Intracerebral haemorrhage expansion: definitions, predictors, and prevention

Andrea Morotti, Gregoire Boulouis*, Dar Dowlatshahi, Qi Li, Michel Shamy, Rustam Al-Shahi Salman, Jonathan Rosand, Charlotte Cordonnier, Joshua N Goldstein, Andreas Charidimou*

Haematoma expansion affects a fifth of patients within 24 h of the onset of acute intracerebral haemorrhage and is associated with death and disability, which makes it an appealing therapeutic target. The time in which active intervention can be done is short as expansion occurs mostly within the first 3 h after onset. Baseline haemorrhage volume, antithrombotic treatment, and CT angiography spot signs are each associated with increased risk of haematoma expansion. Non-contrast CT features are promising predictors of haematoma expansion, but their potential contribution to current models is under investigation. Blood pressure lowering and haemostatic treatment minimise haematoma expansion but have not led to improved functional outcomes in randomised clinical trials. Ultra-early enrolment and selection of participants on the basis of non-contrast CT imaging markers could focus future clinical trials to show clinical benefit in people at high risk of expansion or investigate heterogeneity of treatment effects in clinical trials with broad inclusion criteria.

Introduction

Stroke caused by intracerebral haemorrhage has few therapeutic options, and final haematoma volume is the strongest prognostic determinant of functional outcome.[1] Haematoma expansion occurs, on average, in 20% of patients with intracerebral haemorrhage and worsens functional outcome.[2,3] Although prevention of haematoma expansion might be an appealing therapeutic strategy, no treatments investigated so far have improved functional outcome.[4] A crucial challenge is the rapid identification of patients at highest risk for haematoma expansion at the time they present with intracerebral haemorrhage. Although stopping the ongoing bleeding might improve patient outcomes, there are four important points that should be clarified before future randomised clinical trials can test this hypothesis: the amount of haematoma expansion that is clinically significant; which biomarkers best identify individuals at highest risk for significant haematoma expansion; the interventions that are most effective at stopping bleeding; and the reasons why a successful restriction of haematoma expansion might not improve functional outcome. Novel definitions of haematoma expansion have provided insights into the effect of acute phase treatments, questioning widely accepted cutoffs for defining a clinically significant haematoma expansion.[5]

Some clinical variables can help to predict the risk of haematoma expansion[3] and several non-contrast CT features are promising biomarkers.[6] The use of non-contrast CT can help in stratifying patients according to risk, even in mobile stroke units.[7,8] Furthermore, deep-learning methods might improve imaging-based prediction models and identify the patients who are likely to benefit from effective anti-expansion therapies.[9] The therapeutic time window in which haematoma expansion can be restricted is short and most therapeutic approaches are probably most effective when administered early in the natural history of the disease.[4,10] In this Review, we provide a critical assessment of advances in the past 5 years on the definition of haematoma expansion, clinical effects, outcome prediction, and prevention.

Definition and clinical effects of haematoma expansion

Haematoma expansion, measured as the increase in haematoma volume on serial neuroimaging, is a major cause of early neurological deterioration and poor clinical outcome after intracerebral haemorrhage.[11] However, the relationship between the time of intracerebral haemorrhage onset and risk of expansion is non-linear; the highest expansion risk is seen within the first 3 h and risk plateaus after 6 h.[3] Approximately a fifth of patients with intracerebral haemorrhage, or a third of patients presenting within 6 h of symptom onset, will have haematoma expansion.[3,12] The pathophysiology of haematoma expansion is complex and remains controversial. Different models and biological mechanisms have been proposed that might contribute to active bleeding and haematoma enlargement (figure 1; panel 1).

There have been several approaches to establish a definition for clinically significant haematoma expansion in intracerebral haemorrhage. The first definition proposed a threshold of 40% relative increase or 12·5 mL absolute increase in haematoma volume and was based on a consensus between investigators regarding their ability to visually discriminate differences between baseline (at the time of initial imaging when the diagnosis of intracerebral haemorrhage is made) and follow-up brain scans.[21] An alternative threshold of 33% relative growth was subsequently proposed based on the observed variability in volumetric analysis, which was consistently less than this threshold, and the mathematical relationship between volume and diameter of a sphere (in which a 33% change in volume is related to a 10% change in diameter).[22] Studies published in the past 6 years describe a relationship between the baseline intracerebral haemorrhage volume and the minimal detectable difference in haematoma growth, suggesting that definitions with

Lancet Neurol 2023; 22: 159–71

Published Online October 26, 2022 https://doi.org/10.1016/S1474-4422(22)00338-6

*Contributed equally

Neurology Unit, Department of Neurological Sciences and Vision, Azienda Socio Sanitaria Territoriale Spedali Civili, Brescia, Italy (A Morotti MD); **Diagnostic and Interventional Neuroradiology Department, University Hospital of Tours, Tours, France** (G Boulouis PhD); **Department of Medicine, Division of Neurology, University of Ottawa and Ottawa Hospital Research Institute, Ottawa ON, Canada** (Prof D Dowlatshahi PhD, M Shamy MD MA); **Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China** (Prof Q Li MD PhD); **Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK** (Prof R Al-Shahi Salman PhD); **Division of Neurocritical Care** (Prof J Rosand MD, Prof J N Goldstein MD), **Department of Emergency Medicine** (Prof J N Goldstein), **and Henry and Allison McCance Center for Brain Health** (Prof J Rosand), **Massachusetts General Hospital, Boston, MA, USA; Universite Lille, Inserm, CHU Lille, U1172, LilNCog, Lille Neuroscience and Cognition, F-59000 Lille, France** (Prof C Cordonnier PhD); **Department of Neurology, Boston University Medical Center, Boston University School of Medicine, Boston, MA, USA** (A Charidimou PhD)

Correspondence to: Dr Andrea Morotti, Neurology Unit, Department of Neurological Sciences and Vision, Azienda Socio Sanitaria Territoriale Spedali Civili, Brescia 25123, Italy **andrea.morotti@ASST-spedalicivili.it**

