# European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage

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Received: 14 May 2014; Accepted: 23 May 2014; Published online 24 August 2014

Conflict of interest: Charlotte Cordonnier is an investigator in trial A9951024, funded by Pfizer. A. David Mendelow is director of the Newcastle Neurosurgery Foundation and consultant to Stryker. Karsten Schwerdtfeger participated in the TASALL study, sponsored by Nycomed-Pharma (now Takeda). Thorsten Steiner holds a research grant from Octapharma, owns shares in NovoNordisk receives speaker and consultancy fees from Boehringer Ingelheim, Bayer, BMS Pfizer, and is Chair of the ESO Guidelines Committee. Turgut Tatlisumak holds a research grant from the Helsinki University Central Hospital Research Funds. The remaining authors declare no conflict of interest.

DOI: 10.1111/ijs.12309

***Background*** **Intracerebral hemorrhage (ICH) accounted for 9% to 27% of all strokes worldwide in the last decade, with high early case fatality and poor functional outcome. In view of recent randomized controlled trials (RCTs) of the management of ICH, the European Stroke Organisation (ESO) has updated its evidence-based guidelines for the management of ICH.**
***Method*** **A multidisciplinary writing committee of 24 researchers from 11 European countries identified 20 questions relating to ICH management and created recommendations based on the evidence in RCTs using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.**
***Results*** **We found moderate- to high-quality evidence to support strong recommendations for managing patients with acute ICH on an acute stroke unit, avoiding hemostatic therapy for acute ICH not associated with antithrombotic drug use, avoiding graduated compression stockings, using intermittent pneumatic compression in immobile patients, and using blood pressure lowering for secondary prevention. We found moderate-quality evidence to support weak recommendations for intensive lowering of systolic blood pressure to <140 mmHg within six-hours of ICH onset, early surgery for patients with a Glasgow Coma Scale score 9–12, and avoidance of corticosteroids.**
***Conclusion*** **These guidelines inform the management of ICH based on evidence for the effects of treatments in RCTs. Outcome after ICH remains poor, prioritizing further RCTs of interventions to improve outcome.**

Key words: anticoagulation, antiepileptic treatment, antihypertensive treatment, intracranial hemorrhage, intracranial pressure, management

## Introduction

The worldwide burden of hemorrhagic stroke [i.e. intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH)] has increased between 1990 and 2010 by 47%, as demonstrated in a systematic epidemiological review of 119 studies from high-, low-, and middle-income countries (1). In high-income countries, the incidence, mortality, disability adjusted life years (DALYs) lost, and mortality-to-incidence ratio decreased by 19%, 38%, 39%, and 27%, respectively (Fig. 1). In contrast, the incidence of hemorrhagic stroke increased by 6% in low- and middle-income countries, and the mortality rate decreased by 23%, DALYs lost by 25%, and mortality-to-incidence ratio by 36% (Fig. 1).

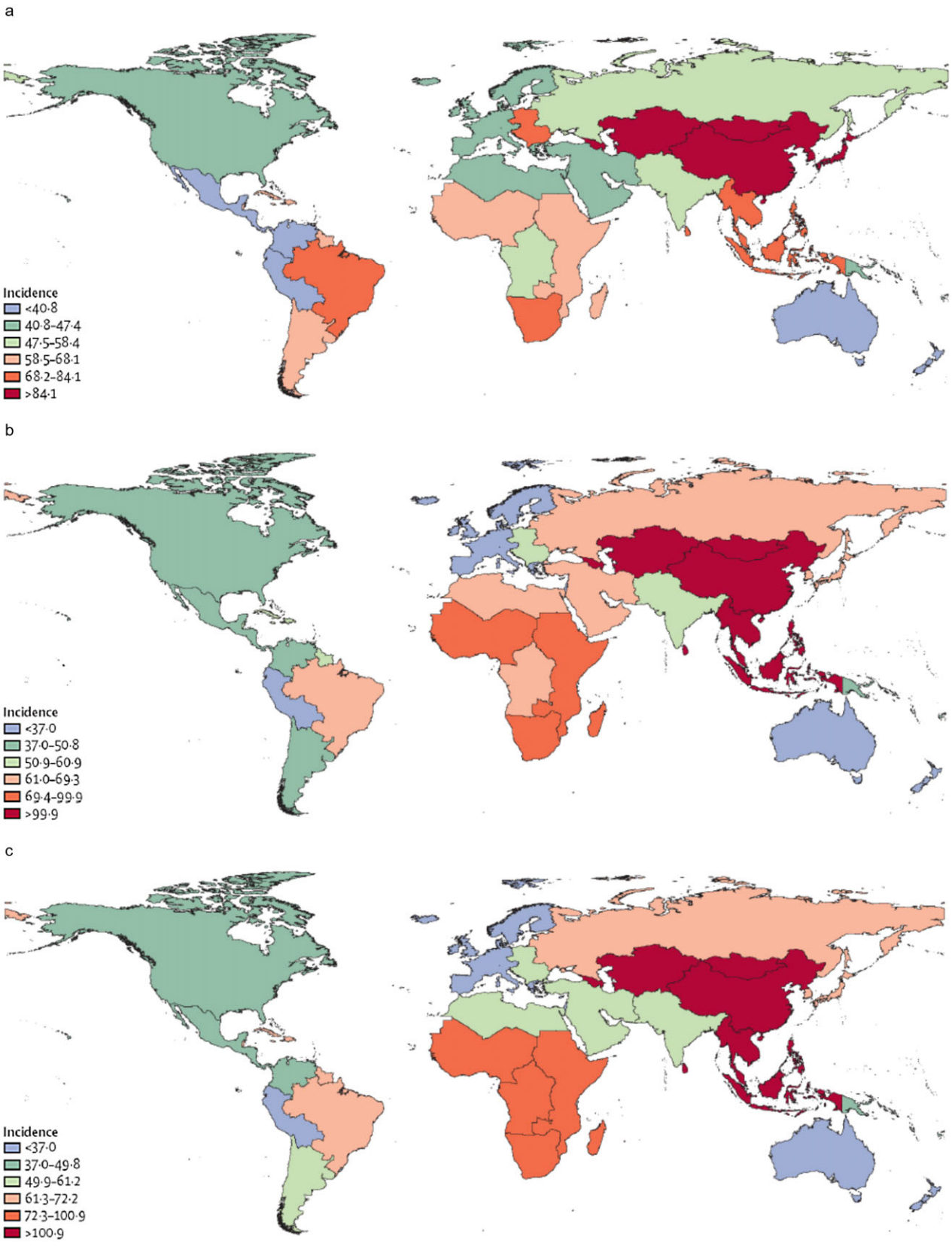


**Fig. 1** Age-standardized incidence of hemorrhagic stroke per 100 000 person-years for 1990 (a), 2005 (b), and 2010 (c). From Feigin *et al.* (1).

