

# Stroke

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**Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults: 2007 Update: A Guideline From the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.**

Joseph Broderick, Sander Connolly, Edward Feldmann, Daniel Hanley, Carlos Kase, Derk Krieger, Marc Mayberg, Lewis Morgenstern, Christopher S. Ogilvy, Paul Vespa and Mario Zuccarello

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## Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults

2007 Update

A Guideline From the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group

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

Joseph Broderick, MD, FAHA, Chair; Sander Connolly, MD, FAHA, Vice-Chair; Edward Feldmann, MD, FAHA; Daniel Hanley, MD, FAHA; Carlos Kase, MD, FAHA; Derk Krieger, MD; Marc Mayberg, MD, FAHA; Lewis Morgenstern, MD, FAHA; Christopher S. Ogilvy, MD; Paul Vespa, MD; Mario Zuccarello, MD

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

**Methods**—A formal literature search of Medline was performed through the end date of August 2006. The results of this search were complemented by additional articles on related issues known to the writing committee. Data were synthesized with the use of evidence tables. The American Heart Association Stroke Council's Levels of Evidence grading algorithm was used to grade each recommendation. Prerelease review of the draft guideline was performed by 5 expert peer reviewers and by the members of the Stroke Council Leadership Committee. It is intended that this guideline be fully updated in 3 years' time.

**Results**—Evidence-based guidelines are presented for the diagnosis of intracerebral hemorrhage, the management of increased arterial blood pressure and intracranial pressure, the treatment of medical complications of intracerebral hemorrhage, and the prevention of recurrent intracerebral hemorrhage. Recent trials of recombinant factor VII to slow initial bleeding are discussed. Recommendations for various surgical approaches for treatment of spontaneous intracerebral hemorrhage are presented. Finally, withdrawal-of-care and end-of-life issues in patients with intracerebral hemorrhage are examined. (*Stroke*. 2007;38:2001-2023.)

**Key Words:** AHA Scientific Statement ■ intracerebral hemorrhage ■ treatment

Intracerebral hemorrhage (ICH) causes 10% to 15% of first-ever strokes, with a 30-day mortality rate of 35% to 52%; half of the deaths occur in the first 2 days.<sup>1-3</sup> In one population study of 1041 ICHs, 50% were deep in location, 35% were lobar, 10% were cerebellar, and 6% were in the brain

stem.<sup>4</sup> Death at 1 year for ICH varies by location of ICH: 51% for deep hemorrhage, 57% for lobar, 42% for cerebellar, and 65% for brain stem.<sup>5</sup> Of the estimated 67 000 patients who had an ICH in the United States during 2002, only 20% are expected to be functionally independent at 6 months.<sup>3</sup>

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**TABLE 1. Definition of Classes and Levels of Evidence Used in AHA Stroke Council 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 recommendation	
Level of Evidence A	Data derived from multiple randomized clinical trials
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts
Diagnostic recommendation	
Level of Evidence A	Data derived from multiple prospective cohort studies employing a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study or 1 or more case-control studies or studies employing a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

At the time the first American Heart Association (AHA) guidelines for the management of spontaneous ICH were published in 1999,<sup>6</sup> only 5 small randomized medical trials and 4 small randomized surgical trials of acute ICH existed. In the past 6 years, 15 pilot and larger randomized medical and surgical trials for ICH/intraventricular hemorrhage (IVH) have been completed or are ongoing, as listed at the National Institute of Neurological Disorders and Stroke-funded Stroke Trials Directory; these are in addition to the ongoing phase III trial of recombinant activated factor VII (rFVIIa).<sup>7,8</sup> The recent dramatic increase in clinical trials of ICH/IVH and the initial findings from these trials provide great hope for new and effective treatments for patients with ICH.

Recommendations follow the AHA Stroke Council's methods of classifying the level of certainty of the treatment effect and the class of evidence (see Table 1 and Figure).

### Emergency Diagnosis and Assessment of ICH and Its Causes

Rapid recognition and diagnosis of ICH are essential because of its frequently rapid progression during the first several hours. The classic clinical presentation includes the onset of a sudden focal neurological deficit while the patient is active, which progresses over minutes to hours. This smooth symptomatic progression of a focal deficit over a few hours is uncommon in ischemic stroke and rare in subarachnoid hemorrhage. Headache is more common with ICH than with ischemic stroke, although less common than in subarachnoid hemorrhage.<sup>9</sup>

Vomiting is more common with ICH than with either ischemic stroke or subarachnoid hemorrhage. Increased blood pressure and impaired level of consciousness are common.<sup>9</sup> However, clinical presentation alone, although helpful, is insufficient to reliably differentiate ICH from other stroke subtypes.

The early risk of neurological deterioration and cardiopulmonary instability in ICH is high. Identification of prognostic

indicators during the first several hours is very important for planning the level of care in patients with ICH. The volume of ICH and grade on the Glasgow Coma Scale (GCS) on admission are the most powerful predictors of death by 30 days.<sup>10</sup> Hydrocephalus was an independent indicator of 30-day death in another study.<sup>11</sup> Conversely, cortical location, mild neurological dysfunction, and low fibrinogen levels have been associated with good outcomes in medium to large ICH.<sup>12</sup>

Because of the difficulty in differentiating ICH from ischemic stroke by clinical measures, emergency medicine personnel triage and transport patients with ICH and ischemic stroke to hospitals similarly. As described below, patients with ICH often have greater neurological instability and risk of very early neurological deterioration than do patients with ischemic stroke and will have a greater need for neurocritical care, monitoring of increased intracranial pressure (ICP), and even neurosurgical intervention. This level of care may exceed that available at some hospitals, even those that meet the criteria for primary stroke centers. Thus, each hospital that evaluates and treats stroke patients should determine whether the institution has the infrastructure and physician support to manage patients with moderate-sized or large ICHs or has a plan to transfer these patients to a tertiary hospital with the appropriate resources.

Initial clinical diagnostic evaluation of ICH at the hospital involves assessment of the patient's presenting symptoms and associated activities at onset, time of stroke onset, age, and other risk factors. The patient or witnesses are questioned about trauma; hypertension; prior ischemic stroke, diabetes mellitus, smoking, use of alcohol and prescription, over-the-counter, or recreational drugs such as cocaine; use of warfarin and aspirin or other antithrombotic therapy; and hematologic disorders or other medical disorders that predispose to bleeding, such as severe liver disease.

The physical examination focuses on level of consciousness and degree of neurological deficit after assessment of

“Estimate of Certainty (Precision) of Treatment Effect”		“Size of Treatment Effect”		
Level A <i>Multiple (3-5) population risk strata evaluated*</i> <i>General consistency of direction and magnitude of effect</i>	Class I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment SHOULD be performed/administered	Class IIa <i>Benefit &gt;&gt; Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	Class IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; Additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	
	Class III <i>Risk ≥ Benefit</i> <i>No additional studies needed</i> Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL	Recommendation in favor of treatment or procedure being useful/effective	Recommendation in favor of treatment or procedure being useful/effective	Recommendation that procedure or treatment not useful/effective and may be harmful
	Recommendation that procedure or treatment is useful/effective	Recommendation in favor of treatment or procedure being useful/effective	Recommendation's usefulness/efficacy less well established	Recommendation that procedure or treatment not useful/effective and may be harmful
Level B <i>Limited (2-3) population risk strata evaluated*</i>	Recommendation that procedure or treatment is useful/effective	Recommendation in favor of treatment or procedure being useful/effective	Recommendation's usefulness/efficacy less well established	
Level C <i>Very limited (1-2) population risk strata evaluated*</i>	Recommendation that procedure or treatment is useful/effective	Recommendation in favor of treatment or procedure being useful/effective	Recommendation's usefulness/efficacy less well established	
Suggested phrases for writing recommendations †	should be recommended	is reasonable	may/might be considered	
	is indicated	can be useful/effective/ beneficial	is not recommended	
	is useful/effective/beneficial	is probably recommended or indicated	is not indicated	
			should not be used	
			is not useful/effective/beneficial	
			may be harmful	

\*Data available from clinical trials or registries about the usefulness/efficacy in different sub-populations, such as gender, age, history of diabetes, history of heart failure, and prior aspirin use. 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. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All recommendations in this guideline have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

Figure. Applying classification of recommendations and level of evidence.

airway, breathing, circulation, and vital signs. In several retrospective studies, elevated systolic blood pressure >160 mm Hg on admission has been associated with growth of the hematoma, but this has not been demonstrated in prospective studies of ICH growth.<sup>13–16</sup> Fever >37.5°C that persists for >24 hours is found in 83% of patients with poor outcomes and correlates with ventricular extension of the hemorrhage.<sup>17</sup>

Brain imaging is a crucial part of the emergent evaluation. Computed tomography (CT) and magnetic resonance scans show equal ability to identify the presence of acute ICH, its size and location, and hematoma enlargement. Deep hemorrhages in hypertensive patients are often due to hypertension, whereas lobar hemorrhages in nonhypertensive elderly patients are often due to cerebral amyloid angiopathy; however, a substantial number of lobar hemorrhages in hypertensive patients may be due to hypertension, and both deep and superficial hemorrhages may be caused by vascular abnormalities and other nonhypertensive causes.

CT may be superior at demonstrating associated ventricular extension, whereas magnetic resonance imaging (MRI) is superior at detecting underlying structural lesions and delineating the amount of perihematomal edema and herniation. A CT scan with contrast may identify an associated aneurysm, arteriovenous malformation, or tumor. CT angiography may provide additional detail in patients with suspected aneurysm or arteriovenous malformation.

CT has also clarified the natural history of ICH. One prospective study of spontaneous ICH in the mid-1990s demonstrated that an increase in volume of >33% is detectable on repeated CT examination in 38% of patients initially scanned within 3 hours after onset. In two thirds of cases with growth in volume of ICH, this increase was evident within 1 hour. Growth of the volume of ICH was associated with early neurological deterioration.<sup>15</sup> Hematoma growth is associated with a nearly 5-fold increase in clinical deterioration, poor outcome, and death.<sup>18</sup> The lobar location of ICH increases the risk of long-term recurrence by a factor of 3.8.<sup>19</sup>

MRI performs as well as CT in identifying ICH. In one multicenter study of acute stroke within 6 hours of onset, gradient-echo MRI was as accurate as CT for the identification of acute hemorrhage and more accurate for identification of chronic hemorrhage.<sup>20</sup> In another under-6-hour multicenter diagnostic trial, MRI showed equivalent performance to CT in ICH identification.<sup>21</sup> MRI is also superior to CT for the identification of associated vascular malformations, especially cavernoma. MRI, however, is not as practical as CT for all presenting patients. One study found that MRI was not feasible in 20% of acute stroke patients because of contraindications to MRI or impaired consciousness, hemodynamic compromise, vomiting, or agitation. Of the patients with acute stroke ineligible for MRI, 73% had an ICH.<sup>22</sup>

Indications for catheter angiography include subarachnoid hemorrhage, abnormal calcifications, obvious vascular abnormalities, and blood in unusual locations, such as the sylvian fissure. Angiography may also be indicated in patients with no obvious cause of bleeding, such as those subjects with isolated IVH.<sup>23</sup> The yield of angiography declines in elderly patients with hypertension and a deep hematoma. The timing

of the angiogram balances the need for a diagnosis with the condition of the patient and the potential timing of any surgical intervention. A critically ill patient with hemorrhage and herniation may require urgent surgery before angiography, whereas the stable patient with imaging features of an aneurysm or arteriovenous malformation should undergo angiography before any intervention.

