Management of spontaneous intracerebral haemorrhages

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In this issue

Stroke at the beginning of the XXIst century
S. Timsit, France

Epidemiology of stroke in Europe and trends for the 21st Century
Y. Béjot, H. Bailly, J. Durier, M. Giroud, France

How is stroke care organised in Europe?
V. Armao, P. Nemanja, V. Caso, Italy

Up-date on specificities of stroke in women
H. Christensen, L. Bentsen, L. Christensen, Denmark

Management of spontaneous intracerebral haemorrhages
B. Casolla, R. Tortuyaux, C. Cordonnier, France

Cerebral venous thrombosis
J.M. Ferro, P. Canhao, D. Aguiar de Sousa, Portugal

Management of acute cerebral ischaemia
S. Moulin, D. Leys, France

Stroke prevention
J.L. Mas, France

Summary

Spontaneous intracerebral haemorrhage is defined as a collection of blood in the cerebral parenchyma that is not caused by trauma. It represents roughly 10–20% of all strokes. The clinical presentation is unspecific and the diagnosis requires brain imaging. ICH is a medical emergency and ICH patients have to be admitted in an acute stroke unit. The priority is to fight against ICH expansion. The first step consists in the administration of a specific antagonist of the antithrombotic treatment when available, and in the strict control of blood pressure. Clinicians should keep in mind that the concept of so-called “primary” ICH is misleading since many causes should be searched for. During follow-up, the risk of recurrence may depend on the underlying vessel disease and blood pressure should be strictly managed. ICH patients are at high risk of dementia: cognitive evaluation should regularly be performed during follow-up.

General data about ICH

Definition
Spontaneous intracerebral haemorrhage (ICH) is defined as a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma [1]. It is a heterogeneous condition resulting from several distinct underlying vasculopathies. Several interacting and overlapping risk factors may play a role in the vessel rupture.

Epidemiology
Haemorrhagic stroke accounts for 11-22% of incident strokes [2], half of all stroke deaths, and ~47 million (42%) of the disability-adjusted life years lost due to stroke [3]. ICH caused by cerebral small vessel diseases accounts for two-thirds of haemorrhagic stroke [4], amounting to > 2 million incident ICH worldwide each year. The risk of ICH increases with age, being 9.6-fold higher in people over 85 years old compared with those less than 45 years of age [5]. Despite a significant improvement in ischaemic stroke management, ICH treatment has not significantly changed. This condition remains associated...
with a high case fatality rate in the first month, ranging from 13 to 61% of patients, with a median of 40% across studies [6]. The clinical and epidemiological scenario of ICH has been changing in the last decades [7–9]. Despite an overall stable incidence of ICH, the incidence among people older than 75 years has increased and the incidence among people younger than 60 years has decreased, with a larger proportion of lobar haemorrhages, suggesting that vasculopathies more strongly associated with the elderly, particularly cerebral amyloid angiopathy (CAA), represent an increasing proportion within the aetiological distribution of ICH [9]. The poor prognosis of ICH may be partly due to our poor understanding of this heterogeneous disease. Do-not-resuscitate (DNR) orders are relatively common in patients with ICH, especially among those with expected poor prognosis. Patients with DNR orders receive less active care [10] and have a worse prognosis [11].

Mechanisms of brain injury

There are several mechanisms of brain injury in ICH, including primary direct mechanical injury to brain parenchyma by the expanding clot and cytotoxic perilesional oedema. Both clot and oedema contribute to the mass effect, determining increased intracranial pressure, which in turn can cause reduced cerebral perfusion and ischaemic injury, and in larger ICH, cerebral herniation. Secondary brain injury after the initial haemorrhage is an important contributing process; however, the exact mechanism remains uncertain. Perilesional oedema is present in at least half of ICH patients, reaching maximum volume 7 to 12 days after onset [12]. The perihematomal regions show delayed perfusion and increased diffusivity, identifying areas of both vasogenic and cytotoxic oedema [13]. Although the precise mechanism of haemorrhage enlargement is not yet defined and may be heterogeneous, blood brain barrier breakdown may be a crucial event [14]. It may contribute to inflammation by promoting leukocyte infiltration. This event may also contribute to vasogenic oedema formation. The plasma protein components of the complement system are normally excluded from the brain by the blood brain barrier, but they may enter the brain after ICH as part of the haemorrhage or following blood brain barrier breakdown [15]. There is mounting evidence that haemoglobin and iron release from the haematoma is a major contributor to ICH-induced brain injury [15].