ICH caused by bleeding, primarily into parenchymal brain tissue, is responsible for 9% to 27% of all strokes worldwide (2). Underlying pathologies can be differentiated into arterial small- and large-vessel disease, venous disease, vascular malformation, and hemostatic disorders, as well as ICH in the context of other diseases and conditions. In cases where no underlying cause is identified with currently available diagnostic tools, ICH may be considered cryptogenic. Case fatality at 1 month is 40%, increasing to 54% at one-year (3,4). With such a poor outcome and so few effective interventions (5,6), optimal management of patients with ICH is a priority.

The European Stroke Initiative (EUSI) last published recommendations on management of ICH in 2006 (7). The European Stroke Organisation (ESO) decided to update these recommendations in view of emerging information on treatment of ICH in randomized controlled trials (RCTs) in recent years. Therefore, we updated these guidelines to provide recommendations for management of ICH based on the findings of RCTs, which we agreed on in consensus using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and with the approval of the ESO executive committee. Section authors (see Appendixes S1 and S2) supplement the recommendations in the guidelines with additional, pertinent information from observational studies and expert opinion. The right to apply the different measures recommended here depends on statutory and professional regulations in respective jurisdictions.

## Methods

A multidisciplinary group of clinical researchers [neurology, neurosurgery, neuroradiology, neuro-intensive care, and the European patient organization Stroke Alliance for Europe (SAFE)] from 11 European countries and Israel was proposed by the Guidelines Committee of the ESO and confirmed by the ESO Executive committee.

Steps undertaken by the working group are summarized below:

1. The group discussed and decided by consensus on specific PICO (patient, intervention, comparator, outcome) therapeutic questions (online Appendix S1) and conducted the entire process of creating these guidelines, guided by the GRADE working group's recommendations (8). This included rating the importance of the outcomes selected, concluded by a majority consensus among the members of the working group.
2. The group identified all available related literature. Given the focus of these guidelines on therapeutic questions, we performed systematic literature searches, guided by the 2011 Centre for Evidence Based Medicine's levels of evidence (9). The Cochrane Stroke Group information specialist (BMT) developed the search strategies using a combination of controlled vocabulary and free-text terms to describe each PICO topic and included a methodological filter to identify RCTs, meta-analyses, and systematic reviews (online Appendix S2). BMT searched the Cochrane Stroke Group Trials Register (to June 2013) (10), the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Reviews of Effects (DARE) (The Cochrane Library 2013 Issue 4), as well as MEDLINE (2008 to June 2013) and EMBASE (2008 to June 2013). To avoid duplication of effort we restricted the MEDLINE and EMBASE searches to articles published after January 2008, as these databases had already been searched to that date on behalf of the Cochrane Stroke Group and all relevant RCTs and systematic reviews added to the Cochrane Stroke Group Trials Register.
3. The group selected eligible studies. For each PICO question, two or three authors (online Appendix S1) independently screened the titles and abstracts of the publications identified by the corresponding electronic search and assessed the full text of potentially relevant studies. We restricted our evidence synthesis to RCTs and systematic reviews and meta-analyses of RCTs relating to 20 PICO questions.
4. The group graded quality of evidence and strength of recommendations. The final summaries of the quality and strength of evidence and recommendations for each PICO question (based on RCT evidence only) were discussed by the whole group, and the recommendations were agreed by a majority consensus of the group of authors (8,11). Quality of evidence was graded into high, moderate, low, and very low as defined in Table 1, strength of recommendation was assessed according to the specific factors indicated in Table 2, and levels of strength of recommendations as given in Table 3, and wording of statements about the effects observed in RCTs made reference to published guidance (13).
5. Section authors generated 'additional information' based on observational studies and ongoing RCTs that were identified by the literature searches or the included RCTs' bibliographies (13,14).

**Table 1** Criteria for assigning grade of evidence (12)

| Grade of evidence | Criteria |
|---|---|
| High quality | Further research is very unlikely to change our confidence in the estimate of effect |
| Moderate quality | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate |
| Low quality | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate |
| Very low quality | Any estimate of effect is very uncertain |

| Summary of recommendations related to functional outcome and mortality (with exemption to 13a, 14b) | Quality of evidence | Strength of recommendation |
|---|---|---|
| **1.** Acute stroke unit care reduces both death and dependency for patients with ICH in comparison with care on a general ward. | High | Strong |
| **2.** In acute ICH within 6 h of 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. | Moderate | Weak |
| **3.** We do not recommend the use of rFVIIa for adults with acute spontaneous ICH not associated with antithrombotic drug use outside RCTs. | High | Strong |
| **4.** In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom to normalize clotting for patients with acute spontaneous ICH who had been on antiplatelet drugs. | Very low | None |
| **5.** In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom to normalize coagulation for patients with acute spontaneous ICH who had been on anticoagulant drugs. | Very low | None |
| **6.** There is no evidence to support surgical intervention on a routine basis to improve outcome after supratentorial ICH in comparison with conservative management, but early surgery may be of value for patients with a GCS score 9–12. | Moderate | Weak |
| **7.** In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom to place an EVD in patients with acute spontaneous ICH. | Very low | None |
| **8.** In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom to use EVD combined with intrathecal thrombolysis in spontaneous ICH. | Very low | None |
| **9.** There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom to perform surgical evacuation in adults with infratentorial ICH. | Low | Weak |
| **10.** In the absence of RCTs we cannot not make strong recommendations about how, when, and for whom invasive monitoring of intracranial pressure should be performed for patients with acute ICH. | Very low | None |
| **11.** There is insufficient evidence from RCTs to make strong recommendations on measures to lower intracranial pressure for adults with acute ICH. | Low | Weak |
| **12.** There is insufficient evidence from RCTs to make strong recommendations on whether, when, and for whom preventive or early fever treatment should be given after acute ICH. | Low | Weak |
| **13a.** We do not recommend short or long graduated compression stockings for the prevention of DVT. We recommend intermittent pneumatic compression to improve outcome and reduce the risk of DVT in immobile patients with ICH. | Moderate | Strong |
| **13b.** There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom anticoagulation should be given to prevent DVT or improve outcome. | Low | Weak |
| **14a.** There is insufficient evidence from RCTs to make strong recommendations on whether preventive antiepileptic treatment should be used after ICH for the prevention of seizures or improvement of outcome in the long term. | Low | Weak |
| **14b.** There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom AEDs should be given to reduce the risk of epilepsy after ICH. | Low | Weak |
| **15.** We do not recommend the use of dexamethasone in patients with acute ICH outside RCTs. | Moderate | Weak |
| **16.** In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom do-not-attempt-resuscitation or withdrawal-of-care orders should be used to reduce suffering after ICH. | Very low | None |
| **17.** We recommend lowering blood pressure for secondary prevention after ICH. | Moderate | Strong |
| **18.** In the absence of RCTs, we cannot make strong recommendations about whether and when to resume antithrombotic drugs after ICH. | Very low | None |