Routine laboratory tests performed in patients with ICH include complete blood count; electrolytes; blood urea nitrogen and creatinine; glucose; electrocardiogram; chest radiography; prothrombin time or international normalized ratio (INR); and activated partial thromboplastin time. A toxicology screen in young or middle-aged persons to rule out cocaine use and a pregnancy test in a woman of childbearing age should also be obtained.

Elevated serum glucose is likely a response to the stress and severity of ICH and is a marker for death, with an odds ratio (OR) of 1.2.<sup>24</sup> Warfarin use, reflected in an elevated prothrombin time or INR, is a risk factor for hematoma expansion (OR 6.2), with expansion continuing longer than in patients not taking warfarin.<sup>25</sup>

Recent studies have identified serum markers that add to the prognostic evaluation of ICH and may provide clues to its pathophysiology. Early neurological deterioration in one study was associated with a temperature >37.5°C, elevated neutrophil count, and serum fibrinogen.<sup>26</sup> Matrix metalloproteinases are matrix-degrading enzymes activated by proinflammatory factors after stroke. Matrix metalloproteinase-9 levels at 24 hours after onset of bleeding correlate with edema, whereas matrix metalloproteinase-3 levels at 24 to 48 hours after bleeding correlate with risk of death. The levels of both enzymes correlate with residual cavity volume.<sup>27</sup> c-Fibronectin is a glycoprotein that is important for platelet adhesion to fibrin and is a marker of vascular damage. Levels of c-fibronectin >6 µg/mL and levels of interleukin-6 (a marker of inflammation) >24 pg/mL were independently associated with ICH enlargement in one study.<sup>18</sup> In another study, levels of tumor necrosis factor-α correlated with perihematomal edema, whereas levels of glutamate correlated with the size of the residual hematoma cavity.<sup>28</sup> The clinical usefulness of these serum markers requires further testing.

## Recommendations for Emergency Diagnosis and Assessment of ICH

### Class I

1. ICH is a medical emergency, with frequent early, ongoing bleeding and progressive deterioration, severe clinical deficits, and subsequent high mortality and morbidity rates, and it should be promptly recognized and diagnosed (*Class I, Level of Evidence A*).
2. CT and magnetic resonance are each first-choice initial imaging options (*Class I, Level of Evidence A*); in patients with contraindications to magnetic resonance, CT should be obtained (*Class I, Level of Evidence A*).

## Treatment of Acute ICH/IVH

### Overall Approach to Treatment of ICH

Potential treatments of ICH include stopping or slowing the initial bleeding during the first hours after onset; removing

blood from the parenchyma or ventricles to eliminate both mechanical and chemical factors that cause brain injury; management of complications of blood in the brain, including increased ICP and decreased cerebral perfusion; and good general supportive management of patients with severe brain injury. Good clinical practice includes management of airways, oxygenation, circulation, glucose level, fever, and nutrition, as well as prophylaxis for deep vein thrombosis. However, because of the lack of definitive randomized trials of either medical or surgical therapies for ICH, until recently, there has been great variability in the treatment of ICH worldwide.

## Medical Treatment of ICH

### Medical Treatment Trials for ICH

Four small randomized trials of medical therapy for ICH were conducted before the 1999 AHA guidelines for management of spontaneous ICH were published.<sup>6</sup> These trials involved steroids versus placebo treatment, hemodilution versus best medical therapy, and glycerol versus placebo.<sup>29–32</sup> None of the 4 studies showed any significant benefit for the 3 therapies. In the study by Pongvarin et al,<sup>31</sup> patients who were treated with steroids were more likely to develop infectious complications than those who received placebo.

The observation that substantial ongoing bleeding occurred in patients with ICH and was linked to neurological deterioration, particularly during the first 3 to 4 hours after onset, dramatically changed the prospects of an effective treatment for ICH.<sup>15</sup> It was this observation that prompted consideration of the use of activated factor VII in patients with spontaneous ICH within the first hours after symptom onset.<sup>33,34</sup> It has also led to renewed interest in the control of blood pressure as a means of decreasing the growth of ICH during the first hours after onset.

Subsequent clinical and animal studies have demonstrated conclusively that the low-density region that is frequently observed surrounding the ICH on the baseline CT during the first several hours after onset is due to extruded serum from clotting blood and that this serum is rich in thrombin.<sup>35–37</sup> This hypodensity also grows during the first 24 hours in parallel with the volume of ICH but has not been independently associated with worse outcome. Proteins and proteases in the serum surrounding the ICH may have potential deleterious effects and could be additional targets for future treatments.

### *Trials of Recombinant Activated Factor VII*

rFVIIa is approved to treat bleeding in patients with hemophilia who have antibodies to factor VIII or IX, and it has been reported to reduce bleeding in patients without coagulopathy as well.<sup>38</sup> Interaction of rFVIIa and tissue factor stimulates thrombin generation. rFVIIa also activates factor X on the surface of activated platelets, which leads to an enhanced thrombin burst at the site of injury.<sup>38,39</sup> Thrombin converts fibrinogen into fibrin, which produces a stable clot. rFVIIa has a half-life of  $\approx 2.6$  hours, and the recommended dose for treatment of bleeding in patients with hemophilia is 90  $\mu\text{g}/\text{kg}$  intravenously every 3 hours.<sup>38</sup>

Two small dose-ranging pilot safety studies and a larger dose-finding phase II study focusing on decreasing the growth of ICHs have been published.<sup>33,34,40</sup> In the 2 small dose-ranging studies, the overall thromboembolic and serious adverse event rate in the 88 patients tested at escalating doses from 5 to 160  $\mu\text{g}/\text{kg}$  was low enough to encourage further testing.

The second larger, randomized, dose-escalation trial included 399 patients with ICH diagnosed by CT within 3 hours after onset who were randomized to receive placebo (96 patients) or rFVIIa 40  $\mu\text{g}/\text{kg}$  body weight (108 patients), 80  $\mu\text{g}/\text{kg}$  (92 patients), or 160  $\mu\text{g}/\text{kg}$  (103 patients) within 1 hour after the baseline scan. The primary outcome measure was the percent change in the volume of the ICH at 24 hours. Clinical outcomes were assessed at 90 days. Hematoma volume increased more in the placebo group than in the rFVIIa groups. The mean increase was 29% in the placebo group, compared with 16%, 14%, and 11% in the groups given rFVIIa 40, 80, and 160  $\mu\text{g}/\text{kg}$ , respectively ( $P=0.01$  for comparison of the 3 rFVIIa groups with the placebo group). Growth in the volume of ICH was reduced by 3.3, 4.5, and 5.8 mL, respectively, in the 3 treatment groups versus that in the placebo group ( $P=0.01$ ). Sixty-nine percent of placebo-treated patients died or were severely disabled (as defined by a modified Rankin Scale score of 4 to 6), compared with 55%, 49%, and 54% of the patients who were given rFVIIa 40, 80, and 160  $\mu\text{g}/\text{kg}$ , respectively ( $P=0.004$  for comparison of the 3 rFVIIa groups with the placebo group). The rate of death at 90 days was 29% for patients who received placebo versus 18% in the 3 rFVIIa groups combined ( $P=0.02$ ). Serious thromboembolic adverse events, mainly myocardial or cerebral infarction, occurred in 7% of rFVIIa-treated patients versus 2% of those given placebo ( $P=0.12$ ). In this moderate-sized phase II trial, treatment with rFVIIa within 4 hours after the onset of ICH limited the growth of the hematoma, reduced the mortality rate, and improved functional outcome at 90 days despite a small increase in the frequency of thromboembolic adverse events. A larger phase III randomized trial of rFVIIa has been completed, and presentation of the results will occur in May 2007 at the American Academy of Neurology Meeting in Boston, Mass.

In addition, several case reports of the use of rFVIIa in the setting of warfarin-associated ICH have been published.<sup>41,42</sup> Although rFVIIa can reverse the elevated INR measurements rapidly, its use in this setting remains investigational. In addition, a normal INR after use of rFVIIa does not imply complete normalization of the clotting system, and the INR may rise again after the initial rFVIIa dose.<sup>43</sup>

### *Recent Pilot Trial of Acute Blood Pressure Management*

The optimal level of a patient's blood pressure should be based on individual factors such as chronic hypertension, ICP, age, presumed cause of hemorrhage, and interval since onset. Theoretically, elevated blood pressure may increase the risk of ongoing bleeding from ruptured small arteries and arterioles during the first hours. Blood pressure is correlated with increased ICP and volume of hemorrhage. However, it has been difficult to determine whether elevated blood pressure is a cause of hemorrhage growth or an effect of

increasing volumes of ICH and increased ICP. A prospective observational study of growth in the volume of ICH did not demonstrate a relationship between baseline blood pressure and subsequent growth of ICH, but frequent early use of hypertensive agents in that study may have obscured any relationship.<sup>15</sup> Conversely, overaggressive treatment of blood pressure may decrease cerebral perfusion pressure (CPP) and theoretically worsen brain injury, particularly in the setting of increased ICP.

Powers and colleagues<sup>44</sup> studied 14 patients with acute supratentorial ICH 1 to 45 mL in size at 6 to 22 hours after onset. Cerebral blood flow (CBF) was measured with positron emission tomography and [<sup>15</sup>O]water. After completion of the first CBF measurement, patients were randomized to receive either nicardipine or labetalol to reduce mean arterial pressure by 15%, and the CBF study was repeated. Mean arterial pressure was lowered by  $-16.7 \pm 5.4\%$  from  $143 \pm 10$  to  $119 \pm 11$  mm Hg. No significant change was observed in either global CBF or periclot CBF. The authors concluded that in patients with small- to medium-sized acute ICHs, autoregulation of CBF was preserved with arterial blood pressure reductions in the range studied.

#### ***Recent Trial of Hyperosmolar Therapy for Treatment of Increased ICP in ICH***

Results of a trial of mannitol for spontaneous ICH were published in 2005.<sup>45</sup> One hundred twenty-eight patients with primary supratentorial ICH within 6 days of onset were randomized to low-dose mannitol or sham therapy. The study group received mannitol 20%, 100 mL every 4 hours for 5 days, tapered in the next 2 days. The control group received sham infusion. At 1 month, 16 patients (25% in each group) died in each group. The primary ( $P=0.80$ ) and secondary end points were not significantly different between the 2 groups. At 3 months, the primary outcome was not significantly different ( $P=0.25$ ) between the groups. In the study group, 23 patients had poor, 18 had partial, and 8 had complete recovery, and in the control group, 18 had poor, 20 had partial, and 9 had complete recovery.

