

## Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

### A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

*The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.*

*Endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Neurocritical Care Society*

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**Purpose**—The aim of this guideline is to present current and comprehensive recommendations for the diagnosis and treatment of spontaneous intracerebral hemorrhage.

**Methods**—A formal literature search of PubMed was performed through the end of August 2013. The writing committee met by teleconference to discuss narrative text and recommendations. Recommendations follow the American Heart Association/American Stroke Association methods of classifying the level of certainty of the treatment effect and the class of evidence. Prerelease review of the draft guideline was performed by 6 expert peer reviewers and by the members of the Stroke Council Scientific Oversight Committee and Stroke Council Leadership Committee.

**Results**—Evidence-based guidelines are presented for the care of patients with acute intracerebral hemorrhage. Topics focused on diagnosis, management of coagulopathy and blood pressure, prevention and control of secondary brain injury and intracranial pressure, the role of surgery, outcome prediction, rehabilitation, secondary prevention, and future considerations. Results of new phase 3 trials were incorporated.

**Conclusions**—Intracerebral hemorrhage remains a serious condition for which early aggressive care is warranted. These guidelines provide a framework for goal-directed treatment of the patient with intracerebral hemorrhage. (*Stroke*. 2015;46:2032–2060. DOI: 10.1161/STR.0000000000000069.)

**Key Words:** AHA Scientific Statements ■ blood pressure ■ coagulopathy ■ diagnosis ■ intracerebral hemorrhage ■ intraventricular hemorrhage ■ surgery ■ treatment

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Spontaneous, nontraumatic intracerebral hemorrhage (ICH) remains a significant cause of morbidity and mortality throughout the world. Although ICH has traditionally lagged behind ischemic stroke and aneurysmal subarachnoid hemorrhage in terms of evidence from clinical trials to guide management, the past decade has seen a dramatic increase in studies of ICH intervention. Population-based studies show that most patients present with small ICHs that are readily survivable with good medical care.<sup>1</sup> This suggests that excellent medical care likely has a potent, direct impact on ICH morbidity and mortality. This guideline serves several purposes. One is to provide an update to the last American Heart Association/American Stroke

Association ICH guideline, published in 2010, incorporating the results of new studies published in the interim.<sup>2</sup> Another equally important purpose is to remind clinicians of the importance of their care in determining ICH outcome and to provide an evidence-based framework for that care.

To make this review brief and readily useful to practicing clinicians, background details of ICH epidemiology are limited, with references provided for readers seeking more details.<sup>1,3,4</sup> Ongoing studies are not discussed substantively because the focus of this guideline is on currently available therapies; however, the increase in clinical studies related to ICH is encouraging, and those interested may go to <http://www.strokecenter.org/trials/> for more information. Also, this

Table 1. Applying Classification of Recommendations and Level of Evidence

SIZE OF TREATMENT EFFECT						
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/ administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> Additional studies with <i>focused objectives needed</i> <b>IT IS REASONABLE</b> to per- form procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>		
				Procedure/ Test	Treatment	
				COR III: No benefit	No Proven Benefit	
				COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients
LEVEL A Multiple populations evaluated*  Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective  ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective  ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established  ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful  ■ Sufficient evidence from multiple randomized trials or meta-analyses		
LEVEL B Limited populations evaluated*  Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective  ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective  ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established  ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful  ■ Evidence from single randomized trial or nonrandomized studies		
LEVEL C Very limited populations evaluated*  Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective  ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective  ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established  ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful  ■ Only expert opinion, case studies, or standard of care		
Suggested phrases for writing recommendations	should  is recommended  is indicated  is useful/effective/beneficial	is reasonable  can be useful/effective/beneficial  is probably recommended or indicated	may/might be considered  may/might be reasonable  usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit	COR III: Harm	
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		is not recommended  is not indicated  should not be performed/ administered/ other  is not useful/ beneficial/ effective	potentially harmful  causes harm associated with excess morbidity/mortality  should not be performed/ administered/ other	

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

guideline is generally concerned with adults, with issues of hemorrhagic stroke in children and neonates covered in a separate American Heart Association scientific statement on "Management of Stroke in Infants and Children."<sup>5</sup>

This document serves to update the last ICH guidelines published in 2010,<sup>2</sup> and the reader is referred to these guidelines for additional relevant references not contained here. The development of this update was purposely delayed for 1 year from the intended 3-year review cycle so that results of 2 pivotal phase 3 ICH clinical trials could be incorporated. Differences from recommendations in the 2010 guideline are specified in the current work. The writing group met by phone to determine subcategories to evaluate. These included 15 sections that covered the following: emergency diagnosis and assessment of ICH and its causes; hemostasis and coagulopathy; blood pressure (BP) management; inpatient management, including general monitoring and nursing care, glucose/temperature/seizure management, and other medical complications; procedures, including management of intracranial pressure (ICP), intraventricular hemorrhage, and the role of surgical clot removal; outcome prediction; prevention of recurrent ICH; rehabilitation; and future considerations. Each subcategory was led by a primary author, with 1 or 2 additional authors making contributions. Full PubMed searches were conducted of all English language articles regarding relevant human disease treatment from 2009 through August 2013. Drafts of summaries and recommendations were circulated to the entire writing group for feedback. Several conference calls were held to discuss individual sections, focusing on controversial issues. Sections were revised and merged by the Chair. The resulting draft was sent to the entire writing group for comment. Comments were incorporated by the Chair and Vice-Chair, and the entire committee was asked to approve the final draft. Changes to the document were made by the Chair and Vice-Chair in response to peer review, and the document was again sent to the entire writing group for suggested changes and approval. Recommendations follow the American Heart Association/American Stroke Association's methods of classifying the level of certainty of the treatment effect and the class of evidence (Tables 1 and 2). All Class I recommendations are listed in Table 3.

### Emergency Diagnosis and Assessment

ICH is a medical emergency. Rapid diagnosis and attentive management of patients with ICH is crucial, because early deterioration is common in the first few hours after ICH onset. More than 20% of patients will experience a decrease in the Glasgow Coma Scale (GCS) of 2 or more points between the prehospital emergency medical services (EMS) assessment and the initial evaluation in the emergency department (ED).<sup>6</sup> Furthermore, another 15% to 23% of patients demonstrate continued deterioration within the first hours after hospital arrival.<sup>7,8</sup> The risk for early neurological deterioration and the high rate of poor long-term outcomes underscore the need for aggressive early management.

### Prehospital Management

Prehospital management for ICH is similar to that for ischemic stroke, as detailed in the recent American Heart Association "Guidelines for the Early Management of Patients With Acute

**Table 2. Definition of Classes and Levels of Evidence Used in AHA/ASA Recommendations**

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study or one or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

AHA/ASA indicates American Heart Association/American Stroke Association.

Ischemic Stroke."<sup>9</sup> The primary objective is to provide airway management if needed, provide cardiovascular support, and transport the patient to the closest facility prepared to care for patients with acute stroke.<sup>10</sup> Secondary priorities for EMS providers include obtaining a focused history regarding the timing of symptom onset (or the time the patient was last normal); information about medical history, medication, and drug use; and contact information for family. EMS providers should provide advance notice to the ED of the impending arrival of a potential stroke patient so that critical pathways can be initiated and consulting services alerted. Advance notice by EMS has been demonstrated to significantly shorten time to computed tomography (CT) scanning in the ED.<sup>11</sup> Two studies have shown that prehospital CT scanning with an appropriately equipped ambulance is feasible and may allow for triage to an appropriate hospital and initiation of ICH-specific therapy.<sup>12,13</sup>

### ED Management

Every ED should be prepared to treat patients with ICH or have a plan for rapid transfer to a tertiary care center. The crucial resources necessary to manage patients with ICH include neurology, neuroradiology, neurosurgery, and critical

**Table 3. Class I Recommendations**

Section	Class I Recommendations
Emergency Diagnosis and Assessment	A baseline severity score should be performed as part of the initial evaluation of patients with ICH ( <i>Class I; Level of Evidence B</i> ). (New recommendation) Rapid neuroimaging with CT or MRI is recommended to distinguish ischemic stroke from ICH ( <i>Class I; Level of Evidence A</i> ). (Unchanged from the previous guideline)
Hemostasis and Coagulopathy, Antiplatelet Agents, and DVT Prophylaxis	Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively ( <i>Class I; Level of Evidence C</i> ). (Unchanged from the previous guideline) Patients with ICH whose INR is elevated because of VKA should have their VKA withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K ( <i>Class I; Level of Evidence C</i> ). (Unchanged from the previous guideline) Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism beginning the day of hospital admission ( <i>Class I; Level of Evidence A</i> ). (Revised from the previous guideline)
Blood Pressure	For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe ( <i>Class I; Level of Evidence A</i> ) and can be effective for improving functional outcome ( <i>Class IIa; Level of Evidence B</i> ). (Revised from the previous guideline)
General Monitoring and Nursing Care	Initial monitoring and management of ICH patients should take place in an intensive care unit or dedicated stroke unit with physician and nursing neuroscience acute care expertise ( <i>Class I; Level of Evidence B</i> ). (Revised from the previous guideline)
Glucose Management	Glucose should be monitored. Both hyperglycemia and hypoglycemia should be avoided ( <i>Class I; Level of Evidence C</i> ). (Revised from the previous guideline)
Seizures and Antiseizure Drugs	Clinical seizures should be treated with antiseizure drugs ( <i>Class I; Level of Evidence A</i> ). (Unchanged from the previous guideline) Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiseizure drugs ( <i>Class I; Level of Evidence C</i> ). (Unchanged from the previous guideline)
Management of Medical Complications	A formal screening procedure for dysphagia should be performed in all patients before the initiation of oral intake to reduce the risk of pneumonia ( <i>Class I; Level of Evidence B</i> ). (New recommendation)
Surgical Treatment of ICH	Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible ( <i>Class I; Level of Evidence B</i> ). (Unchanged from the previous guideline)
Prevention of Recurrent ICH	BP should be controlled in all ICH patients ( <i>Class I; Level of Evidence A</i> ). (Revised from the previous guideline) Measures to control BP should begin immediately after ICH onset ( <i>Class I; Level of Evidence A</i> ). (New recommendation)
Rehabilitation and Recovery	Given the potentially serious nature and complex pattern of evolving disability and the increasing evidence for efficacy, it is recommended that all patients with ICH have access to multidisciplinary rehabilitation ( <i>Class I; Level of Evidence A</i> ). (Revised from the previous guideline)

BP indicates blood pressure; CT, computed tomography; DVT, deep vein thrombosis; EEG, electroencephalography; ICH, intracerebral hemorrhage; INR, international normalized ratio; MRI, magnetic resonance imaging; SBP, systolic blood pressure; and VKA, vitamin K antagonist.

care facilities that include adequately trained nurses and physicians. Consultants should be contacted as quickly as possible while the patient is in the ED, and the clinical evaluation should be performed efficiently, with physicians and nurses working in parallel. Consultation via telemedicine can be a valuable tool for hospitals without on-site presence of consultants.<sup>14,15</sup> Table 4 describes the integral components of the history, physical examination, and diagnostic studies that should be obtained in the ED.

A routine part of the evaluation should include a standardized severity score, because such scales can help streamline assessment and communication between providers. The National Institutes of Health Stroke Scale (NIHSS) score, commonly used for ischemic stroke, may also be useful in ICH.<sup>24,25</sup> However, ICH patients more often have depressed consciousness on initial presentation, and this may diminish the utility of the NIHSS. Numerous grading scales exist specifically for ICH.<sup>26–32</sup> Although the optimal severity scale is not yet clear, the most widely used and externally validated

is the ICH Score.<sup>28,30,33–35</sup> These severity scales should not be used as a singular indicator of prognosis.

After diagnosis, emergency providers should arrange for rapid admission to a stroke unit or neuroscience intensive care unit (at their own hospital if available, or via transfer) and initiate early management while the patient is awaiting this bed. A single-center study found that prolonged patient stays in the ED lead to worse outcomes, although another suggested that early neurocritical care management in the ED may ameliorate this effect.<sup>36,37</sup> Although many centers have critical pathways developed for the treatment of acute ischemic stroke, few have protocols specific to the management of ICH.<sup>38</sup> Such pathways may allow for more efficient, standardized, and integrated management of patients with acute ICH; one is available from the Neurocritical Care Society.<sup>39</sup> These pathways emphasize that urgent treatment of time-sensitive issues including BP lowering and reversal of coagulopathy should be initiated in the ED to which the patient presents rather than waiting until after transfer to an intensive care unit, stroke unit, or other hospital.



**Table 4. Integral Components of the History, Physical Examination, and Workup of the Patient With ICH in the Emergency Department**

	Comments
<b>History</b>	
Time of symptom onset (or time the patient was last normal)	
Initial symptoms and progression of symptoms	
Vascular risk factors	History of stroke or ICH, hypertension, diabetes mellitus, and smoking
Medications	Anticoagulant drugs, antiplatelet agents, antihypertensive medications, stimulants (including diet pills), sympathomimetic drugs
Recent trauma or surgery	Carotid endarterectomy or carotid stenting, because ICH may be related to hyperperfusion after such procedures
Dementia	Associated with amyloid angiopathy
Alcohol or illicit drug use	Cocaine and other sympathomimetic drugs are associated with ICH, stimulants
Seizures	
Liver disease	May be associated with coagulopathy
Cancer and hematologic disorders	May be associated with coagulopathy
<b>Physical examination</b>	
Vital signs	
A general physical examination focusing on the head, heart, lungs, abdomen, and extremities	
A focused neurological examination	A structured examination such as the National Institutes of Health Stroke Scale can be completed in minutes and provides a quantification that allows easy communication of the severity of the event to other caregivers. GCS score is similarly well known and easily computed.
<b>Serum and urine tests</b>	
Complete blood count, electrolytes, blood urea nitrogen and creatinine, and glucose	Higher serum glucose is associated with worse outcome <sup>16,17</sup>
Prothrombin time (with INR) and an activated partial thromboplastin time	Warfarin-related hemorrhages are associated with an increased hematoma volume, greater risk of expansion, and increased morbidity and mortality <sup>18,19</sup>
Cardiac-specific troponin	Elevated troponin levels are associated with worse outcome <sup>20,21</sup>
Toxicology screen to detect cocaine and other sympathomimetic drugs of abuse	Cocaine and other sympathomimetic drugs are associated with ICH
Urinalysis and urine culture, as well as a pregnancy test in a woman of childbearing age	
<b>Other routine tests</b>	
Neuroimaging	CT or MRI; consider contrast-enhanced or vascular imaging
ECG	To assess for active coronary ischemia or prior cardiac injury; ECG abnormalities can mark concomitant myocardial injury <sup>22,23</sup>

CT indicates computed tomography; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; and MRI, magnetic resonance imaging.

