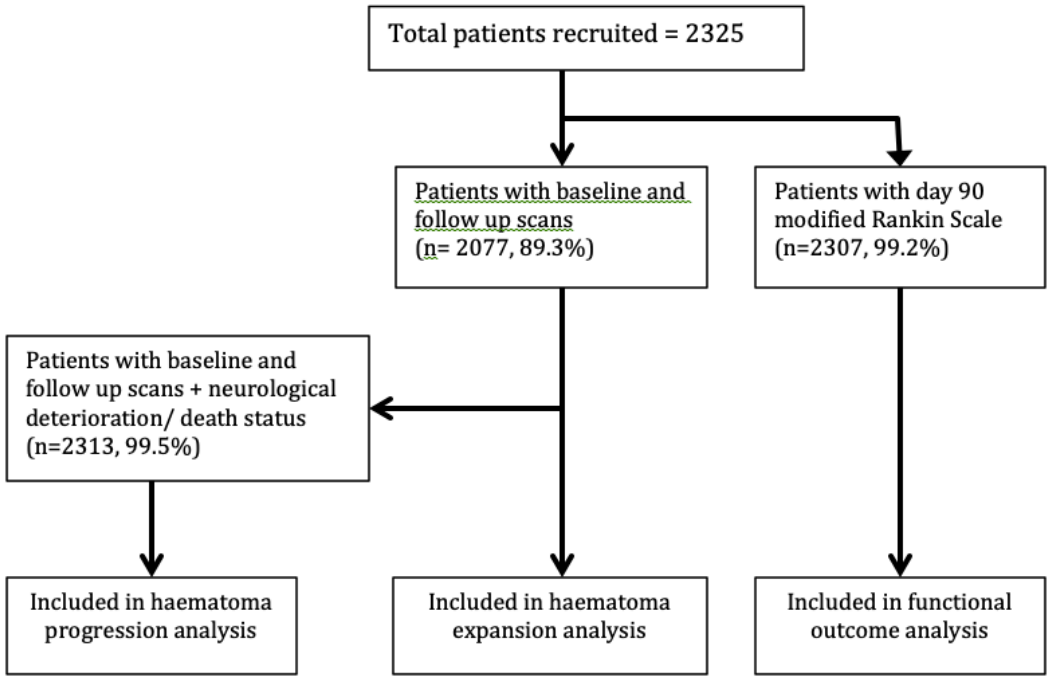


Figure 6–1 Flow chart showing numbers included in analysis

6.6.2 Inter- and intra-rater agreement

For haematoma volume measurement, the intraclass correlation (ICC) using semi-automated segmentation (SAS) method was 0.94 (0.86-0.97).

Intra-observer Cohen's kappa for blend sign was 0.93 (0.79-1.00); black hole was 0.73 (0.45-1.00); island sign 0.85 (0.57-1.00) and hypodensities 0.66 (0.43-0.90). The Fleiss kappa for blend signs was 0.60 (95%CI 0.47-0.74); black hole sign 0.53 (0.41-0.64); island sign 0.64 (0.53-0.75); and hypodensities 0.63 (0.39-0.86).

6.6.3 Characteristics of patients with haematoma expansion

570 patients (27.4%) had haematoma expansion. Patients with haematoma expansion had worse premorbid modified Rankin Scale, worse stroke severity (higher NIHSS and lower GCS), larger baseline haematoma volumes, more lobar location, more likely to have had antiplatelet therapy prior to ICH and a shorter onset to CT time (Table 6-1). Patients with haematoma expansion were more likely to have haematoma with blend sign,

black hole sign, island sign and hypodensities on baseline imaging (Table 6-1).

Table 6-1 Comparison of baseline characteristics in patients with and without haematoma expansion

Variables	All	Haematoma expansion*	No haematoma expansion*	P
Patients randomised	2325	570 (27.4%)	1508 (72.6%)	
Age (years)	68.9 (13.8)	69.5 (13.9)	68.4 (13.7)	0.12
Sex (male)	1301 (56.0%)	332 (58.2%)	833 (55.2%)	0.22
Pre-stroke mRS (/5)	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.012
Glasgow coma scale (/15)	15 [12, 15]	14 [12, 15]	15 [13, 15]	<0.001
NIHSS score [/42]	12.0 [7.0, 19.0]	15 [9, 20]	11 [6, 17]	<0.001
Systolic blood pressure (mmHg)	172.6 (27.2)	173.8 (29.8)	175.5 (29.4)	0.25
Intra-ventricular haemorrhage	704 (30.7%)	147 (25.9%)	465 (30.9%)	0.026
Haematoma location				
Supratentorial lobar	688 (29.6%)	206 (36.3%)	396 (26.4%)	<0.001
Supratentorial deep	1451 (62.4%)	332 (58.6%)	1011 (67.5%)	<0.001
Infratentorial	145 (6.2%)	29 (5.1%)	91 (6.1%)	0.41
Previous antiplatelet therapy	611 (26.3%)	164 (28.8%)	357 (23.7%)	0.016
Onset to CT time (median, hours)	1.9 [1.4, 2.8]	1.8 [1.3, 2.5]	2.0 [1.4, 3.0]	<0.001
Onset to CT time (mean, hours)	2.3 (1.3)	2.0 (1.1)	2.4 (1.4)	<0.001
Haematoma volume				
ICH only, mL [median, IQR]	13.3 [5.5, 32.4]	21.4 [7.7, 44.2]	10.7 [4.9, 23.2]	<0.001
ICH only, categorical				<0.001†
<30 mL	1651 (72.6%)	345 (60.5%)	1213 (80.4%)	
30-60mL	365 (16.1%)	143 (25.1%)	184 (12.2%)	
>60 mL	257 (11.3%)‡	82 (14.4%)	111 (7.4%)	
ICH+IVH [median, IQR]	16.3 [6.3, 37.4]	23.8 [9.1, 50.8]	13.2 [5.3, 29.1]	<0.001
Blend sign	366 (16.1%)	133 (23.3%)	180 (11.9%)	<0.001
Black hole sign	414 (18.2%)	130 (22.8%)	218 (14.5%)	<0.001
Hypodensities	701 (30.2%)	225 (39.5%)	365 (24.3%)	<0.001
Island sign	200 (8.8%)	65 (11.4%)	102 (6.8%)	0.001

Data are mean (standard deviation), median [interquartile range] or number (%). ICH=intracerebral haemorrhage; IVH=intraventricular haemorrhage; mRS= modified Rankin Scale; NIHSS= National Institute of Health Stroke Scale. Statistics are Chi-squared, Mann-Whitney U, Student's t and Mantel-Haenszel test of trend.
*Assessments of haematoma expansion for 2077 patients with valid baseline and follow-up CT scans. †Both Chi-squared and Mantel-Haenszel test of trend's p <0.001. ‡The largest baseline haematoma volume is 206.8 mL; 161 (7.1%) of patients had baseline haematoma volume >75 mL.

6.6.3.1 Prevalence and accuracy of NCCT signs

The prevalence of NCCT signs was: blend sign-366 (16.1%); black hole sign-414 (18.2%); island sign-200 (8.8%) and hypodensities- 701 (30.2%). NCCT signs had low sensitivity (11.4 to 39.5%) and high specificity (76 to 93%) for haematoma expansion with island sign having the highest specificity but lowest sensitivity (Table 6-2). Similarly, NCCT signs had low sensitivity (14-39%) and high specificity (79.5 to 97.6%) for poor functional outcome (Table 6-2). Baseline haematoma volumes were significantly larger in all NCCT signs; patients with black hole sign and hypodensities had shorter onset to CT time while a larger proportion of patients with island signs were taking antiplatelet therapy (Table 6-3).

Table 6-2 Diagnostic accuracy of NCCT signs for haematoma expansion and poor functional outcome

Haematoma expansion	Se	Sp	PPV	NPV	PLR	NLR	Accuracy
Blend sign	23.3% (19.9-27.0)	88.1% (86.3-89.7)	42.5% (37.6-47.5)	75.2% (74.3-76.1)	1.95 (1.60-2.39)	0.87 (0.83-0.91)	70.3% (68.3-72.3)
Black hole sign	22.8% (19.4-26.5)	85.5% (83.7-87.3)	37.4% (32.9-42.0)	74.6% (73.6-75.5)	1.58 (1.30-1.92)	0.90 (0.86-0.95)	68.3% (66.3-70.3)
Hypodensities	39.5% (35.5-43.7)	75.8% (73.5-77.9)	38.1% (35.0-41.4)	76.8% (75.5-78.1)	1.63 (1.42-1.87)	0.80 (0.74-0.86)	65.8% (63.7-67.9)
Island sign	11.4% (8.9-14.3)	93.2% (91.9-94.5)	38.9% (32.2-46.1)	73.6% (72.9-74.2)	1.69 (1.25-2.27)	0.95 (0.92-0.98)	70.8% (68.8-72.7)
Poor functional outcome (modified Rankin Scale of 4 to 6)							
Blend sign	20.1% (17.9-22.4)	88.7% (86.6-90.6)	68.1% (63.5-72.4)	47.9% (47.1-48.8)	1.77 (1.45-2.18)	0.90 (0.87-0.93)	51.2% (49.1-53.3)
Black hole sign	24.0% (21.6-26.5)	88.8% (86.7-90.6)	72.0% (67.8-75.9)	49.2% (48.3-50.2)	2.14 (1.75-2.61)	0.86 (0.82-0.89)	53.4% (51.3-55.4)
Hypodensities	39.2% (36.5-42.0)	79.5% (76.9-81.9)	69.8% (66.8-72.6)	52.0% (50.7-53.4)	1.91 (1.66-2.20)	0.76 (0.72-0.81)	57.5% (55.4-59.5)
Island sign	14.3% (12.4-16.4)	97.8% (96.7-98.6)	88.5% (83.4-92.2)	48.6% (48.0-49.3)	6.39 (4.17-9.78)	0.88 (0.85-0.90)	52.2% (50.1-54.3)

Se=sensitivity; Sp=specificity; PLR=positive likelihood ratio; NLR=negative likelihood ratio.

Table 6-3 Comparison of baseline haematoma volume, onset to CT time and history of antiplatelet between patients with and without noncontrast CT signs

	Baseline HV	Onset to CT time	Prior antiplatelet
Blend +	38.1 [18.2, 68.6]	1.9 [1.4, 3.0]	97 (26.5)
Blend -	10.9 [4.7, 25.4]	1.9 [1.4, 2.8]	493 (25.9)
P	<0.001	0.68	0.80
Black hole +	36.0 [19.6, 62.0]	1.8 [1.3, 2.6]	111 (26.8)
Black hole -	10.5 [4.6, 24.5]	2.0 [1.4, 3.0]	479 (25.8)
P	<0.001	0.003	0.67
Hypodensity +	32.1 [15.7, 59.6]	1.8 [1.3, 2.7]	185 (26.4)
Hypodensity -	8.9 [4.0, 19.2]	2.0 [1.4, 3.0]	407 (25.9)
P	<0.001	0.026	0.79
Island +	64.6 [39.3, 84.5]	2.0 [1.4, 3.1]	69 (34.5)
Island -	11.8 [5.00, 26.4]	1.9 [1.4, 2.8]	521 (25.1)
P	<0.001	0.21	0.004

*Data are median [interquartile range] or number (%). Analyses are Mann-Whitney U test and Chi-squared test. HV =haematoma volume

6.6.3.2 Predictors of haematoma expansion

Univariate logistic regression analysis showed that higher premorbid mRS, prior antiplatelet therapy, lower GCS, lobar location, larger baseline haematoma volume, shorter onset to CT time as well as the presence of blend sign, black hole sign, island sign and hypodensities increased the odds ratio of haematoma expansion (Table 6-4). Multivariable logistic regression models were then constructed to explore the significance of NCCT signs in predicting haematoma expansion. As there was significant overlap between black hole sign and hypodensities, 2 different models were constructed with model 1 including black hole sign and model 2 including hypodensities (Table 6-4). Baseline haematoma volume, onset to CT time and prior antiplatelet therapy were significant predictors of haematoma expansion. Of the NCCT signs, blend sign, black hole and hypodensities were significant independent predictors of haematoma expansion (Table 6-4). The island sign was no longer a significant predictor after adjusting for baseline haematoma volume.

Table 6-4 Binary logistic regression analyses for predictors of haematoma expansion

Variables	**Unadjusted OR**	**p**	**Adjusted OR (Model 1)***	**p**	**Adjusted OR (Model 2)†**	**p**
Age	1.01 (1.00-1.01)	0.12	1.00 (1.00-1.01)	0.42	1.00 (1.00-1.01)	0.36
Sex (male)	1.13 (0.93-1.37)	0.22	1.31 (1.05-1.62)	0.016	1.32 (1.06-1.64)	0.012
Premorbid mRS	1.11 (1.01-1.21)	0.031	1.07 (0.96-1.19)	0.22	1.07 (0.96-1.19)	0.22
Systolic blood pressure (mmHg)	0.998 (0.995-1.001)	0.25	1.000 (0.996-1.004)	0.98	1.000 (0.997-1.004)	0.85
Glasgow Coma Scale (/15)	0.89 (0.85-0.93)	<0.001	0.94 (0.89-0.99)	0.013	0.94 (0.89-0.99)	0.020
Previous antiplatelet therapy	1.31 (1.05-1.62)	0.016	1.27 (1.00-1.62)	0.053	1.28 (1.00-1.64)	0.048
Intraventricular haemorrhage	0.78 (0.63-0.97)	0.026	0.66 (0.52-0.84)	0.001	0.65 (0.51-0.83)	0.001
Supratentorial lobar	1.59 (1.29-1.95)	<0.001	1.07 (0.81-1.40)	0.65	1.07 (0.81-1.40)	0.64
Baseline haematoma volume (per 10 mL increase)	1.17 (1.13-1.22)	<0.001	1.18 (1.12-1.26)	<0.001	1.18 (1.12-1.27)	<0.001
Onset to CT time (hours)	0.79 (0.73-0.86)	<0.001	0.75 (0.69-0.83)	<0.001	0.75 (0.69-0.83)	<0.001
Treatment with tranexamic acid	0.83 (0.68-1.00)	0.053	0.77 (0.63-0.94)	0.010	0.76 (0.62-0.93)	0.009
Blend sign	2.25 (1.75-2.88)	<0.001	1.53 (1.16-2.03)	0.003	1.49 (1.13-1.98)	0.005
Black hole sign	1.75 (1.37-2.23)	<0.001	2.03 (1.34-3.08)	0.001	-	-
Hypodensities	2.04 (1.66-2.51)	<0.001	-	-	2.06 (1.48-2.89)	<0.001
Island sign	1.77 (1.28-2.46)	0.001	0.85 (0.57-1.26)	0.42	0.84 (0.57-1.25)	0.39

*Model 1: adjustment for all variables in unadjusted analysis except hypodensities with addition of black hole X haematoma volume interaction (p=0.004). †Model 2: adjustment for all variables in unadjusted analysis except black hole sign with addition of hypodensities X haematoma volume interaction (p=0.008).

