Stroke 2

Intracerebral haemorrhage: current approaches to acute management

Charlotte Cordonnier, Andrew Demchuk, Wendy Ziai, Craig S Anderson

Acute spontaneous intracerebral haemorrhage is a life-threatening illness of global importance, with a poor prognosis and few proven treatments. As a heterogeneous disease, certain clinical and imaging features help identify the cause, prognosis, and how to manage the disease. Survival and recovery from intracerebral haemorrhage are related to the site, mass effect, and intracranial pressure from the underlying haematoma, and by subsequent cerebral oedema from perihaematomal neurotoxicity or inflammation and complications from prolonged neurological dysfunction. A moderate level of evidence supports there being beneficial effects of active management goals with avoidance of early palliative care orders, well-coordinated specialist stroke unit care, targeted neurointensive and surgical interventions, early control of elevated blood pressure, and rapid reversal of abnormal coagulation.

Lancet 2018; 392: 1257–68

This is the second in a Series of three papers about stroke

University of Lille, Inserm U1171, Degenerative and Vascular Cognitive Disorders, Centre Hospitalier Universitaire Lille, Department of Neurology, Lille, France (Prof C Cordonnier PhD); **Department of Clinical Neurosciences, University of Calgary, AB, Canada** (Prof A Demchuk MD); **The Johns Hopkins University School of Medicine, Baltimore, MD, United States** (W Ziai MD); **The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia** (Prof C S Anderson PhD); **Neurology Department, Royal Prince Alfred Hospital, Sydney, NSW, Australia** (Prof C S Anderson); **The George Institute China at Peking University Health Science Center, Beijing, China** (Prof C S Anderson)

Correspondence to:
Prof Craig Anderson, The George Institute for Global Health, Camperdown, NSW 2050, Australia
canderson@georgeinstitute.org.au

Introduction

Acute spontaneous (non-traumatic) intracerebral haemorrhage is the most common type of spontaneous intracranial haemorrhage (others being subarachnoid haemorrhage and isolated intraventricular haemorrhage) and is the most serious and least treatable form of stroke that affects approximately 2 million people in the world each year.[1] It is a life-threatening and disabling event, usually manifest as a rapidly expanding haematoma arising within the brain parenchyma, with potential extension into the ventricular system and subarachnoid or dural spaces. One in three patients die within the first month of onset, and survivors have varying degrees of residual disability and high risk of recurrent intracerebral haemorrhage, other serious vascular events, and neurological complications such as epilepsy and dementia. As most cases occur in working adults in large populations of low-income and middle-income countries, among whom the prevalence of hypertension and other vascular risk factors is high, intracerebral haemorrhage has enormous social and economic effects from the resultant loss of productive life years. A meta-analysis of available population-based studies showed stable early case fatality for intracerebral haemorrhage between 1980 and 2008.[2] More recent data have shown favourable trends in survival from intracerebral haemorrhage in the Netherlands,[3] the UK,[4] and France,[5] possibly related to the development of specialist-organised stroke unit care. Unfortunately, there is still no medical treatment for acute intracerebral haemorrhage that is clearly beneficial, and the role of surgery remains controversial despite its widespread use in various forms. We review the evidence and offer guidance in the management of intracerebral haemorrhage, for which recent advances provide encouraging information about reducing cerebral injury, preventing complications, and promoting recovery from this complex and challenging illness.

Acute assessment

Intracerebral haemorrhage is difficult to differentiate from acute ischaemic stroke at the bedside, but certain features suggest its diagnosis: rapidly progressive neurological signs and symptoms, headache, vomiting, seizures, and reduced consciousness often disproportionate to focal deficits all suggest mass effect from an underlying haematoma; neck stiffness indicates chemical meningitis from extension of intraventricular haemorrhage into the subarachnoid space. Neuroimaging should be done immediately to confirm the diagnosis of stroke and the underlying pathological process.

Neuroimaging

Neuroimaging done rapidly after presentation, either CT or MRI, is needed to differentiate intracerebral haemorrhage from acute ischaemic stroke (in patients presenting with acute focal neurological symptoms) or tumours—either primary brain tumours (eg, pituitary) or metastasis (eg, renal, melanoma)—which are prone to

Search strategy and selection criteria

We searched PubMed for papers published between Dec 1, 1945, and April 1, 2018. We used the search terms: "intracerebral haemorrhage" or "haemorrhagic stroke" or "intracranial haemorrhage". Two authors independently reviewed all the retrieved articles. In case of disagreements regarding the literature search results, another author was consulted to formulate a mutual consensus. The search focused on articles published in English. We mostly selected publications from the past 5 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search and selected those we judged relevant. Review articles are cited to provide readers with more detail.

Panel 1: **Key management steps in intracerebral haemorrhage**

Brain and vascular imaging

- Imaging should be done to detect an underlying cause that requires early intervention—eg, vascular malformation, cerebral venous thrombosis, vasculitis, reversible cerebral vasoconstrictor syndrome where the likelihood of diagnosis is higher on the basis of patient age (>50 years), intracerebral haemorrhage location (peripheral or cortical), history of hypertension (absent), and presence of cerebral small vessel disease (imaging features)
- CT angiography spot sign predicts haematoma growth but whether this improves upon established clinical and haematoma predictive markers is still to be defined
- MRI can detect chronic microhaemorrhaging and cerebral superficial siderosis, which is helpful for the diagnosis of cerebral amyloid angiopathy

Stroke unit care

Lowering of blood pressure (systolic target <140 mm Hg over 1–2 h)

Correction of haemostatic abnormalities

- Consider whether there is a specific disease (eg, haematological disorder)
- Consider whether this disease is due to a specific anticoagulant drug and whether a reversal agent or antidote is required

Prevention of complications

- Careful identification of deteriorating patients requiring neurosurgical intervention
- Use of intermittent pneumatic compression therapy for venous thromboembolism prophylaxis
- Management of seizures

Search for the cause of the intracerebral haemorrhage

Prevention

- Lower blood pressure to prevent recurrent intracerebral haemorrhage and other serious vascular events
- Consider whether there is a high risk of recurrent intracerebral haemorrhage to prevent starting or restarting antithrombotic treatment to prevent ischaemic events
- Screen for cognitive impairment during follow-up

haemorrhage. Although MRI is the preferred acute stroke imaging tool because of the detail of anatomy and function provided, the high cost and low accessibility mean that it is typically performed in the subacute phase to assess the underlying cause, including the presence and pattern of cerebral small vessel disease.[6] Non-contrast CT is therefore the practical method of confirming the clinical presentation of acute stroke and identifying the volume and location of intracerebral haemorrhage, any intraventricular haemorrhage, and the presence of subarachnoid haemorrhage, which can suggest an aneurysm or cerebral amyloid angiopathy as the underlying vessel disease.[7] Several non-contrast CT markers of the shape and density of intracerebral haemorrhage add to certain clinical features in predicting the likelihood of haematoma growth (or expansion) and prognosis.[8–15]

An underlying vascular lesion, such as an arteriovenous malformation, aneurysm, or dural fistula, occurs in about 15% of adults with acute intracerebral haemorrhage.[16,17] The decision to proceed to more extensive vascular imaging—CT angiography or MRI angiography and intra-arterial digital subtraction angiography—can be made on the probability of finding a structural lesion using simple criteria: patient age, intracerebral haemorrhage location, history of hypertension, and presence of cerebral small vessel disease (panel 1).