How to diagnose an ICH?

Clinical presentation

The clinical presentation of ICH usually includes non-specific symptoms (e.g., headache and/or decreased consciousness) and focal symptoms that vary according to the anatomical distribution of the ICH. Some clinical scales, such as Guy’s Hospital Stroke Score and Siriraj Stroke Score, were proposed for the clinical differential diagnosis between ischaemic and haemorrhagic stroke [16]. Validation studies showed that none of the clinical signs at presentation is reliable for clinical diagnosis of ICH, emphasizing the need for routine neuroimaging evaluation [17].

Neuroimaging

In case of focal and acute neurological deficit, brain-imaging study should be performed as soon as possible. Brain MRI including T2*–gradient echo (or SWI) sequences allows to identify the ICH at the acute phase and can provide information on the surrounding parenchyma. When MRI is not immediately available, a CT scan should be performed. CT scan is as accurate as MRI in the acute phase. Nonetheless, sensibility decreases when CT scan is performed later than one week after ICH, especially for small ICH, because the haemorrhagic component may appear isodense [18,19].

Neuroimaging reveals ICH location: lobar ICH represents about 35% of cases; deep ICH represents about 55% of cases (specifically, caudate nucleus in 5% of patients, putamen in 20% and thalamus in 30%) and 10% in the posterior fossa (brainstem or cerebellum) [20] (figure 1).

Moreover, computed tomography angiography may help in detecting ICH underlying macrovascular cause, including arteriovenous malformation, aneurysm, dural arteriovenous fistula, cavernoma, and cerebral venous sinus thrombosis in about 1 patient out of 4 to 7 [21–23]. Detection of these macrovascular causes may have immediate therapeutic implications. Nevertheless, the best strategy for identifying a macrovascular cause in patients with non-traumatic intracerebral haemorrhage is unknown [24]. In a prospective diagnostic study that enrolled 298 adults (18–70 years), a macrovascular cause was identified in 69 patients (23%) [25]. Accuracy of CT angiography for the detection of macrovascular causes of ICH is modest with a sensitivity of 74% and a specificity of 91% and is less than previously assumed [26]. Therefore, digital subtraction angiography is necessary when the result of CT angiography is negative. In this study, the additional value of MRI/MRA after negative CT angiography consisted mainly of diagnosis of non-macrovascular causes of ICH. Other authors suggest to start with MRI to search for evidence of the underlying vessel disease such as cerebral amyloid angiopathy or deep perforating vasculopathy [27].

The Spot Sign CT angiography (CTA) has been used as a tool to predict haemorrhage enlargement by revealing a spot sign. Spot sign was first described in 1999 and is defined as a contrast extravasation within the haematoma. The supposed cause is continued bleeding from ruptured vessels, but the precise mechanism is still poorly understood [28]. One prospective study suggested that the spot sign may have value to predict ICH enlargement (positive predictive value of 73%, negative predictive value of 84%, sensitivity of 63%, and specificity of 90%). In this study, ICH patients with a spot sign had a worse prognosis than patients without a spot sign [29]. Unfortunately,
the added value of observing a spot sign in clinical routine has not been demonstrated yet.

**Biological tests**

Biological tests rarely detect the cause of ICH. They usually provide indirect information that can contribute to the diagnostic evaluation (e.g., an inflammatory condition in a patient with angiitis, coagulation tests abnormalities, liver enzyme changes in excessive alcohol consumption) or that can drive to a specific therapeutic intervention (e.g., INR > 1.4).

Biological evaluation should include the following tests:

- blood cell counts;
- prothrombin time, international normalized ratio, partial thromboplastin time;
- C-reactive protein, fibrinogen levels, blood cultures (in cases of suspected infection);
- liver enzymes;
- creatinine and blood urea nitrogen levels;
- screening for prothrombotic conditions in cases of cerebral venous thrombosis when indicated. The most common thrombophilic disorders are factor V Leyden mutation, prothrombin G20210A mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency, elevated factor VIII, antiphospholipid antibody syndrome, hyperhomocysteinemia, and activated protein C resistance. An hypercoagulable state should be investigated in patients with unexplained cerebral venous thrombosis [30];
- screening for illicit drugs: cocaine metabolites can be screened in urine within 48 hours of admission [31,32]. Recently, other fluids, such as oral fluid, hair, and sweat, have been used to detect cocaine and its metabolites [33]. The association between ICH and the use of amphetamines, cocaine (and its freebase form crack-cocaine), and ecstasy has been reported with increasing frequency [33,34]. Cocaine-associated ICH is more frequent in males with a high proportion of subcortical ICH [32].