In the receiver operating characteristic (ROC) analysis for haematoma expansion, the area under the curve (AUC) for 3 predictors (haematoma volume, onset to CT time and prior antiplatelet agent) was 0.654. Addition of blend and black hole signs, and blend sign and hypodensities improved the AUC minimally to 0.664 and 0.667 respectively (Figure 6-2).

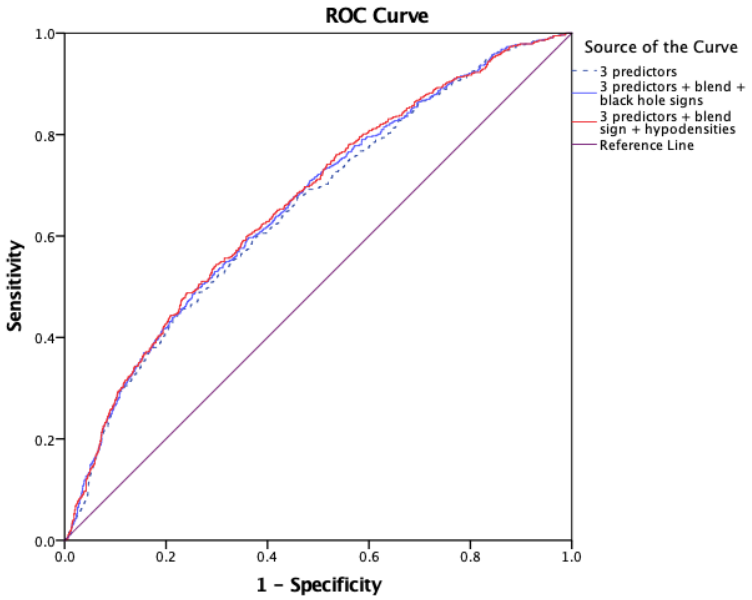


Figure 6–2 Area under the curve (AUC) for 3 predictors (onset to CT, baseline haematoma volume and prior antiplatelet)=0.654. Addition of blend and black hole signs to the predictors increased AUC to 0.664 while addition of blend sign and hypodensities increased AUC to 0.667.

As nearly 10% of patients did not have follow-up CT scans, we analysed haematoma progression and total ICH volume expansion as defined in the methods section as outcomes. Multivariable logistic regression adjusting for variables used in the analysis for haematoma expansion showed that blend sign, black hole sign and hypodensities were significant predictors of haematoma progression and total ICH expansion (Table 6-5)

Table 6-5 Multivariable logistic regression analysis for predictors of haematoma progression and total ICH expansion

Variables	*Adjusted OR (Model 1)	p	†Adjusted OR (Model 2)	p
Haematoma progression				
Blend sign	1.59 (1.20-2.11)	0.001	1.57 (1.19-2.08)	0.002
Black hole sign	1.56 (1.02-2.38)	0.039	-	-
Hypodensities	-	-	1.49 (1.07-2.07)	0.019
Island sign	0.94 (0.63-1.40)	0.76	0.95 (0.63-1.42)	0.79
Total ICH expansion				
Blend sign	1.64 (1.25-2.17)	<0.001	1.60 (1.21-2.12)	0.001
Black hole sign	1.97 (1.30-2.99)	0.001	-	-
Hypodensities	-	-	1.97 (1.41-2.76)	<0.001
Island sign	0.93 (0.63-1.37)	0.72	0.94 (0.64-1.38)	0.73

* Model 1 excludes hypodensities with adjustment for age, sex, premorbid mRS, systolic blood pressure, GCS, presence of IVH on baseline scan, lobar location, baseline haematoma volume, onset to CT time, prior antiplatelet therapy, treatment with tranexamic acid, black hole sign X haematoma volume. †Model 2 excludes black hole sign with adjustment of covariates similar to Model 1.

6.6.3.3 Predictors of functional outcome

1259 patients (54.6%) had poor functional outcome. Older age, female sex, worse premorbid mRS, lower GCS, previous antiplatelet therapy, intraventricular haemorrhage, lobar location, baseline haematoma volume and shorter onset to CT time were significant predictors of functional outcome (Table 6-6). Figure 6-3 illustrates the relation between baseline haematoma volume and functional outcome.

Amongst the NCCT signs, black hole sign, hypodensities and island sign were significant predictors of poor functional outcome after adjustment of prognostic covariates (Table 6-6). This was despite island sign not being significant predictors of haematoma expansion. On the other hand, the blend sign, which was an independent predictor of haematoma expansion, did not predict poor functional outcome. In ordinal regression analysis, only the presence of black hole sign (aOR 1.25, 1.01-1.56; p=0.045) and hypodensities (aOR 1.33, 1.10-1.61; p=0.003) resulted in significant shift towards worse modified Rankin Scale.

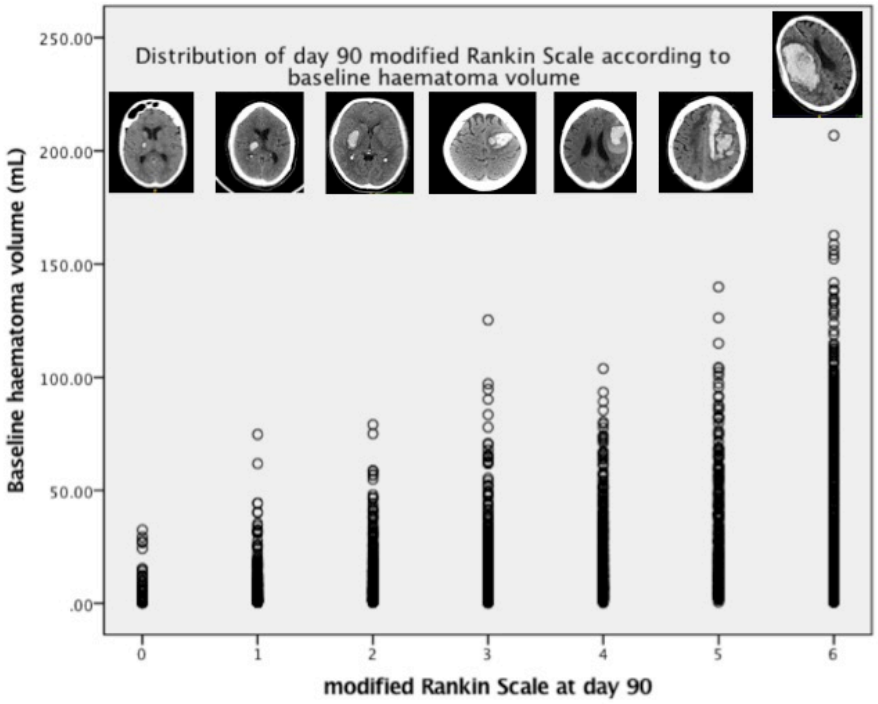


Figure 6–3 Scatter plot of distribution of modified Rankin Scale according to baseline haematoma volumes

Table 6-6 Binary logistic regression analyses for predictors of death and dependency (dichotomised modified Rankin Scale of ≥4)

Variables	**Unadjusted OR**	**p**	**Adjusted OR (Model 1)***	**p**	**Adjusted OR (Model 2)†**	**p**
Age	1.05 (1.05-1.06)	<0.001	1.05 (1.04-1.06)	<0.001	1.05 (1.04-1.06)	<0.001
Sex (male)	0.61 (0.52-0.72)	<0.001	0.76 (0.61-0.95)	0.016	0.77 (0.62-0.96)	0.019
Premorbid mRS	2.02 (1.81-2.25)	<0.001	1.71 (1.50-1.95)	<0.001	1.71 (1.50-1.95)	<0.001
Systolic blood pressure (mmHg)	0.998 (0.995-1.0)	0.104	1.000 (0.996-1.003)	0.81	1.000 (0.996-1.003)	0.87
Glasgow Coma Scale (/15)	0.66 (0.62-0.70)	<0.001	0.77 (0.72-0.82)	<0.001	0.77 (0.73-0.82)	<0.001
Previous antiplatelet therapy	2.20 (1.81-2.67)	<0.001	1.32 (1.02-1.71)	0.036	1.33 (1.02-1.72)	0.034
Intraventricular haemorrhage	3.43 (2.82-4.18)	<0.001	2.24 (1.76-2.87)	<0.001	2.26 (1.77-2.89)	<0.001
Supratentorial lobar	1.55 (1.29-1.86)	<0.001	0.39 (0.29-0.53)	<0.001	0.40 (0.29-0.54)	<0.001
Baseline haematoma volume (per 10 mL increase)	1.58 (1.49-1.68)	<0.001	1.60 (1.47-1.74)	<0.001	1.60 (1.47-1.76)	<0.001
Onset to CT time (hours)	0.91 (0.85-0.97)	0.003	0.87 (0.80-0.94)	0.001	0.87 (0.80-0.94)	0.001
Treatment with tranexamic acid	0.99 (0.84-1.16)	0.89	0.87 (0.71-1.08)	0.23	0.87 (0.70-1.07)	0.18
Blend sign	1.95 (1.54-2.47)	<0.001	1.05 (0.76-1.47)	0.76	1.04 (0.75-1.45)	0.81
Black hole sign	2.49 (1.97-3.15)	<0.001	1.52 (1.10-2.11)	0.012	-	-
Hypodensities	2.50 (2.07-3.03)	<0.001	-	-	1.37 (1.05-1.78)	0.019
Island sign	7.29 (4.68-11.35)	<0.001	2.59 (1.21-5.55)	0.014	2.21 (1.04-4.67)	0.037

*Model 1:Adjustment for all variables on unadjusted analysis except hypodensities with addition of black hole X island interaction. †Model 2: Adjustment for all variables on unadjusted analysis except black hole sign with addition of hypodensities X island interaction.

6.6.4 Effects of tranexamic acid on haematoma expansion and functional outcome

Overall, tranexamic acid reduced the risk of haematoma expansion (adjusted OR 0.77, 0.63-0.94; p=0.01). Similarly, there was significant reduction in haematoma progression (aOR 0.71, 0.59-0.86; p<0.001) and total ICH expansion (aOR 0.82, 0.67-0.99; p=0.047). Logistic regression model stratified by presence of NCCT signs did not show any significant interactions between the presence of signs and the benefit of tranexamic acid in reducing haematoma expansion (Figure 6-4). The effect of tranexamic acid on functional outcome, stratified by presence of NCCT signs is shown in Figure 6-5. Tranexamic acid did not significantly improve functional outcome regardless of the status of NCCT signs.

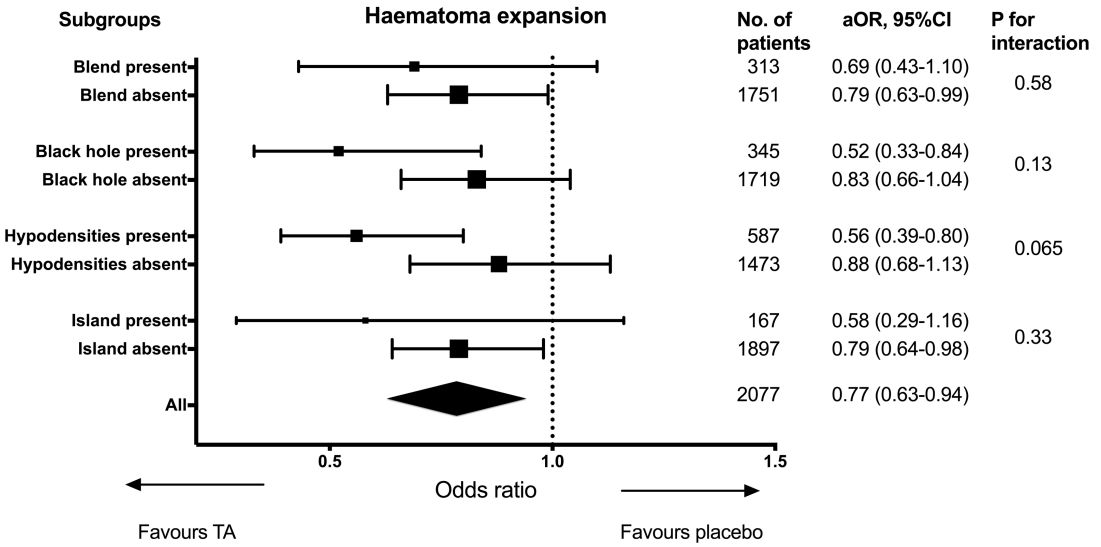


Figure 6-4 Effect of tranexamic acid on haematoma expansion, stratified by presence of NCCT signs

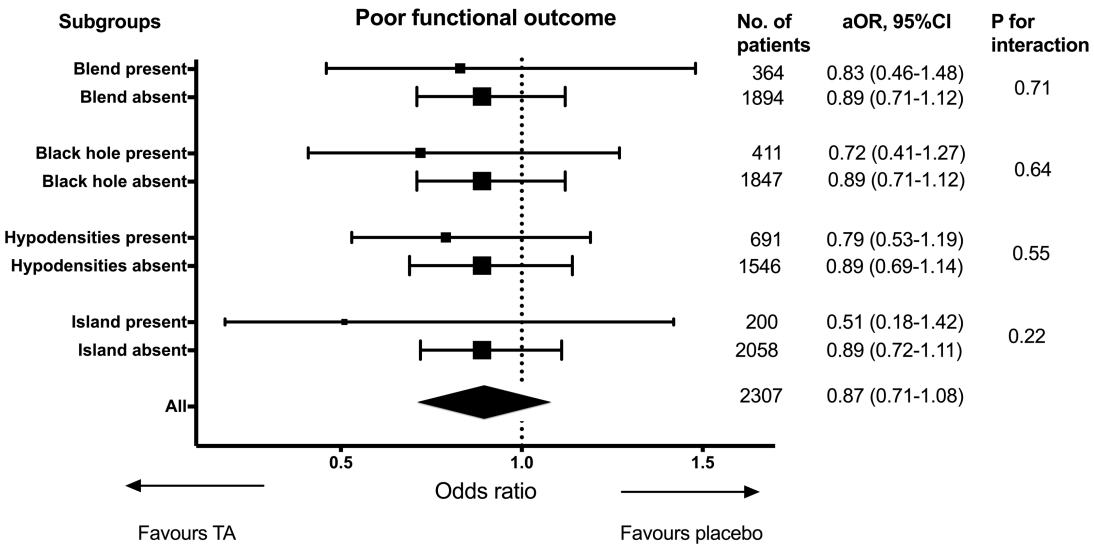


Figure 6-5 Effect of tranexamic acid on functional outcome, stratified by presence of NCCT signs.