CT angiography spot sign

The CT angiography spot sign[18] has been the focus of much attention and is an indicator of an active haemorrhage. Identification of the location of the leak[19] or rate of leakage, via extravasation of contrast material within the haematoma, might assist in understanding the causes of haematoma growth in intracerebral haemorrhage. With some training, the spot sign can be detected reasonably well[20] and indicates a high likelihood of ongoing bleeding, greater risk of further haematoma growth, and poor clinical outcome.[21–24] The spot sign also predicts ongoing bleeding during haematoma evacuation for intracerebral haemorrhage,[25] and a retrospective analysis suggested that patients with surgically treated intracerebral haemorrhage that is spot-sign positive had lower mortality than a conservatively managed group.[26] However, a disadvantage of the standard single phase CT angiography is that it is only a snapshot in time. Because a spot sign can be missed if the images are acquired before the contrast material has had sufficient time to reach the leak point, detection is increased if later arterial, early venous, or delayed phases of the CT angiography are examined.[27,28] Furthermore, the predictive ability of the spot sign for haematoma expansion diminishes when the sign is only seen at later time points. A meta-analysis suggests the predictive ability of the spot sign is better when CT angiography is done within a few hours after intracerebral haemorrhage,[29] and a multiphase CT angiography, which includes a venous phase, can also increase the frequency of detecting a spot sign. A spot sign seen in the initial phase of the CT angiography (arterial) is associated with the greatest risk of haematoma growth, indicating a more

robust leak.[30] Although dynamic CT angiography[31] and CT perfusion[32,33] ensure good detection of contrast extravasation in the brain and might provide a more robust measure of extravasation rate, these methods have a higher radiation dose than single-phase or multiphase CT angiography. Ultimately, however, the clinical utility of the CT angiography spot sign for management of patients with intracerebral haemorrhage has not been defined.

Prognostic scales

The ICH score is the most commonly used prognostic scale that combines demographic and clinical information with the location and volume of intracerebral haemorrhage and presence of intraventricular haemorrhage.[34] Although other scores are available, none are substantially better at predicting outcomes, particularly that of early death.[35] Part of the problem is that loss of consciousness, a prominent feature of intracerebral haemorrhage, complicates the use of neurological assessment scales, such as the National Institutes of Health Stroke Scale. Altered consciousness can also be related to complications such as seizures, dehydration, head injury from falling, cerebral anoxia from airway obstruction, or even cardiac arrest. Scores that include the CT angiography spot sign or other haematoma patterns on non-contrast CT seem to predict haematoma growth, but are not superior to established clinical (ie, neurological severity) and haematoma (ie, haematoma volume, presence of intraventricular haemorrhage) parameters at predicting clinical outcome.[36]

Classification of causes

The notion of primary disease is entrenched in conventional medical practice, but there is no such thing as primary intracerebral haemorrhage in the same way that there is no such thing as primary cerebral infarction. The major risk factors for spontaneous intracerebral haemorrhage are ageing, male sex, high blood pressure, illicit drug use, excessive alcohol consumption (particularly with a binge pattern), and dietary (eg, high salt consumption and low consumption of fruit and fresh vegetables[37]) and genetic factors, which preferentially influence endothelial integrity. Vascular risk factors are often considered as an underlying cause, whereas the actual underlying pathological cause (eg, small vessel disease, amyloid angiopathy, or vascular malformation) in intracerebral haemorrhage is not well acknowledged or goes undetected. Heterogeneous disease entities, such as cerebral amyloid angiopathy, vasculitis, and deep perforating vasculopathy, are often included together only because they share one common complication of acute bleeding into the brain parenchyma. Thus, spontaneous intracerebral haemorrhage should be considered as a heterogeneous condition, for which the attending clinician is required to investigate the cause, the most frequent being deep perforating vasculopathy and sporadic cerebral amyloid angiopathy.

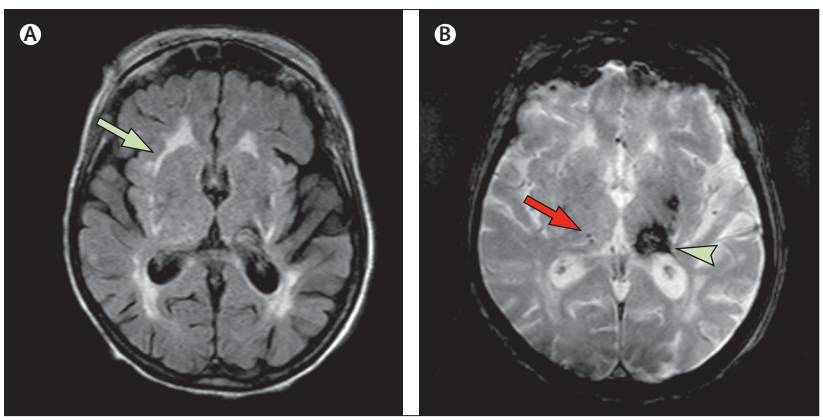

Figure 1: **Brain MRI, axial slices**
(A) Fluid-attenuated inversion recovery sequence showing occlusive features of deep perforating vasculopathy with extensive white-matter hyperintensities (green arrow) and lacunes in the right basal ganglia. (B) T2* gradient echo sequence showing haemorrhagic features of deep perforating vasculopathy with a deep left haematoma (green arrow head) and deep right microhaemorrhages (red arrow).

Deep perforating vasculopathy or arteriolosclerosis

Often called hypertensive intracerebral haemorrhage, deep perforating vasculopathy or arteriolosclerosis is the main cause of intracerebral haemorrhages that are most often located in the basal ganglia, thalamus, and brainstem. How much cerebellar intracerebral haemorrhage relates to hypertension versus cerebral amyloid angiopathy is uncertain. In the absence of prospectively validated diagnostic criteria, clinicians should keep in mind that the presence of risk factors is neither necessary nor sufficient to conclude that a deep intracerebral haemorrhage is due to arteriolosclerosis.[38] Because this vasculopathy has two modalities of expression—haemorrhagic and occlusive—clinicians should search for biomarkers for chronic damage to the brain, such as cerebral white matter lesions, lacunes, microbleeds, or old intracerebral haemorrhage located in the basal ganglia or brainstem. To assess chronic, often silent, lesions dedicated MRI sequences such as fluid-attenuated inversion recovery, gradient echo T2*, or susceptibility-weighted imaging are useful (figure 1). In the absence of features of arteriolosclerosis, even in an elderly patient with hypertension, clinicians should consider searching for other causes, especially for small deep arteriovenous malformations, for which surgical intervention can have beneficial effects.

