Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage

A Statement for Healthcare Professionals From a Special Writing Group of the Stroke Council, American Heart Association

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

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Subarachnoid hemorrhage (SAH) is a common and frequently devastating condition, accounting for ~5% of all strokes and affecting as many as 30,000 Americans each year.1,2 The American Heart Association (AHA) previously published “Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage.”3 Since then, considerable advances have been made in endovascular techniques, diagnostic methods, and surgical and perioperative management paradigms. Nevertheless, outcome for patients with SAH remains poor, with population-based mortality rates as high as 45% and significant morbidity among survivors.4–9 Several multicenter, prospective, randomized trials and prospective cohort analyses have influenced treatment protocols for SAH. However, rapid evolution of newer treatment modalities, as well as other practical and ethical considerations, has meant that rigorous clinical scientific assessment of the treatment protocols has not been feasible in several important areas.

To address these issues, the Stroke Council of the AHA formed a writing group to reevaluate the recommendations for management of aneurysmal SAH. A consensus committee reviewed existing data in this field and prepared the recommendations in 1994.3 In an effort to update those recommendations, a systematic literature review was conducted based on a search of MEDLINE to identify all relevant randomized clinical trials published between June 30, 1994, and November 1, 2006 (search terms: subarachnoid hemorrhage, cerebral aneurysm, trial; Table 1). Each identified article was reviewed by at least 2 members of the writing group. Selected articles had to meet one of the following criteria to be included: randomized trial or nonrandomized concurrent cohort study. Case series and nonrandomized historical cohort studies were reviewed if no studies with a higher level of evidence were available for a particular topic covered in the initial guidelines. These were chosen on the basis of sample size and the relevance of the particular studies to subjects that were covered in the initial guidelines.10 The committee’s recommendations were made by applying the standard AHA evidence rating scheme11,12 (Tables 2 and 3). These recommendations are intended to summarize the best available evidence for treatment of patients with aneurysmal SAH and to identify areas of future research. Treatments for specific patients need to be individualized.

Incidence and Prevalence of Aneurysmal SAH

A large multinational World Health Organization study found that the age-adjusted annual incidence of SAH varied 10-fold between different countries, from 2.0 cases per 100,000 population in China to 22.5 per 100,000 in Finland.13 Community-based studies reported an incidence that ranged from 8.1 per 100,000 in Australia and New Zealand to 23 per 100,000 in Japan.14–16 One Japanese study suggested that if early deaths attributed to SAH were included, the rate would be as high as 32 per 100,000.17 Using data collected from nonfederal hospitals in the United States, the National Hos-
pital Discharge Survey of 199018 reported that 25 000 patients had an SAH during the previous year. Data from Rochester, Minn, for 1975 through 1984 suggest that an additional 12% of persons with SAH do not receive prompt medical attention19 and that many cases of SAH are misdiagnosed.20–26 The annual prevalence of aneurysmal SAH in the United States may therefore exceed 30 000 persons. Population-based studies have indicated that the incidence rate for SAH has not changed dramatically over the past 4 decades,27,28 whereas others have suggested a slight decline in incidence in New Zealand from the 1980s to the 1990s29 and a decreased mortality from SAH in Sweden as a result of declining incidence in men and decreased death rates after SAH in women.30 The incidence of SAH increases with age, occurring most commonly between 40 and 60 years of age (mean age 51 ± 13 years), but SAH can occur from childhood to old age and is 1.6 times higher in women than in men,4,31 although this difference does not carry across all populations.13 Studies have suggested that the gender difference is related to hormonal status, with premenopausal women,32 those of older age at the birth of their first child, and those of older age at the onset of menarche at reduced risk for SAH.33

### Table 1. Randomized Clinical Trials in Aneurysmal SAH: 1995 to 2006 (by Therapeutic Modality)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Therapy</th>
<th>n</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Bergh et al415</td>
<td>2006</td>
<td>Aspirin</td>
<td>161</td>
<td>No less DIND</td>
</tr>
<tr>
<td>Hop et al416</td>
<td>2000</td>
<td>Aspirin</td>
<td>50</td>
<td>No improvement in 4-mo outcome</td>
</tr>
<tr>
<td>Schmid-Elsaesser499</td>
<td>2006</td>
<td>Magnesium</td>
<td>113</td>
<td>No better outcome than nimodipine</td>
</tr>
<tr>
<td>Wong et al476</td>
<td>2006</td>
<td>Magnesium</td>
<td>60</td>
<td>No better outcome</td>
</tr>
<tr>
<td>Van den Bergh et al409</td>
<td>2005</td>
<td>Magnesium</td>
<td>283</td>
<td>Less DCI and poor outcome</td>
</tr>
<tr>
<td>Veyna450</td>
<td>2002</td>
<td>Magnesium</td>
<td>40</td>
<td>No less clinical vasospasm</td>
</tr>
<tr>
<td>Molyneux et al485</td>
<td>2005</td>
<td>GDC</td>
<td>2143</td>
<td>Less mortality/epilepsy, more rebleeding</td>
</tr>
<tr>
<td>Molyneux et al428</td>
<td>2002</td>
<td>GDC</td>
<td>2143</td>
<td>Less mortality, better outcome</td>
</tr>
<tr>
<td>Koivisto et al459</td>
<td>2000</td>
<td>GDC</td>
<td>109</td>
<td>No improvement in 12-mo outcome</td>
</tr>
<tr>
<td>Vanninen501</td>
<td>1999</td>
<td>GDC</td>
<td>109</td>
<td>No improvement in 3-mo outcome</td>
</tr>
<tr>
<td>Vajkoczy et al425</td>
<td>2005</td>
<td>ET antagonist</td>
<td>32</td>
<td>Less incidence/intensity angiographic vasospasm</td>
</tr>
<tr>
<td>Shaw et al426</td>
<td>2000</td>
<td>ET antagonist</td>
<td>420</td>
<td>Trend to less DIND, no better outcome</td>
</tr>
<tr>
<td>Lynch et al428</td>
<td>2005</td>
<td>Statin (simvastatin)</td>
<td>39</td>
<td>Reduced incidence of clinical vasospasm</td>
</tr>
<tr>
<td>Tseng et al429</td>
<td>2005</td>
<td>Statin (pravastatin)</td>
<td>80</td>
<td>Less mortality/incidence of TCD vasospasm</td>
</tr>
<tr>
<td>Anderson502</td>
<td>2006</td>
<td>Hypothermia</td>
<td>1001</td>
<td>No neuropsychological benefit at 3 mo</td>
</tr>
<tr>
<td>Todd et al364</td>
<td>2005</td>
<td>Hypothermia</td>
<td>1001</td>
<td>No improvement in 3-mo outcome</td>
</tr>
<tr>
<td>Karibe503</td>
<td>2000</td>
<td>Hypothermia</td>
<td>24</td>
<td>Immediate CBF improvement</td>
</tr>
<tr>
<td>Hindman504</td>
<td>1999</td>
<td>Hypothermia</td>
<td>114</td>
<td>Improved outcome at 3 and 6 mo</td>
</tr>
<tr>
<td>Diringer505</td>
<td>2004</td>
<td>Normothermia</td>
<td>296</td>
<td>Reduced fever burden with catheter</td>
</tr>
<tr>
<td>Reinen et al427</td>
<td>2004</td>
<td>TD NTG</td>
<td>17</td>
<td>Raised CBF</td>
</tr>
<tr>
<td>Klopfenstein et al469</td>
<td>2004</td>
<td>Drain wean</td>
<td>81</td>
<td>No difference in shunted hydrocephalus</td>
</tr>
<tr>
<td>Wurm et al417</td>
<td>2004</td>
<td>Enoxaparin</td>
<td>117</td>
<td>No less TCD vasospasm</td>
</tr>
<tr>
<td>Sironen et al418</td>
<td>2003</td>
<td>Enoxaparin</td>
<td>170</td>
<td>No improvement in 3-mo outcome</td>
</tr>
<tr>
<td>Moro506</td>
<td>2003</td>
<td>Hydrocortisone</td>
<td>28</td>
<td>Improved sodium balance</td>
</tr>
<tr>
<td>Mori et al498</td>
<td>1999</td>
<td>Fluorocortisone</td>
<td>30</td>
<td>No improvement in 6-mo outcome</td>
</tr>
<tr>
<td>Mayer et al391</td>
<td>1998</td>
<td>5% Albumin</td>
<td>43</td>
<td>Improved sodium balance</td>
</tr>
<tr>
<td>Hamada507</td>
<td>2003</td>
<td>IT urokinase</td>
<td>110</td>
<td>Reduced symptomatic vasospasm</td>
</tr>
<tr>
<td>Findlay508</td>
<td>1995</td>
<td>IT rtPA</td>
<td>91</td>
<td>No decrease in angiographic vasospasm</td>
</tr>
<tr>
<td>Hillman et al440</td>
<td>2002</td>
<td>Tranexamic A</td>
<td>505</td>
<td>Reduced rebleeding, no effect on outcome</td>
</tr>
<tr>
<td>Roos509</td>
<td>2000</td>
<td>Tranexamic A</td>
<td>462</td>
<td>Reduced rebleeding, no effect on outcome</td>
</tr>
<tr>
<td>Egge et al389</td>
<td>2001</td>
<td>Hypervolemia</td>
<td>32</td>
<td>No effect on clinical/TCD vasospasm</td>
</tr>
<tr>
<td>Lennihan et al385</td>
<td>2000</td>
<td>Hypervolemia</td>
<td>82</td>
<td>No less symptomatic vasospasm</td>
</tr>
<tr>
<td>Lanzino et al419</td>
<td>1999</td>
<td>Tirilazad (F-NA)</td>
<td>823</td>
<td>No improvement in 3-mo outcome</td>
</tr>
<tr>
<td>Lanzino et al420</td>
<td>1999</td>
<td>Tirilazad (F-E)</td>
<td>819</td>
<td>No improvement in 3-mo outcome</td>
</tr>
<tr>
<td>Haley et al421</td>
<td>1997</td>
<td>Tirilazad (NA)</td>
<td>897</td>
<td>No improvement in 3-mo outcome</td>
</tr>
<tr>
<td>Kassell et al422</td>
<td>1996</td>
<td>Tirilazad (E)</td>
<td>1015</td>
<td>No improvement in 3-mo outcome</td>
</tr>
<tr>
<td>Saito et al423</td>
<td>1998</td>
<td>Ebselen</td>
<td>286</td>
<td>No less DIND but improved outcome</td>
</tr>
<tr>
<td>Asano et al424</td>
<td>1996</td>
<td>Ebselen</td>
<td>162</td>
<td>Decreased incidence of DIND</td>
</tr>
</tbody>
</table>

DIND indicates delayed ischemic neurological deficits; GDC, Guglielmi detachable coil; ET, endothelin; TD NTG, transdermal nitroglycerin; rtPA, recombinant tissue-type plasminogen activator; F-NA, female patient subgroup—North American cohort; F-E, female patient subgroup—European cohort; NA, North American cohort; and E, European cohort.
be racial differences in risk of SAH. Black Americans are at higher risk than white Americans.34 Maori and Pacific people are at higher risk than white New Zealanders.14 Population-based mortality rates for SAH appear to have declined from the 1970s and 1980s.28 More recent studies have suggested that the trend either is continuing or has leveled off.27 Racial differences in mortality have emerged, with white Americans having a lower mortality rate than black Americans, Hispanic Americans, American Indians/Alaskan Natives, and Asian/Pacific Islanders in the United States.35

### Risk Factors for Aneurysmal SAH

Risk factors for SAH have been studied in a number of settings. Multivariate models have found hypertension, smoking, and heavy alcohol use to be independent risk factors for SAH in the United States, Japan, the Netherlands, Finland, and Portugal. Sympathomimetic drugs, including cocaine and phenylpropanolamine, have been implicated as a cause of SAH. Cocaine-related SAH occurs in younger patients and has an outcome similar to that in other SAH patients. Diabetes does not appear to be a risk factor for SAH. Interestingly, some of the same risk factors for SAH also have been shown to increase the risk of multiple aneurysms (ie, smoking, female gender, hypertension, family history of cerebrovascular disease, and postmenopausal state).48–50

