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

Joshua B. Bederson, E. Sander Connolly, Jr, H. Hunt Batjer, Ralph G. Dacey, Jacques E. Dion, Michael N. Diringer, John E. Duldner, Jr, Robert E. Harbaugh, Aman B. Patel and Robert H. Rosenwasser

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://stroke.ahajournals.org/cgi/content/full/40/3/994

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

Joshua B. Bederson, MD, Chair; E. Sander Connolly, Jr, MD, FAHA, Vice-Chair; H. Hunt Batjer, MD;
Ralph G. Dacey, MD, FAHA; Jacques E. Dion, MD, FRCPC; Michael N. Diringer, MD, FAHA;
John E. Duldner, Jr, MD, MS; Robert E. Harbaugh, MD, FAHA;
Aman B. Patel, MD; Robert H. Rosenwasser, MD, FAHA

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 scheme[11,12] (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 Hospital Discharge Survey of 1990[18] 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 attention[19] and that many cases of SAH are misdiagnosed.[20–26] The annual prevalence of aneurysmal SAH in the United

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

Authors	Year	Therapy	n	Benefit
Van den Bergh et al[415]	2006	Aspirin	161	No less DIND
Hop et al[416]	2000	Aspirin	50	No improvement in 4-mo outcome
Schmid-Elsaesser[499]	2006	Magnesium	113	No better outcome than nimodipine
Wong et al[176]	2006	Magnesium	60	No better outcome
Van den Bergh et al[409]	2005	Magnesium	283	Less DCI and poor outcome
Veyna[500]	2002	Magnesium	40	No less clinical vasospasm
Molyneux et al[185]	2005	GDC	2143	Less mortality/epilepsy, more rebleeding
Molyneux et al[258]	2002	GDC	2143	Less mortality, better outcome
Koivisto et al[259]	2000	GDC	109	No improvement in 12-mo outcome
Vanninen[501]	1999	GDC	109	No improvement in 3-mo outcome
Vajkoczy et al[425]	2005	ET antagonist	32	Less incidence/intensity angiographic vasospasm
Shaw et al[426]	2000	ET antagonist	420	Trend to less DIND, no better outcome
Lynch et al[428]	2005	Statin (simvastatin)	39	Reduced incidence of clinical vasospasm
Tseng et al[429]	2005	Statin (pravastatin)	80	Less mortality/incidence of TCD vasospasm
Anderson[502]	2006	Hypothermia	1001	No neuropsychological benefit at 3 mo
Todd et al[364]	2005	Hypothermia	1001	No improvement in 3-mo outcome
Karibe[503]	2000	Hypothermia	24	Immediate CBF improvement
Hindman[504]	1999	Hypothermia	114	Improved outcome at 3 and 6 mo
Diringer[505]	2004	Normothermia	296	Reduced fever burden with catheter
Reinert et al[427]	2004	TD NTG	17	Raised CBF
Klopfenstein et al[469]	2004	Drain wean	81	No difference in shunted hydrocephalus
Wurm et al[417]	2004	Enoxaparin	117	No less TCD vasospasm
Siironen et al[418]	2003	Enoxaparin	170	No improvement in 3-mo outcome
Moro[506]	2003	Hydrocortisone	28	Improved sodium balance
Mori et al[496]	1999	Fludrocortisone	30	No improvement in 6-mo outcome
Mayer et al[391]	1998	5% Albumin	43	Improved sodium balance
Hamada[507]	2003	IT urokinase	110	Reduced symptomatic vasospasm
Findlay[508]	1995	IT rtPA	91	No decrease in angiographic vasospasm
Hillman et al[140]	2002	Tranexamic A	505	Reduced rebleeding, no effect on outcome
Roos[509]	2000	Tranexamic A	462	Reduced rebleeding, no effect on outcome
Egge et al[389]	2001	Hypervolemia	32	No effect on clinical/TCD vasospasm
Lennihan et al[385]	2000	Hypervolemia	82	No less symptomatic vasospasm
Lanzino et al[419]	1999	Tirilazad (F-NA)	823	No improvement in 3-mo outcome
Lanzino et al[420]	1999	Tirilazad (F-E)	819	No improvement in 3-mo outcome
Haley et al[421]	1997	Tirilazad (NA)	897	No improvement in 3-mo outcome
Kassell et al[422]	1996	Tirilazad (E)	1015	No improvement in 3-mo outcome
Saito et al[423]	1998	Ebselen	286	No less DIND but improved outcome
Asano et al[424]	1996	Ebselen	162	Decreased incidence of DIND

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.

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 1990s[29] 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 ≥50 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] There appear to 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

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

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
	Class IIa: the weight of evidence or opinion is in favor of the procedure or treatment
	Class IIb: usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Therapeutic 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

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,[36,37] Japan,[38] the Netherlands,[39,40] Finland,[41,42] and Portugal.[43] Sympathomimetic drugs, including cocaine[44,45] and phenylpropanolamine,[46] 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.[44] Diabetes does not appear to be a risk factor for SAH.[47] 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 months[14,51] 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,[98] 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 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]

Table 3. Applying Classification of Recommendations and Level of Evidence

	CLASS I *Benefit >>> Risk* **Procedure/Treatment SHOULD be performed/administered**	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *Risk ≥ Benefit* **Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

SIZE OF TREATMENT EFFECT →

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

*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.

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 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,[94,103,106–108] 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.[40,105] 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.[91]

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,[109] 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.[110] However, in a review of the available literature, Wardlaw and White[111] 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,[4–7] and it is recognized that the main determinant of outcome is the severity of the initial bleed.[8,112] 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.[113] 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,[114] 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[115] and 33% in a recent analysis of in-hospital deaths among SAH patients admitted through an emergency department (ED).[102] In a population-based study by Broderick et al,[8] 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.[27,28,30]

There are many influences on outcome after SAH, with wide variations in case fatality rates reported between different countries and regions.[13] 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.[102] Aneurysm factors include size, location in the posterior circulation, and possibly morphology.[116] Institutional factors include the availability of endovascular services,[117] the volume of SAH patients treated,[102,117–119] and the type of facility in which the patient is first evaluated.[120]

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[121]). SAH causes profound reductions in cerebral blood flow (CBF), reduced cerebral autoregulation, and acute cerebral ischemia.[122–126] These pathophysiological processes are linked to raised intracranial pressure and decreased cerebral perfusion pressure,[122,127,128] decreased availability of nitric oxide,[126,129] acute vasoconstriction[123,130,131] and microvascular platelet aggregation,[132] activation of microvascular collagenases, loss of microvascular collagen,[133] and endothelial barrier antigen leading to decreased microvascular perfusion and increased permeability.[132,133] 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 pat-

terns of rebleeding.[134,135] In the prospective Cooperative Aneurysm Study,[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[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 ≈3% per year.[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,[140,141] with high mortality rates. In 1 study, 70% of ultraearly rebleeds occurred within 2 hours of initial SAH.[141] In another study, all preoperative rebleeding occurred within 12 hours of initial SAH.[142] In recent studies, poor neurological status,[142] high Hunt-Hess grade, and larger aneurysm diameter[143] were independent predictors of acute hydrocephalus, intraventricular blood, and the use of ventricular drains.[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.[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 intraobserver and interobserver uniformity or consistency.[9,149–151] Recent reports have tended to use the Glasgow Coma Scale or Glasgow Outcome Scale.[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 neurobehavioral difficulties that impair their social adjustment and ability to return to their previous occupations.[179–183] At least 1 study has suggested that these neurobehavioral deficits are not correlated with tissue loss as seen on recent MRI[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.[179–182,184] In the recent International Subarachnoid Aneurysm Trial (ISAT), written questionnaires were sent to patients to determine a modified Rankin Scale.[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.[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.[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 ≈80% of patients who can give a history, but a warning or sentinel headache is also described by ≈20% of patients.[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.[189,190] The onset of headache may be associated with ≥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[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%.[4] As many as 12% die before receiving medical attention.[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 ≈12%.[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.[21] The most common diagnostic error is failure to obtain a noncontrast cranial CT.[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*.[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.[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.[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.[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.[196] Seizures may occur in up to 20% of patients after SAH, most commonly in the first 24 hours[200] and more commonly in SAH associated with intracerebral hemorrhage, hypertension, and middle cerebral and anterior communicating artery aneurysms.[201]

The cornerstone of SAH diagnosis is the noncontrast cranial CT scan.[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[203–207] and to 57% to 85% 6 days after SAH.[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.[194,195,209,210] Guidelines for the examination and interpretation of CSF obtained from lumbar puncture to evaluate suspected SAH have been published.[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.[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.[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.[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%.[219–222] The variations seen in these studies are due largely to differences in aneurysm size. With aneurysms ≥5 mm, the sensitivity is 85% to 100%, whereas the sensitivity of MRA for detecting aneurysms <5 mm drops to 56%.[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.[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.[225] CTA has a reported sensitivity for aneurysms between 77% and 100% and a specificity between 79% and 100%.[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 ≥5 mm, CTA has a sensitivity between 95% and 100% compared with between 64% and 83% when aneurysms are <5 mm.[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.[83,226] Among aneurysms detected on CTA and then undergoing surgery, 100% correlation was observed between CTA and catheter angiography.[226,232] Velthuis and colleagues[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.[228] 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.[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.[234] CTA has advan-

tages 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.[233,235]

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.[236] Repeat angiography after ≈1 week will disclose a previously unrecognized aneurysm in an additional 1% to 2% of cases.[237] Whether the additional small yield is worth the cost and morbidity of the second angiogram is a source of controversy.[238]

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 first 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 ≥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.[150,239] 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.[144] 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 re-

bleeding 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 pressure[245]; 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 al[242] 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 al[240] 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 studies[250,251] 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 al[252] 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,[257] procedural (30-day) mortality for coiling was 2.0% and disability was 7.4%. In the recently published ISAT,[185,258] 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.[259–265] 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.[265] The same study reported rebleeds in 2 patients with complete angiographic obliteration. ISAT, the only randomized trial comparing endovascular therapy with surgical clipping, reported a 1-year rehemorrhage rate of ≈2.9% in aneurysms treated with endovascular therapy.[185,258] More recently, a Boston Scientific–sponsored research study used phone interviews and public records to try to determine long-term rebleeding in patients undergoing coiling at 9 high-volume centers in the western United States from 1996 to 1998. Although it is unclear what percent of the patients were actually contacted, it appeared that all rebleeding occurred in the first 12 months after treatment and that overall rebleeding was still somewhat more common than with surgical repair.[266]

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.[267] Another study of 61 patients followed up for 1.1 years after treatment found an annual rerupture rate of 2.9%.[268] A study that included 104 patients with ruptured posterior circulation aneurysms documented an annual rate of 0.9%.[269] A small study in 23 patients documented no reruptures during ≈24 patient-years of follow-up.[270] 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.[271–278] 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%.[270] 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.[279]

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.[93,271,280] 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.[281] In a significant proportion of intracranial aneurysms, complete occlusion is not possible on the first endovascular treatment.[256] In a meta-analysis, only 54% of aneurysms were completely occluded, and 88% of aneurysms were >90% occluded after coil embolization.[256]

In the largest published series from North America, Murayama et al[282] 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 1.1% 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.[282]

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.[283] Angiographic follow-up may reveal aneurysm recurrence and provide an opportunity to further treat the aneurysm before it becomes symptomatic.[281,284] 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,[117,255,285,286] and surgical results for these aneurysms are often reported as more favorable than for other lesions.[286–289] However, aneurysms in the posterior cerebral circulation are frequently more difficult to treat with surgery,[73] and comparative observational studies have found better outcomes after coil embolization in these locations.[120,270] 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,[290] and both treatments can lead to a reduction in compressive symptoms.[291]

Aneurysm size has been associated with an increased risk of complications and an increased likelihood of incomplete occlusion. In the Raaymakers et al[73] 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.[282,292–296] 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[271]; however, comparative studies have not evaluated the impact of size on outcome.

In several studies, aneurysm neck size has been an independent predictor of likelihood of complete occlusion and recurrence by coil embolization, particularly when considered relative to the size of the aneurysm.[296–299] 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.[297]

Comorbid medical conditions and complications from an initial SAH may also influence the selection of surgery or endovascular therapy. For example, the presence of a large parenchymal hematoma with mass effect may favor a decision to perform open surgery to reduce intracranial pressure by surgical evacuation of the hematoma. In contrast, a poor neurological grade or evidence of significant brain swelling without mass effect may increase the risk of surgical retraction[300] but has less influence on the difficulty of endovascular therapy.[301] 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, ultrasoft coils,[302] liquid polymer techniques,[303] bioactive or coated coils, the development of techniques using balloons,[304–307] and intravascular stents[308–314] 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,[272] with major reductions in procedural complication rates after the first 5 procedures, at least in the setting of a high-volume academic training program.[315] 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[256,282] and may occur even in aneurysms that appear completely occluded after initial treatment.[271,280] Additional embolization is often possible and may be required to prevent growth and potential SAH.[281,284] 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.[316]

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.[317] When aneurysm occlusion is incomplete, follow-up imaging is often obtained more frequently.[282]

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,[318] 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.[283] 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.[319]

The Cooperative Study[320] evaluated 979 patients who underwent intracranial surgery only.[321] 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,[1] 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,[9] 11.1% of good-grade patients rebled before surgery, and 8 of 644 patients (1.2%) had postoperative bleeds. These results, comparable to those in prior large series,[322,323] have recently been confirmed prospectively in the modern era by Naidech et al,[247] who found that 5.5% bled before surgery despite aggressive management. The authors found that increasing admission Hunt-Hess grade and aneurysm size independently predicted rebleeding.