**Table 2** Factors that affect the strength of a recommendation (12)

| Factor | Examples of strong recommendations | Examples of weak recommendations |
|---|---|---|
| Quality of evidence | Many high-quality randomized trials have shown the benefit of inhaled steroids in asthma | Only case series have examined the utility of pleurodesis in pneumothorax |
| Uncertainty about the balance between desirable and undesirable effects | Aspirin in myocardial infarction reduces mortality with minimal toxicity, inconvenience, and cost | Warfarin in low-risk patients with atrial fibrillation results in small stroke reduction but increased bleeding risk and substantial inconvenience |
| Uncertainty or variability in values and preferences | Young patients with lymphoma will invariably place a higher value on the life-prolonging effects of chemotherapy than on treatment toxicity | Older patients with lymphoma may not place a higher value on the life-prolonging effects of chemotherapy than on treatment toxicity |
| Uncertainty about whether the intervention represents a wise use of resources | The low cost of aspirin as prophylaxis against stroke in patients with transient ischemic attacks | The high cost of clopidogrel and of combination dipyridamole and aspirin as prophylaxis against stroke in patients with transient ischemic attacks |

**Table 3** Grades (levels) of recommendation (12)

| Level of recommendation | Criteria |
|---|---|
| Strong | The desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not |
| Weak | The trade-offs are less certain, either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced |

## Results

The working group formulated 20 PICO questions, each one examining two outcomes – functional outcome and mortality – both of which were rated as of critical importance for all PICO questions.

**(1) For adults with ICH, does management on an acute stroke unit (ASU) in comparison with care on a general ward improve outcome?**

In a meta-analysis of 13 RCTs (3570 patients) of stroke unit care that recruited patients with ICH and ischemic stroke, stroke unit care reduced death or dependency overall [risk ratio (RR) 0·81; 95% confidence interval (CI) 0·47–0·92; $P = 0·0009$; $I^2 = 60\%$], an effect that was comparable for the subgroup of patients with ICH (RR 0·79; 95% CI 0·61–1·00) (15). Therefore, patients with ICH seem to benefit at least as much as patients with ischemic stroke from organized inpatient (stroke unit) care (15). We also sought to evaluate care for ICH in an intensive care unit (ICU), neuro-intensive care unit (NICU), or high-dependency unit (HDU) in comparison to a general ward or an ASU, but there were no RCTs of these care settings.

**Recommendation**
Acute stroke unit care reduces both death and dependency for patients with ICH in comparison with care on a general ward.
**Quality of evidence:** High
**Strength of recommendation:** Strong

**Additional information:** Observational studies have suggested that treatment in stroke units and NICUs is beneficial for patients with ICH (16–21). Factors that may influence this positive effect are more frequent monitoring, more patients receiving oxygen, antipyretics, measures to reduce aspiration, and early nutrition compared with general wards, leading, hence, to a reduction in complications, with fewer patients having chest infection or dehydration (22). Dedicated NICUs allow for more intensive neurological and cardiopulmonary monitoring and medical and nursing care. It is thus conceivable that management of ICH patients in NICUs may further reduce morbidity and mortality and improve short-term and long-term outcome as well (16–19).

**(2) For adults with acute ICH, does altering blood pressure to a particular target or with a specific agent compared with an alternative target or agent improve outcome?**

Blood pressure reduction to a particular target in acute ICH has been explored in one large RCT and two pilot RCTs (23–25).

The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial-2 (INTERACT-2) (23) investigated the effect on functional outcome at three-months of intensive blood pressure reduction, defined as targeting a systolic blood pressure <140 mmHg in less than one-hour within six-hours of symptom onset in comparison with a guideline-based target (systolic <180 mmHg) in 2794 patients (23). 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 [odds ratio (OR) 0·87, 95% CI 0·75–1·01; $P = 0·06$], 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; $P = 0·04$). Intensive treatment with antihypertensive drugs was safe, a finding that is also supported by two previous RCTs (24,25).

**Recommendation**
In acute ICH within 6 h of 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.
**Quality of evidence:** Moderate
**Strength of recommendation:** Weak

**Additional information:** Previous guidelines have included cautionary statements on acute blood pressure reduction in ICH based on the potential risk of a detrimental drop of cerebral blood flow below penumbra values in the vicinity of the ICH. Substudies of the above-mentioned RCTs on acute ICH and smaller studies indicate that blood pressure reduction decreases hematoma expansion but does not affect perihematoma blood flow (26–30). In subacute ICH, only results from small subgroups of patients with ICH are available. The Angiotensin-Receptor Blocker Candesartan for Treatment of Acute Stroke (SCAST) RCT investigated the effects of blood pressure lowering by seven-day candesartan treatment initiated within 30 h after stroke onset on functional outcome and a composite vascular outcome at six-months after stroke. A meta-analysis including SCAST and 10 other RCTs of blood pressure-lowering drugs within the first week of acute stroke found that 'there was no evidence that careful blood pressure lowering with the angiotensin blocker candesartan is beneficial in patients with acute stroke and raised blood pressure', and there was no benefit for the subgroup of patients with ICH (31). In the Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) RCT, hypertensive patients with acute stroke were randomized to lisinopril, labetalol or

placebo within 36 h after stroke onset, but this small RCT demonstrated neither benefit nor harm overall or in the subgroup of patients with ICH (32). Further RCTs are ongoing: ATACH-2 (NCT01176565) and ENOS (NCT00989716).