**How to fight against ICH expansion?**

**Acute stroke unit care**

Acute stroke unit care reduces both the risk of death and dependency in patients with ICH when compared with general ward care [35]. Indeed, a meta-analysis of 13 randomised
controlled trials (RCT) (3570 patients) showed that stroke unit care reduces the overall risk of death or dependency (risk ratio [RR]: 0.81; 95% confidence interval [CI]: 0.47–0.92). The result was comparable in both subgroup of patients with ischaemic stroke and ICH (RR: 0.79; 95% CI: 0.61–1.00) [36].

Patients admitted in the stroke unit may take advantage of the intensive monitoring, care and prevention of complications. Early haemorrhage growth is the most common identifiable factor associated with clinical deterioration [37] and it is frequent: 38% of patients with ICH suffer from more than a 33% growth in the volume of parenchymal haemorrhage during the first 20 hours after the baseline computed tomography (CT) following admission. Haematoma growth mainly occurs within the first 3 to 4 hours after haemorrhage onset [38] (figure 2).

**Blood pressure management**

The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial-2 (INTERACT-2) investigated the effect on functional outcome at three months of intensive blood pressure reduction, compared to guideline-based target (systolic < 180 mmHg) in 2794 patients [39]. Intensive blood pressure reduction was defined as a targeting a systolic blood pressure < 140 mmHg in less than one-hour, within 6 hours of symptom onset [39]. Antihypertensive drugs were used according to local preference. On the primary outcome (modified Rankin Scale score 3–6) intensive blood pressure reduction might be superior (OR: 0.87; 95% CI: 0.75–1.01), but on a prespecified secondary outcome using ordinal analysis of the entire modified Rankin Scale, intensive blood pressure reduction seemed superior (OR: 0.87; 95% CI: 0.77–1.00). Intensive treatment with antihypertensive drugs was safe, a finding that was also supported by two previous RCTs [40,41].

Following the INTERACT-2 publication, European and American guidelines suggested that in acute ICH, within 6 hours of symptom onset, intensive blood pressure reduction (systolic target < 140 mmHg in < 1 h) is safe and may be superior to a systolic target < 180 mmHg. No specific agent can be recommended [35,42]. The recent publication of the ATACH-2 trial [43] may challenge these guidelines. In a prospective randomised trial on 1000 ICH participants (mean age 61.9 years, 56% were Asian) with a mean (± SD) systolic blood pressure of 200.6 ± 27.0 mmHg at baseline, 500 were assigned to intensive treatment (systolic blood pressure target of 110–139 mmHg) and 500 to standard treatment (systolic blood pressure target of 140–179 mmHg). Enrolment was stopped because of futility after a prespecified interim analysis. The primary outcome of death or disability was observed in 38.7% of the participants (186 of 481) in the intensive treatment group and in 37.7% (181 of 480) in the standard-treatment group (RR: 1.04; 95% CI: 0.85–1.27; analysis was adjusted for age, initial GCS score, and presence or absence of intraventricular haemorrhage). Therefore, the authors found that achieving a target systolic blood pressure of 110 to 139 mmHg did not result in a lower rate of death or disability compared with a standard reduction to a target of 140 to 179 mmHg.

**Management of antithrombotic treatment**

ICH in patients under antithrombotic treatment is a frequent clinical condition: in Europe, 44% of patients with ICH took have antithrombotic drugs at hospital admission [44].

**ICH associated with vitamin K antagonist (VKA)**

Warfarin-associated intracerebral haemorrhage represents 15% of ICH [45]. Reversal of anticoagulation in patients with...
Management of spontaneous intracerebral haemorrhages

warfarin-associated ICH is a medical emergency, as anticoagulation is associated with haematoma growth, neurological deterioration, and increased risk of death and major disability [46,47]. In all patients with warfarin-associated ICH confirmed by imaging who have an international standardized ratio (INR) higher than 1.5, administration of intravenous vitamin K is recommended (10 mg is given by slow intravenous infusion, no faster than 1 mg/min, to minimize anaphylactic risk). In addition to vitamin K, prothrombin-complex concentrates (PCC, also called factor IX complex) are administered.

