Recommendations for the Management of Intracranial Haemorrhage – Part I: Spontaneous Intracerebral Haemorrhage

The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee

Key Words
Haemorrhage, intracerebral · European Stroke Initiative, recommendation

Abstract
This article represents the recommendations for the management of spontaneous intracerebral haemorrhage of the European Stroke Initiative (EUSI). These recommendations are endorsed by the 3 European societies which are represented in the EUSI: the European Stroke Council, the European Neurological Society and the European Federation of Neurological Societies.

Introduction

Intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH) are responsible for about 20% of all strokes [1–6]. Within the last 10 years, knowledge in this field has accumulated, based on prospective and randomized controlled trials (RCTs). The concept of rebleeding or growth of haematoma in spontaneous ICH has been prospectively described [7–9], coiling has been shown to be an important therapeutic option in SAH [10], and the molecular mechanisms of consecutive damage after haemorrhage have been further identified. Several RCTs on the treatment of ICH or SAH are available [11–13].

After the publication of the second edition of the European Stroke Initiative (EUSI) Recommendations for acute ischaemic stroke in 2003 [14], the executive committee of the EUSI felt that there were enough data to address recommendations for the treatment of spontaneous ICH, including spontaneous haemorrhage and SAH. In December 2004, members of the executive committee and writing committee met in Heidelberg, Germany, for 2 days and prepared 2 recommendations: part I on ICH and part II on SAH. This article deals with part I: recommendations on the treatment of ICH.

For reasons of practicability and clarity, we decided to publish 2 versions of these recommendations. The short version, which is published here, includes recommendations that refer specifically to ICH (imaging, surgery, spe-
specific aspects of conservative treatments and concomitant treatment of acute complications). The longer version, which will be available on the EUSI homepage (http://www.eusi-stroke.org), will also include recommendations on general treatments and monitoring, as they were published for ischaemic stroke. The recommendations for SAH will be published shortly.

The levels of evidence in this article correspond to those published by the European Federation of Neurological Societies and are listed in Table 1 [15]. In the recommendations we give levels A–C, and, if the data represents good clinical practice or is unknown, we refer to class IV.

**Incidence, Mortality and Prognosis**

ICH accounts for 10–17% of all strokes [6, 16–18]. The incidence of ICH is influenced by racial factors and was found to be higher in Blacks, Hispanics and Asians compared with the white population [16, 19, 20].

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**Table 1. Evidence classification scheme (according to [15])**

<table>
<thead>
<tr>
<th>For therapeutic intervention</th>
<th>For diagnostic procedures</th>
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| **Class I** An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective, randomized, controlled clinical trials with masked outcome assessment in representative populations. The following are required:  
  a. Randomization concealment  
  b. Primary outcome(s) is/are clearly defined  
  c. Exclusion/inclusion criteria are clearly defined  
  d. Adequate accounting for dropouts and crossovers, with numbers sufficiently low to have minimal potential for bias  
  e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences | A prospective study in a broad spectrum of persons with the suspected condition, using a ‘gold standard’ for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy |
| **Class II** Prospective, matched group, cohort study in a representative population with masked outcome assessment that meets criteria a–e above or a randomized controlled trial in a representative population that lacks 1 of the criteria a–e | A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by ‘gold standard’) compared with a broad spectrum of controls, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy |
| **Class III** All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome assessment is independent of patient treatment | Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where the test is applied in a blinded evaluation |
| **Class IV** Evidence from uncontrolled studies, case series, case reports or expert opinion | Any design where the test is not applied in a blinded evaluation or evidence provided by expert opinion alone or in descriptive case series (without controls) |

**Rating of recommendation**

| Level A | Effective, ineffective or harmful – requires at least 1 convincing class I study or at least 2 consistent, convincing class II studies | Established as useful/predictive or not useful/predictive – requires at least 1 convincing class I study or at least 2 consistent, convincing class II studies |
| Level B | Probably effective, ineffective or harmful – requires at least 1 convincing class II study or overwhelming class III evidence | Probably useful/predictive or not useful/predictive – requires at least 1 convincing class II study or overwhelming class III evidence |
| Level C | Possibly effective, ineffective or harmful – rating requires at least 2 convincing class III studies | Possibly useful/predictive or not useful/predictive – requires at least 2 convincing class III studies |
The 30-day mortality is correlated with the size and location of the initial bleeding [7, 21]. Deep haemorrhages are associated with high mortality rates. Equally sized lobar haemorrhages are survived more frequently. In patients with an initial volume of >60 cm³, the mortality rate was 93% for deep haemorrhage and 71% for lobar bleeding. In patients with a volume between 30 and 60 cm³, the mortality rate was 64% for deep haemorrhage, 60% for lobar bleeding and 75% for cerebellar haemorrhages. If the initial volumes were <30 cm³, the mortality rate decreased to 23% for deep haemorrhage, 7% for lobar location and 57% for cerebellar haemorrhages [22].

In retrospective studies, between 35 and 52% of patients were found to have died within 1 month of ICH onset, and only 20% regained functional independence by 6 months [22–24]. Treatment within specialized neurologic/neurosurgical intensive care units can decrease the mortality rate to 28–38% compared with the mortality rates associated with treatment in general intensive care units (ICUs) of 25–83% [25]. Besides volume of ICH and Glasgow Coma Score (GCS) on admission, age >80 years, infratentorial origin of ICH and presence of intraventricular blood were found to be independent predictors of 30-day mortality [26]. However, this finding should be applied with caution, since the single most important factor predicting survival after ICH was the implementation of do-not-resuscitate orders [27]. This may be responsible for a pessimistic overestimation of prognosis in ICH.

**Complications of ICH**

Subsequent increase in bleeding is an early complication after ICH. The frequency of increased bleeding is high, although it is not clear whether the growth of volume is due to rebleeding or continuous bleeding. Brott et al. [7] showed that ‘growth’, defined as a 33% increase in haematoma volume on cerebral computed tomography (CT), occurred in 26% of 103 patients within 4 h after the first symptoms. Another 12% had growth within the following 20 h. Haemorrhage growth was significantly associated with clinical deterioration. These findings are supported by 3 retrospective studies [8, 9, 28]. Enlargements of ICH are also seen when the observation periods are extended up to 48 h, although the frequency diminishes with time from the onset of symptoms [9].

The most important predictor of haematoma enlargement is the time between onset of symptoms and baseline cerebral CT [29]. Other predictors of haemorrhage expansion include initial haematoma volume, irregular shape, liver disease, arterial hypertension, hyperglycaemia, alcohol use and hypofibrinogenaemia, but these have not been confirmed in prospective trials [8, 21].

A total of 36–50% of patients with spontaneous ICH suffer additional intraventricular haemorrhage (IVH) [30, 89, 173]. Tuhrim et al. [30] reported that the 30-day mortality rate was 43% for patients with IVH compared with 9% in patients with only intraparenchymal blood. The intraventricular blood volume was significantly associated with the probability of mortality at day 30. Location of parenchymal origin of ICH, distribution of ventricular blood and total volumes have been reported to be predictors of outcome in patients with spontaneous ICH and intraventricular extension [31, 32]. Furthermore, hydrocephalus was found to be an independent predictor of early mortality [33].

Brain oedema after ICH is observed in the acute and subacute phase and may increase up to 14 days [34, 35]. Shrinking of the haematoma due to clot retraction leads to an accumulation of serum in the early phase [36]. Thrombin and several serum proteins were found to be involved in the inflammatory reaction of the perihematomal zone [37–40]. Factors released from activated platelets at the site of bleeding, such as vascular endothelial growth factor, may interact with thrombin to increase vascular permeability and contribute to the development of oedema [41]. Several studies in spontaneous ICH suggest that the role of perihematomal ischaemia is small at most. Magnetic resonance imaging (MRI) studies found decreased perfusion but no ischaemia in the perilesional zone [42, 43], while positron emission tomography studies found intact autoregulation in the perihematomal area [44] and only a reactive reduction of cerebral blood flow (CBF) consistent with oligaemia and diastasis [44, 45].