The effectiveness of aneurysm clipping in reducing poor outcomes resulting from rebleeding was analyzed by Brilstra et al,[324] 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[325] 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,[326] 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[93] 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%.[93] In ISAT,[185,258] 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.[327–329] In a recent long-term follow-up study,[330] 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%.[331] 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[332–334] and recently has been associated with higher rates of poor outcome.[116] The International Cooperative Study on the Timing of Aneurysm Surgery[335] 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,[336] 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.[185,258] 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%; $P<0.05$).[247]

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.[337–339] However, ischemic sequelae may still occur in those who tolerated test occlu-

sion,[338,339] even if an extracranial-intracranial arterial bypass is performed.[340] 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.[341,342]

Before 1970, carotid ligation was commonly used to treat recently ruptured intracranial aneurysms. A large retrospective study by Nishioka,[343] 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,[344] 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[345] 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.[8,112] 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),[257] 2.6% in the meta-analysis by Raaymakers and colleagues[73] of studies published between 1966 and 1996, 2.5% in the analysis of discharge data from 2200 New York State patients,[118] and 3.0% in a study of California discharge data.[253] Adverse outcomes in survivors were 8.9% in ISUA II,[257] 10.9% in the Raaymakers et al study,[73] 21.3% in the study of New York State discharges,[118] and 22.4% in the study of California discharges.[253]

The only large, prospective, randomized trial to date comparing surgery and endovascular techniques is ISAT,[185,258] 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.[346,347]

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[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 1546 US hospitals, Cross et al[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 9534 SAH cases treated at 70 centers in the University of California Health Systems from 1994 through 1997, Johnston[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[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%.[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[118] limited their analysis to the 5963 patients who underwent treatment of an intracranial aneurysm (2200 unruptured, 3763 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.[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.[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.[102] Bardach et al[348] 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,[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.[116] Low-volume centers have been found to treat SAH with acceptable outcomes.[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.[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.[348] One important issue relevant to the morbidity associated with transfer is aneurysm rebleeding. To address this, Hillman and colleagues[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.[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 intraprocedural 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 occlu-

sion 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.[9,192,365] 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.[241]

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 supraclinoid 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 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 reports[383,384] 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 colleagues[385] 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. Egge et al[389] 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 al[378] reported on prophylactic hyperdynamic therapy and hypertension and observed stable CBF values within 3 weeks after SAH. Darby et al[395] 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 colleagues[399] 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 potential septic episodes; all are extremely important in the management of cerebral vasospasm and its potential for irreversible ischemic damage.[401–405] Mayer et al[391] 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 hyperglyce-

mia[407] 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 $\cdot$ L^{-1} $\cdot$ 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 tirilizad[419–422] has been shown to be ineffective in improving outcome via reductions in vasospasm and delayed ischemic neurological deficits, ebselen,[423,424] endothelin-1a antagonists,[425,426] and nitroglycerin[427] 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 al[430] 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 al[436] 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 al[438] 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. Johnston[117] 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.[439–443] 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 al[446]; 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 al[437] with a subset of patients in a tirilazad 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. Verapamil[447] and other calcium channel blockers[448,449] have increasingly been used with excellent anecdotal results. Although they appear to be safer than papavarine, 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.[450] However, there are no reports indicating that the 2 treatments delivered together are superior in terms of outcome.[156] 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. Re-

ported rates of serious complications range from 2% to 5%.[443,450,451]

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 ≈20% to 30% of patients.[452–455] The ventricular enlargement is often, but by no means always, accompanied by intraventricular blood[456,457]; hydrocephalus without intraventricular hemorrhage is associated with the amount and distribution of cisternal blood.[96,458] Acute hydrocephalus is more frequent in patients with poor clinical grade and higher Fischer Scale scores.[452–455] The clinical significance of acute ventriculomegaly after SAH is uncertain because many patients are apparently asymptomatic and do not deteriorate.[457] Yet, in patients with a diminished level of consciousness, 40% to 80% had some degree of improvement after the procedure.[456,457,459] On the basis of 2 small series, the placement of a ventriculostomy may[146] or may not[148] be associated with rebleeding.

Chronic ventriculomegaly requiring permanent shunting procedures is reported at rates of 18% to 26% of surviving patients.[455,460,461] The need for permanent CSF diversion has been associated with older age, early ventriculomegaly, intraventricular hemorrhage, poor clinical condition on presentation, and female sex.[202,462–465] Two single-center series have suggested that routine fenestration of the lamina terminalis reduces the incidence of chronic hydrocephalus.[207,466] In comparison, rates are no different in patients undergoing clipping or endovascular treatment of their aneurysms.[460,461] Ventriculoatrial, ventriculoperitoneal, or lumboperitoneal shunts may improve clinical status in this group of patients.[467,468] Nevertheless, the speed with which the ventriculostomy is weaned does not appear to affect the need for ultimate shunt placement.[469]

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.[200,470] It is unclear, however, whether all these episodes are truly epileptic in origin.[470,471] More recent retrospective reviews report a low frequency of seizures ranging from 6% to 18%.[472–474] 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.[473] Delayed seizures occurred in ≈7% of patients in another series.[475] Seizures caused by intraarterial papaverine have also been reported.[476] The relationship between seizures and outcome is uncertain because they have been reported to have no impact on outcome[473] or to be associated with worse outcome.[472]

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.[477] 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.[478–480] Nonrandomized studies of craniotomy patients have indicated a benefit of prophylactic anticonvulsants[481–483]; however, the number of patients with SAH in these studies is very small. A study of patients undergoing coil embolization of aneurysms reported no periprocedural seizures and a delayed seizure rate of 3%.[484] Risk factors for seizures after SAH have been noted in several retrospective studies, including middle cerebral artery aneurysms,[485,486] intraparenchymal hematoma,[481,485,487] infarcts,[488] and a history of hypertension.[201] Although retrospective studies have concluded that prophylactic anticonvulsants are of no benefit after SAH,[470,478] 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 IIb, 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.[401,490–492] Uncontrolled prospective studies suggest a relationship of hyponatremia to excessive natriuresis and volume contraction.[402,493] Fluid restriction has been associated with an increased incidence of delayed ischemic deficits,[402] and volume contraction has been linked to symptomatic vasospasm.[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 fluorocortisone to correct hyponatremia and fluid balance. One found that it helped to correct the negative sodium balance but not volume contraction or hyponatremia,[495] and the other reported a reduced need for fluids and improved sodium levels with fluorocortisone.[496] One retrospective study has suggested that 3% saline is effective in correcting hyponatremia.[497] Additional reports suggest that 5% albumin may also be effective.[391]

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."[3] 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

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Ownership Interest	Consultant/ Advisory Board	Other
Joshua B. Bederson	Mt Sinai School of Medicine	None	None	None	None	None	None
E. Sander Connolly, Jr	Columbia University	None	None	None	None	None	None
H. Hunt Batjer	Northwestern Medical Faculty Foundation	None	None	None	None	None	None
Ralph G. Dacey	Washington University School of Medicine	NIH/ NINDS†	None	None	Stereotaxis, Inc*	None	None
Jacques E. Dion	Emory University Hospital	None	None	None	None	None	None
Michael N. Diringer	Washington University	None	None	None	None	None	None
John E. Duldner, Jr	Samaritan Regional Health Center	None	None	None	None	None	None
Robert E. Harbaugh	Dartmouth Hitchcock Medical Center	None	None	None	None	MedCool, Inc*	None
Aman B. Patel	Mt Sinai Hospital	None	None	Boston Scientific*; Cordis*	None	None	None
Robert H. Rossenwasser	Thomas Jefferson University	None	Micrios*	None	Boston Scientific†	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Gavin Britz	University of Washington	None	None	None	None	None	None	None
Gary Ross Duckwiler	University of California at Los Angeles	None	None	None	None	None	None	None
Randall Higashida	University of California, San Francisco	None	None	None	None	None	None	None
R.L. Macdonald	University of Toronto	National Institutes of Health†	Boston Scientific†	Actelion Pharmaceuticals†	None	Brainsgate*	Actelion Pharmaceuticals†	None
Adnan Qureshi	University of Medicine and Dentistry of New Jersey	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

References

1. Graf CJ, Nibbelink DW. Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage: report on a randomized treatment study, 3: intracranial surgery. *Stroke*. 1974;5:557–601.
2. King JT Jr. Epidemiology of aneurysmal subarachnoid hemorrhage. *Neuroimaging Clin N Am*. 1997;7:659–668.
3. Mayberg MR, Batjer HH, Dacey R, Diringer M, Haley EC, Heros RC, Sternau LL, Torner J, Adams HP Jr, Feinberg W. 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. *Stroke*. 1994;25:2315–2328.
4. van Gijn J, Rinkel GJ. Subarachnoid haemorrhage: diagnosis, causes and management. *Brain*. 2001;124(pt 2):249–278.
5. Hijdra A, van Gijn J, Nagelkerke NJ, Vermeulen M, van Crevel H. Prediction of delayed cerebral ischemia, rebleeding, and outcome after aneurysmal subarachnoid hemorrhage. *Stroke*. 1988;19:1250–1256.
6. Hijdra A, Braakman R, van Gijn J, Vermeulen M, van Crevel H. Aneurysmal subarachnoid hemorrhage: complications and outcome in a hospital population. *Stroke*. 1987;18:1061–1067.
7. Hop JW, Rinkel GJ, Algra A, van Gijn J. Changes in functional outcome and quality of life in patients and caregivers after aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2001;95:957–963.
8. Broderick JP, Brott TG, Duldner JE, Tomsick T, Leach A. Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. *Stroke*. 1994;25:1342–1347.
9. Sundt TM Jr, Kobayashi S, Fode NC, Whisnant JP. Results and complications of surgical management of 809 intracranial aneurysms in 722 cases: related and unrelated to grade of patient, type of aneurysm, and timing of surgery. *J Neurosurg*. 1982;56:753–765.
10. Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest*. 1992;102(suppl):305S–311S.
11. Gibbons RJ, Smith S, Antman E, for the American College of Cardiology, American Heart Association. American College of Cardiology/American Heart Association clinical practice guidelines, part I: where do they come from? *Circulation*. 2003;107:2979–2986.
12. Gibbons RJ, Smith SC Jr, Antman E, for the American College of Cardiology, American Heart Association. American College of Cardiology/American Heart Association clinical practice guidelines, part II: evolutionary changes in a continuous quality improvement project. *Circulation*. 2003;107:3101–3107.
13. Ingall T, Asplund K, Mahonen M, Bonita R. A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. *Stroke*. 2000;31:1054–1061.
14. Epidemiology of aneurysmal subarachnoid hemorrhage in Australia and New Zealand: incidence and case fatality from the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS). *Stroke*. 2000;31:1843–1850.
15. Inagawa T, Shibukawa M, Inokuchi F, Tokuda Y, Okada Y, Okada K. Primary intracerebral and aneurysmal subarachnoid hemorrhage in Izumo City, Japan, part II: management and surgical outcome. *J Neurosurg*. 2000;93:967–975.
16. Inagawa T, Takechi A, Yahara K, Saito J, Moritake K, Kobayashi S, Fujii Y, Sugimura C. Primary intracerebral and aneurysmal subarachnoid hemorrhage in Izumo City, Japan, part I: incidence and seasonal and diurnal variations. *J Neurosurg*. 2000;93:958–966.
17. Inagawa T. What are the actual incidence and mortality rates of subarachnoid hemorrhage? *Surg Neurol*. 1997;47:47–52.
18. Graves EJ. Detailed diagnoses and procedures, national hospital discharge survey, 1990. *Vital Health Stat 13*. 1992:1–225.
19. Ingall T, Wiebers D. Natural history of subarachnoid hemorrhage. In: Whisnant JP, ed. *Stroke: Populations, Cohorts, and Clinical Trials*. Boston, Mass: Butterworth-Heinemann Ltd; 1993.
20. Fridriksson S, Hillman J, Landtblom AM, Boive J. Education of referring doctors about sudden onset headache in subarachnoid hemorrhage: a prospective study. *Acta Neurol Scand*. 2001;103:238–242.
21. Kowalski RG, Claassen J, Kreiter KT, Bates JE, Ostapkovich ND, Connolly ES, Mayer SA. Initial misdiagnosis and outcome after subarachnoid hemorrhage. *JAMA*. 2004;291:866–869.
22. Mayer PL, Awad IA, Todor R, Harbaugh K, Varnavas G, Lansen TA, Dickey P, Harbaugh R, Hopkins LN. Misdiagnosis of symptomatic cerebral aneurysm: prevalence and correlation with outcome at four institutions. *Stroke*. 1996;27:1558–1563.
23. Mori K, Kasuga C, Nakao Y, Yamamoto T, Maeda M. Intracranial pseudoaneurysm due to rupture of a saccular aneurysm mimicking a large partially thrombosed aneurysm ("ghost aneurysm"): radiological findings and therapeutic implications in two cases. *Neurosurg Rev*. 2004;27:289–293.
24. Polmear A. Sentinel headaches in aneurysmal subarachnoid haemorrhage: what is the true incidence? A systematic review. *Cephalalgia*. 2003;23:935–941.
25. Toffol GJ, Swiontoniowski M. Stroke in young adults: a continuing diagnostic challenge. *Postgrad Med*. 1992;91:123–128.
26. Vannemreddy P, Nanda A, Kelley R, Baskaya MK. Delayed diagnosis of intracranial aneurysms: confounding factors in clinical presentation and the influence of misdiagnosis on outcome. *South Med J*. 2001;94:1108–1111.
27. Harmsen P, Tsipogianni A, Wilhelmsen L. Stroke incidence rates were unchanged, while fatality rates declined, during 1971–1987 in Göteborg, Sweden. *Stroke*. 1992;23:1410–1415.
28. Ingall TJ, Whisnant JP, Wiebers DO, O'Fallon WM. Has there been a decline in subarachnoid hemorrhage mortality? *Stroke*. 1989;20:718–724.
29. Truelsen T, Bonita R, Duncan J, Anderson NE, Mee E. Changes in subarachnoid hemorrhage mortality, incidence, and case fatality in New Zealand between 1981–1983 and 1991–1993. *Stroke*. 1998;29:2298–2303.
30. Stegmayr B, Eriksson M, Asplund K. Declining mortality from subarachnoid hemorrhage: changes in incidence and case fatality from 1985 through 2000. *Stroke*. 2004;35:2059–2063.
31. Rinkel GJ, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke*. 1998;29:251–256.
32. Longstreth WT, Nelson LM, Koepsell TD, van Belle G. Subarachnoid hemorrhage and hormonal factors in women: a population-based case-control study. *Ann Intern Med*. 1994;121:168–173.
33. Okamoto K, Horisawa R, Kawamura T, Asai A, Ogino M, Takagi T, Ohno Y. Menstrual and reproductive factors for subarachnoid hemorrhage risk in women: a case-control study in Nagoya, Japan. *Stroke*. 2001;32:2841–2844.
34. Broderick JP, Brott T, Tomsick T, Huster G, Miller R. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. *N Engl J Med*. 1992;326:733–736.
35. Ayala C, Greenlund KJ, Croft JB, Keenan NL, Donehoo RS, Giles WH, Kittner SJ, Marks JS. Racial/ethnic disparities in mortality by stroke subtype in the United States, 1995–1998. *Am J Epidemiol*. 2001;154:1057–1063.
36. Qureshi AI, Suri MF, Yahia AM, Suarez JI, Guterman LR, Hopkins LN, Tamargo RJ. Risk factors for subarachnoid hemorrhage. *Neurosurgery*. 2001;49:607–612.
37. Taylor CL, Yuan Z, Selman WR, Ratcheson RA, Rimm AA. Cerebral arterial aneurysm formation and rupture in 20,767 elderly patients: hypertension and other risk factors. *J Neurosurg*. 1995;83:812–819.
38. Kubota M, Yamaura A, Ono J. Prevalence of risk factors for aneurysmal subarachnoid haemorrhage: results of a Japanese multicentre case control study for stroke. *Br J Neurosurg*. 2001;15:474–478.
39. van der Schaaf IC, Ruigrok YM, Rinkel GJ, Algra A, van Gijn J. Study design and outcome measures in studies on aneurysmal subarachnoid hemorrhage. *Stroke*. 2002;33:2043–2046.
40. Teunissen LL, Rinkel GJ, Algra A, van Gijn J. Risk factors for subarachnoid hemorrhage: a systematic review. *Stroke*. 1996;27:544–549.
41. Knekt P, Reunanen A, Aho K, Heliovaara M, Rissanen A, Aromaa A, Impivaara O. Risk factors for subarachnoid hemorrhage in a longitudinal population study. *J Clin Epidemiol*. 1991;44:933–939.
42. Juvela S, Hillbom M, Numminen M, Koskinen P. Cigarette smoking and alcohol consumption as risk factors for aneurysmal subarachnoid hemorrhage. *Stroke*. 1993;24:639–646.
43. Pinto AN, Canhao P, Ferro JM. Seizures at the onset of subarachnoid haemorrhage. *J Neurol*. 1996;243:161–164.
44. Nanda A, Vannemreddy PS, Polin RS, Willis BK. Intracranial aneurysms and cocaine abuse: analysis of prognostic indicators. *Neurosurgery*. 2000;46:1063–1067.
45. Oyesiku NM, Colohan AR, Barrow DL, Reisner A. Cocaine-induced aneurysmal rupture: an emergent negative factor in the natural history of intracranial aneurysms? *Neurosurgery*. 1993;32:518–525.
46. Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, Morgenstern LB, Wilterdink JL, Horwitz RI. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med*. 2000;343:1826–1832.