6.7 Discussion

In the largest prospective randomised controlled trial of haemostatic therapy in intracerebral haemorrhage, we found that blend sign, black hole sign and hypodensities were independent predictors of haematoma expansion. Nevertheless, addition of these signs to more established predictors of onset to CT time, baseline haematoma volume and antiplatelet therapy only marginally improved the AUC. The island sign was not a significant independent predictor of haematoma expansion.

Apart from Li *et al* who first described the blend and black hole signs, two large studies, Boulis *et al* (n=1029) and Morotti *et al* (n=989) found them to be independent predictors of haematoma expansion.[109, 494] A recent meta-analysis of 5 studies (2248 patients) found the pooled sensitivity and specificity of blend sign to be 0.28 (0.16-0.46) and 0.92 (0.88-0.95) respectively.[499] A second meta-analysis of 5 studies (1495 patients) reported a pooled sensitivity and specificity of 0.30 (0.20-0.41) and 0.91 (0.87-0.94) respectively for black hole sign.[500] Our study similarly found blend and black hole signs to be highly specific but not very sensitive for prediction of haematoma expansion.

Hypodensities had been found to be a useful predictor of haematoma expansion and poor functional outcome as well.[109, 494] There is significant overlap between black hole sign and hypodensities where black hole sign is a subset of hypodensities. We found hypodensities to be more sensitive but less specific than black hole. The adjusted odd ratio of hypodensities was similar to that for the black hole sign (aOR 2.06 vs 2.01).

On the other hand, we did not find the island sign to be an independent predictor of haematoma expansion. The island sign was of particular interest as it was found to be very specific, albeit less sensitive, than the other NCCT signs. The island sign was first reported as a predictor of haematoma expansion and poor functional outcome in a single centre study by Li *et al*.[111] Similarly, we found the island sign to have high specificity but low sensitivity in detecting haematoma expansion. However, after accounting for

haematoma volume, the island sign did not independently predict haematoma expansion. This may be because island sign was mostly present in large haematomas (64.6 mL in island sign positive vs 11.8 mL in island sign negative); hence haematoma volume was a significant confounder. Comparatively, the median volume was 30 mL in island sign positive haematoma in Li *et al*.[111] Another reason is the prevalence of island sign in our cohort was relatively low (8.8% compared to 16% in Li *et al*) and the numbers may be inadequately powered to detect a difference.

Black hole sign, hypodensities and island sign independently predicted poor functional outcome, although island sign did not predict haematoma expansion. Conversely, the blend sign that independently predicted haematoma expansion did not predict poor functional outcome. This suggests that although haematoma expansion increased the risk of poor functional outcome, there were other factors that contributed to poor functional outcome. This finding is in keeping with the trial main results where tranexamic acid significantly reduced haematoma expansion, early death (< 7 days) and serious adverse events but did not improve functional outcome at day 90.[231] We hypothesise that one of the mechanism may be the development of perihaematomal oedema. Haematomas with island sign have a larger surface area of contact with the surrounding tissue and this may contribute to more inflammation and cerebral oedema.

While some of the NCCT signs are useful predictors of haematoma expansion, none of the signs reliably predicted clinical benefit of tranexamic acid. This again supports the hypothesis of alternate pathological process contributing to poor outcome. Although tranexamic acid reduced the risk of haematoma expansion, the effect of tranexamic acid is short lasting with a half-life of three hours.[333] It is therefore unlikely that tranexamic acid will have any biological effect on events occurring later such as perihaematomal oedema. In addition, the number of patients with NCCT signs is relatively small and may be inadequately powered to detect a modest benefit of tranexamic acid. The usefulness of the CTA spot sign in predicting clinical benefit of tranexamic acid is being studied in a separate sub-study.[497]

The strength of the study is the large sample size and good availability of CT scans, making this the largest imaging analysis in ICH. There is a large range of haematoma volume from very small to very large haematoma reflective of real world ICH patients. To account for intraventricular extension and missing data, we performed exploratory analysis using total ICH expansion and a composite outcome of haematoma progression (data available in 99.5%) as outcomes. The analyses yielded similar results hence the conclusion is robust.

One limitation of this study is the inter-rater agreement is only moderate (kappa 0.53 to 0.64). The raters were from a range of background (physicians, radiographer and medical student). Although all raters were trained prior to commencing assessment, the interpretation of the NCCT signs may not be as accurate as other studies where the assessments were usually performed by only 2 expert raters.[106, 107, 111, 494] Having more raters also reduced agreement, as it is less likely for 4 raters to completely agree on the presence of on signs compared to two raters. However, our interpretation represents a real world scenario where the raters are likely to have different background and experience.

Recently there is much enthusiasm in exploring the role of NCCT signs in predicting haematoma expansion. We found previously established factors of baseline haematoma volume and onset to CT time to be more significant predictors of haematoma expansion. Addition of NCCT signs only improved the AUC minimally by 0.01 to 0.013. Haematoma volume may be the most important CT marker of haematoma expansion and may be used to better select in future haemostatic trials. Although we have used semi-automated segmentation technique for the volume measurement, simple clinical tool such as the ABC/2 method has been shown previously to be a reliable and feasible method in the context of clinical trials.[501] In view of its prognostic value, calculation of haematoma volume should perhaps be recommended as a routine clinical practice.

6.8 Conclusion

Blend sign, black hole sign and hypodensities predict haematoma expansion while black hole sign, hypodensities and island sign predict poor functional outcome. NCCT signs did not predict a better response to tranexamic acid.

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Chapter 7 Endogenous plasminogen activators are associated with haematoma progression in spontaneous intracerebral haemorrhage

7.1 Publications contributing to chapter:

1. Law ZK, Rakkar K, Scutt P, Appleton JP, Bath PM, Bayraktutan U, Sprigg N. Endogenous plasminogen activators association with haematoma expansion and neurological deterioration in spontaneous intracerebral haemorrhage: findings from the TICH-2 plasma biomarkers sub-study. UK Stroke Forum 2018, Telford, UK. International Journal of Stroke 2018, Vol. 13(3S) 10–65

2. Law ZK, Rakkar K, Scutt P, Appleton JP, Bath PM, Bayraktutan U, Sprigg N. Endogenous plasminogen activators association with haematoma expansion and neurological deterioration in spontaneous intracerebral haemorrhage: findings from the TICH-2 plasma biomarkers sub-study. Division of Clinical Neuroscience Research day, Medical School, University of Nottingham, 18th December 2018

3. Zhe Kang Law, Michael Desborough, Kamini Rakkar, Polly Scutt, Jason P Appleton, Philip M Bath, Ulvi Bayraktutan, Nikola Sprigg. Endogenous plasminogen activators are associated with haematoma progression in spontaneous intracerebral haemorrhage: findings from the TICH-2 plasma biomarkers sub-study (abstract O-066 oral presentation): World Intracranial Haemorrhage Conference, Granada, Spain. 19-21 May 2019

4. Zhe Kang Law, Michael Desborough, Kamini Rakkar, Philip M Bath, Ulvi Bayraktutan, Nikola Sprigg. Elevated plasminogen activators are associated with hematoma progression in spontaneous intracerebral hemorrhage. (Submitted to Stroke)

7.2 Abstract

7.2.1 Background

Endogenous activation of fibrinolysis leads to persistent bleeding in traumatic causes of intracerebral haemorrhage and might explain haematoma growth in spontaneous intracerebral haemorrhage (ICH).

7.2.2 Methods

The Tranexamic acid for IntraCerebral Haemorrhage-2 (TICH-2) trial was a randomised controlled trial that tested the safety and efficacy of tranexamic acid in ICH within 8 hours of onset. In a single-centre substudy, plasma biomarker levels assessing fibrinolysis and haemostasis were measured using specific ELISA assays at baseline, 24 hours and day 7 in patients with ICH and compared with those in healthy controls. Levels in patients with and without haematoma progression (haematoma growth of >33% or 6mL at 24 hours; or early neurological deterioration and death in patients with no repeat CT scan) were compared.

7.2.3 Results

Twenty-two patients and nine healthy controls were recruited into this sub-study. Patients with ICH had significantly higher D-dimer and plasmin-alpha-2-antiplasmin complexes as compared to healthy controls. As compared to patients with no haematoma progression, those who progressed had higher baseline plasma urokinase-type plasminogen activator (uPA), median 555.6 [interquartile range 205.1, 706.4] vs 203.8 [93.6, 430.6] pg/mL (Mann-Whitney U test, p=0.053) and tissue-type plasminogen activator (tPA), 6234.2 [4229, 9251] vs 2801 [2398, 4351] pg/mL (p=0.01), and lower plasminogen, 199 [176.7, 208] vs 218.2 [202.6, 317.6] µg/mL (p=0.032). 24-hour matrix metalloproteinases-9 (MMP-9) was significantly increased in patients with haematoma progression, 270.8 [200.5, 322.6] vs 97.3 [60.3, 207.7] ng/mL (p=0.012) with a further increase on day 7, 656.6 vs 131.8 ng/mL (p<0.001). There were no significant differences in all plasma biomarker levels between patients treated with tranexamic acid and placebo.

7.2.4 Conclusion

Increased baseline uPA and tPA and 24-hour MMP-9 levels were associated with haematoma progression. Larger studies are needed to confirm these findings.

7.3 Background

Spontaneous intracerebral haemorrhage (ICH) is a devastating disorder with a high mortality rate of 40 to 50% at one month.[2] Up to 38% of cases of ICH are complicated by haematoma expansion, which leads to death and worse functional outcome.[86] While several risk factors including shorter onset to CT time, larger initial haematoma volume, prior antiplatelet and anticoagulant therapy were identified as predictors of haematoma expansion, the pathophysiological process underlying it is still poorly understood.[102]

Plasma biomarkers may provide some insight into the pathophysiological mechanisms of intracerebral haemorrhage. Several clinical studies explored the association of plasma biomarkers with haematoma volume and haematoma expansion in spontaneous intracerebral haemorrhage. A lower fibrinogen level was found to be significantly associated with haematoma expansion in a study of 627 patients[87] while other studies found no significant association.[117, 221, 502] Higher plasma thrombin-antithrombin complex levels were found to be associated with more severe ICH and larger haematoma volume in two studies of 60 and 90 patients.[117, 503] However a larger study of 358 patients found that thrombin-antithrombin complex levels were only increased in patients with intraventricular or subarachnoid extension.[221] Higher D-dimer levels were found to be associated with larger haematoma volume, presence of intraventricular and subarachnoid haemorrhage as well as poor outcome after intracerebral haemorrhage.[476, 504] A summary of studies on haemostatic/fibrinolytic factors is illustrated in Table 7-1.

Table 7-1 Human studies of haemostatic/fibrinolytic factors in intracerebral haemorrhage

Studies	No. of participants	Thrombin	Fibrinogen	D-dimer	Plasmin
Fujii 1998*[87]	627	NA	↓fibrinogen, ↑HV	NA	NS
Takahashi 1998*[117]	90	↑TAT, ↑HV	NS	NS	NA
Fujii 2001†[221]	358	↑TAT in IVH/SAH	NS	↑ in IVH/SAH	↑PAP in IVH/SAH
Marti-Fabregas 2010*[502]	90	NS	NS	NS	NS
Wu 2011[503]	60	↑TAT, ↑NIHSS,↓GCS	NA	NA	NA
Delgado 2006[476]	98	NA	NS	↑in larger HV, IVH and SAH	NA
Chiu 2012[504]	170	NA	NA	↑in larger HV, and SAH	NA

*Comparing levels between those with and without haematoma expansion. †Comparing levels with healthy volunteers. HV=haematoma volume; IVH= intraventricular haemorrhage; NA=not available; NS= not significant; PAP= plasmin-antiplasmin complex; SAH= subarachnoid haemorrhage; TAT= thrombin-antithrombin complex

Table 7-2 Roles of MMPs in intracerebral haemorrhage, adapted from Florczak-Rzepka *et al*.[206]

	MMP-2	MMP-3	MMP-9
Haematoma expansion	No[505]	No[505]	Yes[464]
Perihaematomal oedema	Yes[506], No[505]	No[505]	Yes[209, 464, 505, 506]
Neurological deterioration	No[505]	Yes[505]	Yes[209]

Matrix metalloproteinases (MMP-2, -3 and -9) were found to be increased after intracerebral haemorrhage in animal models.[208] MMP-9, also known as gelatinase B, is putatively involved in breaking down of basal lamina, leading to perihaematomal oedema.[208, 329] In human studies, MMP-9 was found to be associated with haematoma expansion (Table 7-2).[206, 464] In addition, MMP-2 and MMP-9 was found to be associated with perihaematomal oedema volume and neurological deterioration.[209, 505] The levels of MMP-2 were the highest at baseline with a gradual decline over the first 7 days while conversely MMP-9 gradually increased after 48 hours and peak at 7 days.[506] On the other hand, MMP-3 was found to be powerful predictor of mortality after intracerebral haemorrhage though no clear relation with haematoma expansion or perihaematomal oedema was found.[505]

The role of fibrinolysis in spontaneous intracerebral haemorrhage had not been established. Fibrinolysis is initiated by two major plasminogen activators, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) in response to tissue injury. TPA and uPA catalyse the cleavage of plasminogen converting it to the active plasmin form.[315] Plasmin binds to polymerised fibrin, leading to the breakdown of cross-linked fibrin and resolution of clot.[316] In theory, premature fibrinolysis and clot breakdown may contribute to haematoma expansion. However, previous studies showed that plasmin-antiplasmin complex, a marker of fibrinolytic activities, was not increased with haematoma growth unless complicated by intraventricular or subarachnoid extension (Table 7-1).[87, 221, 502]

In animal models of traumatic intracranial haemorrhage, endogenous plasminogen activation was found to contribute to delayed expansion of intracranial haemorrhage.[218] In ischaemic stroke, systemic coagulopathy and increased permeability of the blood-brain barrier were observed as probable mechanism of recombinant tissue plasminogen activator (rtPA) induced haemorrhagic transformation.[507] Some effects of plasminogen activators are independent of their actions on plasmin activation. In animal models, rtPA-

induced haemorrhagic transformation may also occur because of metalloproteinases or reactive oxygen species induced breakdown of the blood-brain barrier.[508] In addition, endogenous tPA induced blood-brain barrier opening by binding directly on LDL receptor-related protein (LRP) and N-methyl-D-aspartate (NMDA) on endothelial cells, with subsequent activation of matrix metalloproteinases.[507, 509] Plasminogen activators had not been previously shown to be associated with haematoma expansion in spontaneous intracerebral haemorrhage to the best of our knowledge.