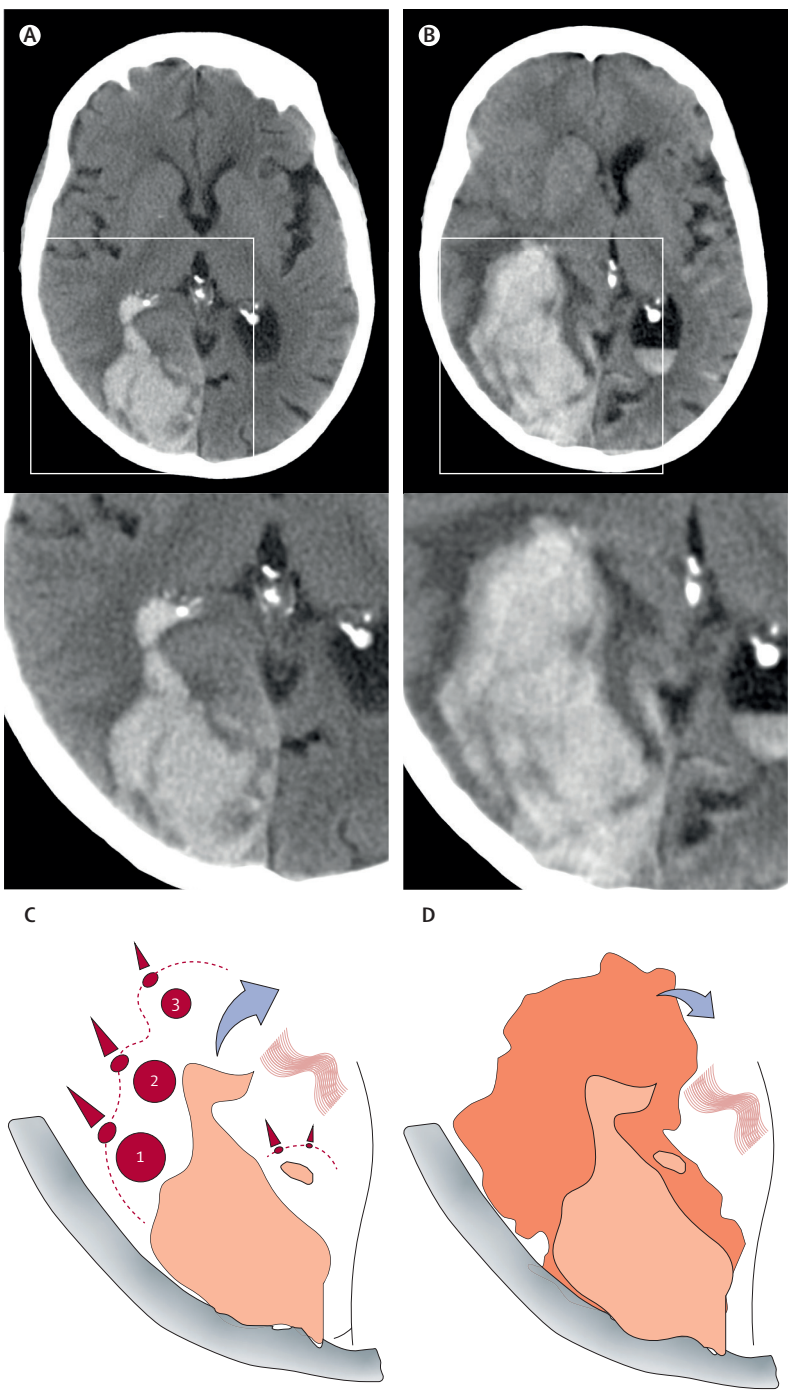

Figure 1: **Baseline and follow-up non-contrast CT with haematoma expansion**
Non-contrast CT in a man aged 68 years with acute intracerebral haemorrhage, imaged at 5 h (A) and 17 h (B) since symptom onset, showing significant intercurrent haemorrhage expansion (70%). (C) Schematic representation of the baseline bleed on initial imaging (highlighted in orange) and the hypothesis of secondary bleedings (numbers 1, 2, and 3) from sequentially active bleeding sites, expanding the mass effect in the direction of the red arrows. The blue arrow represents intraventricular extension, and the red lines show a bundle of fibres representing physical constraint and restricting expansion in a particular direction. (D) Schematic of the final haemorrhage volume, with superimposed co-registered previous bleed size (highlighted in orange).

Panel 1: **Pathophysiology of haematoma expansion**

- The simplest biological model of haematoma expansion assumes that intracerebral haemorrhage originates from a single small vessel rupture event, with haematoma formation continuing until clot stabilisation and mechanical resistance from surrounding brain structures counteract the force of active bleeding[13,14]
- Perihaematomal hypoperfusion is common after intracerebral haemorrhage[15] and might be associated with reduced tissue integrity and reduced resistance to haematoma expansion[16]
- In the avalanche model introduced by Charles Miller Fisher,[17] the mass effect of the initial haemorrhage triggers the rupture of adjacent pathological small vessels around the primary haemorrhage, contributing to further bleeding and leading to the final haematoma volume[14]
- Multiple studies showed that acute intracerebral haemorrhage could be composed of blood regions with different ages, supporting the hypothesis of several bleeding events occurring in a sequential way;[18,19] bleeding from the rupture of secondary vessels has been shown in a proof-of-concept study in mice[20]
- Blood pressure and coagulation status might influence acute intracerebral haemorrhage formation,[20] but whether these two factors have a direct causal effect or are cofactors that influence the extent of blood that extravasate at each rupture site remains unclear

smaller thresholds are most suitable (eg, expansion of less than 3 mL for haematomas with baseline volumes larger than 10 mL, or expansion of less than 6 mL for haematomas with baseline volumes larger than 50 mL).[23] Although these definitions appropriately consider the minimal detectable difference in measurement techniques, they do not consider correlations with clinical outcomes after intracerebral haemorrhage.

When the minimal relevant clinical difference was assessed, any increase in haematoma volume (measured with semi-automated volumetric methods) had a significant effect on outcome. Every 1 mL of haematoma expansion was associated with a 5% increased risk of death or dependency.[24] When the various thresholds for significant haematoma expansion were tested against clinical outcomes, all of them (including 3 mL, 6 mL, 12·5 mL, or 33% relative growth) predicted poor clinical outcome.[2] Moreover, parenchymal haematomas frequently expand into the ventricular space,[25] which can be missed if definitions do not incorporate ventricular expansion,[26] and the relationship between intraventricular haemorrhage expansion and outcome is exponential.[27] Haematoma expansion could also be analysed as a spectrum, with a haematoma shift analysis. This approach might provide novel insights into the pathophysiology of active intracerebral bleeding and the biological effects of therapeutic strategies.[5]

Observational studies and clinical trials require a consensus definition of significant haematoma expansion to facilitate comparisons across studies. The ideal definition would have a volume threshold over the minimal detectable difference of the measurement technique, incorporate intraventricular haemorrhage expansion, and clearly and meaningfully correlate with clinical outcome. However, from the strictly clinical perspective, any measurable increase in haematoma volume is detrimental for patients with intracerebral haemorrhage.

Predictors of intracerebral haemorrhage expansion

Time from onset to first brain imaging

Haematoma expansion is an early event in the natural history of intracerebral haemorrhage; most of the bleeding usually occurs in the first 3–6 h after symptom onset.[13] The relationship between timing of diagnostic imaging and haematoma expansion is not linear and the risk of haematoma expansion declines as the time from symptom onset to baseline non-contrast CT increases,[3] but continues to remain high in patients with anticoagulant-associated intracerebral haemorrhage until the coagulopathy is corrected.[28] In approximately a third of patients with intracerebral haemorrhage, the time of intracerebral haemorrhage onset is unknown and haematoma expansion is common and associated with poor outcome.[29]

Antithrombotic treatment

Patients with underlying coagulopathy are at high risk of haematoma expansion for long periods of time, either because bleeding lasts for a long time or because it is likely to resume once it has stopped.[28] Patients with vitamin K antagonist-associated intracerebral haemorrhage can have a risk of expansion of more than 50% in the first 6 h after symptom onset, continuation of expansion well beyond 24 h, and have more than double the odds of death compared with a patient without coagulopathy.[28] Similarly, direct oral anticoagulant-associated intracerebral haemorrhages have an increased risk of expansion,[30] but the risk is less than that in vitamin K antagonist-associated intracerebral haemorrhages, and clinical outcomes are less severe.[31] Antiplatelet use is also a predictor of haematoma expansion, although the risk is not as high as in intracerebral haemorrhage associated with anticoagulation.[3]

Imaging predictors

Imaging can identify patients at high risk for haematoma expansion. Neuroimaging markers might improve our understanding of the mechanisms of haematoma expansion. Imaging predictors of haematoma expansion rely almost entirely on CT because of its wide availability and preponderant use at the acute phase of stroke. The most important imaging biomarker for risk of haematoma expansion is baseline haemorrhage volume.[3] Patients with moderate to large intracerebral haemorrhage volumes (highest risk around 75 mL baseline volume) at early timepoints from symptom onset are those with the highest risk for haematoma expansion.[3] Ultra-early haematoma growth (defined as baseline haemorrhage volume divided by onset-to-imaging time [mL/h]) is an indirect measure of the speed of bleeding in the hyperacute phase of intracerebral haemorrhage and is a robust predictor of haematoma expansion.[32]

Baseline intracerebral haemorrhage volume can be approximated in clinical practice using the ellipsoid volume formula.[33,34] Alternatively, some new imaging softwares offer easy-to-use, semi-automated, intensity based, planimetric volume measurement tools.[35]

Non-contrast CT offers several other insights into the risk of haematoma expansion by the detection of gradual shape and density features of intracerebral haemorrhage that are associated with high risk.[36] Several terms have been used to describe the extent of irregularity (shape variations) and heterogeneity (density variations).[6] A meta-analysis of non-contrast CT markers showed sensitivities of shape features for haematoma expansion prediction ranging from 32% to 68% and specificities ranging from 47% to 92%.[37] Density features showed sensitivities (28–63%) and specificities (65–89%) of similar magnitude.[37] The role of non-contrast CT markers in predicting haematoma expansion, and as a tool for patient selection for trials, warrants examination in large prospective studies and has the benefit of being generalisable to almost all settings. For now, the accuracy of non-contrast CT markers suggests that they can be used to identify patients at high risk for haematoma expansion.[38]

CT angiography allows the identification of contrast extravasation within the haemorrhage at the arterial phase of injection, which is a marker of ongoing bleeding known as the spot sign.[39] Similar to non-contrast CT features, the sensitivity of the CT angiography spot sign for haematoma expansion remains low, with a pooled estimate of 57% in a meta-analysis based on data from 5085 patients.[40] This modest predictive performance is partly due to the presence of so-called spot mimics[41] and to the challenge of differentiating spots signs that are points of active contrast extravasation from resolved haemorrhages forming fibrin globes secondary to endogenous haemostasis.[17] Although the performance of the spot sign for predicting haematoma expansion can be increased by use of multiphase CT angiography,[42] or repeat delayed acquisitions generally,[43] the need for baseline iodine contrast injection has been an important disadvantage regarding its use in clinical practice and in clinical trials.[44,45]