**Causes**

ICH may be classified into primary (80–85%) and secondary (15–20%) causes. More than 50% of cases of primary ICH are associated with hypertension, and 30% are found in association with cerebral amyloid angiopathy [46]. Secondary ICH may be caused by aneurysms, arteriovenous malformation (AVM), oral anticoagulant treatment (OAT), antiplatelets, coagulopathies, liver cirrhosis, neoplasms, trauma, vasculitis, Moya-moya disease, sinus venous thrombosis, eclampsia or cerebral endometriosis.

ICHs preferentially occur at certain locations which are associated with specific underlying diseases. Thus, deep basal ganglia bleeding is often found in patients...
with hypertensive disease, whereas lobar bleeding is often seen in elderly patients with cerebral amyloid angiopathy [47, 48].

Risk Factors

Arterial hypertension is the most common risk factor for spontaneous ICH, and its frequency has been estimated to be between 70 and 80% [5]. The causative role of hypertension is supported by the high frequency of left ventricular hypertrophy in the autopsies of patients with ICH, although there are clinical series where the history of hypertension, ECG, and chest X-ray evidence have suggested hypertension in only 56% of patients with ICH [49]. The role of hypertension and the beneficial effect of antihypertensive treatment with regard to risk of ICH were verified in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [50]. The relative risk of ICH was reduced by 50% in comparison with the placebo-treated group after 4 years of follow-up [50].

Other risk factors for ICH, in addition to age, hypertension and ethnicity, include cigarette smoking, alcohol consumption and low serum cholesterol levels [51].

In a population-based case-control study, hypercholesterolemia was associated with a lower risk of ICH. However, treatment with statins did not increase the risk of ICH [52]. This may be in contrast to the findings from a recently presented study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels – SPARCL) [212]. The risk of haemorrhagic stroke, including ICH, was 2.5 times higher in smokers [53]. Both the Physicians’ Health Study [54] and the Women’s Health Study [55] confirmed the role of smoking as a risk factor for ICH. For men smoking ≥ 20 cigarettes, the relative risk of ICH was 2.06 [95% confidence interval (CI) 1.08–3.96], and for women smoking ≥ 15 cigarettes it was 2.67 (95% CI 1.04–6.90) [54, 55].

An increasing body mass index was found to be correlated with an increasing IVH volume [56]. Several studies document an increased risk of ICH in relation to alcohol consumption [57, 58]. Spontaneous ICH can probably also be triggered by binge drinking [58].

A variety of coagulopathies can lead to cerebral haemorrhage, and anticoagulation accounts for 4–20% of ICH in different series. Oral anticoagulation increases the risk of ICH by 8- to 11-fold compared with that in patients of similar age who are not on anticoagulation [59–61]. In a meta-analysis of 16 RCTs (n = 55,462), aspirin therapy was shown to increase the risk of ICH (12 events per 10,000) [62]. However, this effect did not outweigh the net benefit of reducing the risk of myocardial infarction (reduction of 137 per 10,000) or of ischaemic stroke (reduction of 39 per 10,000) [62]. The risk of ICH was significantly increased by the combination of aspirin and clopidogrel compared with aspirin alone when given for secondary prevention in high-risk patients with recent ischaemic stroke or transient ischaemic attack [63]. Moreover, Toyoda et al. [64] published a retrospective study in which they found prior antiplatelet use to be an independent predictor of haematoma enlargement measured on the second day of hospitalization.

Cerebral amyloid angiopathy (CAA) is a common cause of ICH in occipital and parietal regions, particularly in elderly persons (>70 years) [59, 65]. In a recent study of genotype and haplotype association, apolipoprotein E4 was found to be independently associated with lobar but not with non-lobar ICH [66]. A variety of illicit drugs are known to cause ICH. Best known of these are amphetamines, cocaine, and phenylpropanolamine, and this possibility should be kept in mind in young patients in whom other causes such as AVM or trauma have been excluded [60, 65]. Also, thrombolysis of cerebral ischaemic infarction may increase the risk of ICH [67]. Brain tumours, vasculitis and various vasculopathies, including sinus thrombosis, are also important causes of ICH [60, 65].

Location and Clinical Symptoms

The clinical presentation of ICH depends on its site, size and speed of development. About 40% of primary ICHs occur in the basal ganglia, 30% in the thalamus, 20% lobar, and about 10% occurring in the cerebellum and pons [7, 11, 13, 68].

The striatum (caudate nucleus and putamen) is the most common site of spontaneous ICH. The most common type of onset is a gradual, smooth progression of symptoms over the course of minutes, and sometimes hours, usually beginning with hemiparesis [65]. The gradual development is due to bleeding from small penetrating vessels under arteriolar or capillary pressure. Another type of onset is an abrupt development of symptoms with a reduced level of consciousness over a few moments.

Bleeding directly in the brain parenchyma rather than the cerebrospinal fluid (CSP) space is painless, owing to the fact that the brain is devoid of pain fibres so that, rather than a headache, the initial bleed causes neurological symptoms based on the region of the bleed. If the haematoma starts in the putamen, it causes contralateral limb weakness and hemisensory symptoms, while bleeding in the thalamus causes greater hemisensory loss and...
hemiparesis. As the bleeding grows, the weakness becomes severer, and sensory symptoms, loss of speech (depending on the site of the bleed) and conjugate eye deviation to the side of the ICH might ensue, together with a reduced level of consciousness. If the haematoma continues to grow, it may lead to coma and death due to increased intracranial pressure (ICP) and compression of brain stem centres. Oculomotor signs such as forced downward gaze, convergence paralysis and unreactive miotic pupils suggest thalamic haemorrhage. The clinical presentation also involves slight contralateral motor hemiparesis and greater hemisensory loss.

Vomiting is a typical sign of ICH, caused by increased intracranial pressure and distortion of brain structures. Nearly half of the patients with hemispheric ICH and more than half of those with intratentorial haemorrhage vomit, while patients with cerebellar haemorrhages almost always vomit early in the clinical course.

Headache is not an invariable symptom of ICH. Patients with small, deep haematomas often have no headache at any time during their illness, while headache is much more common with large haematomas and in those rupturing in the CSF with meningeal irritation. Headache is often accompanied by vomiting and a decreased level of consciousness when the haematoma enlarges, but it may be the sole manifestation of caudate haemorrhage, which is usually accompanied by ventricular extension of haemorrhage.

Several attempts have been made to clinically differentiate supratentorial haemorrhagic from ischaemic stroke [69, 70]. Weir et al. [71] showed that the sensitivity and specificity of scoring systems is not reliable for predicting haemorrhagic stroke. In conclusion the symptoms of haemorrhagic stroke cannot be differentiated from those caused by ischaemic stroke. Imaging is always needed to confirm the diagnosis of ICH.

**Imaging ICH**

The sensitivity of CT in ICH has been proven in several studies [72–74]. Acute haemorrhage is hyperdense, with Hounsfield units (HU) between 40 and 60; the only clinical exceptions are patients with a low haematocrit, due to the low haemoglobin concentration, when even the acute haematoma can be isodense [75]. Over time – with a decrease in HU of 2 HU per day – the haematoma becomes isodense and then hypodense.

The appearance of ICH on MR depends on a variety of technical and biological variables, such as field strength, sequences and age of the haematoma [76]. As a rule of thumb, for a 1.5 Tesla: hyperacute haematoma is isodense on T₁ and hyperintense on T₂-weighted images. During the hyperacute stage, the MR protocol should always include T₂*- and/or proton-density-weighted images. Later (beyond 7 days) the methaemoglobin appears bright on T₁ and T₂-weighted images. In the chronic stage a dark rim of haemosiderin is typical on MR images and is best seen on T₂- or T₂*-weighted images [42].

Analyzing the images, an attempt should be made to differentiate between hypertensive and non-hypertensive ICH, in order to optimize the subsequent diagnostic work-up. Haemorrhages that involve the putamen, globus pallidum, thalamus, internal capsule, periventricular white matter, pons and cerebellum, particularly in a patient with known hypertension, are often attributed to hypertensive small-vessel disease [77]. In these patients further imaging studies investigating the underlying vascular pathology are not necessary. Follow-up with CT or MRI might be necessary, particularly for patients with IVH and for those with clinical deterioration.

Patients with CT evidence of ICH in a location typical for hypertensive ICH (see above), but at a younger age and/or without a history of hypertension, need further diagnostic work-up, which should include MR angiography (MRA), CT angiography (CTA) and/or digital subtraction angiography (DSA). There is also no need for further work-up for patients with lobar haemorrhage, in whom T₂*-weighted MRI is suspicious of an underlying amyloid angiopathy, if it reveals multiple cortical and subcortical old haemorrhages [78].