In the Tranexamic acid for IntraCerebral Haemorrhage-2 (TICH-2) trial, we explored the effect of tranexamic acid, an antifibrinolytic agent, on patients with ICH. Although there was no significance benefit on day 90 modified Rankin Scale, patients who were treated with tranexamic acid had a significant reduction of haematoma expansion.[231] This suggests that endogenous fibrinolysis may have an important role in haematoma expansion. In this single centre sub-study, we explored the role of fibrinolytic process in haematoma expansion by studying several plasma biomarkers.

7.4 Methods

7.4.1 Aims

We explored if there are differences in plasma biomarkers between healthy controls and patients with ICH; and if there are any difference between ICH patients who experienced haematoma progression as compared to those who did not. We also assessed the effects of tranexamic acid on the plasma biomarkers.

7.4.2 Study population

The plasma biomarker sub-study was a single centre sub-study of the TICH-2 trial conducted in Nottingham City Hospital, United Kingdom. The TICH-2 trial was a prospective multi-centre randomised placebo-controlled phase 3 trial which examined the efficacy and safety of tranexamic acid in acute spontaneous ICH. The full details of the trials were published elsewhere.[231]

Patients recruited into the TICH-2 trial were eligible for the sub-study unless there was coagulopathy (prolonged prothrombin time or activated partial thromboplastin time of >1.5 times normal), systemic hypotension (systolic blood pressure < 90mmHg), or admission to intensive care unit.

In addition, healthy controls aged >18 years who were age- and sex-matched to the patients were recruited. Volunteers were not recruited if they had previously had a stroke, intracerebral haemorrhage, venous thromboembolism or medical illness requiring hospitalisation in the preceding three months, or taken tranexamic acid or an anticoagulant in the preceding seven days.

7.4.3 Ethical approvals and consent

Approval from the Nottingham University Hospital NHS Trust ethics committee and Medicine and Healthcare products Regulatory Agency (MHRA) were obtained in form of an amendment to the TICH-2 trial protocol (version 5.0 dated 26th May 2016, available from http://tich-2.org/links/protocol50). For TICH-2 trial participants, additional consent was taken for the sub-study from them or their relatives prior to enrolment. All healthy controls provided their own consent.

7.4.4 Blood sample collection and processing

Venous blood was collected using EDTA tubes at baseline (before the first dose of tranexamic acid or placebo) and at 24-hours and day 7. For healthy controls, only one blood sample was obtained. Blood samples were processed within 30 minutes of venepuncture. Platelet-poor plasma samples were obtained by centrifuging blood samples at 2000 g for 10 minutes at 4 ^{0}C. Plasma samples were then aliquoted and stored at -80 ^{0}C, then analysed in batches.

7.4.5 Assays and protocols

Assays assessed the following:

1) Plasma urokinase-type plasminogen activator (uPA; ab119611, Abcam, Cambridge, UK)
2) Plasma tissue-type plasminogen activator (tPA; ab190812 SimpleStep, Abcam, Cambridge, UK)
3) Plasma plasminogen (AssayMax, St Charles, US)
4) Plasma plasmin-alpha-2-antiplasmin complex (PAP; SKU: HPAPKT-COM, Molecular Innovations, Michigan, US). After activation plasmin rapidly binds with alpha-2 antiplasmin, hence PAP complex was measured instead of plasmin.[510]
5) Plasma D-dimer (ab196269 SimpleStep, Abcam, Cambridge, UK)
6) Plasma fibrinogen antigen (ab208036 SimpleStep, Abcam, Cambridge, UK)
7) Plasma thrombin-antithrombin complex (TAT; SEA831Hu, CloudClone, Texas, US).[117, 221, 503] Thrombin-antithrombin complex has been used as a surrogate for thrombin generation as the plasma half-life of thrombin is very short (56.4 ± 4.7 seconds).[511]
8) Plasma matrix metalloproteinase-2 (MMP-2; KHC3082, Invitrogen, California, US)
9) Plasma matrix metalloproteinase-9 (MMP-9; RK00217, ABclonal, Massachusetts, US)

All assays were sandwich ELISA assays and performed in duplicates according to suppliers' protocol.

7.4.6 Outcomes

Haematoma progression was defined as an increase in haematoma volume on follow-up scan of >33% or > 6 mL from baseline haematoma, or when follow-up scans were not available, early neurological deterioration (≥4 points increase in NIHSS or drop in GCS of ≥ 2) or death before day-2 clinical assessment.

7.4.7 Statistical analysis

7.4.7.1 Sample size calculation

Based a previous study, where mean D-dimer level for placebo group was 3612.5 ng/ml, tranexamic acid group 1125 ng/ml and pooled standard deviation of 1308.6 ng/ml; and assuming an type 1 error (α) of 0.05 and aiming for a power of 90%, the estimated sample size is 8 patients per group.[512, 513] The minimum sample size required is 16 patients and at least 8 healthy controls.

Due to the small sample size, data were assumed to be not normally distributed and this was tested using test of normality including Shapiro-Wilk test, histogram, P-P plot and Q-Q plot. Non-parametric tests (Wilcoxon signed rank test, Mann-Whitney U test and Kruskal-Wallis test) are used for statistical analyses. Data are shown as median [interquartile range, IQR], $p<0.05$ is considered significant and analyses were performed using Statistical Package for the Social Sciences (SPSS version 24, IBM, Armonk, NY).

7.5 Results

Twenty-two patients and nine healthy controls were recruited into the sub-study between August 2016 and September 2017. Plasma samples were collected in all participants for baseline comparison, 19/22 for day 2 (86.4%, 3 patients died by day 2) and 16/22 on day 7 (72.7%, 5 died and one on end-of-life care). The median time from onset to blood sampling for baseline, day 2 and day 7 plasma biomarkers was median 2 [IQR 2.0, 3.0] hours, 26 [23, 30] hours and 150 [142, 156] hours respectively. There were no statistically significant differences in the baseline characteristics between patients with ICH and the volunteers (Table 7-3). Nine patients received tranexamic acid while 13 received placebo. A greater proportion of patients who received tranexamic acid had lobar haemorrhage. Otherwise there were no other difference in baseline characteristics between patients receiving tranexamic acid and placebo. The mean haematoma volume was similar between participants receiving tranexamic acid vs placebo: 31.8 (43.1) mL vs 33.0

(46.8) mL. There were significantly higher baseline D-dimer and PAP levels in ICH patients compared to healthy controls. There were no significant differences in other baseline plasma biomarkers (Table 7-4).

Table 7-3 Baseline characteristics of ICH patients who received tranexamic acid or placebo and healthy controls

Variables	Tranexamic acid	Placebo	All ICH	Healthy controls	P*
Participants (N)	9	13	22	9	
Age (years)	74.8 (13.9)	74.5 (9.5)	74.6 (11.2)	66.9 (13.7)	0.11
Sex (male)	3 (33.3	8 (61.5)	11 (50)	4 (44.4)	0.78
Medical history (%)					
Prior stroke	0 (0)	2 (15.4)	2 (9.1)	0 (0)	0.35
Hypertension	4 (44.4)	8 (61.5)	12 (54.5)	3 (33.3)	0.28
Diabetes mellitus	2 (22.2)	4 (30.8)	6 (27.3)	1 (11.1)	0.33
Hypercholesterolaemia	1 (11.1)	3 (23.1)	4 (18.2)	1 (11.1)	0.63
Ischaemic heart disease	2 (22.2)	3 (23.1)	5 (22.7)	0 (0)	0.12
Atrial fibrillation	1 (11.1)	1 (7.7)	2 (9.1)	0 (0)	0.35
Previous venous thromboembolism	1 (11.1)	0 (0)	1 (4.5)	0 (0)	0.52
Previous intracerebral haemorrhage	1 (11.1)	0 (0)	1 (4.5)	0 (0)	0.52
Peripheral artery disease	0 (0)	1 (7.7)	1 (4.5)	0 (0)	0.52
Prior antiplatelet therapy	2 (22.2)	7 (53.8)	9 (40.9)	2 (22.2)	0.32
Prior statin	2 (22.2)	6 (46.2)	8 (36.4)	1 (11.1)	0.16
Glasgow Coma Scale	15 [12.5, 15]	14 [14, 15]	15 [14, 15]	-	-
NIHSS	11 [2.5, 20]	14 [6.5, 21]	13.5 [5.75, 19.5]	-	-
Haematoma location (%)†				-	-
Supratentorial deep	2 (22.2)	10 (76.9)	12 (54.5)	-	-
Supratentorial superficial	6 (66.7)	3 (23.1)	9 (40.9)	-	-
Infratentorial	1 (11.1)	0 (0)	1 (4.5)	-	-
Intraventricular haemorrhage	1 (11.1)	3 (23.1)	4 (18.2)	-	-
Subarachnoid extension	0 (0)	4 (30.8)	4 (18.2)	-	-
Haematoma volume (mL)	31.8 (43.1)	33.0 (46.8)	32.5 (44.2)	-	-
Perihaematomal oedema volume (mL)	13.5 (19.0)	16.7 (17.2)	15.4 (17.6)	-	-

Data are number (%), median [interquartile range] or mean (standard deviation). NIHSS=National Institute of Health Stroke Scale. *Comparison of ICH participants and volunteers by Chi-squared, Mann-Whitney U or Student t tests.
† Haematoma location differed between participants randomised to tranexamic acid and placebo, p=0.033

Table 7-4 Comparison of baseline and day 2 plasma biomarkers of patients with haematoma progression and no haematoma progression

Biomarkers	Healthy controls	All ICH	P	Baseline			Day 2		
				Haematoma progression (n=7)	No haematoma progression (n=15)	P*	Haematoma progression (n=4)	No haematoma progression (n=15)	P*
tPA (pg/mL)	3217.6 [2547.1, 4083.3]	3688.0 [2646.4, 6263.4]	0.49	6234.2 [4229, 9251]	2801.0 [2398.0, 4351]	0.010	5686.2 [3142.0, 6741.0]	3671.0 [2391.5, 4979.0]	0.19
uPA (pg/mL)	338.9 [97.0, 518.0]	245.9 [99.6, 550.0]	0.90	555.7 [205.1, 706.4]	203.8 [93.6, 430.6]	0.053	321.7 [150.2, 485.9]	141.9 [83.6, 268.0]	0.27
Plasminogen (µg/mL)	212.5 [182.0, 249.4]	211.5 [194.7, 273.1]	0.90	199.0 [176.7, 208.0]	218.2 [202.6, 317.6]	0.032	142.6 [135.7, 148.5]	188.1 [154.6, 213.6]	0.057
PAP (ng/mL)	1.2 [0.9, 1.5]	1.8 [1.1, 2.4]	0.026	1.4 [1.0, 2.6]	1.8 [1.7, 2.3]	0.75	1.1 [0.8, 2.1]	1.4 [0.8, 1.8]	0.69
TAT (ng/mL)	174.5 [159.3, 196.3]	183.5 [169.9, 200.5]	0.46	184.7 [175.1, 196.4]	182.3 [141.4, 220.3]	0.75	197.2 [147.2, 229.8]	182.8 [163.5, 221.9]	0.76
D-dimer (ng/mL)	357.0 [189.5, 425.5]	809.5 [417, 1294.5]	0.002	673 [411, 1279]	1012 [419, 1299]	0.50	271.0 [232.5, 1255.3]	752.0 [561.0, 1108.0]	0.11
Fibrinogen (mg/mL)	5.2 [2.2, 8.1]	4.8 [3.3, 7.2]	0.73	4.8 [3.9, 11.9]	4.5 [3.0, 6.7]	0.55	4.8 [4.0, 6.8]	4.9 [4.0, 8.8]	0.76
MMP-2 (ng/mL)	27.0 [23.0, 30.0]	26.0 [20.5, 27.5]	0.47	26.0 [22.0, 27.0]	24.0 [19.8, 29.8]	0.63	17.0 [8.0, 17.0]	21.0 [15.0, 25.0]	0.65
MMP-9 (ng/mL)	97.0 [77.2, 134.4]	142.0 [81.1, 199.6]	0.28	104.1 [24.4, 200.8]	148.3 [86.1, 199.2]	0.50	270.8 [200.5, 322.6]	97.3 [60.3, 207.7]	0.012

Data are median [interquartile range]. *Mann-Whitney U test is used for analysis. tPA= tissue-type plasminogen activator; uPA= urokinase-type plasminogen activator; PAP=plasmin-α2antiplasmin complex; TAT=thrombin-antithrombin complex; MMP-2 & -9=matrix metalloproteinases-2 & -9

Seven patients (31.8%) had haematoma progression including 3 (13.6%) with haematoma growth > 33% or 6 mL and 3 (13.6%) who died before day 2 and one with neurological deterioration and died on day 5. Patients with haematoma progression had significantly higher baseline tPA and lower plasminogen levels (Table 7-4). Although median uPA level was more than 2 times higher in the haematoma progression group, the difference was not statistically significant (p=0.053). There were no significant differences in baseline PAP, TAT, D-dimer, fibrinogen, MMP-2 and MMP-9 levels between those who had haematoma progression and those had not. There were significantly higher MMP-9 levels in patients with haematoma progression on day 2 (Table 7-4). Similar trend of higher tPA and uPA and lower plasminogen levels was observed on day 2 though the differences were not significant. Figure 7-1 illustrates the trend of tPA, uPA, plasminogen and MMP-9 between baseline, day 2 and day 7. TPA and uPA levels were higher initially in haematoma progression group before gradually declining to levels similar to patients without haematoma progression and healthy controls. Plasminogen levels in haematoma progression reduced further on day 2 before returning to baseline levels on day 7. Conversely, MMP-9 levels between groups were similar at baseline with levels in patients with haematoma progression gradually increase on day 2 and day 7.

Figure 7-2 shows the comparison of plasma biomarkers between the tranexamic acid and placebo group. Apart from day 2 plasminogen level, which was significantly lower in tranexamic acid group, there were no significant differences in plasma biomarkers between both groups.