## Neuroimaging

The abrupt onset of focal neurological symptoms is presumed to be vascular in origin until proven otherwise; however, it is impossible to know whether symptoms are caused by ischemia or hemorrhage on the basis of clinical characteristics alone. Vomiting, systolic BP (SBP) >220 mmHg, severe headache, coma or decreased level of consciousness, and symptom progression over minutes or hours all suggest ICH, although none of these findings are specific; neuroimaging is thus mandatory.<sup>40</sup> CT and magnetic resonance imaging (MRI) are both reasonable for initial evaluation. CT is very sensitive for identifying acute hemorrhage and is considered the “gold standard”; gradient echo and T2\* susceptibility-weighted MRI are as sensitive as CT for detection of acute hemorrhage and are more sensitive for identification of prior hemorrhage.<sup>41,42</sup> Time, cost, proximity to the ED, patient tolerance, clinical status, and MRI availability may, however, preclude emergent MRI in many cases.<sup>43</sup>

The high rate of early neurological deterioration after ICH is related in part to active bleeding that may proceed for hours after symptom onset. Hematoma expansion tends to occur early after ICH and increases risk of poor functional outcome and death.<sup>7,44–49</sup> Among patients undergoing head CT within 3 hours of ICH onset, 28% to 38% have hematoma expansion of greater than one third of the initial hematoma volume on follow-up CT.<sup>7,45</sup> As such, the identification of patients at risk for hematoma expansion is an active area of research. CT angiography (CTA) and contrast-enhanced CT may identify patients at high risk of ICH expansion based on the presence of contrast within the hematoma, often termed a *spot sign*.<sup>50–54</sup> A larger number of contrast spots suggests even higher risk of expansion.<sup>55,56</sup>

Early diagnosis of underlying vascular abnormalities can both influence clinical management and guide prognosis in ICH patients. Risk factors for underlying vascular abnormalities are

age <65 years, female sex, nonsmoker, lobar ICH, intraventricular extension, and absence of a history of hypertension or coagulopathy.<sup>57,58</sup> MRI, magnetic resonance angiography, magnetic resonance venography, and CTA or CT venography can identify specific causes of hemorrhage, including arteriovenous malformations, tumors, moyamoya, and cerebral vein thrombosis.<sup>59–61</sup> CTA has been more widely studied and is highly sensitive and specific for detecting vascular abnormalities.<sup>58,62–64</sup> A catheter angiogram may be considered if clinical suspicion is high or noninvasive studies are suggestive of an underlying lesion.<sup>65</sup> Radiological evidence suggestive of vascular abnormalities as causative for ICH can include the presence of subarachnoid hemorrhage, enlarged vessels or calcifications along the margins of the ICH, hyperattenuation within a dural venous sinus or cortical vein along the presumed venous drainage path,<sup>56</sup> unusual hematoma shape, presence of edema out of proportion to the time of presumed ICH, an unusual hemorrhage location, and the presence of other abnormal structures in the brain (like a mass). Patients with lobar hemorrhage location, age <55 years, and no history of hypertension have a higher likelihood of identification of a secondary cause of ICH from additional MRI beyond noncontrast CT.<sup>66</sup> An magnetic resonance venography or CT venography should be performed if hemorrhage location, relative edema volume, or abnormal signal in the cerebral sinuses on routine neuroimaging suggests cerebral vein thrombosis.

In summary, ICH is a medical emergency that should be diagnosed and managed promptly. Hematoma expansion and early deterioration are common within the first few hours after onset.

### Emergency Diagnosis and Assessment: Recommendations

1. A baseline severity score should be performed as part of the initial evaluation of patients with ICH (*Class I; Level of Evidence B*). (New recommendation)
2. Rapid neuroimaging with CT or MRI is recommended to distinguish ischemic stroke from ICH (*Class I; Level of Evidence A*). (Unchanged from the previous guideline)
3. CTA and contrast-enhanced CT may be considered to help identify patients at risk for hematoma expansion (*Class IIb; Level of Evidence B*), and CTA, CT venography, contrast-enhanced CT, contrast-enhanced MRI, magnetic resonance angiography and magnetic resonance venography, and catheter angiography can be useful to evaluate for underlying structural lesions including vascular malformations and tumors when there is clinical or radiological suspicion (*Class IIa; Level of Evidence B*). (Unchanged from the previous guideline)

### Medical Treatment for ICH

#### Hemostasis and Coagulopathy, Antiplatelets, and Deep Vein Thrombosis Prophylaxis

Underlying hemostatic abnormalities can contribute to ICH. Patients at risk include those taking oral anticoagulant drugs

(OACs), antiplatelet agents, those with acquired or congenital coagulation factor deficiencies, and those with inherited or acquired qualitative or quantitative platelet abnormalities. Patients taking OACs constitute 12% to 20% of patients with ICH,<sup>67–69</sup> a rate that has increased with the aging population and increased use of anticoagulant drugs in recent decades.<sup>67,70</sup> Vitamin K antagonists (VKAs) such as warfarin are the most frequently prescribed OAC, but new agents that do not require laboratory monitoring and do not necessarily prolong coagulation screening tests are being increasingly used, including dabigatran,<sup>71</sup> rivaroxaban,<sup>72</sup> and apixaban.<sup>73</sup> These new agents appear to be associated with a lower risk of ICH than VKAs.<sup>74</sup> It is important that providers caring for ICH patients recognize the use of antithrombotic drugs or of an underlying coagulopathy in the initial evaluation of patients with ICH, so that the treatment strategy can include appropriate interventions.

For patients with a known coagulation factor deficiency or platelet disorder, replacement of the appropriate factor or platelets, often with the assistance of a consultant hematologist, is indicated. If spontaneous ICH occurs in a patient undergoing an intravenous heparin infusion, then protamine sulfate can be given by intravenous injection at a dose of 1 mg per 100 U of heparin (maximum dose 50 mg), with adjustment based on time elapsed since discontinuation of heparin infusion.<sup>75</sup> Similar dosing can be used in patients who are receiving low-molecular-weight heparin; however, reversal may be incomplete.<sup>39</sup>

#### VKA-Related ICH

Guidelines exist for reversal of OACs.<sup>76</sup> For ICH patients taking VKA, rapid correction of the international normalized ratio (INR) is recommended.<sup>76,77</sup> Fresh frozen plasma (FFP), along with vitamin K, has been the mainstay of treatment in the United States for years, but more recently, prothrombin complex concentrates (PCCs), the activated PCC FEIBA (factor VIII inhibitor bypassing activity), and recombinant activated factor VIIa (rFVIIa) have emerged as potential therapies. Administration of intravenous vitamin K alone is insufficient for reversal in the first hours but should be part of all acute VKA reversal strategies in a dose of 5 to 10 mg, usually given slowly via the intravenous route. Onset of action begins by 2 hours and is maximal at ≈24 hours if liver function is normal.<sup>78</sup> FFP administration requires thawing and cross matching, carries a risk of allergic and infectious transfusion reactions, and often requires large volumes for full INR correction. Likelihood of INR correction at 24 hours was linked to time to FFP administration in 1 study, although 17% of patients still did not have an INR <1.4 by this time, which suggests that FFP administered in this manner may be insufficient for rapid correction of coagulopathy.<sup>79</sup> Shortcomings of FFP have led to interest in alternative agents for VKA reversal.

PCCs are plasma-derived factor concentrates originally developed to treat factor IX deficiency (hemophilia B). Three-factor PCC contains factors II, IX, and X whereas 4-factor PCC also contains factor VII. PCC does not require cross matching, can be reconstituted and administered rapidly in a small volume (20–40 mL), and has been processed to

inactivate infectious agents. Several studies have shown that PCCs rapidly normalize the INR (within minutes) in patients taking VKAs.<sup>80–82</sup> Although nonrandomized retrospective reviews and a small case-control study have shown more rapid correction of INR with vitamin K and PCC than vitamin K and FFP, none have clearly demonstrated an improvement in patient clinical outcome with PCC.<sup>83–85</sup> In 1 randomized trial comparing the use of a PCC (Konyne) to supplement FFP versus FFP alone in patients with VKA-related ICH, those who were given FFP alone received a higher volume of FFP and developed more adverse events, primarily attributable to fluid overload.<sup>86</sup> PCCs may increase the risk of thrombotic complications, although this risk appears low.<sup>80</sup> In 2013, the first large phase 3 randomized controlled trial demonstrated noninferiority of 4-factor PCC to FFP for urgent reversal of warfarin in a cohort of 202 patients with acute bleeding (24 of whom had intracranial hemorrhage).<sup>87</sup> In this study, the rate of achieving an INR <1.3 within 30 minutes of completing therapy was 62.2% for PCC and 9.6% for FFP. Thromboembolic event rates were similar (7.8% with PCC and 6.4% with FFP), and fluid overload was more common with FFP (12.8% versus 4.9%). Analogous randomized trials have not been performed to directly evaluate 3-factor and 4-factor PCCs against each other. Additionally, the specific INR target for VKA correction in OAC-related ICH is unclear, with various studies cited here and elsewhere using targets ranging from <1.3 to <1.5.<sup>88</sup>

rFVIIa, licensed to treat hemophilia patients with high titer inhibitors or congenital factor VII deficiency, has garnered attention as a potential treatment for spontaneous and OAC-associated ICH. Although rFVIIa can rapidly normalize INR in the setting of VKA-associated ICH,<sup>89–93</sup> it does not replenish all of the vitamin K–dependent factors and may not restore thrombin generation as effectively as PCCs.<sup>94</sup> Thus, rFVIIa is not currently recommended for routine use in warfarin reversal.<sup>95</sup>

### New Anticoagulant Medication–Related ICH

There are no randomized trials of reversing agents for newer anticoagulants among patients with ICH or other major bleeding complications, and because these agents have only been available for a few years, experience with reversal is limited. Currently available agents in the United States (dabigatran, rivaroxaban, and apixaban) have relatively short half-lives ranging from 5 to 15 hours. Evaluation of the activated partial thromboplastin time and prothrombin time and consultation with a hematologist are reasonable to individualize care. Potential reversal strategies using FEIBA, other PCCs, or rFVIIa might be considered. FFP is of unclear utility, and vitamin K is not useful. It has been suggested that FEIBA or rFVIIa may be better for the direct thrombin inhibitor dabigatran, whereas other PCCs may be better for the factor Xa inhibitors rivaroxaban and apixaban,<sup>96–99</sup> but these data are preliminary. Activated charcoal can be used if the most recent dose of dabigatran, apixaban, or rivaroxaban was taken within the previous couple of hours.<sup>100</sup> Hemodialysis has been noted as an option for dabigatran, but less so for rivaroxaban or apixaban because these are more highly protein bound.<sup>90</sup> Specific antidotes for these medications are in early clinical development.<sup>101</sup>

### Antiplatelet Medication–Related ICH

Studies addressing the effect of prior antiplatelet agent use or platelet dysfunction on ICH growth and outcome have found conflicting results. Reported antiplatelet agent use was not associated with hematoma expansion or clinical outcome in the placebo group of an ICH neuroprotective study.<sup>102</sup> Others have suggested that platelet dysfunction as measured by platelet function assays may be associated with hematoma expansion and clinical outcome.<sup>103,104</sup> Platelet function monitoring could be helpful in assessing exposure to antiplatelet medications and guiding hemostatic interventions, but this approach has not been fully studied. A case series of 45 ICH patients receiving platelet transfusion at the discretion of their physician demonstrated improved platelet reactivity after transfusion with the VerifyNow-ASA assay.<sup>105</sup> Subgroup analysis in those at high risk of hemorrhage growth suggested that platelet transfusion within 12 hours of symptom onset was associated with smaller final hemorrhage outcome and independence at 3 months. Two randomized controlled trials are ongoing to evaluate the effectiveness of platelet transfusion in ICH patients taking antiplatelet agents.<sup>106,107</sup>

### rFVIIa in ICH Not Related to Anticoagulant Agents

rFVIIa has also been tested in patients with non-OAC ICH. Although a phase 2 randomized trial showed that treatment with rFVIIa within 4 hours after ICH onset limited hematoma growth and improved clinical outcome relative to placebo, a subsequent phase 3 trial did not find clinical benefit.<sup>108,109</sup> Use of rFVIIa was associated with an increased frequency of thromboembolic events compared with placebo (7% versus 2%) in the phase 2 trial and significantly more arterial events in the phase 3 trial. It remains to be determined whether rFVIIa might benefit a particular subset of patients with ICH, but currently its benefits in ICH patients, whether or not they are taking an OAC, remain unproven.