For patients with suspected non-hypertensive ICH requiring emergency surgical evacuation, the fastest and most effective technique revealing the underlying vascular pathology is CTA [79]. Alternatively, MRA can be performed [80]. Under such emergency conditions the use of DSA is also acceptable, but it is generally not required. Aneurysms >=3 mm and larger AVMs – not requiring a specific technique – can be recognized using cross-sectional angiographic methods [79–81].

MRI is the optimal technique to demonstrate low-flow vascular malformations (cavernomas), haemorrhagic tumours and other vascular pathologies. CTA or MRA are the methods of choice to demonstrate dural sinus thrombosis as the underlying cause of ICH.

DSA is the optimal technique to demonstrate underlying high-flow vascular malformations. As larger ICH may change the haemodynamics of AVMs to an extent that the malformation cannot be seen on CTA or MRA, DSA can be electively performed in a delayed fashion.
Dural or cortical vein thrombosis can present as ICH with venous infarction. The most sensitive examination technique is MRI in combination with MR venography. DSA may be performed if diagnosis is still uncertain [82].

**Recommendations**

1. The sensitivity for acute intracranial haemorrhage – including SAH – is almost equal between CT and MR, if the MR protocol includes T1*- and/or proton-density-weighted images. However, patient monitoring is still easier using CT (level A).

2. No further imaging studies, except at follow-up (within 24–48 h), are required for patients with ICH in a location typical for hypertensive ICH and with a clinical history characteristic for hypertensive ICH (level B). Follow-up imaging is indicated in all other cases and should be performed 4 weeks after the initial insult.

3. If urgent surgical evacuation of a non-hypertensive ICH is indicated, the underlying vascular pathology should preferably be studied by CTA, or alternatively by MRA or DSA (class IV evidence).

4. If urgent surgical evacuation of a supposedly non-hypertensive ICH is not indicated, the underlying vascular pathology should be investigated by:
   a. MRI if the suspected lesion is a cavernoma or CAA;
   b. CTA or MRA if the suspected lesion is dural sinus thrombosis;
   c. DSA if the suspected lesion is a ruptured aneurysm or a pial or dural AVM.
   These studies may be performed as elective procedures, except if aneurysm rupture is assumed (class IV evidence).

**Emergency Management and General Treatment**

There are 5 main areas in the treatment of acute ICH:

1. General treatment does not substantially differ from the treatment of ischaemic stroke [14]. The neurological status and vital functions (blood pressure, pulse rate, oxygenation and temperature) should be continuously or regularly monitored.

2. Prevention and treatment of complications, which may be either neurological (such as space-occupying oedema or seizures) or medical (such as aspiration, infections, decubital ulcers, DVT or PE).

3. Early secondary prevention to reduce the incidence of early recurrence of ICH. Apart from treatment of increased blood pressure and withholding the use of antithrombotic drugs, early secondary prevention does not substantially differ from secondary prevention in stroke in general; the latter was detailed in the 2003 EUSI recommendations [14].

4. Early rehabilitation is also essential for ICH patients. Again there are no substantial differences to the 2003 EUSI recommendations for acute ischemic stroke [14].

5. Specific therapy directed against the growth of the haematoma that is currently the subject of surgery and ongoing RCTs.

**General Stroke Treatment and Monitoring**

The term 'general treatment' refers to clinical and instrumental monitoring, as well as treatment strategies aimed at stabilizing the acutely ill patient. This not only provides an optimum physiological basis upon which specific therapeutic strategies can be applied [14, 83], but also represents a cornerstone of stroke treatment by treating other medical problems that may significantly influence stroke outcome. All patients with ICH should be treated in stroke units, if such a unit exists in the hospital, or in the ICU if the patient's condition requires this. Stroke unit care reduces mortality and increases the likelihood of good functional outcome of stroke in general [25]. There is consensus that the management of general medical problems is the basis for stroke treatment [14, 83]. It is generally believed that ICH survivors have better neurological and functional prognoses than the survivors of ischaemic stroke [84].

General treatment of patients with stroke and ICH needs monitoring of clinical development and physiological functions. Neurological status is best monitored using validated neurological scales; the National Institute of Health Stroke Scale (NIHSS) [85] and the GCS [86] are the most frequently used. Other scales, such as the Scandinavian Stroke Scale [87] or the Unified Neurological Stroke Scale [213], may also be used. However, it is essential that a centre concentrates on the use of one scale only. The ICH score is an instrument that may allow risk stratification of ICH patients on admission [26].

General management of all stroke patients, including those with ICH, comprises respiratory and cardiac care, fluid and metabolic management and blood pressure control. In addition prophylactic measures concerning deep venous thrombosis (DVT), pulmonary embolism (PE), aspiration pneumonia, other infections and decubital ulcer are part of the general treatment of these patients.

Vital functions, pulmonary function, airway protection, glucose, body temperature, fluid balance, electrolytes and decubital ulcers will be covered in the long version of these recommendations (http://www.eusi-stroke.org/index.shtml) and are mostly comparable with the
Blood Pressure Management

Blood pressure monitoring and treatment is a critical issue in the general treatment of acute ICH, although it remains controversial due to the fact that there are no randomized trials to guide the management. Reducing blood pressure in acute ICH may prevent or retard the growth of the haematoma and also decrease the risk of rebleeding, but reduced cerebral perfusion pressure (CPP) could compromise adequate CBF due to increased intracranial pressure. Qureshi et al. [88] kept the blood pressure of 27 patients with acute ICH below 160 (systolic) and 90 mm Hg (diastolic) in a prospective trial. They found a haematoma growth in 9% of these patients. This is remarkably lower than the number found by Brott et al. [7] in a prospective study that did not primarily target blood pressure measurement. In the study by Brott et al. [7], haematoma growth was observed in 38% of patients within 24 h after onset of symptoms.

Stroke patients are frequently chronically hypertensive, and their brain hydraulic autoregulatory curve is shifted to the right. This means that while in normal individuals CBF is constant at a MAP of approximately 50–150 mm Hg, hypertensive stroke patients can better tolerate higher MAP levels, while they are at risk of critical hypoperfusion for MAP levels usually well tolerated by normotensive individuals [214]. MAP should gradually be reduced below 120 mm Hg in persons with a history of chronic hypertension, but a reduction of >20% should be avoided, and MAP should not be reduced to <84 mm Hg [90].

Based on these limited data, an upper limit of systolic blood pressure of 180 mm Hg and a diastolic blood pressure of 105 mm Hg is recommended for patients with known prior hypertension or signs (ECG, retina) of chronic hypertension. If treatment is necessary, the target blood pressure should be 160/100 mm Hg (or a MAP of 120 mm Hg, see recommendations). In patients without known hypertension, the upper recommended limits are 160/95 mm Hg. If treatment is necessary, the target blood pressure should be 150/90 mm Hg (or a MAP of 110 mm Hg) [90].

These limits and targets should be adapted (increased) to higher values in patients with increased intracranial pressure (ICP), to guarantee a sufficient cerebral perfusion pressure (CPP = MAP – ICP) of at least 60 to 70 mm Hg, however, these are data derived from traumatic brain injury.

Other indications for immediate antihypertensive therapy: treatment may be appropriate in the setting of concomitant acute myocardial ischaemia (although extreme lowering of blood pressure is deleterious for myocardial infarction patients as well), cardiac insufficiency, acute renal failure, acute hypertensive encephalopathy or aortic arch dissection.

In patients with ischaemic stroke, sublingual calcium antagonists should be avoided because of the risk of an abrupt reduction in blood pressure [91], possible ischaemic steal [83, 92–95] and overshoot hypertension. However, it is possible that these concepts may not apply to spontaneous ICH because there is no evidence of an ischaemic penumbra [42, 43, 45]. Nevertheless, oral, sublingual, and intravenous administration of calcium antagonists should be used carefully because of their rapid and excessive hypotensive effect. The same may be true for subcutaneous clonidine. In both cases the duration of action is hard to predict. Oral captopril (6.25–12.5 mg) has been recommended as an oral first-line drug [96], but it has a short duration of action and can have an abrupt effect.