### **Specific Medical Therapies**

#### ***Blood Pressure Management***

The previous AHA recommendation for the management of blood pressure after ICH outlined the important concept of selecting a target blood pressure on the basis of individual patient factors,<sup>6</sup> such as baseline blood pressure, presumed cause of hemorrhage, age, and elevated ICP. The primary rationale for lowering the blood pressure is to avoid hemorrhagic expansion from potential sites of bleeding. This is especially true for hemorrhage resulting from a ruptured aneurysm or arteriovenous malformation, in which the risk of continued bleeding or rebleeding is presumed to be highest. However, in primary ICH, in which a specific large-vessel vasculopathy is not apparent, the risk of hemorrhagic expansion with mild blood pressure elevation may be lower and must be balanced with the theoretical risks of inducing cerebral ischemia in the edematous region that surrounds the hemorrhage. This theoretical risk has been somewhat

mutated by prospective observational studies in both animals and human beings<sup>44,46</sup> that have dispelled the concept of major ischemia in the edematous tissue surrounding the hemorrhage. Nevertheless, some controversy persists on the basis of human MRI—apparent diffusion coefficient studies of the perihemorrhagic region,<sup>47</sup> which indicate a rim of tissue at risk for secondary ischemia in large hematomas with elevated ICP.

Nonetheless, for primary ICH, little prospective evidence exists to support a specific blood pressure threshold. The previous recommendation was to maintain a systolic blood pressure  $\leq 180$  mm Hg and/or mean arterial pressure  $< 130$  mm Hg. The evidence to support any specific recommendation can be briefly summarized as follows: (1) Isolated systolic blood pressure  $\leq 210$  mm Hg is not clearly related to hemorrhagic expansion or to neurological worsening.<sup>48</sup> (2) Reduction in mean arterial pressure by 15% (mean  $142 \pm 10$  to  $119 \pm 11$  mm Hg) does not result in CBF reduction in humans as measured by positron emission tomography.<sup>44</sup> (3) In one prospective observational study,<sup>49</sup> reduction of systolic blood pressure to a target  $< 160/90$  mm Hg was associated with neurological deterioration in 7% of patients and with hemorrhagic expansion in 9% but was associated with a trend toward improved outcome in those patients in whom systolic blood pressure was lowered within 6 hours of hemorrhage onset. (4) Baseline blood pressure was not associated with growth of ICH in the largest prospective study of ICH growth and in the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial.<sup>15,16,50</sup> (5) Hemorrhagic enlargement occurs more frequently in patients with elevated systolic blood pressure, but it is not known whether this is an effect of increased growth of ICH with associated increases in ICP or a contributing cause to the growth of ICH.<sup>51</sup> (6) A rapid decline in blood pressure during the acute hospitalization was associated with increased death rate in one retrospective study.<sup>52</sup> (7) Experience in traumatic brain hemorrhage, as well as spontaneous ICH, supports preservation of the CPP  $> 60$  mm Hg.<sup>53–56</sup>

Thus, whether more aggressive control of blood pressure during the first hours after onset of ICH can decrease bleeding without compromising the perfusion of brain surrounding the ICH remains unknown. The Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) Pilot Study, begun in 2005, has been funded by the National Institute of Neurological Disorders and Stroke to investigate the control of blood pressure in patients with ICH. This study will involve a 3-dose–tiered trial of reducing systolic blood pressure to 3 predetermined levels: 170 to 200, 140 to 170, and 110 to 140 mm Hg. In addition, the phase III randomized international INTERACT study (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage) is planned to begin in 2006. The goal of this study is to determine whether lowering high blood pressure levels after the start of ICH will reduce the chances of a person dying or surviving with a long-term disability. The study includes patients with acute stroke due to spontaneous ICH with at least 2 systolic blood pressure measurements of  $\geq 150$  mm Hg and  $\leq 220$  mm Hg recorded 2 or more minutes apart and who are able to commence a

randomly assigned blood pressure–lowering regimen within 6 hours of ICH onset.

### **Brain Supportive Therapy in ICH: ICP and CPP/Glucose Control/Prevention and Treatment of Seizures/Body Temperature**

#### *Monitoring of Neurological and Cardiopulmonary Function*

The sudden eruption of an intracranial hemorrhage destroys and displaces brain tissue and can induce an increase in ICP. The dynamics of ICH after appearance of the primary lesion include hematoma growth, perihematomal edema and/or ischemia, hydrocephalus, or secondary IVH. All of these complications also can potentially increase ICP and mass effect, resulting in neurological deterioration.<sup>56</sup>

The patient's neurological status should be assessed frequently with the use of standard stroke scales such as the National Institutes of Health Stroke Scale (NIHSS)<sup>57</sup> and coma scales such as the GCS.<sup>58</sup> Blood pressure can be monitored adequately with an automated cuff, whereas continuous monitoring of systemic arterial pressure should be considered in patients who require continuous intravenous administration of antihypertensive medications and in patients whose neurological status is deteriorating. Airway and oxygenation can be assessed per respiratory status and pulse oximetry. Cardiopulmonary instability in association with increased ICP is to be avoided to minimize deleterious effects in patients with limited autoregulatory capacity. The vast majority of ICH patients are admitted to intensive care units because of their impaired consciousness, elevated blood pressure, and frequent need for intubation. It has been reported that admission of ICH patients to a neuroscience intensive care unit may result in a reduced mortality rate.<sup>59</sup> Although these findings are preliminary and require further study, they have important implications for decisions about organization of critical care services provided by hospitals.

Multimodal monitoring to assess metabolic and hemodynamic variables can provide crucial information at the cellular level. Continuous or frequent assessment of variables in terms of CBF, brain tissue oxygenation, and intracerebral microdialysis provide critical basic physiological information about brain function in patients with acute brain injury, but the efficacy of these measures in patients with ICH has not been tested in randomized clinical trials.

The information provided by standard CT or MRI is static, and it is not practical to perform frequent imaging studies in these patients. Fiberoptic ICP monitors within the brain parenchyma and ventricular catheters can detect dynamic changes but are typically preferentially used in patients in whom there is a high suspicion of ICP or who are clinically deteriorating.<sup>60</sup>

Transcranial Doppler sonography has the potential to assess mass effect and track ICP changes.<sup>61</sup> Increased ICP and decreased CPP give rise to typical changes in the Doppler waveform obtained by transcranial insonation (ie, a decrease in diastolic velocity and an increase in the pulsatility index). Information on the relation of radiological data to 1 or more specific transcranial Doppler variables and on the clinical utility of radiological data is still sparse. Whether an increase

in pulsatility index reflects intracranial hypertension or mass effect in patients with ICH requires confirmation by other means.

#### *Treatment of ICP*

Treatment of intracranial hypertension has evolved around patients with head injuries and may not apply to the specifics of patients with ICH. The "Lund protocol" assumes a disruption of the blood–brain barrier and recommends manipulations to decrease the hydrostatic and increase the osmotic forces that favor maintenance of fluid within the vascular compartment.<sup>62</sup> The other primary approach, CPP-guided therapy, focuses on maintaining a CPP of >70 mm Hg to minimize reflex vasodilation or ischemia and has become a popular treatment for intracranial hypertension.<sup>55,56,63,64</sup> However, cerebral ischemia and hypoxia may still occur with CPP-guided therapy, and concern remains that blood pressure elevation to maintain CPP may advance intracranial hypertension. A recent study on this matter concluded that the majority of patients did have increases in ICP when their mean arterial pressure was elevated therapeutically.<sup>65</sup>

Despite long-standing debates, no controlled clinical trial has demonstrated the superiority of either approach. In today's neurological critical care environment, various potent treatments to combat intracranial hypertension are available, but these are far from perfect and are associated with serious adverse events. Nonselective hyperventilation may enhance secondary brain injury; mannitol can cause intravascular volume depletion, renal failure, and rebound intracranial hypertension; barbiturates are associated with cardiovascular and respiratory depression and prolonged coma; and cerebrospinal fluid (CSF) drainage via intraventricular catheter insertion may result in intracranial bleeding and infection and tissue shifts. Systemic cooling to 34°C can be effective in lowering refractory intracranial hypertension but is associated with a relatively high rate of complications, including pulmonary, infectious, coagulation, and electrolyte problems.<sup>66</sup> A significant rebound in ICP also appears to occur when induced hypothermia is reversed.<sup>67</sup>

The exact frequency of increased ICP in patients with ICH is not known. Many patients with smaller ICHs will likely not have increased ICP and require no measures to decrease ICP, as is the case for many patients with ischemic stroke. However, for those patients with clinical evidence of increased ICP, a balanced approach to ICP makes use of any of the approaches detailed below, with appropriate monitoring safeguards in a critical care unit. A balanced approach begins with simple and less aggressive measures, such as head positioning, analgesia, and sedation, and then progresses to more aggressive measures as clinically indicated. In general, the more aggressive the measures, the more critical is the need to monitor ICP and CPP. No randomized clinical trial has demonstrated the efficacy of monitoring ICP and CPP in the setting of ICH.

#### *Head-of-Bed Elevation*

Elevation of the head of the bed to 30° improves jugular venous outflow and lowers ICP. The head should be midline, and head turning to either side should be avoided. In patients



who are hypovolemic, elevation of the head of the bed may be associated with a fall in blood pressure and an overall fall in CPP; therefore, care must be taken initially to exclude hypovolemia. The position of the arterial pressure transducer will also need to be adjusted to ensure reliable measurements of CPP.

#### *CSF Drainage*

The role of ventriculostomy has never been studied prospectively, and its use has been associated with very high mortality<sup>68</sup> and morbidity<sup>69</sup> rates. When an intraventricular catheter is used to monitor ICP, CSF drainage is an effective method for lowering ICP, particularly in the setting of hydrocephalus. When an intraventricular catheter is used to monitor ICP, CSF drainage is an effective method for lowering ICP. This can be accomplished by intermittent drainage for short periods in response to elevations in ICP. The principal risks associated with ventriculostomy are infection and hemorrhage. Most studies report rates of bacterial colonization rather than symptomatic infection that range from 0% to 19%.<sup>60,70</sup> The incidence of ventriculostomy-associated bacterial meningitis varies between 6% and 22%.<sup>70,71</sup>

#### *Analgesia and Sedation*

Intravenous sedation is needed in unstable patients who are intubated for maintenance of ventilation and control of airways, as well as for other procedures. Sedation should be titrated to minimize pain and increases in ICP, yet should enable evaluation of the patient's clinical status. This is usually accomplished with intravenous propofol, etomidate, or midazolam for sedation and morphine or alfentanil for analgesia and antitussive effect.

#### *Neuromuscular Blockade*

Muscle activity may further raise ICP by increasing intrathoracic pressure and obstructing cerebral venous outflow. If the patient is not responsive to analgesia and sedation alone, neuromuscular blockade is considered. However, the prophylactic use of neuromuscular blockade in patients without proven intracranial hypertension has not been shown to improve outcome. It is associated with an increased risk of complications such as pneumonia and sepsis and can obscure seizure activity.