There has also long been interest in the influence of meteorological and temporal factors on the incidence of SAH. Studies have provided variable results, but there appears to be a somewhat higher incidence of SAH in the winter months14,51 and in the spring.52 This, however, was not found in a Japanese study.53 Finally, another study found a modest correlation between atmospheric pressure and change in pressure and number of SAHs per day.54

Certain genetic syndromes have also been associated with an increased risk of SAH and support the concept of inherited susceptibility to aneurysm formation. These include autosomal dominant polycystic kidney disease and type IV Ehlers-Danlos syndrome.55–60 These syndromes support the theory of inherited susceptibility to aneurysm formation.61–76 In a small review of published sibships with SAH, angiography performed in asymptomatic siblings found an aneurysm in one third of cases.77 This finding is in contrast to the true familial intracranial aneurysm syndrome, which occurs when 2 first- through third-degree relatives have intracranial aneurysms.10,78–83 This is associated with SAH at a younger age, a high incidence of multiple aneurysms, and hemorrhages among siblings and mother-daughter pairings.78,83,84 In family members with the familial intracranial aneurysm syndrome, the risk of harboring an unruptured aneurysm was 8%73 with a relative risk of 4.2.85 A study of 23 families with familial SAH found that having ≥3 affected relatives tripled the risk of SAH. When magnetic resonance angiography (MRA) was used to screen 8680 asymptomatic individuals for intracranial aneurysms, the overall incidence of aneurysms was 7.0% but rose to 10.5% in those with a family history of SAH.86 However, another magnetic resonance imaging (MRI) study reported that 4% of relatives of sporadic SAH patients had aneurysms.87 In a large case-control study,88 family history was found to be an independent risk factor for SAH. The specific genes involved have not yet been identified, and when polymorphisms in matrix metalloproteinase genes were studied, they had no relationship to the development of aneurysms.89

Finally, in patients who have been treated for a ruptured aneurysm, the annual rate of new aneurysm formation is 1% per year to 2% per year.81,84,90–95 Patients with multiple intracranial aneurysms may be particularly susceptible to new aneurysm formation.47,93,96 It is not clear whether this is due to genetic or acquired factors.

### Prevention of SAH

Because no randomized controlled trials have specifically examined whether treatment of medical risk factors reduces the occurrence of SAH, available evidence is derived from observational cohort studies. It has been suggested that control of these major risk factors may have a greater impact on SAH in younger than in older patients.97 Hypertension is a common risk factor for hemorrhagic stroke. In a review by Collins et al., an average reduction in diastolic blood pressure of 6 mm Hg by antihypertensive medication produced an aggregate 42% reduction in stroke incidence. However, there are few data on aneurysmal SAH in these

### Table 2. Definitions of Classes and Levels of Evidence Used in AHA Stroke Council Recommendations

<table>
<thead>
<tr>
<th>Class</th>
<th>Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment</td>
</tr>
<tr>
<td>Class IIa</td>
<td>The weight of evidence or opinion is in favor of the procedure or treatment</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence or opinion</td>
</tr>
<tr>
<td>Class III</td>
<td>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</td>
</tr>
</tbody>
</table>

**Therapeutic recommendations**

| 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/prognostic recommendations**

| Level of Evidence A | Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator |
| Level of Evidence B | Data derived from a single grade A study or ≥1 case-control studies or studies using a reference standard applied by an unmasked evaluator |
| Level of Evidence C | Consensus opinion of experts |
studies because of limited sample size for SAH events. Although there has been a marked improvement in blood pressure control in the general population, there has been little change in the incidence of SAH during that time.99–101 Regardless of whether hypertension control reduces the incidence of SAH, it may reduce the severity; untreated hypertension appears to be an independent risk factor for poor outcome after SAH.102 Similarly, only indirect evidence exists to indicate that smoking cessation reduces risk for SAH. In a case-control study,103 former smokers had a lower relative risk than light or moderate smokers, and there was an inverse relationship between time since the last cigarette and risk of SAH. In a prospective study of 117,006 women, it was observed that former smokers also had a lower relative risk of SAH than current smokers and that duration since quitting was associated with a decreased risk.104

Because of the poor prognosis from SAH and the relatively high frequency of asymptomatic intracranial aneurysms, the role of elective screening has been a subject of discussion in the literature. In evaluations of the clinical efficacy of screening for asymptomatic intracranial aneurysms, the costs of screening should be weighed against the risks and consequences of SAH. Several assumptions must be made to estimate these costs, for example, about how an aneurysm would be managed if detected, although this unrealistically simplifies the medical decision-making process. Several factors, including aneurysm incidence, risk of rupture (natural history), and risk of treatment, influence the analysis of cost-effectiveness for asymptomatic unruptured aneurysms.73,85,93,105 Of these factors, the risk of rupture is the most important. To date, there have been no population-based clinical studies of cost-effectiveness of screening for intracranial aneurysms. Therefore, screening for asymptomatic intracranial aneurysms in the general population is currently not supported by the available literature. Patients

Table 3. Applying Classification of Recommendations and Level of Evidence

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>Suggested phrases for writing recommendations</th>
<th>Should</th>
<th>Is recommended</th>
<th>Is indicated</th>
<th>Is useful/effective/beneficial</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Multiple populations evaluated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Limited populations evaluated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Very limited populations evaluated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Only consensus opinion of experts, case studies, or standard of care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, 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 guideline recommendations 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.
with environmental risk factors such as cigarette smoking and alcohol use have an increased incidence of SAH, but this has not been associated with an increased incidence of intracranial aneurysms, and general screening for aneurysms does not appear to be warranted in this population either.

In populations with the familial intracranial aneurysm syndrome, although screening detects an increased incidence of intracranial aneurysms, the cost-effectiveness of screening has not been demonstrated. Until the efficacy of screening has been evaluated in a population-based clinical study, most studies suggest that screening should be considered on an individual basis. In contrast to asymptomatic individuals, the annual rate of new aneurysm formation in patients treated for aneurysmal SAH is 1% to 2%. In this group, late radiological evaluation of this population has been considered reasonable by some.

Nevertheless, the appropriate techniques for aneurysm detection screening remain a matter of debate. Many of the issues pertaining to screening for incidental aneurysm also pertain to detecting ruptured aneurysm and are discussed below in the section on diagnosis. Although early studies have suggested that MRA may miss aneurysms detected by conventional angiographic techniques, data suggest that MRA combined with computed tomography (CT) angiography (CTA) is comparable to conventional angiography in detecting aneurysms. Another small prospective study suggested that digital subtraction angiography and MRA were complementary. However, in a review of the available literature, Wardlaw and White concluded that “quality of data testing their [MRA and CTA] accuracy is limited.” Thus, until better data become available, the appropriate technique for initial screening should be individualized; however, when it is clinically imperative to know if an aneurysm exists, catheter angiography remains the gold standard.

As discussed, the case fatality rate for aneurysmal SAH remains high, and it is recognized that the main determinant of outcome is the severity of the initial bleed. If SAH could be prevented before aneurysm rupture, poor outcomes related to SAH could theoretically be avoided. However, because only a minority of asymptomatic aneurysms go on to rupture and because all aneurysm treatments carry some risk, the management of patients harboring an unruptured aneurysm remains controversial. Recommendations were published for the management of unruptured intracranial aneurysms in 2000. Subsequent advances in treatment modalities and better understanding of the natural history of unruptured intracranial aneurysms have occurred, and a separate writing committee has been commissioned to update these recommendations.

**Prevention of SAH: Summary and Recommendations**

1. The relationship between hypertension and aneurysmal SAH is uncertain. However, treatment of high blood pressure with antihypertensive medication is recommended to prevent ischemic stroke, intracerebral hemorrhage, and cardiac, renal, and other end-organ injury (Class I, Level of Evidence A).
2. Cessation of smoking is reasonable to reduce the risk of SAH, although evidence for this association is indirect (Class IIa, Level of Evidence B).
3. Screening of certain high-risk populations for unruptured aneurysms is of uncertain value (Class IIb, Level of Evidence B); advances in noninvasive imaging may be used for screening, but catheter angiography remains the gold standard when it is clinically imperative to know if an aneurysm exists.

**Natural History and Outcome of Aneurysmal SAH**

An estimated 6700 annual in-hospital deaths from aneurysmal SAH occur in the United States, with evidence that incidence rates remain relatively stable, but death rates from SAH may have declined during the past several decades in other geographic locations. The mortality rate for SAH in the 1966 Cooperative Study on Intracranial Aneurysms was 50% at 29 days and 33% in a recent analysis of in-hospital deaths among SAH patients admitted through an emergency department (ED). In a population-based study by Broderick et al, the 30-day mortality rate among all patients who suffered SAH was 45%, with the majority of deaths occurring in the first days after SAH. Other studies have suggested slightly declining mortality rates in this and other countries.

There are many influences on outcome after SAH, with wide variations in case fatality rates reported between different countries and regions. The factors that strongly influence outcome after SAH can be divided into patient factors, aneurysm factors, and institutional factors. Patient factors include the severity of initial hemorrhage, age, sex, time to treatment, and medical comorbidities such as untreated and treated hypertension, atrial fibrillation, congestive heart failure, coronary artery disease, and renal disease. Aneurysm factors include size, location in the posterior circulation, and possibly morphology. Institutional factors include the availability of endovascular services, the volume of SAH patients treated, and the type of facility in which the patient is first evaluated.

Of patient factors, by far the most important determinant of poor outcome is the deleterious effect of acute SAH on the brain (reviewed by Sehba and Bederson). SAH causes profound reductions in cerebral blood flow (CBF), reduced cerebral autoregulation, and acute cerebral ischemia. These pathophysiological processes are linked to raised intracranial pressure and decreased cerebral perfusion pressure, decreased availability of nitric oxide, acute vasoconstriction and microvascular platelet aggregation, activation of microvascular collagenases, loss of microvascular collagen, and endothelial barrier antigen leading to decreased microvascular perfusion and increased permeability. Despite recent advances in the understanding of the mechanisms of SAH-induced brain injury, few effective treatments exist, and further research is needed.

Recurrent hemorrhage remains a serious consequence of aneurysmal SAH, with a case fatality rate of ~70% for
persons who rebleed, and is currently the most treatable cause of poor outcomes. Previous studies delineated several patterns of rebleeding.\textsuperscript{134,135} In the prospective Cooperative Aneurysm Study,\textsuperscript{136} rebleeding was maximal (4\%) on the first day after SAH and then constant at a rate of 1\% per day to 2\% per day over the subsequent 4 weeks. Several prospective follow-up cohorts\textsuperscript{137,138} have demonstrated that the risk of rebleeding with conservative therapy is between 20\% and 30\% for the first month after hemorrhage and then stabilizes at a rate of \(\approx 3\%\) per year.\textsuperscript{139} Several potential risk factors for acute rebleeding have been identified from prospective and retrospective studies. A longer interval from hemorrhage to admission and treatment, higher initial blood pressure, and worse neurological status on admission have been related to recurrent hemorrhage in the first 2 weeks after SAH. Recent evidence indicates that the risk of “ultraearly rebleeding” (within 24 hours of initial SAH) may be 15\%, which is considerably higher than previously recognized,\textsuperscript{140,141} with high mortality rates. In 1 study, 70\% of ultraearly rebleeds occurred within 2 hours of initial SAH.\textsuperscript{141} In another study, all preoperative rebleeding occurred within 12 hours of initial SAH.\textsuperscript{142} In recent studies, poor neurological status,\textsuperscript{142} high Hunt-Hess grade, and larger aneurysm diameter\textsuperscript{143} were independent predictors of acute hydrocephalus, intraventricular blood, and the use of ventricular draining.\textsuperscript{137–139,143–147} Recent data suggest that when preoperative ventriculostomy is followed by early treatment of the ruptured aneurysm, the risk of rebleeding is not increased by the ventriculostomy.\textsuperscript{148}

Numerous systems have been reported for grading the clinical outcome in patients with SAH from a ruptured intracranial aneurysm, but the current literature remains substantially deficient with respect to triage and triage uniformity or consistency.\textsuperscript{9,149–151} Recent reports have tended to use the Glasgow Coma Scale or Glasgow Outcome Scale.\textsuperscript{149,150,152–178} It should be noted that the Glasgow Coma Scale was designed to predict outcome after head injury and has not been fully assessed in outcome after SAH. In addition, patients who have no grossly evident neurological deficits after SAH frequently have subtle cognitive or neuropsychological deficits that impair their social adjustment and ability to return to their previous occupations.\textsuperscript{179–183} At least 1 study has suggested that these neuropsychological deficits are not correlated with tissue loss as seen on recent MRI;\textsuperscript{184} therefore, it is likely that they are due to a diffuse effect of SAH. At the present time there is no standardized method of measuring these deficits in patients with SAH, and a wide variety of standard neuropsychological tests have been used by a variety of investigators.\textsuperscript{179–182,184} In the recent International Subarachnoid Aneurysm Trial (ISAT), written questionnaires were sent to patients to determine a modified Rankin Scale.\textsuperscript{185,186} Perhaps the most meaningful and simplest measure of the effect of these deficits is whether the patient is able to return to his or her previous occupation.\textsuperscript{182} It is reasonable to recommend that studies reporting on SAH contain as a minimum the admission Glasgow Coma Scale score and factors commonly believed to influence prognosis as discussed previously.\textsuperscript{150}

Natural History and Outcome of Aneurysmal SAH: Summary and Recommendations

1. The severity of the initial bleed should be determined rapidly because it is the most useful indicator of outcome after aneurysmal SAH, and grading scales that rely heavily on this factor are helpful in planning future care with family and other physicians (Class I, Level of Evidence B).