47. Adams HP Jr, Putman SF, Kassell NF, Torner JC. Prevalence of diabetes mellitus among patients with subarachnoid hemorrhage. *Arch Neurol*. 1984;41:1033–1035.
48. Qureshi AI, Suarez JI, Parekh PD, Sung G, Geocadin R, Bhardwaj A, Tamargo RJ, Ulatowski JA. Risk factors for multiple intracranial aneurysms. *Neurosurgery*. 1998;43:22–26.
49. Juvela S. Risk factors for multiple intracranial aneurysms. *Stroke*. 2000; 31:392–397.
50. Ellamushi HE, Grieve JP, Jager HR, Kitchen ND. Risk factors for the formation of multiple intracranial aneurysms. *J Neurosurg*. 2001;94: 728–732.
51. Inagawa T. Seasonal variation in the incidence of aneurysmal subarachnoid hemorrhage in hospital- and community-based studies. *J Neurosurg*. 2002;96:497–509.
52. Gallerani M, Portaluppi F, Maida G, Chieregato A, Calzolari F, Trapella G, Manfredini R. Circadian and circannual rhythmicity in the occurrence of subarachnoid hemorrhage. *Stroke*. 1996;27:1793–1797.
53. Oyoshi T, Nakayama M, Kuratsu J. Relationship between aneurysmal subarachnoid hemorrhage and climatic conditions in the subtropical region, Amami-Oshima, in Japan. *Neurol Med Chir (Tokyo)*. 1999;39: 585–590.
54. Buxton N, Liu C, Dasic D, Moody P, Hope DT. Relationship of aneurysmal subarachnoid hemorrhage to changes in atmospheric pressure: results of a prospective study. *J Neurosurg*. 2001;95:391–392.
55. Unruptured intracranial aneurysms: risk of rupture and risks of surgical intervention: International Study of Unruptured Intracranial Aneurysms Investigators. *N Engl J Med*. 1998;339:1725–1733.
56. Locksley HB. Natural history of subarachnoid hemorrhage, intracranial aneurysms and arteriovenous malformations. *J Neurosurg*. 1966;25: 321–368.
57. Yasui N, Magarisawa S, Suzuki A, Nishimura H, Okudera T, Abe T. Subarachnoid hemorrhage caused by previously diagnosed, previously unruptured intracranial aneurysms: a retrospective analysis of 25 cases. *Neurosurgery*. 1996;39:1096–1100.
58. Ferguson GG, Peerless SJ, Drake CG. Natural history of intracranial aneurysms. *N Engl J Med*. 1981;305:99.
59. Hsiang JN, Liang EY, Lam JM, Zhu XL, Poon WS. The role of computed tomographic angiography in the diagnosis of intracranial aneurysms and emergent aneurysm clipping. *Neurosurgery*. 1996;38: 481–487.
60. Vieco PT, Morin EE 3rd, Gross CE. CT angiography in the examination of patients with aneurysm clips. *AJNR Am J Neuroradiol*. 1996;17: 455–457.
61. Ruggieri PM, Poulos N, Masaryk TJ, Ross JS, Obuchowski NA, Awad IA, Braun WE, Nally J, Lewin JS, Modic MT. Occult intracranial aneurysms in polycystic kidney disease: screening with MR angiography. *Radiology*. 1994;191:33–39.
62. Black WC. Intracranial aneurysm in adult polycystic kidney disease: is screening with MR angiography indicated? *Radiology*. 1994;191:18–20.
63. Lozano AM, Leblanc R. Cerebral aneurysms and polycystic kidney disease: a critical review. *Can J Neurol Sci*. 1992;19:222–227.
64. Fehlings MG, Gentili F. The association between polycystic kidney disease and cerebral aneurysms. *Can J Neurol Sci*. 1991;18:505–509.
65. Gabow PA, Schrier RW. Pathophysiology of adult polycystic kidney disease. *Adv Nephrol Necker Hosp*. 1989;18:19–32.
66. Kato T, Hattori H, Yorifuji T, Tashiro Y, Nakahata T. Intracranial aneurysms in Ehlers-Danlos syndrome type IV in early childhood. *Pediatr Neurol*. 2001;25:336–339.
67. Schievink WI. Genetics and aneurysm formation. *Neurosurg Clin N Am*. 1998;9:485–495.
68. de Paepe A, van Landegem W, de Keyser F, de Reuck J. Association of multiple intracranial aneurysms and collagen type III deficiency. *Clin Neurol Neurosurg*. 1988;90:53–56.
69. Ruigrok YM, Rinkel GJ, Wijmenga C. Familial intracranial aneurysms. *Stroke*. 2004;35:e59–60.
70. Wills S, Ronkainen A, van der Voet M, Kuivaniemi H, Helin K, Leinonen E, Frosen J, Niemela M, Jaaskelainen J, Hernesniemi J, Tromp G. Familial intracranial aneurysms: an analysis of 346 multiplex Finnish families. *Stroke*. 2003;34:1370–1374.
71. Kasuya H, Onda H, Takeshita M, Hori T, Takakura K. Clinical features of intracranial aneurysms in siblings. *Neurosurgery*. 2000;46: 1301–1305; discussion 1305–1306.
72. Stehbens WE. Familial intracranial aneurysms: an autopsy study. *Neurosurgery*. 1998;43:1258–1259.
73. Raaymakers TW, Rinkel GJ, Ramos LM. Initial and follow-up screening for aneurysms in families with familial subarachnoid hemorrhage. *Neurology*. 1998;51:1125–1130.
74. Huang TY, Lin CL, Chang CZ, Howng SL. Familial intracranial aneurysms. *Kaohsiung J Med Sci*. 1998;14:242–246.
75. Schievink WI. Genetics of intracranial aneurysms. *Neurosurgery*. 1997; 40:651–662.
76. Ronkainen A, Hernesniemi J, Ryynanen M, Puranen M, Kuivaniemi H. A ten percent prevalence of asymptomatic familial intracranial aneurysms: preliminary report on 110 magnetic resonance angiography studies in members of 21 Finnish familial intracranial aneurysm families. *Neurosurgery*. 1994;35:208–212.
77. Alberts MJ, Quinones A, Graffagnino C, Friedman A, Roses AD. Risk of intracranial aneurysms in families with subarachnoid hemorrhage. *Can J Neurol Sci*. 1995;22:121–125.
78. Sarti C, Tuomilehto J, Salomaa V, Sivenius J, Kaarsalo E, Narva EV, Salmi K, Torppa J. Epidemiology of subarachnoid hemorrhage in Finland from 1983 to 1985. *Stroke*. 1991;22:848–853.
79. Asari S, Ohmoto T. Natural history and risk factors of unruptured cerebral aneurysms. *Clin Neurol Neurosurg*. 1993;95:205–214.
80. Juvela S, Porras M, Heiskanen O. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *J Neurosurg*. 1993;79: 174–182.
81. Winn HR, Almaani WS, Berga SL, Jane JA, Richardson AE. The long-term outcome in patients with multiple aneurysms: incidence of late hemorrhage and implications for treatment of incidental aneurysms. *J Neurosurg*. 1983;59:642–651.
82. Dorsch NW, Young N, Kingston RJ, Compton JS. Early experience with spiral CT in the diagnosis of intracranial aneurysms. *Neurosurgery*. 1995;36:230–236.
83. Vieco PT, Shuman WP, Alsofrom GF, Gross CE. Detection of circle of Willis aneurysms in patients with acute subarachnoid hemorrhage: a comparison of CT angiography and digital subtraction angiography. *AJR Am J Roentgenol*. 1995;165:425–430.
84. King JT Jr, Berlin JA, Flamm ES. Morbidity and mortality from elective surgery for asymptomatic, unruptured, intracranial aneurysms: a meta-analysis. *J Neurosurg*. 1994;81:837–842.
85. Ronkainen A, Miettinen H, Karkola K, Papinaho S, Vanninen R, Puranen M, Hernesniemi J. Risk of harboring an unruptured intracranial aneurysm. *Stroke*. 1998;29:359–362.
86. Kojima M, Nagasawa S, Lee YE, Takeichi Y, Tsuda E, Mabuchi N. Asymptomatic familial cerebral aneurysms. *Neurosurgery*. 1998;43: 776–781.
87. Raaymakers TW. Aneurysms in relatives of patients with subarachnoid hemorrhage: frequency and risk factors: MARS Study Group: Magnetic Resonance Angiography in Relatives of Patients With Subarachnoid Hemorrhage. *Neurology*. 1999;53:982–988.
88. Kissela BM, Sauerbeck L, Woo D, Khoury J, Carrozzella J, Pancioli A, Jauch E, Moomaw CJ, Shukla R, Gebel J, Fontaine R, Broderick J. Subarachnoid hemorrhage: a preventable disease with a heritable component. *Stroke*. 2002;33:1321–1326.
89. Zhang B, Dhillon S, Geary I, Howell WM, Iannotti F, Day IN, Ye S. Polymorphisms in matrix metalloproteinase-1, -3, -9, and -12 genes in relation to subarachnoid hemorrhage. *Stroke*. 2001;32:2198–2202.
90. Rinne JK, Hernesniemi JA. De novo aneurysms: special multiple intracranial aneurysms. *Neurosurgery*. 1993;33:981–985.
91. Inagawa T, Hirano A. Autopsy study of unruptured incidental intracranial aneurysms. *Surg Neurol*. 1990;34:361–365.
92. Zacks DJ, Russell DB, Miller JD. Fortuitously discovered intracranial aneurysms. *Arch Neurol*. 1980;37:39–41.
93. David CA, Vishteh AG, Spetzler RF, Lemole M, Lawton MT, Partovi S. Late angiographic follow-up review of surgically treated aneurysms. *J Neurosurg*. 1999;91:396–401.
94. Miller CA, Hill SA, Hunt WE. "De novo" aneurysms: a clinical review. *Surg Neurol*. 1985;24:173–180.
95. Peterson EW, Cardoso ER. The blood-brain barrier following experimental subarachnoid hemorrhage, part 2: response to mercuric chloride infusion. *J Neurosurg*. 1983;58:345–351.
96. Hasan D, Tanghe HL. Distribution of cisternal blood in patients with acute hydrocephalus after subarachnoid hemorrhage. *Ann Neurol*. 1992; 31:374–378.
97. Broderick JP, Viscoli CM, Brott T, Kernan WN, Brass LM, Feldmann E, Morgenstern LB, Wilterdink JL, Horwitz RI, for the Hemorrhagic Stroke Project Investigators. Major risk factors for aneurysmal subarach-

noid hemorrhage in the young are modifiable. *Stroke*. 2003;34:1375–1381.

98. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood pressure, stroke, and coronary heart disease, part 2: short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet*. 1990;335:827–838.

99. Klag MJ, Whelton PK, Seidler AJ. Decline in US stroke mortality: demographic trends and antihypertensive treatment. *Stroke*. 1989;20:14–21.

100. Cooper R, Sempos C, Hsieh SC, Kovar MG. Slowdown in the decline of stroke mortality in the United States, 1978–1986. *Stroke*. 1990;21:1274–1279.

101. Broderick JP, Phillips SJ, Whisnant JP, O'Fallon WM, Bergstralh EJ. Incidence rates of stroke in the eighties: the end of the decline in stroke? *Stroke*. 1989;20:577–582.

102. Cross DT 3rd, Tirschwell DL, Clark MA, Tuden D, Derdeyn CP, Moran CJ, Dacey RG Jr. Mortality rates after subarachnoid hemorrhage: variations according to hospital case volume in 18 states. *J Neurosurg*. 2003;99:810–817.

103. Longstreth WT Jr, Nelson LM, Koepsell TD, van Belle G. Cigarette smoking, alcohol use, and subarachnoid hemorrhage. *Stroke*. 1992;23:1242–1249.

104. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, Speizer FE, Hennekens CH. Smoking cessation and decreased risk of stroke in women. *JAMA*. 1993;269:232–236.

105. Magnetic Resonance Angiography in Relatives of Patients With Subarachnoid Hemorrhage Study Group. Risks and benefits of screening for intracranial aneurysms in first-degree relatives of patients with sporadic subarachnoid hemorrhage. *N Engl J Med*. 1999;341:1344–1350.

106. Crawley F, Clifton A, Brown MM. Should we screen for familial intracranial aneurysm? *Stroke*. 1999;30:312–316.

107. Yoshimoto Y, Wakai S. Cost-effectiveness analysis of screening for asymptomatic, unruptured intracranial aneurysms: a mathematical model. *Stroke*. 1999;30:1621–1627.

108. Bonita R. Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case-control study. *Stroke*. 1986;17:831–835.

109. Gouliamos A, Gotsis E, Vlahos L, Samara C, Kapsalaki E, Rologis D, Kapsalakis Z, Papavasiliou C. Magnetic resonance angiography compared to intra-arterial digital subtraction angiography in patients with subarachnoid haemorrhage. *Neuroradiology*. 1992;35:46–49.

110. Jager HR, Mansmann U, Hausmann O, Partzsch U, Moseley IF, Taylor WJ. MRA versus digital subtraction angiography in acute subarachnoid haemorrhage: a blinded multireader study of prospectively recruited patients. *Neuroradiology*. 2000;42:313–326.

111. Wardlaw JM, White PM. The detection and management of unruptured intracranial aneurysms. *Brain*. 2000;123(pt 2):205–221.

112. Hop JW, Rinkel GJ, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. *Stroke*. 1997;28:660–664.

113. Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC Jr, Brott T, Hademenos G, Chyatte D, Rosenwasser R, Caroselli C. Recommendations for the management of patients with unruptured intracranial aneurysms: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke*. 2000;31:2742–2750.

114. Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. *Neurology*. 1998;50:1413–1418.

115. Mount LA. *Practical Applications*. Philadelphia, Pa: Lippincott; 1969.

116. Schievink WI, Wijdicks EF, Piepgras DG, Chu CP, O'Fallon WM, Whisnant JP. The poor prognosis of ruptured intracranial aneurysms of the posterior circulation. *J Neurosurg*. 1995;82:791–795.

117. Johnston SC. Effect of endovascular services and hospital volume on cerebral aneurysm treatment outcomes. *Stroke*. 2000;31:111–117.

118. Berman MF, Solomon RA, Mayer SA, Johnston SC, Yung PP. Impact of hospital-related factors on outcome after treatment of cerebral aneurysms. *Stroke*. 2003;34:2200–2207.

119. Johnston SC, Dudley RA, Gress DR, Ono L. Surgical and endovascular treatment of unruptured cerebral aneurysms at university hospitals. *Neurology*. 1999;52:1799–1805.

120. Johnston SC, Wilson CB, Halbach VV, Higashida RT, Dowd CF, McDermott MW, Applebury CB, Farley TL, Gress DR. Endovascular and surgical treatment of unruptured cerebral aneurysms: comparison of risks. *Ann Neurol*. 2000;48:11–19.

121. Sehba FA, Bederson JB. Mechanisms of acute brain injury after subarachnoid hemorrhage. *Neurol Res*. 2006;28:381–398.

122. Bederson JB, Germano IM, Guarino L. Cortical blood flow and cerebral perfusion pressure in a new noncraniotomy model of subarachnoid hemorrhage in the rat. *Stroke*. 1995;26:1086–1091.

123. Bederson JB, Levy AL, Ding WH, Kahn R, DiPerna CA, Jenkins AL 3rd, Vallabhajosyula P. Acute vasoconstriction after subarachnoid hemorrhage. *Neurosurgery*. 1998;42:352–360.

124. Kamiya K, Kuyama H, Symon L. An experimental study of the acute stage of subarachnoid hemorrhage. *J Neurosurg*. 1983;59:917–924.

125. Prunell GF, Mathiesen T, Svendgaard NA. Experimental subarachnoid hemorrhage: cerebral blood flow and brain metabolism during the acute phase in three different models in the rat. *Neurosurgery*. 2004;54:426–436.

126. Sehba FA, Ding WH, Chereshnev I, Bederson JB. Effects of S-nitrosoglutathione on acute vasoconstriction and glutamate release after subarachnoid hemorrhage. *Stroke*. 1999;30:1955–1961.

127. Nornes H. The role of intracranial pressure in the arrest of hemorrhage in patients with ruptured intracranial aneurysm. *J Neurosurg*. 1973;39:226–234.

128. Nornes H. Cerebral arterial flow dynamics during aneurysm haemorrhage. *Acta Neurochir (Wien)*. 1978;41:39–48.

129. Sehba FA, Schwartz AY, Chereshnev I, Bederson JB. Acute decrease in cerebral nitric oxide levels after subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2000;20:604–611.

130. Jackowski A, Crockard A, Burnstock G, Russell RR, Kristek F. The time course of intracranial pathophysiological changes following experimental subarachnoid haemorrhage in the rat. *J Cereb Blood Flow Metab*. 1990;10:835–849.

131. Takahashi S. Correlation of vasospasm and intracranial metabolism under experimental subarachnoid hemorrhage, part 1: in reference with the acid-base-balance of cerebral blood and cerebrospinal fluid [in Japanese]. *No To Shinkei*. 1978;30:777–787.

132. Sehba FA, Mostafa G, Friedrich V Jr, Bederson JB. Acute microvascular platelet aggregation after subarachnoid hemorrhage. *J Neurosurg*. 2005;102:1094–1100.

133. Sehba FA, Mostafa G, Knopman J, Friedrich V Jr, Bederson JB. Acute alterations in microvascular basal lamina after subarachnoid hemorrhage. *J Neurosurg*. 2004;101:633–640.

134. Locksley HB. Natural history of subarachnoid hemorrhage, intracranial aneurysms and arteriovenous malformations: based on 6368 cases in the cooperative study. *J Neurosurg*. 1966;25:219–239.

135. van Crevel H. Pitfalls in the diagnosis of rebleeding from intracranial aneurysm. *Clin Neurol Neurosurg*. 1980;82:1–9.

136. Kassell NF, Torner JC. Aneurysmal rebleeding: a preliminary report from the Cooperative Aneurysm Study. *Neurosurgery*. 1983;13:479–481.

137. Richardson AE, Jane JA, Yashon D. Prognostic factors in the untreated course of posterior communicating aneurysms. *Arch Neurol*. 1966;14:172–176.

138. Henderson WG, Torner JC, Nibbelink DW. Intracranial aneurysms and subarachnoid hemorrhage: report on a randomized treatment study, IV-B: regulated bed rest: statistical evaluation. *Stroke*. 1977;8:579–589.

139. Winn HR, Richardson AE, Jane JA. The long-term prognosis in untreated cerebral aneurysms, I: the incidence of late hemorrhage in cerebral aneurysm: a 10-year evaluation of 364 patients. *Ann Neurol*. 1977;1:358–370.

140. Hillman J, Fridriksson S, Nilsson O, Yu Z, Saveland H, Jakobsson KE. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. *J Neurosurg*. 2002;97:771–778.

141. Ohkuma H, Tsurutani H, Suzuki S. Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management. *Stroke*. 2001;32:1176–1180.

142. Laidlaw JD, Siu KH. Poor-grade aneurysmal subarachnoid hemorrhage: outcome after treatment with urgent surgery. *Neurosurgery*. 2003;53:1275–1280.

143. Wijdicks EF, Vermeulen M, Murray GD, Hijdra A, van Gijn J. The effects of treating hypertension following aneurysmal subarachnoid hemorrhage. *Clin Neurol Neurosurg*. 1990;92:111–117.

144. Torner JC, Kassell NF, Wallace RB, Adams HP Jr. Preoperative prognostic factors for rebleeding and survival in aneurysm patients receiving

antifibrinolytic therapy: report of the Cooperative Aneurysm Study. *Neurosurgery*. 1981;9:506–513.

145. Vermeulen M, Lindsay KW, Murray GD, Cheah F, Hijdra A, Muizelaar JP, Schannong M, Teasdale GM, van Crevel H, van Gijn J. Antifibrinolytic treatment in subarachnoid hemorrhage. *N Engl J Med*. 1984; 311:432–437.

146. Pare L, Delfino R, Leblanc R. The relationship of ventricular drainage to aneurysmal rebleeding. *J Neurosurg*. 1992;76:422–427.

147. Juvela S. Rebleeding from ruptured intracranial aneurysms. *Surg Neurol*. 1989;32:323–326.

148. McIver JI, Friedman JA, Wijdicks EF, Piepgras DG, Pichelmann MA, Toussaint LG 3rd, McClelland RL, Nichols DA, Atkinson JL. Preoperative ventriculostomy and rebleeding after aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2002;97:1042–1044.

149. Rosen DS, Macdonald RL. Grading of subarachnoid hemorrhage: modification of the World Federation of Neurosurgical Societies scale on the basis of data for a large series of patients. *Neurosurgery*. 2004;54: 566–575.

150. Rosen DS, Macdonald RL. Subarachnoid hemorrhage grading scales: a systematic review. *Neurocrit Care*. 2005;2:110–118.

151. Saveland H, Hillman J, Brandt L, Edner G, Jakobsson KE, Algers G. Overall outcome in aneurysmal subarachnoid hemorrhage: a prospective study from neurosurgical units in Sweden during a 1-year period. *J Neurosurg*. 1992;76:729–734.

152. Badjatia N, O'Donnell J, Baker JR, Huang D, Ayata C, Greer DM, Carter BS, Ogilvy CS, McDonald CT. Achieving normothermia in patients with febrile subarachnoid hemorrhage: feasibility and safety of a novel intravascular cooling catheter. *Neurocrit Care*. 2004;1:145–156.

153. Boet R, Chan MT, Poon WS, Wong GK, Wong HT, Gin T. Intravenous magnesium sulfate to improve outcome after aneurysmal subarachnoid hemorrhage: interim report from a pilot study. *Acta Neurochir Suppl*. 2005;95:263–264.

154. Chieregato A, Fainardi E, Morselli-Labate AM, Antonelli V, Compagnone C, Targa L, Kraus J, Servadei F. Factors associated with neurological outcome and lesion progression in traumatic subarachnoid hemorrhage patients. *Neurosurgery*. 2005;56:671–680.

155. Collignon FP, Friedman JA, Piepgras DG, Pichelmann MA, McIver JI, Toussaint LG 3rd, McClelland RL. Serum magnesium levels as related to symptomatic vasospasm and outcome following aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2004;1:441–448.

156. Coyne TJ, Montanera WJ, Macdonald RL, Wallace MC. Percutaneous transluminal angioplasty for cerebral vasospasm after subarachnoid hemorrhage. *Can J Surg*. 1994;37:391–396.

157. Egge A, Waterloo K, Sjoholm H, Ingebrigtsen T, Forsdahl S, Jacobsen EA, Romner B. Outcome 1 year after aneurysmal subarachnoid hemorrhage: relation between cognitive performance and neuroimaging. *Acta Neurol Scand*. 2005;112:76–80.

158. Juvela S, Siironen J. D-dimer as an independent predictor for poor outcome after aneurysmal subarachnoid hemorrhage. *Stroke*. 2006;37: 1451–1456.

159. Kato Y, Sano H, Dong PT, Panji N, Itezawa Y, Hayashi J, Kanno T. The effect of clipping and coiling in acute severe subarachnoid hemorrhage after International Subarachnoid Aneurysmal Trial (ISAT) results. *Minim Invasive Neurosurg*. 2005;48:224–227.

160. Klimo P Jr, Kestle JR, MacDonald JD, Schmidt RH. Marked reduction of cerebral vasospasm with lumbar drainage of cerebrospinal fluid after subarachnoid hemorrhage. *J Neurosurg*. 2004;100:215–224.

161. Kusumi M, Yamada M, Kitahara T, Endo M, Kan S, Iida H, Sagiuchi T, Fujii K. Rerupture of cerebral aneurysms during angiography: a retrospective study of 13 patients with subarachnoid hemorrhage. *Acta Neurochir (Wien)*. 2005;147:831–837.

162. Lang EW, Diehl RR, Mehdorn HM. Cerebral autoregulation testing after aneurysmal subarachnoid hemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. *Crit Care Med*. 2001;29:158–163.