#### *Osmotic Therapy*

The most commonly used agent is mannitol, an intravascular osmotic agent that can draw fluid from both edematous and nonedematous brain tissue. In addition, it increases cardiac preload and CPP, thus decreasing ICP through cerebral autoregulation. Mannitol decreases blood viscosity, which results in reflex vasoconstriction and decreased cerebrovascular volume. The major problems associated with mannitol administration are hypovolemia and the induction of a hyperosmotic state. Target serum osmolality has often been recommended as 300 to 320 mOsm/kg, but definitive data on the effectiveness of specific thresholds are lacking.

The use of hypertonic saline solutions has been shown to reduce ICP in a variety of conditions, even in cases refractory to treatment with hyperventilation and mannitol. In terms of hypertonic saline, many issues remain to be clarified, includ-

ing its exact mechanism of action, the best mode of administration, and the concentration to be given.<sup>72,73</sup>

#### *Hyperventilation*

Hyperventilation is one of the most effective methods available for the rapid reduction of ICP. The CO<sub>2</sub> reactivity of intracerebral vessels is one of the normal mechanisms involved in the regulation of CBF. Experimental studies using a pial window technique have clearly demonstrated that the action of CO<sub>2</sub> on cerebral vessels is exerted via changes in extracellular fluid pH.<sup>74</sup> Molecular CO<sub>2</sub> and bicarbonate ions do not have independent vasoactivity on these vessels. As a result, hyperventilation consistently lowers ICP. Despite the effectiveness of hyperventilation in lowering ICP, broad and aggressive use of this treatment modality to substantially lower PCO<sub>2</sub> levels has fallen out of favor, primarily because of the simultaneous effect on lowering CBF. Another characteristic of hyperventilation that limits its usefulness as a treatment modality for intracranial hypertension is the transient nature of its effect. Because the extracellular space of the brain rapidly accommodates to the pH change induced by hyperventilation, the effects on CBF and on ICP are short-lived. In fact, after a patient has been hyperventilated for >6 hours, rapid normalization of arterial PCO<sub>2</sub> can cause a significant rebound increase in ICP. The target levels of CO<sub>2</sub> for hyperventilation are 30 to 35 mm Hg. Lower levels of CO<sub>2</sub> are not recommended.<sup>75</sup>

#### *Barbiturate Coma*

Barbiturates in high doses are effective in lowering refractory intracranial hypertension but ineffective or potentially harmful as a first-line or prophylactic treatment in patients with brain injuries. High-dose barbiturate treatment acts by depressing cerebral metabolic activity. This results in a reduction in CBF, which is coupled to metabolism, and a fall in ICP. The use of barbiturates in the treatment of refractory intracranial hypertension requires intensive monitoring and is associated with a significant risk of complications,<sup>76</sup> the most common being hypotension. Cerebral electrical activity should ideally be monitored during high-dose barbiturate treatment, preferably on a continuous basis, with burst suppression activity providing a physiological end point for dose titration.

#### *Management of Glucose*

High blood glucose on admission predicts an increased 28-day case-fatality rate in both nondiabetic and diabetic patients with ICH.<sup>24</sup> In some studies, hyperglycemia in acute stroke has been considered a manifestation of premorbid diabetic glucose metabolism<sup>77,78</sup> or a stress reaction or has been associated with other mechanisms.<sup>79</sup> The amount of evidence to support the stress hypothesis of poststroke hyperglycemia is increasing.

The AHA guidelines for the early management of ischemic stroke published in 2003 indicated that there is general agreement to recommend control of hypoglycemia or hyperglycemia after stroke.<sup>80</sup> Until further data from ongoing trials became available, a judicious approach to management of hyperglycemia was recommended. The only target provided in these guidelines was that markedly elevated glucose levels be lowered to <300 mg/dL (<16.63 mmol/L). More aggres-

sive lowering of hyperglycemia in acute stroke is currently being tested in randomized trials.

### **Antiepileptic Drugs**

Seizures occur commonly after ICH and may be nonconvulsive. The frequency of observed seizures after ICH depends on the extent of monitoring. In a recently published large clinical series of 761 subsequent patients, early seizures occurred in 4.2% of patients, and 8.1% had seizures within 30 days after onset. Lobar location was significantly associated with the occurrence of early seizures.<sup>81</sup> In a cohort of ICH patients undergoing continuous electrophysiological monitoring in a neurocritical care unit, electrographic seizures occurred in 18 (28%) of 63 patients with ICH during the initial 72 hours after admission. Seizures were independently associated with increased midline shift after intraparenchymal hemorrhage.<sup>82</sup> ICH-related seizures are often nonconvulsive and are associated with higher NIHSS scores, a midline shift, and a trend toward poor outcome.<sup>82</sup>

Treatment of clinical seizures in ICH patients during the hospitalization should include intravenous medications to control seizures quickly, as for any hospitalized patient. Initial choice of medications includes benzodiazepines such as lorazepam or diazepam, followed directly by intravenous fos-phenytoin or phenytoin. The European Federation of Neurological Societies guidelines provide a detailed step approach to address more refractory cases of status epilepticus.<sup>83</sup>

A brief period of antiepileptic therapy soon after ICH onset may reduce the risk of early seizures, particularly in patients with lobar hemorrhage.<sup>81</sup> Choice of medication for prophylaxis should include one that can be administered intravenously as needed during the hospitalization and orally after discharge.

### **Temperature Management**

Cerebral temperature has been recognized as a strong factor in ischemic brain damage. Laboratory investigations have shown that hypothermia ameliorates brain damage.<sup>84</sup> The classic mechanism proposed for this protection is redistribution of oxygen and lowering of glucose consumption sufficient to permit tolerance to prolonged periods of oxygen deprivation. In terms of applying therapeutic cooling to patients with ICH, experimental research indicates that thrombin-induced brain edema formation is significantly reduced by induced hypothermia in the rat.<sup>85,86</sup> Inhibition of thrombin-induced blood-brain barrier breakdown and inflammatory response by hypothermia appear to contribute to brain protection in this model. Therapeutic cooling may provide an approach to potentially reduce edema after ICH. In another experimental study, delayed and prolonged cooling failed to reduce residual blood volume and improve functional outcome in the rat. Although these results do not exclude possible beneficial effects of hypothermia, such as ICP reduction, tissue that is quickly lost after ICH will not likely be salvaged.<sup>87</sup>

By contrast, fever worsens outcome in several experimental models of brain injury.<sup>88,89</sup> The incidence of fever after basal ganglionic and lobar ICH is high, especially in patients with ventricular 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>17</sup> Rossi et al<sup>90</sup> found that fever is associated with increases in intracranial volume homeostasis, which causes intracranial hypertension. These data provide a rationale for aggressive treatment of fever to normal levels in patients with ICH.

Therapeutic cooling has been investigated in acute brain injuries in terms of controlling ICP and as a possible neuroprotectant strategy.<sup>91</sup> Cooling to 32°C to 34°C can be effective in lowering refractory intracranial hypertension but, particularly with longer-term use (24 to 48 hours), is associated with a relatively high rate of complications, including pulmonary, infectious, coagulation, and electrolyte problems.<sup>92</sup> There also appears to be a risk for rebound intracranial hypertension when induced hypothermia is reversed too quickly.<sup>67</sup>

## **Recommendations for Initial Medical Therapy**

### *Class I*

1. **Monitoring and management of patients with an ICH should take place in an intensive care unit setting because of the acuity of the condition, frequent elevations in ICP and blood pressure, frequent need for intubation and assisted ventilation, and multiple complicating medical issues (Class I, Level of Evidence B).**
2. **Appropriate antiepileptic therapy should always be used for treatment of clinical seizures in patients with ICH (Class I, Level of Evidence B).**
3. **It is generally agreed that sources of fever should be treated and antipyretic medications should be administered to lower temperature in febrile patients with stroke (Class I, Level of Evidence C).**
4. **As for patients with ischemic stroke,<sup>93</sup> early mobilization and rehabilitation are recommended in patients with ICH who are clinically stable (Class I, Level of Evidence C).**

### *Class II*

1. **Treatment of elevated ICP should include a balanced and graded approach that begins with simple measures, such as elevation of the head of the bed and analgesia and sedation. More aggressive therapies to decrease elevated ICP, such as osmotic diuretics (mannitol and hypertonic saline solution), drainage of CSF via ventricular catheter, neuromuscular blockade, and hyperventilation, generally require concomitant monitoring of ICP and blood pressure with a goal to maintain CPP >70 mm Hg (Class IIa, Level of Evidence B).**
2. **Evidence indicates that persistent hyperglycemia (>140 mg/dL) during the first 24 hours after stroke is associated with poor outcomes, and thus it is generally agreed that hyperglycemia should be treated in patients with acute stroke. Guidelines for ischemic stroke suggest that elevated glucose concentrations (>185 mg/dL and possibly >140 mg/dL) probably should trigger administration of insulin, similar to the procedure in other acute situations accompanied by hyperglycemia. Use of these guidelines for ICH as well is reasonable. The results of ongoing research should**

clarify the management of hyperglycemia after stroke (Class IIa, Level of Evidence C).

3. Until ongoing clinical trials of blood pressure intervention for ICH are completed, physicians must manage blood pressure on the basis of the present incomplete evidence. Current suggested recommendations for target blood pressures in various situations and potential medications are listed in Tables 2 and 3 and may be considered (Class IIb, Level of Evidence C).
4. Treatment with rFVIIa within the first 3 to 4 hours after onset to slow progression of bleeding has shown promise in one moderate-sized phase II trial; however, the efficacy and safety of this treatment must be confirmed in phase III trials before its use in patients with ICH can be recommended outside of a clinical trial (Class IIb, Level of Evidence B).
5. A brief period of prophylactic antiepileptic therapy soon after ICH onset may reduce the risk of early seizures in patients with lobar hemorrhage (Class IIb, Level of Evidence C).

### Prevention of Deep Vein Thrombosis and Pulmonary Embolism

Deep vein thrombosis and pulmonary emboli are relatively common preventable causes of morbidity and mortality in patients with acute ICH. In a prospective randomized rFVIIa trial, 2 (2.1%) of the 96 patients who received placebo developed a pulmonary embolism on days 7 to 11 (1 fatal).<sup>34</sup> Four (1.3%) of the 303 patients treated with rFVIIa had pulmonary embolism (1 fatal), and an additional patient had a deep vein thrombosis. In a retrospective study of 1926 patients with ICH, 1.6% had a clinical diagnosis of venous thromboembolism as documented by the *International Classification of Diseases—9th Revision* clinical modification (ICD-9-CM) codes.<sup>94</sup> Studies using fibrinogen scanning or MRI to detect occult venous thrombosis report high frequencies (10% to 50%) of deep vein thrombosis in acute stroke patients with hemiplegia.<sup>95</sup>

The question is how to prevent and treat these venous thromboembolic complications without increasing the risk of intracranial rebleeding. Anticoagulants, platelet antiaggregants, unfractionated heparin and low-molecular-weight heparins/heparinoids, and use of mechanical methods such as

**TABLE 2. Suggested Recommended Guidelines for Treating Elevated Blood Pressure in Spontaneous ICH**

1.	If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes.
2.	If SBP is >180 mm Hg or MAP is >130 mm Hg and there is evidence of or suspicion of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep cerebral perfusion pressure >60 to 80 mm Hg.
3.	If SBP is >180 mm Hg or MAP is >130 mm Hg and there is not evidence of or suspicion of elevated ICP, then consider a modest reduction of blood pressure (eg, MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg) using intermittent or continuous intravenous medications to control blood pressure, and clinically reexamine the patient every 15 minutes.