Markers of active contrast extravasation have been also reported in patients imaged with acute phase MRI, but the evidence remains scant for this method.[46] The severity and subtype of the underlying cerebral small vessel

disease evaluated with MRI has been linked to baseline intracerebral haemorrhage volumes, and to the rates of haematoma expansion.[47] However, whether the patterns and pace for haematoma expansion differ in cerebral amyloid angiopathy-related or arteriolosclerosis-related haemorrhages is not known and requires further research. Approaches used in the past 5 years implementing supervised machine-learning algorithms have shown preliminary encouraging results, but their implementation both for clinical and research settings is unlikely in the near future.[48,49]

Tools and scores

Multiple prediction scores have been developed to identify patients at risk of haematoma expansion.[50] There is substantial overlap between different prediction scores, including various clinical risk factors, non-contrast CT, CT angiography imaging predictors, and a range of laboratory markers. Baseline intracerebral haemorrhage volume and non-contrast CT timing seem to be the two commonly included core predictors in these scores.[3,50] In derivation cohorts (often selected populations), prediction scores have shown high performance based on C-statistics (0·7–0·9); however, in validation cohorts, their discriminative ability was suboptimal (0·6–0·8).[50–52] The only prediction scores that achieved a C-statistic value of more than 0·8 are those including the CT angiography spot sign. However, their applicability is currently poor as CT angiography is not often done in clinical settings.[3,50]

Several issues restrict the applicability and diagnostic yield of prediction algorithms. First, studies have used different definitions of haematoma expansion and several scores were derived from retrospective analyses. Second, few studies quantified discrimination and calibration statistics and many still lack external validation. Third, there is substantial heterogeneity in the studied populations. Finally, several scores are too time consuming for routine clinical use and require expertise in intracerebral haemorrhage imaging for the analysis of CT angiography and non-contrast CT features of haematoma expansion. In a large individual patient data meta-analysis, four simple clinical risk factors emerged as independent predictors of haematoma expansion: time from symptom onset to baseline non-contrast CT and baseline intracerebral haemorrhage volume, and antiplatelet and anticoagulant use, with a C-index of 0·78 (95% CI 0·75–0·82).[3] Addition of CT angiography spot sign increased the C-index by only 0·05 (0·03–0·07). Four to five simple clinical predictors that are readily available to every clinician might have an acceptable discrimination for haematoma expansion.[3]

In summary, different tools are available for haematoma expansion prediction, but their application in clinical decision making and patient selection for randomised controlled trials remains to be established. Large-scale prospective studies and advanced imaging tools incorporating automated analysis of imaging features are needed to establish a high discriminative ability and an optimal balance between sensitivity and specificity. Future studies should also investigate if the implementation of prediction models in clinical practice can improve the management and outcomes of patients.

Prevention of intracerebral haemorrhage expansion

Early identification and management of intracerebral haemorrhage is crucial, with a strong focus on minimising haematoma expansion and neurological deterioration. Available medical approaches include blood pressure control, reversal of any associated coagulopathy, care in a dedicated stroke unit or neurointensive care unit, and brain imaging.[38]

Patients with suspected intracerebral haemorrhage should have rapid and accurate diagnosis with non-contrast CT (and ideally CT angiography; figure 2), which will also allow for calculation of haemorrhage volume and identify the presence of non-contrast CT markers or a spot sign.[38,54] Early interventions to restrict haematoma expansion should include rapid control of hypertension, although the optimal systolic blood pressure target remains unclear.[38,54,55] Patients presenting with anticoagulant-related intracerebral haemorrhage should have their anticoagulation withheld and should be considered for immediate reversal with management specific to the antithrombotic agent used.[38,54] Admission to a dedicated stroke unit is associated with a better outcome than admission to an intensive care unit or general ward in patients with mild or moderate severity haemorrhages without ventilation and intensive care needs.[38] Once stable, patients should have ongoing management of blood pressure, cerebral oedema, intracranial pressure issues, and seizures.[38,54]

Blood pressure lowering

Acute elevation of systolic blood pressure (known as acute hypertensive response) is common after intracerebral haemorrhage and has been independently associated with haematoma expansion and poor outcome,[1] therefore representing a compelling target for intervention. Several large randomised controlled trials have examined the safety and efficacy of early intensive blood pressure reduction to a systolic blood pressure target of less than 140 mmHg in patients with intracerebral haemorrhage.

A meta-analysis of individual patient data from randomised clinical trials showed that intensive systolic blood pressure lowering is safe and clearly reduced haematoma expansion, but this reduction did not lead to improved functional outcome.[56] This meta-analysis observed heterogeneity according to treatment strategy and drug, suggesting an increased effect when the antihypertensive treatment is titrated to an intensive

target (rather than using a fixed dose) and when α and β adrenoreceptors blockers are used.[56] The median time from intracerebral haemorrhage symptom onset to randomisation was 3·8 h and early treatment was not associated with improved outcome. However, the inclusion of patients with intracerebral haemorrhage treated with topical nitrates, which are potentially harmful, in a prehospital setting might have offset the benefits of a more rapid treatment than in-hospital treatment.[56]

The time-sensitivity of medical interventions targeting haematoma expansion has been shown in a secondary analysis of the ATACH2 trial (NCT01176565), in which rapid intensive blood pressure lowering (within 2 h from intracerebral haemorrhage symptom onset) reduced haematoma expansion and improved functional outcome.[57] Post-hoc analyses of ATACH2 showed that patients with imaging markers of haematoma expansion (CT angiography spot sign and non-contrast CT markers) were not more likely to benefit from intensive systolic blood pressure lowering than patients with no imaging markers.[58,59] This study might have been underpowered to detect a significant heterogeneity of effect, given that only 10% of the participants received a CT angiography before randomisation.[56] Another possible explanation is the suboptimal diagnostic performance of imaging markers (all non-contrast CT features had sensitivity of less than 50% for haematoma expansion).[58] Furthermore, previous trials compared an intensive blood pressure reduction strategy with a conventional blood pressure reduction strategy and the lack of comparison with a group with no blood pressure treatment might have minimised the true effects of blood pressure lowering.

To summarise, the optimal systolic blood pressure target in patients with acute intracerebral haemorrhage remains debated and, despite evidence of reduced haematoma expansion in intensively treated patients, this approach has not consistently led to better outcomes.[55,56] Intensive systolic blood pressure reduction (target 120–139 mm Hg) is relatively safe, other than having a potential risk of renal injury, and might improve functional outcome and restrict haematoma expansion in patients with elevated systolic blood pressure (150–220 mm Hg) presenting early (ideally treated within 2 h from symptom onset) and with intracerebral haemorrhage of mild to moderate severity.[60] Achieving the systolic blood pressure target smoothly, without fluctuations and rapid large drops (≥70 mm Hg in 1 h), is associated with improved outcome.[61,62]