163. Okten AI, Gezercan Y, Ergun R. Traumatic subarachnoid hemorrhage: a prospective study of 58 cases [in Turkish]. *Ulus Travma Acil Cerrahi Derg*. 2006;12:107–114.

164. Qureshi AI, Suarez JI, Bhardwaj A, Yahia AM, Tamargo RJ, Ulatowski JA. Early predictors of outcome in patients receiving hypervolemic and hypertensive therapy for symptomatic vasospasm after subarachnoid hemorrhage. *Crit Care Med*. 2000;28:824–829.

165. Qureshi AI, Sung GY, Razumovsky AY, Lane K, Straw RN, Ulatowski JA. Early identification of patients at risk for symptomatic vasospasm

after aneurysmal subarachnoid hemorrhage. *Crit Care Med*. 2000;28: 984–990.

166. Reinprecht A, Czech T, Asenbaum S, Podreka I, Schmidbauer M. Low cerebrovascular reserve capacity in long-term follow-up after subarachnoid hemorrhage. *Surg Neurol*. 2005;64:116–120.

167. Rosen D, Novakovic R, Goldenberg FD, Huo D, Baldwin ME, Frank JI, Rosengart AJ, Macdonald RL. Racial differences in demographics, acute complications, and outcomes in patients with subarachnoid hemorrhage: a large patient series. *J Neurosurg*. 2005;103:18–24.

168. Rothoerl RD, Axmann C, Pina AL, Woertgen C, Brawanski A. Possible role of the C-reactive protein and white blood cell count in the pathogenesis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg Anesthesiol*. 2006;18:68–72.

169. Sadamitsu D, Kuroda Y, Nagamitsu T, Tsuruta R, Inoue T, Ueda T, Nakashima K, Ito H, Maekawa T. Cerebrospinal fluid and plasma concentrations of nitric oxide metabolites in postoperative patients with subarachnoid hemorrhage. *Crit Care Med*. 2001;29:77–79.

170. Sarrafzadeh AS, Sakowitz OW, Kiening KL, Benndorf G, Lanksch WR, Unterberg AW. Bedside microdialysis: a tool to monitor cerebral metabolism in subarachnoid hemorrhage patients? *Crit Care Med*. 2002; 30:1062–1070.

171. Satoh A, Nakamura H, Kobayashi S, Miyata A, Matsutani M. Management of severe subarachnoid hemorrhage: significance of assessment of both neurological and systemic insults at acute stage. *Acta Neurochir Suppl*. 2005;94:59–63.

172. Schuiling WJ, de Weerd AW, Dennesen PJ, Algra A, Rinkel GJ. The simplified acute physiology score to predict outcome in patients with subarachnoid hemorrhage. *Neurosurgery*. 2005;57:230–236.

173. Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. *N Engl J Med*. 2006;354:387–396.

174. Toussaint LG 3rd, Friedman JA, Wijdicks EF, Piepgras DG, Pichelmann MA, McIver JI, McClelland RL, Nichols DA, Meyer FB, Atkinson JL. Survival of cardiac arrest after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2005;57:25–31.

175. Weiss N, Sanchez-Pena P, Roche S, Beaudeux JL, Colonne C, Coriat P, Puybasset L. Prognosis value of plasma S100B protein levels after subarachnoid aneurysmal hemorrhage. *Anesthesiology*. 2006;104: 658–666.

176. Wong GK, Chan MT, Boet R, Poon WS, Gin T. Intravenous magnesium sulfate after aneurysmal subarachnoid hemorrhage: a prospective randomized pilot study. *J Neurosurg Anesthesiol*. 2006;18:142–148.

177. Jennett B. Predicting outcome after head injury. *J R Coll Physicians Lond*. 1975;9:231–237.

178. Jennett B, Teasdale G, Knill-Jones R. Prognosis after severe head injury. *Ciba Found Symp*. 1975:309–324.

179. Vilkki J, Holst P, Ohman J, Servo A, Heiskanen O. Social outcome related to cognitive performance and computed tomographic findings after surgery for a ruptured intracranial aneurysm. *Neurosurgery*. 1990; 26:579–584.

180. Vilkki J, Holst P, Ohman J, Servo A, Heiskanen O. Cognitive deficits related to computed tomographic findings after surgery for a ruptured intracranial aneurysm. *Neurosurgery*. 1989;25:166–172.

181. Sonesson B, Ljunggren B, Saveland H, Brandt L. Cognition and adjustment after late and early operation for ruptured aneurysm. *Neurosurgery*. 1987;21:279–287.

182. Ropper AH, Zervas NT. Outcome 1 year after SAH from cerebral aneurysm: management morbidity, mortality, and functional status in 112 consecutive good-risk patients. *J Neurosurg*. 1984;60:909–915.

183. Ljunggren B, Sonesson B, Saveland H, Brandt L. Cognitive impairment and adjustment in patients without neurological deficits after aneurysmal SAH and early operation. *J Neurosurg*. 1985;62:673–679.

184. Romner B, Sonesson B, Ljunggren B, Brandt L, Saveland H, Holtas S. Late magnetic resonance imaging related to neurobehavioral functioning after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 1989;25: 390–396.

185. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, Sandercock P, for the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet*. 2005;366:809–817.

186. Rankin J. Cerebral vascular accidents in patients over the age of 60, II: prognosis. *Scott Med J*. 1957;2:200–215.

187. Bassi P, Bandera R, Loiero M, Tognoni G, Mangoni A. Warning signs in subarachnoid hemorrhage: a cooperative study. *Acta Neurol Scand*. 1991;84:277–281.

188. Weir B. Antifibrinolytics in subarachnoid hemorrhage: do they have a role? No. *Arch Neurol*. 1987;44:116–118.

189. Schievink WI. Intracranial aneurysms. *N Engl J Med*. 1997;336:28–40.

190. Yano K, Reed DM, MacLean CJ. Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. *Stroke*. 1989;20:1460–1465.

191. Fontanarosa PB. Recognition of subarachnoid hemorrhage. *Ann Emerg Med*. 1989;18:1199–1205.

192. Kassell NF, Kongable GL, Torner JC, Adams HP Jr, Mazuz H. Delay in referral of patients with ruptured aneurysms to neurosurgical attention. *Stroke*. 1985;16:587–590.

193. Mayberg MR. Warning leaks and subarachnoid hemorrhage. *West J Med*. 1990;153:549–550.

194. Edlow JA. Diagnosis of subarachnoid hemorrhage in the emergency department. *Emerg Med Clin North Am*. 2003;21:73–87.

195. Edlow JA. Diagnosis of subarachnoid hemorrhage. *Neurocrit Care*. 2005;2:99–109.

196. Jakobsson KE, Saveland H, Hillman J, Edner G, Zygmunt S, Brandt L, Pellettieri L. Warning leak and management outcome in aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 1996;85:995–999.

197. Hauerberg J, Andersen BB, Eskesen V, Rosenorn J, Schmidt K. Importance of the recognition of a warning leak as a sign of a ruptured intracranial aneurysm. *Acta Neurol Scand*. 1991;83:61–64.

198. Juvela S. Minor leak before rupture of an intracranial aneurysm and subarachnoid hemorrhage of unknown etiology. *Neurosurgery*. 1992;30:7–11.

199. Leblanc R. The minor leak preceding subarachnoid hemorrhage. *J Neurosurg*. 1987;66:35–39.

200. Sundaram MB, Chow F. Seizures associated with spontaneous subarachnoid hemorrhage. *Can J Neurol Sci*. 1986;13:229–231.

201. Ohman J. Hypertension as a risk factor for epilepsy after aneurysmal subarachnoid hemorrhage and surgery. *Neurosurgery*. 1990;27:578–581.

202. Vale FL, Bradley EL, Fisher WS 3rd. The relationship of subarachnoid hemorrhage and the need for postoperative shunting. *J Neurosurg*. 1997;86:462–466.

203. Morgenstern LB, Luna-Gonzales H, Huber JC Jr, Wong SS, Uthman MO, Gurian JH, Castillo PR, Shaw SG, Frankowski RF, Grotta JC. Worst headache and subarachnoid hemorrhage: prospective, modern computed tomography and spinal fluid analysis. *Ann Emerg Med*. 1998;32(pt 1):297–304.

204. van der Wee N, Rinkel GJ, Hasan D, van Gijn J. Detection of subarachnoid haemorrhage on early CT: is lumbar puncture still needed after a negative scan? *J Neurol Neurosurg Psychiatry*. 1995;58:357–359.

205. Sidman R, Connolly E, Lemke T. Subarachnoid hemorrhage diagnosis: lumbar puncture is still needed when the computed tomography scan is normal. *Acad Emerg Med*. 1996;3:827–831.

206. Sames TA, Storrow AB, Finkelstein JA, Magoon MR. Sensitivity of new-generation computed tomography in subarachnoid hemorrhage. *Acad Emerg Med*. 1996;3:16–20.

207. Tomasello F, d'Avella D, de Divitiis O. Does lamina terminalis fenestration reduce the incidence of chronic hydrocephalus after subarachnoid hemorrhage? *Neurosurgery*. 1999;45:827–831.

208. van Gijn J, van Dongen KJ. The time course of aneurysmal haemorrhage on computed tomograms. *Neuroradiology*. 1982;23:153–156.

209. Wood MJ, Dimeski G, Nowitzke AM. CSF spectrophotometry in the diagnosis and exclusion of spontaneous subarachnoid haemorrhage. *J Clin Neurosci*. 2005;12:142–146.

210. Shah KH, Edlow JA. Distinguishing traumatic lumbar puncture from true subarachnoid hemorrhage. *J Emerg Med*. 2002;23:67–74.

211. UK National External Quality Assessment Scheme for Immunochemistry Working Group. National guidelines for analysis of cerebrospinal fluid for bilirubin in suspected subarachnoid haemorrhage. *Ann Clin Biochem*. 2003;40(pt 5):481–488.

212. Wijdicks EF, Kerkhoff H, van Gijn J. Long-term follow-up of 71 patients with thunderclap headache mimicking subarachnoid haemorrhage. *Lancet*. 1988;2:68–70.

213. Markus HS. A prospective follow up of thunderclap headache mimicking subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*. 1991;54:1117–1118.

214. Wiesmann M, Mayer TE, Yousry I, Medele R, Hamann GF, Bruckmann H. Detection of hyperacute subarachnoid hemorrhage of the brain by using magnetic resonance imaging. *J Neurosurg*. 2002;96:684–689.

215. Mitchell P, Wilkinson ID, Hoggard N, Paley MN, Jellinek DA, Powell T, Romanowski C, Hodgson T, Griffiths PD. Detection of subarachnoid haemorrhage with magnetic resonance imaging. *J Neurol Neurosurg Psychiatry*. 2001;70:205–211.

216. Yuan MK, Lai PH, Chen JY, Hsu SS, Liang HL, Yeh LR, Chen CK, Wu MT, Pan HB, Yang CF. Detection of subarachnoid hemorrhage at acute and subacute/chronic stages: comparison of four magnetic resonance imaging pulse sequences and computed tomography. *J Chin Med Assoc*. 2005;68:131–137.

217. van Gijn J, van Dongen KJ. Computed tomography in the diagnosis of subarachnoid haemorrhage and ruptured aneurysm. *Clin Neurol Neurosurg*. 1980;82:11–24.

218. van Gijn J, van Dongen KJ. Computerized tomography in subarachnoid hemorrhage: difference between patients with and without an aneurysm on angiography. *Neurology*. 1980;30:538–539.

219. Huston J 3rd, Nichols DA, Luetmer PH, Goodwin JT, Meyer FB, Wiebers DO, Weaver AL. Blinded prospective evaluation of sensitivity of MR angiography to known intracranial aneurysms: importance of aneurysm size. *AJNR Am J Neuroradiol*. 1994;15:1607–1614.

220. Schuierer G, Huk WJ, Laub G. Magnetic resonance angiography of intracranial aneurysms: comparison with intra-arterial digital subtraction angiography. *Neuroradiology*. 1992;35:50–54.

221. Anzalone N, Triulzi F, Scotti G. Acute subarachnoid haemorrhage: 3D time-of-flight MR angiography versus intra-arterial digital angiography. *Neuroradiology*. 1995;37:257–261.

222. Horikoshi T, Fukamachi A, Nishi H, Fukasawa I. Detection of intracranial aneurysms by three-dimensional time-of-flight magnetic resonance angiography. *Neuroradiology*. 1994;36:203–207.

223. Atlas SW. Magnetic resonance imaging of intracranial aneurysms. *Neuroimaging Clin N Am*. 1997;7:709–720.

224. Wilcock D, Jaspan T, Holland I, Cherryman G, Worthington B. Comparison of magnetic resonance angiography with conventional angiography in the detection of intracranial aneurysms in patients presenting with subarachnoid haemorrhage. *Clin Radiol*. 1996;51:330–334.

225. Vieco PT. CT angiography of the intracranial circulation. *Neuroimaging Clin N Am*. 1998;8:577–592.

226. Korogi Y, Takahashi M, Katada K, Ogura Y, Hasuo K, Ochi M, Utsunomiya H, Abe T, Imakita S. Intracranial aneurysms: detection with three-dimensional CT angiography with volume rendering: comparison with conventional angiographic and surgical findings. *Radiology*. 1999;211:497–506.

227. Hope JK, Wilson JL, Thomson FJ. Three-dimensional CT angiography in the detection and characterization of intracranial berry aneurysms. *AJNR Am J Neuroradiol*. 1996;17:439–445.

228. Alberico RA, Patel M, Casey S, Jacobs B, Maguire W, Decker R. Evaluation of the circle of Willis with three-dimensional CT angiography in patients with suspected intracranial aneurysms. *AJNR Am J Neuroradiol*. 1995;16:1571–1578.