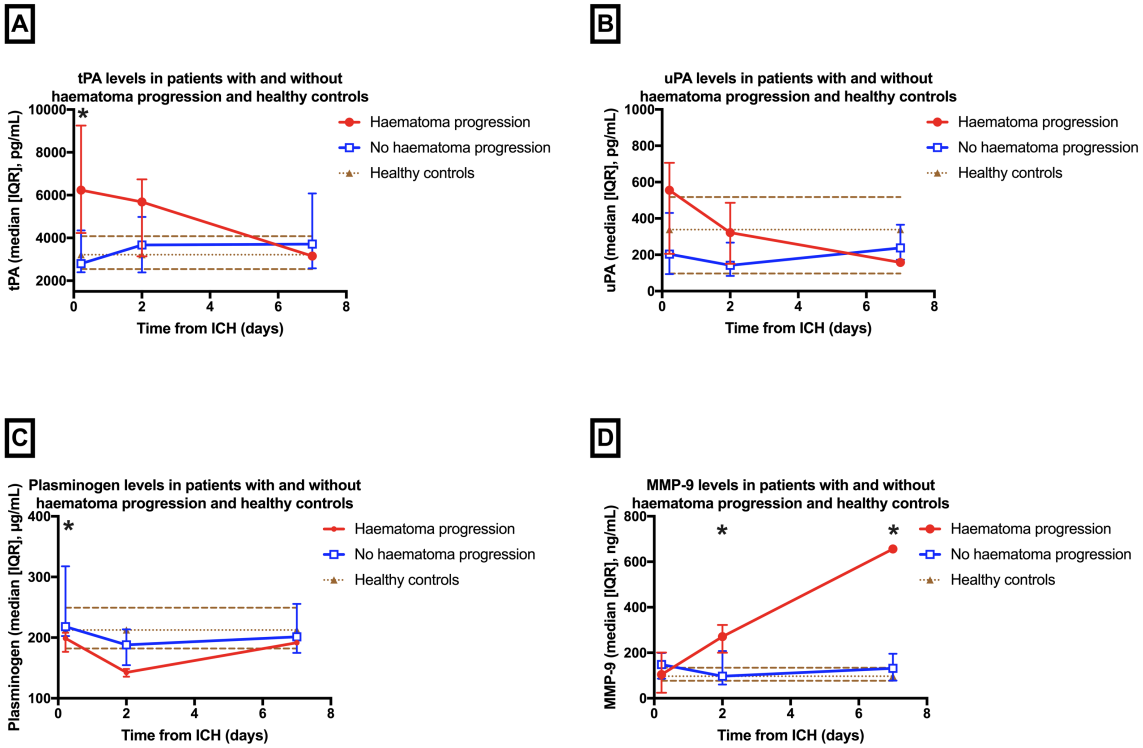


Figure 7–1 illustrates trend of tissue-type plasminogen activator (tPA), urokinase-type plasminogen activator (uPA), plasminogen and matrix metalloproteinase-9 (MMP-9) between baseline, day 2 and day 7. TPA and uPA levels were higher initially in haematoma progression group before gradually declining to levels similar to patients without haematoma progression and healthy controls. Plasminogen levels were lower in haematoma progression with further reduction on day 2 before returning to baseline levels on day 7. MMP-9 levels between groups were similar at baseline with levels in patients with haematoma progression gradually increase on day 2 and day 7. Note only one patient with haematoma progression was alive at day 7 and had levels analysed. * Indicates $p<0.05$ on Mann-Whitney U test comparison between haematoma progression and no haematoma progression. There was no difference in all baseline, day 2 and day 7 levels between the no haematoma progression group and healthy controls.

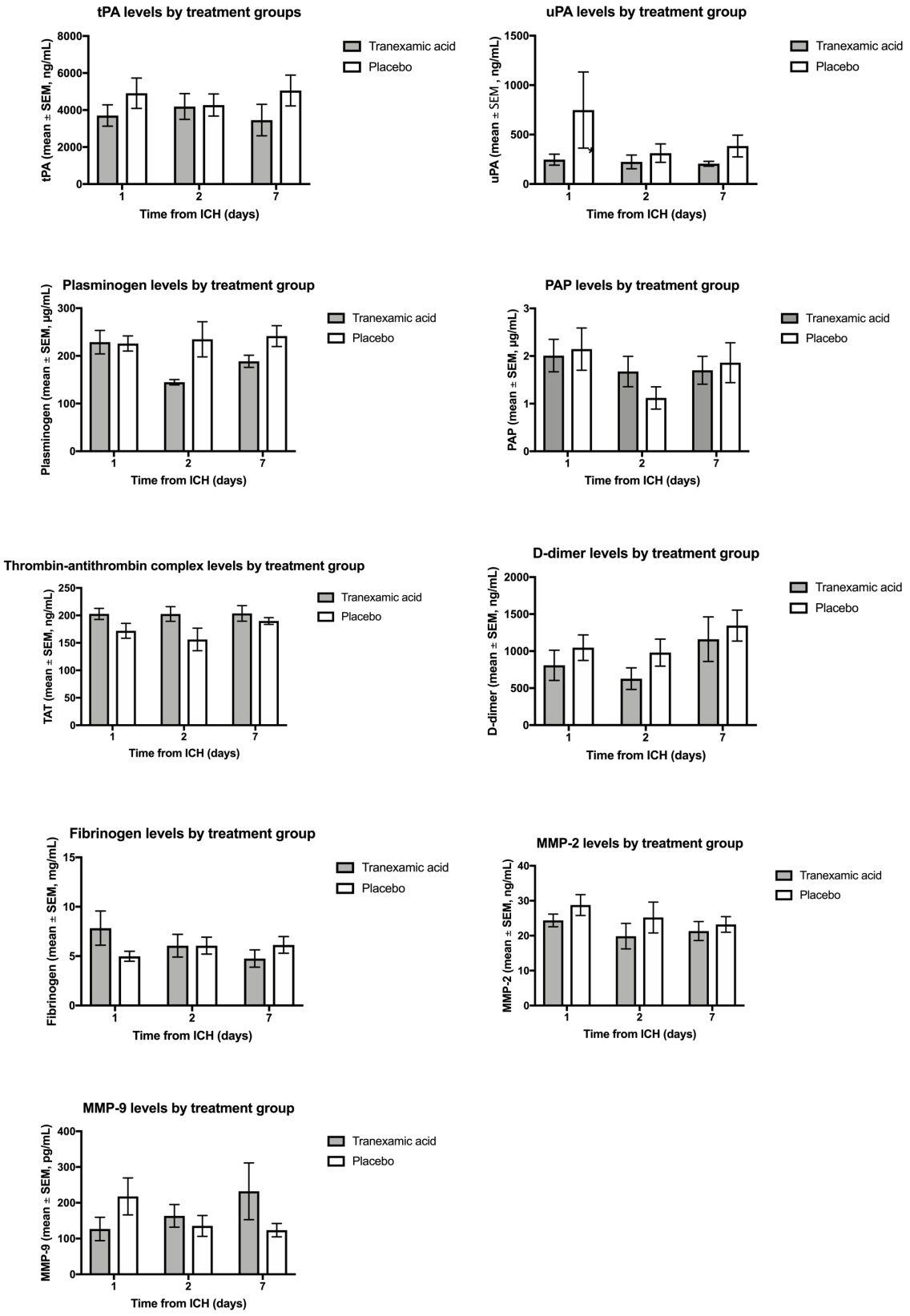


Figure 7–2 shows comparison of plasma biomarkers between tranexamic acid and placebo at baseline, 24 hours and day 7. There was no significant difference except for 24-hour plasminogen, which was lower in tranexamic acid group. *P<0.05.

7.6 Discussion

In this plasma biomarker sub-study of the TICH-2 trial, we found that patients with ICH had higher D-dimer and PAP levels, both markers of fibrinolysis, as compared to healthy controls. In ICH patients, elevated endogenous plasminogen activators, tPA and uPA, and reduced plasminogen levels at baseline were associated with haematoma progression. On the other hand, tPA, uPA and plasminogen levels in patients who did not have haematoma progression were similar to healthy controls. These results suggest endogenous plasminogen activators may play a role in haematoma progression in ICH. These findings have not been previously reported in patients with spontaneous ICH. MMP-9 levels at days 2 and 7 increased in participants with progression as compared to those with no progression. No differences were seen for D-dimer, PAP, TAT, fibrinogen and MMP-2.

D-dimer and PAP levels were not significantly higher in patients with haematoma progression despite elevated tPA and uPA. This finding is in agreement with several previous studies, which reported no difference in D-dimer and PAP levels between patients with and without haematoma growth.[476, 502, 504] One possible explanation is that systemic activation of the fibrinolytic system only occurs when there is intraventricular or subarachnoid extension, as supported by two studies, which showed significantly higher D-dimer and PAP in patients with intraventricular or subarachnoid extension:[221, 504] unfortunately our study only had 4 cases of intraventricular haemorrhage and subarachnoid extension so we cannot test this hypothesis. Alternatively, tPA and uPA may have acted via a plasmin-independent pathway. In animal models of ischaemic stroke, tPA and uPA up-regulate MMP-9, induce oxidative stress and inflammation, and disrupt the blood-brain barrier via plasmin-independent pathways, and so lead to haemorrhagic transformation.[337 508 514, 515] Similarly, in animal models of ICH, tPA and uPA increased haematoma expansion via the MMP-9 pathway.[516] In the current study, there was a progressive rise of MMP-9 levels on day 2 and day 7 in patients with haematoma progression, lending support to a plasminogen activators-MMP-9 effect hypothesis.

Tranexamic acid inhibits tPA and uPA activities but higher doses of tranexamic acid paradoxically potentiate uPA action.[517, 518] TPA levels peak soon after injury while the slower release of uPA means it peaks later at approximately 9 hours.[218] The delayed potentiation of uPA activities may explain why administration of tranexamic acid after 3 hours in postpartum haemorrhage and major trauma did not reduce bleeding-related death.[519] In our study, there was no difference in both tPA and uPA levels on day 2, possibly because blood sampling was performed at approximately 24 hours, when levels may have naturally declined in both tranexamic acid and placebo groups.

Tranexamic acid did not have significant effect on D-dimer levels in our study. Tranexamic acid had been found to lower D-dimer levels in major trauma, cardiac surgery, spinal surgery and postpartum haemorrhage.[512, 520-522] These are conditions with systemic fibrinolysis and high levels of D-dimer (>3000 ng/mL).[512, 520-522] However, D-dimer was only mildly elevated (median 810 ng/mL) in our cohort and may not be a good marker of the effects of tranexamic acid in intracerebral haemorrhage.

The strength of this study is its novelty in exploring the role of plasminogen activators in intracerebral haemorrhage, a mechanism that was not described previously. We also compared the effect of tranexamic acid on a broad range of plasma markers while previous studies mostly limited reports to effects on D-dimer. A main limitation of the current study was that it is exploratory in nature, and has a small sample size. Covariate-adjusted regression analysis, which would have allowed us to account for effects of variables such as haematoma volume, was not feasible due to the small sample size. Further, we did not measure inhibitors of fibrinolysis such as thrombin activatable fibrinolysis inhibitor (TAFI). Finally, due to the dynamic nature of spontaneous ICH, repeated sampling within the first 24 hours might have picked up more rapid changes in biomarker levels.

In conclusion, the role of uPA and tPA in haematoma progression in ICH needs to be further explored with larger studies. If the relation is proven

significant, there may be a role of using plasma biomarkers to target haemostatic treatment in ICH.

Chapter 8 Discussion and conclusion

8.1 Overview of the thesis

The main purpose of this thesis was to explore whether tranexamic acid has a beneficial effect in patients with acute spontaneous intracerebral haemorrhage. The thesis started with description of what we know about intracerebral haemorrhage, its complications and management (Chapter 1). The next two chapters (2 and 3) established what is known about the use of tranexamic acid and other haemostatic therapies in intracerebral haemorrhage. Chapter 4 described the clinical assessment tools used in the results chapters with more chapter-specific methods described in Chapter 5, 6 and 7. Chapter 5 described the predictors of neurological deterioration and seizures and the effects of tranexamic acid on both clinical outcomes. In Chapter 6, I explored the use of noncontrast CT signs as predictors of haematoma expansion and whether the use of these signs would help predict response to tranexamic acid. Chapter 7 explored the association of several plasma biomarkers with haematoma expansion and the effect of tranexamic acid on these biomarkers. The following summarises the key findings in each chapter.

8.1.1 Chapter 1 Background and literature review

The first chapter described the poor prognosis associated with intracerebral haemorrhage and the lack of definitive treatment. Current management strategy involved blood pressure reduction, reversal of anticoagulation, admission to stroke care unit, avoidance of early do not attempt resuscitation (DNAR) order and neurosurgery for selected patients.[288] One of the main complications of intracerebral haemorrhage in the acute stage is haematoma expansion, which leads to death and dependency.[86, 90, 91] Haematoma expansion can theoretically be ameliorated by reduction of blood pressure or haemostatic therapy.[383] Intensive reduction of blood pressure, though now established to be safe, did not significantly improved outcome in intracerebral haemorrhage.[161, 162, 253] Recombinant activated factor VII (rFVIIa) had been studied in several large randomised controlled trials but did not show

significant benefit.[265] A reduction in risk of haematoma expansion with rFVIIa was offset by an increase in thromboembolic events. Tranexamic acid had been effective in reducing bleeding-related death in polytrauma and post-partum haemorrhage.[342,370] There were several small studies that showed tranexamic acid as a promising haemostatic therapy in intracerebral haemorrhage. [390,391,393,394] With this background knowledge in mind, the next 2 chapters (2 and 3) systematically explored the available evidence for use of tranexamic acid and haemostatic therapies in intracerebral haemorrhage.

8.1.2 Chapter 2: Systematic review: Treatment of intracerebral haemorrhage with tranexamic acid – A review of current evidence and ongoing trials.

In this chapter, I performed a systematic review of literature searching for randomised controlled trials that explored the efficacy of tranexamic acid in spontaneous intracerebral haemorrhage.[523] The search included publications/ trial registers up till 13 May 2016. Two randomised controlled trials that included 54 patients were identified. One RCT reported reduction in haematoma expansion but did not test for statistical significance in difference in functional outcome between patients treated with tranexamic acid and placebo.[394] The second trial was a feasibility trial that was not designed to test efficacy.[393] In addition, there were six ongoing randomised controlled trials including the Tranexamic acid in IntraCerebral Haemorrhage-2 (TICH-2) trial. The conclusion was that there was no evidence up to the time of systematic review to support the use of tranexamic acid in spontaneous intracerebral haemorrhage.