PCC contains the vitamin K-dependent coagulation factors (factors II and VII in variable amounts, IX, and X). Those that contain relatively little factor VII are called three-factor PCC, while those that contain factor VII are called four-factor PCC. PCCs normalize the INR more rapidly than infusion of FFP or vitamin K alone, often within 10 minutes of administration [48]. However, vitamin K should be administered to all patients with warfarin-associated ICH, because the effect of PCCs is transient (hours) [48]. In terms of correcting the INR, fixed dose PCC regimens appear to be non-inferior to variable dose regimens based on bodyweight and INR. In France, guidelines suggest to use a 25 UI factor IX/kg when the INR is not known at admission, or to adapt the dosage according to the INR (table I) [49].

In some countries, fresh frozen plasma (FFP) may be an alternative. The infusion rate for FFP depends on the patient’s ability to tolerate the volume load of the plasma. Observational non-randomized data suggest that the combination of FFP and PCC could be interesting [50]. However to date, it cannot be recommended. While normalization of the INR is recommended, optimal haemostatic management remains controversial. A recent study assessed the safety and efficacy of FFP versus PCC in patients with VKA-ICH [51]. Fifty-four patients were randomly assigned (26 to FFP and 28 to PCC) and 50 received study drug (23 FFP and 27 PCC). In this multicentre, prospective, randomised, open-label, blinded-endpoint trial, the primary endpoint was the proportion of patients with INR 1.2 or lower within 3 h of treatment initiation. The trial was terminated, after inclusion of 50 patients after a safety analysis because of safety concerns: six serious adverse events were judged to be FFP related (four cases of haematoma expansion, one anaphylactic reaction, and one ischaemic stroke) and two PCC related (ischaemic stroke and pulmonary embolism). Two (9%) of 23 patients in the FFP group versus 18 (67%) of 27 in the PCC group reached the primary endpoint (adjusted OR: 30.6; 95% CI: 4.7–197.9).

Although an effect of PCC on clinical outcomes remains to be shown, these data favour the use of PCC over FFP in terms of reversal effect on INR values.

The use of recombinant factor VIIa (rFVIIa) is not recommended for treatment of warfarin-associated ICH [42].

ICH associated with direct oral anticoagulant (DOAC)

DOAC are an interesting alternative to improve the net clinical benefit of oral anticoagulants. In a meta-analysis of phase III RCT (RE-LY, ROCKET-AF, ARISTOTLE, AVEROES and ENGAGE), intracranial haemorrhages were less frequent in patients treated with DOAC than in patients treated with VKA (RR: 0.46; 95% CI: 0.36–0.57) [52]. In an observational German multicentre study of 61 patients with NOAC associated ICH, the authors reported an overall mortality of 28% at 3 months, and 65% of survivors had an unfavourable outcome (modified Rankin Scale score, 3–6) [53]. These data highlight the fact that even if less frequent, NOAC-ICH remains as severe as VKA-ICH. Strategies of reversal of NOAC are still not evidence-based. However, the development of specific antidote is promising.

Idarucizumab, the first novel antidote against direct thrombin inhibitor dabigatran was approved by US FDA in October 2015 and is now available in France. A phase III trial on Idarucizumab also confirms the reversal effect on dabigatran anticoagulant effect [54]. Andexanet alfa (PRT064445), a specific reversal agent against factor Xa inhibitors, showed a complete reversal of anticoagulant activity of apixaban and rivaroxaban, within minutes after administration and without adverse effects, in two recently completed parallel phase III trials (ANNEXA-A and ANNEXA-R respectively) [55]. Andexanet alfa is currently studied in the phase IV trial (ANNEXA-4). Ariapinze (PER-977), the third reversal agent, has shown promising activity against edoxaban, dabigatran, apixaban, rivaroxaban, as well as subcutaneous fondaparinux and low molecular weight heparin [56,57].

In the clinical setting of a NOAC-ICH, data on the timing of last administration and renal function are very important to obtain. If the drug was administered within the last 48 hours (when renal function is normal), then the drug has to be considered as active without waiting for specific dosages. Clinicians should not refer to usual coagulation tests that are altered. Few data are currently available on the benefit-risk balance of reversal agents.