**(3) For adults with acute ICH not associated with antithrombotic drug use, do hemostatic drugs compared with standard care improve outcome at six-months?**

For patients who had not been on antithrombotic drugs at the time of acute spontaneous ICH, the hemostatic drug recombinant activated factor VII (rFVIIa) diminished hematoma growth in meta-analyses of RCTs (33–35). However, published and unpublished (NCT00266006) RCTs did not show that rFVIIa reduced the risk of death or disability after acute spontaneous ICH, but they did show that rFVIIa increased the risk of arterial thromboembolic events (33,34,36,37). A small RCT of rFVIIa after early surgery for spontaneous ICH did not demonstrate an effect on ICH growth or clinical outcome (38). A small RCT of tranexamic acid in ICH demonstrated neither benefit nor safety concerns (39).

**Recommendation**
We do not recommend the use of rFVIIa for adults with acute spontaneous ICH not associated with antithrombotic drug use outside ongoing trials.
**Quality of evidence:** High
**Strength of recommendation:** Strong

**Additional information:** Further RCTs are ongoing that look at efficacy of tranexamic acid or rFVIIa in spontaneous ICH (ISRCTN50867461, ISRCTN29749408, NCT01702636, and NCT00810888).

**(4) For adults with acute ICH associated with antiplatelet drug use, do hemostatic drugs compared with standard care improve outcome at six-months?**

A recent systematic review, which we updated for these guidelines, did not identify any completed RCTs of treatments for acute spontaneous ICH in patients who had been on antiplatelet drugs (40).

**Recommendation**
In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom to normalize clotting for patients with acute spontaneous ICH who had been on antiplatelet drugs.
**Quality of evidence:** Very low
**Stength of recommendation:** None

**Additional information:** The concept of platelet transfusion in patients with spontaneous ICH in association with antiplatelet drug use is to replace nonfunctional by functional thrombocytes and thus to increase the chance of hemostasis. We found one RCT ($n = 22$) on the use of thrombocytes in traumatic ICH (41). In this RCT, platelet transfusion had no effect on platelet function or ICH progression. However, the small size of this RCT or use of only one-unit of platelets may explain these findings. Two RCTs of platelet transfusion in ICH are ongoing (NCT00699621 and The Netherlands National Trial Register NTR1303).

**(5) For adults with ICH associated with anticoagulant drug use, do hemostatic drugs compared with standard care improve outcome at six-months?**

The outcome after acute ICH is worse for patients who were taking anticoagulant drugs at the time of the ICH, so in addition to stopping anticoagulant drugs, urgent measures are usually undertaken to reverse the effects of vitamin K antagonists for patients with an elevated international normalized ratio (INR). One RCT compared fresh-frozen plasma alone versus factor IX complex concentrate and fresh-frozen plasma for ICH related to the use of warfarin, but it was not restricted to ICH (42). A RCT found fast lowering of the INR but no difference in clinical outcomes with 40 IU/kg versus 25 IU/kg four-factor prothrombin complex concentrate (43). We could not identify RCTs that have compared clinical outcomes after treatment with fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) (44).

**Recommendation**
In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom to normalize coagulation for patients with acute spontaneous ICH who had been on anticoagulant drugs.
**Quality of evidence:** Very low
**Strength of recommendation:** None

**Additional information:** Although we did not find any RCTs relevant to this PICO question, clinical observational and pharmacological data have led to standard clinical practice in acute ICH being the administration of 5–10 mg intravenous vitamin K to patients on vitamin K antagonists or intravenous protamine sulfate to patients on heparin. For patients who were taking vitamin K antagonists at the time of an ICH and who have an elevated INR, anticoagulant medication is stopped, intravenous vitamin K is given, and either fresh-frozen plasma (e.g. 20 ml/kg) or prothrombin complex concentrate (e.g. 25–40 IU/kg) is added to prevent hematoma expansion. The risk of a thrombotic event occurring due to the normalization of coagulation for shorter periods of time than a week is considered low for most indications compared with the possible benefit of stopping hematoma expansion or re-bleeding (45). Ongoing RCTs are comparing fresh-frozen plasma with prothrombin complex concentrate (NCT00928915) and rFVIIa with fresh-frozen plasma or prothrombin complex concentrate (NCT00222625).

ICH is also associated with the use of novel oral anticoagulants (NOACs – apixaban, dabigatran, edoxaban, rivaroxaban). There is no specific antidote available for any of the NOACs, and clinical experience with hemostatic agents in NOAC-associated bleeding is scarce. An expert opinion on management of bleeding emergencies associated with NOAC therapy has been published in a

consensus paper (46). Three phase 2 RCTs on safety, tolerability, pharmacokinetics, and pharmacodynamics of factor-II- and factor-Xa-inhibitor-antidotes were conducted but have not been published (NCT01688830, NCT01758432, NCT01826266), and a phase III trial on an antidote for dabigatran is ongoing (NCT02104947).

**(6) For adults with supratentorial ICH, does surgical hematoma evacuation compared with conservative management improve outcome?**

The STICH-1 RCT compared hematoma evacuation (within 24 h of randomization) with best medical treatment in 1033 patients with supratentorial ICH and found that early surgery did not seem superior (47). The STICH-2 RCT compared the effect of early hematoma evacuation (within 12 h of randomization) with best medical treatment in 601 patients with lobar ICH without intraventricular extension, and early surgery was not superior to medical treatment (OR 0·86, 95% CI 0·62–1·20; $P = 0·37$) (48). In a meta-analysis of STICH-2 with 14 other RCTs of surgery for supratentorial ICH in any location, early surgery was superior (OR 0·74, 95% CI 0·64–0·86), but there was significant heterogeneity between the RCTs ($P = 0·0002$), which mandates cautious interpretation of the pooled estimate (48). Surgery for lobar ICH without intraventricular hemorrhage (IVH) did not seem superior in this meta-analysis (OR 0·78, 95% CI 0·59–1·02) (48). A meta-analysis of individual patient data, based on 2186 patients in 8 out of 14 RCTs published 1985–2012 before STICH II, found that surgery seemed effective in patients with a higher consciousness level [especially Glasgow Coma Scale (GCS) score 9–12] and in patients who were randomized to surgery within eight-hours of ICH symptom onset (49).