8.1.3 Chapter 3: Systematic review: Haemostatic therapies for acute spontaneous intracerebral haemorrhage

This Cochrane systematic review was slightly different from the previous chapter as it included any form of haemostatic therapy as intervention of interest. The searches included publications/ trial registers up till November 2017. The interventions were classified into clotting factors, antifibrinolytic agents and platelet transfusion. Twelve randomised controlled trials (RCTs)

were included involving 1732 participants. There were seven RCTs of clotting factors versus placebo/control (1480 participants), three RCTs of antifibrinolytic agents versus placebo/control (57 participants), one RCT of platelet transfusion versus control (190 participants) and one RCT of clotting factors versus fresh frozen plasma (five participants). Clotting factors and antifibrinolytic agents did not improve outcome in patients with intracerebral haemorrhage. On the other hand, platelet transfusion was found to be harmful and should be avoided. There were six ongoing RCTs of tranexamic acid in intracerebral haemorrhage including TICH-2. However, the six RCTs were not exactly the same one as identified in Chapter 2. One planned RCT (EsICH) has changed its design to an observational study while a new RCT (TRANSACT) has been registered since Chapter 2 systematic review was published but has not started recruiting.[426] With the exception of TICH-2, all ongoing trials are still not completed at the time of writing of this chapter. The implications on research in terms of tranexamic acid in intracerebral haemorrhage was that more data from the ongoing trials were needed to make conclusions.[524] The Cochrane systematic review is due for update on 1st March 2020.

8.1.4 Chapter 4: Clinical assessments used in the Tranexamic acid in Intracerebral Haemorrhage-2 (TICH-2) trial

This chapter described the clinical assessment methods used in the TICH-2 trial including NIHSS, mRS, Barthel index, EuroQoL-5D-HUS, EuroQoL-VAS, ZDS and TICS-m all of which are common outcome measures in stroke trials.

8.1.5 Chapter 5: Clinical effects of tranexamic acid on neurological deterioration and seizures

The first section of Chapter 5 explored the predictors of neurological deterioration in the first 7 days after intracerebral haemorrhage. Neurological deterioration was further divided into early (<48 hours) and late (48 hours to 7 days). The hypothesis was that early deteriorations were largely driven by haematoma expansion, which occurs early, and late deteriorations were

attributed to development of perihaematomal oedema and medical complications. I found that previous intracerebral haemorrhage, higher systolic blood pressure, higher NIHSS, larger baseline haematoma volume, intraventricular haemorrhage, subarachnoid extension, midline shift, lobar location, antiplatelet therapy and leukoaraiosis were all significant predictors of early neurological deterioration. Older age, previous intracerebral haemorrhage, higher NIHSS, larger baseline haematoma volume predicted late neurological deterioration. While some factors were associated with reduced neurological reserve i.e. older age and previous intracerebral haemorrhage and leukoaraiosis, many of these factors were known risk factors for haematoma expansion (shorter onset to CT, antiplatelet therapy and larger haematoma volume). Haematoma expansion was 3 times more common in patients with neurological deterioration. Radiologically confirmed haematoma expansion was found in nearly 60% of patients with early neurological deterioration. Hence haematoma expansion was an important if not the most prominent factor contributing to neurological deterioration.

In addition, in patients who had early neurological deterioration, 18% had further neurological deterioration while one-fifth had neurological improvement on repeat assessment, indicating that the neurological deterioration was transient. Patients with further neurological deterioration were older, had more severe stroke, larger haematoma volume and greater haematoma expansion rate and absolute haematoma growth than those with transient neurological deterioration. Transient neurological deterioration was previously studied in ischaemic stroke and increased the risk of poor functional outcome despite being transient.[467] Our cohort was the first to look at transient neurological deterioration in intracerebral haemorrhage and showed that the risk of poor functional outcome at day 90 was increased but not the risk of death if compared to patients with no neurological deterioration. However, this exploratory analysis was limited by absence of repeat assessment in nearly one-third of patients.

Tranexamic acid significantly reduced haematoma expansion (aOR 0.77, 95%CI 0.63-0.94) but there was no significant reduction in growth of

perihaematomal oedema (PHO). At the same time, tranexamic acid reduced the risk of early (aOR 0.75, 95%CI 0.59-0.96; p=0.022) but not late neurological deterioration (aOR 0.73 95%CI 0.49-1.08; p=0.12). This suggests that the reduction in risk of neurological deterioration was attributable to the reduction in haematoma expansion.

Neurological deterioration is an important intermediate outcome as it was independently associated with an increased risk of death and dependency, disability, cognition, depression and quality of life scores at day 90. But more importantly it increases the risk of early death (< 7 days) by more than 30 times. The findings from this chapter were in keeping with the results from the main TICH-2 paper, which showed that tranexamic acid reduced early death and serious adverse events in the first seven days.[231] However this did not translate into improvement in functional outcome at day 90. In summary, tranexamic acid, through a reduction in risk of haematoma expansion, improved early outcomes but did not translate to long-term functional improvement.

There were several strengths in this study. Firstly, this was one of the largest studies of neurological deterioration in intracerebral haemorrhage. Only the INTERACT-2 trial had a larger sample size.[470] We defined neurological deterioration by comparing NIHSS and GCS at baseline, day 2 and day 7 but also take into account investigator reported neurological deterioration. To minimise data loss in those with missing NIHSS/GCS, I screened the SAE reports for indication of neurological deterioration (a decline in GCS/ increase in NIHSS) outside the scheduled assessments. As a result the status of neurological deterioration within the first week was available in more than 99% of the patients. We also looked at transient neurological deterioration, which was previously only reported in one study involving patients with ischaemic stroke.[467]

The second section of this chapter addressed the concerns regarding the increased risk of seizures with tranexamic acid. Although the risk of seizure was previously reported to be increased with tranexamic acid, most of the

previous studies involved patients who underwent cardiac surgery and were given high dose of tranexamic acid.[382] The risk of seizures is increased in intracerebral haemorrhage and whether tranexamic acid increases the risk further was not known. In our cohort, the incidence of seizures within 90 days of intracerebral haemorrhage was 8.3%, which was similar to previously reported incidence.[26-32] Lobar haematoma was a consistent risk factor of post-ICH seizures, while haematoma size was not. Younger age was also an independent predictor of early seizures. This was the first study based on RCT data that looked at risk of seizure with tranexamic acid in spontaneous intracerebral haemorrhage population. It was also the largest study of seizure in intracerebral haemorrhage to date and hence provided further data on risk factors of seizures in intracerebral haemorrhage. Reassuringly, the risks of any, early and late seizures in intracerebral haemorrhage were not increased with tranexamic acid compared with placebo. The incidence of seizure did not increase whether full dose or less than full dose was given. The incidence of seizure was also not increased in patients with renal impairment. This indicates that intravenous dose of tranexamic acid up to 2 g (or approximately 28 mg/kg total dose; or 14 mg/kg loading and 1.8 mg/kg/hour for 8 hours in a 70 kg adult) was safe in intracerebral haemorrhage.

8.1.6 Chapter 6: Noncontrast CT signs as predictors of haematoma expansion, functional outcome and response to tranexamic acid in acute spontaneous intracerebral haemorrhage

Haematoma expansion occurs in approximately one-third of patients with intracerebral haemorrhage.[86] To better research haemostatic agents, we need to target patients at greatest risk of haematoma expansion. Several established factors include shorter onset to CT time, larger haematoma volume, previous antiplatelet or anticoagulant therapy.[102] CT angiography spot sign was also predictive but advanced imaging was not readily available.[38] Several noncontrast CT (NCCT) signs such as blend sign, black hole sign, hypodensities and island sign had been found to be predictive of haematoma expansion and poor functional outcome.[106, 107, 109, 111,495, 496] In this chapter, I examined if these signs predict haematoma expansion and

poor functional outcome in our cohort. I also sought to examine if the presence of these NCCT signs predict better response to tranexamic acid. NCCT signs had relatively low sensitivity and high specificity. I found that blend, black hole and hypodensities were independent predictors of haematoma expansion while island sign was not. On other hand, black hole sign, hypodensities and island sign were independent predictors of poor functional outcome. However, receiver operating characteristic (ROC) curves analysis showed that addition of NCCT signs only marginally improved the area under the curve (AUC) compared to if only haematoma volume, onset to CT time and history of antiplatelet therapy were used. Subgroup analysis by the presence of NCCT signs showed that NCCT signs did not predict better response to tranexamic acid in terms of reduction in haematoma expansion and improvement in functional outcome. Although patients with black hole signs and hypodensities had significant reduction in haematoma expansion, while those without these signs did not, the interaction was not significant. This was indicative that the subgroup analysis was underpowered.

Our cohort was the largest RCT of haemostatic therapy in intracerebral haemorrhage to date. The availability of imaging data was relatively good compared to other RCTs in intracerebral haemorrhage. Nearly 90% (2077 patients) had a baseline and repeat CT scan which allowed the presence of haematoma expansion to be assessed. In comparison, the availability of repeat CT scan was 95% (800/841) in FAST trial, 87% (869/1000) in ATACH-2 and 32% (893 /2839) in INTERACT-2.[102,223,470] This makes the current study the largest imaging analysis in intracerebral haemorrhage. A recent individual patient data meta-analysis included 5435 patients from 36 studies.[102] Our cohort would make up nearly 40% of the total number in this IPDMA. Our cohort would be a valuable addition to existing literature on haematoma expansion in intracerebral haemorrhage. As there was no restriction on haematoma size for inclusion in the trial, our cohort had a wide range of haematoma volume from very small to very large which reflected a real-world scenario. In addition, we also explored total ICH expansion and haematoma progression. Haematoma progression was a composite outcome that consisted of haematoma expansion; and death or neurological

deterioration in patients who did not have a repeat CT. This was based on the assumption that most patients who died or had neurological deterioration within the first 24 hours had clinically significant haematoma expansion. This further increased the data availability to more than 99%. The use of haematoma progression as a composite outcome in intracerebral haemorrhage had not been used in previous studies, though this was published in the TICH-2 CT angiography spot sign sub-study statistical analysis plan.[497] The predictive value of NCCT signs for total ICH expansion and haematoma progression was similar compared to haematoma expansion, adding robustness to our conclusion. As none of the assessors of NCCT signs were expert neuroradiologists, the inter-rater agreement was only moderate to substantial. However, this reflected a real-world scenario where the clinician and local investigators are mostly not neuroradiologists. This meant NCCT signs could be utilised reliably as inclusion criteria in clinical trials or as a prognostic sign in clinical practice when assessed by non-neuroradiologists.

The NCCT signs had been the focus of research recently with many studies reporting them as reliable predictors of haematoma expansion and poor functional outcome and possible alternative to CTA spot sign.[106, 107, 109, 111,495, 496] With the exception of the island sign, the findings in this chapter were in agreement with previous studies, where blend sign, black hole sign and hypodensities independently predicted haematoma expansion. However, the addition of NCCT signs to known predictors of haematoma expansion (onset to CT time, baseline haematoma volume, history of antiplatelet or anticoagulant) only marginally improved the predictive probability. This meant that it might be equally or more useful to measure baseline haematoma volume. Haematoma volume measurement should be advocated as a routine practice.

8.1.7 Endogenous plasminogen activators are associated with haematoma progression in spontaneous intracerebral haemorrhage

This chapter described an exploratory plasma biomarker sub-study of the TICH-2 trial. The process of fibrinolysis is initiated by two major plasminogen activators, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) in response to tissue injury. TPA and uPA catalyse the cleavage of plasminogen converting it to active form plasmin.[315] Plasmin then binds to polymerised fibrin, leading to the breakdown of cross-linked fibrin and resolution of clot.[316] In addition, plasmin, tPA and uPA may also induce proinflammatory response through a myriad of mechanisms including through activation of MMPs.[328]

Intracerebral haemorrhage occurs with rupture of an intracranial vessel. The subsequent haematoma expansion was thought to be caused by shearing on surrounding blood vessels by an expanding haematoma, a theory known as the “avalanche” theory.[183] On the other hand, haemostasis is secured by platelet plug followed by fibrin clot formation. The rationale for antifibrinolytic agent in intracerebral haemorrhage was to prevent premature endogenous fibrinolysis that may lead to haematoma expansion. Endogenous fibrinolysis was reported to cause delayed intracerebral haemorrhage in animal models of traumatic brain injury.[218] Acute release of tPA and a delayed release of uPA was associated with persistent intracerebral haemorrhage.[218] However, fibrinolysis as a mechanism of haematoma expansion in spontaneous intracerebral haemorrhage had not been previously proven.

The novel findings in this chapter were uPA and tPA levels were significantly higher in patients with haematoma progression. These were elevated in the acute setting before gradual decline on day 2 and normalisation by day 7. This suggests that endogenous plasminogen activators may play a role in haematoma expansion, hence supporting the rationale of treatment with an antifibrinolytic agent. There was also a significant association between increased day 2 and day 7 MMP-9 levels with haematoma expansion. Tranexamic acid did not have any significant effect on any of the plasma

biomarkers. One possible reason was the repeat blood sampling was timed at 24-hours, when plasma biomarkers in both tranexamic acid and placebo groups would have naturally normalised. Furthermore, the sample size was small and may not be adequately powered to detect a difference.

8.2 Future work and directions

Spontaneous intracerebral haemorrhage is a devastating condition for which effective treatment remains elusive. Haematoma expansion is a common complication in the acute stage and is an obvious treatment target. Tranexamic acid is a potential haemostatic agent that had a modest effect on reduction of haematoma expansion but did not have significant effect on functional outcome in TICH-2.[231] This may be because the modest reduction in haematoma growth (1.4 mL) may not translate into significant clinical benefit. A larger sample size is needed to detect a modest treatment effect.[525] In addition, the broad selection criteria meant that patients who may not benefit from tranexamic acid were enrolled into the trial.[525] This thesis looked at the effect of tranexamic acid from clinical, radiological and biochemical perspectives and also reviewed published literature. Work outlined in this thesis may suggest improvement to future research or clinical practice, as discussed in the following.

Firstly, to better select patients at risk of haematoma expansion, neuroimaging findings are important. Findings from Chapter 6 were in keeping with previous studies that showed that blend sign, black hole sign and hypodensities were predictive of haematoma expansion[107,109, 494] but island sign was not. Haematoma volume was found to be a confounder as the mean haematoma volume of patients with island sign was much larger than those with no island sign. More studies are needed to validate island signs as a predictor of haematoma expansion. CT angiography spot sign was previous reported as a predictor of haematoma expansion. A subgroup analysis of TICH-2 patients with CT angiography is ongoing.[497]

Several predictive scoring systems for haematoma expansion had been developed in the past taking into account factors such as baseline haematoma volume, onset to CT time, history of antiplatelet or anticoagulant use, intraventricular extension, GCS, NIHSS, CTA spot sign, blend sign and hypodensities. [526-529] Future studies should examine further examine and compare the predictive capabilities of these scoring systems.[530] Regardless of scoring systems used or whether one or more NCCT signs were included, baseline haematoma volume was an important risk factor. Therefore baseline haematoma volume should probably be a selection criterion in future trials. Although the risk of haematoma expansion increases with larger baseline volume, patients with very large haematoma (> 60 mL) should probably be excluded, as the prognosis is poor.[95,102] The ABC/2 method is a simple bedside tool and can be performed in under a minute.[531] This method had excellent agreement with the semi-automated segmentation method.[532] Alternatively, the largest diameter of a haematoma correlates with functional outcome and may be an even easier substitute to haematoma volume measurement.[533] Haematoma volume is an important prognostic factor that should be taken into consideration in clinical decision-making. Hence, quantitative or semi-quantitative measurement of haematoma volume should form part of standard clinical care in addition to its use in research. However, to the best of our knowledge, this was not a routine practice in most hospitals.