Intravenous antihypertensive drugs with a short half-life time can be used as first-line treatment for optimal therapeutic control (table 2). In the USA and Canada intravenous labetalol (10–80 mg), which is not available everywhere in Europe, or esmolol, nicardipin and enalapril are frequently recommended. Intravenous urapidil is also increasingly used. Finally sodium nitroprusside is sometimes necessary, despite some major side effects, such as reflex tachycardia, coronary artery ischaemia, antiplatelet action and increasing ICP, which may also lead to a decrease in CPP [97]. Intravenous treatment of hypertension should always be accompanied by continuous blood pressure monitoring. In an ICU, blood pressure monitoring with an intra-arterial line is advisable [98]. Intravenous antihypertensive drugs that may be used in acute ICH are listed in table 2.

Prevention of DVT and PE

The prevention of DVT/PE is of major importance in the care of every stroke patient [112], and patients with ICH are no exception. Although graded compression stockings are effective in surgical patients, their efficacy in haemorrhagic stroke patients has not been verified [113–115]. While subcutaneous heparin and low-molecular-weight heparin (LMWH) reduce venous thromboembolism, it is possible that their effect is counterbalanced...
by an increase in haemorrhagic complications. In patients with ICH such agents are usually withheld during the early days and administered only in patients at high risk of DVT or PE, at half of the normal dose [116]. Depending on the choice of the drug, either activated prothrombin time or anti-factor Xa tests should be used to monitor the level of anticoagulation. The initial use of intermittent pneumatic compression devices for DVT/PE prophylaxis in patients with acute ICH has recently been recommended by the experts of the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy [116]. Only in 1 small trial was low-dose heparin (5,000 U) given subcutaneously to patients with ICH on day 2. These patients were compared with patients who had received their first dose of heparin either on day 4 or day 10. There was a significantly lower incidence of PE in the patients who had received early heparin on day 2, while the number of patients with intracranial rebleeding was not increased [117]. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy panel of experts recommends that in neurologically stable patients a low dose of subcutaneous heparin (or LMWH) can be started on the second day after the onset of acute ICH [116].

Table 2. Intravenous antihypertensive drugs that may be used in acute intracerebral haemorrhage (modified from [96])

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset of action</th>
<th>Duration of action</th>
<th>Comments</th>
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<tr>
<td><strong>Adrenergic inhibitors</strong></td>
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<tr>
<td>Labetalol</td>
<td>20–80 mg bolus every 10 min, up to 300 mg; 0.5–2.0 mg/min infusion</td>
<td>5–10 min</td>
<td>3–6 h</td>
<td>Indicated in ischaemic and haemorrhagic stroke; contraindicated in acute heart failure</td>
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<tr>
<td>Esmolol</td>
<td>250–500 µg/kg/min bolus, then 50–100 µg/kg/min infusion</td>
<td>1–2 min</td>
<td>10–30 min</td>
<td>Indicated in stroke and aortic dissection; contraindicated in bradycardia, AV block, heart failure and bronchospasm</td>
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<td>Urapidil</td>
<td>12.5–25 mg bolus; 5–40 mg/h infusion</td>
<td>3–5 min</td>
<td>4–6 h</td>
<td>Indicated in most hypertensive emergencies including stroke; avoid in coronary ischaemia</td>
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<td><strong>Vasodilators</strong></td>
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<td>Nitroprusside*</td>
<td>0.2–10 µg/kg/min as infusion</td>
<td>within seconds</td>
<td>2–5 min</td>
<td>Indicated in most hypertensive emergencies including stroke, when diastolic blood pressure &gt;140 mm Hg; contra-indicated in high ICP</td>
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<tr>
<td>Nicardipine</td>
<td>5–15 mg/h infusion</td>
<td>5–10 min</td>
<td>0.5–4 h</td>
<td>Indicated in stroke; contraindicated in acute heart failure, coronary ischaemia and aortic stenosis</td>
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<tr>
<td>Enalaprilat</td>
<td>1.25–5 mg every 6 h</td>
<td>15–30 min</td>
<td>6–12 h</td>
<td>Indicated in acute left ventricular failure; avoid in acute MI and hypotension</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10–20 mg bolus</td>
<td>10–20 min</td>
<td>1–4 h</td>
<td>Indicated in eclampsia; avoid in tachycardia and coronary ischaemia</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>0.1–0.3 µg/kg/min infusion</td>
<td>&lt;5 min</td>
<td>30 min</td>
<td>Indicated in most hypertensive emergencies including stroke; avoid in glaucoma, tachycardia and portal hypertension</td>
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<tr>
<td><strong>Diuretics</strong></td>
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<tr>
<td>Furosemide</td>
<td>20–40 mg bolus</td>
<td>2–5 min</td>
<td>2–3 h</td>
<td>Avoid in hypokalemia, eclampsia and pheochromocytoma</td>
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</tbody>
</table>

* Nitroprusside is contraindicated in patients with high ICP. AV = Atrioventricular; MI = myocardial infarction.
Treatment of Complications

Management of Increased ICP

Increased ICP, brain oedema and mass effect are associated with high morbidity and mortality after ICH. Some patients with suspected intracranial hypertension and a decreasing level of consciousness might require invasive ICP monitoring, although its added value beyond clinical or radiological monitoring has not yet been proven. The aim of treating elevated ICP is to maintain the CPP above 60–70 mm Hg, as CPP = MAP – ICP.

The main methods of medical decompression for increased ICP include: controlled hyperventilation, osmotic diuretics and intravenous barbiturates (table 3). These techniques are most useful for bridging the time to surgery, if the latter is planned. At the current stage corticosteroids are not recommended [5, 99]. A recent review of 206 patients with ICH in 5 trials found no statistically significant influence of corticosteroids on death or clinical outcome [100]. However, the authors point out that these results should be interpreted with caution because of relevant methodological differences in the studies. They conclude that further RCTs are needed with various clinical settings, e.g. time and dosage of intervention.

The aim of therapeutic hyperventilation is to achieve arterial pCO₂ levels of 30–35 mm Hg. The beneficial effects of controlled hyperventilation are transient, and this method is usually most useful in the first hours after its institution. The lack of reduction of increased ICP with hyperventilation means that it is a poor prognostic sign for ICH patients.

Mannitol produces a rapid lowering of ICP, and this effect is already observed within 20 min of administering an intravenous bolus, which suggests that this effect may be independent from subsequent diuresis. Mannitol (20%) at a dose of 0.75–1 g/kg is given as an intravenous bolus, followed by a dose of 0.25–0.5 g/kg every 3–6 h, depending on the neurological status, fluid balance and serum osmolality. Serum osmolality will increase with repeated doses of mannitol and should be maintained between 300 and 320 mosm/l. Mannitol may cause renal failure and electrolyte disturbances [101]. Measuring the osmolar gap correlates better with mannitol serum concentrations than osmolality. A normal osmolar gap concentration was shown to indicate sufficient clearance for repeating mannitol [102–104].

If intracranial hypertension cannot be controlled with osmotic therapy and hyperventilation, induced barbiturate coma may be considered [105]. Barbiturates have been shown to reduce CBF and metabolism, which results in a decline in ICP. Barbiturate coma should be induced with pentobarbital (loading dose of 3–10 mg/kg, by infusing at a rate of 1 mg/kg per min) or thiopental (loading dose of 10 mg/kg) followed by continuous infusion. The doses should be adapted to a burst suppression pattern in continuous electroencephalography (EEG) monitoring [106]. Experience with high doses of barbiturates in ICH patients is still limited, and further clinical studies are needed.