2. Case review and prospective cohorts have shown that for untreated, ruptured aneurysms, there is at least a 3\% to 4\% risk of rebleeding in the first 24 hours—and possibly significantly higher—with a high percentage occurring immediately (within 2 to 12 hours) after the initial ictus, a 1\% per day to 2\% per day risk in the first month, and a long-term risk of 3\% per year after 3 months. Urgent evaluation and treatment of patients with suspected SAH are therefore recommended (Class I, Level of Evidence B).

3. In the triage of patients for aneurysm repair, factors that may be considered in determining the risk of rebleeding include severity of the initial bleed, interval to admission, blood pressure, gender, aneurysm characteristics, hydrocephalus, early angiography, and the presence of a ventricular drain (Class IIb, Level of Evidence B).

Clinical Manifestations and Diagnosis of Aneurysmal SAH

The clinical presentation of aneurysmal SAH is one of the most distinctive in medicine. The sine qua non of SAH in an awake patient is the complaint of “the worst headache of my life,” described by \(\approx 80\%\) of patients who can give a history, but a warning or sentinel headache is also described by \(\approx 20\%\) of patients.\textsuperscript{187,188} Most intracranial aneurysms remain asymptomatic until they rupture. Although aneurysmal SAH occurs frequently during physical exertion or stress, SAH can occur at any time.\textsuperscript{189,190} The onset of headache may be associated with \(\geq 1\) additional signs and symptoms, including nausea and/or vomiting, stiff neck, a brief loss of consciousness, or focal neurological deficits (including cranial nerve palsies). Fontanarosa\textsuperscript{191} retrospectively studied 109 patients with proven SAH and found headache in 74\%, nausea or vomiting in 77\%, loss of consciousness in 53\%, and nuchal rigidity in 35\%.\textsuperscript{4} As many as 12\% die before receiving medical attention.\textsuperscript{189}

Despite the classic presentation of SAH, individual findings occur inconsistently, and because the type of headache from SAH is sufficiently variable, misdiagnosis or delayed diagnosis is common. Misdiagnosis of SAH occurred in as many as 64\% of cases before 1985, with more recent data suggesting an SAH misdiagnosis rate of \(\approx 12\%\).\textsuperscript{4,21,192–195} Misdiagnosis was associated with a nearly 4-fold higher likelihood of death or disability at 1 year in patients with minimal or no neurological deficit at the initial visit.\textsuperscript{21} The most common diagnostic error is failure to obtain a noncontrast cranial CT.\textsuperscript{21,194–196}

Patients may report symptoms consistent with a minor hemorrhage before a major rupture, which has been called a sentinel bleed or warning leak.\textsuperscript{197} The majority of these minor hemorrhages occur within 2 to 8 weeks before overt SAH. The headache associated with a warning leak is usually milder than that associated with a major rupture, but it may last for a few days.\textsuperscript{198,199} Nausea and vomiting may occur, but meningismus is uncommon after a sentinel hemorrhage.
Among 1752 patients with aneurysm rupture from 3 series, 340 (20%; range, 15% to 37%) had a history of a sudden severe headache before the event leading to admission.\textsuperscript{187,197,198} The importance of recognizing a warning leak cannot be overemphasized. Headache is a common presenting chief complaint in the ED, and SAH accounts for only 1% of all headaches evaluated in the ED.\textsuperscript{194} Therefore, a high index of suspicion is warranted because diagnosis of the warning leak or sentinel hemorrhage before a catastrophic rupture may be lifesaving.\textsuperscript{196} Seizures may occur in up to 20% of patients after SAH, most commonly in the first 24 hours\textsuperscript{200} and more commonly in SAH associated with intracerebral hemorrhage, hypertension, and middle cerebral and anterior communicating artery aneurysms.\textsuperscript{201}

The cornerstone of SAH diagnosis is the noncontrast cranial CT scan.\textsuperscript{202} The probability of detecting a hemorrhage is proportional to the clinical grade and the time from hemorrhage. In the first 12 hours after SAH, the sensitivity of CT for SAH is 98% to 100%, declining to 93% at 24 hours\textsuperscript{203–207} and to 57% to 85% 6 days after SAH.\textsuperscript{195,208} Because the diagnostic sensitivity of CT scanning is not 100%, diagnostic lumbar puncture should be performed if the initial CT scan is negative. Proper technique, proper specimen handling, and correct interpretation of the cerebrospinal fluid (CSF) results are critical for accurate diagnosis. Key factors for the examination of CSF include an understanding of the timing of lumbar puncture in relation to SAH, red and white blood cell counts, the presence of xanthochromia, and detection of bilirubin.\textsuperscript{194,195,209,210} Guidelines for the examination and interpretation of CSF obtained from lumbar puncture to evaluate suspected SAH have been published.\textsuperscript{211} A normal CT scan and CSF examination exclude a warning leak in most cases and predict a more favorable prognosis in the setting of severe and/or sudden headache.\textsuperscript{212,213} It has been recommended that patients with a normal CT scan and CSF examination be offered reassurance, symptomatic headache treatment, and appropriate consultative referral as indicated.\textsuperscript{195}

Use of MRI in the diagnosis of SAH has evolved. MRI techniques using proton-density–weighted images or fluid-attenuated inversion recovery images have improved the diagnosis of acute SAH.\textsuperscript{4,214–218} However, the practical limitations of MRI in the emergency setting are routine availability, logistics (including difficulty in scanning of acutely ill patients), sensitivity to motion artifact, patient compliance, longer study time, and cost. Generally speaking, these factors limit the use of MRI in acute SAH. MRI can be used to obtain more information about the brain and to search for other causes of SAH. MRI and MRA are alternatives to evaluate patients with SAH and negative catheter angiography and in patients with a negative CT scan with equivocal lumbar puncture results.

MRA in SAH has evolved over the past decade but has not replaced catheter-based angiography as the initial test for aneurysm identification and localization. The practical limitations discussed earlier apply to MRA, as do other technological factors. Factors such as aneurysm size, acquisition sequences used, and the type of postprocessed images used for MRA interpretation can influence MRA results. The sensitivity of 3-dimensional time-of-flight MRA for cerebral aneurysms is between 55% and 93%.\textsuperscript{219–222} The variations seen in these studies are due largely to differences in aneurysm size. With aneurysms \( \geq 5 \) mm, the sensitivity is 85% to 100%, whereas the sensitivity of MRA for detecting aneurysms \(< 5 \) mm drops to 56%.\textsuperscript{219,221,223,224} MRA also has limitations in the characterization of the aneurysm neck and its relationship to the parent vessels. MRA does not require iodinated contrast and ionizing radiation. This may be helpful in the evaluation of patients during pregnancy. MRA may also be an acceptable modality for initial screening in patients without SAH, as described above.\textsuperscript{86,87}

CTA is a rapid, readily available, less invasive alternative to catheter angiography and has demonstrated sensitivities approaching equivalence to catheter angiography for larger aneurysms. The technique uses a rapid intravenous injection of iodinated contrast with image acquisition during the arterial phase in the area of interest. Images from a CTA should extend from just below the foramen magnum to above the circle of Willis and middle cerebral artery bifurcation. The success of CTA depends in part on imaging through the area of interest during maximal contrast dose. Post–image processing techniques can provide valuable 3-dimensional information for developing treatment strategies. Interpretation of CTA should not be based on reconstructed images alone. The source images should be the major basis of interpretation, and the 3-dimensional reconstructed images should be used to clarify specific questions.\textsuperscript{225} CTA has a reported sensitivity for aneurysms between 77% and 100% and a specificity between 79% and 100%,\textsuperscript{83,226–231} The sensitivity and specificity of CTA for aneurysm detection depend on aneurysm location and size, radiologist experience, image acquisition, and the presentation of the images. For aneurysms \( \geq 5 \) mm, CTA has a sensitivity between 95% and 100% compared with between 64% and 83% when aneurysms are \(< 5 \) mm.\textsuperscript{83,226,227–231} Vessel tortuosity decreases the specificity of CTA, leading to misinterpretation as an intracranial aneurysm. This occurs most frequently in the region of the middle cerebral artery bifurcation, anterior communicating artery, and the posterior inferior cerebellar arteries. Radiologist experience is an important factor in the practical accuracy of CTA in detecting cerebral aneurysms. The sensitivity and specificity for the detection of cerebral aneurysms are increased with more experienced observers.\textsuperscript{83,226} Among aneurysms detected on CTA and then undergoing surgery, 100% correlation was observed between CTA and catheter angiography.\textsuperscript{226,232} Velthuis and colleagues\textsuperscript{232} found that CTA is equal to catheter angiography in 80% to 83% of cases. In 74% of patients, catheter angiography performed after CTA did not reveal any additional information.\textsuperscript{226} From these data, many neurosurgeons operate on the basis of CTA alone in cases in which the risk of delaying surgery for a catheter study is not justified. A smaller number of neurosurgeons have used these data to justify routine surgery on CTA alone.\textsuperscript{233}

CTA can also be used to supplement information obtained by catheter angiography. CTA is better able to define aneurysmal wall calcification, intraluminal aneurysm thrombosis, orientation of aneurysm with respect to intraparenchymal
hemorrhage, and the relationship of the aneurysm with bony landmarks. CTA has been shown to be effective in determining the presence of severe vasospasm but is less accurate in detecting mild and moderate vasospasm. CTA has advantages related to rapid image acquisition and its widespread availability, which can make it suitable for critically ill patients. Disadvantages of CTA include the need for iodinated contrast dye administration, the possibility of bony artifact that interferes with image quality, and the inability to study small distal vessels. Artifact interference from metal limits the use of CTA in patients with previous aneurysm clips or coils. The use of CTA continues to evolve, and in the future, CTA will increasingly supplement or selectively replace conventional angiography in the management of acute SAH.

Selective catheter cerebral angiography is currently the standard for diagnosing cerebral aneurysms as the cause of SAH. Approximately 20% to 25% of cerebral angiograms performed for SAH will not indicate a source of bleeding. Repeat angiography after \( \approx 1 \) week will disclose a previously unrecognized aneurysm in an additional 1% to 2% of cases. Whether the additional small yield is worth the cost and morbidity of the second angiogram is a source of controversy.

**Manifestations and Diagnosis of SAH: Summary and Recommendations**

1. SAH is a medical emergency that is frequently misdiagnosed. A high level of suspicion for SAH should exist in patients with acute onset of severe headache (Class I, Level of Evidence B).
2. CT scanning for suspected SAH should be performed (Class I, Level of Evidence B), and lumbar puncture for analysis of CSF is strongly recommended when the CT scan is negative (Class I, Level of Evidence B).
3. Selective cerebral angiography should be performed in patients with SAH to document the presence and anatomic features of aneurysms (Class I, Level of Evidence B).
4. MRA and CTA may be considered when conventional angiography cannot be performed in a timely fashion (Class IIb, Level of Evidence B).