### Thromboprophylaxis in ICH Patients

Patients with ICH have a high risk of thromboembolic disease.<sup>110</sup> Women and blacks may be at greater risk.<sup>110–112</sup> In a randomized trial of 151 ICH patients, intermittent pneumatic compression together with elastic stockings reduced the occurrence of asymptomatic deep vein thrombosis (DVT) after ICH compared with elastic stockings alone (4.7% versus 15.9%).<sup>113</sup> The CLOTS trials (Clots in Legs or Stockings After Stroke) consisted of 3 different randomized trials (CLOTS 1, 2, and 3) that assessed several different treatments, including graduated compression stockings versus none, thigh-high graduated compression stockings versus calf-high stockings, and intermittent pneumatic compression versus none.<sup>114–117</sup> CLOTS 1 enrolled 2518 stroke patients (232 with ICH) and found that thigh-high compression stockings did not reduce DVT, pulmonary embolism (PE), or death.<sup>115</sup> CLOTS 2 found that DVT was more common in patients who had below-knee graduated compression stockings than in those with thigh-high graduated compression stockings.<sup>114</sup> Finally, CLOTS 3 enrolled 2876 patients (376 with ICH) and found that intermittent pneumatic compression begun as early as the day of hospital admission reduced the occurrence of proximal DVT, with



the effect being particularly prominent in patients with hemorrhagic stroke (6.7% versus 17.0%, odds ratio [OR], 0.36; 95% confidence interval, [CI] 0.17–0.75).<sup>116</sup> A meta-analysis of anticoagulant drugs for thromboprophylaxis that included 1000 ICH patients from 4 trials (2 randomized) and evaluated the early use of enoxaparin or heparin (from 1 to 6 days after admission) found a reduction in PE (1.7% versus 2.9%; relative risk [RR], 0.37; 95% CI, 0.17–0.80), a nonsignificant reduction in mortality (16.1% versus 20.9%; RR, 0.76; 95% CI, 0.57–1.03), but no difference in DVT (4.2% versus 3.3%; RR, 0.77; 95% CI, 0.44–1.34) or hematoma enlargement (8.0% versus 4.0%; RR, 1.42; 95% CI, 0.57–3.53).<sup>118</sup>

ICH patients who develop DVT or PE may be considered for full systemic anticoagulation or placement of an inferior vena cava (IVC) filter. Given the generally accepted recurrence rate of nonfatal PE is 12% to 15% in nontreated patients (not specific to ICH), observation alone is not recommended. Only very limited information is available to guide decision making on IVC filter placement versus anticoagulation, as well as the optimal anticoagulation regimen.<sup>119</sup> Considerations include the posthemorrhage date on which DVT/PE is diagnosed, documentation of stable hematoma size on neuroimaging, lobar versus deep hematoma location, and the practical ability to remove an IVC filter at a later date. General guidelines for the use of IVC filters in the setting of acute DVT suggest a conventional course of anticoagulant therapy if the risk of bleeding resolves; however, these are not ICH specific.<sup>120</sup>

### Hemostasis and Coagulopathy, Antiplatelet Agents, and DVT Prophylaxis: Recommendations

1. Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively (*Class I; Level of Evidence C*). (Unchanged from the previous guideline)
2. Patients with ICH whose INR is elevated because of VKA should have their VKA withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K (*Class I; Level of Evidence C*). PCCs may have fewer complications and correct the INR more rapidly than FFP and might be considered over FFP (*Class IIb; Level of Evidence B*). rFVIIa does not replace all clotting factors, and although the INR may be lowered, clotting may not be restored in vivo; therefore, rFVIIa is not recommended for VKA reversal in ICH (*Class III; Level of Evidence C*). (Revised from the previous guideline)
3. For patients with ICH who are taking dabigatran, rivaroxaban, or apixaban, treatment with FEIBA, other PCCs, or rFVIIa might be considered on an individual basis. Activated charcoal might be used if the most recent dose of dabigatran, apixaban, or rivaroxaban was taken <2 hours earlier. Hemodialysis might be considered for dabigatran (*Class IIb; Level of Evidence C*). (New recommendation)
4. Protamine sulfate may be considered to reverse heparin in patients with acute ICH (*Class IIb; Level of Evidence C*). (New recommendation)

5. The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is uncertain (*Class IIb; Level of Evidence C*). (Revised from the previous guideline)
6. Although rFVIIa can limit the extent of hematoma expansion in noncoagulopathic ICH patients, there is an increase in thromboembolic risk with rFVIIa and no clear clinical benefit in unselected patients. Thus, rFVIIa is not recommended (*Class III; Level of Evidence A*). (Unchanged from the previous guideline)
7. Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism beginning the day of hospital admission (*Class I; Level of Evidence A*). Graduated compression stockings are not beneficial to reduce DVT or improve outcome (*Class III; Level of Evidence A*). (Revised from the previous guideline)
8. After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset (*Class IIb; Level of Evidence B*). (Unchanged from the previous guideline)
9. Systemic anticoagulation or IVC filter placement is probably indicated in ICH patients with symptomatic DVT or PE (*Class IIa; Level of Evidence C*). The decision between these 2 options should take into account several factors, including time from hemorrhage onset, hematoma stability, cause of hemorrhage, and overall patient condition (*Class IIa; Level of Evidence C*). (New recommendation)

### BP and Outcome in ICH

Elevated BP is very common in acute ICH<sup>121,122</sup> because of a variety of factors, including stress, pain, increased ICP, and premonitory acute or persistent elevations in BP. High SBP is associated with greater hematoma expansion, neurological deterioration, and death and dependency after ICH.<sup>122–124</sup> Compared with ischemic stroke, in which consistent U- or J-shaped associations between SBP nadir of 140 and 150 mm Hg and poor outcome have been shown,<sup>125</sup> only 1 study of ICH has shown a poor outcome at low SBP levels (<140 mm Hg).<sup>126</sup>

### Safety of Early Intensive BP-Lowering Treatment

Observational studies with advanced neuroimaging have shown no significant ischemic penumbra in ICH,<sup>127</sup> with the perihematomal rim of low attenuation seen on CT being related to extravasated plasma.<sup>128</sup> A randomized clinical trial using CT perfusion in primarily small and medium ICH found no clinically significant reduction in cerebral blood flow within the perihematomal region related to early intensive BP lowering to an SBP target of <140 mm Hg within several hours of ICH.<sup>129</sup> In a clinical cohort of 211 patients who received a standard protocol of nicardipine-based BP lowering to reach an SBP target of <160 mm Hg at a mean of 30 minutes (range, 15–45 minutes) within 3 hours of the onset of ICH, the best outcomes were seen in the group with the lowest achieved SBP (<135 mm Hg).<sup>124</sup> Both the Antihypertensive Treatment



of Acute Cerebral Hemorrhage (ATACH) trial, a 4-tier dose-escalation study of intravenous nicardipine-based BP lowering in 80 patients within 3 hours of ICH,<sup>130</sup> and the pilot phase Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT1) trial in 404 mainly Chinese patients within 6 hours of ICH<sup>131</sup> found rapid reduction of SBP to <140 mmHg to be safe.<sup>132,133</sup> Most recently, the main phase INTERACT2 trial has shown no increase in death or serious adverse events from early intensive BP lowering in eligible patients with elevated SBP.<sup>134</sup> Several observational studies have demonstrated that small ischemic lesions identified on diffusion-weighted MRI are common after ICH; however, the impact on outcome and relationship with BP lowering vary across studies.<sup>135</sup>

### Efficacy of Early Intensive BP-Lowering Treatment

The largest randomized clinical trial evaluating the efficacy of intensive BP lowering is INTERACT2, a phase 3 trial undertaken in 2839 patients with SBP between 150 and 220 mmHg within 6 hours of ICH.<sup>134</sup> Among 2794 participants for whom the primary outcome could be determined, 719 of 1382 participants (52.0%) receiving intensive treatment (to an SBP target of <140 mmHg within 1 hour of randomization and for a duration of 7 days, following protocols that included locally available intravenous agents) compared with 785 of 1412 participants (55.6%) receiving standard treatment (SBP <180 mmHg) had a primary outcome of death or major disability (modified Rankin scale score  $\geq 3$ ; OR, 0.87; 95% CI, 0.75–1.01;  $P=0.06$ ). Analysis of secondary end points indicated significantly better functional recovery on an ordinal analysis of scores on the modified Rankin scale (OR for greater disability, 0.87; 95% CI, 0.77 to 1.00;  $P=0.04$ ) and better physical and mental health–related quality of life on the EQ-5D scale (mean health utility scores, intensive group  $0.60 \pm 0.39$  versus standard group  $0.55 \pm 0.40$ ;  $P=0.002$ ) from intensive treatment.

Although INTERACT2 demonstrated consistency of the treatment effect across several prespecified patient subgroups, there was no clear relationship between outcome and the time from onset of ICH to commencing treatment and no significant effect of intensive BP-lowering treatment on hematoma growth. Moreover, only one third of patients achieved the target SBP level within 1 hour (half achieved the target by 6 hours), and most (75%) presented with mild to moderate size (<20 mL) hematomas.

Overall, current evidence indicates that early intensive BP lowering is safe and feasible and that surviving patients show modestly better functional recovery, with a favorable trend seen toward a reduction in the conventional clinical end point of death and major disability. It is therefore reasonable for ICH patients similar to those enrolled in INTERACT2 to receive early treatment targeted to an SBP level <140 mmHg to improve their chances of achieving better functional recovery should they survive the condition. There are fewer data available pertaining to the safety and effectiveness of such treatment in patients with very high BP (sustained SBP >220 mmHg) on presentation, large and more severe ICH, and those requiring

surgical decompression. Because the speed and degree of BP reduction will vary according to the agent and method of delivery (bolus versus infusion) and clinical features, the choice of agent should take into account the practicability, pharmacological profile, potential side effects, and cost.

### BP: Recommendations

1. For ICH patients presenting with SBP between 150 and 220 mmHg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mmHg is safe (*Class I; Level of Evidence A*) and can be effective for improving functional outcome (*Class IIa; Level of Evidence B*). (Revised from the previous guideline)
2. For ICH patients presenting with SBP >220 mmHg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring (*Class IIb; Level of Evidence C*). (New recommendation)

## Inpatient Management and Prevention of Secondary Brain Injury

### General Monitoring

Patients with ICH are frequently medically and neurologically unstable, particularly within the first few days after onset. Care of ICH patients in a dedicated neuroscience intensive care unit is associated with a lower mortality rate.<sup>136</sup> Many patients in the INTERACT2 study were cared for in a dedicated stroke unit rather than an intensive care unit.<sup>134</sup> Frequent vital sign checks, neurological assessments, and continuous cardiopulmonary monitoring including a cycled automated BP cuff, electrocardiographic telemetry, and pulse oximetry probe should be standard. Continuous intra-arterial BP monitoring should be considered in patients receiving intravenous vasoactive medications.

### Nursing Care

The specific nursing care required for ICH patients in intensive care units may include (1) surveillance and monitoring of ICP, cerebral perfusion pressure (CPP), and hemodynamic function; (2) titration and implementation of protocols for management of ICP, BP, mechanical ventilation, fever, and serum glucose; and (3) prevention of complications of immobility through positioning, airway maintenance, and mobilization within physiological tolerance. The consensus document from the Brain Attack Coalition on comprehensive stroke centers delineates these as specific areas of monitoring and complication prevention in which nurses should be trained.<sup>137</sup> This document also recommends that nurses be trained in detailed assessment of neurological function, including standardized scales such as the NIHSS, GCS, and the Glasgow Outcome Scale.

In a Canadian study of 49 hospitals that included ICH patients, a higher proportion of registered nurses at the hospital and better nurse-physician communication were independently associated with lower 30-day mortality even after adjustment for disease severity, comorbidities, and hospital

characteristics.<sup>138</sup> In a Swedish study of 86 hospitals, stroke unit care was associated with a lower risk of death or institutional living after 3 months in patients with ICH (OR, 0.60; 95% CI, 0.54–0.68).<sup>139</sup>

## General Monitoring and Nursing Care: Recommendation

- 1. Initial monitoring and management of ICH patients should take place in an intensive care unit or dedicated stroke unit with physician and nursing neuroscience acute care expertise (Class I; Level of Evidence B).** (Revised from the previous guideline)

## Glucose Management

High blood glucose on admission predicts an increased risk of mortality and poor outcome in patients with ICH, independent of the presence of diabetes mellitus.<sup>140–144</sup> A randomized trial showing improved outcomes with tight glucose control (range, 80–110 mg/dL) using insulin infusions in mainly surgical critical care patients<sup>141</sup> has increased the use of this therapy. However, more recent studies have demonstrated an increased incidence of systemic and cerebral hypoglycemic events and possibly even an increased risk of mortality in patients treated with this regimen.<sup>145–148</sup> A cluster randomized trial of a set of interventions (managing glucose, fever, and swallowing dysfunction in stroke units) found improved outcomes in a mixed cohort of ischemic and hemorrhagic stroke patients.<sup>149</sup> At present, the optimal management of hyperglycemia in ICH and the target glucose level remains to be clarified. Hypoglycemia should be avoided.

## Glucose Management: Recommendation

- 1. Glucose should be monitored. Both hyperglycemia and hypoglycemia should be avoided (Class I; Level of Evidence C).** (Revised from the previous guideline)

## Temperature Management

Fever worsens outcome in experimental models of brain injury.<sup>150,151</sup> Fever is common after ICH, especially in patients with intraventricular hemorrhage. In patients surviving the first 72 hours after hospital admission, the duration of fever is related to outcome and appears to be an independent prognostic factor in these patients.<sup>152</sup> Fever may also be associated with hematoma growth, although a cause-effect relationship is unclear.<sup>153</sup> Although these data provide a rationale for treatment of fever in ICH patients, maintenance of normothermia has not been clearly demonstrated as beneficial to outcome.<sup>149,154</sup> Preliminary animal and human studies have suggested that therapeutic cooling may reduce perihematomal edema.<sup>155,156</sup> However, treatment with mild hypothermia should be considered investigational in ICH at this time.<sup>157</sup>

## Temperature Management: Recommendation

- 1. Treatment of fever after ICH may be reasonable (Class IIb; Level of Evidence C).** (New recommendation)

## Seizures and Antiseizure Drugs

The frequency of clinical seizures early (within 1 week) after ICH is as high as 16%, with the majority occurring at or near onset.<sup>158,159</sup> Cortical involvement of ICH is the most important risk factor for early seizures.<sup>158–160</sup> In a large single-center study, prophylactic antiseizure drugs significantly reduced the number of clinical seizures after lobar ICH.<sup>161</sup> Prospective and population-based studies, however, have shown no association between clinical seizures and neurological outcome or mortality.<sup>159,160,162–164</sup>

Studies of continuous electroencephalography (EEG) report electrographic seizures in 28% to 31% of select cohorts of ICH patients, despite most having received prophylactic antiseizure medications.<sup>160,164</sup> The clinical impact of subclinical seizures detected on EEG is unclear.