**Recommendation**
There is no evidence to support surgical intervention on a routine basis to improve outcome after supratentorial ICH in comparison with conservative management, but early surgery may be of value for patients with a GCS score 9–12.
**Quality of evidence:** Moderate
**Strength of recommendation:** Weak

**Additional information:** The Minimally Invasive Surgery plus Recombinant Tissue Plasminogen Activator (MISTIE) II RCT compared minimally invasive surgery plus recombinant tissue plasminogen activator with medical treatment in 118 patients with acute supratentorial ICH and found reductions in hematoma and edema volume from intervention, but no overall difference in clinical outcomes (50). MISTIE III is ongoing to investigate clinical outcome (modified Rankin Scale at three-months) and safety (mortality, rebleeding, and infection at one-month) (NCT01827046).

**(7) For adults with supratentorial ICH, does drainage of cerebrospinal fluid (CSF) by using an external ventricular drain (EVD) compared with no EVD improve outcome?**

No RCTs have compared EVD vs. no EVD for acute ICH.

**Recommendation**
In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom to place an EVD in patients with acute spontaneous ICH.
**Quality of evidence:** Very low
**Strength of recommendation:** None

**Additional information:** It seems reasonable to apply an EVD in case of clinical or neuroradiological signs of hydrocephalus, which is supported indirectly by small non-randomized studies of intraventricular fibrinolysis for IVH compared with no treatment (5,51–55). Endoscopy compared with EVD for thalamic ICH with ventricular extension reduced length of stay and the need for shunting, but there was no difference in clinical outcome (51).

**(8) For adults with supratentorial ICH, does EVD with intraventricular thrombolysis compared with EVD with placebo improve outcome?**

We could not identify RCTs that looked at clinical outcomes of patients treated with EVD and intraventricular thrombolysis compared with EVD and placebo.

**Recommendation**
In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom to use EVD combined with intrathecal thrombolysis in spontaneous ICH.
**Quality of evidence:** Very low
**Stength of recommendation:** None

**Additional information:** Gubucz *et al.* report a prospective RCT on intraventricular urokinase in 16 patients with EVDs for IVH with hydrocephalus and ICH compared with 11 treated with EVDs alone (56). The one-year survival rate was significantly higher in the urokinase-treated group ($P = 0·014$). Based on these limited data, patients with spontaneous ICH, ventricular extension and clinical and/or neuroradiological signs of hydrocephalus may be considered for EVD combined with fibrinolytic agent. At the same time patients, should be considered for randomization in RCTs that use ventricular thrombolysis or lavage.

The Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR) III RCT is ongoing (NCT00784134).

**(9) For adults with infratentorial, ICH does surgical hematoma evacuation compared with conservative management improve outcome?**

We identified one RCT concerning infratentorial ICH, which compared two different surgical techniques (paramedian suboccipital mini-craniectomy vs. large suboccipital craniectomy) showing that a mini-craniectomy resulted in fewer complications, but not a better outcome (57). We found no RCTs comparing surgical clot evacuation with CSF drainage alone or conservative management in nonaneurysmal posterior fossa ICH.

**Recommendation**
There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom surgical evacuation should be performed in adults with infratentorial ICH.
**Quality of evidence:** Low
**Strength of recommendation:** Weak

**Additional information:** Small, retrospective, observational studies suggest that initial neurological condition, level of consciousness, evidence of brain stem compression, and a tight posterior fossa on imaging are associated with outcome and might influence the decision to evacuate infratentorial ICH (58). The following indications for surgery have been proposed: obliteration of the fourth ventricle regardless of clinical symptoms or ICH size (59), GCS score <14 (60,61), hematoma diameter >30–40 mm (60,61), and hematoma volume not less than 7 $cm^3$ (62). Observational studies of the effect of surgery on cerebellar ICH have been inconsistent (61,63–66). An EVD usually is inserted in cases of infratentorial ICH with associated hydrocephalus (59). In a retrospective study on 39 cases of ICH within posterior fossa, CSF-drainage alone frequently required a second operation for hematoma evacuation (66).

**(10) For adults with ICH, does intracranial pressure (ICP) monitoring improve outcome in comparison to no ICP monitoring?**

We could not identify any completed RCTs of ICP monitoring for acute spontaneous ICH.

**Recommendation**
In the absence of RCTs we cannot not make strong recommendations about how, when, and for whom invasive monitoring of intracranial pressure should be performed for patients with acute ICH.
**Quality of evidence:** Very low
**Strength of recommendation:** None

**Additional information:** Clear treatment thresholds for ICP have not been identified. An observational study of ICP recordings in 100 patients with IVH and ICH of less than 30 ml who required an EVD found that the percentage of readings above 30 mmHg was an independent predictor of mortality ($P < 0{\cdot}001$) and poor modified Rankin Scale score at 30 days ($P = 0{\cdot}01$) (67). ICP measurement can be considered in selected patients with ICH and/or IVH, informed by the reported risks of complications. Interestingly, a retrospective case analysis of 38 patients with traumatic brain injury in whom a parenchymal ICP monitor was placed by nonsurgeon neurointensivists did not reveal major technical complications, major intracranial hemorrhage, or infections related to the monitoring probe. The authors state that these outcomes were comparable to published data from a systematic literature search (68). Clear treatment thresholds for ICP have not been identified. Further, prospective RCTs are needed to demonstrate whether monitoring of single ICP or a concept of multivariable monitoring is a more effective alternative (69–72).

**(11) For adults with ICH, do nonsurgical interventions to lower ICP compared with standard care or other treatments improve outcome?**

Glycerol (73) and mannitol (74) were tested in RCTs with no apparent benefits. Glycerol was given to 107 ICH patients as an intravenous infusion (500 ml of 10% glycerol in saline) over four-hours for six consecutive days, and 109 patients with ICH received saline only as placebo treatment, but at six-months, all outcome measures, including mortality, neurological scores, and handicap, were similar in both groups (73). Treatment with glycerol was associated with hemolysis, but this adverse event was usually subclinical (73). Another RCT randomized 128 supratentorial ICH patients to either mannitol (20%, 100 ml every four-hours for five-days, tapered in the next two-days) or sham infusion (74). One-month case fatality and disability at three-months were similar between the 65 treated patients and 63 controls (74).

No RCTs were found for a large variety of nonsurgical and surgical measures commonly applied in clinical practice for lowering raised ICP in ICH patients: head elevation, osmotic therapy with several agents, hyperventilation, analgesia, sedation, general anesthesia with barbiturates, neuromuscular blockade, hypothermia, shunting for hydrocephalus and cerebrospinal fluid drainage in cerebellar ICH with brainstem compression, and craniectomy with or without simultaneous evacuation of hematoma.