**Emergency Evaluation and Preoperative Care**

Limited consideration has been given to the care of SAH in the hyperacute setting. For at least two thirds of patients, the medical contact after acute SAH is made by emergency medical services. The rapid assessment and transport model widely adopted to optimize thrombolytic therapy in acute ischemic stroke needs to be broadened and reemphasized for hemorrhagic stroke. Although not all patients with SAH transported to the ED have focal neurological deficits, patients with \( \geq 1 \) signs and symptoms, including headache, abnormal level of consciousness, or vomiting, should be considered by emergency medical services personnel to have SAH. Emergency medical services personnel should receive continuing education regarding the importance of rapid neurological assessment when altered level of consciousness is encountered. A mechanism for rapid transport and advanced notification of the ED should be maintained. Unnecessary on-scene delays should be avoided.

The initial focus in the evaluation of SAH is to ensure and maintain an adequate airway, breathing, and circulation. Although the majority of SAH patients will not present with airway compromise, the potential for neurological deterioration is significant, and airway surveillance is paramount. If endotracheal intubation is necessary because of a change in the level of consciousness, an inability to protect the airway, or a respiratory compromise, it should be performed in accordance with established protocols. Rapid sequence intubation protocols are recommended. Specific attention should be given to preoxygenation, pharmacological blunting of reflex dysrhythmia, and avoidance of unnecessary fluctuations in blood pressure. Endotracheal intubation should be followed by placement of a nasogastric or orogastric tube to reduce the chance of aspiration. Appropriate levels of oxygenation without hyperventilation should be maintained and periodically assessed with oximetry and arterial blood gas analysis. A complete medical history should be obtained and a physical examination performed. Special attention should be given to risk factors for SAH, and toxicology screens should be obtained in younger patients or in those with a history of substance abuse. Factors known to influence prognosis such as age, preexisting hypertension, time of admission after SAH, and blood pressure at admission should be recorded.

Numerous systems for grading the clinical condition of patients after SAH have been reported. These include the Hunt and Hess Scale, Fisher Scale, Glasgow Coma Scale, and World Federation of Neurological Surgeons Scale. Substantial deficits remain in the literature regarding the grading of patients with SAH. Most grading scales were derived retrospectively, and the intraobserver and interobserver variabilities have seldom been assessed. Although choosing a neurological assessment scale for SAH is controversial, it has been recommended that emergency care providers evaluate SAH patients with one of these accepted scales and record it in the ED. If definitive expertise is not directly available to manage an SAH patient at the hospital providing initial care, expedient transfer to an appropriate referral center should be considered.

**Emergency Evaluation and Preoperative Care: Summary and Recommendations**

1. The degree of neurological impairment using an accepted SAH grading system can be useful for prognosis and triage (Class IIa, Level of Evidence B).
2. A standardized ED management protocol for the evaluation of patients with headaches and other symptoms of potential SAH currently does not exist and should probably be developed (Class IIa, Level of Evidence C).

**Medical Measures to Prevent Rebleeding After SAH**

Bedrest is a prescribed element in the treatment protocol of SAH aimed at reducing rebleeding. Despite continued inclusion in current treatment protocols, by itself it does not abate the risk of rebleeding. It may be included as a component...
of a broader treatment strategy, along with more definitive measures.138,144,240–244

To date, no well-controlled studies exist that answer whether blood pressure control in acute SAH influences rebleeding. A retrospective review of the influence of rebleeding showed that it occurred less frequently in patients treated with antihypertensive medication, yet blood pressures were still higher in the treated group.143 Alternately, rebleeding may be related to variations or changes in blood pressure rather than to absolute blood pressure245; 1 report found an increase in blood pressure before rebleeding.141 In a retrospective review of 179 patients admitted within 24 hours of SAH, 17% experienced rehemorrhage that was associated with a systolic blood pressure >150 mm Hg.246 Interpretation of this finding is confounded, however, by the observation that blood pressure was higher closer to the time of initial SAH, as was the incidence of rebleeding. Another study found a rehemorrhage rate of 13.6% in the ambulance or referring hospital with a peak incidence within 2 hours of the initial bleed. Rebleeding was more common in those with a systolic blood pressure >160 mm Hg.141 Another large retrospective study reported a rebleeding rate of 6.9% after admission but no relationship to blood pressure.247 Interpretation of these studies is limited by variable times of observation and variable use of antihypertensives,248 although all attempted to repair the aneurysm within 24 hours of admission. When blood pressure is elevated, short-acting continuous-infusion intravenous agents with a reliable dose-response relationship and favorable safety profile are desirable. To reduce blood pressure, nicardipine, labetalol, and esmolol appear to meet these criteria best. It is reasonable to avoid sodium nitroprusside in many neurological emergencies because of its tendency to raise intracranial pressure and cause toxicity with prolonged infusion.

The role of antifibrinolytic therapy in the prevention of rebleeding has been investigated since 1967. Among 30 publications, only half were randomized studies with concurrent controls; 11 studies used acceptable randomization. Adams et al242 reviewed the antifibrinolytic experience from 3 studies (2 randomized studies and 1 prospective phase IV study), which consistently showed a significant reduction in rebleeding among treated patients compared with nonantifibrinolytic control subjects. However, nearly one third of treated patients in these trials were worse at 14 days compared with at the time of admission. A multicenter, randomized, double-blind, placebo-controlled study using tranexamic acid showed that rebleeding was reduced by >60% in the treatment group, but an increased rate of cerebral infarction in these patients offset any improvement in overall outcome.144 Similar findings were reported by Kassell et al240 in a nonrandomized, controlled study; a 40% reduction in rebleeding in patients receiving antifibrinolytic therapy was offset by a 43% increase in focal ischemic deficits. In a double-blind, placebo-controlled trial of tranexamic acid,249 there was no difference in rebleeding between groups, and an increase in cerebral ischemia was seen for treated patients, although the sample size was not sufficient to demonstrate significance. Retrospective studies250,251 have shown similar results regardless of the duration of antifibrinolytic therapy with either epsilon aminocaproic acid (36 g/d) or tranexamic acid (6 to 12 g/d).

Increased use of early aneurysm treatment combined with prophylactic treatment of cerebral vasospasm may reduce the ischemic complications of antifibrinolytic agents while maintaining the benefit of reduced preoperative bleeding rates. In a prospective, randomized trial of the antifibrinolytic drug tranexamic acid, early rebleeding rates and adverse outcomes were reduced when the drug was administered immediately after the diagnosis of SAH.140

Medical Measures to Prevent Rebleeding After SAH: Summary and Recommendations

1. Blood pressure should be monitored and controlled to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure (Class I, Level of Evidence B).
2. Bedrest alone is not enough to prevent rebleeding after SAH. It may be considered a component of a broader treatment strategy, along with more definitive measures (Class IIb, Level of Evidence B).
3. Although older studies demonstrated an overall negative effect of antifibrinolytics, recent evidence suggests that early treatment with a short course of antifibrinolytic agents combined with a program of early aneurysm treatment followed by discontinuation of the antifibrinolytic and prophylaxis against hypovolemia and vasospasm may be reasonable (Class IIb, Level of Evidence B), but further research is needed. Furthermore, antifibrinolytic therapy to prevent rebleeding may be considered in certain clinical situations, eg, in patients with a low risk of vasospasm and/or a beneficial effect of delaying surgery (Class IIb, Level of Evidence B).

Surgical and Endovascular Methods for Treatment of Ruptured Cerebral Aneurysms

In 1991, Guglielmi et al252 described the technique of occluding aneurysms from an endovascular approach with electrolytically detachable platinum coils (Guglielmi detachable coils). Guglielmi detachable coils are introduced directly into the aneurysm through a microcatheter and detached from a stainless steel microguidewire by an electric current. The aneurysm is packed with several coils. The coils induce thrombosis, thereby excluding the aneurysm from the circulation. As clinical experience with the technique has increased and technological advances in coil design and adjunctive methods have improved, endovascular treatment has been used with increasing frequency. Improved outcomes have been linked to hospitals that provide endovascular services.102,117,118,253 However, even in centers where endovascular services are available, their use varies greatly; some centers perform surgical clipping only when coiling cannot be performed, and others perform endovascular therapy in only 1% of treated patients or when certain angiographic criteria are met.118,254,255

The procedural risk of endovascular coil embolization was previously reviewed in a meta-analysis of case series published from January 1990 through March 1997 including a total of 1256 patients.256 In that article, aneurysmal perforation was observed in 2.4% and ischemic complications in
8.5%; these procedural complications were permanent in 3.7%. Outcome after SAH is related primarily to severity of the initial bleed, confounding the interpretation of the impact of procedural risk on final clinical outcome. The effect of procedural complications of both endovascular and open surgical methods on clinical outcome is delineated more clearly in studies of treatment of unruptured aneurysms. In the recently published International Study of Unruptured Intracranial Aneurysms, procedural (30-day) mortality for coiling was 2.0% and disability was 7.4%. In the recently published ISAT, procedural complications were not reported, but 2-month combined endovascular mortality and disability was 25.4%. Of course, this number combines the morbidity and mortality of the hemorrhage and its treatment.

Procedural efficacy for treatment of an intracranial aneurysm is determined by 2 factors: the rebleeding rate and the angiographic recurrence rate of the treated aneurysm. Several case studies have documented the rates of SAH after coil embolization of ruptured aneurysms. Seven case series included ruptured aneurysms in all locations that provided adequate information to estimate annual rerupture rates. If these case series are combined, a late rerupture rate of 0.9% per year can be estimated after coil embolization of ruptured aneurysms in various locations. A recent study of 431 patients undergoing coiling of a ruptured aneurysm found an early rebleeding rate of 1.4% with 100% mortality. The same study reported rebleeds in 2 patient-years of follow-up, corresponding to a rate of 1.3% rerupture of an incompletely occluded aneurysm during 74.8 months after treatment and that overall rebleeding was still somewhat more common than with surgical repair.

Four additional studies have provided detailed information on hemorrhage after coil embolization of ruptured aneurysms arising from the posterior circulation. In a study of 34 ruptured distal basilar artery aneurysms, there was a single rerupture of an incompletely occluded aneurysm during 74.8 patient-years of follow-up, corresponding to a rate of 1.3% per year. Another study of 61 patients followed up for 1.1 years after treatment found an annual rerupture rate of 2.9%. A study that included 104 patients with ruptured posterior circulation aneurysms documented an annual rate of 0.9%. A small study in 23 patients documented no reruptures during ≥24 patient-years of follow-up. When these studies are combined, a 1.4% annual rerupture rate is estimated for aneurysms arising from the posterior circulation that have been treated with endovascular coiling.

Some series that have reported SAHs during long-term follow-up after coil embolization either have not provided length of follow-up or have not distinguished between ruptured and unruptured aneurysms at the time of initial treatment. Calculation of rerupture rates from this collection of studies is not possible. Accumulating evidence indicates that several factors contribute to aneurysm recurrence and hemorrhage after endovascular treatment. The most important of these are aneurysm size and shape and history of SAH from the treated aneurysm. In a cohort study of previously ruptured aneurysms >2 cm in diameter, 1 rerupture occurred in 36 patient-years of follow-up, corresponding to an annual rupture rate of 2.7%. In another report, an overall annual hemorrhage rate of 1.8% was reported after coil embolization in a consecutive series of ruptured and unruptured aneurysms. Aneurysm size was an important predictor of hemorrhage risk, with 33% of giant aneurysms, 4% of large aneurysms, and no small aneurysms presenting with new hemorrhage during an average of 3.5 years of follow-up. A similar series found an overall annual hemorrhage rate of 1.4% over 141 patient-years, with degree of occlusion an important predictor.

Case reports and series have demonstrated that even when aneurysms appear to be completely occluded after surgery or endovascular treatment, recurrence and rupture may occur later. However, the majority of hemorrhages after treatment reported in patients with postprocedural angiography have occurred in incompletely occluded aneurysms. Aneurysm growth appears to be more frequent when complete occlusion is not achieved, with an incidence of 49% in 1 series of 178 incompletely occluded aneurysms treated by endovascular techniques. In a significant proportion of intracranial aneurysms, complete occlusion is not possible on the first endovascular treatment. In a meta-analysis, only 54% of aneurysms were completely occluded, and 88% of aneurysms were >90% occluded after coil embolization.