Cerebral amyloid angiopathy

Cerebral amyloid angiopathy is characterised by the presence of amyloid-β protein within cortical and leptomeningeal blood vessel walls, and is a common cause of a lobar intracerebral haemorrhage. Indeed, cerebral amyloid angiopathy is associated with a high risk of rebleeding of about 9% per year;[39] however, some

Panel 2: Clues for underlying causes of intracerebral haemorrhage

Deep perforating vasculopathy
- Haematoma located in the basal ganglia or brainstem; microbleeds or old intracerebral haemorrhage in the basal ganglia or brainstem; white matter lesions; lacunes

Cerebral amyloid angiopathy
- Lobar intracerebral haemorrhage; cortico-subcortical microbleeds; cortical superficial siderosis; apolipoprotein E ε4; cognitive decline; transient focal neurological episodes

Brain arteriovenous malformation
- Extension to other brain compartments; flow voids; calcification

Intracranial arterial aneurysm
- Disproportionate subarachnoid extension

Cavernous malformation
- Small, homogeneous intracerebral haemorrhage with no extension to other brain compartments

Intracranial venous thrombosis
- Headaches preceding intracerebral haemorrhage onset; intracerebral haemorrhage close to sinuses or veins; high relative oedema volume; onset in pregnancy or postpartum

Dural arteriovenous fistula
- Subarachnoid or subdural extension; abnormal dilated cortical vessels

Haemorrhagic transformation of cerebral infarction
- Substantial areas of acute ischaemic lesions adjacent to the intracerebral haemorrhage or diffuse acute ischaemic lesions in other arterial territories

Severe clotting factor deficiency such as haemophilia
- Abnormal coagulation tests

Tumour (primary/metastasis)
- Large perihaematomal oedema

Vasculitis
- Headaches; small acute ischaemic lesions in different arterial territories; focal diffuse arterial stenosis

Infective endocarditis
- Acute ischaemic lesions in different arterial territories; small irregular arterial aneurysms; diffuse brain microbleeds

Posterior reversible encephalopathy syndrome
- Thunderclap headaches; parietal and occipital asymmetrical oedematous lesions

patients with extensive multifocal cortical superficial siderosis might have up to a 26% yearly risk of bleeding.[40] Such patients also have a high risk of cognitive decline and dementia.[41] The widely used MRI-based modified Boston criteria have excellent sensitivity and good specificity for cerebral amyloid angiopathy, requiring the patient to be aged over 55 years, have one previous lobar intracerebral haemorrhage, or lobar cerebral microbleeds, or cortical superficial siderosis.[42] The Edinburgh CT and genetic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy have since been developed,[43] with a three-variable model using two non-contrast CT features (subarachnoid haemorrhage and finger-like haematoma projections) and an apolipoprotein E (APOE) genotype to predict moderate or severe cerebral amyloid angiopathy. The Edinburgh sensitive rule-out criteria and specific rule-in criteria based on non-contrast CT and APOE genotype are potentially widely applicable for diagnostic, prognostic, and therapeutic decisions in everyday clinical practice if MRI is contraindicated, intolerable, or unavailable. Diagnosis of cerebral amyloid angiopathy in vivo is a challenge in the absence of a histological sample. Moreover, in the absence of a specific curative treatment, such patients should be managed in the same manner as a patient with any other type of spontaneous intracerebral haemorrhage. However, a key clinical dilemma yet to be solved is how best to assess the balance of benefits and risks of starting or restarting antithrombotic drugs in these high-risk patients.[44]

Other causes

Although cerebral amyloid angiopathy and deep perforating vasculopathy might be responsible for most (around 80%) cases of non-traumatic intracerebral haemorrhage, clinicians should consider searching for other causes (panel 2). Some causes will require urgent management—for example, intensive anticoagulation for cerebral venous thrombosis.

Organisation of care

Intracerebral haemorrhage is a medical emergency in which most patients benefit from an early active management plan. Various studies of health record data show that premature use of orders for do-not-resuscitate, withdrawal of care, or palliative care (which includes narcotic use) independently predict mortality, after adjustment for conventional clinical prognostic factors.[45,46] Active care includes monitoring, early screening for dysphagia, maintenance of physiological control, including avoidance of high blood glucose concentrations, and timely intervention for neurological deterioration, secondary complications, and adverse events. Patients with critical care needs, such as mechanical ventilation and ventriculostomy, are ideally managed in an intensive care or high-dependency unit, where there is a high nurse to patient ratio and specialised care and expertise. For all other patients, management within a specialist acute stroke unit can reduce the risks of death and dependency after intracerebral haemorrhage compared with general ward care. A meta-analysis of 13 randomised controlled

trials involving 3570 patients with intracerebral haemorrhage showed that stroke unit care provides an overall 20% reduction in the risk of poor outcome, which is comparable to the treatment effect seen in patients with acute ischaemic stroke.[47]

Medical management

Blood pressure control

Hypertension after intracerebral haemorrhage is common and multiple factors contribute to the hypertensive response, including stress of the acute event, or prior variability and peaks in systolic blood pressure that might trigger the event. Because hypertension, defined as elevated systolic blood pressure (>140 mm Hg), is modifiable and associated with haematoma growth and poor recovery, it seems reasonable that early intensive lowering of blood pressure could improve clinical outcomes through the attenuation of haematoma growth as the most plausible mechanistic action. However, the evidence to date is not so definitive. An international clinical trial (INTERACT2)[48] of 2829 patients with generally mild to moderately severe intracerebral haemorrhage showed that early intensive lowering of blood pressure to a systolic target of less than 140 mm Hg led to modest improvements in functional outcomes and health-related quality of life without substantial harms, compared with the contemporaneous standard (systolic target <180 mm Hg) within several hours of onset.[48] However, a second trial (ATACH-II)[49] involving 1000 patients of similar demographic and clinical parameters did not show any benefits of a more intensive blood pressure lowering regimen and raised concerns over an increase in renal adverse events of such treatment.[49] These discordant results might be largely explained by differences in the manner in which blood pressure was managed. INTERACT2 took a pragmatic approach and allowed various drugs, on the basis of local availability and familiarity, to be used to lower blood pressure over several hours, whereas ATACH-II had a more intensive blood pressure lowering protocol based on a single intravenous agent (nicardipine) and the investigators, probably influenced by the updating of guidelines, also intensively managed the blood pressure of control patients.

Systematic reviews and meta-analyses of these and other, much smaller, clinical trials have not shown any effect of early intensive blood pressure lowering on clinical outcomes, despite there being a modest attenuation of haematoma growth overall and no clear effect on haematoma growth in either INTERACT2 or ATACH-II.[50–53] However, these studies were unable to account for differences in blood pressure management. Indirect evidence for beneficial effects of early intensive blood pressure lowering in intracerebral haemorrhage comes from several other sources. First, secondary analyses of INTERACT2, in which participants on antithrombotic treatment and who received blood pressure lowering treatment early after onset, had greater attenuation of haematoma growth compared with other patients.[54] Second, studies of intracerebral haemorrhage associated with anticoagulation have shown that early control of elevated blood pressure is at least as effective as the use of reversal agents.[55] Finally, a large clinical trial of the early use of the haemostatic drug tranexamic acid in intracerebral haemorrhage showed a significant prespecified subgroup interaction for baseline systolic blood pressure lower than 170 mm Hg and a beneficial effect of the treatment.[56] Thus, the evidence is reasonably strong to recommend intensive blood pressure lowering (target systolic blood pressure range 130–140 mm Hg within 6 h of onset) for most patients with intracerebral haemorrhage, as it is practical, safe, and might improve functional outcome. Even so, more research is needed to assess the effects of this treatment in certain subgroups of patients with intracerebral haemorrhage: those presenting very early (<1 h) after onset, those who undergo neurosurgery, and when treatment is combined with the use of haemostatic agents or reversal of anticoagulation.

Intracerebral haemorrhage associated with antiplatelet therapy

In high-income countries, more than a quarter of patients with intracerebral haemorrhage are on prior antiplatelet therapy;[57] these patients have a worse prognosis than those not on antiplatelet therapy,[58] potentially because of greater haematoma growth.[59] Thus, it seems plausible that haemostasis could be improved in these patients by replacing non-functioning platelets via platelet transfusion. However, a randomised trial of 190 patients treated with antiplatelet therapy who had acute intracerebral haemorrhage (<6 h after intracerebral haemorrhage onset) showed an increased risk of poor outcome after receiving platelet transfusion.[60] Thus, it seems reasonable to avoid platelet transfusion in the context of intracerebral haemorrhage associated with antiplatelet therapy.