Data from Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) and World Maternal Antifibrinolytic Trial (WOMAN) trial also suggest a time-dependent effect of tranexamic acid and the need to rapidly include patients in future trials.[519] However, utilising radiological selection criteria will likely increase time to recruitment, due to the need to perform radiological assessments at site or centrally.

To address the underpowered sample size, future trials would need to be larger. However, by being more selective using radiological findings and only recruiting patients who presented early, we are likely to limit recruitment rate. This may also limit the number of investigators, as they would need to be

trained on measurement of haematoma volume and identification of NCCT signs. Automated analysis of haematoma volume and NCCT signs may improve recruitment time and rate but it not widely available yet. Techniques for automated measurement of haematoma volume were already developed though not widely available for use in clinical practice.[534-536]

Pooling of data with meta-analysis had been used to improve evidence synthesis that was otherwise limited by insufficient sample size of individual trials. While working on chapter 2, our team had managed to made contact with most of the trialists involved in randomised controlled trials of tranexamic acid in intracerebral haemorrhage to form a collaboration. The main purpose of the collaboration was to embark on an individual patient data meta-analysis (IPDMA) once the trials are completed. We have co-authored an IPDMA protocol that was published in PROSPERO.[537] Chapter 3's Cochrane systematic review needs to be updated to include results from TICH-2 and other completed or published RCTs. A repeat systematic search is due 1st March 2020 to identify any new studies. The other trials were still ongoing and were expected to be completed in 2019/2020 (personal communication during European Stroke Organisation Conference 2018, Gothenburg, Sweden). However, the trials were estimated to add another 200 to 300 patients to the patient pool and therefore not expected to drastically change the conclusion.

In addition, a separate collaboration aiming for an IPDMA of tranexamic acid in intracranial haemorrhage were formed with the Clinical Randomisation of an Antifibrinolytic in Significant Head injury-3 (CRASH-3) team.[538] Although traumatic intracranial/intracerebral haemorrhage is a different condition than spontaneous intracerebral haemorrhage, this collaboration may perhaps identify if the effect of tranexamic acid is dependent on the aetiology of the haemorrhage.

A different timing of functional outcome assessment may be considered in the future. As discussed in Chapter 4, recovery after intracerebral haemorrhage may take more than 3 months, especially if higher cortical

functions were affected.[451] Many ICH trials had used modified Rankin Scale at 6 months as outcome assessment including STICH and CLEAR III trials.[224, 275] In fact, the MISTIE III trial assessed the primary outcome of modified Rankin Scale even later at one year.[226] The TICH-2 day 365 follow-up sub-study may address delayed recovery but extraneous events such as accidents, recurrent intracerebral haemorrhage or ischaemic heart disease may affect the functional outcome. As for radiological outcomes, haematoma progression may be a more sensitive outcome than haematoma expansion in future trials as this may limit loss of data.

The work from chapter 5 highlight the complex nature of the temporal evolution of intracerebral haemorrhage and the limitations faced by clinicians in investigating neurological deterioration in acute intracerebral haemorrhage. Haematoma expansion is the most common complication identified in patients with neurological deterioration. However, a substantial proportion of patients did not have repeat neuroimaging. In addition, nearly 20% of deterioration occurred after 48 hours, when haematoma expansion was reportedly rare. It is not known if cerebral oedema contributed to late neurological deterioration. The perihaematomal oedema (PHO) volume at 24 hour was not associated with increased risk of early or late neurological deterioration. PHO volume continues to grow till 2 to 3 weeks after intracerebral haemorrhage[478] but CT scans within this time window was not part of the trial protocol. A subgroup of patients underwent MRI at day 5 as part of TICH-2 MRI sub-study and the results may provide more insight into processes occurring in subacute stage of intracerebral haemorrhage. However, there was probably selection bias, as patients enrolled into the MRI sub-study had milder stroke and were stable enough to undergo an MRI. The results of MRI sub-study were not covered in this thesis.

As neurological deterioration heralded poor outcomes, future studies should also include repeat neuroimaging in subacute stage of intracerebral haemorrhage where feasible, to better study the evolution of neurological deterioration in intracerebral haemorrhage. However, the practically of performing repeat CT scans in patients with neurological deterioration

remains challenging as they may be medically unfit or on end of life care pathway.

Clinical and radiological assessments in intracerebral haemorrhage may be restricted by ethical consideration in avoiding further test in patients whom prognosis were perceived to be dismal. However, DNAR order should probably be deferred for a few days, as a substantial proportion (20%) of patients with early neurological deterioration subsequently improved. Patients at risk of neurological deterioration should be more closely monitored for medical complications such as pneumonia as well, as these were common and treatable causes of neurological deterioration.

The results from the seizure section provided reassurance that tranexamic acid did not increase the risk of seizure in intracerebral haemorrhage. The findings also highlight that lobar haemorrhage increased the risk of seizures and future trials of primary seizure prophylaxis in intracerebral haemorrhage should perhaps include patients with lobar haemorrhage only. Including EEG as a routine investigation in post-ICH seizures may improve the diagnosis of subclinical seizures but continuous EEG is not readily available.[135, 136]

Lastly, the plasma biomarker sub-study provided novel mechanistic evidence that endogenous fibrinolysis may be important in spontaneous intracerebral haemorrhage. The association between elevated baseline tPA and uPA and day 2 MMP-9 levels with haematoma progression would need to be studied in larger studies. Tranexamic acid did not have any significant effect on tPA and uPA levels possibly because repeat assays were sampled at 24 hours when the levels would have naturally declined independent of treatment assignment. Due to the dynamic changes in tPA and uPA levels within 24 hours of intracerebral haemorrhage, future studies should perform serial measurements of their levels in the first day. The effect of tranexamic acid on tPA and uPA in spontaneous intracerebral haemorrhage should be further studied as tranexamic acid may potentiate uPA activities that peak later (approximately 9 hours after onset).[218] Increased uPA activities were postulated as a possible reason for lack of benefit of tranexamic acid in

postpartum haemorrhage and major trauma.[518] An alternative antifibrinolytic agent, aprotinin, may be preferable in patients with late presentation, as it inhibits both tPA and uPA.[518] This needs to be studied further. One problem faced in the plasma biomarker sub-study was that it was initiated in later stage of the trial and logistical difficulties in storing and transporting blood samples prevented involvement of more centres in the sub-study. The recruitment of patients in the sub-study may be improved in future, if they were included as an optional sub-study from the inception of a trial. The feasibility of using plasma biomarkers to predict haematoma expansion in clinical practice and research remains to be examined. Even if any of the plasma biomarkers were established to be useful in the future, the assays would need to be performed rapidly to influence decision-making in clinical practice or research.

In short, future trials of tranexamic acid in intracerebral haemorrhage may take two approaches: include stricter criteria to better select patients who may benefit but risk low recruitment; or use broad selection criteria to try to improve recruitment. Perhaps a sensible approach would be to employ some exclusion criteria such as age of ≥80 years, haematoma volume of > 60 mL or presence of intraventricular haemorrhage as recommended by Hemorrhagic Stroke Academia Industry (HEADS)[539], with addition of one or more NCCT signs as selection criteria.

As tranexamic acid reduced haematoma expansion but did not have any significant biological effect beyond 24 hours, a factorial trial combining tranexamic acid in acute stage and an anti-oedema agent in the sub-acute stage may improve the yield of a positive trial. In fact, as any one treatment modality alone may not improve outcome in intracerebral haemorrhage, a bundled care approach may be the way forward. A “bundle” may consist of a combination of haemostatic therapy/ reversal of anticoagulation, blood pressure reduction, early neurosurgical referral, avoidance of DNAR and prevention of medical complication. One such trial, The Third, Intensive Care Bundle With Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial

(INTERACT-3) is already ongoing but did not include haemostatic therapy as part of treatment.[540]

8.3 Conclusion

This thesis explored haematoma expansion in intracerebral haemorrhage from clinical, radiological and biochemical perspectives. There were clinical, radiological and biochemical signals supporting the benefit of tranexamic acid in intracerebral haemorrhage. In addition, certain clinical, radiological and biochemical markers may be used to better select patients at risk of haematoma expansion.

Tranexamic acid is a widely available, easy to administer, low-cost and safe treatment. As there is some evidence that tranexamic acid may be beneficial in selected patients with acute intracerebral haemorrhage, there is a role for more clinical trials of tranexamic acid.

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Appendix

Appendix 1: MEDLINE Search Strategy (1946 -13 May 2016)

No.	Searches	Results
1	randomized controlled trial/	431538
2	randomization/	88992
3	Clinical Trial/	506013
4	(clin$ adj25 trial$).ti,ab.	343905
5	((singl$ or doubl$ or trebl$ or tripl$) adj5(blind$ or mask$)).ti,ab.	154093
6	placebo$.ti,ab.	185080
7	random$.ti,ab.	886872
8	or/1-7	1542988
9	Animal/ not Human/	4286513
10	8 not 9	1399817
11	exp basal ganglia hemorrhage/ or intracranial hemorrhages/ or cerebral hemorrhage/ or intracranial hemorrhage, hypertensive/ or cerebrovascular disorders/	77433
12	((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa) adj10 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.	52644
13	11 or 12	109368
14	(antifibrinolytic$ or tranexamic acid or acide tranexamique or acido tranexamico or acidum tranexamicum or tranexamsaeure or tranexamic acid or tranhexamic acid or trans AMCHA or trans-4-Aminomethyl cyclohexanecarboxylic acid or trans-4-aminomethylcyclohexane-1-carboxylic acid or trans-Amcha or trans-Tranexamic acid or Cyklokapron or Lysteda).tw.	4611
15	exp Antifibrinolytic Agents/	23593
16	14 or 15	25587
17	10 and 13 and 16	115

Appendix 2: EMBASE Search Strategy (1974 - 13 May 2016)

No.	Searches	Results
1	Randomized Controlled Trial/	403135
2	Randomization/	70305
3	Controlled Study/	4915321
4	control group/	88952
5	exp Clinical Trial/	1088127
6	Double Blind Procedure/	130646
7	Single Blind Procedure/	22048
8	placebo/	286997
9	experimental design/	12380
10	drug comparison/	131042
11	types of study/	733
12	research subject/	6058
13	Comparative Study/	709627
14	random$.tw.	1080912
15	(controlled adj5 (trial$ or stud$)).tw.	346989
16	(clinical$ adj5 trial$).tw.	377205
17	((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.	1625034
18	(quasi-random$ or quasi random$ or pseudorandom$ or pseudo random$).tw.	4707
19	((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.	190472
20	placebo$.tw.	237352
21	controls.tw.	887837
22	or/1-21	7989162
23	basal ganglion hemorrhage/ or brain hemorrhage/ or brain ventricle hemorrhage/ or cerebellum hemorrhage/	75648
24	((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa) adj10 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.	70348
25	23 or 24	107223
26	(antifibrinolytic$ or tranexamic acid or acide tranexamique or acido tranexamico or acidum tranexamicum or tranexamsaeure or tranexmic acid or tranhexamic acid or trans AMCHA or trans-4-Aminomethyl cyclohexanecarboxylic acid or trans-4-aminomethylcyclohexane-1-carboxylic acid or trans-Amcha or trans-Tranexamic acid or Cyklokapron or Lysteda).tw.	6180
27	22 and 25 and 26	133

Appendix 3: CENTRAL Search Strategy (1974 - 13 May 2016)

No	Searches	Results
1	MeSH descriptor: [Cerebral Hemorrhage] explode all trees	778
2	MeSH descriptor: [Basal Ganglia Hemorrhage] explode all trees	15
3	MeSH descriptor: [Intracranial Hemorrhage, Hypertensive] this term only	18
4	MeSH descriptor: [Intracranial Hemorrhages] explode all trees	1540
5	((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa) adj10 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$))	43
6	#1 or #2 or #3 or #4 or #5	1576
7	MeSH descriptor: [Tranexamic Acid] explode all trees	510
8	MeSH descriptor: [Antifibrinolytic Agents] explode all trees	545
9	(antifibrinolytic* or anti fibrinolytic* or antiplasmin* or plasmin inhibitor* or tranexamic or cyclohexanecarboxylic acid* or trans- 4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or kabi 2161 or transamin or exacyl or anvitoff or spotof or cyklokapron or ugurol or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or TXA)	2863
10	(Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Cyklokapron or Cymin or Dubatran or Examic or Existat or Extam or Fibran or Hemstate or Lysteda or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nixa-500 or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or T Stat or Tanmic or Temsyl-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or Trance Inj or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Tranxi or Trapic or Traxage or Traxamic or Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic)	820
11	#7 or #8 or #9 or #10	3635
12	#6 and #11	69

Appendix 4: Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 11) in the Cochrane Library (searched 27 November 2017)

#1 [mh hemostatics]

#2 [mh "Blood Coagulation Factors"]

#3 [mh ^hemostasis/DE] or [mh ^"blood coagulation"/DE] or [mh ^fibrinolysis/DE] or [mh "platelet activation"/DE] or [mh antithrombins] or [mh ^thrombin/AI]

#4 ((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag*) near/5 (drug* or agent* or treat* or therap*)):ti,ab

#5 (antifibrinolytic* or coagulat* next factor* or clotting next factor* or aminocaproic next acid or 6-aminocaproic next acid or "tranexamic acid" or aprotinin or factor next VII* or "factor 7" or "factor 7a" or NovoSeven or thrombin next inhib* or argatroban):ti,ab

#6 [mh ^"platelet transfusion"] or [mh ^"blood component transfusion"]

#7 [mh ^"blood platelets"]

#8 (infus* or transfus*):ti,ab

#9 #7 and #8

#10 ((platelet* or thrombocyte* or blood component*) near/5 (transfus* or infus*)):ti,ab

#11 #1 or #2 or #3 or #4 or #5 or #6 or #9 or #10

#12 [mh "basal ganglia haemorrhage"] or [mh ^"intracranial hemorrhages"] or [mh ^"cerebral haemorrhage"] or [mh ^"intracranial hemorrhage, hypertensive"]

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

#14 (ICH or ICHs):ti,ab

#15 #12 or #13 or #14

#16 #11 and #15

Appendix 5: MEDLINE Ovid (1946 to 27 November 2017)

1. exp hemostatics/

2. exp Blood Coagulation Factors/

3. hemostasis/de or blood coagulation/de or fibrinolysis/de or exp platelet activation/de or exp antithrombins/ or thrombin/ai

4. ((haemosta$ or hemosta$ or antihaemorrhag$ or antihemorrhag$) adj5 (drug$ or agent$ or treat$ or therap$)).tw.