Most studies suggest that prophylactic antiseizure drugs (primarily phenytoin) are associated with increased death and disability in ICH,<sup>165–167</sup> although a recent study found no association between antiseizure drugs and outcome in those who survived beyond 5 days after ICH, which highlights the possible influence of confounding in previous reports.<sup>166</sup> A small randomized trial of 1-month prophylactic treatment with valproic acid showed no reduction in incident seizures over 1-year follow-up (19.5% in the treatment group, 22.2% in the placebo group;  $P=0.8$ ).<sup>168</sup> Prophylactic anticonvulsant medication has thus not been demonstrated to be beneficial.

Clinical seizures or electrographic seizures in patients with a change in mental status should be treated with antiseizure drugs. Continuous EEG monitoring should be considered in ICH patients with depressed mental status that is disproportionate to the degree of brain injury.

Epilepsy occurs in up to 10% of young patients (18–50 years) with ICH; the risk of poststroke epilepsy may be less in older patients.<sup>169,170</sup> Risk factors for epilepsy include stroke severity, cortical location of the hematoma, and delayed initial seizures.<sup>169,170</sup> There are no data to suggest that early use of antiseizure drugs will prevent lesion-related epilepsy.

## Seizures and Antiseizure Drugs: Recommendations

- 1. Clinical seizures should be treated with antiseizure drugs (Class I; Level of Evidence A).** (Unchanged from the previous guideline)
- 2. Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiseizure drugs (Class I; Level of Evidence C).** (Unchanged from the previous guideline)
- 3. Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status that is out of proportion to the degree of brain injury (Class IIa; Level of Evidence C).** (Revised from the previous guideline)
- 4. Prophylactic antiseizure medication is not recommended (Class III; Level of Evidence B).** (Unchanged from the previous guideline)

## Management of Medical Complications

The frequency of medical complications after acute stroke is high, although there is substantially more information reported for ischemic stroke than ICH. In a trial of the safety and tolerability of NXY-059 (CHANT [Cerebral Hematoma and NXY Treatment]) in patients with spontaneous ICH, at least 1 adverse event was reported in 88% of the placebo-treated patients, 40% of which were serious (ie, resulted in prolonged hospitalization, were immediately life threatening, or were fatal). The most common complications were pneumonia (5.6%), aspiration (2.6%), respiratory failure/distress (2%), PE (1.3%), and sepsis (1.7%).<sup>171</sup> Approximately 50% of deaths after stroke are attributed to medical complications, usually after 7 days of hospitalization. Stroke patients who experience medical complications while in the hospital have increased mortality up to 4 years after the initial event.

Dysphagia and aspiration are major risk factors for the development of pneumonia. Dysphagia is defined by swallowing impairment of the upper digestive tract and includes impairments in swallowing efficiency and safety, with delays in the timing of movements, reduced range of movements, and frank aspiration. Aspiration in this population is a sign of severe dysphagia and refers to abnormal entry of fluid, particulate exogenous substances, or endogenous secretions into the airways. In a retrospective study that included 90 Japanese ICH patients, 68% could not tolerate oral feeding.<sup>172</sup> In another German study of 208 ICH patients, 25% of patients required percutaneous endoscopic gastrostomy.<sup>173</sup> In this study, GCS, occlusive hydrocephalus, mechanical ventilation, and sepsis were independent risk factors for dysphagia and percutaneous endoscopic gastrostomy placement. In a prospective multicenter study, use of a formal screening protocol for dysphagia (eg, water swallow test) for all patients admitted with ischemic stroke was associated with a significantly reduced risk of pneumonia compared with no formal screen (OR, 0.10; 95% CI, 0.30–0.45).<sup>174</sup> The pneumonia rate of sites with a formal dysphagia screen was 2.4% versus 5.4% of those without a screen, a 3% absolute risk reduction.

Serious cardiac events and cardiac death after stroke may be caused by acute myocardial infarction (MI), heart failure, ventricular arrhythmias including ventricular tachycardia/fibrillation, and cardiac arrest. Concurrent stroke and MI are not uncommon. Recent data from the prospective Austrian Stroke Unit Registry, which included 4984 ICH patients, found that 0.3% of patients had an MI over a median duration of 3 days.<sup>175</sup> These patients not only experienced higher in-hospital mortality but also had greater complications, including pneumonia and progressive stroke. History of prior MI and severity of deficits on admission are associated with the occurrence of MI. In a meta-analysis of 65 996 stroke patients with a mean follow-up of  $\approx 3.5$  years,<sup>176</sup> the annual risk of MI was 2.2%. For ICH patients, an elevated troponin level  $>0.4$  ng/mL was found in 15% within 24 hours of admission and was associated with increased in-hospital mortality.<sup>21</sup> In another study of 49 patients with supratentorial ICH, excluding those who died within 12 hours or were moribund, 20%

had elevated troponin levels, although this was not associated with 30-day mortality.<sup>177</sup>

Heart failure can occur as the result of myocardial ischemia, infarction, stress-induced cardiomyopathy, or uncontrolled hypertension in the setting of acute ICH. Neurogenic pulmonary edema is an increase in interstitial and alveolar fluid in the setting of an acute central nervous system injury well documented in subarachnoid hemorrhage but prevalent in ICH as well.<sup>178</sup> Neurogenic pulmonary edema presents abruptly and progresses quickly after the neurological insult. Radiographically, it is indistinguishable from cardiogenic pulmonary edema. Resolution usually occurs within several days. Intubation with mechanical ventilator support is often required for airway protection and maximum oxygen delivery. ICH patients may be at risk for acute respiratory distress syndrome from multiple different origins<sup>179</sup>; however, at present, ways to prevent this have not been studied. When ICH patients develop acute respiratory distress syndrome, it is reasonable to use ventilation strategies used in non-neurological patients (such as low-tidal-volume ventilation)<sup>180</sup>; however, attention should be paid to avoid ICP elevations or inadequate cerebral oxygen delivery.

Other medical complications in ICH patients include acute kidney injury, hyponatremia, gastrointestinal bleeding, impaired nutritional status, urinary tract infections, and post-stroke depression. Acute nephropathy (defined in a study by Oleinik et al<sup>181</sup> as a rise in creatinine of at least 25% or 0.5 mg/dL to a level of at least 1.5 mg/dL) occurred in 41 of 539 ICH patients (8%) admitted to a single institution over a 5-year period and was no more frequent in those who underwent CT angiography,<sup>181</sup> which suggests that kidney injury was a result of overall medical status rather than this particular procedure. Screening and monitoring are keys to detecting these events. Management at this time is focused on prevention and targeting these complications as they arise. Because of limited information regarding ICH-specific issues related to ventilator-associated events, acute respiratory distress syndrome management, and acute kidney injury, these should be considered areas for future study. The identification of preventive or treatment strategies for other medical complications will also require further studies focused on ICH patients.

## Management of Medical Complications: Recommendations

1. A formal screening procedure for dysphagia should be performed in all patients before the initiation of oral intake to reduce the risk of pneumonia (*Class I; Level of Evidence B*). (New recommendation)
2. Systematic screening for myocardial ischemia or infarction with electrocardiogram and cardiac enzyme testing after ICH is reasonable (*Class IIa; Level of Evidence C*). (New recommendation)

## Procedures/Surgery

### ICP Monitoring and Treatment

Limited data exist regarding the frequency of elevated ICP and its management in patients with ICH.<sup>182–185</sup> A recently reported



cohort study of 243 consecutive ICH patients described ICP monitoring in 57 (23%), of whom 40 (70%) had at least 1 episode of intracranial hypertension (defined as an ICP >20 mm Hg).<sup>185</sup> In a randomized trial of intraventricular thrombolysis in 100 patients with intraventricular hemorrhage (IVH) and ICH smaller than 30 mm<sup>3</sup>, ICP was >20 mm Hg at the time of ventricular catheter (VC) insertion in 14 patients.<sup>184</sup> Overall, however, ICP was not frequently elevated during monitoring and VC drainage in these patients. There is evidence for differential pressure gradients in at least some cases of ICH, so that ICP may be elevated in and around the hematoma but not distant from it.<sup>186</sup> Because the usual causes of elevated ICP are hydrocephalus from IVH or mass effect from the hematoma (or surrounding edema), patients with small hematomas and limited IVH usually will not require treatment to lower ICP. Increased ICP also may be more common in younger patients and those with supratentorial ICH.<sup>185</sup> Hydrocephalus is associated with worsened outcome in acute ICH.<sup>187–189</sup> Among 902 patients with follow-up data who were randomized into the international Surgical Trial for Intracerebral Haemorrhage (STICH), 377 had IVH, and 208 of these had hydrocephalus (23% of all patients, 55% of those with IVH).<sup>190</sup>

ICP is measured by use of devices inserted into the brain parenchyma or cerebral ventricles. Fiber optic technology can be used in both types of devices. A VC inserted into the lateral ventricle allows for drainage of cerebrospinal fluid (CSF), which can help reduce ICP. A parenchymal ICP device is inserted into the brain parenchyma and allows for monitoring of ICP, but not CSF drainage. The absence of published studies showing that management of elevated ICP has an effect on ICH outcome makes the decision whether to monitor and treat elevated ICP unclear in patients with ICH. Risks associated with ICP monitors include infection and intracranial hemorrhage. The risk of hemorrhage or infection is thought to be higher with VC than with parenchymal catheters, although data on these rates are not derived from patients with ICH but principally from those with traumatic brain injury or aneurysmal subarachnoid hemorrhage. In a 1997 series of 108 intraparenchymal devices, the rate of infection was 2.9% and the rate of intracranial hemorrhage was 2.1% (15.3% in patients with coagulopathies).<sup>191</sup> Two of 22 patients (9%) patients in the placebo arm of a trial of intraventricular thrombolysis developed ventriculitis, but these patients had multiple intrathecal injections, which could potentially increase the risk of infection.<sup>184</sup> Before insertion of a monitoring device, the patient's coagulation status should be evaluated. Prior use of antiplatelet agents may justify platelet transfusion before the procedure, and the use of warfarin may require reversal of coagulopathy before placement. The decision to use a VC or a parenchymal catheter device should be based on whether there is a need to drain CSF to treat hydrocephalus or elevated ICP.

Because of limited data regarding indications for monitoring and treatment of ICP in ICH, management principles for elevated ICP are usually generalized from those for traumatic brain injury, in which current guidelines recommend placement of an ICP monitor in patients with a GCS score of 3 to 8 and maintenance of an ICP <20 mm Hg and a CPP of 50 to 70 mm Hg, depending on the status of cerebral autoregulation.<sup>192–194</sup> Data from small, retrospectively analyzed cohorts

of ICH patients suggest that rising ICP and declining CPP are associated with mortality.<sup>184,195,196</sup> In 1 study of multimodality monitoring in 18 ICH patients, CPP <70 to 80 mm Hg was associated with brain tissue hypoxia and poor outcome.<sup>195</sup> Thus, ICP monitoring and subsequent treatment might be considered in ICH patients with a GCS score of ≤8 that is presumed related to hematoma mass effect, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus.

Methods of treating elevated ICP are generally borrowed from traumatic brain injury guidelines as well. Basic principles include elevation of the head of the bed to 30°, the use of mild sedation, and avoidance of collar-endotracheal tube ties that might constrict cervical veins.<sup>197</sup> Mannitol or hypertonic saline may be used to treat acute ICP elevations, and hypertonic saline may be more effective.<sup>198</sup> In patients with CSF outflow obstruction caused by hydrocephalus or a trapped ventricle, CSF drainage should be considered. Hematoma evacuation and decompressive craniectomy (DC) are options for treating elevated ICP and are discussed in the section on Surgical Treatment of ICH. Salvage therapies might include barbiturate coma or mild hypothermia. Corticosteroids should not be used, because they are not effective in ICH and increase complications.<sup>199</sup>

Small case series have described the use of brain tissue oxygen and cerebral microdialysis monitoring in patients with ICH.<sup>195,200,201</sup> Because of the small numbers of patients and limited data, no recommendation can be made regarding the use of these technologies at this time.

## ICP Monitoring and Treatment: Recommendations

1. **Ventricular drainage as treatment for hydrocephalus is reasonable, especially in patients with decreased level of consciousness (Class IIa; Level of Evidence B).** (Revised from the previous guideline)
2. **Patients with a GCS score of ≤8, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus might be considered for ICP monitoring and treatment. A CPP of 50 to 70 mm Hg may be reasonable to maintain depending on the status of cerebral autoregulation (Class IIb; Level of Evidence C).** (Unchanged from the previous guideline)
3. **Corticosteroids should not be administered for treatment of elevated ICP in ICH (Class III; Level of Evidence B).** (New recommendation)

## Intraventricular Hemorrhage

IVH occurs in ≈45% of patients with spontaneous ICH and is an independent factor associated with poor outcome.<sup>190,202,203</sup> Pooled analysis of 13 studies found IVH in association with ICH increased the risk of death from 20% without to 51% with IVH.<sup>204</sup> IVH can be primary, confined to the ventricles, or secondary, originating as an extension of an ICH. Most IVH is secondary and related to hypertensive hemorrhages involving the basal ganglia and thalamus.<sup>202,205</sup> Although the insertion of a VC should theoretically aid in drainage of blood and CSF from the ventricles, VC use alone may be ineffective because of difficulty maintaining catheter patency and the



slow removal of intraventricular blood.<sup>188</sup> Thus, there has been recent interest in the use of thrombolytic agents as adjuncts to VC use in the setting of IVH.