229. Liang EY, Chan M, Hsiang JH, Walkden SB, Poon WS, Lam WW, Metreweli C. Detection and assessment of intracranial aneurysms: value of CT angiography with shaded-surface display. *AJR Am J Roentgenol*. 1995;165:1497–1502.

230. Ogawa T, Okudera T, Noguchi K, Sasaki N, Inugami A, Uemura K, Yasui N. Cerebral aneurysms: evaluation with three-dimensional CT angiography. *AJNR Am J Neuroradiol*. 1996;17:447–454.

231. Wilms G, Guffens M, Gryspeerdt S, Bosmans H, Maaly M, Boulanger T, Van Hoe L, Marchal G, Baert A. Spiral CT of intracranial aneurysms: correlation with digital subtraction and magnetic resonance angiography. *Neuroradiology*. 1996;38(suppl 1):S20–S25.

232. Velthuis BK, Rinkel GJ, Ramos LM, Witkamp TD, Berkelbach van der Sprenkel JW, Vandertop WP, van Leeuwen MS. Subarachnoid hemorrhage: aneurysm detection and preoperative evaluation with CT angiography. *Radiology*. 1998;208:423–430.

233. Velthuis BK, Van Leeuwen MS, Witkamp TD, Ramos LM, Berkelbach van Der Sprenkel JW, Rinkel GJ. Computerized tomography angiography in patients with subarachnoid hemorrhage: from aneurysm detection to treatment without conventional angiography. *J Neurosurg*. 1999;91:761–767.

234. Anderson GB, Ashforth R, Steinke DE, Findlay JM. CT angiography for the detection of cerebral vasospasm in patients with acute subarachnoid hemorrhage. *AJNR Am J Neuroradiol*. 2000;21:1011–1015.

235. Matsumoto M, Sato M, Nakano M, Endo Y, Watanabe Y, Sasaki T, Suzuki K, Kodama N. Three-dimensional computerized tomography angiography-guided surgery of acutely ruptured cerebral aneurysms. *J Neurosurg*. 2001;94:718–727.

236. Cioffi F, Pasqualin A, Cavazzani P, Da Pian R. Subarachnoid haemor-rhage of unknown origin: clinical and tomographical aspects. *Acta Neurochir (Wien)*. 1989;97:31–39.

237. Forster DM, Steiner L, Hakanson S, Bergvall U. The value of repeat pan-angiography in cases of unexplained subarachnoid hemorrhage. *J Neurosurg*. 1978;48:712–716.

238. Gilbert JW, Lee C, Young B. Repeat cerebral pan-angiography in subarachnoid hemorrhage of unknown etiology. *Surg Neurol*. 1990;33:19–21.

239. Oshiro EM, Walter KA, Piantadosi S, Witham TF, Tamargo RJ. A new subarachnoid hemorrhage grading system based on the Glasgow Coma Scale: a comparison with the Hunt and Hess and World Federation of Neurological Surgeons Scales in a clinical series. *Neurosurgery*. 1997;41:140–147.

240. Kassell NF, Torner JC, Adams HP Jr. Antifibrinolytic therapy in the acute period following aneurysmal subarachnoid hemorrhage: pre-liminary observations from the Cooperative Aneurysm Study. *J Neurosurg*. 1984;61:225–230.

241. Kassell NF, Boarini DJ, Adams HP Jr, Sahs AL, Graf CJ, Torner JC, Gerk MK. Overall management of ruptured aneurysm: comparison of early and late operation. *Neurosurgery*. 1981;9:120–128.

242. Adams HP Jr, Nibbelink DW, Torner JC, Sahs AL. Antifibrinolytic therapy in patients with aneurysmal subarachnoid hemorrhage: a report of the Cooperative Aneurysm Study. *Arch Neurol*. 1981;38:25–29.

243. Nishioka H, Torner JC, Graf CJ, Kassell NF, Sahs AL, Goettler LC. Cooperative Study of Intracranial Aneurysms and Subarachnoid Hem-orrhage: a long-term prognostic study, II: ruptured intracranial aneu-rysms managed conservatively. *Arch Neurol*. 1984;41:1142–1146.

244. Nishioka H, Torner JC, Graf CJ, Kassell NF, Sahs AL, Goettler LC. Cooperative Study of Intracranial Aneurysms and Subarachnoid Hem-orrhage: a long-term prognostic study, III: subarachnoid hemorrhage of undetermined etiology. *Arch Neurol*. 1984;41:1147–1151.

245. Stornelli SA, French JD. Subarachnoid hemorrhage: factors in prognosis and management. *J Neurosurg*. 1964;21:769–780.

246. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Koike T, Tanaka R. Ultra-early rebleeding in spontaneous subarachnoid hemorrhage. *J Neurosurg*. 1996;84:35–42.

247. Naidech AM, Janjua N, Kreiter KT, Ostapkovich ND, Fitzsimmons BF, Parra A, Commichau C, Connolly ES, Mayer SA. Predictors and impact of aneurysm rebleeding after subarachnoid hemorrhage. *Arch Neurol*. 2005;62:410–416.

248. Rose JC, Mayer SA. Optimizing blood pressure in neurological emer-gencies. *Neurocrit Care*. 2004;1:287–299.

249. Tsementzis SA, Hitchcock ER, Meyer CH. Benefits and risks of antifi-brinolytic therapy in the management of ruptured intracranial aneu-rysms: a double-blind placebo-controlled study. *Acta Neurochir (Wien)*. 1990;102:1–10.

250. Pinna G, Pasqualin A, Vivenza C, Da Pian R. Rebleeding, ischaemia and hydrocephalus following anti-fibrinolytic treatment for ruptured cerebral aneurysms: a retrospective clinical study. *Acta Neurochir (Wien)*. 1988;93:77–87.

251. Wijdicks EF, Hasan D, Lindsay KW, Brouwers PJ, Hatfield R, Murray GD, van Gijn J, Vermeulen M. Short-term tranexamic acid treatment in aneurysmal subarachnoid hemorrhage. *Stroke*. 1989;20:1674–1679.

252. Guglielmi G, Vinuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach, part 2: preliminary clinical experience. *J Neurosurg*. 1991;75:8–14.

253. Bardach NS, Zhao S, Gress DR, Lawton MT, Johnston SC. Association between subarachnoid hemorrhage outcomes and number of cases treated at California hospitals. *Stroke*. 2002;33:1851–1856.

254. Raftopoulos C, Goffette P, Vaz G, Ramzi N, Scholtes JL, Wittebole X, Mathurin P. Surgical clipping may lead to better results than coil embo-lization: results from a series of 101 consecutive unruptured intracranial aneurysms. *Neurosurgery*. 2003;52:1280–1287.

255. Raftopoulos C, Mathurin P, Boscherini D, Billa RF, Van Boven M, Hantson P. Prospective analysis of aneurysm treatment in a series of 103 consecutive patients when endovascular embolization is considered the first option. *J Neurosurg*. 2000;93:175–182.

256. Brilstra EH, Rinkel GJ, van der Graaf Y, van Rooij WJ, Algra A. Treatment of intracranial aneurysms by embolization with coils: a sys-tematic review. *Stroke*. 1999;30:470–476.

257. Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC, for the International Study of Unruptured Intracranial Aneurysms Investigators.

258. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, Holman R, for the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet*. 2002;360:1267–1274.

259. Koivisto T, Vanninen R, Hurskainen H, Saari T, Hernesniemi J, Vapalahti M. Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms: a prospective randomized study. *Stroke*. 2000;31:2369–2377.

260. Byrne JV. Long-term outcomes of Guglielmi detachable coil packing for acutely ruptured cerebral aneurysms. *AJNR Am J Neuroradiol*. 1999;20:1184.

261. Cognard C, Weill A, Castaings L, Rey A, Moret J. Intracranial berry aneurysms: angiographic and clinical results after endovascular treatment. *Radiology*. 1998;206:499–510.

262. Uda K, Goto K, Ogata N, Izumi N, Nagata S, Matsuno H. Embolization of cerebral aneurysms using Guglielmi detachable coils: problems and treatment plans in the acute stage after subarachnoid hemorrhage and long-term efficiency. *Neurol Med Chir (Tokyo)*. 1998;38:143–152.

263. Graves VB, Strother CM, Duff TA, Perl J 2nd. Early treatment of ruptured aneurysms with Guglielmi detachable coils: effect on sub-sequent bleeding. *Neurosurgery*. 1995;37:640–647.

264. Casasco AE, Aymard A, Gobin YP, Houdart E, Rogopoulos A, George B, Hodes JE, Cophignon J, Merland JJ. Selective endovascular treatment of 71 intracranial aneurysms with platinum coils. *J Neurosurg*. 1993;79:3–10.

265. Sluzewski M, van Rooij WJ. Early rebleeding after coiling of ruptured cerebral aneurysms: incidence, morbidity, and risk factors. *AJNR Am J Neuroradiol*. 2005;26:1739–1743.

266. CARAT Investigators. Rates of delayed rebleeding from intracranial aneurysms are low after surgical and endovascular treatment. *Stroke*. 2006;37:1437–1442.

267. Bavinzski G, Killer M, Gruber A, Reinprecht A, Gross CE, Richling B. Treatment of basilar artery bifurcation aneurysms by using Guglielmi detachable coils: a 6-year experience. *J Neurosurg*. 1999;90:843–852.

268. Eskridge JM, Song JK. Endovascular embolization of 150 basilar tip aneurysms with Guglielmi detachable coils: results of the Food and Drug Administration multicenter clinical trial. *J Neurosurg*. 1998;89:81–86.

269. Lempert TE, Malek AM, Halbach VV, Phatouros CC, Meyers PM, Dowd CF, Higashida RT. Endovascular treatment of ruptured posterior circulation cerebral aneurysms: clinical and angiographic outcomes. *Stroke*. 2000;31:100–110.

270. Gruber DP, Zimmerman GA, Tomsick TA, van Loveren HR, Link MJ, Tew JM Jr. A comparison between endovascular and surgical man-agement of basilar artery apex aneurysms. *J Neurosurg*. 1999;90:868–874.

271. Raymond J, Roy D. Safety and efficacy of endovascular treatment of acutely ruptured aneurysms. *Neurosurgery*. 1997;41:1235–1245.

272. Malisch TW, Guglielmi G, Vinuela F, Duckwiler G, Gobin YP, Martin NA, Frazee JG. Intracranial aneurysms treated with the Guglielmi detachable coil: midterm clinical results in a consecutive series of 100 patients. *J Neurosurg*. 1997;87:176–183.

273. Murayama Y, Vinuela F, Duckwiler GR, Gobin YP, Guglielmi G. Embolization of incidental cerebral aneurysms by using the Guglielmi detachable coil system. *J Neurosurg*. 1999;90:207–214.

274. Vinuela F, Duckwiler G, Mawad M. Guglielmi detachable coil embo-lization of acute intracranial aneurysm: perioperative anatomical and clinical outcome in 403 patients. *J Neurosurg*. 1997;86:475–482.

275. Guglielmi G, Vinuela F, Duckwiler G, Dion J, Lylyk P, Berenstein A, Strother C, Graves V, Halbach V, Nichols D, et al. Endovascular treatment of posterior circulation aneurysms by electrothrombosis using electrically detachable coils. *J Neurosurg*. 1992;77:515–524.

276. Makoui AS, Smith DA, Evans AJ, Cahill DW. Early aneurysm recur-rence after technically satisfactory Guglielmi detachable coil therapy: is early surveillance needed? Case report. *J Neurosurg*. 2000;92:355–358.

277. Manabe H, Fujita S, Hatayama T, Suzuki S, Yagihashi S. Rerupture of coil-embolized aneurysm during long-term observation: case report. *J Neurosurg*. 1998;88:1096–1098.

278. Tateshima S, Murayama Y, Gobin YP, Duckwiler GR, Guglielmi G, Vinuela F. Endovascular treatment of basilar tip aneurysms using

Guglielmi detachable coils: anatomic and clinical outcomes in 73 patients from a single institution. *Neurosurgery*. 2000;47:1332–1339.

279. Kuether TA, Nesbit GM, Barnwell SL. Clinical and angiographic outcomes, with treatment data, for patients with cerebral aneurysms treated with Guglielmi detachable coils: a single-center experience. *Neurosurgery*. 1998;43:1016–1025.

280. Mawad M. Subarachnoid hemorrhage due to late recurrence of a previously unruptured aneurysm after complete endovascular occlusion. *AJNR Am J Neuroradiol*. 1998;19:1810–1811.

281. Hayakawa M, Murayama Y, Duckwiler GR, Gobin YP, Guglielmi G, Vinuela F. Natural history of the neck remnant of a cerebral aneurysm treated with the Guglielmi detachable coil system. *J Neurosurg*. 2000; 93:561–568.

282. Murayama Y, Nien YL, Duckwiler G, Gobin YP, Jahan R, Frazee J, Martin N, Vinuela F. Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. *J Neurosurg*. 2003;98:959–966.

283. Farb RI, Nag S, Scott JN, Willinsky RA, Marotta TR, Montanera WJ, Tomlinson G, Terbrugge KG. Surveillance of intracranial aneurysms treated with detachable coils: a comparison of MRA techniques. *Neuroradiology*. 2005;47:507–515.

284. Mericle RA, Wakhloo AK, Lopes DK, Lanzino G, Guterman LR, Hopkins LN. Delayed aneurysm regrowth and recanalization after Guglielmi detachable coil treatment: case report. *J Neurosurg*. 1998;89: 142–145.

285. Regli L, Dehdashti AR, Uske A, de Tribolet N. Endovascular coiling compared with surgical clipping for the treatment of unruptured middle cerebral artery aneurysms: an update. *Acta Neurochir Suppl*. 2002;82: 41–46.

286. Regli L, Uske A, de Tribolet N. Endovascular coil placement compared with surgical clipping for the treatment of unruptured middle cerebral artery aneurysms: a consecutive series. *J Neurosurg*. 1999;90: 1025–1030.