### Table 3. Escalation scheme for treatment of ICP (modified from [215])

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid situations that may lead to an elevation or aggravation of intracranial pressure: pain, fever, psychological stress, physical stress (e.g. body positioning), hypo-natremia and hypertension</td>
<td></td>
</tr>
<tr>
<td>Elevation of body positioning up to 30°</td>
<td></td>
</tr>
<tr>
<td>Mannitol (20%), intravenous, 100 ml (bolus), up to 6 times per day</td>
<td></td>
</tr>
<tr>
<td>Hyper-HAES (NaCl 7.5%; HES 6%), intravenous, 150 ml bolus</td>
<td></td>
</tr>
<tr>
<td>Muscle relaxants (e.g. vecuronium), titrate to effect</td>
<td>CPP &gt;60–70 mm Hg&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>THAM buffer, intravenous (central line), 1 mmol/kg bolus; 0.25 mmol/kg as permanent infusion</td>
<td>Serum osmolality &lt;320 mmol/l</td>
</tr>
<tr>
<td>Consider haematoma evacuation with or without decompressive hemicraniectomy</td>
<td>Serum sodium &lt;155 mmol/l</td>
</tr>
<tr>
<td>Barbiturates (thiopental), intravenous, 250–500 mg bolus</td>
<td>pH &lt;7.5–7.55</td>
</tr>
<tr>
<td>Hyperventilation, increasing respiratory rate and tidal volume</td>
<td>Caution: tissue necrosis (central line needed)</td>
</tr>
</tbody>
</table>

<sup>a</sup> When a monitoring probe is in place, CPP should be kept >70 mm Hg. HES = Hydroxyethyl starch; PaO₂ = partial pressure of oxygen.
Seizure

In a prospective study the incidence of post-haemorrhagic seizures – as demonstrated by continuous EEG – was found to be higher than that for ischaemic stroke. Eighteen of 63 (28%) patients with ICH showed EEG evidence of seizures compared with 3 of 46 (6%) patients who had suffered ischaemic stroke [107]. Seizures occurred in 21% of subcortical haemorrhage. Seizures were associated with neurological worsening and with an increase in midline shift. The rate of increase on the NIHSS was significantly higher in patients with seizures. Age and initial NIHSS were independent predictors of outcome [107].

In another prospective study, 32 of 761 (4.2%) patients had their clinically detected seizure at the onset of the haemorrhage or within 24 h [108]. Twenty-five patients (3.8%) had their first seizures within 29 days. Of the 32 patients with immediate (within 24 h) seizure, 1 had a recurrent seizure within the next 29 days, though it is not clear whether this patient did receive prophylactic treatment. The occurrence of seizures was elevated in patients with lobar location and small-sized ICH. Early seizures were associated with lobar location and neurological complications, mainly rebleeding. In this study the prophylactic use of antiepileptic treatment in patients with lobar location did lead to a reduction in seizures.

In an older study all epileptic seizures (17%; 19 of 112) occurred at ICH onset [109]. In this study there was no association between seizure and the size of the haemorrhage, but there was an association if the blood had extended into the cerebral cortex.

Furthermore non-convulsive seizure or status epilepticus has been detected in 28% of stuporous or comatose patients [110, 111].

Recommendations

1 All patients with acute ICH should preferably be treated in stroke units or in the ICU if the patient’s condition requires this. Stroke unit care reduces mortality and increases the likelihood of good functional outcome of stroke in general [25]. Continuous cardiac monitoring is recommended in the first 48–72 h of stroke onset, particularly in patients with previous known cardiopathies, history of arrhythmias, unstable blood pressure, clinical signs/symptoms of heart failure, abnormal baseline ECG and haemorrhage involving the insular cortex (level C).

2 Immediate antihypertensive therapy is recommended in cases of ICH and heart failure, aortic dissection, acute myocardial infarction and acute renal failure, but it should be applied cautiously (class IV evidence).

3 Routine blood pressure lowering is not recommended. Treatment is recommended if blood pressure is elevated above the following levels, confirmed by repeated measurements (class IV evidence):
   a Patients with known history of hypertension or signs (ECG, retina) of chronic hypertension: systolic blood pressure >180 mm Hg and/or diastolic blood pressure >105 mm Hg. If treated, target blood pressure should be 170/100 mm Hg (or a MAP of 125 mm Hg).
   b Patients without known hypertension: systolic blood pressure >160 mm Hg and/or diastolic blood pressure >95 mm Hg. If treated, target blood pressure should be 150/90 mm Hg (or a MAP of 110 mm Hg).
   c A reduction of MAP by >20% should be avoided.
   d These limits and targets should be adapted to higher values in patients undergoing monitoring of increased ICP, to guarantee a sufficient CPP >70 mm Hg. Recommended drugs for blood pressure treatment: intravenous labetolol or urapidil, intravenous sodium nitroprusside or nitroglycerin, and captopril (per os). Avoid oral nifedipine and any drastic blood pressure decrease (table 2).

4 Continuous ICP monitoring should be considered in patients who need mechanical ventilation for further therapeutic options (class IV evidence).

5 Medical treatment of elevated ICP should be started if deterioration can be related to increasing oedema (on CCT or MRI; class IV evidence).

6 Medical treatment of elevated ICP includes glycerol, mannitol, hyper-HAES. Short-term hyperventilation can be initiated intermittently for ICP crisis (class IV evidence).

7 Compression stockings and intermittent pneumatic compression are recommended for prevention of thromboembolism in patients with disabling limb weakness from the beginning of treatment (class IV evidence). Low-dose subcutaneous heparin or LMWH should be considered after 24 h, especially in patients who are at high risk of thromboembolism (class IV evidence).

8 Early prophylactic treatment of seizures is not recommended for all patients, but may be considered for selected patients with lobar ICH. In all other cases seizures should only be treated if they occur (level C). If seizures occur, a step-wise administration of antiepileptic drugs is generally recommended (table 4). Antiepileptic treatment should be continued for 30 days. After this time treatment should be reduced and eventually discontinued. If seizures reoccur, patients should receive chronic treatment with anticonvulsants.

9 Other general measures (control of hyperglycaemia, hypothermia, fluid management and nutrition, prevention of aspiration pneumonia and bed sores) are the same as for patients with ischaemic stroke [14].

10 Early mobilization is recommended unless intracranial hypertension is present.

11 Early rehabilitation is recommended in patients with neurological deficits and should follow the same principles as in patients with ischaemic stroke (class IV evidence).
Specific Treatment

Surgery

ICH represents a heterogeneous group of pathological conditions, which deserve differentiation in order to clarify the different surgical treatment options. Surgical treatments should be considered separately according to whether the haemorrhage is supratentorial or infratentorial and according to the presence or absence of aneurysms or other causes of spontaneous ICH.

Supratentorial Non-Aneurysmal ICH

Twelve prospective RCTs have been published on surgery for supratentorial non-aneurysmal ICH [11, 118–128]. These are summarized in figure 1. The overall odds ratio (OR) for death from these trials is 0.85 (95% CI 0.71–1.02) [129]. There is thus some trend in favour of early surgery. The adverse effect of ventricular blood [30] has not been considered in any of these trials, so the effect of surgery on pure parenchymal ICH, without ventricular haemorrhage, has yet to be determined.

The largest of these trials was the International Surgical Trial in Intracerebral Haemorrhage (STICH), and this showed in 1,033 patients that early surgery (within 24 h) was no different from initial conservative treatment (OR 0.89; 95% CI 0.66–1.19) [11]. Clinical observation (with or without ICP/CPP monitoring) is therefore a reasonable management policy initially.

Prespecified post-hoc analysis in the STICH trial showed that 2 subgroups – deterioration in consciousness (from a GCS of between 9 and 12) and location (deep vs. superficial) – approached significant benefit with early surgery, which permits the following considerations: consider craniotomy if there is deterioration from a GCS of between 9 and 12 and/or if the clot is superficial (<1 cm from the surface). Deep-seated haematomas do not benefit from craniotomy. Stereotactic aspiration may be considered. Both of these procedures certainly call for more trials [125].
### Recommendations for the Management of Intracranial Haemorrhage