Animal studies and clinical series have reported that intraventricular administration of fibrinolytic agents, including urokinase, streptokinase, and recombinant tissue-type plasminogen activator (rtPA), in IVH may reduce morbidity and mortality by accelerating blood clearance and clot lysis.<sup>206–214</sup> Retrospective analysis of 42 consecutive patients with IVH, 88% attributable to primary ICH, who were treated with intraventricular urokinase found death occurred in 21 patients (50%) and ventriculitis in 11 (26%).<sup>206</sup> Another prospective study compared 48 patients with IVH (caused by ICH in 40 [83%]) treated with intraventricular rtPA to 49 matched control patients treated with VC alone.<sup>207</sup> Mortality was reduced from 30% to 10% in the group treated with rtPA, with 2 patients in the rtPA group diagnosed with ventriculitis. In a small prospective trial, 16 patients with IVH and ICH <30 mm<sup>3</sup> were randomized to VC or VC plus urokinase.<sup>214</sup> Clearance of IVH was faster with urokinase. Mortality at 6 months was 14% with urokinase and 44% with VC alone ( $P=0.22$ ), and there were no significant differences between groups in requirement for permanent shunts or ventriculitis. Meta-analysis of 4 randomized and 8 observational studies of patients with IVH secondary to spontaneous ICH treated with VC ( $n=149$ ) or VC with intraventricular fibrinolysis ( $n=167$ ) found a significant decrease in mortality from 47% to 23% (pooled Peto OR, 0.32; 95% CI, 0.19–0.52), with the difference occurring principally in patients treated with urokinase.<sup>209</sup> There was no difference in complications or need for permanent CSF diversion between subjects treated with intraventricular fibrinolytic agents and VC alone. Studies with rtPA have used various dose regimens ranging from 1 to 4 mg every 8 to 12 hours.<sup>184,215–218</sup>

The largest trial of intraventricular fibrinolysis to date is the CLEAR-IVH trial (Clot Lysis: Evaluating Accelerated Resolution of IVH).<sup>184,217,218</sup> CLEAR-IVH included 100 patients (22 placebo, 78 rtPA) with IVH attributable to spontaneous ICH <30 mm<sup>3</sup>.<sup>184,217–219</sup> Overall, bacterial ventriculitis occurred in 3 patients with rtPA (4%) and 2 with placebo (9%). Patients treated with rtPA had significantly lower intracranial pressures, fewer VC obstructions that required replacement, and nonsignificantly shorter duration of VC requirement. There was symptomatic rebleeding in 9 rtPA patients (12%) and 1 patient given placebo (5%;  $P=0.33$ ). Permanent CSF diversion was required in 14% of placebo and 6% of rtPA patients ( $P=0.27$ ). Median 30-day modified Rankin scale score was 5 in both groups, and mortality was 19%, with no significant difference between placebo and rtPA. The phase 3 randomized CLEAR III trial is in progress.

There are now reports of alternative procedures for IVH, such as endoscopic surgical evacuation and ventriculostomy.<sup>220–223</sup> A comparison of 48 patients with IVH secondary to ICH and other causes and treated with endoscopic removal of IVH found 17% required permanent CSF diversion compared with 50% of 48 historical control patients treated with VC alone. Outcome on the modified Rankin scale was similar. Two randomized trials have been reported comparing endoscopic removal of IVH with VC in patients with IVH secondary to primary ICH <30 mm<sup>3</sup>.<sup>221,223</sup> In 1 of the studies,

urokinase was also used in both treatment groups.<sup>223</sup> Among the 46 patients treated with endoscopy compared with 44 treated with VC, mortality was not significantly different. One study reported improved outcome on the Glasgow Outcome Scale at 2 months with endoscopy but did not report the rate of permanent CSF diversion.<sup>223</sup> The other suggested lower rates of permanent CSF diversion after endoscopy.<sup>221</sup> Other reported management strategies for IVH include early ventriculoperitoneal shunting,<sup>224</sup> endoscopic third ventriculostomy,<sup>225</sup> or lumbar drainage.<sup>189</sup> In a study comparing 16 patients treated with VC and lumbar drainage for ICH with IVH to 39 historical control patients treated with VC alone, patients managed with VC plus lumbar drainage had a longer median duration of external CSF drainage but were significantly less likely to require permanent CSF diversion.<sup>189</sup>

## IVH: Recommendations

1. **Although intraventricular administration of rtPA in IVH appears to have a fairly low complication rate, the efficacy and safety of this treatment are uncertain (Class IIb; Level of Evidence B).** (Revised from the previous recommendation)
2. **The efficacy of endoscopic treatment of IVH is uncertain (Class IIb; Level of Evidence B).** (New recommendation)

## Surgical Treatment of ICH (Clot Removal)

The role of surgery for most patients with spontaneous ICH remains controversial. The theoretical rationale for hematoma evacuation revolves around the concepts of preventing herniation, reducing ICP, and decreasing the pathophysiological impact of the hematoma on surrounding tissue by decreasing mass effect or the cellular toxicity of blood products. Randomized trials comparing surgery to conservative management have not demonstrated a clear benefit for surgical intervention. Moreover, the generalizability of the results of these trials can be questioned, because patients at risk for herniation were likely excluded and the largest and most recent studies had high rates of treatment group crossover from conservative management to surgery. Since the last guidelines, 2 prospective randomized trials and 3 meta-analyses have been completed that compared surgery versus conservative treatment for ICH.<sup>226–229</sup> Several other studies have examined minimally invasive approaches compared with craniotomy. Additionally, recent retrospective studies have suggested a possible role for craniectomy in ameliorating increased ICP caused by ICH.<sup>230–234</sup> In addition, the current recommendations do not apply to intracranial hemorrhage caused by trauma or underlying structural lesions such as aneurysms and arteriovenous malformations, because these patients were not included in the described ICH surgery trials.

## Craniotomy for Supratentorial Hemorrhage

On the basis of inconclusive evidence from prior trials, STICH was undertaken to determine whether early surgery reduces mortality and improves neurological outcome compared with conservative management for supratentorial ICH when the treating neurosurgeon determined that uncertainty of preferred

treatment was present.<sup>235</sup> In this trial, 1033 patients from 83 centers in 27 countries were randomized to early surgery (<24 hours of randomization) or initial conservative treatment. A favorable outcome on the 8-point extended Glasgow Outcome Scale at 6 months was used as the primary end point. Good outcome was dichotomized, with lower expectations set for those with worse prognosis. Twenty-six percent of the patients in the surgical arm achieved a favorable outcome compared with 24% in the medical arm. STICH found no overall statistically significant difference in mortality or functional outcome between treatment groups. Notably, 26% of patients initially assigned to conservative management ultimately underwent surgery. Subgroup analysis suggested that patients with lobar hemorrhages within 1 cm of the cortical surface might benefit from surgery. Additional subgroup analysis suggested that the risk for a poor outcome was increased for patients who presented as comatose (GCS score  $\leq 8$ ). On the basis of these observations, the STICH II trial was undertaken.<sup>226,236</sup>

The STICH II trial addressed the question of whether early surgery would be beneficial for conscious patients with superficial lobar hemorrhage of 10 to 100 mm<sup>3</sup> within 1 cm of the cortical surface and without IVH and who were admitted within 48 hours of ictus. Seventy-eight centers in 27 countries participated. The study randomized patients to early surgery (within 12 hours of randomization) plus medical management or medical management alone. The primary outcome was a prognosis-based dichotomized (favorable or unfavorable) outcome of the extended Glasgow Outcome Scale. Forty-one percent of patients in the early surgery group had a favorable outcome compared with 38% in the medical arm; this difference was not statistically significant. A nonprespecified subgroup analysis that included only patients with a poor prognosis (as defined by a specific equation used in STICH) showed that such patients were more likely to have a favorable outcome with early surgery; however, there was no advantage to early surgery for patients in the good prognosis category. A nonsignificant survival advantage was noted for the surgical arm. Twenty-one percent of patients randomized to initial medical management ultimately underwent surgery, with the most common reason described as patient deterioration. The STICH II authors performed an updated meta-analysis of surgical trials reporting on 3366 patients.<sup>228</sup> A significant advantage for surgery was shown when all patients were considered, but there was significant heterogeneity in the data. Thus, early hematoma evacuation has not been shown to be beneficial in the 2 largest randomized trials, but high crossover rates of patients to surgical intervention, narrow patient-based inclusion criteria, and the focus of STICH and STICH II on early surgery leave unclear whether surgery may benefit specific groups of patients with supratentorial ICH.

### Craniotomy for Posterior Fossa Hemorrhage

Because of the narrow confines of the posterior fossa, deterioration can occur quickly in cerebellar hemorrhage caused by obstructive hydrocephalus or local mass effect on the brainstem. Several nonrandomized studies have suggested that patients with cerebellar hemorrhages >3 cm in diameter

or patients in whom cerebellar hemorrhage is associated with brainstem compression or hydrocephalus have better outcomes with surgical decompression.<sup>237–239</sup> Attempting to control ICP via means other than hematoma evacuation, such as VC insertion alone, is considered insufficient, is not recommended, and may actually be harmful, particularly in patients with compressed cisterns.<sup>239</sup> In contrast to cerebellar hemorrhage, evacuation of brainstem hemorrhages may be harmful in many cases. Given the broad lack of clinical equipoise for surgical evacuation of cerebellar hemorrhages, especially those >3 cm in diameter occurring in potentially salvageable patients, it is unlikely that a randomized trial could be conducted to compare surgery versus conservative treatment.

### Craniectomy for ICH

The potential of DC to improve outcomes for patients with ICH has not been well studied. On the basis of the results of the first STICH trial, several authors have suggested that outcomes could potentially be improved with DC for selected patients with high ICP and mass effect related to ICH.<sup>232–234,240</sup> Patients in these studies tended to be those in coma (GCS score <8) and those who had significant midline shift, large hematomas, or ICP that did not normalize with medical management. One study of DC without hematoma evacuation matched 12 consecutive patients with supratentorial ICH to control subjects via propensity score.<sup>232</sup> Median hematoma volume was 61.3 mm<sup>3</sup>, and median preoperative GCS score was 8. Three patients in the study group died compared with 8 in the control group, whereas 9 patients had a study-defined good outcome. Another study on DC without hematoma evacuation included 5 patients with recalcitrant elevated ICP.<sup>234</sup> This small cohort fared better than matched control subjects from the authors' institutional prospective ICH database. A retrospective study of DC in addition to hematoma evacuation for both putaminal and lobar ICH found that patients with putaminal hemorrhage had greater reduction in midline shift and a trend toward better neurological outcome than matched control subjects.<sup>240</sup> A systematic review of studies in which DC was performed in the setting of spontaneous ICH suggested that DC with hematoma evacuation might be safe and might improve outcomes.<sup>233</sup>

### Minimally Invasive Surgical Evacuation of ICH

Several recent randomized studies have compared minimally invasive aspiration to standard craniotomies and suggested better outcomes with less invasive approaches.<sup>227,231,241–243</sup> A meta-analysis of 12 clinical trials suggested superiority of minimally invasive approaches over craniotomy, but methodological issues with this analysis have been raised.<sup>229,244</sup> A recent randomized study of 465 patients compared needle aspiration of basal ganglia hemorrhages (25–40 mm<sup>3</sup>) to medical management alone. Although there was no significant impact on mortality, 3-month neurological outcome was better in the aspiration group.<sup>227</sup> The Minimally Invasive Surgery Plus Recombinant Tissue-Type Plasminogen Activator for ICH Evacuation Trial II (MISTIE II) aimed to determine the safety of minimally invasive surgery plus rtPA in the setting of ICH. This study compared 79 surgical patients with 39

medical patients. The study demonstrated a significant reduction in perihematomal edema in the hematoma evacuation group with a trend toward improved outcomes.<sup>231</sup> A randomized phase 3 clinical trial of minimally invasive hematoma evacuation (MISTIE III) is currently in progress.

### Timing of Surgery

Timing of surgery for ICH remains controversial. Randomized prospective trials to date have reported on a wide time frame for surgery that ranges from 4 to 96 hours after symptom onset.<sup>226,235,245,246</sup> Subgroup analyses of patients in STICH II suggested a trend toward better outcome for patients operated on before 21 hours from ictus.<sup>226</sup> An individual patient meta-analysis of 2186 patients from 8 trials of surgery for ICH found that surgery improved outcome if performed within 8 hours of hemorrhage.<sup>247</sup> Ultra-early craniotomy (within 4 hours from ictus) was associated with an increased risk of rebleeding in a study that involved 24 patients.<sup>248</sup>

### Surgical Treatment of ICH: Recommendations

1. Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible (*Class I; Level of Evidence B*). Initial treatment of these patients with ventricular drainage rather than surgical evacuation is not recommended (*Class III; Level of Evidence C*). (Unchanged from the previous guideline)
2. For most patients with supratentorial ICH, the usefulness of surgery is not well established (*Class IIb; Level of Evidence A*). (Revised from the previous guideline) Specific exceptions and potential subgroup considerations are outlined below in recommendations 3 through 6.
3. A policy of early hematoma evacuation is not clearly beneficial compared with hematoma evacuation when patients deteriorate (*Class IIb; Level of Evidence A*). (New recommendation)
4. Supratentorial hematoma evacuation in deteriorating patients might be considered as a life-saving measure (*Class IIb; Level of Evidence C*). (New recommendation)
5. DC with or without hematoma evacuation might reduce mortality for patients with supratentorial ICH who are in a coma, have large hematomas with significant midline shift, or have elevated ICP refractory to medical management (*Class IIb; Level of Evidence C*). (New recommendation)
6. The effectiveness of minimally invasive clot evacuation with stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain (*Class IIb; Level of Evidence B*). (Revised from the previous guideline)

### Outcome Prediction and Withdrawal of Technological Support

Observational and epidemiological studies have identified a wide range of factors associated with outcome after acute ICH; identification of these factors led to the development of models to predict mortality and functional outcome. These

prediction models include individual patient characteristics such as score on the GCS or NIHSS, age, hematoma volume and location, and the presence and amount of IVH.<sup>26,30,249–256</sup> None of these prediction models, however, account for the impact of care limitations such as do-not-attempt-resuscitation (DNAR) orders or the withdrawal of technological support.