However, in the setting of life-threatening haemorrhages, including ICH:

- for patients treated with dabigatran, idarucizumab should be administered (double bolus intravenously: 2.5 g with a 15 minutes interval);

### Table 1

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<tr>
<th>INR</th>
<th>Dose of PCC</th>
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<tr>
<td>Unknown</td>
<td>25 UI factor IX/kg</td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>32 UI factor IX/kg</td>
</tr>
<tr>
<td>2.5 ≤ INR ≤ 3.5</td>
<td>25 UI factor IX/kg</td>
</tr>
<tr>
<td>1.5 ≤ INR ≤ 2.5</td>
<td>18 UI factor IX/kg</td>
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Target: INR < 1.5 using 10 mg vitamin K and PCC; INR control at 30 minutes and 6 hours.
ICH associated with Heparin
Protamine sulfate is recommended for urgent treatment of patients with heparin-associated ICH [42]. Protamine sulfate can be administered by slow intravenous infusion (1 mg per 100 UI heparin, maximum dose 50 mg).

ICH associated with antiplatelet agents
Antiplatelet therapy may slightly increase the incidence of ICH [8]. In high-income countries, more than one quarter of patients with incident ICH takes antiplatelet therapy before ICH [44]. People taking antiplatelet therapy before ICH have a 27% (95% CI: 10-47) increase in the odds of death in comparison to people with ICH who had not taken anti-thrombotic drugs [58]. Observational analyses suggest that pre-ICH antiplatelet therapy use and reduced platelet activity may worsen outcome by increasing the risk of early ICH volume growth [59], which is an important determinant of outcome [37]. Therefore, platelet transfusion was an interesting strategy in theory. Unfortunately, in a recent randomised trial gathering 190 patients with ICH associated with antiplatelet agents, the odds of death or dependence at three months were higher after platelet transfusion compared to standard care (adjusted common OR 2.05; 95% CI: 1.18 to 3.56) [60]. These important results suggest that platelet transfusion should not be performed in this setting.

Surgical indications
According to the European guidelines, evacuation of supratentorial ICH in the first 96 hours is not recommended. In the STICH study, the 503 patients assigned to early (median time to surgery was 30 hours after haemorrhage onset) surgical haematoma evacuation were slightly more likely to have a favourable outcome at six months compared to those managed with initial conservative treatment, but the trend did not reach statistical significance [61]. STICH II trial found that rates of unfavourable outcomes at six months were similar in the 307 conscious patients treated with early (within 48 hours of onset) surgical haematoma evacuation versus the 294 patients treated conservatively (59 versus 62%) [62]. Surgical indications are reserved to patients with life-threatening mass effect, a Glasgow Coma Scale score 9–12 [42]. Because of the questionable efficacy of surgery, it should only be considered as a life saving procedure. Ongoing studies are focusing on the development of new mini-invasive surgical techniques.

In patients with cerebellar haemorrhage, surgical decompression is indicated for patients with a clinical deterioration, signs of brainstem compression and/or hydrocephalus [35,42]. Patients with intraventricular extension of the ICH should be closely monitored because of the high risk for hydrocephalus, especially if the third and fourth ventricles are involved.

Neurologic deterioration may occur abruptly. External ventricular drainage should be performed in patients with neurologic deterioration and hydrocephalus.

How to prevent complications?
Deep venous thrombosis and thromboembolism
Patients hospitalised for an ICH are at high risk of deep venous thrombosis and thromboembolic complications [63]. Patients with ICH should receive intermittent pneumatic compression for prevention of venous thromboembolism since the first day of hospitalisation [35,64]. Low molecular weight subcutaneous heparin can be administered starting from the 1st-6th day of ICH, after check of the stability of the ICH [65].

In case of pulmonary embolism or deep venous thrombosis, an inferior vena cava filter can be an alternative to anticoagulants to prevent new pulmonary embolism. However, there is no RCT to clarify the management of a deep vein thrombosis in the acute phase of ICH. Therapeutic decision will be based on individual benefit-risk ratio assessment [66].

Early epileptic seizures
The EGASIS RCT showed an augmentation of pneumonia and death with the use of dexamet. In another RCT, 36 patients were treated with valproic acid for one month, with a clinical benefit on early epileptic seizures without consequence on late epileptic seizures [67].

According to the European recommendation, there is no evidence to recommend a preventive treatment [35].