In the largest published series from North America, followed up 818 patients with 916 coiled aneurysms over 11 years and found that only 55% of aneurysms could be completely occluded. They analyzed the factors leading to incomplete initial occlusion and later recurrence and determined that aneurysm size and shape were the critical variables. Excluding patients from their first 5 years, in which there may have been a learning curve related to initial experience, permitted analysis of their most recent 665 aneurysms in 558 patients over 6 years. In small aneurysms (4- to 10-mm diameter) with small necks (≤4 mm), incomplete coiling occurred in 25.5%, with recurrence in 11.1% of completely coiled aneurysms and 21% of incompletely coiled aneurysms. In small aneurysms with wide necks (>4-mm diameter), incomplete coiling occurred in 59%, with recurrence in 7.5% of completely coiled aneurysms and 29.4% of incompletely coiled aneurysms. In large aneurysms (11- to 25-mm diameter), incomplete coiling occurred in 56%, with recurrence in 30% of completely coiled aneurysms and 44% of incompletely coiled aneurysms. With giant aneurysms (>25 mm in diameter), incomplete occlusion occurred in 63%, with recurrence in 42% of completely coiled aneurysms and 60% of incompletely coiled aneurysms.

The high initial incomplete obliteration and late recurrence rates in aneurysms treated with endovascular techniques, even in the most experienced centers, work to offset the lower procedural complication rate demonstrated in recent studies (see below). However, clinical morbidity and management
outcome may not be fully reflected in discussions limited to procedural outcomes. For example, most patients with incomplete aneurysm obliteration do not rebleed. Therefore, demonstration of efficacy requires long-term follow-up of both clinical and angiographic outcomes. A recent report suggests that gadolinium-enhanced MRA can serve as an alternative to catheter angiography as a means of follow-up. Angiographic follow-up may reveal aneurysm recurrence and provide an opportunity to further treat the aneurysm before it becomes symptomatic. The risks, costs, and inconvenience of serial follow-up angiography and treatment should be considered in evaluations of the efficacy of endovascular methods. Although the degree of aneurysmal obliteration does not appear to be a complete surrogate for hemorrhage risk after treatment, it is an important goal of treatment by both endovascular coil embolization and surgical clip ligation.

Because of their morphology, middle cerebral artery aneurysms can be difficult to treat by coil embolization, and surgical results for these aneurysms are often reported as more favorable than for other lesions. However, aneurysms in the posterior cerebral circulation are frequently more difficult to treat with surgery, and comparative observational studies have found better outcomes after coil embolization in these locations. Aneurysms in the cavernous segment and the internal carotid artery are also difficult to treat with surgery but may be treated relatively easily with coil embolization, and both treatments can lead to a reduction in compressive symptoms.

Aneurysm size has been associated with an increased risk of complications and an increased likelihood of incomplete occlusion. In the Raaymakers et al meta-analysis, the risk of disability and mortality for giant aneurysms (>25 mm) was demonstrated with endovascular techniques as well. As described above, complete aneurysm occlusion is far less likely in larger aneurysms with wide necks, and additional embolizations are often required during follow-up. Very small aneurysms such as those with a diameter <2 or 3 mm can also be technically difficult to treat by coil embolization, and intraoperative rupture may be more frequent; however, comparative studies have not evaluated the impact of size on outcome.

In several studies, aneurysm neck size has been an independent predictor of complete occlusion and recurrence by coil embolization, particularly when considered relative to the size of the aneurysm. Neck diameters of <5 mm and a ratio of neck diameter to the largest aneurysm dimension of <0.5 have been associated with better outcomes in terms of rates of complications and likelihood of complete occlusion by coil embolization.

Comorbid medical conditions and complications from an initial SAH may also influence the selection of surgery or endovascular therapy. Combined strategies involving acute aneurysm coiling and surgical decompression of brain swelling or hemorrhage can also be used successfully.

Advances in technology are likely to alter the proportion of aneurysms that are treatable by endovascular techniques. Introduction of coils with complex shapes and 3-dimensional structures, ultrastiff coils, liquid polymer techniques, bioactive or coated coils, the development of techniques using balloons, and intravascular stents to support coil occlusion are examples of improvements that have broadened the indications for coil embolization. New adjuvant techniques may also carry greater procedural risks that will influence outcome.

The skills of the treating practitioner and institution are important contributors to outcome, as discussed previously. Endovascular coil embolization improves with experience of the practitioner, with major reductions in procedural complication rates after the first 5 procedures, at least in the setting of a high-volume academic training program. The selection of appropriate candidates for endovascular coil embolization is a complex process that involves integration of information about the patient’s medical condition, the characteristics of the aneurysm, evolving techniques and equipment, and the skills and experience of the available practitioners.

Aneurysm recurrence is not uncommon after endovascular coiling and may occur even in aneurysms that appear completely occluded after initial treatment. Additional embolization is often possible and may be required to prevent growth and potential SAH. Follow-up imaging provides an opportunity to identify incompletely treated aneurysms before SAH or other symptoms occur and should be considered in patients with incompletely coiled aneurysms. A variable number of aneurysms will require additional treatment after coil embolization. When complete treatment is not possible with coil embolization, open surgery may be indicated.

Few data are available to define the appropriate timing of follow-up imaging. After apparently complete occlusion, many practitioners prescribe a follow-up angiogram in 6 months, with additional follow-up imaging based on the aneurysm appearance. In a recent study of 501 aneurysms in 466 patients followed up for >1 year, recurrence was found in 33.6% of patients and appeared at a mean time interval of 12.3 months after endovascular treatment. Approximately 50% of the recurrences would have been missed by a program of angiographic follow-up at 6 months after treatment, so long-term angiographic monitoring of aneurysms treated by endovascular methods was considered mandatory. When aneurysm occlusion is incomplete, follow-up imaging is often obtained more frequently.

Catheter angiography has been the preferred imaging modality for follow-up after coil embolization. Given the small risk of permanent complications with catheter angiography (recently estimated at <0.1% in this setting) and its cost, a noninvasive screening test to identify patients with recanalization after coil embolization is highly desirable but is complicated by the characteristics of the platinum coils. Although MRA can identify residual aneurysm neck,
platinum coils are associated with artifacts that may preclude reliable imaging of the treated aneurysms with MRA and CTA; recent advances in gadolinium-enhanced MRA could very well validate noninvasive MRA as a method of choice in the follow-up of coil-embolized aneurysms. Plain skull radiographs may identify patients with aneurysm recanalization. In a study of 60 patients, evidence of coil compaction correlated well with MRA and catheter angiography.

The Cooperative Study evaluated 979 patients who underwent intracranial surgery only. Nine of 453 patients (2%) rebled after surgery; nearly half (n = 4) of these hemorrhages occurred in patients with multiple aneurysms. In the Randomized Treatment Study, surgery (either clipping or wrapping of the aneurysm) performed within the first 3 months after SAH significantly lowered rebleeding during this interval compared with bedrest, hypotension, or carotid ligation. Long-term rebleeding was significantly reduced by either intracranial surgery or completed carotid ligation. In a large retrospective series reported by Sundt et al, who calculated a risk reduction of 19% in patients undergoing surgery versus conservative management. In this study, age >65 years was a significant predictor of surgical complications. Feuerberg et al retrospectively examined 715 patients operated on between 1970 and 1980. Twenty-seven patients (3.8%) showed incomplete obliteration on follow-up angiography; only 1 patient rebled during 266 person-years of follow-up. However, in another case series reported by Lin et al, 19 patients with incompletely clipped aneurysms were readmitted for regrowth of the aneurysm; 17 had a recurrent hemorrhage.

In a recent study of 102 patients with 160 surgically treated aneurysms followed up for a mean of 4.4 years, David et al found that the rate of complete obliteration on postoperative angiography was 91.8%. For completely clipped aneurysms, the rate of aneurysm recurrence was 0.5%, with no recurrent hemorrhages. For incompletely clipped aneurysms with a typical “dog-ear” residual, the annual hemorrhage rate was 1.9%. This rate is similar to the overall hemorrhage rate after endovascular coiling reported above. For incompletely clipped aneurysms with a broad residual neck, there was a 19% annual recurrence rate and a 3.8% recurrent hemorrhage rate. For all incompletely clipped aneurysms, the annual recurrence rate was 2.9%, and the recurrent hemorrhage rate was 1.5%. For all clipped aneurysms regardless of the presence of residual aneurysm filling, the annual risk of recurrent hemorrhage was 0.26%. In ISAT, posttreatment SAH occurred at an annualized rate of 0.9% with surgical clipping compared with 2.9% with endovascular treatment. Currently available evidence indicates that the rate of incomplete obliteration and recurrence is significantly lower with surgical clipping than with endovascular treatment.

Anecdotal clinical series have reported a reduction in rebleeding after external wrapping or coating of intracranial aneurysms. In a recent long-term follow-up study, the rebleeding rate was 11.7% (upper confidence limit, 19.8%) at 6 months and 17.8% (upper confidence limit, 28.9%) at 6 months to 10 years. On the basis of the sample size, this rate was not significantly different from the rate of rebleeding for conservatively treated aneurysms. Another small series with a mean follow-up of 11.2 years demonstrated an overall risk of rebleeding of 33%. The available data suggest that wrapping or coating of intracranial aneurysms does not prevent rebleeding and that studies are of insufficient size to conclude a consistently lower rate of rebleeding than that for conservative management.

Increased time to treatment is associated with increased rates of preoperative rebleeding in retrospective and prospective studies and recently has been associated with higher rates of poor outcome. The International Cooperative Study on the Timing of Aneurysm Surgery analyzed management in 3521 patients, 83% of whom underwent surgical repair of the ruptured aneurysm. Timing of surgery after SAH was significantly related to the likelihood of preoperative rebleeding (0 to 3 days, 5.7%; 4 to 6 days, 9.4%; 7 to 10 days, 12.7%; 11 to 14 days, 13.9%; and 15 to 32 days, 21.5%). Postoperative rebleeding did not differ among time intervals (1.6% overall). Nevertheless, there was no significant difference in overall outcome in this study related to timing of surgery. In the randomized trial of nimodipine conducted by Ohman and Heiskanen, patients who underwent early surgery had a significantly lower preoperative rebleed rate than those who underwent later surgery (3% versus 11%). In recent years, there has been a trend toward early surgery for ruptured aneurysms, especially in good- and moderate-grade patients. In addition, early surgery facilitates the aggressive therapy of vasospasm (see below). Endovascular treatments can theoretically be performed at the time of the initial diagnostic angiogram, thereby saving additional time without increasing risk. There is evidence that time from SAH to treatment is shorter in patients undergoing endovascular coiling. For example, in ISAT, the mean time to treatment was 1.1 days for endovascular coiling versus 1.8 days for surgery; in that study, there were fewer preoperative rebleeds in the endovascular group. This difference in the time to repair for open versus endovascular surgery may explain in part the lower pretreatment rebleed rate of coiling compared with clipping (2.5% versus 5.5%; P < 0.05).

Ideally, decisions about whether to clip or coil an aneurysm are made jointly by an experienced cerebrovascular surgeon and an endovascular specialist during the initial diagnostic angiogram. When appropriate, endovascular treatment should be performed at the time of the diagnostic angiogram, thereby potentially reducing the time to treatment and the risk of rebleeding by many hours. Aneurysms can be treated by occluding the parent artery, the artery from which it arises; however, occlusion of intracranial arteries may lead to ischemia, particularly in the
face of recent SAH. Ischemic consequences of parent artery occlusion can be predicted by temporarily inflating a balloon to occlude the vessel and evaluating the effects on brain function and hemodynamics. However, ischemic sequelae may still occur in those who tolerated test occlusion even if an extracranial-intracranial arterial bypass is performed. Parent arteries can be occluded with surgical clips or endovascular techniques and can be performed as an extension of a test occlusion. This involves the use of systemic heparinization during the procedure, which can be problematic in the face of recent SAH. This approach has been used most commonly for aneurysms that cannot be treated by direct surgical clipping or coil embolization when the risk of not treating is very high.