Intracerebral haemorrhage associated with anticoagulation

Roughly 15% of intracerebral haemorrhage is associated with the use of anticoagulant treatment.[61] Warfarin-associated intracerebral haemorrhage is associated with increased haematoma volumes,[62] haematoma growth,[63] and worse clinical outcomes compared with other intracerebral haemorrhage.[64] Despite a lower rate of intracerebral haemorrhage associated with direct oral anticoagulants than with warfarin,[65] when intracerebral haemorrhage occurs the use of direct oral anticoagulants is also associated with worse outcomes compared with patients with intracerebral haemorrhage without anticoagulation. However, the prognosis for intracerebral haemorrhage associated with direct oral anticoagulants is better than that for intracerebral haemorrhage associated with warfarin.[66] The concept of time is brain is

relevant for anticoagulation-related intracerebral haemorrhage.[55] A moderate level of evidence indicates that these patients should receive reversal agents as soon as possible.[67] In patients with an international normalised ratio (INR) greater than or equal to 1·4 at admission who are treated with vitamin K antagonists, where available, 4-factor prothrombin complex concentrate is preferable to fresh frozen plasma.[68] Vitamin K injection is also recommended as standard treatment, despite insufficient supporting evidence. The aim of the reversal treatment is to obtain an INR lower than 1·4 as soon as possible. INR values should be followed up at 3–6 h intervals for the first 24 h to detect rebound coagulopathy and further need for reversal if necessary. In patients treated with direct oral anticoagulants, when available, specific reversal drugs can be used (idarucizumab for dabigatran and andexanet-alpha for factor Xa inhibitors). In the absence of specific reversal agents, 4-factor prothrombin complex concentrate can be used.

Haemostatic strategies

The rationale for using haemostatic drugs is to reduce early haematoma growth, with recombinant factor VIIa (rFVIIa) being the main therapy tested in patients presenting within 4 h of intracerebral haemorrhage onset.[69,70] Although a major clinical trial showed that a dose of 80 mg/kg significantly reduced haematoma growth compared with placebo,[70] this result did not translate into a clinical benefit as seen in an earlier trial,[69] and resulted in an excess of serious thromboembolic events. Exploratory analysis of this trial suggested benefit in a highly selected group of patients who present within 2·5 h of intracerebral haemorrhage onset with small intracerebral haemorrhage and without intraventricular haemorrhage,[71] but the practicality of readily identifying such a group and the high cost of rFVIIa greatly limit the utility of this treatment. Results of two unpublished trials of rFVIIa in a highly targeted group of patients with intracerebral haemorrhage and high likelihood of haematoma growth based on CT angiography spot sign confirm the predictive value of the spot sign for haematoma growth but did not show any effect on haematoma growth. Furthermore, the slow patient recruitment further emphasises the poor practicality of this potent treatment. The absence of an effect of rFVIIa might have been due to late initiation of treatment: less than half of the patients were treated within 3 h of onset of intracerebral haemorrhage because of the delay between the initial CT and drug administration. Further unpublished data from the Canadian trial "Spot Sign" Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy (SPOTLIGHT, NCT01359202), showed that most haematoma growth occurred between baseline and the immediate post-drug CT, rather than at the conventional follow-up CT at 24 h. These data suggest that much of the haematoma growth is brisk and very early after onset of intracerebral haemorrhage, before rapidly plateauing and sometimes contracting by 24 h, which is indicative of a logarithmic pattern of bleeding.

The second international Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2) trial compared the use of intravenous tranexamic acid (1 mg bolus followed by an infusion of another 1 mg over a period of 8 h) with matching placebo in 2325 patients with intracerebral haemorrhage (<8 h after onset).[56] Although the trial did not show any effect of tranexamic acid on the primary outcome of functional recovery at 90 days, there was a significant reduction in deaths within 7 days (but not at 90 days) and serious adverse events, and a modest attenuation (1 mL) of haematoma growth between the baseline and 24 h non-contrast CT. TICH-2 was probably underpowered to detect a benefit of tranexamic acid, which, given the safety profile and low cost, could be a widely applicable option for treatment for intracerebral haemorrhage.

Complications

Seizures

The risk of seizures is relatively high (around 5–10%) after intracerebral haemorrhage, more so than it is for acute ischaemic stroke,[72] and even higher if subclinical seizures are also considered.[73] Early seizures (<7 days after intracerebral haemorrhage onset) are due to the cerebral trauma of intracerebral haemorrhage and do not seem to influence recovery.[74] Prophylactic use of antiepilepsy drugs is not recommended because of uncertainty over the balance of potential benefits (eg, improved recovery) and harms (eg, sedation). In those patients who do experience an early seizure, antiepilepsy drugs are usually prescribed for 3–6 months to prevent further seizures. Patients with late seizures (>7 days after intracerebral haemorrhage onset),[74] the likelihood of which is estimated from the CAVE score[75] (cortical involvement [C], young age, ie, <65 years [A], small haematoma volume [V], and early seizures, <7 days, [E]), are managed with antiepilepsy drugs in the same manner as any other patients with epilepsy.

Cerebral oedema

Disruption of the blood–brain barrier and leakage of fluids and proteins contribute to cerebral oedema after intracerebral haemorrhage, which increases over several days and can further damage the brain. Early oedema formation (within hours of intracerebral haemorrhage) involves hydrostatic pressure and clot retraction, with movement of serum from the clot into the surrounding tissue. A second phase (within days) involves the coagulation cascade and thrombin production, which induces inflammatory cell infiltration, mesenchymal cell proliferation and scar formation, and evolves into inflammation and leucocyte infiltration from a breakdown of the blood–brain barrier. Haemoglobin breakdown and iron release are major contributors to intracerebral haemorrhage-induced brain injury.[76] None

of the commonly used treatments for cerebral oedema (steroids, mannitol, glycerol, hyperventilation) have been proven to be effective at lowering intracranial pressure or preventing perihaematoma oedema in intracerebral haemorrhage[72] (figure 2). Non-randomised feasibility studies suggest hypertonic saline and mild hypothermia might reduce perihaematoma oedema.[77,78] Studies to assess new approaches targeting inflammation (fingolimod [NCT02175225], deferoxamine) and the use of decompressive hemicraniectomy (NCT02258919) are ongoing.

The effect of raised intracranial pressure in intracerebral haemorrhage is not well understood, as it is not always the immediate cause of death,[79] might be related to mortality only in comatose patients,[80,81] and has no reported relation with long-term outcome.[82] However, observational studies suggest that raised intracranial pressure is not uncommon, and intracranial pressure more than 20–30 mm Hg is significantly associated with early mortality and poor functional recovery in comatose patients with supratentorial intracerebral haemorrhage and in aggressively managed patients with obstructive intraventricular haemorrhage and catheter drainage.[83,84] Guidelines for the management of intracerebral haemorrhage recommend invasive intracranial pressure monitoring in patients who are comatose, or who have transtentorial herniation, large intraventricular haemorrhage, or hydrocephalus.[67,84] However, there is uncertainty over the appropriate management of raised intracranial pressure in intracerebral haemorrhage, and principles relevant to traumatic brain injury are often empirically applied. Increasing attention is being given to dynamic cerebral autoregulation and the potential for individualising treatment.[85] Similarly, although a large cluster crossover clinical trial has shown no differences in outcomes between the lying-flat and the sitting-up head position in acute stroke,[86] the sitting-up head position is often used in patients with large intracerebral haemorrhage in the belief that this position might reduce intracranial pressure and improve cardiopulmonary function.