SBP indicates systolic blood pressure; MAP, mean arterial pressure.

**TABLE 3. Intravenous Medications That May Be Considered for Control of Elevated Blood Pressure in Patients With ICH**

Drug	Intravenous Bolus Dose	Continuous Infusion Rate
Labetalol	5 to 20 mg every 15 min	2 mg/min (maximum 300 mg/d)
Nicardipine	NA	5 to 15 mg/h
Esmolol	250 $\mu$ g/kg IVP loading dose	25 to 300 $\mu$ g $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup>
Enalapril	1.25 to 5 mg IVP every 6 h*	NA
Hydralazine	5 to 20 mg IVP every 30 min	1.5 to 5 $\mu$ g $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup>
Nipride	NA	0.1 to 10 $\mu$ g $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup>
Nitroglycerin	NA	20 to 400 $\mu$ g/min

IVP indicates intravenous push; NA, not applicable.

\*Because of the risk of precipitous blood pressure lowering, the enalapril first test dose should be 0.625 mg.

intermittent pneumatic compression and graduated compression stockings are options with varying strengths of evidence for preventing venous thromboembolism in patients with ischemic stroke. However, almost all of the evidence for these various options comes from studies of patients with ischemic stroke or other causes of immobility. One recent trial randomized patients with ICH to compression stockings versus compression stockings plus intermittent pneumatic compression. Asymptomatic deep vein thrombosis by ultrasonography was detected at day 10 in 15.9% of patients wearing elastic stockings alone and in 4.7% in the combined group (relative risk 0.29 [95% confidence interval {CI} 0.08 to 1.00]).<sup>96</sup>

Boer and colleagues<sup>97</sup> reported a small randomized trial comparing 68 patients with ICH who were randomized to receive low-dose heparin (5000 U of heparin-sodium subcutaneously 3 times per day) beginning on the tenth day of treatment (group 1), the fourth day (group 2), or the second day (group 3) after ICH onset. Group 1 served as the control group because heparin treatment beginning on day 10 was the standard treatment protocol in the intensive care unit. All patients received basic intensive care medication and regular diagnostic evaluations. Group 3 patients showed a statistically significant reduction in the number of pulmonary emboli when compared with the other 2 groups. No overall increase in the incidence of rebleeding was observed in any of the 3 groups. The incidence of deep vein thrombosis was higher in the first few days of treatment than at 10 days, but this difference was not significant.<sup>97</sup>

A separate issue from primary prevention of deep vein thrombosis and embolism is what to do for patients with ICH who develop deep vein thrombosis or pulmonary embolism. The rate of recurrent ICH during the initial 3 months after an acute ICH is  $\approx$ 1%.<sup>98–100</sup> A theoretical analysis estimated that anticoagulation increases the risk of recurrent ICH 2-fold compared with the recurrence risk of ICH overall.<sup>100</sup> However, the challenge of selecting therapy for an individual patient is to balance the risk of subsequent life-threatening thromboembolism against the risk of recurrence of ICH, in which the mortality rate is >50%. The risk of ICH recurrence also likely varies by location and age, but few prospective data are available (eg, higher risk in patients with lobar ICH due to suspected amyloid angiopathy).<sup>101</sup>

Another option is the interruption of the inferior vena cava by the placement of a filter.<sup>102</sup> Vena cava filters may reduce the incidence of pulmonary embolism in patients with proximal deep vein thrombosis in the first several weeks but have a longer-term risk of increased venous thromboembolism.<sup>102,103</sup> No randomized clinical trial has compared vena cava filters with anticoagulation in patients with ICH or ischemic stroke.

During anticoagulation, good control of blood pressure substantially reduces the risk of recurrent ICH. The randomized PROGRESS trial (Perindopril pROtection aGainst REcurrent Stroke Study)<sup>104,105</sup> documented a 50% reduction of the risk of recurrence among ICH survivors by lowering systolic blood pressure by 11 mm Hg.

## Recommendations for Prevention of Deep Vein Thrombosis and Pulmonary Embolism

### Class I

1. Patients with acute primary ICH and hemiparesis/hemiplegia should have intermittent pneumatic compression for prevention of venous thromboembolism (Class I, Level of Evidence B).
2. Treatment of hypertension should always be part of long-term therapy because such therapy decreases the risk of recurrent ICH (Class I, Level of Evidence B).

### Class II

1. After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered in patients with hemiplegia after 3 to 4 days from onset (Class IIb, Level of Evidence B).
2. Patients with an ICH who develop an acute proximal venous thrombosis, particularly those with clinical or subclinical pulmonary emboli, should be considered for acute placement of a vena cava filter (Class IIb, Level of Evidence C).
3. The decision to add long-term antithrombotic therapy several weeks or more after placement of a vena cava filter must take into consideration the likely cause of the hemorrhage (amyloid [higher risk of recurrent ICH] versus hypertension), associated conditions with increased arterial thrombotic risk (eg, atrial fibrillation [AF]), and the overall health and mobility of the patient (Class IIb, Level of Evidence B).

## ICH Related to Coagulation and Fibrinolysis: Management of Acute ICH and Restarting Antithrombotic Therapy

In recent reports, ICH occurs with a frequency of approximately 0.3% to 0.6% per year in patients undergoing chronic warfarin anticoagulation.<sup>105</sup> Furthermore, warfarin accounts for a substantial proportion of the cases of ICH who present to general hospitals: Among patients with supratentorial ICH admitted to the Massachusetts General Hospital over a 7-year period, 23.4% were taking warfarin<sup>106</sup>; figures between 6% and 16% were reported in earlier series.<sup>107–109</sup>

For warfarin-related ICH, the main risk factors are age, history of hypertension, intensity of anticoagulation,<sup>110,111</sup> and associated conditions such as cerebral amyloid angiopa-

thy<sup>112</sup> and leukoaraiosis.<sup>113</sup> An elevation of the INR above the therapeutic range of 2 to 3 has been associated with a steady increase in the frequency of ICH, especially above values of 3.5 to 4.5<sup>111,114</sup>; The risk of ICH nearly doubles for each increase of 0.5 points in the INR above 4.5.<sup>114</sup> The degree of elevation of the INR also correlates with hematoma expansion and prognosis (death and functional outcome). Although the increase of ICH risk with excessive prolongation of the INR is well documented, most warfarin-related ICHs occur with INRs in the recommended therapeutic range.<sup>110</sup> Cerebral amyloid angiopathy is probably a common underlying pathology in elderly patients with warfarin-related lobar ICH.<sup>112</sup> Leukoaraiosis, despite its high frequency in patients with cerebrovascular disease and hypertension, is a likely risk factor for warfarin-related ICH. It was present in 92% of a series of patients with ICH taking warfarin (which had been prescribed after an episode of ischemic stroke), compared with 48% of a control group of patients without ICH taking warfarin after ischemic stroke.<sup>113</sup> The management issues in warfarin-related ICH are the need to rapidly reverse the coagulation defect to minimize further hematoma growth and the need for and feasibility of reinstating oral anticoagulation. The measures available to counteract the warfarin effect include the use of vitamin K<sub>1</sub>, fresh frozen plasma (FFP), prothrombin complex concentrate, and rFVIIa. Vitamin K<sub>1</sub> is given intravenously at a dose of 10 mg.<sup>115</sup> The intravenous injection entails a small risk of anaphylaxis, which is reduced by the slower-acting subcutaneous injection route.<sup>116</sup> Vitamin K<sub>1</sub> should not be used alone because it takes hours (at least 6) for vitamin K<sub>1</sub> to normalize the INR.<sup>117</sup> FFP can be given to replenish the vitamin K–dependent coagulation factors inhibited by warfarin. It is an effective way of correcting the INR, and it acts more quickly than vitamin K<sub>1</sub>; however, its use at the recommended dose of 15 to 20 mL/kg involves the infusion of potentially large volumes of plasma, which not only may take several hours to be infused (with the potential for continuing hematoma enlargement) but can also lead to volume overload and heart failure.<sup>118</sup> In addition, the concentration of clotting factors in FFP varies substantially, and thus the degree of effectiveness of different batches of FFP is unpredictable. Finally, circulating levels of factor IX may remain low (and thus result in incomplete hemostasis) despite replacement of all other clotting factors with FFP.<sup>119</sup> These limitations, particularly the sometimes lengthy process of normalizing the INR in the emergency life-threatening situation of warfarin-related ICH, make the FFP approach impractical.

This has stimulated the search for better options. Prothrombin complex concentrate contains high levels of vitamin K–dependent factors (II, VII, and X), and factor IX complex concentrate contains factors II, VII, IX, and X. These preparations have the advantage of requiring smaller volumes of infusion than FFP and correcting the coagulopathy faster.<sup>120,121</sup> Their disadvantage is the risk of inducing thromboembolic complications, ranging from superficial thrombophlebitis, deep vein thrombosis and pulmonary embolism, and arterial thrombosis to disseminated intravascular coagulation. Concerns about viral transmission have been minimized by the current rigorous screening of blood products.

The ability of rFVIIa to rapidly normalize the INR in subjects anticoagulated with warfarin<sup>43</sup> and the recent report of a beneficial effect in patients with spontaneous ICH<sup>34,41,42</sup> suggest that this option should be tested in warfarin-related ICH. A small study of 7 patients with warfarin-related ICH treated with rFVIIa at a dose between 15 and 90  $\mu\text{g}/\text{kg}$  showed a rapid reduction of INR after single injections.<sup>41</sup> Because of the short half-life of rFVIIa (2.6 hours),<sup>122</sup> the initial rapid response at times required repeated injections of the factor to maintain the INR in the normal range. Given the significant increase in thromboembolic complications (7% versus 2% in the control group) in patients with “spontaneous” ICH treated with rFVIIa,<sup>34</sup> concern is warranted about a potentially larger risk with the use of this procoagulant agent in subjects prone to embolism, such as those with prosthetic heart valves or chronic AF. Randomized controlled trials of rFVIIa, as well as the other various options for treatment of warfarin-related ICH, are needed.