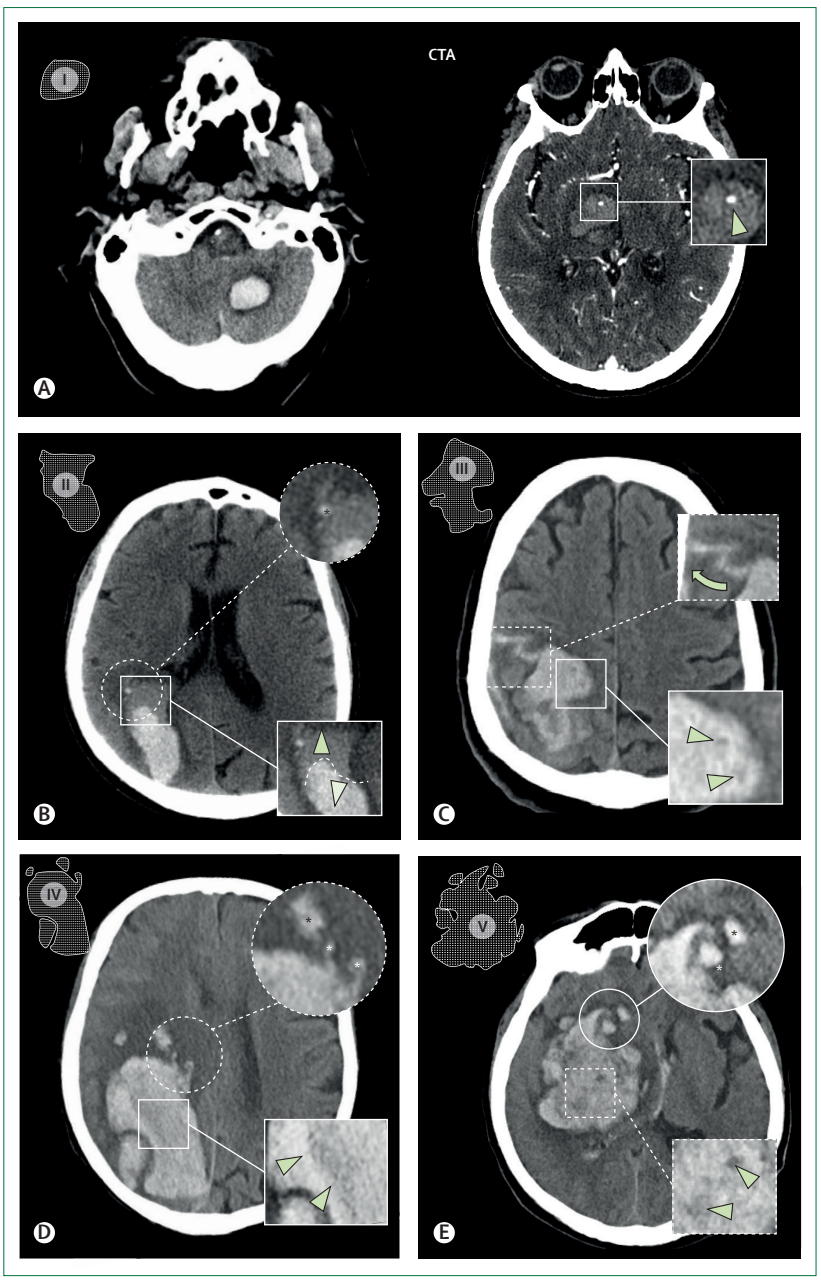

Figure 2: **Imaging markers of intracerebral haemorrhage expansion**
Non-contrast CT slices (A-E) and CT angiography. (A-E) Increasing shape irregularity on non-contrast CT, with the corresponding Barras' scale for irregularity shown in the top left corner of all panels (range I–V; V represents the highest degree of shape irregularity).[53] The circular insets depict shape features, including island signs (black or white asterisks) and satellite signs (black asterisks). The arrowheads in square insets depict density features, including blend sign (B), hypodensities (C–E), and swirl sign (E). The first inset (C) shows subarachnoid extension (green arrow), and the arrowhead (CTA) points at a spot sign. CTA=CT angiography.

Haemostatic therapy

Randomised clinical trials of haemostatic therapy for patients with intracerebral haemorrhage have assessed the effects of reversing coagulopathy or the effects of haemostatic agents in the absence of known coagulopathy (the two most studied agents are recombinant activated factor VIIa and tranexamic acid; table).

Recombinant activated factor VIIa, if administered within 3 h of onset, reduces haematoma expansion by approximately 4 mL. Unfortunately, this effect has not yet led to improved outcome (FAST trial, NCT00127283).[66] This trial might not have adequately targeted the subset of patients at highest risk of haematoma expansion.[66] To further investigate this lack of a positive outcome,

	Location	Sample size, n; setting	Study cohort	Intervention	Comparator	Outcome
Haemostatic treatment						
rFVIIa for haemorrhagic stroke trial (FASTEST, NCT03496883)[7]	Canada, Germany, and the USA	860; mobile stroke units	Intracerebral haemorrhage volume 2–60 mL within 2 h of onset	rFVIIa 80 µg/kg	Placebo	Haematoma growth after 24 h; mRS at 180 days from symptom onset
Stopping haemorrhage with tranexamic acid for hyperacute onset presentation including mobile stroke units (STOP-MSU, NCT03385928)[8]	Australia, Finland, New Zealand, Taiwan, and Viet Nam	326; hospitals and mobile stroke units	Intracerebral haemorrhage volume <70 mL within 2 h of onset	Tranexamic acid 1 g for 10 min, then 1 g infusion for 8 h	Placebo	Haematoma growth by 18–30 h (≥33% or ≥6 mL increase from baseline volume); death at 7 days from symptom onset; mRS at 90 days from symptom onset
Tranexamic acid for intracerebral haemorrhage 3 (TICH-3, ISRCTN97695350)	Worldwide	5500; hospitals	Intracerebral haemorrhage volume <60 mL within 4·5 h of onset or symptom discovery	Tranexamic acid 1 g for 10 min, then 1 g infusion for 8 h	Placebo	Death at 7 days from symptom onset; mRS at 180 days from symptom onset
Indian trial of tranexamic acid in spontaneous intracerebral hemorrhage (INTRINSIC, CTRIREF/2021/12/049694)	India, Philippines, Sri Lanka, and Viet Nam	3600; hospitals	Intracerebral haemorrhage volume <60 mL within 4·5 h of onset	Tranexamic acid 1 g for 10 min, then 1 g infusion for 8 h	Standard of care	Death at 7 days from symptom onset; mRS at 90 days from symptom onset
Tranexamic acid for hematoma expansion and peri-hematomal edema in patients with acute itntracerebral hemorrhage (THE-ICHChiCTR1900027065)	China	2400; hospitals	Intracerebral haemorrhage volume <60 mL within 4·5 h of onset	Tranexamic acid 1 g for 10 min, then 1 g infusion for 8 h	Placebo	Death at 7 days from symptom onset; mRS at 90 days from symptom onset
Blood pressure lowering						
The third intensive care bundle with blood pressure reduction in acute cerebral haemorrhage trial (INTERACT3, NCT03209258)[63]	China	8360; hospitals	No volume limit within 6 h of onset	Intensive care bundle including Intensive blood pressure lowering (systolic target <140 mm Hg), glucose control (target 6·1–7·8 mmol/L for non-diabetic individuals; 7·8–10·0 mmol/L for diabetic patients), treatment of pyrexia (target temperature ≤37·5°C), and reversal of anticoagulation (target international normalised ratio <1·5)	Usual care	mRS at 180 days from symptom onset
Intensive ambulance-delivered blood pressure reduction in hyper-acute stroke trial (INTERACT4, NCT03790800)[64]	China	3116; ambulances	No volume limit within 24 h of time last seen well	Intensive blood pressure lowering to a target systolic blood pressure of <140 mm Hg within 30 min	Guideline-recommended blood pressure management according to local protocols	mRS at 90 days from symptom onset
The intracerebral haemorrhage acutely decreasing arterial pressure trial II (ICH-ADAPT II, NCT02281838)[65]	Canada	270; hospitals	No volume limit within 6 h of intracerebral haemorrhage onset	Blood pressure lowering to a target systolic blood pressure of <140 mm Hg	Blood pressure lowering to a systolic blood pressure of 180 mm Hg	DWI lesions on MRI; absolute haematoma growth 24 h after randomisation

DWI=diffusion weighted imaging. mRS=modified Rankin scale. rFVIIa=recombinant factor VIIa.

Table: **Ongoing randomised clinical trials targeting haematoma expansion in patients with intracerebral haemorrhage**

two trials used the CT angiography spot sign to target individuals at highest risk of expansion, but were stopped early and found no change in outcome (SPOTLIGHT, NCT01359202; STOP-IT, NCT00810888).[44] As patients were enrolled up to 6·5 h after intracerebral haemorrhage onset, the time period in which haemostatic therapy was administered could have been too long. The ongoing FASTEST trial (NCT03496883) will investigate treatment with recombinant activated factor VIIa within 2 h of onset.[7]

Tranexamic acid has also been studied; the largest trial (TICH-2, ISRCTN93732214) suggested reduced mortality with early administration after intracerebral haemorrhage symptom onset, but found no effect on mortality after 30 days.[67] The ongoing TICH-3 trial (ISRCTN97695350) will be larger and potentially better powered than the TICH-2 trial to detect a mortality effect. Similarly, the STOP-MSU trial (NCT03385928) will evaluate the use of tranexamic acid in mobile stroke units, and might show that ultra-early therapy is crucial.[8]

A meta-analysis of several tranexamic acid trials, including participants with traumatic intracerebral haemorrhage, found that tranexamic acid, like recombinant activated factor VIIa, reduces haemorrhage expansion without consistently leading to improved outcome.[68] Furthermore, there is no evidence that patients with specific imaging features derive benefit from treatment with tranexamic acid.[45,69–71]

Procoagulant therapy might be most beneficial when offered as part of a treatment bundle (a group of co-administered treatments), including intensive blood pressure reduction.[72] Consistent with this hypothesis, a subgroup analysis of the TICH-2 trial suggested that tranexamic acid might be more effective in patients with systolic blood pressure of less than 170 mm Hg than in those with higher systolic blood pressure.[67] A treatment bundle approach to intracerebral haemorrhage is being studied in the ongoing INTERACT3 trial (NCT03209258).[63] For patients with intracerebral haemorrhage and coagulopathy, the risk of haematoma expansion is even higher than if they weren't coagulopathic.[3] The best evidence for coagulopathy reversal comes from studies of vitamin K antagonists, comparing plasma (slow reversal) to prothrombin complex concentrate (rapid reversal).[73] The INCH trial (NCT00928915) found that prothrombin complex concentrate significantly reduces haematoma expansion.[73] However, this trial was stopped early and was therefore underpowered to achieve its primary outcome, but provided the most promising data available that rapid anticoagulation reversal could reduce haematoma expansion enough to improve outcome.