Venous thromboembolism

As in other immobile patients, those with intracerebral haemorrhage are at high risk of thromboembolic events and should be mobilised cautiously as soon as possible after the event.[87] A large clinical trial has shown that intermittent pneumatic compression can reduce the risk of deep vein thrombosis and improve survival,[88] and another showed that compression stockings are ineffective and harmful, and should be avoided.[89] It is common practice to use intermittent pneumatic compression during the first few days and to wait at least 24–48 h before using prophylactic low-molecular-weight heparin or heparinoids in the persistently immobile patient,[67] because of concerns that heparin could contribute to worsening outcome, possibly by increasing the risk of rebleeding of the intracerebral haemorrhage.[90]

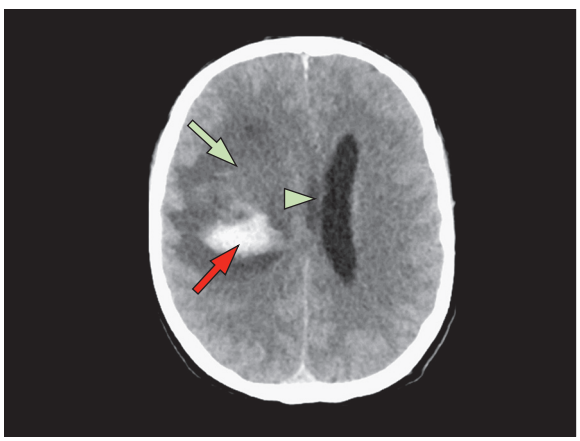

Figure 2: **Non-contrast CT scan, axial slice, 8 days after intracerebral haemorrhage.**
Image shows deep right haematoma (red arrow) surrounded by perihaematomal oedema (green arrow) with mass effect and midline shift (green arrow head).

Neurosurgery

Craniectomy for evacuation of the haematoma

Surgical evacuation of cerebellar intracerebral haemorrhage in patients who are rapidly deteriorating from brainstem compression is accepted practice despite there being no randomised assessment of this strategy.[91,92] For supratentorial intracerebral haemorrhage, early evacuation (<24 h after onset of haemorrhage) with standard craniotomy is considered life saving in deteriorating patients, but is not clearly beneficial in deeply comatose or otherwise stable patients. In the first large clinical trial on surgical management of intracerebral haemorrhage, there was no overall benefit from early surgery compared with initial conservative treatment.[93] Another trial in highly selected patients (Glasgow coma scale [GCS] score 8–15, no intraventricular haemorrhage) with superficial intracerebral haemorrhage (<1 cm of the cortical surface) also showed no benefit of early surgery on poor outcome (death or disability at 6 months) compared with best medical treatment.[94] However, both of these trials were complicated by high crossover from initial conservative to surgical intervention in deteriorating patients, which probably compromised the statistical power to detect a net benefit of surgery. An individual patient data meta-analysis suggests an overall modest benefit of surgery, and that the greatest benefit is in patients who are aged 50–69 years, treated early (within 8 h of onset), have moderately large (20–50 mL) haematomas, and whose level of consciousness is impaired but still responsive (GCS score 9–12).[95] Further subgroup analysis also did not show a significant benefit of craniotomy in patients with lobar intracerebral haemorrhage and no intraventricular haemorrhage.[94]

External ventricular drainage

Intraventricular haemorrhage is an independent determinant of prognosis in intracerebral haemorrhage, as blood breakdown products promote inflammatory meningitis and hydrocephalus, and a worse outcome related to increased intraventricular haemorrhage volume.[96–97] External ventricular drain, with or without controlled irrigation of a lytic agent such as alteplase, improves the chances of survival in a deteriorating patient with a reduced level of consciousness from rapid clearance of intraventricular haemorrhage.[67] However, there is uncertainty over the critical threshold volume of intraventricular haemorrhage that determines the need for insertion of external ventricular drain, and insertion rates vary widely within and between countries.[98–100] Moreover, the absence of benefit of external ventricular drain on functional outcome seen in clinical trials might be due to the lack of effect of this intervention on the cerebral injury associated with intracerebral haemorrhage or insufficient intraventricular haemorrhage removal.[101–103] Other promising strategies under investigation for removing large volumes of intraventricular haemorrhage include controlled lumbar drainage and more targeted intraventricular surgical techniques.[104,105]

Minimally invasive surgery

Minimally invasive surgery, with non-contrast CT-guided insertion of a catheter or stylet to decompress the haematoma, is standard clinical practice in China, where rates of intracerebral haemorrhage are high, access to neurosurgery is often poor, and there is acceptance of broader based discipline expertise in the techniques. Minimally invasive surgery using various techniques has now become a mainstream concept in high-income countries for the surgical management of intracerebral haemorrhage, especially deep intracerebral haemorrhage, to minimise the parenchymal injury that occurs in accessing the haematoma. Meta-analyses of clinical trials from different settings, comparing stereotactic puncture or endoscopic drainage with other treatments (both craniotomy and conservative treatment), have shown improved outcomes from minimally invasive surgery.[93,105,106] Whether decompression removes the toxic effects of the haematoma in stable patients, by combining minimally invasive surgery and instillation of a lytic agent, and improves clinical outcomes in intracerebral haemorrhage is under investigation.[107] These data and other efforts have already influenced various neurosurgical approaches, including endoscopic evacuation without thrombolysis and minimally invasive surgery with focused ultrasound, which are also undergoing testing in clinical trials.

Secondary prevention

Intracerebral haemorrhage has a high risk of recurrence—about 5% per year.[40] Several trials have shown long-term benefits from blood pressure lowering (systolic target <140 mm Hg) for the secondary prevention of intracerebral haemorrhage and other serious vascular events, and the effects on recurrent intracerebral haemorrhage are much greater than for prevention of ischaemic stroke for the same degree of blood pressure reduction.[108] The stronger effect of blood pressure lowering on intracerebral haemorrhage as compared with ischaemic stroke is consistent with the large reductions in risk of intracerebral haemorrhage seen in trials of blood pressure lowering in patients with hypertension, and the stronger epidemiological association of usual blood pressure and rates of intracerebral haemorrhage, particularly in Asian populations.[109] Whether more intensive blood pressure control (target systolic <130 or <120 mm Hg) confers even greater benefits over potential cardiac and renal harms, whether the benefits of blood pressure lowering are consistent across different types of intracerebral haemorrhage, and how best to achieve blood pressure control and long-term adherence all require further randomised assessment. Having survived an intracerebral haemorrhage, patients, families, and clinicians are naturally concerned about the risk of a recurrence. However, the risk of having an acute ischaemic stroke is at least as frequent, which raises a therapeutic dilemma as to the net clinical benefit of antithrombotic agents after intracerebral haemorrhage. Clinical trials assessing the benefit to risk ratio of restarting antiplatelet agents in patients already taking antiplatelets before an intracerebral haemorrhage are ongoing. The hypothesis in these clinical trials is that for most patients with intracerebral haemorrhage, the risk of ischaemic cerebral events is much higher than the risk of another intracerebral haemorrhage. To date, however, only observational non-randomised data are available to guide therapy and these data are consistently in favour of restarting antiplatelet therapies, as the benefits of preventing ischaemic events clearly outweighs the increased risk of intracerebral haemorrhage.[110] Of course, the benefit to risk ratio can differ according to the severity of underlying cerebral small vessel disease, and patients with large numbers of cerebral microbleeds seem to have a higher risk of recurrent intracerebral haemorrhage than patients with deep perforating vasculopathy.[111] As part of general vascular risk management, appropriate attention should be given to cessation of smoking, management of diabetes, and lifestyle advice concerning regular exercise, social activities, and a reduction in dietary salt. Whether the clear benefits of lipid-lowering therapy in patients at high risk of atherothrombotic disease is offset by the tiny potential increased risk of intracerebral haemorrhage associated with low levels of cholesterol is controversial.[112] Statins should therefore be continued or initiated in those for whom there are clear long-term benefits in preventing atherosclerotic vascular disease,[113] but whether statins otherwise improve functional

recovery from intracerebral haemorrhage is uncertain. In the context of atrial fibrillation, the same dilemma applies regarding the question of whether to begin on oral anticoagulants or not in patients with intracerebral haemorrhage, and clinical trials are ongoing.[114,115]