In instances of ICH that result from the use of intravenous heparin, management involves rapid normalization of the activated partial thromboplastin time by protamine sulfate. The recommended dose is 1 mg per 100 U heparin, and the dose needs to be adjusted according to the time elapsed since the last heparin dose. If heparin is stopped for 30 to 60 minutes, the protamine sulfate dose is 0.5 to 0.75 mg per 100 U heparin, down to 0.375 to 0.5 mg per 100 U heparin after 60 to 120 minutes off heparin and 0.25 to 0.375 mg per 100 U heparin if it was stopped >120 minutes from the time of the protamine sulfate injection. Protamine sulfate is given by slow intravenous injection, not to exceed 5 mg/min, with a total dose not to exceed 50 mg. A faster rate of infusion can produce severe systemic hypotension.

The issue of reinstatement of anticoagulation after warfarin-related ICH applies primarily to those who began taking warfarin for the prevention of cardiogenic embolism associated with either prosthetic heart valves or chronic AF. In view of the documented rates of cerebral embolism of 5% per year in patients who have nonvalvular AF without history of stroke,<sup>123</sup> 12% per year in patients who have AF with prior ischemic stroke events,<sup>124</sup> and at least 4% per year in patients with prosthetic mechanical heart valves,<sup>125</sup> re-anticoagulation with warfarin is often a consideration after warfarin-related ICH. This difficult decision should balance the prevention of ischemic stroke and the risk of recurrent ICH.<sup>126</sup> Unfortunately, no data are available on rates of ICH recurrence while warfarin treatment is being given. In an aggregate group of 114 patients with ICH in 3 clinical series,<sup>127–129</sup> reversal of anticoagulation with FFP and discontinuation of warfarin after ICH for a mean of 7 to 10 days was associated with embolism in 6 patients (5%). Rebleeding on reinstatement of anticoagulation between 7 and 10 days from ICH onset occurred in 1 patient (0.8%). The use of prothrombin complex concentrate for reversal of anticoagulation in an aggregate group of 78 patients from 7 clinical series<sup>119,130–135</sup> resulted in 4 thromboembolic events (5%), and continued hematoma expansion occurred in 5 subjects (6%). Data on the rate of thromboembolism with the use of rFVIIa in this setting are not currently available. These limited data suggest that reversal of anticoagulation with FFP or prothrombin

complex concentrate after ICH in patients with prosthetic heart valves or chronic nonvalvular AF is associated with a low frequency of embolic events over periods of 7 to 10 days, after which reinstatement of warfarin anticoagulation appears to be safe.<sup>136</sup>

One decision analysis, using quality-of-life years as the outcome, compared the risk of restarting anticoagulation in patients with chronic AF who had a lobar or deep hemorrhage.<sup>100</sup> In general, elderly patients with a lobar hemorrhage likely due to amyloid angiopathy had a much higher projected risk of a poor outcome with continuation of warfarin. In patients with a small deep ICH, the risk was similar for restarting and withholding warfarin.

The clinical dilemma of whether and when to restart anticoagulants in patients with ICH who have cardioembolic risk will not be solved until prospectively generated data on rates of ICH recurrence after warfarin reinstatement become available. However, for patients with a lower risk of cerebral infarction (eg, AF without prior ischemic stroke) and a higher risk of amyloid angiopathy (eg, an elderly patient with lobar ICH, particularly with evidence of small microbleeds on MRI), antiplatelet agents may be a better choice for prevention of ischemic stroke than warfarin.

### ICH Related to Fibrinolysis

Thrombolytic treatment for acute ischemic stroke was followed by symptomatic ICH in 3% to 9% of patients treated intravenously with tissue-type plasminogen activator (tPA),<sup>77,137–139</sup> 6% of patients treated with a combination of intravenous and intra-arterial tPA,<sup>140</sup> and 10.9% of those who were treated with intra-arterial prourokinase in a controlled clinical trial.<sup>141</sup> In addition, ICH occurred in 0.5% to 0.6% of patients treated with thrombolytic agents for other acute arterial and venous occlusions, with higher rates among the elderly.<sup>142,143</sup>

The onset of ICH after fibrinolysis carries a poor prognosis because the hemorrhages tend to be massive, can be multifocal, and are associated with a 30-day death rate of 60% or more.<sup>138,144</sup> No reliable data are available to guide the clinician in the choice of effective measures to control ICH in this setting.<sup>145</sup> Current recommended therapy includes the infusion of platelets (6 to 8 U) and cryoprecipitate that contains factor VIII to rapidly correct the systemic fibrinolytic state created by tPA.<sup>80,146</sup> The guidelines for the surgical treatment of ICH after fibrinolysis for acute ischemic stroke are the same as those followed for ICH in general but should be initiated only after a sufficient infusion of platelets and cryoprecipitate has stabilized intracranial bleeding.

### Recommendations for the Management of ICH Related to Coagulation and Fibrinolysis

#### *Class I*

1. Protamine sulfate should be used to reverse heparin-associated ICH, with the dose depending on the time from cessation of heparin (*Class I, Level of Evidence B*).
2. Patients with warfarin-associated ICH should be treated with intravenous vitamin K to reverse the

effects of warfarin and with treatment to replace clotting factors (*Class I, Level of Evidence B*).

#### Class II

1. Prothrombin complex concentrate, factor IX complex concentrate, and rFVIIa normalize the laboratory elevation of the INR very rapidly and with lower volumes of fluid than FFP but with greater potential of thromboembolism. FFP is another potential choice but is associated with greater volumes and much longer infusion times (*Class IIb, Level of Evidence B*).
2. The decision to restart antithrombotic therapy after ICH related to antithrombotic therapy depends on the risk of subsequent arterial or venous thromboembolism, the risk of recurrent ICH, and the overall state of the patient. For patients with a comparatively lower risk of cerebral infarction (eg, AF without prior ischemic stroke) and a higher risk of amyloid angiopathy (eg, elderly patients with lobar ICH) or with very poor overall neurological function, an antiplatelet agent may be an overall better choice for prevention of ischemic stroke than warfarin. In patients with a very high risk of thromboembolism in whom restarting warfarin is considered, warfarin therapy may be restarted at 7 to 10 days after onset of the original ICH (*Class IIb, Level of Evidence B*).
3. Treatment of patients with ICH related to thrombolytic therapy includes urgent empirical therapies to replace clotting factors and platelets (*Class IIb, Level of Evidence B*).

### Surgical Treatment of ICH/IVH

#### Craniotomy

Of all the surgical therapies described for treating ICH, craniotomy has been the most extensively studied, with 7 of the 9 randomized controlled surgical trials reporting results with craniotomy either primarily or exclusively. Two of these studies were conducted with limited access to contemporary medical and surgical technologies, which limits their relevance. Of the remaining 5, all but one are small, single-center studies that randomized fewer than 125 patients in total. Although none of these small studies found convincing evidence of surgical benefit, one concluded that for patients presenting with mild to moderate alterations in consciousness (GCS score 7 to 10), surgery might reduce the risk of death without improving functional outcome,<sup>147</sup> and another suggested that ultra-early evacuation might improve the 3-month NIHSS score.<sup>148</sup>

The insights of these smaller trials are important in light of the single large multicenter trial, the International Surgical Trial in Intracerebral Haemorrhage (STICH), which randomized 1033 patients from 107 centers over an 8-year period, beginning in 1995.<sup>149</sup> Patients were eligible if randomized within 72 hours and operated on within 96 hours of ictus for a clot >2 cm in diameter. Patients in very poor condition (GCS score <5) were excluded. Patients were randomized if the neurosurgeon was uncertain of the benefit of surgery, with 50% randomly assigned to a policy of either early surgery or initial medical management. Primary outcomes were the incidence of death and disability as measured by the extended

Glasgow Outcome Scale (GOS) at 6 months, and secondary outcomes were death, the Barthel Index (BI), and the modified Rankin scale (mRS) at 6 months. To increase study power, patients with an expected poor prognosis on the basis of age, admission GCS score, and hemorrhage volume were analyzed with different extended GOS, mRS, and BI cutoffs. In addition, several prespecified subgroup analyses were included.

Five hundred six patients were randomized to surgery and 530 to medical therapy, with groups being well matched for all known variables. Twenty-six percent of the medical arm ultimately crossed over to surgery. This crossover was due to rebleeding or deterioration in 85% of crossover subjects, and craniotomy was used in 85% of those subjects who crossed over to surgery. By contrast, only 75% of patients in the primary surgical arm underwent craniotomy, with the others being treated with less invasive surgical techniques. Ninety-three percent of patients were available for analysis at 6 months.

In an intention-to-treat analysis, surgery within 96 hours of ictus was associated with a statistically insignificant absolute benefit of 2.3% (95% CI -3.2% to 7.7%) in 6-month prognosis-dichotomized extended GOS. Death (absolute benefit 1.2% [-4.9% to 7.2%]), mRS (absolute benefit 4.7% [-1.2% to 10.5%]), and BI (absolute benefit 4.1% [-1.4% to 9.5%]) showed similar statistically insignificant trends in favor of surgery. Subgroup analysis identified those subjects with GCS score of 9 to 12, those with lobar clots, and those with clots <1 cm from the surface that may have been helped by early surgery, but this did not reach statistical significance. In contrast, those presenting in deep coma (GCS score 5 to 8) tended to do better with medical management. Together, the data from both STICH and the other smaller trials suggest that surgery does not appear to be helpful in treating most supratentorial ICH and is probably harmful in those patients presenting in coma. Having said this, surgery, particularly craniotomy, may be helpful in treating those lobar clots within 1 cm of the surface that present in patients with milder deficits (GCS score  $\geq$ 9), because both craniotomy and surface location were associated with a 29% relative benefit in functional outcome when compared with medical management. Confirmation of these conclusions will require further trials.

These randomized trials of surgery did not include patients with cerebellar hemorrhage. As discussed in the 1999 AHA guidelines for management of spontaneous ICH,<sup>6</sup> nonrandomized treatment series of patients with cerebellar hemorrhage report good outcomes for surgically treated patients who have large (>3 cm) cerebellar hemorrhages or cerebellar hemorrhages with brain stem compression or hydrocephalus.<sup>150-156</sup> In these patients, medical management alone often results in bad outcomes. Smaller cerebellar hemorrhages without brain stem compression that are managed medically do reasonably well in the case series. For these reasons, neurosurgeons and neurologists have advocated that large cerebellar hemorrhages with compression of the brain stem or obstruction of the fourth ventricle should be removed surgically as soon as possible.

### Minimally Invasive Surgery

The purported advantages of minimally invasive clot evacuation over conventional craniotomy include (1) reduced operative time, (2) the possibility of performance under local anesthesia, and (3) reduced tissue trauma, especially for deep lesions. Together, these advantages may also facilitate earlier evacuation of ICH than is possible or practical with conventional craniotomy. On the other hand, the reduced surgical exposure, the inability to treat structural lesions (arteriovenous malformation or aneurysm), the potential for rebleeding related to the use of fibrinolytics, and the possibility of an increased risk of infection related to prolonged indwelling catheters are limitations of this approach. Despite the fact that fewer data exist for these techniques than for craniotomy, we present an overview of the various minimally invasive techniques.