**Recommendation**
There is insufficient evidence from RCTs to make strong recommendations on measures to lower intracranial pressure for adults with acute ICH.
**Quality of evidence:** Low
**Strength of recommendation:** Weak

**Additional information:** Hypertonic saline (3%) was tested in one nonrandomized feasibility study in patients with supratentorial ICH, leading to less perihematomal edema and a trend in mortality figures in favor of treatment when compared with 64 historical controls (75). Invasive mild hypothermia (35°C) started within 12 h of symptom onset for 10 days in 10 patients with ICH resulted in reduced peri-hematomal edema volumes and increased the chance of survival when compared with 25 patients who were not treated (76). Several nonrandomized studies compared decompressive craniectomy plus hematoma evacuation with hematoma evacuation alone with conflicting results (77–79).

**(12) For adults with ICH, does prevention and early treatment of fever (by pharmacological or physical means) compared with conventional fever management improve outcome?**

Occurrence of fever has been associated with worsened outcome in acute stroke including ICH (80). One prospective large RCT of prophylactic acetaminophen – the Paracetamol (Acetaminophen) in Stroke RCT (PAIS-1) – included 1400 patients, of whom 11% had an ICH (81). Paracetamol did not

seem superior overall (adjusted OR 1·20, 95% CI 0·96–1·50) or in the subgroup of patients with ICH (81). Two RCTs looked at feasibility and effectiveness of different catheter-based cooling systems to either prevent fever or lower elevated body temperature. Both RCTs demonstrated feasibility and resulted in higher effectiveness of the catheter-based cooling, but the RCTs were too small to evaluate clinical outcome, and less than 25% of the studied patients had acute ICH (82,83).

**Recommendation**
There is insufficient evidence from RCTs to make strong recommendations on whether, when, and for whom preventive or early fever treatment should be given after acute ICH.
**Quality of evidence:** Low
**Strength of recommendation:** Weak

**Additional information:** Several smaller observational studies (76,84–91) have investigated the feasibility and effects of different cooling strategies in ICH, and an institutional standard operating procedure for fever treatment has been published (92). Most of these trials were undertaken to study the neuroprotective effects of hypothermia and were not specifically aimed at fever control. Moreover, many of the studies were performed in an ICU setting with a mixed case selection of patients and numbers of ICH being too small to reach any valid conclusion on this specific disease. An ICU-based retrospective case–control study of 40 ICH patients treated with temperature modulation to prevent fever failed to show any benefit versus matched historical controls but increased length of mechanical ventilation in these patients (93). RCTs of stroke unit treatment found that administration of antipyretics was one of few measurable differences in care. However, the administration of antipyretics or other measures to control fever in patients with ICH could not be linked to improvement in outcome in those RCTs (94,95). Meanwhile the PAIS-II RCT has been started (NTR2365), an RCT designed to examine the effect of acetaminophen in acute stroke patients, including ICH patients, with a body temperature of 36·5°C or higher (96). Fever is associated with death and disability in stroke, and there are no data to suggest that this would be different in ICH. Based on circumstantial evidence and lack of data suggesting harm in large RCTs, early treatment of fever with antipyretics may be considered in clinical practice. Preventive treatment of fever is not recommended outside RCTs.

**(13a) For adults with ICH, do physical or pharmacological interventions to prevent deep vein thrombosis/pulmonary embolism (DVT/PE) compared with standard care reduce symptomatic DVT/PE?**
**(13b) For adults with ICH, do physical or pharmacological interventions to prevent DVT/PE compared with standard care improve outcome?**

We defined 'symptomatic DVT/PE' as second outcome to approach the question of preventive measurements against thromboembolic events. This outcome was ranked as critical. Since a Cochrane systematic review of RCTs of graduated compression stockings (GCS) to prevent DVT was published (97), several RCTs have been conducted. Routine care plus thigh-length graduated compression stockings (TL-GCS) was compared with routine care in the CLOTS-1 multicenter RCT in stroke, and TL-GCS increased the risk of skin defects without preventing DVT (98). In the CLOTS-2 trial in stroke, proximal DVT occurred more often in patients with below-knee stockings than in those with TL-GCS (99).

In the VICTORIAh RCT of 151 seemingly immobile patients with ICH, elastic stockings combined with intermittent pneumatic compression (IPC) seemed superior to elastic stockings alone for the prevention of asymptomatic DVT (4% vs. 16·9%; RR 0·29, 95% CI 0·08 to 1·00; $P = 0·03$), although there was no evidence of an effect on clinical outcomes (100). In the CLOTS-3 RCT comparing IPC versus no IPC for immobile patients with stroke, IPC was superior for the prevention of the primary outcome of proximal DVT within 30 days (8·5% vs. 12·1%; OR 0·65, 95% CI 0·51–0·84; $P = 0·001$), patients with ICH seemed to benefit at least as much as patients with ischemic stroke (OR 0·36, 95% CI 0·17–0·75 vs. OR 0·72, 95% CI 0·55–0·93; $P = 0·057$), and IPC may be superior for the prevention of death within six-months (adjusted HR 0·86, 95% CI 0·74–0·99; $P = 0·042$) (101).

Two small RCTs investigated anticoagulation for the prevention of venous thromboembolism in patients with acute ICH (102,103). One RCT compared subcutaneous low-molecular-weight heparin (enoxaparin sodium 40 mg/day) with long compression stockings in 75 patients with ICH and found no differences in hematoma enlargement, systemic bleeding, or asymptomatic DVT (103). Another RCT (not blinded) compared low-dose subcutaneous unfractionated heparin started early (day 4) or late (day 10) for 68 patients with spontaneous ICH and did not demonstrate a difference in hemorrhagic or thromboembolic events between the two groups (102); whether the comparison with the third group starting heparin on day 2 was randomized is unclear (102).

**Recommendations:**
We do not recommend short or long graduated compression stockings for the prevention of DVT. We recommend intermittent pneumatic compression to improve outcome and reduce the risk of DVT in immobile patients with ICH.
**Quality of evidence:** Moderate
**Strength of recommendations:** Strong
There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom anticoagulation should be given to prevent DVT or improve outcome.
**Quality of evidence:** Low
**Strength of recommendation:** Weak

**Additional information:** Subcutaneous low-dose, unfractionated heparin after acute ICH DVT prophylaxis did not show harm, but was not superior to elastic stockings, in a nonrandomized comparison (200 with heparin plus elastic stockings vs. 258 with elastic stockings only) (104). A retrospective study included

73 patients with ICH and/or IVH who were treated with LMWH or UFH within 7 days of ictus. Two patients (2·7%) suffered from significant hematoma growth, but no PEs or DVTs occurred (105).