Before 1970, carotid ligation was commonly used to treat recently ruptured intracranial aneurysms. A large retrospective study by Nishioka, however, demonstrated a high number of intervention failures and a rebleed rate of 7.8% for patients who received carotid ligation. In the Cooperative Aneurysm Randomized Treatment Study, carotid ligation did not lead to a significant improvement in mortality or rebleeding in the acute period (1 month after SAH) compared with regulated bedrest in the intent-to-treat analysis; however, only 67% of patients randomly selected to receive carotid ligation actually received it. In the treatment-accomplished subgroup, a significantly lower rate of mortality and rebleeding was evident as early as 1 month after carotid ligation, and no rebleeds occurred in the group that received carotid ligation during follow-up in patients surviving 6 months. Long-term follow-up demonstrated a benefit for carotid ligation in reducing rebleeding at 3 years and mortality at 5 years. A recent review by Taylor et al of pooled long-term follow-up results from several uncontrolled series concluded that the risk of rebleeding was lower than expected after carotid ligation for untreated ruptured aneurysms. In summary, compared with conservative therapy, carotid ligation may produce a decrease in rebleeding; however, the rate of treatment failures (ie, rebleeding plus complications of therapy) likely exceeds that of direct surgical treatment of the aneurysm.

The major determinant of outcome after surgical or endovascular treatment of a ruptured aneurysm is the preoperative neurological status of the patient, which is determined by the severity of the initial hemorrhage. It may be possible to estimate the clinical consequences of complications attributable to an operation from data regarding surgery for unruptured aneurysms. In this group of patients, in-hospital mortality rates vary from 1.8% to 3.0% in large multicenter studies, including 0.2% to 1.8% in the International Study of Unruptured Intracranial Aneurysms (ISUA II), 2.6% in the meta-analysis by Raaymakers and colleagues of studies published between 1966 and 1996, 2.5% in the analysis of discharge data from 2200 New York State patients, and 3.0% in a study of California discharge data. Adverse outcomes in survivors were 8.9% in ISUA II, 10.9% in the Raaymakers et al study, 21.3% in the study of New York State discharges, and 22.4% in the study of California discharges.

The only large, prospective, randomized trial to date comparing surgery and endovascular techniques is ISAT, which selected 2143 of 9559 SAH patients for randomization into endovascular or surgical aneurysm treatment on the basis of a preoperative estimation that the ruptured aneurysm could be treated successfully by either modality. Evaluation at 1 year demonstrated no significant difference in mortality rates (8.1% versus 10.1%, endovascular versus surgical). Greater disability rates in surgical versus endovascular patients (21.6% versus 15.6%) meant that combined morbidity and mortality was significantly greater in surgically treated patients than in those treated with endovascular techniques (30.9% versus 23.5%; absolute risk reduction, 7.4%; P=0.0001). These results suggest that for the types of patients selected for randomization in ISAT and for surgeons and interventional neuroradiologists with similar outcomes, endovascular coiling is associated with better outcomes at 1 year than surgical clipping. Unfortunately, there are few, if any, data on what constituted a randomizable aneurysm other than it being in the anterior circulation in a young, awake patient. The authors of ISAT indicate that longer-term follow-up is vital to answer the question of durability of benefit. During the relatively short follow-up period in ISAT, the rebleeding rate was 2.9% for coiling versus 0.9% for surgery; 139 coiled patients required additional treatment compared with 31 patients treated by clipping. This occurred despite a bias for coiling in that none of the clipped aneurysms underwent intraoperative angiography, which is an increasingly common practice in specialized cerebrovascular centers in the United States, and many did not even undergo postoperative angiography.

The preceding analysis and the recommendations that follow pertain to patients with ruptured aneurysms. There have been no randomized comparisons of coiling and clipping for unruptured aneurysms, and it important to recognize that the recommendations of this writing group should not be extended to patients with these lesions.

**Surgical/Endovascular Treatment of Ruptured Aneurysms: Summary and Recommendations**

1. Surgical clipping or endovascular coiling should be performed to reduce the rate of rebleeding after aneurysmal SAH (Class I, Level of Evidence B).
2. Wrapped or coated aneurysms and incompletely clipped or coiled aneurysms have an increased risk of rehemorrhage compared with those that are completely occluded and therefore require long-term follow-up angiography. Complete obliteration of the aneurysm is recommended whenever possible (Class I, Level of Evidence B).
3. For patients with ruptured aneurysms judged by an experienced team of cerebrovascular surgeons and endovascular practitioners to be technically amenable to both endovascular coiling and neurosurgical clipping, endovascular coiling can be beneficial (Class I, Level of Evidence B). Nevertheless, it is reasonable to consider individual characteristics of the patient and the aneurysm in deciding the best means of repair, and management of patients in centers offering both techniques is probably indicated (Class IIa, Level of Evidence B).
4. Although previous studies showed that overall outcome was not different for early versus delayed surgery after SAH, early treatment reduces the risk of rebleeding after SAH, and newer methods may increase the effectiveness of early aneurysm treatment. Early aneurysm treatment is reasonable and is probably indicated in the majority of cases (**Class IIa, Level of Evidence B**).

**Hospital Characteristics and Systems of Care**

Studies of outcome after SAH\(^\text{102,117,118,253}\) have demonstrated a relationship between outcome and the volume of patients managed by an individual hospital. In a study of 16,399 patients admitted to 1,546 US hospitals, Cross et al\(^\text{102}\) found that 82% of hospitals admitted <19 SAH patients annually and 64% admitted <10 such patients; the 30-day mortality rate was significantly greater in hospitals admitting <10 SAH patients than for those admitting >35 SAH patients (39% versus 27%; odds ratio, 1.4). Two factors associated with better outcomes in the high-volume hospitals were greater use of endovascular services and a higher percentage of patients transferred from other hospitals. Only 34% of all patients admitted with SAH were treated with surgical or endovascular techniques for an aneurysm in this study.

In a study of 9,534 SAH cases treated at 70 centers in the University of California Health Systems from 1994 through 1997, Johnston\(^\text{117}\) found that although high-volume hospitals had lower mortality rates, this was perhaps influenced by the increased use of endovascular services and the higher rates of transfer from other institutions at the high-volume hospitals. Institutions that used coil embolization more frequently had lower in-hospital mortality rates, with a 9% reduction in risk for every 10% of cases treated with endovascular techniques. In addition, there was a 16% reduction in risk of in-hospital death at institutions that used angioplasty for vasospasm. Whether improved outcomes were due to endovascular therapy or to other aspects of multidisciplinary care at high-volume hospitals could not be answered by that analysis. In a study of 12,804 patients admitted for SAH to 390 California hospitals, Bardach et al\(^\text{253}\) found that the mortality rate in the lowest-volume hospitals was greater than that in the highest-volume hospitals (49% versus 32%; \(P<0.001\)). They also found greater use of endovascular services at the high-volume hospitals, but this factor did not independently predict good outcomes. The proportion of all SAH patients who underwent treatment of an aneurysm was only 29%.\(^\text{253}\)

In an analysis of 13,399 SAH cases admitted to 257 hospitals in the state of New York from 1995 through 2000, Berman et al\(^\text{118}\) limited their analysis to the 5,963 patients who underwent treatment of an intracranial aneurysm (2,200 unruptured, 3,763 ruptured) by surgery or endovascular techniques. The overall in-hospital death rate was 14% for ruptured aneurysms. Hospitals performing >35 annual aneurysm procedures had lower death rates than low-volume hospitals, but the effect was modest for ruptured aneurysms (odds ratio, 0.94; \(P=0.03\)) compared with unruptured aneurysms (odds ratio, 0.89; \(P<0.0001\)). Greater use of endovascular services had no impact on patients with ruptured aneurysms but was beneficial in unruptured aneurysms.

Taken together, these analyses indicate that treatment volume is an important determinant of outcome for intracranial aneurysms. This effect may be more important for patients with unruptured aneurysms than for those with ruptured aneurysms. Despite the fact that patients treated at institutions that provide endovascular treatment of post-SAH vasospasm have a 16% greater chance of good outcome, the fact that overall ruptured aneurysm volume is not as great a predictor may reflect the overwhelming importance of bleed severity on overall outcome.\(^\text{8,112}\) Procedural volume may seem more important for surgical clipping than for endovascular therapy for a variety of reasons, but perhaps the most important reason for this apparent discrepancy revolves around the fact that published results of endovascular treatment come primarily from high-volume centers, whereas results of surgical clipping come from both high- and low-volume centers.\(^\text{118}\)

Although the results described above might support a policy that promotes regionalization of care for SAH patients, it is uncertain whether the benefits of receiving care at a high-volume center would outweigh the costs and risks of transfer.\(^\text{102}\) Bardach et al\(^\text{253}\) performed a cost-utility analysis, estimating that transferring an SAH patient from a low- to a high-volume hospital would result in a gain of 1.60 quality-adjusted life-years at a cost of $10,548 per quality-adjusted life-year. However, interhospital transfers may have a negative impact on outcomes in other neurological conditions,\(^\text{349}\) and patients with SAH may be particularly susceptible to complications associated with transfer because of the time dependence of outcome related to early rebleeding and the sensitivity of unsecured aneurysms to fluctuations in blood pressure. In addition, some SAH patients with acute hydrocephalus may benefit from early placement of a ventricular drain at the initial hospital.\(^\text{116}\) Low-volume centers have been found to treat SAH with acceptable outcomes.\(^\text{350}\) High-volume centers may already be taxed in terms of the severity of illness of their patients and the availability of resources and staff.\(^\text{351}\) Nevertheless, further studies should be performed that would include a more detailed prospective cohort analysis delineating the differences in outcomes between low- and high-volume hospitals and the risks associated with transfer.\(^\text{348}\) One important issue relevant to the morbidity associated with transfer is aneurysm rebleeding. To address this, Hillman and colleagues\(^\text{140}\) examined the ability of tranexamic acid, a short-acting antifibrinolytic agent, to reduce the incidence of early rebleeding during transfer. They randomized 505 patients and showed a reduction in early rebleeding from 10.8% to 2.4%, along with an 80% reduction in mortality. Furthermore, favorable Glasgow Outcome Scale score increased from 70.15% on average to 74.8%. If these data can be verified, use of these strategies may save more lives than curing vasospasm.

As described in the preceding paragraphs, accumulating evidence suggests that endovascular treatments are associated with lower complication rates and higher recurrence rates than surgical clipping. In addition, there is a 16% reduction in risk of in-hospital death at institutions that use angioplasty for vasospasm.\(^\text{117}\) Therefore, choosing the optimum aneurysm...
treatment for each patient requires the availability of experienced cerebrovascular and endovascular surgeons.

Hospital Characteristics and Systems of Care: Summary and Recommendations

1. Early referral to high-volume centers that have both experienced cerebrovascular surgeons and endovascular specialists is reasonable (Class IIa, Level of Evidence B).