Most patients who die of ICH do so during the initial acute hospitalization, and these deaths usually occur in the setting of withdrawal of support because of presumed poor prognosis.<sup>257,258</sup> Palliative care is an important aspect of care for patients with severe ICH and their families whether or not withdrawal of support is being pursued, and this is discussed in substantially more detail in the recently released American Heart Association scientific statement on “Palliative and End-of-Life Care in Stroke.”<sup>259</sup> Several studies, however, have identified withdrawal of medical support and other early care limitations, such as DNAR orders within the first day of hospitalization, as independent predictors of outcome.<sup>260–262</sup> By definition, a DNAR order means that there should be no attempt at resuscitation should a cardiopulmonary arrest occur. In practical use, however, DNAR orders are a proxy for overall lack of aggressive care when administered early after ICH, and the overall aggressiveness of ICH care at a hospital is associated with patient outcomes, even after controlling for specific individual characteristics.<sup>136,261,263</sup> The decision to limit care early after ICH may therefore result in self-fulfilling prophecies of poor outcome, and studies show that current outcome prediction models are overly pessimistic because of the failure to account for these care limitations.<sup>264,265</sup>

Prognostication early after ICH is often desired by physicians, patients, and families, but existing prognostic models are biased by limitation-of-care decisions. Providers should therefore be cautious about offering precise prognoses early after ICH, especially if the purpose of prognostication is to consider withdrawal of support or DNAR orders.<sup>266</sup> Aggressive, guideline-concordant therapy is thus recommended for patients with ICH who do not have advanced directives specifying that such care should not be undertaken.

### Outcome Prediction and Withdrawal of Technological Support: Recommendation

1. Aggressive care early after ICH onset and postponement of new DNAR orders until at least the second full day of hospitalization is probably recommended (*Class IIa; Level of Evidence B*). Patients with preexisting DNAR orders are not included in this recommendation. Current prognostic models for individual patients early after ICH are biased by failure to account for the influence of withdrawal of support and early DNAR orders. DNAR status should not limit appropriate medical and surgical interventions unless otherwise explicitly indicated (*Class III; Level of Evidence C*). (Revised from the previous guideline)

### Prevention of Recurrent ICH

Patients with ICH are at high risk of a recurrent event and of other major vascular disease.<sup>267</sup> The cumulative risk of



ICH recurrence is 1% to 5% per year.<sup>267–269</sup> In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), the hazard ratio (HR) for ICH recurrence among subjects with prior ICH relative to a first ICH in subjects with prior ischemic stroke was 6.60 (95% CI, 4.50–9.68).<sup>267</sup> Although the risk of ICH recurrence is highest in the first year after the initial event, the ongoing risk extends for years, particularly in patients with lobar ICH.<sup>269,270</sup>

### Risk Factors

Hypertension, older age, and location of the initial hemorrhage (deep versus lobar) are important risk factors for ICH recurrence.<sup>269,271</sup> High BP is associated with an increase in the recurrence of both deep and lobar hemorrhages.<sup>271</sup> Increased risk in the elderly is attributed to a higher prevalence of cerebral amyloid angiopathy (CAA) and increased use of antithrombotic medications with accumulating comorbidities.<sup>272</sup> CAA is a recognized risk factor for recurrent ICH, particularly in lobar locations.<sup>271</sup> Carriers of the apolipoprotein E  $\epsilon$ 2 or  $\epsilon$ 4 alleles,<sup>273</sup> patients with previous ICH before the presenting ICH,<sup>274</sup> and patients with a greater number of microbleeds (particularly microbleeds in lobar brain locations) on gradient echo MRI appear to be at higher risk for ICH recurrence.<sup>272,275</sup> In whites, most of the initial and recurrent hemorrhages tend to be lobar, whereas deep hemorrhages (both initial and recurrent) are more common in Asians.<sup>269,276</sup> A history of ischemic stroke, particularly of the small-vessel “lacunar” type, which shares a common pathogenesis with ICH, might also be a predictor of ICH recurrence.<sup>277,278</sup>

### BP Management

Among the preceding risk factors, only BP and the use of antithrombotic agents are modifiable. In PROGRESS, treatment with perindopril (4 mg daily) and indapamide reduced baseline BP by an average of 12 mmHg systolic and 5 mmHg diastolic and lowered the risks of first and recurrent ICH (adjusted HR, 0.44 [95% CI, 0.28–0.69] and 0.37 [95% CI, 0.10–1.38], respectively), as well as other vascular events.<sup>267,273,279</sup> In that trial, the lowest risk of stroke recurrence was seen among patients with the lowest follow-up BP levels (median, 112 mmHg systolic and 72 mmHg diastolic)<sup>280</sup>; those with prior ICH derived the greatest benefit, and the size of the benefit was directly related to the degree of BP lowering, with no clear evidence of a lower threshold below which the benefit attenuated or even reversed, as is seen for ischemic stroke or coronary artery disease. Results of the Secondary Prevention of Small Subcortical Strokes (SPS3) study have shown that the greatest benefit of “more intensive” BP lowering is on the prevention of ICH in patients with established small-vessel stroke disease and that lowering target SBP to <130 mmHg significantly reduced the risk of ICH (risk reduction, 60%; HR, 0.37;  $P=0.03$ ),<sup>281</sup> which suggests that ICH patients should have their BP lowered to or beyond the targets currently recommended in other high-risk groups (<130 mmHg systolic and 80 mmHg diastolic in the presence of diabetes mellitus, heart failure, or chronic kidney disease).<sup>282</sup> Other factors, such as BP variability, the presence of obstructive sleep apnea,<sup>283,284</sup> obesity, and other lifestyle modifications, should also be

considered despite the lack of systematic data regarding their effect on ICH recurrence. Frequent alcohol use (>2 drinks per day)<sup>285</sup> and illicit drug use have been linked to elevated BP and ICH<sup>286</sup> and should be avoided in ICH patients. Tobacco use is also associated with increased ICH risk<sup>287–291</sup> and should be discontinued.

The optimal timing for initiating BP lowering after ICH to prevent recurrence is unknown. In INTERACT2, rapid reduction of SBP to <140 mmHg within a few hours was safe, which indicates that such treatment can be safely initiated as soon as possible after ICH onset.<sup>134</sup>

### Management of Antithrombotic Drugs

The rising use of anticoagulant agents in an aging population is associated with increased risk of ICH and its recurrence.<sup>292</sup> There is a marked paucity of prospective population-based data on the risk of ICH recurrence and mortality after reinitiation of warfarin. In a cohort of 284 consecutive patients with warfarin-related ICH in the Registry of the Canadian Stroke Network, mortality rates were lower in those who restarted warfarin in the hospital: 31.9% versus 54.4% at 30 days ( $P<0.001$ ) and 48% versus 61% at 1 year ( $P=0.04$ ), and the rates of bleeding events were not increased.<sup>293</sup> In a retrospective cohort study of 2869 ICH patients, of whom 234 had warfarin-associated ICH, the HR for recurrent ICH with resumption of warfarin was 5.6 (95% CI, 1.8–17.2) during a median 69-week follow-up period.<sup>294</sup> In another study of 48 patients with warfarin-associated ICH, of 23 patients who began taking warfarin again, 1 had a recurrent ICH and 2 subsequently had traumatic intracranial hemorrhage, whereas none who did not restart warfarin had recurrent intracranial bleeding. However, 5 patients in the nonrestarted group developed thromboembolism (2 with stroke) compared with none in the group who restarted warfarin.<sup>295</sup> Using a Markov decision model and estimates for 1-year risk of ICH recurrence of 15% after lobar ICH versus 2.1% for deep ICH, Eckman et al<sup>296</sup> found that withholding anticoagulation improved quality-adjusted life-year expectancy by 1.9 quality-adjusted life-years after lobar ICH and 0.3 quality-adjusted life-years after deep ICH, which led to the conclusion that anticoagulation should be avoided after lobar ICH but can be considered in patients with deep hemorrhage if the risk of thromboembolism is particularly high. CAA is an important cause of warfarin-associated lobar ICH in the elderly. The presence of microbleeds might increase the risk of ICH recurrence in warfarin users, although there are no prospective data. In a pooled analysis of ICH and ischemic stroke or transient ischemic attack patients, microbleeds were more frequent in warfarin users with ICH than in nonwarfarin users (OR, 2.7; 95% CI, 1.6–4.4;  $P<0.001$ ) but were not more frequent in warfarin users with ischemic stroke or transient ischemic attack (OR, 1.3; 95% CI, 0.9–1.7;  $P=0.33$ ;  $P$  difference between pooled OR, 0.01), and the presence of microbleeds was associated with a higher risk of subsequent ICH (OR, 12.1; 95% CI, 3.4–42.5;  $P<0.001$ ).<sup>297</sup>

The optimal timing for resumption of anticoagulation after ICH, if necessary, is uncertain, and no randomized trial data are available to guide the decision. Several observational studies of patients with anticoagulant-related ICH found



low rates of cardioembolic events while not receiving anticoagulation therapy or recurrent ICH when anticoagulation was resumed,<sup>298–300</sup> but the results are limited by relatively small sample sizes and short durations of follow-up. A larger study of 234 patients with warfarin-related ICH followed up for a median of 34 weeks found that the risk of rebleeding with early resumption of anticoagulation exceeded the risk of thromboembolism from withholding it, whereas later, the opposite was true.<sup>294</sup> A survival model based on these data found that the total risk of ischemic plus hemorrhagic stroke was minimized when anticoagulation was reinitiated after  $\approx 10$  weeks, and the authors suggested a delay of at least 1 month after ICH.<sup>294</sup> In practice, the timing often depends on the indication for anticoagulation. In patients with prosthetic heart valves, early resumption of anticoagulation may be necessary because of the high risk of embolism. Although there are conflicting reports regarding the risk of ICH recurrence with antiplatelet use, particularly in patients with lobar ICH,<sup>272,301</sup> antiplatelet monotherapy<sup>302</sup> or percutaneous left atrial appendage closure<sup>303</sup> might be safer alternatives to warfarin in some patients with atrial fibrillation. Antiplatelet agents do not appear to dramatically increase the risk of hematoma expansion<sup>52,102</sup> and therefore appear to be generally safe for use after ICH, including ICH caused by CAA. Although dabigatran, rivaroxaban, and apixaban are reported to convey a lower risk of ICH than warfarin in atrial fibrillation patients,<sup>71,72,304</sup> their usefulness as alternatives to warfarin after ICH remains to be determined.

Meta-analyses suggest that aspirin use is associated with modest increases in ICH incidence<sup>305</sup> and mortality,<sup>306</sup> but the absolute ICH risk in unselected populations appears to be small relative to the absolute numbers of MIs and ischemic strokes prevented.<sup>305</sup> A small observational study found that antiplatelet use was common after ICH and did not appear to be associated with an increase in the risk of ICH recurrence in 127 survivors of lobar hemorrhage (HR, 0.8; 95% CI, 0.3–2.3;  $P=0.73$ ) and 80 survivors of deep hemorrhage (HR, 1.2; 95% CI, 0.1–14.3;  $P=0.88$ ).<sup>307</sup>

There are conflicting reports regarding the use of statins in patients with ICH.<sup>308–312</sup> In the Stroke Prevention With Aggressive Reduction in Cholesterol Levels (SPARCL) study, the benefit of high-dose atorvastatin in reducing recurrent ischemic stroke was offset in part by an increased risk of ICH. Secondary analysis found that statin treatment, increasing age, and having ICH as the qualifying stroke for study enrollment were factors associated with later ICH occurrence.<sup>308</sup> However, a meta-analysis of 31 randomized controlled trials that included 91 588 statin-treated patients found no significant association between statin use and ICH (OR, 1.08; 95% CI, 0.88–1.32;  $P=0.47$ ); all strokes and all-cause mortality were significantly reduced with statin therapy.<sup>310</sup> A Markov analysis evaluating the risks and benefits of statin therapy in patients with prior ICH concluded that if statin use does increase the risk of ICH, avoidance of statins should be considered in patients with ICH, particularly those with lobar ICH.<sup>311</sup> Concordant with these conclusions, statin use and age were independently associated with the presence and number of microbleeds, especially in

cortical locations, in ICH patients.<sup>313</sup> In contrast, continued statin use after ICH was associated with early neurological improvement and reduced 6-month mortality in a small retrospective study.<sup>312</sup> There are no data on whether the reported propensity for ICH with statin use is dose dependent. It remains unclear whether statins should be continued or discontinued in ICH patients.