For patients taking direct oral anticoagulants, single arm trials have found that specific reversal agents appear to be associated with effective haemostasis,[74–76] and a randomised clinical trial of oral anticoagulant-associated intracerebral haemorrhage is ongoing (NCT03661528). Direct oral anticoagulant reversal can be presumed to have the same benefit as vitamin K antagonist reversal, but with a shorter timeframe for treatment, as oral anticoagulants have shorter half-lives than vitamin K antagonists.[77]

How to treat patients taking antiplatelet agents is not clear. The largest trial of platelet transfusion (NTR1303), the most common reversal method, found poor outcomes in those treated, suggesting that platelet transfusion causes more harm than benefit.[78] Future studies of alternative agents, such as desmopressin, specifically targeted at patients with platelet dysfunction might be more promising.[79]

Overall, procoagulant agents, such as recombinant activated factor VIIa and tranexamic acid, appear to reduce haematoma expansion. However, there is no clear evidence regarding who will benefit from their use. Rapid vitamin K antagonist reversal with prothrombin complex concentrate might reduce haematoma expansion enough to improve outcome, and many investigators believe that oral anticoagulant reversal will eventually be shown to offer similar benefits. Haemostatic therapy is a promising therapeutic strategy to reduce haematoma expansion, but it should be administered to patients at highest risk of haematoma expansion. Furthermore, the optimal use of haemostatic therapy might not be in isolation, but as part of a multimodal approach to reducing expansion in the first 2 h after intracerebral haemorrhage.

Clinical trial design

Several trials targeting haematoma expansion did not show an overall clinical benefit on functional outcome.[56,66,67] Although this lack of benefit could be the result of minimal reductions in haematoma expansion from the interventions, it might also suggest that the potential for clinical benefit is being diluted by the inclusion of participants who will not have haematoma expansion, by the adverse effects of the tested treatments, or by the array of non-haematoma expansion-related factors that can influence outcome. The ideal intracerebral haemorrhage trial design targeting haematoma expansion should attempt to enrich the study cohort with patients at highest risk of haematoma expansion through the application of careful clinical and radiographic criteria. This enriched population can be achieved by refining prediction tools with machine learning techniques or treating patients early during the haematoma expansion using mobile stroke units. However, even within 2 h from symptom onset, most intracerebral haemorrhage patients do not have haematoma expansion,[57] suggesting that some risk stratification is needed in these ultra-early presenters. Haematoma expansion predictors might not only help the selection of patients for explanatory randomised controlled trials, but also the selection of patients to be used in subgroup analyses to investigate heterogeneity of treatment effect in more inclusive trials.

Informed consent in intracerebral haemorrhage trials

Obtaining prospective informed consent to participate in clinical trials from patients with intracerebral haemorrhage is often impossible, as they might be aphasic, unconscious, or otherwise incapable. The inclusion of only the participants who are capable of consenting can bias trial results by excluding the most severely affected patients.[80,81] Depending on the jurisdiction, several approaches for enrolment with exceptions from standard informed consent are available: surrogate consent (from a legally authorised representative), deferred consent (in which the patient or a surrogate consent after enrolment), and advance consent (in which at-risk patients are asked to consent before they have an intracerebral haemorrhage). Unfortunately, there is substantial variability in consent practices across and within jurisdictions, and these inconsistencies present ethical and methodological

challenges to the implementation of clinical trials in this field.

Surrogate consent is commonly accepted in many countries, although it was difficult to obtain in practice during COVID-19 restrictions, and can delay the administration of time-sensitive treatments by 20 min or more.[82] A systematic review found that surrogates were wrong about the preferences of patients 32% of the time. Restricting enrolment to patients who arrive in emergency departments with substitute decision makers is known to bias research results, lowering their validity and generalisability.[83] During the COVID-19 pandemic, remote decision making was common and accepted. The initiation of remote consent procedures in some trials during the pandemic led to increased rates of recruitment, although similar rates have not yet been seen in acute stroke trials.[84] Deferred consent can overcome reduced validity and generalisability, although patients could be enrolled in trials against their wishes. However, several studies from the past 3 years suggest that patients and surrogates in stroke trials are accepting of deferred consent,[85–87] including the SPOTLIGHT trial for intracerebral haemorrhage.[88] Advance consent could also support trial participation decisions. Identifying patients at risk for intracerebral haemorrhage before an intracerebral haemorrhage occurs is likely to be both feasible and ethically acceptable, although this approach has not yet been attempted in a trial. Future research assessing consent procedures for acute stroke and intracerebral haemorrhage trials should advance consent practices, producing an ethically defensible, equitable, and efficient system of trial enrolment.[89]

Intracerebral haemorrhage treatment has been recognised as a research priority by patients and caregivers, but their involvement in stroke research remains restricted.[90] Future research should incorporate patient-reported outcome measures and assess the functional outcomes that matter most to patients with intracerebral haemorrhage.[91,92]

Conclusions and future directions

Blood pressure lowering and haemostatic treatment successfully reduced haematoma expansion in several randomised trials without consistently leading to improved outcomes. Several reasons could explain this discrepancy. The simplest explanation is that haematoma expansion might not be a reasonable therapeutic target to improve outcome.[93] The effect size of haematoma expansion prevention on functional recovery is evidently small in unselected patients, and patients will need to be precisely triaged to potentially benefit from anti-expansion treatments.

Several factors have been advanced as alternative hypotheses for the absence of clinical improvement after haematoma expansion-targeted strategies. First, the small reduction in haematoma expansion might have been insufficient to improve prognosis, especially in patients with moderate to large baseline haematoma volume. However, patients with small volume growth often qualify as so-called expanders if a relative haematoma expansion definition is used, even in cases of small absolute increases in total volume that have little clinical significance. The analysis and interpretation of haematoma expansion as a spectrum could allow for a more precise distinction between different degrees of haemorrhage enlargement and provide novel insights into the efficacy of treatment strategies.[5] Second, the benefit of haematoma expansion restriction might have been offset by treatment-related side-effects.[66,94] Third, patients might have been treated when most of the bleeding has already occurred.[4] Fourth, participants selection might have led to the inclusion of many patients at low risk of haematoma expansion, diluting the potential benefits of prevention treatments. Fifth, the presenting haematoma might be either large enough or in a crucial anatomical location to account for the severity of the final outcome, irrespective of any subsequent haematoma expansion. Finally, haematoma expansion is an important prognostic determinant,[2] but other mechanisms also influence brain recovery in patients with intracerebral haemorrhage. One approach to overcome this issue might be the use of combined endpoints; for instance, combining radiological haematoma expansion with clinical deterioration or unfavourable functional outcome in a composite outcome, with a predefined hierarchy between different endpoints.[95] The win ratio might be a valuable statistical method to account for the unequal clinical relevance of multiple endpoints included in composite outcomes.[96,97]

Improvement of haematoma expansion prediction

Available prediction tools lack large-scale prospective validation studies, and their diagnostic accuracy can be improved (panel 2). Deep learning is an area of technological development and its applications in predicting haematoma expansion might reform current approaches to diagnosis and management. A prediction model including automated imaging analysis techniques provided a confidence score for the prediction of the risk of haematoma expansion.[9] A retrospective, single-centre, observational study that used a support vector machine model from routinely available variables reported high sensitivity (0·81) and high specificity (0·85) for predicting risk of haematoma expansion, with good overall discriminative ability (area under curve 0·89).[49] Future studies should focus on developing simple and fast prediction tools, preferably with the assistance of automated analysis, to quickly identify patients at high risk of haematoma expansion. These approaches could improve personalised care in the management of intracerebral haemorrhage. Prospective validation of previously proposed models and techniques is needed before automated approaches can be successfully used in clinical practice or for the

Panel 2: Predictors of intracerebral haemorrhage expansion

Time from intracerebral haemorrhage onset to first brain imaging

- Non-linear relationship between the risk of haematoma expansion and the time from symptom onset to first brain imaging
- The probability of haematoma expansion is increased in patients who are initially scanned within 3–6 h from symptom onset

Antithrombotic treatment

- Anticoagulant-associated intracerebral haemorrhages have usually large volumes and elevated risk of haematoma expansion (>50%)
- Antiplatelet treatment also increases the probability of haemorrhage expansion, although the risk is lower than in anticoagulant-associated haemorrhages