Anesthetic Management During Surgical and Endovascular Treatments

The many goals of intraoperative anesthetic management during aneurysm treatment are beyond the scope of this review. They include the use of hemodynamic management (blood pressure control) to limit the risk of intra procedural aneurysm rupture, as well as several different strategies to protect the brain against ischemic injury. Induced hypotension has been used to prevent intraoperative aneurysm rupture. Although the efficacy of this technique has not been studied systematically, there is evidence that it may adversely affect CBF during surgery and even outcome. CBF was decreased during induced hypotension in patients with impaired autoregulation.352 In an earlier retrospective study (n=112), increased risk of early and delayed neurological deficits was associated with a systolic arterial blood pressure <60 mm Hg with longer periods of hypotension.353 Existing data suggest that there could be potential harm from induced hypotension without any evidence regarding benefit. Numerous pharmacological agents and strategies have been used to promote cerebral protection during intracranial cerebrovascular procedures,354–359 although none has been clearly shown to improve outcome.357,360

Temporary vascular occlusion is frequently used during aneurysm surgery to prevent intraoperative rupture of large or difficult-to-approach aneurysms. In a retrospective review of 185 operations with uniform anesthetic management, outcome did not differ with or without vascular occlusion.361 Induced hypertension is used to improve CBF in settings such as vasospasm and carotid endarterectomy but has not been well studied during vessel occlusion in aneurysm surgery. In selected patients with giant aneurysms, particularly of the basilar artery, deep hypothermia with circulatory arrest under cardiopulmonary extracorporeal circulation has been shown to be an acceptable technique at selected centers with significant experience.362,363

Systemic hypothermia has been used in several clinical settings to protect the brain against ischemic injuries and was recently studied in a multicenter, randomized controlled trial of intraoperative cooling during open craniotomy for ruptured cerebral aneurysms. This study failed to demonstrate in patients with good Hunt-Hess grade any statistically significant influence of hypothermia on the duration of stay in the intensive care unit, total length of hospitalization, rates of death at follow-up, destination at discharge, or neurological outcome. Nevertheless, despite an increased incidence of bacteremia in the hypothermia group, hypothermia appeared to be safe for the most part, and issues surrounding the power of the study to detect less dramatic benefits of hypothermia remain unresolved.364

Anesthetic Management: Summary and Recommendations

1. Minimizing the degree and duration of intraoperative hypotension during aneurysm surgery is probably indicated (Class IIa, Level of Evidence B).
2. There are insufficient data on pharmacological strategies and induced hypertension during temporary vessel occlusion to make specific recommendations, but there are instances when their use may be considered reasonable (Class IIb, Level of Evidence C).
3. Induced hypothermia during aneurysm surgery may be a reasonable option in some cases but is not routinely recommended (Class III, Level of Evidence B).

Management of Cerebral Vasospasm After SAH

Cerebral vasospasm is the delayed narrowing of large-capacitance arteries at the base of the brain after SAH, which is often associated with radiographic or CBF evidence of diminished perfusion in the distal territory of the affected artery. After aneurysmal SAH, angiographic vasospasm is seen in 30% to 70% of patients, with a typical onset 3 to 5 days after the hemorrhage, maximal narrowing at 5 to 14 days, and a gradual resolution over 2 to 4 weeks.365,366 In about one half of cases, vasospasm is manifested by the occurrence of a delayed neurological ischemic deficit, which with equal likelihood may resolve or progress to cerebral infarction.3,192,363 In contemporary series, 15% to 20% of such patients suffer stroke or die of vasospasm despite maximal therapy.367,368 Looked at another way, vasospasm appears to account for nearly 50% of the deaths in patients surviving to treatment after SAH, with rebleeding and complications of aneurysm repair being responsible for the vast majority of the balance.341

Often, the development of a new focal deficit, unexplained by hydrocephalus or rebleeding, is the first objective sign of symptomatic vasospasm. In addition, unexplained increases in mean arterial pressure may occur as cerebral arterial autoregulation attempts to improve cerebral circulation to prevent ischemia. Increasingly, investigators have recognized that “symptomatic” vasospasm leading to delayed cerebral infarction can occur without obvious symptoms in comatose patients.369 As a result, the index of suspicion needs to be higher in poor-grade patients even with subtle changes in neurological examination.

Monitoring for vasospasm with transcranial Doppler (TCD) technology, in addition to clinical observation in the intensive care unit, has been controversial. The literature is inconclusive regarding its sensitivity and specificity. TCD monitoring is an examination that is operator dependent and requires the establishment of critical thresholds and quality control at each institution.370–372 Absolute values of TCD readings can be misleading in the setting of hypertension/hypervolemia/hemodynamic (“triple-H”) therapy, but the Lindegaard ratios (ratio of the velocity in the brain vessel of choice to the velocity in the ipsilateral extracranial internal
carotid artery) have been shown to be helpful in following trends.373–377 Ratios in the range of 5 to 6 for the supracholinid internal carotid, anterior cerebral artery, middle cerebral artery, and vertebrobasilar system have been demonstrated to indicate severe spasm and should be treated on the basis of the clinical situation.378 These trends have been shown to be useful in guiding therapy; however, other modalities such as diffusion perfusion, MRI, and xenon-CT cerebral perfusion studies have been advantageous in guiding management and may be complementary.377,379,380 Whether the use of TCD to treat SAH improves outcome has not been adequately demonstrated. Many centers continue to rely on cerebral angiography for the diagnosis of vasospasm, especially since the development of new interventional radiological treatment (see below). However, the American Academy of Neurology Expert Committee believes that the literature provides Type (see below). However, the American Academy of Neurology Expert Committee believes that the literature provides Type A, Class II level evidence supporting the use of TCD on the basis of the fact that although sensitivity and specificity are quite variable and depend on the vessel of interest, severe spasm can be identified with fairly high reliability.381,382

Early management of the ruptured aneurysm has been shown to reduce in-hospital rebleeding and certainly allows more aggressive and early management of cerebral vasospasm by hemodynamic therapy and interventional management if indicated.383 The goal for the management of cerebral vasospasm is to reduce the threat of ischemic neuronal damage by controlling intracranial pressure, decreasing the metabolic rate of oxygen use, and improving CBF. In improving CBF, hypertensive hypervolemic therapy has become a mainstay in the management of cerebral vasospasm. Nevertheless, despite reports385,386 indicating improvement in neurological status after the institution of this regimen, only 1 randomized study has been performed to assess efficacy.385 This is perhaps due in part to the fact that hypovolemia, hypotension, and hemoconcentration are so obviously detrimental and in part to the fact that these therapies quickly became part of routine management almost as soon as they were popularized in the academic literature.386–388 However, both increases and decreases in CBF have been reported after volume expansion among patients who have experienced an SAH, leading investigators to ask whether prophylactic hypervolemia is any more effective than prophylactic normovolemia in preventing the onset of spasm.383 Using a stratified treatment randomization scheme, which took into account the number of days since the SAH and the postoperative Hunt-Hess grade, Lennihan and colleagues385 showed that although those treated with hypervolemic therapy (n=41) received significantly more fluid and exhibited higher pulmonary artery diastolic pressures and central venous pressures than normovolemic patients (n=41), there was no difference between the 2 groups in mean global CBF (xenon washout), minimal regional CBF, or symptomatic spasm during the treatment period. In addition, 14- and 90-day functional outcomes were similar. Egg et al389 also performed a randomized prospective trial (n=32 patients) to consider the issue of prophylactic volume expansion and hyperdynamic therapy before the onset of symptoms. Sixteen patients received hypervolemic therapy; the other half received normovolemic therapy. All patients were monitored for a minimum of 12 days and followed up with single-photon emission CT scanning and clinical observation. They also did not observe any difference between the 2 groups with respect to cerebral vasospasm, as observed clinically, on TCD recordings, or in CBF. One-year clinical follow-up, according to the Glasgow Coma Scale, did not demonstrate any significant group differences. In their study, costs were higher and complications were more frequent for the hyperdynamic therapy group. Taken together, these 2 small, single-center, prospective randomized studies strongly suggest that avoiding hypovolemia is advisable, but there is no evidence that prophylactic hyperdynamic therapy is of any utility.

Nevertheless, given the inability of these small studies to detect small improvements owing to a lack of statistical power, many centers in North America continue to advocate prophylactic volume expansion as a means to improve CBF, and numerous reports advocate the use of either in-dwelling pulmonary artery catheters to maximize cardiac output and cardiac index or central venous catheters in patients with no preexisting cardiac disease.386,390–394 Mizuno et al378 reported on prophylactic hyperdynamic therapy and hypertension and observed stable CBF values within 3 weeks after SAH. Darby et al395 observed that dopamine-induced hypertension was able to achieve increased CBF in ischemic noninfarcted territories without producing an increase in mean global CBF. Thus, although it appears relatively certain that induced arterial hypertension can be extremely useful in reversing deficits once they occur, the data supporting the finding that prophylactic hypertension lessens the incidence of symptomatic spasm are considerably weaker.396 Given that the initiation of hemodynamic therapy is associated with significant risks, including the possibility of cardiac failure, electrolyte abnormality, cerebral edema, bleeding diathesis resulting from dilution of clotting factors, and potential but apparently rare rupture of unsecured unruptured aneurysms, we conclude that prophylactic hemodynamic therapy needs further study before it can be routinely advocated.397,398

Compared with hypervolemia and hypertension, hemodilution has received comparatively little direct attention. Most patients become relatively hemodiluted because of procedural blood loss and volume expansion, and many investigators have advocated a hematocrit of 0.28 to 0.32 as ideal.383 Nevertheless, recent studies have questioned whether intentional lowering of the hematocrit to this level is actually beneficial. Ekelund and colleagues399 showed in a small single-center case series that although isovolemic hemodilution increased global CBF, it did so at the expense of significant reductions in oxygen delivery capacity and that hypervolemic hemodilution decreased both parameters. However, although intentionally decreasing the hematocrit may be harmful, increasing data from prospectively maintained single-center databases suggest that transfusion may be an independent predictor of poor outcome.400 Given this conclusion, we can only infer that too little information exists on hemodilution to specifically advocate either therapeutic phlebotomy or transfusion for patients in general.

It is imperative to avoid systemic and metabolic insults such as hyperglycemia, acidosis, electrolyte fluctuations, hypoxia, and hyperthermia and to aggressively manage po-
tential septic episodes; all are extremely important in the management of cerebral vasospasm and its potential for irreversible ischemic damage.401–405 Mayer et al401 reported on 43 patients with aneurysmal SAH who were treated with different fluid protocols, suggesting that perhaps 5% albumin helped prevent sodium and fluid losses associated with cerebral salt wasting. That group has also found fever to be an independent predictor of poor outcome, but no definitive prospective trials exist to support these common-sense recommendations.406 Similar things can be said for hyperglycemia407 despite the Class I data on the benefit of insulin drip therapy in a mixed intensive care unit population.408 One exception may be magnesium levels. Hypomagnesemia appears to be common after an SAH and has been associated with both poor outcome and vasospasm.409 Moreover, a large placebo-controlled trial of continuous intravenous infusion for 14 days (64 mmol - L\(^{-1}\) - d\(^{-1}\)) appears to suggest that magnesium may reduce delayed cerebral ischemia by as much as 34%. Poor outcomes at 3 months were reduced by 23%, and the relative risk of a good outcome was 3.4 (95% CI, 1.3 to 8.9) for treated patients.409 These results clearly call for a larger phase III trial.

Calcium channel blockers, particularly nimodipine, have been approved for use in this country on the basis of the initial report of a reduction in morbidity and an improvement in functional outcome in these patients. However, the reduction in morbidity and improvement in functional outcome may have been due to cerebral protection more than an actual effect on the cerebral vasculature because there has been no demonstrated reduction in angiographic vasospasm in patients taking this medication.3,410 Interestingly, nicardipine, an intravenous preparation of a similar L-type calcium channel blocker, showed a 30% reduction in spasm but no improvement in outcome.411

The use of clot removal and intrathecal agents to promote fibrinolysis has been reported in the literature; however, complications associated with this management have offset the benefit in terms of functional outcome, morbidity, and mortality at 6 months.412,413 Small-scale trials have additionally looked at the effect of head shaking, which presumably aids in clot dissolution. A recent trial of 230 patients showed a reduction in permanent ischemic neurological deficit from 8.8% to 2.5% with associated improvements in the modified Rankin Scale that were statistically significant.414 Further study is needed.

Although treatment of patients with aspirin,415,416 enoxaparin,417,418 and tirofiban419–422 has been shown to be ineffective in improving outcome via reductions in vasospasm and delayed ischemic neurological deficits, ebselen,423–425 endothelin-1a antagonists,426,427 and nitroglycerin427 have all shown some promise. In addition, preliminary studies examining the roles of statins (both simvastatin and pravastatin) have suggested a potential to reduce vasospasm and improve mortality.428,429

In 1984, Zubkov et al430 described techniques for balloon angioplasty. They described endovascular techniques for mechanically dilating spastic cerebral vessels via microcatheters. Balloon angioplasty has been shown to be effective in reversing cerebral vasospasm in large proximal conducting vessels with thick muscular walls, whereas angioplasty is not effective or safe in distal perforating branches beyond second-order segments.268,431,432 The theoretical goal of balloon angioplasty is to increase the CBF distal to the area of stenosis. Although many advances have been made in interventional procedures, there are still significant risks associated with angioplasty of cerebral vessels such as vessel occlusion, vessel rupture, thrombus formation, and aneurysm clip displacement.341,433–435

Newell et al436 described angioplasty for the treatment of symptomatic vasospasm after SAH in 1989. They demonstrated feasibility, safety, and angiographic efficacy. A summation of studies indicated that angioplasty is effective in reducing angiographic spasm, that it does promote an increase in CBF, that there is a reduction in deficit, and that balloon angioplasty is superior to papaverine in terms of durability and efficacy, although it is limited in small vessel pathology. What has not been demonstrated in a prospective, randomized fashion is that angioplasty for the management of cerebral vasospasm has improved ultimate outcome.437 The timing of the management of cerebral vasospasm has been evaluated. Rosenwasser et al438 reported that early therapy, perhaps performed at <2 hours, may be advantageous in terms of promoting not only angiographic improvement but, more important, sustained clinical improvement. Johnston117 performed an analysis on the effects of endovascular services and hospital volume on cerebral aneurysm outcomes. This analysis demonstrated that patients treated with angioplasty for cerebral vasospasm had a 16% reduction in risk of in-hospital death compared with institutions without this capability.