#### Cerebrovascular Disease 2006;22:294–316

**Surgery in Intracerebral Haemorrhage**

**Comparison:** 01 Surgery vs. Control

**Outcome:** 02 Death

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto OR 95% CI</th>
<th>Weight %</th>
<th>Peto OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKissock et al. [119], 1961</td>
<td>58/89</td>
<td>46/91</td>
<td>1.81 (1.01–3.27)</td>
<td>9.83</td>
<td></td>
</tr>
<tr>
<td>Auer et al. [118], 1989</td>
<td>21/50</td>
<td>35/50</td>
<td>0.32 (0.15–0.71)</td>
<td>5.54</td>
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</tr>
<tr>
<td>Juvela et al. [120], 1989</td>
<td>12/26</td>
<td>10/26</td>
<td>1.36 (0.46–4.05)</td>
<td>2.88</td>
<td></td>
</tr>
<tr>
<td>Batjer et al. [121], 1990</td>
<td>4/8</td>
<td>11/13</td>
<td>0.20 (0.03–1.33)</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Chen et al. [122], 1992</td>
<td>15/64</td>
<td>11/63</td>
<td>1.44 (0.61–3.40)</td>
<td>4.64</td>
<td></td>
</tr>
<tr>
<td>Morgenstern et al. [123], 1998</td>
<td>3/17</td>
<td>4/17</td>
<td>0.71 (0.14–3.63)</td>
<td>1.27</td>
<td></td>
</tr>
<tr>
<td>Zuccarello et al. [124], 1999</td>
<td>2/9</td>
<td>3/11</td>
<td>0.77 (0.11–5.62)</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Cheng et al. [128], 2001</td>
<td>26/266</td>
<td>34/234</td>
<td>0.64 (0.37–1.09)</td>
<td>11.73</td>
<td></td>
</tr>
<tr>
<td>Teernstra et al. [125], 2003</td>
<td>20/36</td>
<td>20/34</td>
<td>0.88 (0.34–2.25)</td>
<td>3.87</td>
<td></td>
</tr>
<tr>
<td>Hosseini et al. [127], 2003</td>
<td>3/20</td>
<td>9/17</td>
<td>0.19 (0.05–0.72)</td>
<td>1.84</td>
<td></td>
</tr>
<tr>
<td>Hattori et al. [126], 2004</td>
<td>9/121</td>
<td>20/121</td>
<td>0.42 (0.20–0.92)</td>
<td>5.70</td>
<td></td>
</tr>
<tr>
<td>Mendelow et al. [11], 2005</td>
<td>173/477</td>
<td>189/505</td>
<td>0.95 (0.73–1.23)</td>
<td>50.88</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

|              | 1,183        | 1,182        | 100.00 | 0.85 (0.71–1.02) |

**Total events:** 346 (Treatment), 392 (Control)

- **Test for heterogeneity:** $\chi^2 = 26.29$, d.f. = 11 (p = 0.006), F = 58.2%
- **Test for overall effect:** $Z = 1.73$ (p = 0.08)

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**Fig. 1.** Meta-analysis of the 12 prospective RCTs in spontaneous supratentorial ICH for death [from ref. 129].

### Cerebellar Non-Aneurysmal ICH

Cerebellar haemorrhage causes damage in 2 ways: it may produce direct compression of the cerebellum and brainstem with relevant symptoms and signs, or it may produce hydrocephalus. Clot evacuation should be considered if there is neurological dysfunction or radiological evidence of obliteration of CSF spaces infratentorially [130]. Surprisingly good results have been reported with surgical evacuation of cerebellar haematoma, but the optimal timing has not been established, and there are no prospective RCTs of surgery in cerebellar haemorrhage. By contrast there is universal clinical agreement for ventricular drainage for hydrocephalus at any time after ictus [131]. For this reason ventricular drainage and evacuation of the cerebellar haematoma should be considered if hydrocephalus occurs or if haematoma are $\geq 2–3$ cm in diameter, although advanced age and coma mitigate against favourable outcomes. However, it should be borne in mind that all these data are derived from personal experience or retrospective studies.

### Intraventricular Haemorrhage

The outcome from ICH is much worse with intraventricular haemorrhage (IVH) [132]. This has not been taken into account in any of the surgical trials in ICH to date [133]. With IVH, hydrocephalus is common, but blood clots will often block the drainage catheters. For this reason methods to maintain their patency have been evaluated. Intraventricular thrombolysis with urokinase or recombinant tissue plasminogen activator via external ventricular drainage seems to be effective [134, 135]. More trials are needed, and several are being conducted.

### Treatment of Hydrocephalus

Hydrocephalus may occur with any type of intracranial haemorrhage. With SAH, it is often the non-obstructive or ‘communicating’ type of hydrocephalus, while with IVH or parenchymal haemorrhage it is more likely to be of the obstructive or ‘non-communicating’ type, and with cerebellar haemorrhage it is always obstructive.

The methods of treatment depend on the type of hydrocephalus, although all types can be treated with ven-
tricular access. The communicating type of hydrocephalus can be treated via the lumbar route, which is less invasive (no risk of epilepsy or brain haemorrhage).

Methods of treatment include observation if it is mild and does not cause any disturbance of consciousness. External drainage can be ventricular or via the lumbar route if it is a communicating type of hydrocephalus. Lumbar drainage is definitely contraindicated with all types of obstructive hydrocephalus or if the aetiology is in doubt. Intraventricular thrombolysis trials have been encouraging [135], but not in infants [136].

Internal drainage is achieved with a ventricular peritoneal or a lumbar peritoneal shunt if the hydrocephalus is of the communicating type. Endoscopic third ventriculostomy is seldom successful with hydrocephalus associated with acute haemorrhage [137], except perhaps in neonates [138]. Favourable results have been described in case series with intraoperative opening of the lamina terminalis and Lilliequist’s membrane [139, 140]. There are no efficacy trials comparing any type of drainage with non-intervention or different routes of CSF access. There are a few trials comparing different shunt types, but these have failed to show any difference. Antibiotic prophylaxis has been shown to be effective in CSF shunt operations [141].

ICH Caused by AVM

Approximately half of all cerebral AVMs present with a haemorrhage [142]. The long-term risk of rebleeding was found to be as high as 18% in the first year after the initial haemorrhage [142, 143]. However, the immediate short-term risk of bleeding may be relatively low. Thus, surgical or endovascular AVM repair should not be considered as an emergency in the same way that it is for aneurysm rupture. Unless a feeding artery aneurysm is identified as the bleeding source, the best approach in most cases is to stabilize the patient, minimize exposure to acute perioperative complications and then address AVM treatment within 4–12 weeks of the bleed. This is because during the acute phase of bleeding, a procedural complication may lead to much more harm than would be the case if it were to occur several weeks later. Management options include observation, embolization, surgical excision or stereotactic radiotherapy. Combinations of these treatments afford the best results and have to be considered at the time of the haemorrhage [144]. No prospective RCTs have been conducted, but surgeons agree that surgical treatment of the AVM may be facilitated by the presence of the clot, so timing of the surgery of the AVM should take place within about 2–3 months of the ictus if the surgeon is to take advantage of the dissection created by the haematoma.

With unruptured AVMs, a trial of surgery compared with conservative treatment has been initiated [145].

In general, endovascular embolization is an optional treatment modality for the treatment of the underlying vascular pathology, including aneurysm, AVM and dural AVM, but excluding cavernoma [136, 137]. The goal of the endovascular embolization of an AVM or dural AVM is to eliminate or reduce the size of, and blood flow through, the AVM nidus, either as a sole treatment or as a preoperative method [146, 147].

ICH Caused by Cavernous Angiomas

Cavernous angiomas are structural vascular lesions of the brain and spinal cord that occasionally bleed. The estimated annual bleeding rate is 0.7% per year and per lesion [148–150]. Patients with 1 previous haemorrhage had an annual 4.5% risk of rebleeding [216]. Usually the consecutive haematoma is not life-threatening, because cavernomas are part of the low-pressure system. The latter is the reason for the often negative DSA findings. In less than 10% of patients, angiography reveals the vascular malformation. The highest diagnostic sensitivity is given by T2*-weighted MR sequences [148, 149]. In up to 30%, cavernomas are associated with developmental venous anomalies, and vice versa. All patients with a cavernoma should therefore have a contrast-enhanced MR scan in order to rule out an accompanying developmental venous anomaly. This is specifically important if the cavernoma is a candidate for surgical removal.

The treatment options in cavernomas depend mainly on the natural course of the lesion, as well as its location and surgical accessibility. The latter depends on the skill of the surgeon and the position of the lesion relative to eloquent areas of the brain [151]. In general the therapeutic strategies include:

- Observation of patients with asymptomatic or inaccessible lesions (class IV evidence).
- Surgical excision of symptomatic and accessible lesions (class IV evidence).
- Radiosurgery for progressively symptomatic but surgically inaccessible lesions (class IV evidence).