Baseline intracerebral haemorrhage volume

- There is a linear relationship between baseline volume and risk of haematoma expansion, which peaks at around 75 mL, and then declines with larger volumes
- Easy to assess in clinical practice with the ellipsoid volume formula. For the ellipsoid volume formula, select the CT slice with the largest intracerebral haemorrhage area and measure the longest diameter (A) and the longest perpendicular diameter (B); obtain (C) by multiplying slice thickness by the number of slices in which the haematoma is detectable; intracerebral haemorrhage volume can be obtained by multiplying A × B × C and dividing by two; all measures should be taken in cm and the final volume should be reported in cm^3 or mL[34]
- Ultra-early haematoma growth (baseline haemorrhage volume divided by onset-to-imaging time [mL/h]) is an indirect indicator of the speed of bleeding

CT angiography spot sign

- Presence of ≥1 focus of contrast extravasation within the haematoma, with any size or shape, and density more than 120 Hounsfield units (HU)
- Contrast extravasation inside the haemorrhage, with a diameter ≥1·5 mm, spot or serpiginous shape, no connection with vessels outside the haemorrhage, no corresponding hyperdensity on non-contrast CT, and density double than the density of the surrounding haematoma
- Increased frequency of computed tomography angiography spot sign and diagnostic accuracy early after symptom onset

Non-contrast CT intracerebral haemorrhage shape features

- Irregular shape: ≥2 margin irregularities, connected or not with the haematoma borders, and rated on the axial non-contrast CT slice with the largest haemorrhage surface
- Island sign: ≥3 scattered small bleedings that are all separate from the haemorrhage or ≥4 small haematomas that might be connected with the main haemorrhage
- Satellite sign: small haemorrhage (max diameter <10 mm) that is not connected to the main haematoma, with a clear separation (1–20 mm distance)
- Subarachnoid haemorrhage: extension of parenchymal bleeding into the subarachnoid space; associated with haematoma expansion only in lobar haemorrhages
- Satellite signs and subarachnoid haemorrhage lack external validation

Non-contrast CT intracerebral haemorrhage density features

- Fluid level: hypoattenuating area above and hyperattenuating area below a straight line of separation (compared with the brain parenchyma); this marker lacks external validation
- Blend sign: hypoattenuating area adjacent to a hyperattenuating area, clear margin between the two regions, and density difference greater than 18 HU
- Black hole sign: hypoattenuating region encapsulated in the haemorrhage with a density difference >28 HU (compared with the surrounding haemorrhage)
- Hypodensity: any hypodense region within the haemorrhage and no connection with surrounding structures; does not require density measures and can be detected with visual inspection
- Swirl sign: any region of hypoattenuation or isoattenuation compared with the brain parenchyma, encapsulated or not in the haematoma, with any morphology
- Heterogeneous density: ≥3 regions of low attenuation compared with the haemorrhage, rated on the axial slice with the largest haematoma surface

identification of patients with intracerebral haemorrhage at high risk of haematoma expansion in randomised controlled trials.

Intracerebral haemorrhage treatment in mobile stroke units

Mobile stroke units have achieved shorter time from onset to treatment in patients with ischaemic stroke, associated with better outcome compared with traditional in-hospital treatment in emergency wards.[98] Blood pressure lowering and haemostatic therapies are the most promising medical therapies for restricting haematoma expansion in patients with acute intracerebral haemorrhage, and mobile stroke units are an appealing approach to facilitate timely delivery of these time-sensitive therapeutic options.[99] Mobile stroke units might also optimise prehospital triage of patients with intracerebral haemorrhage, allowing fast transport to facilities with neurosurgery and neurological intensive care services. Mobile stroke units also have the potential

Panel 3: Priorities for future research

Definition of haematoma expansion

- Identify a haematoma expansion definition that incorporates intraventricular haemorrhage, with a cutoff more than the minimal detectable difference and a strong correlation with functional outcome
- Analyse and compare data from previous trials targeting haematoma expansion with different haematoma expansion definitions
- Apply the haematoma expansion shift concept to distinguish different degrees of haematoma enlargement
- Achieve a consensus definition of haematoma expansion for future studies

Prediction of haematoma expansion

- External validation of imaging markers and prediction scores
- Comparison of different markers and scores with discrimination, calibration, and net reclassification tests
- Assessment of the added value of multimodal imaging (non-contrast CT with CT angiography)
- Integration of conventional imaging markers with deep learning and automated analysis techniques

Outcome measures

- Test composite outcomes (ie, haematoma expansion-associated clinical deterioration or haematoma expansion-associated poor outcome) with a predefined hierarchy between different combined outcomes, or with a statistical approach that accounts for the unequal clinical relevance of different endpoints, such as the win ratio
- Incorporate patient-reported outcome measures

Search strategy and selection criteria

We searched PubMed for articles published in English without date restrictions. The initial literature search was done on June 1, 2022, with a combination of keywords and MeSH terms including: "intracerebral haemorrhage expansion", "intracerebral hemorrhage expansion", "haematoma expansion" "hematoma expansion", "ICH expansion" OR "intracerebral haemorrhage growth", "intracerebral hemorrhage growth", "haematoma growth", "hematoma growth", and "ICH growth". Additional articles were identified from the bibliographies of included manuscripts. The final reference list was generated on the basis of originality and relevance for the purposes of this Review. We did not include studies on patients with intracerebral haemorrhage secondary to vascular malformations or studies on surgical approaches to restrict haematoma expansion.

to maximise enrolment of patients with intracerebral haemorrhage in clinical trials with a short time for therapeutic intervention. Two ongoing trials are using mobile stroke units to include patients within 2 h of intracerebral haemorrhage onset[7,8] and could provide important data on the feasibility, benefits, and cost-effectiveness of intracerebral haemorrhage management in the prehospital setting.

In conclusion, prevention of haematoma expansion remains a plausible target for improving intracerebral haemorrhage outcomes, but uncertainty regarding the efficacy of haematoma expansion-targeted treatments remains. Standardisation of both the definition of haematoma expansion and outcome measures is needed to maximise future research efforts and to obtain comprehensive evidence on the biological and clinical effects of medical therapies targeting active bleeding (panel 3). Easy-to-use non-contrast CT imaging markers and advanced deep learning-based techniques might improve patient selection in randomised clinical trials and, eventually, in clinical practice. Mobile stroke units and alternatives to standard informed consent are promising approaches to expand the number of patients eligible for future trials and to increase the number of patients receiving early treatment to restrict haematoma expansion.

Contributors

AM, GB, and AC planned the Review. AM, GB, DD, QL, MS, JR, JNG, and AC contributed to the literature search and article selection, wrote sections of the manuscript, and revised the final version of the manuscript. GB designed and made the figures. RA-SS and CC contributed to the literature search and article selection and revised the final version of the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

DD has served on an advisory board for AstraZeneca Canada and holds a patent for the software Computerized Automatic Recognition of Leakage. CC declares grants from the French Ministry of Health (NCT03243175 and TICH3-Fr Trial [ISRCTN97695350]); speaker fees from Bristol Myers Squibb (BMS) and Amgen; and is a steering committee member of international trials (BMS and Biogen) and data safety monitoring boards for University of Caen Normandy (FivHema), University of Glasgow (ATTEST-2), and Assistance des Hopitaux de Paris (BLITZ). JR has received research funding from the National Institutes of Health, the American Heart Association, and NovoNordisk; and consulting fees from Takeda Pharmaceuticals, Boehringer Ingelheim, and Pfizer. JNG has received research funding from Pfizer, Octapharma, and Takeda; consulting fees from CSL Behring, Alexion, NControl, and Cayuga; and declares NControl and Cayuga stock options. All other authors declare no competing interests.

References

1 Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. *Lancet* 2018; **392:** 1257–68.

2 Dowlatshahi D, Demchuk AM, Flaherty ML, Ali M, Lyden PL, Smith EE. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. *Neurology* 2011; **76:** 1238–44.

3 Al-Shahi Salman R, Frantzias J, Lee RJ, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet Neurol* 2018; **17:** 885–94.

4 Broderick JP, Grotta JC, Naidech AM, et al. The story of intracerebral hemorrhage: from recalcitrant to treatable disease. *Stroke* 2021; **52:** 1905–14.

5 Yogendrakumar V, Ramsay T, Menon BK, Qureshi AI, Saver JL, Dowlatshahi D. Hematoma expansion shift analysis to assess acute intracerebral hemorrhage treatments. *Neurology* 2021; **97:** e755–64.

6 Morotti A, Boulouis G, Dowlatshahi D, et al. Standards for detecting, interpreting, and reporting noncontrast computed tomographic markers of intracerebral hemorrhage expansion. *Ann Neurol* 2019; **86:** 480–92.

7 Naidech AM, Grotta G, Elm J, et al. Recombinant factor VIIa for hemorrhagic stroke treatment at earliest possible time (FASTEST): protocol for a phase III, double-blind, randomized, placebo-controlled trial. *Int J Stroke* 2022; **17:** 806–09.