## Prevention of Recurrent ICH: Recommendations

1. When stratifying a patient's risk for recurrent ICH may affect management decisions, it is reasonable to consider the following risk factors for ICH recurrence: (1) lobar location of the initial ICH; (2) older age; (3) presence and number of microbleeds on gradient echo MRI; (4) ongoing anticoagulation; and (5) presence of apolipoprotein E  $\epsilon 2$  or  $\epsilon 4$  alleles (*Class IIa; Level of Evidence B*). (Revised from the previous guideline)
2. BP should be controlled in all ICH patients (*Class I; Level of Evidence A*). (Revised from the previous guideline) Measures to control BP should begin immediately after ICH onset (*Class I; Level of Evidence A*). (New recommendation) A long-term goal of BP <130 mm Hg systolic and 80 mm Hg diastolic is reasonable (*Class IIa; Level of Evidence B*). (New recommendation)
3. Lifestyle modifications, including avoidance of alcohol use greater than 2 drinks per day, tobacco use, and illicit drug use, as well as treatment of obstructive sleep apnea, are probably beneficial (*Class IIa; Level of Evidence B*). (Revised from previous guideline)
4. Avoidance of long-term anticoagulation with warfarin as a treatment for nonvalvular atrial fibrillation is probably recommended after warfarin-associated spontaneous lobar ICH because of the relatively high risk of recurrence (*Class IIa; Level of Evidence B*). (Unchanged from the previous guideline)
5. Anticoagulation after nonlobar ICH and antiplatelet monotherapy after any ICH might be considered, particularly when there are strong indications for these agents (*Class IIb; Level of Evidence B*). (Revised from the previous guideline)
6. The optimal timing to resume oral anticoagulation after anticoagulant-related ICH is uncertain. Avoidance of oral anticoagulation for at least 4 weeks, in patients without mechanical heart valves, might decrease the risk of ICH recurrence (*Class IIb; Level of Evidence B*). (New recommendation) If indicated, aspirin monotherapy can probably be restarted in the days after ICH, although the optimal timing is uncertain (*Class IIa; Level of Evidence B*). (New recommendation)
7. The usefulness of dabigatran, rivaroxaban, or apixaban in patients with atrial fibrillation and past ICH to decrease the risk of recurrence is uncertain (*Class IIb; Level of Evidence C*). (New recommendation)
8. There are insufficient data to recommend restrictions on the use of statins in ICH patients (*Class IIb; Level of Evidence C*). (Unchanged from the previous guideline)

## Rehabilitation and Recovery

Knowledge of differences in the natural history of recovery patterns and prognosis for residual disability and functioning between ICH and ischemic stroke is complicated by the lower rate of ICH compared with ischemic stroke and the lumping of subarachnoid hemorrhage and ICH together in many studies. There are also problems associated with the insensitivity of many of the outcome measures used in rehabilitation to allow detection of clinically meaningful differences between groups. Even so, there is growing evidence that patients with ICH make slightly greater and faster gains in recovery than patients with ischemic stroke.<sup>31,314–317</sup>

In general, recovery is more rapid in the first few weeks but may continue for many months after ICH,<sup>28,316</sup> with approximately half of all survivors remaining dependent on others for activities of daily living.<sup>30</sup> However, patients vary in their speed and degree of recovery, and there is no hard rule as to when recovery ends. Cognition, mood, motivation, and social support all influence recovery, and it is difficult to separate intrinsic from adaptive recovery. A simple prognostic score that uses age, ICH volume and location, level of consciousness at admission, and pre-ICH cognitive impairment has been shown to predict independence at 90 days.<sup>30</sup> Such scores are useful across all patients, but prognostic imaging techniques may also be useful with lesions in specific functional areas.<sup>318</sup> Given that ICH is often located in lobar regions and complicated by intraventricular extension, some patients with specific cognitive deficits or delayed recovery that is disproportionate to the size of the lesion may require specialized therapy in rehabilitation.<sup>27</sup>

The provision of stroke rehabilitation services has received considerable attention in recent years. In part this represents a need to tailor services to ensure optimal recovery for patients, and in part it is attributable to fiscal pressures on costly health services. Given strong evidence for the benefits of well-organized, multidisciplinary inpatient (stroke unit) care in terms of improved survival, recovery, and returning home compared with care provided in conventional nondedicated stroke wards,<sup>319</sup> efforts have been made to extend this service model of coordinated care into the community. Specifically, early supported hospital discharge and home-based rehabilitation programs have been shown to be cost-effective,<sup>319</sup> whereas home-based therapy for stable patients has been shown to produce comparable outcomes to conventional outpatient rehabilitation.<sup>320</sup> Comprehensive stroke units that include rehabilitation services demonstrate improved outcomes compared with other models of stroke unit care.<sup>321</sup>

The majority of studies do not differentiate ICH patients from those with ischemic stroke. However, a recent randomized trial in 364 patients in China was specific to ICH, in which a 3 stage in-hospital rehabilitation program was compared to standard ward and medical care. Improvement was significantly greater for the rehabilitation group, measured by Fugl-Meyer and Barthel scales over 6 months, with the greatest improvement evident in the first month after stroke.<sup>322</sup> A similar result was seen in an Australian trial of very early mobilization in 72 patients, but the number of ICH patients

was too small to make any sensible comparisons to those with ischemic stroke.<sup>323</sup>

The success of rehabilitation depends on caregiver training and support; however, the likely configuration of services in any region will depend on available resources and funding options. A key portion of rehabilitation should include education for the patient and caregiver regarding secondary stroke prevention and means to achieve rehabilitation goals. Rehabilitation programs should consider lifestyle changes, depression, and caregiver burden as important issues to address with the patient and caregivers.

## Rehabilitation and Recovery: Recommendations

1. **Given the potentially serious nature and complex pattern of evolving disability and the increasing evidence for efficacy, it is recommended that all patients with ICH have access to multidisciplinary rehabilitation (Class I; Level of Evidence A).** (Revised from the previous guideline)
2. **Where possible, rehabilitation can be beneficial when begun as early as possible and continued in the community as part of a well-coordinated (“seamless”) program of accelerated hospital discharge and home-based resettlement to promote ongoing recovery (Class IIa; Level of Evidence B).** (Unchanged from the previous guideline)

## Future Considerations

As documented above, the acute treatment of spontaneous ICH remains under intense investigation. Thanks largely to INTERACT2,<sup>134</sup> acute lowering of BP can now be considered safe and potentially effective for improving outcome in most instances of ICH. Ongoing and future studies in this area, such as ATACH II,<sup>324</sup> will seek to solidify the evidence for efficacy of BP lowering and refine the BP ranges and targets that should be applied in practice. These studies will also address other outstanding questions, such as whether the spot sign or other neuroimaging findings identify patients more likely to benefit from BP lowering.<sup>325</sup>

Although current evidence does not establish a general strategy of early surgery for supratentorial ICH, studies will continue to seek subgroups of patients who benefit. Another major focus in future years will be determining whether minimally invasive surgery<sup>231</sup> can provide the advantages of hematoma removal with less surgical trauma and therefore greater net benefit to patients. Another rational but still unproven approach to acute ICH treatment is neuroprotection of surrounding brain tissue from the toxic effects of the hematoma. The translation of biological data on neuroprotection from animals to human ICH patients may face the same difficulties encountered by the ischemic stroke neuroprotection field, such as identifying the correct animal model system and a clinically relevant time frame for treatment.<sup>326</sup> Emerging methods such as prehospital administration of candidate neuroprotectants<sup>327</sup> should increase the range of feasible treatment approaches and time windows for acute ICH.

As targeted treatments for acute ICH continue to be analyzed, it is important to note that many of the gains seen in

ICH outcome have resulted from improved hospital care. Improvements in hospital care tend to be incremental rather than revolutionary but can sum to substantial benefits to patients and remain a key part of future ICH research.

Acute ICH treatment, like acute ischemic stroke treatment, is fundamentally limited in its ability to reduce stroke-related disability; for this reason, it is improved ICH prevention and recovery that has the greatest potential for reducing overall disease burden. In the area of ICH prevention, BP control can be considered as established treatment.<sup>273,328</sup> There remains no

disease-modifying treatment for prevention of CAA-related ICH; however, this is a major goal for ongoing and future trials. Another important question to be addressed is the possible role of the newer direct OACs in patients at increased ICH risk and the identification of the subgroup that might derive the greatest benefit from the reduced tendency of these agents to trigger intracranial bleeding.<sup>72,73,304</sup> Finally, there are no specific treatments or therapies established for enhancing post-ICH recovery, which highlights a tremendous opportunity for improving outcome from this devastating form of stroke.

## Disclosures

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\*Modest.

†Significant.

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## Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

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## AHA/ASA Guideline

## 脳内出血の管理に関するガイドライン

## Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

*The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.**Endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Neurocritical Care Society*

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本ガイドラインは英文 *Stroke* 誌 7 月号に掲載された脳内出血 (ICH) の管理に関する米国心臓協会/米国脳卒中協会 (AHA/ASA) ガイドラインで、2010 年のガイドライン (*Stroke* 41:2108-2129, *Stroke* 日本語版 Vol.5, No.3, 35-39) の改訂版である。推奨には AHA/ASA のエビデンスクラスとレベルが用いられている (表 1)。ICH の治療法は虚血性脳卒中の治療ほど注目されていないが、微小出血 (microbleeds: MB) の認識、スポットサインによる再出血の予測、再出血予防のための血圧管理など新しい動きがある。本稿には救急診断からリハビリテーションにおよぶ項目で提唱された全ての推奨を表 2 から表 11 に掲載しているが、表自体は英文原著の表と関係がないことにご注意いただきたい。また紙面が限られているため、以下の要約は新しい推奨の簡単な紹介に限定させていただいた。

救急診断と評価 (表 2) では、意識障害のため ICH 患者に NIHSS が使いにくく、病状が急速に悪化することが多いため、来院時にまず ICH の重症度スコアを評価すべきとしている。現時点で NIHSS のように普遍化されたスケールはないが、ICH Score (*Neurology* 2009;73:1088) はその一つである。止血と凝固障害への対応 (表 3) では、主として薬剤性凝固障害につき述べられており、新しい経口抗凝固薬 (NOAC) 服用者に対する FEIBA や血液透析の適応が述べられ、一時注目された活性型第 VII 因子は ICH には一般的に推奨されないとしている。NOAC の新しい拮抗薬についてはまだ

臨床試験の段階であり、記載はない。血圧の管理 (表 4) では INTERACT2 試験の結果を受けて、収縮期血圧が 150 ~ 220mmHg の場合に 140mmHg まで下げることが安全であり、220mmHg 以上の場合には薬剤の持続点滴とモニタリングで急激に低下させることを推奨している。入院管理と二次的脳損傷の予防 (表 5) では ICH 患者の管理に ICU に加えて設備の整った SCU が加えられている。ICH 患者では持続した発熱が転帰に影響を及ぼすとされることから、発熱の治療には肯定的であるが、軽度であっても低体温療法はまだ研究の段階であるとしている。内科的合併症の管理 (表 6) では、誤嚥性肺炎予防のため、経口摂取前に嚥下障害のスクリーニング (例えば飲水テスト) をすることが推奨され、脳卒中後に急性心筋梗塞、心不全、心室性不整脈が起こることから、心電図および血中心筋酵素のスクリーニングが新たに勧められている。ICH 後の頭蓋内圧亢進症の治療 (表 7) には副腎皮質ステロイドを禁忌とする一文が加えられた。ICH と脳室内出血の脳外科的治療 (表 8) において、早期の血腫除去は臨床的な悪化後の血腫除去と比較して明らかな有益性を認めないが、悪化した患者では救命手段として考慮することが認められ、開頭減圧術により死亡率の低下が期待されるとしている。生命維持処置 (表 9) について新しい推奨はない。ICH の再発予防 (表 10) については ICH 発症直後から血圧コントロールが推奨され、長期的には 130 以下 /80mmHg が妥当としている。ICH 後の経口抗凝固薬の開始時期はまだ確定し

ていないが、機械弁のない患者では4週間は待つよう推奨されている。心房細動をもつ ICH 患者の再発予防のための NOAC の有用性はまだ確立されていないが、アスピリンの単独投与は発症数日後には再開に肯定的であ

る。リハビリテーション(表 11)の新しい推奨はないが、全ての ICH 患者が集学的リハビリテーションを受けられるよう推奨レベルが格上げされた。

(文責：柳原武彦)

表 1 AHA/ASA の推奨に用いられているエビデンスの分類とレベルの定義

クラス I	手技または治療法の有用性および有効性を示すエビデンス、または一般的合意がある。
クラス II	手技または治療法の有用性および有効性に関して相反するエビデンス、または意見の相違がある。
クラス IIa	エビデンスまたは意見は手技または治療法を支持する。
クラス IIb	エビデンスまたは意見による有用性および有効性の確立が十分でない。
クラス III	手技または治療法の有用性および有効性がなく、場合によっては有害となりうることを示すエビデンス、または一般的合意がある。
治療に関する推奨	
エビデンスレベル A	複数の無作為臨床試験またはメタ解析から得られたデータ
エビデンスレベル B	単一の無作為試験または複数の非無作為試験から得られたデータ
エビデンスレベル C	専門家の意見、症例研究または標準的治療
診断に関する推奨	
エビデンスレベル A	盲検化された評価者による参照基準を用いた複数の前向きコホート研究から得られたデータ
エビデンスレベル B	単一のグレード A 試験、1 つ以上の症例対照研究、または盲検化されていない評価者による参照基準を用いた複数の試験から得られたデータ
エビデンスレベル C	専門家の意見

AHA/ASA : American Heart Association/American Stroke Association

表 2 救急診断と評価に関する推奨

推 奨	エビデンスのクラスとレベル
1. 脳内出血 (ICH) 患者の初期評価の一環として、ベースライン重症度スコアを算定すべきである	クラス I ; エビデンスレベル B (新たな推奨)
2. 虚血性脳卒中と ICH の鑑別のために CT または MRI による迅速な脳神経画像検査が推奨される	クラス I ; エビデンスレベル A (前回のガイドラインから変更なし)
3. 血腫拡大のリスクを有する患者を特定できるよう CTA および造影 CT を考慮してもよい	クラス IIb ; エビデンスレベル B
また、血管奇形や腫瘍など根底にある構造的病変が臨床的にまたは画像から疑われる場合、その評価のために CTA、CT 静脈造影法、造影 CT、造影 MRI、MR 血管造影法、MR 静脈造影法、カテーテル血管造影法が有用と考えられる	クラス IIa ; エビデンスレベル B (前回のガイドラインから変更なし)