5. (antifibrinolytic$ or coagulat$ factor$ or clotting factor$ or aminocaproic acid or 6-aminocaproic acid or tranexamic acid or aprotinin or factor VII$ or factor 7 or factor 7a or NovoSeven or thrombin inhib$ or argatroban).tw,nm.

6. platelet transfusion/

7. blood component transfusion/

8. blood platelets/ and (infus$ or transfus$).tw.

9. ((platelet$ or thrombocyte$ or blood component$) adj5 (transfus$ or infus$)).tw.

10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11. exp basal ganglia hemorrhage/ or intracranial hemorrhages/ or cerebral hemorrhage/ or intracranial hemorrhage, hypertensive/

12. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or stroke or apoplex$) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.

13. 11 or 12 or (ICH or ICHs).tw.

14. 10 and 13

15. Randomized Controlled Trials as Topic/

16. random allocation/

17. Controlled Clinical Trials as Topic/

18. control groups/

19. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/

20. double-blind method/

21. single-blind method/

22. Placebos/

23. placebo effect/

24. Drug Evaluation/

25. Research Design/

26. randomized controlled trial.pt.

27. controlled clinical trial.pt.

28. clinical trial.pt.

29. random$.tw.

30. (controlled adj5 (trial$ or stud$)).tw.

31. (clinical$ adj5 trial$).tw.

32. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

33. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

34. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

35. placebo$.tw.

36. controls.tw.

37. or/15-36

38. 14 and 37

39. exp animals/ not humans.sh.

40. 38 not 39

Appendix 6: EMBASE Ovid (1974 to 27 November 2017)

1. exp hemostatic agent/ or exp antifibrinolytic agent/ or exp blood clotting factor/ or exp thrombin inhibitor/

2. hemostasis/

3. exp blood clotting/

4. thrombocyte activation/

5. 2 or 3 or 4

6. drug effect/ or dt.fs.

7. 5 and 6

8. ((haemosta$ or hemosta$ or antihaemorrhag$ or antihemorrhag$) adj5 (drug$ or agent$ or treat$ or therap$)).tw.

9. (antifibrinolytic$ or coagulat$ factor$ or clotting factor$ or aminocaproic acid or 6-aminocaproic acid or tranexamic acid or aprotinin or factor VII$ or factor 7 or factor 7a or NovoSeven or thrombin inhib$ or argatroban).tw.

10. thrombocyte transfusion/

11. blood component therapy/

12. exp thrombocyte/ and (infus$ or transfus$).tw.

13. ((platelet$ or thrombocyte$ or blood component$) adj5 (transfus$ or infus$)).tw.

14. 1 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. basal ganglion hemorrhage/ or brain hemorrhage/ or brain ventricle hemorrhage/ or cerebellum hemorrhage/

16. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or stroke or apoplex$) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.

17. 15 or 16 or (ICH or ICHs).tw.

18. 14 and 17

19. randomized controlled trial/

20. "randomized controlled trial (topic)"/

21. Randomization/

22. Controlled Study/

23. control group/

24. exp clinical trial/

25. Double Blind Procedure/

26. Single Blind Procedure/ or triple blind procedure/

27. placebo/

28. drug dose comparison/

29. drug comparison/

30. "types of study"/

31. random$.tw.

32. (controlled adj5 (trial$ or stud$)).tw.

33. (clinical$ adj5 trial$).tw.

34. ((control or treatment or experiment$ or interventionl) adj5 (group$ or subject$ or patient$)).tw.

35. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

36. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

37. placebo$.tw.

38. controls.tw.

39. or/19-38

40. 18 and 39

41. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)

42. 40 not 41

Appendix 7: US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov for Chapter 3

Study Type: Intervention

Study results: All studies

Recruitment: All studies

Age group: Adults & seniors

Condition: (cerebral haemorrhage OR intracerebral haemorrhage OR intracranial haemorrhage OR intraparenchymal haemorrhage OR parenchymal haemorrhage OR intraventricular haemorrhage OR haemorrhagic stroke OR ICH OR intracerebral bleed)

Intervention (performed as four separate searches, and then de-duplicated, due to the word limit for search criteria): haemostatics OR haemostasis OR haemostatic agents OR haemostatic therapy OR haemostatic treatment OR antihaemorrhagic agent OR antihaemorrhagic therapy OR antihaemorrhagic treatment OR antihaemorrhage agent OR antihaemorrhage therapy OR blood clotting OR blood coagulation factors OR blood coagulation OR coagulation factors OR thrombin OR platelet activation OR thrombocyte activation OR platelet transfusion OR blood component transfusion OR thrombocyte transfusion OR antifibrinolytic agents OR antifibrinolysis OR tranexamic acid OR aminocaproic acid OR 6-aminocaproic acid OR aprotinin OR factor VIIa OR factor VII OR Factor 7a OR factor 7 or NovoSeven Or argatroban OR thrombin inhibitor OR desmopressin OR fresh frozen plasma OR FFP OR prothrombin complex concentrates OR PCC

Appendix 8: World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)

Condition: brain haemorrhage OR cerebral haemorrhage OR intracerebral haemorrhage OR intracranial haemorrhage OR intraparenchymal haemorrhage OR intraventricular haemorrhage OR cerebellar haemorrhage OR parenchymal haemorrhage OR infratentorial haemorrhage OR supratentorial haemorrhage OR basal ganglia haemorrhage OR basal ganglion haemorrhage OR thalamic haemorrhage OR putaminal haemorrhage OR posterior fossa haemorrhage OR hemispheric haemorrhage OR haemorrhagic stroke OR haemorrhagic apoplexy brain haematoma OR cerebral haematoma OR intracerebral haematoma OR intracranial haematoma OR intraparenchymal haematoma OR intraventricular haematoma OR cerebellar haematoma OR parenchymal haematoma OR infratentorial haematoma OR supratentorial haematoma OR basal ganglia haematoma OR basal ganglion haematoma OR thalamic haematoma OR putaminal haematoma OR posterior fossa haematoma OR hemispheric haematoma OR brain bleed OR cerebral bleed OR intracerebral bleed OR intracranial bleed OR intraparenchymal bleed OR parenchymal bleed OR intraventricular bleed OR cerebellar bleed OR infratentorial bleed OR supratentorial bleed OR basal ganglia bleed OR putaminal bleed OR posterior fossa bleed OR hemispheric bleed OR ICH OR ICHs

Intervention: haemostatics OR haemostasis OR haemostatic agents OR haemostatic therapy OR haemostatic treatment OR antihaemorrhagic agent OR antihaemorrhagic therapy OR antihaemorrhagic treatment OR antihaemorrhage agent OR antihaemorrhage therapy OR antihaemorrhage treatment OR blood clotting OR blood coagulation factors OR blood coagulation OR coagulation factors OR thrombin OR platelet activation OR thrombocyte activation OR platelet transfusion OR blood component transfusion OR thrombocyte transfusion OR antifibrinolytic agents OR antifibrinolysis OR tranexamic acid OR aminocaproic acid OR 6-aminocaproic acid OR aprotinin OR factor VIIa OR factor VII OR Factor 7a OR factor 7 or NovoSeven Or argatroban OR thrombin inhibitor OR desmopressin OR fresh frozen plasma OR FFP OR prothrombin complex concentrates OR PCC

Appendix 9: National Institute of Health Stroke Scale

	Component	Score
1a	Level of consciousness	0
		1
		2
		3
1b	Level of consciousness questions	0
		1
		2
1c	Level of consciousness commands	0
		1
		2
2	Gaze	0
		1
		2
3	Visual field	0
		1
		2
4	Facial	0
		1
		2
		3
5a	Motor arm-left	0
		1
		2
		3
		4
5b	Motor arm-right	0
		1
		2
		3
		4
6a	Motor leg-left	0
		1
		2
		3
		4
6b	Motor leg-right	0
		1
		2
		3
		4
7	Ataxia	0
		1
		2
8	Sensory	0
		1
		2
9	Best language	0
		1
		2
		3
10	Dysarthria	0
		1
		2
11	Extinction	0
		1
		2

Appendix 10: Telephone interview for cognitive status-modified version (TICS-m)

	Score
Orientation	
What **day** of the week is it?	
What is today's **date**?	
What is the **month**?	
What is the **year**?	
What **season** are we in?	
What is your age?	
What is your telephone number (code and number)?	
Registration/Free Recall	
I am going to read you a list of 10 words. Please listen carefully and try to remember them. When I am done, tell me as many as you can in any order. Ready?" "Now, tell me all of the words that you can remember"	
Cabin	
Pipe	
Elephant	
Chest	
Silk	
Theatre	
Watch	
Whip	
Pillow	
Giant	
Attention/ Calculation	
"Please take 7 away from 100. Now continue to take 7 away from what you have left over until I ask you to stop."	
93	
86	
79	
72	
65	
Please count backwards from 20 to 1	
Comprehension, Semantic and Recent Memory	
What do people usually use to cut paper?	
What is the prickly green plant found in the desert?	
What is the name of the reigning monarch (or head of state)?	
What is the surname of the current Prime Minister?	
What is the opposite direction to East?	
Language/Repetition	
Please say this: "**Methodist Episcopal**"	
Delayed recall	
Please repeat the list of 10 words I read earlier	
Cabin	
Pipe	
Elephant	
Chest	
Silk	
Theatre	
Watch	
Whip	
Pillow	
Giant	

Score 1 for each correct and 0 if incorrect; Max score 39 points

Appendix 11: The Barthel Index

Activities	Score
Feeding	
0 = unable	
5 = needs help cutting, spreading butter, etc., or requires modified diet	
10 = independent	
Bathing	
0 = dependent	
5 = independent (or in shower)	
Grooming	
0 = needs to help with personal care	
5 = independent face/hair/teeth/shaving (implements provided)	
Dressing	
0 = dependent	
5 = needs help but can do about half unaided	
10 = independent (including buttons, zips, laces, etc.)	
Bowels	
0 = incontinent (or needs to be given enemas)	
5 = occasional accident	
10 = continent	
Bladder	
0 = incontinent, or catheterized and unable to manage alone	
5 = occasional accident	
10 = continent	
Toilet use	
0 = dependent	
5 = needs some help, but can do something alone	
10 = independent (on and off, dressing, wiping)	
Transfer (Bed to chair and back)	
0 = unable, no sitting balance	
5 = major help (one or two people, physical), can sit	
10 = minor help (verbal or physical)	
15 = independent	
Mobility (On level surfaces)	
0 = immobile or < 50 yards	
5 = wheelchair independent, including corners, > 50 yards	
10 = walks with help of one person (verbal or physical) > 50 yards	
15= independent (but may use any aid; for example, stick) > 50 yards	
Stairs	
0 = unable	
5 = needs help (verbal, physical, carrying aid)	
10 = independent	

Score range 0-100

Appendix 12: EuroQoL-5D

Please indicate which of the following statements best describes your own health state today:

Mobility	
I have no problem walking about.	Level 1
I have some problems walking about.	Level 2
I am confined to bed.	Level 3
Self-care	
I have no problem with self-care.	Level 1
I have some problems washing or dressing myself.	Level 2
I am unable to wash or dress myself.	Level 3
Usual activities (e.g. work, study, housework, family or leisure activities)	
I have no problem performing my usual activities.	Level 1
I have some problems performing my usual activities.	Level 2
I am unable to perform my usual activities.	Level 3
Pain/discomfort	
I have no pain or discomfort.	Level 1
I have moderate pain or discomfort.	Level 2
I have extreme pain or discomfort.	Level 3
Anxiety/ depression	
I am not anxious or depressed.	Level 1
I am moderately anxious or depressed.	Level 2
I am extremely anxious or depressed.	Level 3

EuroQoL- Visual Analogue Scale

To help people say how good or bad a health state is, we have a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst you can imagine is marked by 0. We would like you to indicate on this scale how good or bad your own health is today, in your opinion?

Appendix 13: Zung Depression Rating Scale (short version)

	Seldom or never	Some of the time	Good part of the time	Most of the time
I feel down-hearted and blue	1	2	3	4
I have trouble sleeping at night	1	2	3	4
I get tired for no reason	1	2	3	4
I find it difficult to make decisions	1	2	3	4
My life is somewhat empty	1	2	3	4
Morning is when I feel best	4	3	2	1
I can eat as much as I used to	4	3	2	1
I feel hopeful about the future	4	3	2	1
I feel that I am useful and needed	4	3	2	1
I still enjoy the things I used to do	4	3	2	1

Short Zung IDS Index = 100 x Total / 40

Appendix 14: Work flow for sample collection, preparation and storage

1. Take consent for plasma biomarkers sub-study at the same time consent for main TICH-2 sub-study is taken.

2. Take baseline blood samples as soon as possible after consent, preferably with other routine clinical blood test and before randomised treatment is given. However, randomised treatment should not be unnecessarily delayed. Take 10ml of venous blood in 3 EDTA (purple) tube and one sodium citrate (blue) tube.

3. Sodium citrate blood samples should be sent to NHS clinical lab for D-Dimer, fibrinogen and coagulation profile, quote TICH-2 research code.

4. Two EDTA tube should be labelled with patient's trial ID (main study ID or sub-study ID). Fill up hard copy CRF for sub-study. Sub-study ID will be generated online after randomisation and be entered into CRF.

5. Process EDTA blood samples within 30 minutes at the Clinical Science Building.

6. Get P1000 precision pipette, 10 two-mLs sterile Eppendorfs and 10 pipette tips from C29.





7. Centrifuge samples using refrigerated centrifugation- 3500 RPM X 10 minutes at 4^0Celsius.



8. Aliquot supernatant (plasma) into 10 Eppendorfs, 350 µL each. Use P1000 pipette, set at 350 (see picture).

9. Label Eppendorfs using permanent marker- cryoware pen.

10. Store plasma samples (Eppendorfs) in B06 -80^0Celsius freezer.

11. Record in freezer log.

12. Update the time and date samples were taken in the sub-study CRF. The same CRF will be used for baseline, day 2 and day 7/ discharge blood samples.

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