8 Yassi N, Zhao H, Churilov L, et al. Tranexamic acid for intracerebral haemorrhage within 2 hours of onset: protocol of a phase II randomised placebo-controlled double-blind multicentre trial. *Stroke Vasc Neurol* 2022; **7:** 158–65.

9 Teng L, Ren Q, Zhang P, Wu Z, Guo W, Ren T. Artificial intelligence can effectively predict early hematoma expansion of intracerebral hemorrhage analyzing noncontrast computed tomography image. *Front Aging Neurosci* 2021; **13:** 632138.

10 Toyoda K, Yoshimura S, Fukuda-Doi M, et al. Intensive blood pressure lowering with nicardipine and outcomes after intracerebral hemorrhage: an individual participant data systematic review. *Int J Stroke* 2022; **17:** 494–505.

11 You S, Zheng D, Delcourt C, et al. Determinants of early versus delayed neurological deterioration in intracerebral hemorrhage. *Stroke* 2019; **50:** 1409–14.

12 Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013; **368:** 2355–65.

13 Schlunk F, Greenberg SM. The pathophysiology of intracerebral hemorrhage formation and expansion. *Transl Stroke Res* 2015; **6:** 257–63.

14 Gunda B, Böjti P, Kozák LR. Hyperacute spontaneous intracerebral hemorrhage during computed tomography scanning. *JAMA Neurol* 2021; **78:** 365–66.

15 Qureshi AI, Hanel RA, Kirmani JF, Yahia AM, Hopkins LN. Cerebral blood flow changes associated with intracerebral hemorrhage. *Neurosurg Clin N Am* 2002; **13:** 355–70.

16 Morotti A, Busto G, Bernardoni A, Tamborino C, Fainardi E. Association between perihematomal cerebral blood volume and intracerebral hemorrhage expansion: a computed tomography perfusion study. *Ann Neurol* 2019; **85:** 943–47.

17 Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. *J Neuropathol Exp Neurol* 1971; **30:** 536–50.

18 Li Y, Ren S, Wang L, et al. Is the CT blend sign composed of two parts of blood with different age? *Neurocrit Care* 2021; **35:** 367–78.

19 Boulouis G, Morotti A, Charidimou A, Dowlatshahi D, Goldstein JN. Noncontrast computed tomography markers of intracerebral hemorrhage expansion. *Stroke* 2017; **48:** 1120–25.

20 Schlunk F, Böhm M, Boulouis G, et al. Secondary bleeding during acute experimental intracerebral hemorrhage. *Stroke* 2019; **50:** 1210–15.

21 Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. *Stroke* 1996; **27:** 1783–87.

22 Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* 1997; **28:** 1–5.

23 Rodriguez-Luna D, Boyko M, Subramaniam S, et al. Magnitude of hematoma volume measurement error in intracerebral hemorrhage. *Stroke* 2016; **47:** 1124–26.

24 Delcourt C, Huang Y, Arima H, et al. Hematoma growth and outcomes in intracerebral hemorrhage: the INTERACT1 study. *Neurology* 2012; **79:** 314–19.

25 Maas MB, Nemeth AJ, Rosenberg NF, Kosteva AR, Prabhakaran S, Naidech AM. Delayed intraventricular hemorrhage is common and worsens outcomes in intracerebral hemorrhage. *Neurology* 2013; **80:** 1295–99.

26 Dowlatshahi D, Deshpande A, Aviv RI, et al. Do intracerebral hemorrhage nonexpanders actually expand into the ventricular space? *Stroke* 2018; **49:** 201–03.

27 Yogendrakumar V, Ramsay T, Fergusson D, et al. New and expanding ventricular hemorrhage predicts poor outcome in acute intracerebral hemorrhage. *Neurology* 2019; **93:** e879–88.

28 Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. *Neurology* 2004; **63:** 1059–64.

29 Morotti A, Boulouis G, Charidimou A, et al. Hematoma expansion in intracerebral hemorrhage with unclear onset. *Neurology* 2021; **96:** e2363–71.

30 Purrucker JC, Haas K, Rizos T, et al. Early clinical and radiological course, management, and outcome of intracerebral hemorrhage related to neworal anticoagulants. *JAMA Neurol* 2016; **73:** 169–77.

31 Kurogi R, Nishimura K, Nakai M, et al. Comparing intracerebral hemorrhages associated with direct oral anticoagulants or warfarin. *Neurology* 2018; **90:** e1143–49.

32 Rodriguez-Luna D, Coscojuela P, Rubiera M, et al. Ultraearly hematoma growth in active intracerebral hemorrhage. *Neurology* 2016; **87:** 357–64.

33 Kothari RU, Brott T, Broderick JP, et al. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* 1996; **27:** 1304–05.

34 Newman GC. Clarification of abc/2 rule for ICH volume. *Stroke* 2007; **38:** 862.

35 Schlunk F, Kuthe J, Harmel P, et al. Volumetric accuracy of different imaging modalities in acute intracerebral hemorrhage. *BMC Med Imaging* 2022; **22:** 9.

36 Morotti A, Arba F, Boulouis G, Charidimou A. Noncontrast CT markers of intracerebral hemorrhage expansion and poor outcome: a meta-analysis. *Neurology* 2020; **95:** 632–43.

37 Arba F, Rinaldi C, Boulouis G, Fainardi E, Charidimou A, Morotti A. Noncontrast computed tomography markers of cerebral hemorrhage expansion: diagnostic accuracy meta-analysis. *Int J Stroke* 2021; published online Nov 29. https://doi.org/10.1177/17474930211061639

38 Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke* 2022; **53:** e282–361.

39 Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. *Lancet Neurol* 2012; **11:** 307–14.

40 Phan TG, Krishnadas N, Lai VWY, et al. Meta-analysis of accuracy of the spot sign for predicting hematoma growth and clinical outcomes. *Stroke* 2019; **50:** 2030–36.

41 Gazzola S, Aviv RI, Gladstone DJ, et al. Vascular and nonvascular mimics of the CT angiography "spot sign" in patients with secondary intracerebral hemorrhage. *Stroke* 2008; **39:** 1177–83.

42 Rodriguez-Luna D, Coscojuela P, Rodriguez-Villatoro N, et al. Multiphase CT angiography improves prediction of intracerebral hemorrhage expansion. *Radiology* 2017; **285:** 932–40.

43 Ciura VA, Brouwers HB, Pizzolato R, et al. Spot sign on 90-second delayed computed tomography angiography improves sensitivity for hematoma expansion and mortality: prospective study. *Stroke* 2014; **45:** 3293–97.

44 Gladstone DJ, Aviv RI, Demchuk AM, et al. Effect of recombinant activated coagulation factor VII on hemorrhage expansion among patients with spot sign-positive acute intracerebral hemorrhage: the SPOTLIGHT and STOP-IT randomized clinical trials. *JAMA Neurol* 2019; **76:** 1493–501.

45 Meretoja A, Yassi N, Wu TY, et al. Tranexamic acid in patients with intracerebral haemorrhage (STOP-AUST): a multicentre, randomised, placebo-controlled, phase 2 trial. *Lancet Neurol* 2020; **19:** 980–87.

46 Schindlbeck KA, Santaella A, Galinovic I, et al. Spot sign in acute intracerebral hemorrhage in dynamic T1-weighted magnetic resonance imaging. *Stroke* 2016; **47:** 417–23.

47 Boulouis G, van Etten ES, Charidimou A, et al. Association of key magnetic resonance imaging markers of cerebral small vessel disease with hematoma volume and expansion in patients with lobar and deep intracerebral hemorrhage. *JAMA Neurol* 2016; **73:** 1440–47.

48 Liu J, Xu H, Chen Q, et al. Prediction of hematoma expansion in spontaneous intracerebral hemorrhage using support vector machine. *EBioMedicine* 2019; **43:** 454–59.

49 Wang T, Song N, Liu L, et al. Efficiency of a deep learning-based artificial intelligence diagnostic system in spontaneous intracerebral hemorrhage volume measurement. *BMC Med Imaging* 2021; **21:** 125.

50 Yogendrakumar V, Moores M, Sikora L, et al. Evaluating hematoma expansion scores in acute spontaneous intracerebral hemorrhage: a systematic scoping review. *Stroke* 2020; **51:** 1305–08.

51 Poli L, Leuci E, Costa P, et al. Validation and comparison of noncontrast CT scores to predict intracerebral hemorrhage expansion. *Neurocrit Care* 2020; **32:** 804–11.

52 Li Z, You M, Long C, et al. Hematoma expansion in intracerebral hemorrhage: an update on prediction and treatment. *Front Neurol* 2020; **11:** 702.