**(14a) For adults with ICH, do prophylactic antiepileptic drugs (AEDs) compared with no AEDs reduce the occurrence of seizures/epilepsy or improve outcome?**

The EGASIS (Early GABA-Ergic Activation Study In Stroke) RCT included 880 acute stroke patients and looked at the neuroprotective properties of diazepam (10 mg twice daily for 3 days) versus placebo. The RCT looked at adverse events but did not report epileptic seizures. In the 95 ICH patients, the frequencies of pneumonia and death were higher in the diazepam group than in the placebo group: 35% vs. 10% and 22% vs. 12%, respectively (106).

In an RCT, 72 patients were treated for one-month with either valproic acid or placebo immediately after a spontaneous ICH. Patients treated with valproic acid were less likely to suffer from early seizures. However, there was no difference regarding the overall seizure rates in both groups during follow-up up over one-year (107). Patients treated with valproic acid exhibited improved neurological function as measured by the National Institutes of Health Stroke Scale (NIHSS) at one-year (4·4 ± 5·1 vs. 8·6 ± 6·1, $P = 0·002$) (107).

**Recommendation:**
There is insufficient evidence from RCTs to make strong recommendations on whether preventive antiepileptic treatment should be used after ICH for the prevention of seizures or improvement of outcome in the long term.
**Quality of evidence:** Low
**Strength of recommendation:** Weak

**Additional information:** The reported incidence of post-ICH seizures ranges from 3% to 17% (108–113), increasing to 42% when subclinical seizures are considered (114). Onset seizures occur in 8%, and altogether, early seizures, that is, occurring within the first seven-days, affected 14% of an observational cohort of 522 spontaneous ICH (115). Early seizures have not been associated with worsened neurological outcome or mortality (115). Retrospective data suggest that prophylactic AED use was associated with poor outcome, independent of other established predictors (116). Phenytoin prophylaxis was also associated with poor outcome (117).

**(14b) For patients with ICH suffering from an early seizure, do long-term AEDs compared with no AEDs reduce the risk of epilepsy?**

We defined 'risk of epilepsy' as second outcome to approach the question on prophylactic AED treatment. This outcome was ranked as critical. The EGASIS-RCT looked at possible neuroprotective properties of diazepam versus placebo in acute stroke patients (106), but although adverse events were recorded, the RCT did not specifically report epileptic seizures.

**Recommendation:**
There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom AEDs should be given to reduce the risk of epilepsy after ICH.
**Quality of evidence:** Low
**Strength of recommendation:** Weak

**(15) For adults with ICH, do corticosteroids compared with standard care improve outcome?**

Based on the effects of corticosteroids on edema in brain tumors, with improvement or resolution of symptoms, dexamethasone has been widely used in patients with ICH. We identified six RCTs that investigated a possible beneficial effect of steroid treatment on outcome in patients with ICH. Five (118–122) of these six RCTs were included in a Cochrane analysis (123), and the sixth RCT was published in 2008 (124). The total number of patients included was between 20 and 93 in the five RCTs in the Cochrane analysis (123) and 200 in the sixth RCT (124). Duration of follow-up was between two- and five-weeks in four RCTs (118,121,122,124), two- and four-months in one RCT (120) and six-months in another (119). In all RCTs treatment consisted of dexamethasone, in varying dosages, for 48 h (120), 9–10 days (119,121,122,124), or 16 days (118).

Meta-analysis of the four studies that reported one-month case mortality showed no difference in the risk of death: 57 of 92 patients (62%) allocated to dexamethasone treatment had died, compared with 50 of 94 patients (53%) in the control group (RR 1·14, 95% CI 0·91–1·42) (123). In one RCT, 49% of patients who received dexamethasone treatment had died at 21 days in comparison with 23% of patients treated with placebo ($P < 0·05$) (124), but there are methodological concerns about this RCT. The methods section states that 200 patients (100 in each treatment arm) were included, whereas in the results section the number of patients in the dexamethasone group was 144 and in the placebo group 81. Also, patients who died within 48 h were excluded, but it is unclear whether this event was similarly frequent in the two treatment groups (124). There was also no beneficial effect of dexamethasone on 6-month case fatality (one study, 20 patients, RR 0·60, 95% CI 0·19–1·86) (119) or on poor outcome after one-month (four studies, 146 patients, RR 0·95, 95% CI 0·83–1·09) (118,120,121,123). There was no significant difference in infections, exacerbation of diabetes and gastrointestinal bleeding between treatment and control groups (123).

**Recommendation:**
We do not recommend the use of dexamethasone in patients with acute ICH outside RCTs.
**Quality of evidence:** Moderate
**Strength of recommendation:** Weak

**(16) For adults with ICH does the use of do-not-attempt-resuscitation (DNAR) or withdrawal-of-care (WOC) orders compared with no use of DNAR or WOC orders reduce suffering?**

We did not find RCTs addressing this question.

**Recommendation**
In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom DNAR or WOC orders should be used to reduce suffering after ICH.
**Quality of evidence:** Very low
**Strength of recommendation:** None

**Additional information:** The case fatality rate at 1 month in patients with ICH is 40%, and the one-year and five-year survival rates were found to be 46% and 29% (3,4). Various models to predict outcome after ICH are in use (125–127). There are conceptual differences between DNAR and WOC in the hopelessly ill. While DNAR is predetermined and usually limits the extent of resuscitation efforts in the event of a cardiac arrest, WOC emerges during care for the hopelessly ill based on the predicted outcome, age, and comorbidity in conjunction with patient and or family choices. While actual DNAR and WOC orders can be abstracted from most patients' charts, the appropriateness of the initial level of care in response to the catastrophe is more difficult to ascertain. The resulting bias contaminates the observed outcome and complicates the assessment of responses to specific treatments in patients with severe ICH (128,129).

Despite these biases, the level of medical support provided remains the single most important prognostic variable of an observed outcome in ICH (128,130). Current evidence from prospective series and retrospective analyses suggests that existing DNAR orders and WOC increase and hasten mortality in adult patients after ICH. The perception of the appropriateness of initial level of care provided to adult ICH patients varies between professionals and lay people, while the perception of DNAR and WOC generally agrees (131).