The main indication for surgical removal of a cavernoma is the prevention of haemorrhage. Therefore many surgical groups recommend surgical removal of a cavernoma if it is located in a non-eloquent brain area and is easily accessible [153]. However, it is quite difficult to predict the natural course of an individual cavernoma, and therefore it is impossible to balance the individual bleeding risk of the individual patient against the morbidity and mortality of a surgical procedure.
Haemostatic Therapy

The use of haemostatic agents to control bleeding has been tried in ICH or SAH with various agents (triamterene, 2-aminocaproic acid, aprotinin) [154–156]. These trials could not demonstrate safety or efficacy. Recombinant factor VIIa (rFVIIa) was developed for the treatment of patients with haemophilia and was thus also used to stop intracerebral bleeding in these patients [157, 158]. FVIIa initiates coagulation at the site of vessel disruption. It may thus lead to thrombotic side effects.

Two prospective, randomized, placebo-controlled, dose-escalating, phase IIa trials demonstrated safety and feasibility for the use of rFVIIa in 88 patients with spontaneous ICH within 4 h after the first symptoms [12, 159].

In a prospective, randomized, placebo-controlled trial, 400 patients with spontaneous ICH were treated with rFVIIa (40, 80, 160 μg/kg) within 4 h of ictus. The diagnosis had to be confirmed within 3 h. Patients with any history of ischaemic events were excluded. The treatment of ICH with rFVIIa within 4 h of onset limited the haematoma expansion, decreased the mortality and improved the 3-month clinical outcome, despite a significant 5% increase in arterial thromboembolic events within the group receiving the highest dose (160 μg/kg) [13]. Possibly or probably (as opposed to unlikely) treatment-related thromboembolic severe adverse events that were fatal or disabling occurred in 2.0% of rFVIIa-treated patients compared with 2.1% in the placebo group.

Recommendations for specific treatment of acute ICH

1 Consider craniotomy if there is deterioration in consciousness (from a GCS level of between 12 and 9 to ≤ 8), if the ICH is superficial (the clot is subcortical ≤ 1 cm from the surface and does not reach the deep basal ganglia), or if it is located in the cerebellum (level C).

2 Deep-seated haematomas do not benefit from craniotomy. Stereotactic aspiration may be considered (class IV evidence), especially if a mass effect is present.

3 Management options of AVM include observation, embolization, surgical excision or focused radiotherapy. Combinations of these treatments afford the best results and have to be considered at the time of the haemorrhage. Surgical treatment takes place within about 2–3 months of the ictus if surgical excision is to be undertaken (class IV evidence).

   If patients have an impaired level of consciousness and a haematoma of at least 3 cm in diameter, consider emergency evacuation of the clot with excision of the AVM in the same operation, if it is possible (class IV evidence).

4 Pending further data on efficacy and safety, rFVIIa should not be used outside a phase III trial. A phase III trial is needed to confirm the beneficial effect of rFVIIa in ICH (level B).

5 External drainage for hydrocephalus can be ventricular or via the lumbor route if it is a communicating type of hydrocephalus (class IV evidence). Lumbar drainage is definitely contraindicated with all types of obstructive hydrocephalus or if the aetiology is in doubt.

6 Intraventricular thrombolysis trials may be considered if an external ventriculair drainage becomes necessary (class IV evidence), but not in infants.

Special Aspects in the Management of ICH

Treatment of ICH Related to Oral Anticoagulants

The annual risk of ICH in patients who are on OAT is between 0.3 and 3.7% when the international normalized ratio (INR) is in the range between 2.0 and 4.5 [160]. The annual risk in the placebo groups was about 0.1% [161–163]. Every elevation of 0.5 INR units increases the risk for major bleedings (intracranial or fatal) by 1.4 [164].

A rather high annual risk of a thromboembolic complication of 5–10% without OAT, a figure representative of high-risk patients with mechanical valves, can be translated as a 2-week risk of 0.2–0.4%, i.e. a rather low risk. This risk should be compared with the very high risk of early rebleeding, especially in patients with OAT-related ICH. Rebleeding was found in 16% (9/75) of patients with ICH who were not on OAT, compared with 54% (7/13) in those on OAT, and occurred up to 7 days [165].

A few studies actually support this view and have indicated that the rate of embolic events is low, even in high-risk patients, if OAT is interrupted for up to 10–14 days [166–168]. Other studies have indicated that ICH in patients on OAT has a severer prognosis with larger bleeds and a higher case fatality than ICH in patients not receiving OAT [165, 169]. Furthermore the use of warfarin is associated with a worse outcome in patients with ICH [160]. Flibotte et al. [165] found that the use of warfarin significantly increases the likelihood of death when controlling for baseline ICH and IVH volumes. In addition the use of warfarin and increased intensity of anticoagulation are independent predictors of 3-month mortality [170].

Based on these experiences, it has been suggested that INR should be normalized emergently in all patients who suffer an OAT-associated ICH. Principally, this can be achieved by administration of prothrombin complex concentrate (PCC), fresh-frozen plasma (FFP) or vita-
min K, but there are no randomized trials comparing the different methods [171–173].

It is necessary to combine PCC or FFP treatment with vitamin K, since the half-lives of warfarin and phenprocoumon (24 h and up to 7 days, respectively) are much longer than that of the vitamin–K-dependent factors. The dosages of PCC and FFP are specified in table 5. Further details regarding dosages should be obtained from the manufacturers. Repeat measurement of coagulation status and a haematology consultation should be obtained in the acute phase.

rFVIIa was used to lower the INR in volunteers who had received acenocoumarol and in patients treated with warfarin and excessively elevated INRs [174, 175]. However, it must be remembered that the INR might not reflect the actual status of all vitamin-K-dependent coagulation factors [176]. The lack of therapeutic alternatives has increased the interest in off-label use of rFVIIa. The substance has been used alone or in combination with FFP in 2 small retrospective series of patients with spontaneous ICH [177, 178].

Although there are no RCTs available, there are some guidelines on the treatment of OAT-related ICH [179–182].

Considerations concerning whether and when to resume therapeutic anticoagulation in patients who have suffered OAT-related ICH include whether intracranial bleeding has been fully arrested, the estimated existing risk of thromboembolism and the presumed pathophysiology of the ICH, which will determine the risk of haemorrhage recurrence [166–168, 183–186]. The indication for secondary prophylactic treatment with OAT should be carefully re-evaluated after an ICH before restarting it. Currently the EUSI is recommending the preventive use of anticoagulation for patients who have had an embolic stroke associated with atrial fibrillation, prosthetic heart valves or other proven cardioembolic sources [14]. In a state-transition decision model stratified by location of haemorrhage, it was found that in patients with atrial fibrillation and a lobar location of ICH, restarting anticoagulation would not lead to a benefit in terms of quality-adjusted life years because the risk of rebleeding and a higher chance of death would outweigh the risk of occurrence of cerebral ischaemia. This was different for patients with deep location ICH [185].

Antiplatelet-associated ICH seems to be a rare event in the primary prevention of cardiovascular events, as shown in a recently published meta-analysis [187]. However, there was a net benefit from primary prevention of cardiovascular events with aspirin. There are no data supporting any use of platelet replacement.

**Recommendations**

In patients with an OAT-associated ICH and an INR >1.4:

1. OAT should be discontinued, and the INR should be normalized with PCC or FFP. Intravenous vitamin K should be added (class IV evidence).

2. After having re-checked the indication for anticoagulation (following the EUSI recommendations on ischaemic stroke) OAT may be continued after 10–14 days, depending on the perceived risk of thromboembolic occlusion and ICH recurrence (class IV evidence).

**Prevention of Recurrence: Modification of Risk Factors**

**Antihypertensive Treatment**

Earlier studies suggested that hypertensive ICHs rarely rebleed [188, 189], but in recent reports the rate of recurrent hypertensive ICH varied from 4.0 to 5.4% [190, 191], and in one report it was 2.9% per year [192]. About 70% of recurrent haemorrhagic strokes can be fatal.

There is good evidence that blood pressure is a determinant of the risk of stroke among both normotensive and hypertensive individuals [193]. However, there was no strong evidence until recently that reducing blood pressure after stroke reduces the risk of new vascular events or death. A meta-analysis from 9 RCTs on antihypertensive drugs, in which a small number of stroke survivors had been included, led to an estimated relative risk reduction for stroke of 29% (95% CI: 5–47%) [194], but these trials suffered severe limitations. In most trials ICH patients were either not included or were not prospectively studied (e.g. PATS, HOPE) [195–197].