287. Suzuki J, Yoshimoto T, Kayama T. Surgical treatment of middle cerebral artery aneurysms. *J Neurosurg*. 1984;61:17–23.

288. Khanna RK, Malik GM, Qureshi N. Predicting outcome following surgical treatment of unruptured intracranial aneurysms: a proposed grading system. *J Neurosurg*. 1996;84:49–54.

289. Rinne J, Hernesniemi J, Niskanen M, Vapalahti M. Analysis of 561 patients with 690 middle cerebral artery aneurysms: anatomic and clinical features as correlated to management outcome. *Neurosurgery*. 1996;38:2–11.

290. Halbach VV, Higashida RT, Dowd CF, Urwin RW, Balousek PA, Lempert TE, Hieshima GB. Cavernous internal carotid artery aneurysms treated with electrolytically detachable coils. *J Neuroophthalmol*. 1997; 17:231–239.

291. Halbach VV, Higashida RT, Dowd CF, Barnwell SL, Fraser KW, Smith TP, Teitelbaum GP, Hieshima GB. The efficacy of endosaccular aneurysm occlusion in alleviating neurological deficits produced by mass effect. *J Neurosurg*. 1994;80:659–666.

292. Cognard C, Weill A, Spelle L, Piotin M, Castaings L, Rey A, Moret J. Long-term angiographic follow-up of 169 intracranial berry aneurysms occluded with detachable coils. *Radiology*. 1999;212:348–356.

293. Gruber A, Killer M, Bavinzski G, Richling B. Clinical and angiographic results of endosaccular coiling treatment of giant and very large intracranial aneurysms: a 7-year, single-center experience. *Neurosurgery*. 1999;45:793–803.

294. Casasco A, George B. Endovascular treatment of saccular intracranial aneurysm. *J Neurosurg Sci*. 1998;42(suppl 1):125–126.

295. McDougall CG, Halbach VV, Dowd CF, Higashida RT, Larsen DW, Hieshima GB. Endovascular treatment of basilar tip aneurysms using electrolytically detachable coils. *J Neurosurg*. 1996;84:393–399.

296. Turjman F, Massoud TF, Sayre J, Vinuela F. Predictors of aneurysmal occlusion in the period immediately after endovascular treatment with detachable coils: a multivariate analysis. *AJNR Am J Neuroradiol*. 1998; 19:1645–1651.

297. Debrun GM, Aletich VA, Kehrli P, Misra M, Ausman JI, Charbel F. Selection of cerebral aneurysms for treatment using Guglielmi detachable coils: the preliminary University of Illinois at Chicago experience. *Neurosurgery*. 1998;43:1281–1295.

298. Hope JK, Byrne JV, Molyneux AJ. Factors influencing successful angiographic occlusion of aneurysms treated by coil embolization. *AJNR Am J Neuroradiol*. 1999;20:391–399.

299. Fernandez-Zubillaga A, Guglielmi G, Vinuela F, Duckwiler GR. Endovascular occlusion of intracranial aneurysms with electrically detachable coils: correlation of aneurysm neck size and treatment results. *AJNR Am J Neuroradiol*. 1994;15:815–820.

300. Yundt KD, Grubb RL Jr, Diringer MN, Powers WJ. Cerebral hemodynamic and metabolic changes caused by brain retraction after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 1997;40:442–450.

301. Kremer C, Groden C, Hansen HC, Grzyska U, Zeumer H. Outcome after endovascular treatment of Hunt and Hess grade IV or V aneurysms: comparison of anterior versus posterior circulation. *Stroke*. 1999;30: 2617–2622.

302. Malek AM, Higashida RT, Phatouros CC, Dowd CF, Halbach VV. Treatment of an intracranial aneurysm using a new three-dimensional-shape Guglielmi detachable coil: technical case report. *Neurosurgery*. 1999;44:1142–1144.

303. Yang X, Wu Z, Li Y, Tang J, Sun Y, Liu Z, Yin K. Re-evaluation of cellulose acetate polymer: angiographic findings and histological studies. *Surg Neurol*. 2001;55:116–122.

304. Levy DI, Ku A. Balloon-assisted coil placement in wide-necked aneurysms: technical note. *J Neurosurg*. 1997;86:724–727.

305. Mericle RA, Wakhloo AK, Rodriguez R, Guterman LR, Hopkins LN. Temporary balloon protection as an adjunct to endosaccular coiling of wide-necked cerebral aneurysms: technical note. *Neurosurgery*. 1997; 41:975–978.

306. Aletich VA, Debrun GM, Misra M, Charbel F, Ausman JI. The remodeling technique of balloon-assisted Guglielmi detachable coil placement in wide-necked aneurysms: experience at the University of Illinois at Chicago. *J Neurosurg*. 2000;93:388–396.

307. Malek AM, Halbach VV, Phatouros CC, Lempert TE, Meyers PM, Dowd CF, Higashida RT. Balloon-assist technique for endovascular coil embolization of geometrically difficult intracranial aneurysms. *Neurosurgery*. 2000;46:1397–1406.

308. Higashida RT, Smith W, Gress D, Urwin R, Dowd CF, Balousek PA, Halbach VV. Intravascular stent and endovascular coil placement for a ruptured fusiform aneurysm of the basilar artery: case report and review of the literature. *J Neurosurg*. 1997;87:944–949.

309. Mericle RA, Lanzino G, Wakhloo AK, Guterman LR, Hopkins LN. Stenting and secondary coiling of intracranial internal carotid artery aneurysm: technical case report. *Neurosurgery*. 1998;43:1229–1234.

310. Sekhon LH, Morgan MK, Sorby W, Grinnell V. Combined endovascular stent implantation and endosaccular coil placement for the treatment of a wide-necked vertebral artery aneurysm: technical case report. *Neurosurgery*. 1998;43:380–383.

311. Lavine SD, Larsen DW, Giannotta SL, Teitelbaum GP. Parent vessel Guglielmi detachable coil herniation during wide-necked aneurysm embolization: treatment with intracranial stent placement: two technical case reports. *Neurosurgery*. 2000;46:1013–1017.

312. Lownie SP, Pelz DM, Fox AJ. Endovascular therapy of a large vertebral artery aneurysm using stent and coils. *Can J Neurol Sci*. 2000;27: 162–165.

313. Wakhloo AK, Lanzino G, Lieber BB, Hopkins LN. Stents for intracranial aneurysms: the beginning of a new endovascular era? *Neurosurgery*. 1998; 43:377–379.

314. Phatouros CC, Sasaki TY, Higashida RT, Malek AM, Meyers PM, Dowd CF, Halbach VV. Stent-supported coil embolization: the treatment of fusiform and wide-neck aneurysms and pseudoaneurysms. *Neurosurgery*. 2000;47:107–113.

315. Singh V, Gress DR, Higashida RT, Dowd CF, Halbach VV, Johnston SC. The learning curve for coil embolization of unruptured intracranial aneurysms. *AJNR Am J Neuroradiol*. 2002;23:768–771.

316. Thornton J, Dovey Z, Alazzaz A, Misra M, Aletich VA, Debrun GM, Ausman JI, Charbel FT. Surgery following endovascular coiling of intracranial aneurysms. *Surg Neurol*. 2000;54:352–360.

317. Raymond J, Guilbert F, Weill A, Georganos SA, Juravsky L, Lambert A, Lamoureux J, Chagnon M, Roy D. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. *Stroke*. 2003;34:1398–1403.

318. Derdeyn CP, Graves VB, Turski PA, Masaryk AM, Strother CM. MR angiography of saccular aneurysms after treatment with Guglielmi detachable coils: preliminary experience. *AJNR Am J Neuroradiol*. 1997;18:279–286.

319. Cottier JP, Bleuzen-Couthon A, Gallas S, Vinikoff-Sonier CB, Bertrand P, Domengie F, Barantin L, Herbreteau D. Follow-up of intracranial aneurysms treated with detachable coils: comparison of plain radiographs, 3D time-of-flight MRA and digital subtraction angiography. *Neuroradiology*. 2003;45:818–824.

320. Sahs AL, Perret GE, Locksley HB, Nishioka H, eds. *Intracranial Aneurysms and Subarachnoid Hemorrhage: A Cooperative Study*. Philadelphia, Pa: JB Lippincott Co; 1969.

321. Skultety FM, Nishioka H. The results of intracranial surgery in the treatment of aneurysms. In: Sahs AL, Perret GE, Locksley HB, Nishioka H, eds. *Intracranial Aneurysms and Subarachnoid Hemorrhage: A Cooperative Study*. Philadelphia, Pa: JB Lippincott Co; 1969:173–193.

322. Samson DS, Hodosh RM, Reid WR, Beyer CW, Clark WK. Risk of intracranial aneurysm surgery in the good grade patient: early versus late operation. *Neurosurgery*. 1979;5:422–426.

323. Winn HR, Richardson AE, O'Brien W, Jane JA. The long-term prognosis in untreated cerebral aneurysms, II: late morbidity and mortality. *Ann Neurol*. 1978;4:418–426.

324. Brilstra EH, Algra A, Rinkel GJ, Tulleken CA, van Gijn J. Effectiveness of neurosurgical clip application in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2002;97:1036–1041.

325. Feuerberg I, Lindquist C, Lindqvist M, Steiner L. Natural history of postoperative aneurysm rests. *J Neurosurg*. 1987;66:30–34.

326. Lin T, Fox AJ, Drake CG. Regrowth of aneurysm sacs from residual neck following aneurysm clipping. *J Neurosurg*. 1989;70:556–560.

327. Dutton J. Acrylic investment of intracranial aneurysms: a report of 12 years' experience. *J Neurosurg*. 1969;31:652–657.

328. Hugosson R. The value of reinforcing intracranial aneurysms with plastic coating. *Acta Chir Scand*. 1975;141:182–186.

329. Mount LA, Antunes JL. Results of treatment of intracranial aneurysms by wrapping and coating. *J Neurosurg*. 1975;42:189–193.

330. Todd NV, Tocher JL, Jones PA, Miller JD. Outcome following aneurysm wrapping: a 10-year follow-up review of clipped and wrapped aneurysms. *J Neurosurg*. 1989;70:841–846.

331. Minakawa T, Koike T, Fujii Y, Ishii R, Tanaka R, Arai H. Long term results of ruptured aneurysms treated by coating. *Neurosurgery*. 1987;21:660–663.

332. Auer LM. Unfavorable outcome following early surgical repair of ruptured cerebral aneurysms: a critical review of 238 patients. *Surg Neurol*. 1991;35:152–158.

333. Kassell NF, Drake CG. Timing of aneurysm surgery. *Neurosurgery*. 1982;10:514–519.

334. Chyatte D, Fode NC, Sundt TM Jr. Early versus late intracranial aneurysm surgery in subarachnoid hemorrhage. *J Neurosurg*. 1988;69:326–331.

335. Kassell NF, Torner JC, Jane JA, Haley EC Jr, Adams HP. The International Cooperative Study on the Timing of Aneurysm Surgery, part 2: surgical results. *J Neurosurg*. 1990;73:37–47.

336. Ohman J, Heiskanen O. Timing of operation for ruptured supratentorial aneurysms: a prospective randomized study. *J Neurosurg*. 1989;70:55–60.

337. Cloughesy TF, Nuwer MR, Hoch D, Vinuela F, Duckwiler G, Martin N. Monitoring carotid test occlusions with continuous EEG and clinical examination. *J Clin Neurophysiol*. 1993;10:363–369.

338. Brunberg JA, Frey KA, Horton JA, Deveikis JP, Ross DA, Koeppe RA. [^{15}O]H2O positron emission tomography determination of cerebral blood flow during balloon test occlusion of the internal carotid artery. *AJNR Am J Neuroradiol*. 1994;15:725–732.

339. Linskey ME, Jungreis CA, Yonas H, Hirsch WL Jr, Sekhar LN, Horton JA, Janosky JE. Stroke risk after abrupt internal carotid artery sacrifice: accuracy of preoperative assessment with balloon test occlusion and stable xenon-enhanced CT. *AJNR Am J Neuroradiol*. 1994;15:829–843.

340. Abruzzo T, Joseph GJ, Owens DS, Dawson RC 3rd, Reid J, Barrow DL. Prevention of complications resulting from endovascular carotid sacrifice: a retrospective assessment. *Neurosurgery*. 2000;46:910–916.

341. Higashida RT, Halback VV, Dormandy B, Bell JD, Hieshima GB. Endovascular treatment of intracranial aneurysms with a new silicone microballoon device: technical considerations and indications for therapy. *Radiology*. 1990;174(pt 1):687–691.

342. Larson JJ, Tew JM Jr, Tomsick TA, van Loveren HR. Treatment of aneurysms of the internal carotid artery by intravascular balloon occlusion: long-term follow-up of 58 patients. *Neurosurgery*. 1995;36:26–30.

343. Nishioka H. Results of the treatment of intracranial aneurysms by occlusion of the carotid artery in the neck. *J Neurosurg*. 1966;25:660–704.

344. Sahs AL, Nibbelink DW, Torner JC, eds. *Aneurysmal Subarachnoid Hemorrhage: Report of the Cooperative Study*. Baltimore, Md: Urban & Schwarzenberg; 1981.

345. Taylor W, Miller JD, Todd NV. Long-term outcome following anterior cerebral artery ligation for ruptured anterior communicating artery aneurysms. *J Neurosurg*. 1991;74:51–54.

346. Tang G, Cawley CM, Dion JE, Barrow DL. Intraoperative angiography during aneurysm surgery: a prospective evaluation of efficacy. *J Neurosurg*. 2002;96:993–999.

347. Harbaugh RE, Heros RC, Hadley MN. More on ISAT. *Lancet*. 2003;361:783–784.

348. Bardach NS, Olson SJ, Elkins JS, Smith WS, Lawton MT, Johnston SC. Regionalization of treatment for subarachnoid hemorrhage: a cost-utility analysis. *Circulation*. 2004;109:2207–2212.