Conclusion

We recognise that this Series paper including practice recommendations is constrained by our interpretation of the evidence in a critical illness that is particularly challenging to study. Research indicates several therapeutic avenues of benefit in intracerebral haemorrhage modelled around an active management plan, aggressive supportive care, early blood pressure control, and targeted surgery as a life-preserving strategy. Emerging data support a shift in management towards much earlier initiation of medical treatments in intracerebral haemorrhage, and in particular for haemostatic treatment when the rate of haematoma growth is highest. The concept of time is brain, developed for the management of acute ischaemic stroke, applies readily to the management of acute intracerebral haemorrhage. Initiation of haemostatic treatment within the first few hours after onset, using deferral or waiver of informed consent or even earlier initiation using a prehospital setting with mobile stroke unit technologies, require evaluation. For patients with intracerebral haemorrhage presenting at later or unwitnessed time windows, refining the approach of spot sign detection through newer imaging techniques, such as multi-phase CT angiography,[30] might prove useful, as has been shown with the use of CT perfusion in the detection of viable cerebral ischaemia in patients with acute ischaemic stroke who present in a late window.[116,117] Ultimately, the best treatment of intracerebral haemorrhage is prevention and effective detection, management, and control of hypertension across the community and in high-risk groups will have the greatest effect on reducing the burden of intracerebral haemorrhage worldwide.

Contributors

All authors assisted with the collection of research data for this Series paper and contributed to the content. CC and CSA wrote the first drafts of the manuscript. All authors made important comments on subsequent revisions and approved the final submission.

Declaration of interests

AD has received honoraria from Portola. WZ has received consultant fees from Headsense Inc. CSA has received speaker fees and travel reimbursement from Takeda and Amgen. CC declares no competing interests.

References

1 Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health* 2013; **1:** e259–81.

2 van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol* 2010; **9:** 167–76.

3 Jolink WM, Klijn CJ, Brouwers PJ, Kappelle LJ, Vaartjes I. Time trends in incidence, case fatality, and mortality of intracerebral hemorrhage. *Neurology* 2015; **85:** 1318–24.

4 Gonzalez-Perez A, Gaist D, Wallander MA, McFeat G, Garcia-Rodriguez LA. Mortality after hemorrhagic stroke: data from general practice (The Health Improvement Network). *Neurology* 2013; **81:** 559–65.

5 Bejot Y, Grelat M, Delpont B, et al. Temporal trends in early case-fatality rates in patients with intracerebral hemorrhage. *Neurology* 2017; **88:** 985–90.

6 Smith EE, Nandigam KR, Chen YW, et al. MRI markers of small vessel disease in lobar and deep hemispheric intracerebral hemorrhage. *Stroke* 2010; **41:** 1933–38.

7 Rodrigues MA, Samarasekera N, Lerpiniere C, et al. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. *Lancet Neurol* 2018; **17:** 232–40.

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

9 Blacquiere D, Demchuk AM, Al-Hazzaa M, et al. Intracerebral hematoma morphologic appearance on noncontrast computed tomography predicts significant hematoma expansion. *Stroke* 2015; **46:** 3111–116.

10 Li Q, Zhang G, Huang YJ, et al. Blend sign on computed tomography: novel and reliable predictor for early hematoma growth in patients with intracerebral hemorrhage. *Stroke* 2015; **46:** 2119–23.

11 Li Q, Zhang G, Xiong X, et al. Black hole sign: novel imaging marker that predicts hematoma growth in patients with intracerebral hemorrhage. *Stroke* 2016; **47:** 1777–81.

12 Li Q, Liu QJ, Yang WS, et al. Island sign: an imaging predictor for early hematoma expansion and poor outcome in patients with intracerebral hemorrhage. *Stroke* 2017; **48:** 3019–25.

13 Li Q, Yang WS, Wang XC, et al. Blend sign predicts poor outcome in patients with intracerebral hemorrhage. *PLoS One* 2017; **12:** e0183082.

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

15 Li Q, Yang WS, Chen SL, et al. Black hole sign predicts poor outcome in patients with intracerebral hemorrhage. *Cerebrovasc Dis* 2018; **45:** 48–53.

16 Delgado Almandoz JE, Schaefer PW, et al. Diagnostic accuracy and yield of multidetector CT angiography in the evaluation of spontaneous intraparenchymal cerebral hemorrhage. *Am J Neuroradiol* 2009; **30:** 1213–21.

17 Bekelis K, Desai A, Zhao W, et al. Computed tomography angiography: improving diagnostic yield and cost effectiveness in the initial evaluation of spontaneous nonsubarachnoid intracerebral hemorrhage. *J Neurosurg* 2012; **117:** 761–66.

18 Wada R, Aviv RI, Fox AJ, et al. CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. *Stroke* 2007; **38:** 1257–62.

19 Orito K, Hirohata M, Nakamura Y, et al. Leakage sign for primary intracerebral hemorrhage: a novel predictor of hematoma growth. *Stroke* 2016; **47:** 958–63.

20 Huynh TJ, Flaherty ML, Gladstone DJ, et al. Multicenter accuracy and interobserver agreement of spot sign identification in acute intracerebral hemorrhage. *Stroke* 2014; **45:** 107–12.

21 Delgado Almandoz JE, Yoo AJ, Stone MJ, et al. Systematic characterization of the computed tomography angiography spot sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion: the spot sign score. *Stroke* 2009; **40:** 2994–3000.

22 Delgado Almandoz JE, Yoo AJ, Stone MJ, et al. The spot sign score in primary intracerebral hemorrhage identifies patients at highest risk of in-hospital mortality and poor outcome among survivors. *Stroke* 2010; **41:** 54–60.

23 Park SY, Kong MH, Kim JH, Kang DS, Song KY, Huh SK. Role of "spot sign" on CT angiography to predict hematoma expansion in spontaneous intracerebral hemorrhage. *J Korean Neurosurg Soc* 2010; **48:** 399–405.

24 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:** 307–71.

25 Brouwers HB, Raffeld MR, van Nieuwenhuizen KM, et al. CT angiography spot sign in intracerebral hemorrhage predicts active bleeding during surgery. *Neurology* 2014; **83:** 883–89.

26 Kim HT, Lee JM, Koh EJ, Choi HY. Surgery versus conservative treatment for spontaneous supratentorial intracerebral hemorrhage in spot sign positive patients. *J Korean Neurosurg Soc* 2015; **58:** 309–15.