Late epileptic seizures
Data on late epileptic seizures are sparse. Late epileptic seizures are defined as occurring later than 7 days after the acute event. In an ICH cohort of 325 patients, incidence of late epileptic seizures was 4 for 100 patients-year (95% CI: 3–6) with a median time of onset of 9 months (IQR 3–23) [68]. Predicting factors of late epileptic seizures were the cortical involvement of the ICH, the presence and the number of lobar brain micro-bleeds. Patients with a first late seizure are at high risk of developing epilepsy. Therefore, anti-epileptic treatment can be introduced. Levels of recommendation are weak since no RCT have been performed.

And then?
Risk of recurrent ICH
ICH survivors have a risk of ICH recurrence. A recent meta-analysis showed that the annual rate of ICH recurrence was 2.0–2.4% in five studies and that the long-term rate of recurrence for early survivors, in mostly hospital-based studies, varied from 1.3 to 7.4% per year (with durations ranging from 1 to 7 years) [69]. Focusing on ICH location, lobar ICH carries a higher risk of recurrent haemorrhage compared with non-lobar ICH, which is more likely to be recurrent lobar ICH [70]. The higher rate
Management of spontaneous intracerebral haemorrhages

of ICH recurrence after lobar ICH than after non-lobar ICH is possibly due to the nature of the underlying vessel disease. Indeed, a high proportion of patients with lobar ICH suffer from cerebral amyloid angiopathy [71,72]. Another recent meta-analysis [69] has demonstrated that the risk of an ischaemic event after ICH is at least as frequent as the recurrence of ICH. Indeed, ICH survivors have frequently the same risk factors as for ischaemic events like arterial hypertension (60%), diabetes mellitus (15%) and are smokers (16%) [8,9].

Find the cause

Despite an apparent stability of incidence over the past decades, the profile of ICH has changed: there are fewer deep ICH associated with pre-stroke hypertension, whereas the increasing age of the population associated with a more extensive use of antithrombotic drugs leads to an increase of lobar ICH. Deep perforating vasculopathy remains the most important cause of ICH, followed by cerebral amyloid angiopathy, these two aetiologies accounting for nearly 70% of all ICH cases (table II). Recent scientific evidence has highlighted new aspects of the pathophysiology of such disorders; nevertheless, the morbidity and mortality of ICH remain extremely high. Clinicians should keep in mind that the concept of primary ICH is misleading since many causes should be searched for (figure 2) [4].

Control blood pressure

Efforts to control blood pressure over the long-term are likely to significantly reduce the risk of recurrent ICH. American guidelines published in 2015 suggest a goal blood pressure of < 130/80 mmHg in all patients [42]. In the PROGRESS study, a modest reduction in blood pressure of 9/4 mmHg decreased the rate of ICH by 50 percent (95% CI: 26%–67%) in patients with prior stroke treated with perindopril alone or in association with indapamide (Hazard ratio [HR] adjusted: 0.44; 95% CI: 0.28–0.69). In the subgroup of 611 patients with prior ICH, data did not reach statistical significance for ICH recurrence but there was a similar 49% risk

<table>
<thead>
<tr>
<th>Table II Causes of ICH</th>
<th>Key signs</th>
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<tr>
<td>Aetiology</td>
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<tr>
<td>Deep perforating vasculopathy</td>
<td>Chronic hypertension; Deep ICH associated with deep microbleeds and white matter lesions</td>
</tr>
<tr>
<td>CAA</td>
<td>Age ≥ 55 years, Boston criteria; Lobar ICH with cortical micro-emboli, lobar microbleeds and/or cortical superficial siderosis</td>
</tr>
<tr>
<td>Brain arteriovenous malformation</td>
<td>Seizures and focal neurological deficits; Diagnosis is made by CTA/MRI and confirmed by conventional DSA</td>
</tr>
<tr>
<td>Cerebral cavernoma</td>
<td>Seizures and focal neurological deficits; Diagnosis is made by MRI</td>
</tr>
<tr>
<td>Dural arteriovenous fistula</td>
<td>Pulsatile tinnitus; Secondary lesion (post-thrombotic, traumatic or neoplastic occlusion of a major sinus)</td>
</tr>
<tr>
<td>Haemorrhagic transformation</td>
<td>15% of patients with cerebral infarction; Vascular risk factors; Heterogeneous haemorrhagic lesion confined to a single arterial territory</td>
</tr>
<tr>
<td>Cerebral venous thrombosis</td>
<td>Prothrombotic conditions; Multiple focal haemorrhages close to venous sinuses</td>
</tr>
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<td>Reversible cerebral vasoconstriction syndrome</td>
<td>Women; Thunderclap headache; Arterial constriction and dilatation spontaneously reversible</td>
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<tr>
<td>Primary or systemic vasculitis</td>
<td>Signs of vasculitis; Multifocal white matter lesions, segmental occlusion, collateral vessel formation, and prolonged circulation</td>
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<tr>
<td>Infective endocarditis</td>
<td>Signs of sepsis; Systemic embolism</td>
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<tr>
<td>Brain tumours and brain metastases</td>
<td>Previous history of tumour and histological confirmation</td>
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reduction of recurrence (95% CI 18%–68%) in the treated group, showing a positive trend for deep and lobar ICH (HR adjusted: 0.37; 95% CI: 0.10–1.38) [73]. A subsidiary analysis of the PROGRESS trial showed a benefit for all types of ICH [74].