**(17) For adults who had suffered an ICH, does subsequent blood pressure-lowering therapy compared with standard care improve outcome?**

Pharmacological blood pressure lowering by the angiotensin-converting enzyme inhibitor perindopril (4 mg/day) plus the diuretic indapamide (2·5 mg/day) improved outcome by reducing the relative risk of recurrent stroke by 28% (95% CI 17–38%) in a mixed population of patients with stroke and transient ischemic attack in the PROGRESS RCT (132). In this RCT, patients with ICH benefited as much as other stroke subtypes, and there was no difference in effect according to whether patients were hypertensive after their stroke or not. A subgroup analysis demonstrated an absolute risk reduction in the risk of recurrent ICH from 2% to 1% in patients with ICH (RR reduction 50%; 95% CI 26 to 67) and the RR reduction for recurrent stroke of any type in patients with ICH was 49% (95% CI 18 to 68) (133). *Post hoc* analyses from PROGRESS indicate that blood pressure reduction lowers the risk of ICH occurring after a first stroke, especially in patients also receiving antithrombotic therapy (134). There was no difference in the effect of blood pressure reduction on subgroups according to the presumed underlying cause of ICH (134). PROGRESS enrolled patients up to five-years after stroke onset, and there was no significant difference in the effects of antihypertensive therapy by time from stroke onset (132). There is no evidence from RCTs for other antihypertensive drug classes after ICH.

**Recommendation**
We recommend lowering blood pressure for secondary prevention after ICH.
**Quality of evidence:** Moderate
**Strength of recommendation:** Strong

**Additional information:** There is no evidence on a specific blood pressure target or choice of antihypertensive drug, as this varies between RCTs (132,134–136). Adherence to antihypertensive treatment after stroke relates to support from carers (137) and health professionals as well as a realistic perception of risk and benefits of the treatment; however, nonadherence is frequently reported (138).

**(18) For adults with ICH who had been on antithrombotic drugs for thrombotic disease before their ICH, does continuation of antithrombotic drugs compared with discontinuation of antithrombotic drugs improve outcome?**

The proportion of patients with ICH who had been taking antithrombotic drugs for thrombotic diseases before the time of their ICH increased over time in one community-based study (139). Short-term outcome appears worse for patients who have been taking antiplatelet drugs (140) or anticoagulant drugs pre-ICH. However, the dilemma for the patients who survive is whether to resume their antithrombotic drugs for secondary prevention against thrombotic diseases or to discontinue their antiplatelet drugs lest they should raise the risk of recurrent ICH and/or worsen the outcome of any recurrence. RCTs have not been performed to address this treatment dilemma.

**Recommendation**
In the absence of RCTs to address these treatment dilemmas, we cannot make firm recommendations about whether and when to resume antithrombotic drugs after ICH.
**Quality of evidence:** Very low
**Strength of recommendation:** None

**Additional information:** Small observational case series and literature reviews have not found a relevant effect on the risk of recurrent ICH from restarting antiplatelet drugs in survivors of ICH (141–145). Similarly, only observational studies address whether, when, and in whom to restart oral anticoagulation after ICH (45,142,145–148). Suggested timings for restarting these drugs range from not earlier than 14 days up to 10 to 30 weeks (45,149). A RCT to address the dilemma about whether to restart or stop antiplatelet drugs after ICH is underway (ISRCTN71907627, www.RESTARTtrial.org). Alternatives to restarting antithrombotic drugs, such as left atrial appendage

occlusion (150,151), could be an alternative for managing patients in atrial fibrillation with a high risk of cardioembolic stroke after acute ICH.

## Discussion

We found moderate- to high-quality evidence, based on single RCTs or meta-analyses of RCTs, lending support to acute stroke unit care, intensive blood pressure lowering within six-hours of ICH onset, intermittent pneumatic compression in immobile patients with ICH, and secondary prevention with blood pressure lowering for ICH survivors.

No moderate- to high-quality evidence supports the use of acute hemostatic therapies as used in RCTs so far. Benefit from prevention of hematoma expansion seemed to be counterbalanced by thromboembolic complications with no overall benefit, and there were design issues with the studies we reviewed (36,152,153).

Although RCTs have investigated surgical hematoma evacuation, and the Cochrane review found overall benefit, limitations of RCT design and statistical heterogeneity have led many, including us, to be cautious in recommending surgery. Ongoing and future RCTs are needed to further investigate different methods of hematoma evacuation and the effects in particular subgroups using rigorous methods.

RCTs are also warranted to test the effectiveness of corticosteroids, as the RCTs performed so far have been too small, and the timing of intervention might have been too late to draw definitive conclusions. RCTs seem warranted to address the seven important clinical questions that we identified as being devoid of any published RCT evidence at present (see Summary of Recommendations).

The strengths of this guideline include its systematic approach to searching the literature and guidance by the GRADE recommendations. We decided to base these guidelines primarily on RCTs and meta-analyses of RCTs to avoid the problems of assessing nonrandomized observational studies, with their inherent problems of selection bias and other confounders. We considered whether there are any interventions for ICH that are so effective in observational studies that RCTs appear unnecessary (154) to prove their effectiveness. We did not identify such studies for acute supratentorial ICH. However, there was consensus that surgery in posterior fossa ICH with direct brainstem compression and placement of EVD in patients with clinical and radiological signs of hydrocephalus may be procedures so beneficial that they cannot be ethically evaluated in RCTs in the majority of patients with these conditions.

The limitations of our approach reflect the paucity of RCTs on patients with ICH. However, because clinicians often wish for guidance in the absence of high-quality RCTs in diseases with such high morbidity and mortality as ICH, there is further guidance on what to do in the Additional information' sections, based on observational data and views within the writing group. Furthermore, the GRADE approach only allows for strong or weak recommendations, but in instances where there are one or a few RCTs, we might have liked to use an intermediate category.

ICH outcome remains poor; existing interventions that are known to be effective have only modest absolute effects; and the global burden of ICH will rise. There is therefore a need for further RCTs to inform management, and we have previously identified research priorities (6). Results from the ongoing RCTs will hopefully further improve outcome after ICH.

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## Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Appendix S1.** ESO-ICH Guidelines Working Group.

**Appendix S2.** ESO ICH Guidelines search strategies.