27 Rodriguez-Luna D, Dowlatshahi D, Aviv RI, et al. Venous phase of computed tomography angiography increases spot sign detection, but intracerebral hemorrhage expansion is greater in spot signs detected in arterial phase. *Stroke* 2014; **45:** 734–39.

28 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.

29 Dowlatshahi D, Brouwers HB, Demchuk AM, et al. Predicting intracerebral hemorrhage growth with the spot sign: the effect of onset-to-scan time. *Stroke* 2016; **47:** 695–700.

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

31 Dowlatshahi D, Wasserman JK, Momoli F, et al. Evolution of computed tomography angiography spot sign is consistent with a site of active hemorrhage in acute intracerebral hemorrhage. *Stroke* 2014; **45:** 277–80.

32 Koculym A, Huynh TJ, Jakubovic R, Zhang L, Aviv RI. CT perfusion spot sign improves sensitivity for prediction of outcome compared with CTA and postcontrast CT. *Am J Neuroradiol* 2013; **34** (suppl 1)**:** 965–70.

33 Wang B, Yan S, Xu M, et al. Timing of occurrence is the most important characteristic of spot sign. *Stroke* 2016; **47:** 1233–38.

34 Hemphill 3rd JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 2001; **32:** 891–97.

35 Heeley E, Anderson CS, Woodward M, et al. Poor utility of grading scales in acute intracerebral hemorrhage: results from the INTERACT2 trial. *Int J Stroke* 2015; **10:** 1101–7.

36 Huynh TJ, Aviv RI, Dowlatshahi D, et al. Validation of the 9-point and 24-point hematoma expansion prediction scores and derivation of the PREDICT A/B scores. *Stroke* 2015; **46:** 3105–10.

37 Du H, Li L, Bennet D, et al. Fresh fruit consumption and major cardiovascular disease in China. *N Engl J Med* 2016; **374:** 1332–43.

38 Jackson CA, Sudlow CL. Is hypertension a more frequent risk factor for deep than for lobar supratentorial intracerebral haemorrhage? *J Neurol Neurosurg Psychiatry* 2006; **77:** 1244–52.

39 Charidimou C, Boulouis G, Roongpiboonsopit D, et al. Cortical superfical siderosis multifocality in cerebral amyloid angiopathy: a prospective study. *Neurology* 2017; **89:** 2128–35.

40 Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2014; **85:** 660–67.

41 Moulin S, Labreuche J, Bombois S, et al. Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study. *Lancet Neurol* 2016; **15:** 820–29.

42 Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* 2010; **74:** 1346–50.

43 Rodrigues MA, Samarasekera N, Lerpiniere C, et al. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. *Lancet Neurol* 2018; **17:** 231–40.

44 Banerjee G, Carare R, Cordonnier C, et al. The increasing impact of cerebral amyloid angiopathy: essential new insights for clinical practice. *J Neurol Neurosurg Psychiatry* 2017; **88:** 982–94.

45 Parry-Jones AR, Paley L, Bray BD, et al. Care-limiting decisions in acute stroke and association with survival: analyses of UK national quality register data. *Int J Stroke* 2016; **11:** 321–331.

46 Zahuranec DB, Morgenstern LB, Sanchez BN, et al. Do-not-resuscitate orders and predictive models after intracerebral hemorrhage. *Neurology* 2010; **75:** 626–633.

47 Langhorne P, Fearon P, Ronning OM, et al. Stroke unit care benefits patients with intracerebral hemorrhage: systematic review and meta-analysis. *Stroke* 2013; **44:** 3044–49.

48 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.

49 Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 2016; **375:** 1033–43.

50 Tsivgoulis G, Katsanos AH, Butcher KS, et al. Intensive blood pressure reduction in acute intracerebral hemorrhage: a meta-analysis. *Neurology* 2014; **83:** 1523–29.

51 Boulouis G, Morotti A, Goldstein JN, et al. Intensive blood pressure lowering in patients with acute intracerebral haemorrhage: clinical outcomes and haemorrhage expansion. systematic review and meta-analysis of randomised trials. *J Neurol Neurosurg Psychiatry* 2017; **88:** 339–345.

52 Lattanzi S, Cagnetti C, Provinciali L, et al. How should we lower blood pressure after cerebral hemorrhage? A systematic review and meta-analysis. *Cerebrovascular Dis* 2017; **43:** 207–213.

53 Gong S, Lin C, Zhang D, et al. Effects of intensive blood pressure reduction on acute intracerebral hemorrhage: a systematic review and meta-analysis. *Sci Rep* 2017; **7:** 10694.

54 Song L, Sandset EC, Arima H, et al. Early blood pressure lowering in patients with intracerebral haemorrhage and prior use of antithrombotic agents: pooled analysis of the INTERACT studies. *J Neurol Neurosurg Psychiatry* 2016; **87:** 1330–35.

55 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.

56 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.

57 Lovelock CE, Molyneux AJ, Rothwell PM. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. *Lancet Neurol* 2007; **6:** 487–93.

58 Thompson BB, Bejot Y, Caso V, et al. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology* 2010; **75:** 1333–42.

59 Naidech AM, Jovanovic B, Liebling S, et al. Reduced platelet activity is associated with early clot growth and worse 3-month outcome after intracerebral hemorrhage. *Stroke* 2009; **40:** 2398–401.

60 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.

61 Bejot Y, Cordonnier C, Durier J, Aboa-Eboule C, Rouaud O, Giroud M. Intracerebral haemorrhage profiles are changing: results from the Dijon population-based study. *Brain* 2013; **136:** 658–64.

62 Flaherty ML, Tao H, Haverbusch M, et al. Warfarin use leads to larger intracerebral hematomas. *Neurology* 2008; **71:** 1084–89.

63 Cucchiara B, Messe S, Sansing L, Kasner S, Lyden P. Hematoma growth in oral anticoagulant related intracerebral hemorrhage. *Stroke* 2008; **39:** 2993–96.

64 Dequatre-Ponchelle N, Henon H, Pasquini M, et al. Vitamin K antagonists-associated cerebral hemorrhages: what are their characteristics? *Stroke* 2013; **44:** 350–55.

65 Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin: a meta-analysis of randomised trials. *Lancet* 2014; **383:** 955–62.

66 Inohara T, Xian Y, Liang L, et al. Association of intracerebral hemorrhage among patients taking non-vitamin K antagonist *vs* vitamin K antagonist oral anticoagulants with in-hospital mortality. *JAMA* 2018; **319:** 463–73.

67 Hemphill JC, 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015; **46:** 2032–60.

68 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.

69 Mayer S, Brun N, Broderick J, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005; **352:** 777–85.

70 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.

71 Mayer SA, Davis SM, Skolnick BE, et al. Can a subset of intracerebral hemorrhage patients benefit from hemostatic therapy with recombinant activated factor VII? *Stroke* 2009; **40:** 833–40.

72 Schreuder FH, Sato S, Klijn CJ, Anderson CS. Medical management of intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry* 2017; **88:** 76–84.

73 Carrera E, Michel P, Despland PA, et al. Continuous assessment of electrical epileptic activity in acute stroke. *Neurology* 2006; **67:** 99–104.

74 De Herdt V, Dumont F, Henon H, et al. Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome. *Neurology* 2011; **77:** 1794–800.

75 Haapaniemi E, Strbian D, Rossi C, et al. The CAVE score for predicting late seizures after intracerebral hemorrhage. *Stroke* 2014; **45:** 1971–76.