With microcatheter technology improving and superselective techniques having advanced over the last decade, it has become possible to selectively catheterize third- and fourth-order cerebral vessels and to administer high doses of vasodilators such as papaverine into vessels that cannot be treated with balloon angioplasty.439–442 Superselective slow infusion of vasodilators has been reported to reduce the risks associated with earlier methods of delivery, including brainstem depression, hypotension, aggravation of vasospasm, seizures, respiratory arrest, transient hemiparesis, and elevated intracranial pressure.439,444 The doses of papaverine reported in the literature are infused at a concentration of 3 mg/mL at 6 to 9 L/min for a total dose of up to 300 mg per vascular territory.445 It is strongly advised that intracranial pressure, as well as other physiological and neurophysiological parameters, be monitored. The use of intraarterial papaverine was reported by Kassell et al446; their study indicated, in a small number of patients, improved angiographic reversal of spasm and a 50% clinical improvement. However, in other studies by Polin et al447 with a subset of patients in a tirofiban trial, although papaverine demonstrated angiographic reversal in cerebral vasospasm, there was no correlation to the severity of the spasm, timing of intervention, papaverine dose, or dose of the study drug. Verapamil447 and other calcium channel blockers448,449 have increasingly been used with excellent anecdotal results. Although they appear to be safer than papavine, their utility is not established at this point.
There are numerous reports in the literature in which a combination of balloon angioplasty and vasodilator infusion was used to treat vasospastic cerebral vessels distal to vessels that can be treated with mechanical angioplasty. However, there are no reports indicating that the 2 treatments delivered together are superior in terms of outcome. The major complication associated with papaverine is elevated intracranial pressure. All reports have indicated that intracranial pressure can be controlled with brief hyperventilation, mannitol, barbiturate therapy, and/or ventricular drainage. Reported rates of serious complications range from 2% to 5%.

Management of Cerebral Vasospasm: Summary and Recommendations

1. Oral nimodipine is indicated to reduce poor outcome related to aneurysmal SAH (Class I, Level of Evidence A). The value of other calcium antagonists, whether administered orally or intravenously, remains uncertain.

2. Treatment of cerebral vasospasm begins with early management of the ruptured aneurysm, and in most cases, maintaining normal circulating blood volume and avoiding hypovolemia are probably indicated (Class IIa, Level of Evidence B).

3. One reasonable approach to symptomatic cerebral vasospasm is volume expansion, induction of hypertension, and hemodilution (triple-H therapy) (Class IIa, Level of Evidence B).

4. Alternatively, cerebral angioplasty and/or selective intraarterial vasodilator therapy may be reasonable after, together with, or in the place of triple-H therapy, depending on the clinical scenario (Class IIb, Level of Evidence B).

Management of Hydrocephalus Associated With SAH

The literature regarding hydrocephalus in SAH consists of a number of case series, most of which are retrospective. Acute hydrocephalus (ventricular enlargement within 72 hours) is reported to occur in approximately 20% to 30% of patients. The ventricular enlargement is often, but by no means always, accompanied by intraventricular blood; hydrocephalus without intraventricular hemorrhage is associated with the amount and distribution of cisternal blood. Acute hydrocephalus is more frequent in patients with poor clinical grade and higher Fischer Scale scores. The clinical significance of acute ventriculomegaly after SAH is uncertain because many patients are apparently asymptomatic and do not deteriorate. Yet, in patients with a diminished level of consciousness, 40% to 80% had some degree of improvement after the procedure. On the basis of 2 small series, the placement of a ventriculostomy may or may not be associated with rebleeding.

Chronic ventriculomegaly requiring permanent shunting procedures is reported at rates of 18% to 26% of surviving patients. The need for permanent CSF diversion has been associated with older age, early ventriculomegaly, intraventricular hemorrhage, poor clinical condition on presentation, and female sex. Two single-center series have suggested that routine fenestration of the lamina terminalis reduces the incidence of chronic hydrocephalus. In comparison, rates are no different in patients undergoing clipping or endovascular treatment of their aneurysms. Ventriculotrial, ventriculoperitoneal, or lumboventricular shunts may improve clinical status in this group of patients. Nevertheless, the speed with which the ventriculostomy is weaned does not appear to affect the need for ultimate shunt placement.

Management of Hydrocephalus: Summary and Recommendations

1. Temporary or permanent CSF diversion is recommended in symptomatic patients with chronic hydrocephalus after SAH (Class I, Level of Evidence B).

2. Ventriculostomy can be beneficial in patients with ventriculomegaly and diminished level of consciousness after acute SAH (Class IIa, Level of Evidence B).

Management of Seizures Associated With SAH

The risk and implications of seizures associated with SAH are not well defined, and the need for and efficacy of routinely administered anticonvulsants after SAH are not well established. A large number of seizure-like episodes have been associated with aneurysmal rupture. It is unclear, however, whether all these episodes are truly epileptic in origin. More recent retrospective reviews report a low frequency of seizures ranging from 6% to 18%. Another retrospective review found that the majority of early seizures occurred before medical presentation and that in-hospital seizures were rare for patients given prophylactic anticonvulsants. Delayed seizures occurred in approximately 7% of patients in another series. Seizures caused by intraarterial papaverine have also been reported. The relationship between seizures and outcome is uncertain because they have been reported to have no impact on outcome or to be associated with worse outcome.

Recent reports indicate that nonconvulsive seizures may occur in SAH patients. One series of selected patients who underwent continuous EEG monitoring found that 19% of stuporous or comatose patients had nonconvulsive seizures an average of 18 days after SAH. All were receiving prophylactic anticonvulsants, and all died. The routine use of prophylactic anticonvulsants during the perioperative period has been addressed in several studies, but none has clearly established their use as beneficial. Nonrandomized studies of craniotomy patients have indicated a benefit of prophylactic anticonvulsants, however, the number of patients with SAH in these studies is very small. A study of patients undergoing coil embolization of aneurysms reported no procedural seizures and a delayed seizure rate of 3%. Risk factors for seizures after SAH have been noted in several retrospective studies, including middle cerebral artery aneurysms, intraparenchymal hematoma, infarcts, and a history of hypertension. Although retrospective studies have concluded that prophylactic anticonvulsants are of no benefit after SAH, the studies had small numbers
of patients, and anticonvulsant levels were not routinely monitored. One retrospective study investigated the impact of the use of prophylactic anticonvulsants (phenytoin) on cognitive outcome and found that phenytoin burden was independently associated with worse cognitive function at 3 months after hemorrhage.489

Management of Seizures: Summary and Recommendations

1. The administration of prophylactic anticonvulsants may be considered in the immediate posthemorrhagic period (Class I, Level of Evidence B).
2. The routine long-term use of anticonvulsants is not recommended (Class III, Level of Evidence B) but may be considered for patients with risk factors such as prior seizure, parenchymal hematoma, infarct, or middle cerebral artery aneurysms (Class IIb, Level of Evidence B).

Management of Hyponatremia and Volume Contraction

The reported incidence of hyponatremia after SAH ranges from ≈10% to 30%. Hyponatremia is more common in patients with poor clinical grade, anterior communication artery aneurysms, and hydrocephalus and may be an independent risk factor for poor outcome.491–493 Uncontrolled prospective studies suggest a relationship of hyponatremia to excessive natriuresis and volume contraction.494 In several uncontrolled studies, the development of volume contraction was found to be ameliorated by the administration of large amounts of fluids (hypervolemic therapy).493,495 Two randomized, controlled trials have been performed to evaluate the ability of fludrocortisone to correct hyponatremia and fluid balance. One found that it helped to correct the negative sodium balance but not volume contraction or hyponatremia,496 and the other reported a reduced need for fluids and improved sodium levels with fludrocortisone.497 One retrospective study has suggested that 3% saline is effective in correcting hyponatremia.498 Additional reports suggest that 5% albumin may also be effective.499

Management of Hyponatremia: Summary and Recommendations

1. Administration of large volumes of hypotonic fluids and intravascular volume contraction should generally be avoided after SAH (Class I, Level of Evidence B).
2. Monitoring volume status in certain patients with recent SAH using some combination of central venous pressure, pulmonary artery wedge pressure, fluid balance, and body weight is reasonable, as is treatment of volume contraction with isotonic fluids (Class IIa, Level of Evidence B).
3. The use of fludrocortisone acetate and hypertonic saline is reasonable for correcting hyponatremia (Class IIa, Level of Evidence B).
4. In some instances, it may be reasonable to reduce fluid administration to maintain a euvolemic state (Class IIb, Level of Evidence B).

Compliance With Previous SAH Guidelines

In 1994, a special writing group of the AHA Stroke Council developed “Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage.” These guidelines were intended to provide a framework for patient management and a foundation for research. Translating the guidelines into clinical practice and assessing whether the guidelines have influenced treatment of SAH are important considerations for healthcare providers. Whether the guidelines have reduced the variability in treatment of SAH or resulted in improved outcome would provide additional vital information. Recently, a multicenter (100 centers) retrospective study evaluated 20 indexes of compliance from the 1994 guidelines.498 The indexes were assessed before the guidelines and for 4 years after publication of the guidelines, including a 1-year period of adoption. Seven of the indexes demonstrated 100% compliance during all 3 periods. Five of the 13 remaining indexes were associated with low preguideline compliance rates: use of prophylactic anticonvulsants (27.7%), administration of nimodipine (18.5%), surgical clipping of the aneurysm (59.2%), ordering bedrest (57.9%), and use of TCD sonography (31.8%). Among these 5 indexes, there was a significant increase in the rates of compliance in the postguideline period compared with the preguideline period in the use of prophylactic anticonvulsants (P=0.0002), the administration of nimodipine (P<0.0001), and the use of TCD (P=0.01). There was no significant change in rates of surgical clipping over the guideline periods, and there was a reduction in the rate of bedrest prescribed at admission.

Summary and Conclusions

The current standard of practice calls for microsurgical clipping or endovascular coiling of the aneurysm neck whenever possible. Treatment morbidity is determined by numerous factors, including patient, aneurysm, and institutional factors. Favorable outcomes are more likely in institutions that treat high volumes of patients with SAH, in institutions that offer endovascular services, and in selected patients whose aneurysms are coiled rather than clipped. Optimal treatment requires availability of both experienced cerebrovascular surgeons and endovascular surgeons working in a collaborative effort to evaluate each case of SAH.
## Disclosures

### Writing Group Disclosures

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**Key Words:** AHA Scientific Statements ■ aneurysm ■ angiography ■ cerebrovascular disorders ■ hemorrhage ■ stroke ■ surgery ■ vasospasm
Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Statement for Healthcare Professionals From a Special Writing Group of the Stroke Council, American Heart Association

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An erratum has been published regarding this article. Please see the attached page for:
/content/40/7/e518.full.pdf
In the scientific statement by Bederson et al, “Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Statement for Healthcare Professionals From a Special Writing Group of the Stroke Council, American Heart Association,” which published ahead of print on January 22, 2009, and appeared in the March 2009 issue,¹ a correction was needed.

The American Academy of Neurology affirmed the value of this statement. The following text has been added on page 994 under the title of the statement: “The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.”

This correction has been made to the current online version of the article, which is available at http://stroke.ahajournals.org/cgi/content/full/40/3/994.

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