The STICH trial suggests that subjects treated with any noncraniotomy approach in the trial had a worse outcome than those treated with conservative management (OR 1.3), but the confidence interval included 1 (95% CI 0.78 to 2.35). It is unclear whether the pathology chosen for these approaches was less ideal for intervention, because patients with deep hemorrhages and those in poor neurological condition (both of which fared worse in the trial) were likely those most commonly chosen for minimally invasive techniques.

### Endoscopic Aspiration

Endoscopic aspiration of supratentorial hemorrhage has been studied in a small, single-center randomized trial.<sup>157</sup> One hundred patients between 30 and 80 years of age, with hemorrhages at least 10 mL in volume, received treatment within 48 hours of onset via burr hole and continuous neuroendoscopic lavage of the hematoma cavity with artificial CSF at a pressure of 10 to 15 mm Hg. The mixture of blood clots and blood-stained CSF was removed by suction at regular intervals. Oozing vessels in the wall of the hematoma were coagulated with a laser built into the system, and the entire procedure was under direct visual control. More than 90% of the clot was evacuated in 15% of patients and between 70% and 90% in 30% of patients, with all patients having at least a 50% reduction in size. At 6 months, the mortality rate of the surgical group (42%) was significantly lower than that of the medical group (70%,  $P=0.01$ ). A good outcome with minimal or no deficit was also seen more frequently in the surgically treated group. In patients with large hematomas (50 mL), quality of life was not affected by surgery, but the mortality rate was significantly lower. By contrast, endoscopic evacuation of smaller hematomas led to a significantly better quality of life versus those treated medically, but survival was similar for the 2 groups. Moreover, the benefit was mainly limited to patients with lobar hematomas and patients <60 years of age.

### Thrombolytic Therapy and Aspiration of Clots

Zuccarello et al<sup>148</sup> reported a single-center randomized pilot trial of conservative therapy (11 subjects) or very early surgical removal of the ICH (9 subjects) within 24 hours of onset and 3 hours of randomization. Subjects with deep hemorrhages who underwent surgery were treated with instillation of urokinase into the bed of the clot ( $n=4$ ).<sup>148</sup> Patients

who underwent stereotactic removal of the ICH did well (3-month BI scores of 100, 100, 90, and 85), which suggests that this approach was, as the animal studies had shown,<sup>158</sup> safe and feasible. The effect of an infused thrombolytic on outcome has been demonstrated by Niizuma et al,<sup>159</sup> who reported 81% of 175 patients with putaminal hemorrhage resumed useful lives. A number of nonrandomized studies using this approach reported aspiration rates ranging from 30% to 90% of the initial hematoma<sup>157,160–162</sup> and rebleeding rates comparable to those seen with conventional craniotomy<sup>163</sup> (range 0% to 10%; mean 4% of 392 cases).<sup>157,159–162,164</sup>

Finally, a multicenter randomized controlled trial ( $n=71$  patients)<sup>165</sup> examined the utility of stereotactic urokinase infusion when administered within 72 hours for those patients presenting with GCS score  $\geq 5$  and clots of  $\geq 10$  mL. Treated patients received 5000 IU of urokinase every 6 hours for a maximum of 48 hours. Primary end points were death and degree of functional handicap (measured with the mRS) at 6 months. The median reduction in volume of ICH from baseline was 40% in the surgical group and 18% in the medical group. The rebleeding rate was 35% in the urokinase group and 17% in the conservatively managed group. A significant reduction in death (40%) was found in the treated group, but no statistically significant difference in functional outcome scores was detected at different intervals of treatment.

In 1999, urokinase became unavailable in the United States because of reports of the potential for viral contamination during pharmacological preparation, which prompted investigators to examine the use of intraventricular instillation of tPA for clot evacuation in patients with severe IVH. Rohde et al<sup>166</sup> reported that IVH disappeared earlier (1 to 3 days) with tPA than with urokinase (5 to 8 days). Compared with ventriculostomy alone, IVH treated with the addition of tPA decreased the mortality rate from a range of 60% to 90% to only 5%.<sup>166</sup> Other similar studies have indicated that the use of intraventricular tPA might improve the prognosis in patients with large IVHs.<sup>167,168</sup> The review of the current literature suggests that the use of intraventricular fibrinolytics carries a low incidence of complications, which usually consist of infections and hemorrhage.<sup>167–170</sup>

More recently, tPA has been used in the treatment of ICH. In a pig model of ICH, Wagner et al<sup>171</sup> reported that hematoma aspiration after fibrinolysis with tPA resulted in >70% removal of the clot and marked reduction of perihematoma edema. In pilot human trials, Lippitz et al,<sup>172</sup> Schaller et al,<sup>173</sup> and Vespa et al<sup>174</sup> reported that daily administration of tPA into the hematoma cavity beginning 12 to 24 hours after stereotactic placement of a catheter resulted in an average 85% reduction in the hematoma volume by 2 to 4 days after onset. Lippitz et al<sup>172</sup> used a standard dose of 3 mg of tPA dissolved in 3 mL of 0.9% saline solution; depending on the volume of residual hematoma after the first injection, tPA was repeated every 24 hours for 1 to 3 days. Schaller et al<sup>173</sup> calculated the dose of tPA relative to the maximum diameter of the hematoma; 1 cm of hematoma diameter equaled 1 mg of tPA. Repeated doses of tPA were administered every 24 hours for an additional 48 hours if hematoma remained. Vespa et al<sup>174</sup> described the improvement in

midline shift and NIHSS score with tPA treatment of ICH, as well as a lower mortality rate compared with a matched historical control cohort. No systemic side effects, including intracranial bleeding or rebleeding, were reported.

Given these results, a multicenter, randomized, controlled and stratified study comparing administration of tPA into the clot cavity versus conventional medical treatment has recently been funded by the National Institutes of Health. This study (Minimally Invasive Stereotactic Surgery + rt-PA for ICH Evacuation [MISTIE]) will test the following hypotheses: (1) Early use of minimally invasive surgery plus tPA for 3 days is safe for treatment of ICH and (2) early use of minimally invasive surgery plus tPA for 3 days produces clot size reduction compared with medically treated patients.

#### *Other Mechanical Devices and Radiographic Guidance*

In 1978, Backlund and von Holst<sup>175</sup> described a new instrument for stereotactic evacuation of hematomas, which consisted of a 4-mm cannula in which there was an Archimedes screw. Suction was applied to aspirate the clot into the cannula, while the rotating screw would morcellate the hematoma. Using this technique, others were able to almost completely evacuate ICHs in 13 of 16 patients in their series<sup>176</sup>; however, 81% of these patients died. After these pioneering reports, several modifications to the device were described.<sup>177–179</sup> Other innovative devices included a specially designed ultrasonic aspirator,<sup>180</sup> a modified nucleotome,<sup>181,182</sup> and a double-track aspiration system.<sup>183,184</sup> Although some of these approaches showed interesting results, especially when combined with real-time radiographic confirmation of clot removal with CT or ultrasound, they have not become popular.<sup>161</sup> This is somewhat surprising, because Kanaya and Kuroda<sup>161</sup> reported that rebleeding after surgery was seen in 10% of patients who underwent craniotomy but in only 5% to 6% of patients who underwent CT- or ultrasound-guided aspiration. Moreover, on average, CT-guided aspiration removed 71% of the original hematoma, and ultrasound-guided aspiration removed 81%. The percentage of hemorrhage removed did not significantly vary with the timing of the operation.<sup>161</sup>

#### **Early Clot Evacuation**

The decision about when to operate remains controversial. One key issue has been the lack of consensus on the time frame of what constitutes “early surgery.” Clinical studies have reported a wide variability in the timing of surgery, ranging from within 7 hours up to 72 hours from the onset of symptoms to time of operation.<sup>147–149,185,186</sup> Such time variance among the studies has made direct comparison and analysis of the impact of surgical timing difficult. Although most randomized and nonrandomized studies did not demonstrate statistical significance in the mortality and functional outcome between the surgical and conservative treatment groups, some clinical evidence indicates that performance of surgery in the “ultra-early” stage ( $\leq 7$  hours) may, in fact, be beneficial.

#### *“Ultra-Early” Stage*

In a retrospective review with historical controls, Kaneko and colleagues<sup>186</sup> reported the surgical removal of 100 putaminal

hemorrhages within 7 hours of symptom onset. Sixty of the hemorrhages were treated within 3 hours of onset. These patients had a baseline GCS score of 6 to 13, and most patients had a hematoma volume of  $>20$  to 30 mL. Patients with mild symptoms or GCS scores of  $\leq 5$  were treated conservatively. At 6 months, 7 (7%) had died, whereas 15 (15%) had fully recovered, and 35 (35%) were living independently at home. On the basis of these encouraging findings, a small, single-center randomized trial of craniotomy within 4 hours was performed.<sup>187</sup> Despite a mean time to the operating room of 191 minutes (range 95 to 240 minutes), the 6-month death rate was higher for patients who underwent surgery (36% versus 29%,  $P=NS$ ); functional outcomes in survivors were no different ( $P=0.88$ ). Interestingly, 4 of 11 who underwent ultra-early operation suffered acute rebleeding, of whom 75% died, which led the authors to suggest that the early rebleeding seen in the absence of operation might actually be facilitated by craniotomy. They suggest that surgery with concomitant use of rFVIIa might solve this problem.<sup>188</sup>

#### *Within 12 Hours*

As part of the same ultra-early surgical trial above, a third arm of patients underwent craniotomy within 12 hours of ictus ( $n=17$ ).<sup>187</sup> Interestingly, the mortality rate was only 18%, compared with the 29% seen in the medically managed group ( $P=NS$ ), and early postoperative clot recurrence was markedly reduced. Nevertheless, outcome was not noticeably improved.

In the small, randomized study by Zuccarello et al<sup>148</sup> of 20 subjects, those randomized to operation had the surgery at a mean of 8 hours and 25 minutes from symptom onset. The likelihood of a good outcome (primary outcome measure: GOS score  $>3$ ) for the surgical treatment group (56%) did not differ significantly from the medical treatment group (36%), although it trended in favor of surgery. No significant difference in mortality rate was seen at 3 months. Analysis of the secondary 3-month outcome measures showed a nonsignificant trend toward a better outcome in the surgical treatment group for the median GOS, BI, and mRS scores and a significant difference in the NIHSS score (4 versus 14;  $P=0.04$ ).

#### *Within 24 Hours*

Tan et al<sup>189</sup> conducted a prospective trial within 24 hours, matching 34 patients with hypertensive basal ganglia hemorrhage and comparable hematoma volume and GCS scores to either surgery or conservative treatment. Seventeen patients were treated surgically. Eight patients died (47%), and no statistical difference was seen in patient survival. At 3, 6, and 12 months, there was no statistical difference in functional outcomes (using the BI score) between the 2 groups.