76 Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. *Lancet Neurol* 2006; **5:** 53–63.

77 Wagner, I, Hauer, EM, Staykov, D. Effects of continuous hypertonic saline infusion on perihemorrhagic edema evolution. *Stroke* 2011; **42:** 1540–45.

78 Kollmar, R, Staykov, D, Dorfler, A, Schellinger, PD, Schwab, S, Bardutzky, J. Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage. *Stroke* 2010; **41:** 1684–89.

79 Ropper AH, King RB. Intracranial pressure monitoring in comatose patients with cerebral hemorrhage. *Arch Neurol* 1984; **41:** 725–28.

80 Janny P, Papo I, Chazal J, Colnet G, Barretto LC. Intracranial hypertension and prognosis of spontaneous intracerebral hematomas; a correlative study of 60 patients. *Acta Neurochir* 1982; **61:** 181–86.

81 Fernandes HM, Siddique S, Banister K, et al. Continuous monitoring of ICP and CPP following ICH and its relationship to clinical, radiological and surgical parameters. *Acta Neurochir Suppl* 2000; **76:** 463–66.

82 Ziai WC, Melnychuk E, Thompson CB, Awad I, Lane K, Hanley DF. Occurrence and impact of intracranial pressure elevation during treatment of severe intraventricular hemorrhage. *Crit Care Med* 2012; **40:** 1601–08.

83 Sykora M, Steinmacher S, Steiner T, Poli S, Diedler J. Association of intracranial pressure with outcome in comatose patients with intracerebral hemorrhage. *J Neurol Sci* 2014; **342:** 141–45.

84 Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke* 2014; **9:** 840–55.

85 Diedler J, Santos E, Poli S, Sykora M. Optimal cerebral perfusion pressure in patients with intracerebral hemorrhage: an observational case series. *Cri Care* 2014; **18:** R51.

86 Anderson CS, Arima H, Lavados P, et al. Cluster-randomised, crossover trial of head positioning in acute stroke. *N Engl J Med* 2017; **376:** 2437–47.

87 AVERT Collaborative Group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet* 2015; **386:** 48–55.

88 Dennis M, Sandercock P, et al. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet* 2013; **382:** 516–24.

89 Dennis M, Sandercock PA, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet* 2009; **373:** 1958–65.

90 Munoz-Venturelli P, Wang X, Lavados PM, et al. Prophylactic heparin in acute intracerebral hemorrhage: a propensity score-matched analysis of the INTERACT2 study. *Int J Stroke* 2016; **11:** 549–56.

91 Kobayashi S, Sato A, Kageyama Y, Nakamura H, Watanabe Y, Yamaura A. treatment of hypertensive cerebellar hemorrhage: surgical or conservative management? *Neurosurgery* 1994; **34:** 246–50.

92 Salvati M, Cervoni L, Raco A, Delfini R. Spontaneous cerebellar hemorrhage: clinical remarks on 50 cases. *Surg Neurol* 2001; **55:** 156–61.

93 Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet* 2005; **365:** 387–97.

94 Mendelow AD, Gregson BA, Rowan EN, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet* 2013; **382:** 397–408.

95 Gregson BA, Broderick JP, Auer LM, et al. Individual patient data subgroup meta-analysis of surgery for spontaneous supratentorial intracerebral hemorrhage. *Stroke* 2012; **43:** 1496–504.

96 Phan TG, Koh M, Vierkant RA, Wijdicks EF. Hydrocephalus is a determinant of early mortality in putaminal hemorrhage. *Stroke* 2000; **31:** 2157–62.

97 Diringer MN, Edwards DF, Zazulia AR. Hydrocephalus: a previously unrecognized predictor of poor outcome from supratentorial intracerebral hemorrhage. *Stroke* 1998; **29:** 1352–57.

98 Moradiya Y, Murthy SB, Newman-Toker DE, Hanley DF, Ziai WC. Intraventricular thrombolysis in intracerebral hemorrhage requiring ventriculostomy: a decade-long real-world experience. *Stroke* 2014; **45:** 2629–35.

99 Herrick DB, Ullman N, Nekoovaght-Tak S, et al. Determinants of external ventricular drain placement and associated outcomes in patients with spontaneous intraventricular hemorrhage. *Neurocrit Care* 2014; **21:** 426–34.

100 Lovasik BP, McCracken DJ, McCracken CE, et al. The effect of external ventricular drain use in intracerebral hemorrhage. *World Neurosurg* 2016; **94** (suppl C)**:** 309–18.

101 Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treating severe stroke: results of the CLEAR III trial, a randomised, controlled trial. *Lancet* 2017; **389:** 603–61.

102 Nieuwkamp DJ, de Gans K, Rinkel GJ, Algra A. Treatment and outcome of severe intraventricular extension in patients with subarachnoid or intracerebral hemorrhage: a systematic review of the literature. *J Neurol* 2000; **247:** 117–21.

103 Baker AD, Rivera Perla KM, Yu Z, et al. Fibrinolytic for treatment of intraventricular hemorrhage: a meta-analysis and systematic review. *Int J Stroke* 2018; **13:** 11–23.

104 Chen C-C, Liu C-L, Tung Y-N, et al. Endoscopic surgery for intraventricular hemorrhage (IVH) caused by thalamic hemorrhage: comparisons of endoscopic surgery and external ventricular drainage (EVD) surgery. *World Neurosurg* 2011; **75:** 264–68.

105 Li Y, Zhang H, Wang X, et al. Neuroendoscopic surgery versus external ventricular drainage alone or with intraventricular fibrinolysis for intraventricular hemorrhage secondary to spontaneous supratentorial hemorrhage: a systematic review and meta-analysis. *PLoS One* 2013; **8:** e80599.

106 Zhou X, Chen J, Li Q, et al. Minimally invasive surgery for spontaneous supratentorial intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *Stroke* 2012; **43:** 2923–30.

107 Hanley DF, Thompson RE, Muschelli J, et al. Safety and efficacy of minimally invasive surgery plus recombinant tissue plasminogen activator in intracerebral haemorrhage evacuation (MISTIE): a randomised phase 2 trial. *Lancet Neurol* 2016; **15:** 1228–37.

108 Wang J-W, Li J-P, Song Y-L, et al. Stereotactic aspiration versus craniotomy for primary intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *PLoS One* 2014; **9:** e107614.

109 Lacey B, Lewington S, Clarke R, et al. Age-specific association between blood pressure and vascular and non-vascular chronic diseases in 0·5 million adults in China: a prospective cohort study. *Lancet Glob Health* 2018; **6:** e641–49.

110 Lau KK, Lovelock CE, Li L, et al. Antiplatelet treatment after transient ischemic attack and ischemic stroke in patients with cerebral microbleeds in 2 large cohorts and an updated systematic review. *Stroke* 2018; **49:** 1434–42.

111 Charidimou A, Imaizumi T, Moulin S, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: a meta-analysis. *Neurology* 2017; **89:** 820–29.

112 Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016; **388:** 2532–61.

113 Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63:** 2889–34.

114 Murphy SB, Gupta A, Merkler AE, et al. Restarting anticoagulant therapy after intracranial hemorrhage: a systematic review and meta-analysis. *Stroke* 2017; **48:** 1594–600.

115 Cordonnier C. Balancing risks versus benefits of anticoagulants in stroke prevention. *Lancet Neurol* 2018; **17:** 487–88.

116 Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018; **378:** 11–21.

117 Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018; **378:** 708–18.