The PROGRESS was a double-blind, randomized trial comparing perindopril (4 mg daily), with or without indapamide (2–2.5 mg daily), versus placebo for the prevention of recurrent ischaemic stroke in individuals with a history of non-disabling cerebrovascular disease (minor stroke or transient ischaemic attack), irrespective of blood pressure [50]. Antihypertensive treatment was initialized at least 2 weeks after stroke. The PROGRESS study included 6,105 patients and showed that lowering blood pressure by an average of 9/4 mm Hg with perindopril-based therapy decreased the risk of recurrent stroke by 28% versus placebo. Patients receiving both perindopril and indapamide had a mean drop in blood pressure of 12/5 mm Hg and a 43% reduction in the risk
of stroke. Interestingly the observed benefit was achieved regardless of blood pressure at entry and the type of stroke. These beneficial effects were present in all stroke subtypes, but were greater in haemorrhagic strokes (relative risk reduction 50%; 95% CI: 33–74%) and in Asians. The combination therapy prevented 1 recurrent stroke for 14 patients treated during a 5-year period. A recent systematic review of blood pressure reduction in the prevention of stroke recurrences, including ICHs, revealed a positive association between the magnitude of blood pressure reduction and the risk of vascular events [198].

Alcohol Consumption

The association between alcohol consumption and stroke is complex and may differ between Caucasian and other populations, e.g. Japanese. In the Honolulu Heart Program, heavy drinkers had a 3 times higher risk of haemorrhagic stroke (SAH or ICH) than non-drinkers [199]. A case-control study in a multiethnic population suggested that moderate consumption (up to 2 drinks of spirits, 2 cans of beer or 2 glasses of wine, equivalent to 20–30 g of ethyl alcohol per day) was associated with a decreased risk of ischaemic stroke, while heavy alcohol consumption was associated with an increased risk of ischaemic and haemorrhagic stroke [200]. A recent meta-analysis produced similar results by showing that heavy alcohol drinking (>60 g/day) increases the relative risk of stroke, while light or moderate alcohol consumption may be protective against total and ischaemic stroke [201]. A consumption of <12 g of alcohol per day was associated with a reduced risk of total stroke (relative risk 0.83) and ischaemic stroke (relative risk 0.80), and a moderate consumption of alcohol (12–24 g/day) was associated with a reduced relative risk of ischaemic stroke (0.72) [201]. However, there is no evidence to support any alcohol consumption in the prevention of ICH.

Antiplatelet Agents

Patients with ICH who have preceding or ensuing ischaemic disease (coronary artery syndrome, ischaemic stroke, peripheral arterial disease) or are at risk for ischaemia (symptomatic carotid stenosis, cerebral microangiopathy) may need secondary prophylaxis with antiplatelet drugs [14]. Viswanathan et al. [202] recently published reviewed data from consecutive survivors of primary ICH enrolled in a longitudinal, single-centre prospective cohort study. A total of 207 patients were included; 39 subjects had a recurrent ICH during a median follow-up of 19.5 months. The frequency of recurrent bleeding was significantly higher when patients had their first ICH located in lobar structures, compared with when the initial bleed was located in the basal ganglia. However, there was no difference in bleeding recurrence when patients who had received antiplatelets after the index bleeding were compared with those who had not. Furthermore it is known that small vessel disease is a risk factor for both ischaemic stroke and ICH. In particular, cerebral amyloid angiopathy is a risk factor for ICH, and some studies have looked into the risk of secondary ICH.

Table 5. Recommendation for the treatment of anticoagulation-associated ICH

<table>
<thead>
<tr>
<th>Normalization of INR (&lt;1.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCC</td>
</tr>
<tr>
<td>10–30 (–50) U/kg. Measure INR after 15 min.</td>
</tr>
<tr>
<td>If INR is still ≥ 1.5 consider redosing</td>
</tr>
<tr>
<td>with reduced dose.</td>
</tr>
<tr>
<td>FFP</td>
</tr>
<tr>
<td>10 ml/kg will reduce an INR of 4.2 to 2.4,</td>
</tr>
<tr>
<td>an INR of 3.0 to 2.1, or an INR of 2.4 to 1.8.</td>
</tr>
<tr>
<td>To reduce an INR of 4.2 to 1.4 would require</td>
</tr>
<tr>
<td>40 ml/kg.</td>
</tr>
<tr>
<td>Vitamin K</td>
</tr>
<tr>
<td>1–2 × 5–10 mg p.o. or i.v.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normalization of PTT after heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protamine sulphate</td>
</tr>
<tr>
<td>1.0–1.5 ml protamine sulfate</td>
</tr>
<tr>
<td>inactivates 1,000 IU heparin</td>
</tr>
<tr>
<td>of the total amount applied</td>
</tr>
<tr>
<td>within the last 4 h.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevention of deep vein thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression stockings</td>
</tr>
<tr>
<td>Low-dose heparin/heparinoids</td>
</tr>
</tbody>
</table>

i.v. = Intravenous; p.o. = per os; PTT = prothrombin time.

a There are large variations between products. Further details should be obtained from manufacturers.
b Caution: anaphylactic reactions with i.v. application.
in patients with pre-existing small vessel disease and in patients with cerebral ischaemia. Thus, it was suspected that cerebral small vessel disease and the intake of aspirin are associated with an increased risk of ICH in patients with an ischaemic infarct of arterial origin [203]. However, an analysis of 9 RCTs did not confirm this association [204]. Hypertension additionally increases the risk of ICH [205]. However, no increase in the risk of ICH was found among aspirin users. Other antiplatelet drugs – such as clopidogrel or the combination of dipyridamole and aspirin – have also been shown to be effective in the secondary prophylaxis of vascular events. The risk of rebleeding was not increased by either of these two substances [206, 207]. Adding aspirin to clopidogrel in high-risk patients is associated with increased risk of life-threatening major bleeding [211]. Furthermore pre-treatment with aspirin before thrombolysis with recombinant tissue plasminogen activator did not increase the risk of ICH, if the selection criteria for thrombolysis were applied properly [208]. In conclusion all of these studies provide only indirect information. The risk of ICH in patients who are on secondary prophylaxis with aspirin after ICH is not known. No definitive answer can be given to this problem, as there is insufficient evidence.


**Recommendations: special aspects of secondary prevention after ICH**

1. Diagnosis and control of hypertension after ICH is strongly recommended as the most effective means to decrease morbidity, mortality and recurrence due to spontaneous ICH (level A).

2. After ICH, blood pressure should be lowered, irrespective of its level, with a diuretic and an angiotensin-converting enzyme inhibitor, subject to toleration of the treatment (level A). The effectiveness of other classes of blood-pressure-lowering drugs has not yet been established by controlled trials.

3. Despite the lack of evidence, persons with elevated body mass index should take a weight-reducing diet, those with hypertension should reduce their salt intake, and smokers should quit smoking (class IV evidence).

4. Excessive use of alcohol must be discouraged (class IV evidence).

5. After ICH, antiplatelet treatment has to be individualized, depending on the presence of ischaemic vascular diseases or their perceived risk on the one hand, and the anticipated risk of ICH recurrence on the other (class IV evidence).

**Conclusion**

These recommendations were set up in a period of transition: Knowledge of pathophysiology, diagnosis and possible therapies in patients with intracerebral haemorrhage has drastically increased within the last few years. Still, most of the recommendations cannot be based on level A evidence. At this point it is possible though to identify more clearly those areas of research priority [217]. For example, surgical treatment of patients with spontaneous ICH cannot be recommended on the basis of current trials, but these trials enable us to define target populations more clearly in the future. Acute growth has been identified as the acute problem of ICH in the first few hours. Further studies are needed to identify the role of treatments that prevent or limit growth, to the precise timing of various treatments and the role of hypertension.

**References**


European Stroke Initiative (EUSI) Executive Committee and the EUSI Writing Committee: Recommendations for the Management of Intracranial Haemorrhage


Recommemndations for the Management of Intracranial Haemorrhage


Ayala C, Greenlund KJ, Croft JB, Keenan NL, Donehoes RS, Giles WH, Kittern SJ, Marks JS: Racial/ethnic disparities in mor-


Recommendations for the Management of Intracranial Haemorrhage