#### *Within 48 Hours*

Juvela et al<sup>147</sup> reported 52 patients treated for supratentorial ICH in a prospective randomized trial. Twenty-six patients were assigned to the surgical group and underwent craniotomy, with the median time from bleeding to operation being 14.5 hours (range 6 to 48 hours). At 6 months, 12 patients (46%) had died, and only 1 patient (4%) was living indepen-



dently at home. No statistically significant difference in mortality and morbidity rates was found between the treatment groups, and it was concluded that spontaneous supratentorial ICH should be treated conservatively.

#### **Within 96 Hours**

In the STICH trial, Mendelow and colleagues<sup>149</sup> compared “early” surgery with initial conservative treatment for 1033 patients with ICH. As noted above, the average time from the onset of symptoms to surgery was 30 hours (range 16 to 49 hours), and the average time for only 16% (74 of 465 patients) was fewer than 12 hours. At 6 months, good functional outcome was 26% (n=122) for the surgical group, which was not significant when compared with the medical group (24%; OR 0.89, 95% CI 0.66 to 1.19). The absolute 2.3% (−3.2% to 7.7%) and relative 10% (−13% to 7.7%) benefits for early surgery over initial conservative medical treatment were also found to be nonsignificant.

#### **Decompressive Craniotomy**

This technique has been reported to be beneficial in a number of conditions, including hemispheric stroke and ICH associated with aneurysmal subarachnoid hemorrhage. Such surgery can effectively lower ICP but may reduce the risk of mortality at the expense of unacceptably high levels of morbidity. To date, no prospective randomized controlled trials show a convincing beneficial effect on outcome for any of the possible indications, much less for spontaneous ICH, for which the literature review found only a single case series.<sup>190</sup> In that series, 12 consecutive patients (mean age 50 years [range 19 to 76 years]) with hypertensive ICH were treated with decompressive hemicraniectomy. Eleven patients (92%) survived to discharge, and 6 of them (54.5%) had a good functional outcome, defined as an mRS of 0 to 3 (mean follow-up 17.13 months, range 2 to 39 months). Of note, 3 of the 7 patients with pupillary abnormalities made a good recovery, as did 4 of the 8 with clots >60 mL. Although these data are uncontrolled and preliminary, they call for further rigorous controlled trials, which may identify a subgroup of patients in whom this technique might prove to be worthwhile.

#### **Recommendations for Surgical Approaches**

##### *Class I*

1. **Patients with cerebellar hemorrhage >3 cm who are deteriorating neurologically or who have brain stem compression and/or hydrocephalus from ventricular obstruction should have surgical removal of the hemorrhage as soon as possible (Class I, Level of Evidence B).**

##### *Class II*

1. **Although stereotactic infusion of urokinase into the clot cavity within 72 hours of ictus apparently reduces the clot burden and risk of death, rebleeding is more common, and functional outcome is not improved; therefore, its usefulness is unknown (Class IIb, Level of Evidence B).**
2. **Although theoretically attractive, the usefulness of minimally invasive clot evacuation utilizing a variety of**

**mechanical devices and/or endoscopy awaits further testing in clinical trials; therefore, its current usefulness is unknown (Class IIb, Level of Evidence B).**

3. **For patients presenting with lobar clots within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered (Class IIb, Level of Evidence B).**

##### *Class III*

1. **The routine evacuation of supratentorial ICH by standard craniotomy within 96 hours of ictus is not recommended (Class III, Level of Evidence A). (See possible Class II exception above for patients presenting with lobar clots within 1 cm of the surface.)**

#### **Recommendations for Timing of Surgery**

##### *Class II*

1. **No clear evidence at present indicates that ultra-early craniotomy improves functional outcome or mortality rate. Operative removal within 12 hours, particularly when performed by less-invasive methods, has the most supportive evidence, but the number of subjects treated within this window is very small (Class IIb, Level of Evidence B). Very early craniotomy may be associated with an increased risk of recurrent bleeding (Class IIb, Level of Evidence B).**

##### *Class III*

1. **Delayed evacuation by craniotomy appears to offer little if any benefit with a fairly high degree of certainty. In those patients presenting in coma with deep hemorrhages, removal of ICH by craniotomy may actually worsen outcome and is not recommended (Class III, Level of Evidence A).**

#### **Recommendation for Decompressive Craniectomy**

##### *Class II*

1. **Too few data currently exist to comment on the potential of decompressive craniectomy to improve outcome in ICH (Class IIb, Level of Evidence C).**

#### **Withdrawal of Technological Support**

Several published articles on prognosis of spontaneous supratentorial ICH have been published. They all share a common limitation: They do not consider the use of early do-not-resuscitate (DNR), do-not-attempt-to-resuscitate, or not-for-resuscitation orders. Although the exact terminology varies among different countries, the primary issue about when and how to withdraw technological support is the same. Because withdrawing life-sustaining support is the most common immediate cause of death in ICH,<sup>191</sup> the use of early DNR orders biases predictive models to make ICH outcome look worse than it would if full care was provided.<sup>192</sup> Although physicians may concur on the appropriate circumstances for DNR use in ICH,<sup>193</sup> these decisions are based on these prediction papers that do not account for early DNR use. Recently, several studies have documented how the use of early (within the first 24 to 48 hours) DNR orders biases

predictive models of ICH outcome and may falsely lead to the belief that outcome from ICH is universally bleak.<sup>192</sup> DNR orders are extremely common in ICH.<sup>194</sup>

Although a DNR order by definition means no aggressive treatment should a cardiopulmonary arrest occur, in practical use, it is associated with an overall lack of aggressiveness of care.<sup>195</sup> Hemphill and colleagues<sup>196</sup> found that a given hospital's rate of early DNR usage was very predictive of patient death independent of the individual patient's clinical characteristics or personal DNR status. This again implies that the overall aggressiveness of ICH care at a hospital is critically important in determining patients' outcome.

### Recommendation for Withdrawal of Technological Support

#### *Class II*

1. We recommend careful consideration of aggressive full care during the first 24 hours after ICH onset and postponement of new DNR orders during that time (*Class IIb, Level of Evidence B*). Patients with previous DNR orders are not included in this recommendation. In all cases, physicians and nurses caring for ICH patients who are given DNR status should be reminded that the designation relates only to the circumstance of cardiopulmonary arrest and that patients should receive all other appropriate medical and surgical interventions.

### Prevention of Recurrent ICH

The high morbidity and mortality rates of ICH mandate a rigorous identification of risk factors to decrease its recurrence. Although age cannot be treated, age >65 years has been found to have an OR of 2.8 for recurrence of ICH, which provides useful prognostic information for patients and perhaps points their physicians to the need for aggressive risk factor reduction.<sup>197</sup>

Hypertension remains the most important target for ICH prevention. The OR for ICH in one study was 3.5 with untreated hypertension but only 1.4 for treated hypertension,

which suggests that treatment of hypertension can prevent ICH.<sup>198</sup> More direct evidence comes from a study of 4736 patients >60 years of age with isolated systolic hypertension, wherein treatment resulted in an adjusted relative risk of 0.46 for ICH, and the benefit was observed within 1 year.<sup>199</sup> In the PROGRESS cohort of 6105 patients with prior cerebrovascular events, treatment with a perindopril-based regimen reduced the ICH risk from 2% to 1% over 3.9 years of follow-up.<sup>104</sup>

Data on how and when to switch from intravenous medications used to control blood pressure in ICH patients during the hospitalization to oral long-term medications are not available. This change in antihypertensive regimen often begins after the patient is clinically stable, able to swallow medication or to take oral medications through a gastrointestinal tube, and near discharge from the acute care hospital.

Smoking (particularly in the young), heavy alcohol use, and cocaine use have also been associated with an increased risk of ICH and should be strongly discouraged after ICH.<sup>200–204</sup>

### Recommendations for Prevention of Recurrent ICH

#### *Class I*

1. Treating hypertension in the nonacute setting is the most important step to reduce the risk of ICH and probably recurrent ICH as well (*Class I, Level of Evidence A*).
2. Smoking, heavy alcohol use, and cocaine use are risk factors for ICH, and discontinuation should be recommended for prevention of ICH recurrence (*Class I, Level of Evidence B*).

### Future Considerations

The first scientifically proven treatments for acute ICH are likely to become a reality during the next 5 years, and possibly sooner for some. New trials of antihypertensive therapy, surgical removal of ICH, and other adjunctive therapies are ongoing, but sustained efforts are needed to decrease the high morbidity and mortality rates associated with this deadly type of stroke.

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Sander Connolly	Columbia University	None	None	None	None	APT Therapeutics; Boston Scientific; Johnson & Johnson; Maxigen, Inc; Merck, Inc; Paragenics, Inc; Shinogi, Inc; Thrombogenics, Inc	None
Edward Feldmann	Brown University	None	None	Bristol-Myers Squibb/Sanofi; Boehringer Ingelheim	None	Medical-legal consulting, for both plaintiffs and defendants, with regard to the causes, evaluation, and treatment of ICH	Medical-legal consulting for both plaintiffs and defendants regarding to the causes, evaluation, and treatment of stroke
Daniel Hanley	Johns Hopkins University	Abbott; Genentech	None	Beecham; Bristol-Myers Squibb/Sanofi; Boehringer Ingelheim; GlaxoSmithKline	None	Bayer; Boehringer Ingelheim; Boston Scientific; Centocor-Lilly; Genentech; Hoechst-Marion Merrell Dow; Janssen Knoll Pharmaceutical; Medvance; NMT Medical; Neuron Therapeutics; Novartis; Pharmacia; Pharmos; Pharma Solvay	None
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Derk Krieger	Cleveland Clinic Foundation	None	None	Bristol-Myers Squibb	None	Medcool, Inc; Boston Scientific, Inc; McNeil Pharmaceuticals	None
Marc Mayberg	Seattle Neuroscience Institute	None	None	None	Pulsar Vascular	Northstar Medical	None
Lewis Morgenstern	University of Michigan	None	None	AstraZeneca; Novo Nordisk	None	Merck	None
Christopher S. Ogilvy	Massachusetts General Hospital	Alberta Heritage Foundation; American Association of Neurological Surgeons/Congress of Neurological Surgeons; Center for Integration of Medicine and Innovative Technology	None	None	None	None	None
Paul Vespa	University of California, Los Angeles	None	None	PDL	None	The Medicines Company	None
Mario Zuccarello	Mayfield Clinic	None	None	None	None	None	None

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Michael Diring	Washington University School of Medicine	NINDS	None	None	None	None	Novo Nordisk	None
Donald D. Heistad	University of Iowa College of Medicine	NIH	None	None	None	None	None	None
Edward C. Jauch	University of Cincinnati College of Medicine	Biosite	None	Boehringer Ingelheim	None	None	AstraZeneca; Biosite; Genentech; Johnson & Johnson; Novo Nordisk	None
Stephan Mayer	Columbia University	Novo Nordisk	None	Novo Nordisk; PDL BioPharma	None	None	Novo Nordisk; PDL BioPharma	None

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