53 Barras CD, Tress BM, Christensen S, et al. Density and shape as CT predictors of intracerebral hemorrhage growth. *Stroke* 2009; **40:** 1325–31.

54 Shoamanesh A, Patrice Lindsay M, Castellucci LA, et al. Canadian stroke best practice recommendations: management of spontaneous intracerebral hemorrhage, 7th edition update 2020. *Int J Stroke* 2021; **16:** 321–41.

55 Sandset EC, Anderson CS, Bath PM, et al. European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. *Eur Stroke J* 2021; **6:** XLVIII–LXXXIX.

56 Moullaali TJ, Wang X, Sandset EC, et al. Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *J Neurol Neurosurg Psychiatry* 2022; **93:** 6–13.

57 Li Q, Warren AD, Qureshi AI, et al. Ultra-early blood pressure reduction attenuates hematoma growth and improves outcome in intracerebral hemorrhage. *Ann Neurol* 2020; **88:** 388–95.

58 Morotti A, Brouwers HB, Romero JM, et al. Intensive blood pressure reduction and spot sign in intracerebral hemorrhage: a secondary analysis of a randomized clinical trial. *JAMA Neurol* 2017; **74:** 950–60.

59 Morotti A, Boulouis G, Romero JM, et al. Blood pressure reduction and noncontrast CT markers of intracerebral hemorrhage expansion. *Neurology* 2017; **89:** 548–54.

60 Moullaali TJ, Wang X, Martin RH, et al. Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. *Lancet Neurol* 2019; **18:** 857–64.

61 Wang X, Di Tanna GL, Moullaali TJ, et al. J-shape relation of blood pressure reduction and outcome in acute intracerebral hemorrhage: a pooled analysis of INTERACT2 and ATACH-II individual participant data. *Int J Stroke* 2022; published online Jan 5. https://doi.org/10.1177/17474930211064076

62 Minhas JS, Moullaali TJ, Rinkel GJE, Anderson CS. Blood pressure management after intracerebral and subarachnoid hemorrhage: the knowns and known unknowns. *Stroke* 2022; **53:** 1065–73.

63 Song L, Hu X, Ma L, et al. INTEnsive care bundle with blood pressure reduction in acute cerebral hemorrhage trial (INTERACT3): study protocol for a pragmatic stepped-wedge cluster-randomized controlled trial. *Trials* 2021; **22:** 943.

64 Song L, Chen C, Chen X, et al. INTEnsive ambulance-delivered blood pressure Reduction in hyper-ACute stroke Trial (INTERACT4): study protocol for a randomized controlled trial. *Trials* 2021; **22:** 885.

65 Gioia L, Klahr A, Kate M, et al. The intracerebral hemorrhage acutely decreasing arterial pressure trial II (ICH ADAPT II) protocol. *BMC Neurol* 2017; **17:** 100.

66 Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008; **358:** 2127–37.

67 Sprigg N, Flaherty K, Appleton JP, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet* 2018; **391:** 2107–15.

68 Jiao X, Li M, Li L, Hu X, Guo X, Lu Y. Early tranexamic acid in intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *Front Neurol* 2021; **12:** 721125.

69 Nie X, Liu J, Liu D, et al. Haemostatic therapy in spontaneous intracerebral haemorrhage patients with high-risk of haematoma expansion by CT marker: a systematic review and meta-analysis of randomised trials. *Stroke Vasc Neurol* 2021; **6:** 170–79.

70 Liu J, Nie X, Gu H, et al. Tranexamic acid for acute intracerebral haemorrhage growth based on imaging assessment (TRAIGE): a multicentre, randomised, placebo-controlled trial. *Stroke Vasc Neurol* 2021; **6:** 160–69.

71 Law ZK, Ali A, Krishnan K, et al. Noncontrast computed tomography signs as predictors of hematoma expansion, clinical outcome, and response to tranexamic acid in acute intracerebral hemorrhage. *Stroke* 2020; **51:** 121–28.

72 Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA* 2015; **313:** 824–36.

73 Steiner T, Poli S, Griebe M, et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *Lancet Neurol* 2016; **15:** 566–73.

74 Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal—full cohort analysis. *N Engl J Med* 2017; **377:** 431–41.

75 Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor xa inhibitors. *N Engl J Med* 2019; **380:** 1326–35.

76 Demchuk AM, Yue P, Zotova E, et al. Hemostatic efficacy and anti-fxa (factor xa) reversal with andexanet alfa in intracranial hemorrhage: ANNEXA-4 substudy. *Stroke* 2021; **52:** 2096–105.

77 Kessler CM, Goldstein JN. A new strategy for uncontrollable bleeding after treatment with rivaroxaban or apixaban. *Clin Adv Hematol Oncol* 2019; **17** (suppl 15)**:** 1–20.

78 Baharoglu MI, Cordonnier C, Al-Shahi Salman R, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet* 2016; **387:** 2605–13.

79 Feldman EA, Meola G, Zyck S, et al. Retrospective assessment of desmopressin effectiveness and safety in patients with antiplatelet-associated intracranial hemorrhage. *Crit Care Med* 2019; **47:** 1759–65.

80 Hotter B, Ulm L, Hoffmann S, et al. Selection bias in clinical stroke trials depending on ability to consent. *BMC Neurol* 2017; **17:** 206.

81 Tu JV, Willison DJ, Silver FL, et al. Impracticability of informed consent in the Registry of the Canadian Stroke Network. *N Engl J Med* 2004; **350:** 1414–21.

82 Lindley RI, Kane I, Cohen G, Sandercock PA. Factors influencing the use of different methods of consent in a randomized acute stroke trial: the Third International Stroke Trial (IST-3). *Int J Stroke* 2022; **15:** 553–58.

83 Bjarnason NH, Kampmann JP, Lewis BS, Yuval R, Halon DA, Flugelman MY. Selection bias introduced by the informed consent process. *Lancet* 2003; **361:** 1990–91.

84 Almeida-Magana R, Maroof H, Grierson J, et al. E-consent—a guide to maintain recruitment in clinical trials during the COVID-19 pandemic. *Trials* 2022; **23:** 388.

85 van den Bos N, van den Berg SA, Caupain CMM, et al. Patient and proxies' attitudes towards deferred consent in randomised trials of acute treatment for stroke: a qualitative survey. *Eur Stroke J* 2021; **6:** 395–402.

86 Koopman I, Verbaan D, Vandertop WP, et al. Deferred consent in an acute stroke trial from a patient, proxy, and physician perspective: a cross-sectional survey. *Neurocrit Care* 2022; **36:** 621–29.

87 Shamy MCF, Dewar B, Chevrier S, et al. Deferral of consent in acute stroke trials. *Stroke* 2019; **50:** 1017–20.

88 Shamy M, Dewar B, Fitzpatrick T, et al. Deferral of consent: recent lessons from Canadian acute stroke trials. *Stroke* 2021; **52:** e326–27.

89 Shamy M, Dewar B, Niznick N, Nicholls S, Dowlatshahi D. Advanced consent for acute stroke trials. *Lancet Neurol* 2021; **20:** 170.

90 Leira EC, Kaldjian LC, Ludwig BR, et al. Lack of international consensus on ethical aspects of acute stroke trials. *J Stroke Cerebrovasc Dis* 2012; **21:** 200–04.

91 The Lancet Neurology. Patient-reported outcomes in the spotlight. *Lancet Neurol* 2019; **18:** 981.

92 Reeves M, Lisabeth L, Williams L, et al. Patient-reported outcome measures (PROMs) for acute stroke: rationale, methods and future directions. *Stroke* 2018; **49:** 1549–56.

93 Haussen DC, Selim M. Targeting hematoma expansion in ICH: illusions of hope or hope to disillusion. *Neurology* 2012; **79:** 298–99.

94 Toyoda K, Koga M, Yamamoto H, et al. Clinical outcomes depending on acute blood pressure after cerebral hemorrhage. *Ann Neurol* 2019; **85:** 105–13.
95 Mayer SA, Frontera JA, Jankowitz B, et al. Recommended primary outcomes for clinical trials evaluating hemostatic agents in patients with intracranial hemorrhage: a consensus statement. *JAMA Netw Open* 2021; **4:** e2123629.
96 Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Stat Med* 1999; **18:** 1341–54.
97 Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J* 2012; **33:** 176–82.
98 Hariharan P, Tariq MB, Grotta JC, Czap AL. Mobile stroke units: current evidence and impact. *Curr Neurol Neurosci Rep* 2022; **22:** 71–81.
99 Cooley SR, Zhao H, Campbell BCV, et al. Mobile stroke units facilitate prehospital management of intracerebral hemorrhage. *Stroke* 2021; **52:** 3163–66.