What about statin?
There are insufficient data to recommend general restrictions on the use of statin agents. Two meta-analyses did not find any evidence that statins were associated with an increased risk of ICH [75,76]. A recent meta-analysis suggests a potential benefit of statin use on ICH outcome, through a GTPase regulation mechanism [77]. Nevertheless, a number of studies have found an inverse relationship between total and LDL-cholesterol and the risk of ICH. Given the conflicting data, it seems reasonable to weigh the benefits and possible risks of statin therapy in individual patients who are otherwise at risk for ICH recurrence.

When and in whom should we restart antithrombotic drugs?
The question of when to restart anticoagulation in patients at high risk for embolic events who have suffered from an ICH has not been definitively answered and the indication must be evaluated on an individual basis. It is reasonable to consider risk factors for recurrent ICH when evaluating the risk/benefit ratio regarding resumption of oral anticoagulation. In patients with atrial fibrillation with an ICH related to CAA, oral anticoagulation should not be (re)introduced (the risk of cerebral bleeding overtakes the risk of embolic events). Despite the lack of randomised data for patients who require anticoagulation soon after an ICH, the AHA/ASA guidelines suggest that oral anticoagulants may be resumed three to four weeks after ICH onset with rigorous monitoring and maintenance of INRs in the lower limit of the therapeutic range [42]. No data are available regarding the use of direct oral anticoagulants or of left atrial appendage occlusion [78,79]. Indeed, patients with a previous history of ICH were excluded from all pivotal randomised clinical trials on these alternative strategies.

Data on resumption of antiplatelet drugs after ICH are limited. In the setting of primary prevention of cardiovascular diseases, antiplatelet agents should not be (re)started. The use of aspirin in case of robust and validated indications (such as myocardial infarction) is probably safe after an ICH. The timing of antiplatelet resumption is however largely empiric. The AHA/ASA guidelines state that antiplatelets should be discontinued for at least one or two weeks [42]. The trial RESTART (REstart or STop Antithrombotics Randomised Trial) is an ongoing randomised clinical trial that will evaluate the net clinical benefit of restarting or not antiplatelet drugs after ICH.

Cognitive evaluation
Stroke and dementia are tightly related. About 1 in 10 stroke patients already have dementia when the stroke occurs, 1 in 10 patients will develop dementia after their first ever stroke and this percentage increases dramatically in patients with recurrent strokes [80]. Data from ICH cohort are scarce but suggest that pre-existing dementia can be found in 16% [81]. In patients that are not demented at admission, the risk of developing post-ICH dementia is high. Indeed, incidence of post-ICH dementia is around 28,3% 4 years after the ICH [82]. Therefore, screening of pre-existing dementia at admission may be of interest with tools such as the IQCODE. During follow-up, cognition should be regularly screened.

Conclusion
In conclusion, ICH remains the most devastating type of stroke. Like in patients with ischaemic strokes: time is brain. ICH patients should be considered as a medical emergency and admitted to acute stroke units. Researchers should test new strategies that not only try to fight against haematoma expansion but that also target brain oedema. During follow-up prevention of ICH recurrence and of cognitive decline should be the goal of future research.

Disclosure of interest: the authors declare that they have no competing interest.

References
Management of spontaneous intracerebral haemorrhages