表 3 止血と凝固障害、抗血小板薬、深部静脈血栓症予防に関する推奨

推 奨	エビデンスのクラスとレベル
1. 重度の凝固因子欠乏症患者および重度の血小板減少症患者には、適切な凝固因子および血小板補充療法を行うべきである。	クラス I ; エビデンスレベル C (前回のガイドラインから変更なし)
2. ビタミン K 拮抗薬 (VKA) により INR が高値の脳内出血 (ICH) 患者では、VKA 投与を中止し、ビタミン K 依存性因子の補充療法、INR の補正、ビタミン K の静脈内投与を行うべきである。	クラス I ; エビデンスレベル C
プロトロンビン複合体濃縮製剤 (PCC) は新鮮凍結血漿 (FFP) と比較して合併症が少なく、INR を迅速に補正するため、FFP ではなく PCC を考慮してもよいだろう。	クラス IIb ; エビデンスレベル B
遺伝子組換え活性型第 VII 因子製剤 (rFVIIa) はすべての凝固因子を補充するものではなく、INR は低下するが、in vivo において凝固能は回復しない可能性があるため、ICH における VKA の中和に rFVIIa は推奨されない。	クラス III ; エビデンスレベル C (前回のガイドラインから変更)
3. ダビガトラン、リバーロキサバンまたはアビキサパンを服用している ICH 患者では、症例によっては、血液凝固因子抗体迂回活性複合体 (FEIBA)、その他の PCC または rFVIIa の投与を考慮してもよいだろう。直近のダビガトラン、アビキサパンまたはリバーロキサパンの服用から 2 時間未満であれば活性炭を使用してもよいだろう。ダビガトランについては血液透析を考慮してもよいかもしれない。	クラス IIb ; エビデンスレベル C (新たな推奨)
4. 急性 ICH 患者では、ヘパリンの中和にプロタミン硫酸塩を考慮してもよいだろう。	クラス IIb ; エビデンスレベル C (新たな推奨)
5. 抗血小板薬の投与歴を有する ICH 患者における血小板輸血の有用性は確定していない。	クラス IIb ; エビデンスレベル C (前回のガイドラインから変更)
6. 凝固障害のない ICH 患者において、rFVIIa は血腫の拡大を制限するが、FVIIa には血栓塞栓症のリスクの増加が認められるため、非選択的な患者には明らかな臨床的有益性はない。したがって、rFVIIa は推奨されない。	クラス III ; エビデンスレベル A (前回のガイドラインから変更なし)
7. 静脈血栓塞栓症予防のため、ICH 患者には入院当日から間欠的空気圧迫法を行うべきである。	クラス I ; エビデンスレベル A
深部静脈血栓症 (DVT) の低減または転帰の改善に、段階式着圧ストッキングは有効ではない。	クラス III ; エビデンスレベル A (前回のガイドラインから変更)

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表3 止血と凝固障害、抗血小板薬、深部静脈血栓症予防に関する推奨（前ページより続く）

推 奨	エビデンスのクラスとレベル
8. 発症後1～4日間可動不能な患者では、静脈血栓症の予防のため、止血の確認後、低分子量ヘパリンまたは未分画ヘパリンの低用量皮下投与を考慮してもよい。	クラスIIb；エビデンスレベルB (前回のガイドラインから変更なし)
9. 症候性DVTまたは肺塞栓症(PE)を有するICH患者には、抗凝固薬の全身投与または下大静脈フィルター留置の適応があるだろう。	クラスIIa；エビデンスレベルC
この2つの選択肢からの決定には、出血後の時間、血腫の安定性、出血の原因、患者の総合的状态などいくつかの要素を考慮すべきである。	クラスIIa；エビデンスレベルC (新たな推奨)

表4 血圧に関する推奨

推 奨	エビデンスのクラスとレベル
1. 収縮期血圧(SBP)が150～220 mmHgで急性期降圧療法が禁忌でない脳内出血(ICH)患者では、SBP 140 mm Hgまでの急激な降圧は安全である。 また、このような降圧処置は機能的転帰の改善に有効と考えられる。	クラスI；エビデンスレベルA,  クラスIIa；エビデンスレベルB (前回のガイドラインから変更)
2. SBPが220 mm Hgを超えるICH患者では、持続静注による積極的な降圧および頻回な血圧測定を考慮するのが妥当かもしれない。	クラスIIb；エビデンスレベルC (新たな推奨)

表5 入院管理と二次的脳損傷の予防に関する推奨

推 奨	エビデンスのクラスとレベル
1. 脳内出血(ICH)患者の初期のモニタリングおよび管理は、医師および神経系疾患の急性期看護知識をもった看護師がいる集中治療室またはstroke unitで行うべきである。	クラスI；エビデンスレベルB (前回のガイドラインから変更)
2. 血糖値をモニタリングすべきである。高血糖および低血糖はいずれも回避すべきである。	クラスI；エビデンスレベルC (前回のガイドラインから変更)
3. ICH後の発熱の治療は妥当と考えられる。	クラスIIb；エビデンスレベルC (新たな推奨)
4. 臨床的けいれん発作には抗てんかん薬を投与すべきである。	クラスI；エビデンスレベルA (前回のガイドラインから変更なし)
精神状態の変化を呈し、脳波検査で脳波的けいれん発作波が認められる患者には抗てんかん薬を投与すべきである	クラスI；エビデンスレベルC (前回のガイドラインから変更なし)
脳損傷の程度と不釣り合いな意識レベルの低下を呈するICH患者は持続的脳波モニタリングの適応があるだろう。	クラスIIa；エビデンスレベルC (前回のガイドラインから変更)
抗てんかん薬の予防的投与は推奨されない。	クラスIII；エビデンスレベルB (前回のガイドラインから変更なし)

表6 内科的合併症の管理に関する推奨

推 奨	エビデンスのクラスとレベル
1. 経口摂取の開始前に、肺炎のリスクを軽減するためすべての患者に対して嚥下障害の正式なスクリーニングを行うべきである	クラスI；エビデンスレベルB (新たな推奨)
2. 脳内出血後の心電図および心筋酵素検査による心筋虚血または心筋梗塞の系統的なスクリーニングは妥当である	クラスIIa；エビデンスレベルC (新たな推奨)

表7 頭蓋内圧モニタリングと頭蓋内圧亢進症の治療に関する推奨

推 奨	エビデンスのクラスとレベル
1. 水頭症の治療としての脳室ドレナージは、特に意識レベルが低下した患者には妥当である	クラスIIa；エビデンスレベルB (前回のガイドラインから変更)
2. グラスゴー コーマ スケールが8以下の患者、テント切痕ヘルニアの臨床的所見を有する患者、あるいは重度の脳室内出血または水頭症を有する患者では、頭蓋内圧のモニタリングおよび治療を考慮してもよいだろう。脳自動調節能に応じて、脳灌流圧50～70 mm Hgを維持するのが適切だろう。	クラスIIb；エビデンスレベルC (前回のガイドラインから変更なし)
3. 脳内出血における頭蓋内圧亢進症の治療に副腎皮質ステロイドを投与すべきではない	クラスIII；エビデンスレベルB (新たな推奨)

表8 脳内出血と脳室内出血の脳外科的治療に関する推奨

推 奨	エビデンスのクラスとレベル
1. 脳室内出血(IVH)における組換え型組織プラスミノゲン活性化因子(rt-PA)の脳室内投与は合併症発症率がかなり低いように思われるが、その有効性および安全性は確実でない。	クラスIIb；エビデンスレベルB (前回の推奨から変更)
IVHの内視鏡治療の有効性は確実でない。	クラスIIb；エビデンスレベルB (新たな推奨)

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表 8 脳内出血と脳室内出血の脳外科的治療に関する推奨（前ページより続く）

推 奨	エビデンスのクラスとレベル
2. 神経学的悪化を認める小脳出血患者、または脳幹圧迫および脳室閉塞による水頭症またはそのいずれかを有する小脳出血患者では、できるだけ速やかに出血の外科的除去を行うべきである。 このような患者では、外科的除去ではなく脳室ドレナージによる初期治療は推奨されない。	クラス I；エビデンスレベル B  クラス III；エビデンスレベル C (前回のガイドラインから変更なし)
3. テント上脳内出血患者の大部分において、手術の有用性は十分に確立されていない。  具体的な例外および考慮すべきサブグループを推奨 4～7 に示す。	クラス IIb；エビデンスレベル A (前回のガイドラインから変更)
4. 早期の血腫除去は患者が悪化した時点での血腫除去と比較して明らかな有益性は認められない。	クラス IIb；エビデンスレベル A (新たな推奨)
5. 悪化した患者では救命手段としてテント上血腫除去を考慮してもよいだろう。	クラス IIb；エビデンスレベル C (新たな推奨)
6. 血腫除去の併用の有無に関わらず、開頭減圧術 (DC) により、昏睡状態にある、著明な正中偏位を伴う大きな血腫を有する、または内科的治療に抵抗性の頭蓋内圧亢進を有するテント上脳内出血患者の死亡率が低下するかもしれない。	クラス IIb；エビデンスレベル C (新たな推奨)
7. 血栓溶解薬併用の有無に関わらず定位的吸引または内視鏡的吸引による低侵襲的血栓除去の有効性は確実でない。	クラス IIb；エビデンスレベル B (前回のガイドラインから変更)

表 9 転帰予測と生命維持支援の中止に関する推奨

推 奨	エビデンスのクラスとレベル
1. 脳内出血 (ICH) 発症後早期の積極的な治療および新たな延命治療中止 (DNAR) 指示の少なくとも入院 2 日目までの延期は推奨されるだろう。  DNAR の指示が既に出されている患者はこの推奨の対象とならない。現在の ICH 発症後早期の個々の患者の予後予測モデルには、生命維持支援の中止および早期の DNAR 指示の影響を考慮していないというバイアスがかかっている。特に明示されていない限り、DNAR 指示の有無が適切な内科的介入および外科的介入を制限すべきではない。	クラス IIa；エビデンスレベル B  クラス III；エビデンスレベル C (前回のガイドラインから変更)

表 10 脳内出血の再発予防に関する推奨

推 奨	エビデンスのクラスとレベル
1. 脳内出血 (ICH) 再発のリスクを層別化することが治療方針の決定に影響を及ぼす場合には、以下の ICH 再発の危険因子を考慮に入れることが妥当である。(1) 最初の ICH をきたした脳葉の位置、(2) 高齢であること、(3) グラディエントエコー MRI での微小出血の有無および数、(4) 抗凝固療法を実施中であるか否か、(5) アポリポ蛋白 E の ε2 または ε4 アレルの有無。	クラス IIa；エビデンスレベル B (前回のガイドラインから変更)
2. すべての ICH 患者において血圧をコントロールすべきである。  血圧コントロールは ICH 発症後直ちに開始すべきである。  収縮期血圧 130 mm Hg 未満、拡張期血圧 80 mm Hg 未満を長期目標とすることが妥当である。	クラス I；エビデンスレベル A (前回のガイドラインから変更)  クラス I；エビデンスレベル A (新たな推奨)  クラス IIa；エビデンスレベル B (新たな推奨)
3. 1 日 2 杯を超える飲酒、喫煙および違法薬物の使用を抑える等の生活習慣の改善とともに、閉塞性睡眠時無呼吸の治療は有益だろう。	クラス IIa；エビデンスレベル B (前回のガイドラインから変更)
4. ワルファリンに関連する自然発症の脳葉性 ICH 後は再発のリスクが比較的高いため、非弁膜症性心房細動の治療としてワルファリンによる長期抗凝固療法は避けたほうがよいだろう。	クラス IIa；エビデンスレベル B (前回のガイドラインから変更なし)
5. 非脳葉性 ICH 後の抗凝固療法および全ての ICH 後の抗血小板薬単独投与は、特にこれらの薬剤に強い適応がある場合には考慮してもよいだろう。	クラス IIb；エビデンスレベル B (前回のガイドラインから変更)
6. 抗凝固療法に関連する ICH 後の経口抗凝固療法再開の最適時期は確立していない。機械弁を植え込んでいない患者では、少なくとも 4 週間は経口抗凝固療法を抑えることにより ICH 再発のリスクが低下する可能性がある。 アスピリン単独投与が適応となる場合には、最適時期は確定していないが、ICH 発症から数日後に投与を再開することが有益と思われる。	クラス IIb；エビデンスレベル B (新たな推奨)  クラス IIa；エビデンスレベル B (新たな推奨)
7. 心房細動を有し、ICH の既往がある患者の再発リスクを低下させるためのダビガトラン、リバーロキサパンまたはアピキサパンの有用性は確立していない。	クラス IIb；エビデンスレベル C (新たな推奨)
8. ICH 患者においてスタチン剤の使用制限を推奨するデータは不十分である。	クラス IIb；エビデンスレベル C (前回のガイドラインから変更なし)

表 11 リハビリテーションと回復に関する推奨

推 奨	エビデンスのクラスとレベル
1. 機能障害が重篤で、かつ進行パターンが複雑であり、リハビリテーションの有効性を示すエビデンスが蓄積されていることから、すべての脳内出血患者に集学的リハビリテーションを受けさせることが推奨される。	クラス I；エビデンスレベル A (前回のガイドラインから変更)
2. 可能であれば、リハビリテーションをできるだけ速やかに開始し、連携のとれた (シームレスな) 早期退院と在宅復帰プログラムの一環として継続することは、回復を促進するために有益と考えられる。	クラス IIa；エビデンスレベル B (前回のガイドラインから変更なし)