349. Gordon HS, Rosenthal GE. Impact of interhospital transfers on outcomes in an academic medical center: implications for profiling hospital quality. *Med Care*. 1996;34:295–309.

350. Naso WB, Rhea AH, Poole A. Management and outcomes in a low-volume cerebral aneurysm practice. *Neurosurgery*. 2001;48:91–99.

351. Matz PG. Editorial comment: spontaneous subarachnoid hemorrhage: volume, experience, and outcome. *Stroke*. 2003;34:2206–2207.

352. Farrar JK, Gamache FW Jr, Ferguson GG, Barker J, Varkey GP, Drake CG. Effects of profound hypotension on cerebral blood flow during surgery for intracranial aneurysms. *J Neurosurg*. 1981;55:857–864.

353. Hitchcock ER, Tsementzis SA, Dow AA. Short- and long-term prognosis of patients with a subarachnoid haemorrhage in relation to intra-operative period of hypotension. *Acta Neurochir (Wien)*. 1984;70:235–242.

354. Bendtsen AO, Cold GE, Astrup J, Rosenorn J. Thiopental loading during controlled hypotension for intracranial aneurysm surgery. *Acta Anaesthesiol Scand*. 1984;28:473–477.

355. Batjer HH, Frankfurt AI, Purdy PD, Smith SS, Samson DS. Use of etomidate, temporary arterial occlusion, and intraoperative angiography in surgical treatment of large and giant cerebral aneurysms. *J Neurosurg*. 1988;68:234–240.

356. McDermott MW, Durity FA, Borozny M, Mountain MA. Temporary vessel occlusion and barbiturate protection in cerebral aneurysm surgery. *Neurosurgery*. 1989;25:54–61.

357. Ravussin P, de Tribolet N. Total intravenous anesthesia with propofol for burst suppression in cerebral aneurysm surgery: preliminary report of 42 patients. *Neurosurgery*. 1993;32:236–240.

358. Ogilvy CS, Carter BS, Kaplan S, Rich C, Crowell RM. Temporary vessel occlusion for aneurysm surgery: risk factors for stroke in patients protected by induced hypothermia and hypertension and intravenous mannitol administration. *J Neurosurg*. 1996;84:785–791.

359. Cheng MA, Theard MA, Tempelhoff R. Intravenous agents and intraoperative neuroprotection: beyond barbiturates. *Crit Care Clin*. 1997;13:185–199.

360. Drummond JC. Brain protection during anesthesia: a reader's guide. *Anesthesiology*. 1993;79:877–880.

361. Jabre A, Symon L. Temporary vascular occlusion during aneurysm surgery. *Surg Neurol*. 1987;27:47–63.

362. Spetzler RF, Hadley MN, Rigamonti D, Carter LP, Raudzens PA, Shedd SA, Wilkinson E. Aneurysms of the basilar artery treated with circulatory arrest, hypothermia, and barbiturate cerebral protection. *J Neurosurg*. 1988;68:868–879.

363. Solomon RA, Smith CR, Raps EC, Young WL, Stone JG, Fink ME. Deep hypothermic circulatory arrest for the management of complex anterior and posterior circulation aneurysms. *Neurosurgery*. 1991;29:732–737.

364. Todd MM, Hindman BJ, Clarke WR, Torner JC, for the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) Investigators. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med*. 2005;352:135–145.

365. Heros RC, Zervas NT, Varsos V. Cerebral vasospasm after subarachnoid hemorrhage: an update. *Ann Neurol*. 1983;14:599–608.

366. Fisher CM, Roberson GH, Ojemann RG. Cerebral vasospasm with ruptured saccular aneurysm: the clinical manifestations. *Neurosurgery*. 1977;1:245–248.

367. Haley EC Jr, Kassell NF, Torner JC. The International Cooperative Study on the Timing of Aneurysm Surgery: the North American experience. *Stroke*. 1992;23:205–214.

368. Longstreth WT Jr, Nelson LM, Koepsell TD, van Belle G. Clinical course of spontaneous subarachnoid hemorrhage: a population-based study in King County, Washington. *Neurology*. 1993;43:712–718.

369. Claassen J, Hirsch LJ, Kreiter KT, Du EY, Connolly ES, Emerson RG, Mayer SA. Quantitative continuous EEG for detecting delayed cerebral

ischemia in patients with poor-grade subarachnoid hemorrhage. *Clin Neurophysiol*. 2004;115:2699–2710.

370. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg*. 1982;57:769–774.

371. Aaslid R, Huber P, Nornes H. Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. *J Neurosurg*. 1984;60:37–41.

372. Aaslid R, Huber P, Nornes H. A transcranial Doppler method in the evaluation of cerebrovascular spasm. *Neuroradiology*. 1986;28:11–16.

373. Ekelund A, Saveland H, Romner B, Brandt L. Is transcranial Doppler sonography useful in detecting late cerebral ischaemia after aneurysmal subarachnoid haemorrhage? *Br J Neurosurg*. 1996;10:19–25.

374. Grosset DG, Straiton J, du Trevou M, Bullock R. Prediction of symptomatic vasospasm after subarachnoid hemorrhage by rapidly increasing transcranial Doppler velocity and cerebral blood flow changes. *Stroke*. 1992;23:674–679.

375. Lindegaard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P. Cerebral vasospasm diagnosis by means of angiography and blood velocity measurements. *Acta Neurochir (Wien)*. 1989;100:12–24.

376. Vora YY, Suarez-Almazor M, Steinke DE, Martin ML, Findlay JM. Role of transcranial Doppler monitoring in the diagnosis of cerebral vasospasm after subarachnoid hemorrhage. *Neurosurgery*. 1999;44:1237–1247.

377. Klingelhofer J, Dander D, Holzgraefe M, Bischoff C, Conrad B. Cerebral vasospasm evaluated by transcranial Doppler ultrasonography at different intracranial pressures. *J Neurosurg*. 1991;75:752–758.

378. Mizuno M, Nakajima S, Sampei T, Nishimura H, Hadeishi H, Suzuki A, Yasui N, Nathal-Vera E. Serial transcranial Doppler flow velocity and cerebral blood flow measurements for evaluation of cerebral vasospasm after subarachnoid hemorrhage. *Neurol Med Chir (Tokyo)*. 1994;34:164–171.

379. Schuknecht B, Fandino J, Yuksel C, Yonekawa Y, Valavanis A. Endovascular treatment of cerebral vasospasm: assessment of treatment effect by cerebral angiography and transcranial colour Doppler sonography. *Neuroradiology*. 1999;41:453–462.

380. Sloan MA, Haley EC Jr, Kassell NF, Henry ML, Stewart SR, Beskin RR, Sevilla EA, Torner JC. Sensitivity and specificity of transcranial Doppler ultrasonography in the diagnosis of vasospasm following subarachnoid hemorrhage. *Neurology*. 1989;39:1514–1518.

381. Sloan MA, Alexandrov AV, Tegeler CH, Spencer MP, Caplan LR, Feldmann E, Wechsler LR, Newell DW, Gomez CR, Babikian VL, Lefkowitz D, Goldman RS, Armon C, Hsu CY, Goodin DS, for the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2004;62:1468–1481.

382. Lysakowski C, Walder B, Costanza MC, Tramer MR. Transcranial Doppler versus angiography in patients with vasospasm due to a ruptured cerebral aneurysm: a systematic review. *Stroke*. 2001;32:2292–2298.

383. Solomon RA, Fink ME, Lennihan L. Early aneurysm surgery and prophylactic hypervolemic hypertensive therapy for the treatment of aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 1988;23:699–704.

384. Awad IA, Carter LP, Spetzler RF, Medina M, Williams FC Jr. Clinical vasospasm after subarachnoid hemorrhage: response to hypervolemic hemodilution and arterial hypertension. *Stroke*. 1987;18:365–372.

385. Lennihan L, Mayer SA, Fink ME, Beckford A, Paik MC, Zhang H, Wu YC, Klebanoff LM, Raps EC, Solomon RA. Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: a randomized controlled trial. *Stroke*. 2000;31:383–391.

386. Keller TS, McGillicuddy JE, LaBond VA, Kindt GW. Modification of focal cerebral ischemia by cardiac output augmentation. *J Surg Res*. 1985;39:420–432.

387. Kosnik EJ, Hunt WE. Postoperative hypertension in the management of patients with intracranial arterial aneurysms. *J Neurosurg*. 1976;45:148–154.

388. Pritz MB, Giannotta SL, Kindt GW, McGillicuddy JE, Prager RL. Treatment of patients with neurological deficits associated with cerebral vasospasm by intravascular volume expansion. *Neurosurgery*. 1978;3:364–368.

389. Egge A, Waterloo K, Sjoholm H, Solberg T, Ingebrigtsen T, Romner B. Prophylactic hyperdynamic postoperative fluid therapy after aneurysmal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled study. *Neurosurgery*. 2001;49:593–605.

390. Levy ML, Giannotta SL. Cardiac performance indices during hypervolemic therapy for cerebral vasospasm. *J Neurosurg*. 1991;75:27–31.

391. Mayer SA, Solomon RA, Fink ME, Lennihan L, Stern L, Beckford A, Thomas CE, Klebanoff LM. Effect of 5% albumin solution on sodium balance and blood volume after subarachnoid hemorrhage. *Neurosurgery*. 1998;42:759–767.

392. Origitano TC, Wascher TM, Reichman OH, Anderson DE. Sustained increased cerebral blood flow with prophylactic hypertensive hypervolemic hemodilution ("triple-H" therapy) after subarachnoid hemorrhage. *Neurosurgery*. 1990;27:729–739.

393. Maroon JC, Nelson PB. Hypovolemia in patients with subarachnoid hemorrhage: therapeutic implications. *Neurosurgery*. 1979;4:223–226.

394. Medlock MD, Dulebohn SC, Elwood PW. Prophylactic hypervolemia without calcium channel blockers in early aneurysm surgery. *Neurosurgery*. 1992;30:12–16.

395. Darby JM, Yonas H, Marks EC, Durham S, Snyder RW, Nemoto EM. Acute cerebral blood flow response to dopamine-induced hypertension after subarachnoid hemorrhage. *J Neurosurg*. 1994;80:857–864.

396. Muizelaar JP, Becker DP. Induced hypertension for the treatment of cerebral ischemia after subarachnoid hemorrhage: direct effect on cerebral blood flow. *Surg Neurol*. 1986;25:317–325.

397. Shimoda M, Oda S, Tsugane R, Sato O. Intracranial complications of hypervolemic therapy in patients with a delayed ischemic deficit attributed to vasospasm. *J Neurosurg*. 1993;78:423–429.

398. Trumble ER, Muizelaar JP, Myseros JS, Choi SC, Warren BB. Coagulopathy with the use of hetastarch in the treatment of vasospasm. *J Neurosurg*. 1995;82:44–47.

399. Ekelund A, Reinstrup P, Ryding E, Andersson AM, Molund T, Kristiansson KA, Romner B, Brandt L, Saveland H. Effects of iso- and hypervolemic hemodilution on regional cerebral blood flow and oxygen delivery for patients with vasospasm after aneurysmal subarachnoid hemorrhage. *Acta Neurochir (Wien)*. 2002;144:703–712.

400. Smith MJ, Le Roux PD, Elliott JP, Winn HR. Blood transfusion and increased risk for vasospasm and poor outcome after subarachnoid hemorrhage. *J Neurosurg*. 2004;101:1–7.

401. Hasan D, Wijdicks EF, Vermeulen M. Hyponatremia is associated with cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. *Ann Neurol*. 1990;27:106–108.

402. Wijdicks EF, Vermeulen M, ten Haaf JA, Hijdra A, Bakker WH, van Gijn J. Volume depletion and natriuresis in patients with a ruptured intracranial aneurysm. *Ann Neurol*. 1985;18:211–216.

403. Wijdicks EF, Vermeulen M, Hijdra A, van Gijn J. Hyponatremia and cerebral infarction in patients with ruptured intracranial aneurysms: is fluid restriction harmful? *Ann Neurol*. 1985;17:137–140.

404. Nelson PB, Seif SM, Maroon JC, Robinson AG. Hyponatremia in intracranial disease: perhaps not the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *J Neurosurg*. 1981;55:938–941.

405. Kraus JJ, Metzler MD, Coplin WM. Critical care issues in stroke and subarachnoid hemorrhage. *Neurol Res*. 2002;24(suppl 1):S47–S57.

406. Claassen J, Vu A, Kreiter KT, Kowalski RG, Du EY, Ostapkovich N, Fitzsimmons BF, Connolly ES, Mayer SA. Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. *Crit Care Med*. 2004;32:832–838.

407. Dorhout Mees SM, van Dijk GW, Algra A, Kempink DR, Rinkel GJ. Glucose levels and outcome after subarachnoid hemorrhage. *Neurology*. 2003;61:1132–1133.

408. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345:1359–1367.

409. van den Bergh WM, Algra A, van Kooten F, Dirven CM, van Gijn J, Vermeulen M, Rinkel GJ, for the MASH Study Group. Magnesium sulfate in aneurysmal subarachnoid hemorrhage: a randomized controlled trial. *Stroke*. 2005;36:1011–1015.

410. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Chou SN, Kelly DL, Weir BK, Crabbe RA, Lavik PJ, Rosenbloom SB, Dorsey FC, Ingram CR, Mellits DE, Bertsch LA, Boisvert DP, Hundley MB, Johnson RK, Strom JA, Transou CR. Cerebral arterial spasm: a controlled trial of nimodipine in patients with subarachnoid hemorrhage. *N Engl J Med*. 1983;308:619–624.

411. Haley EC Jr, Kassell NF, Torner JC, Truskowski LL, Germanson TP. A randomized trial of two doses of nicardipine in aneurysmal subarachnoid hemorrhage: a report of the Cooperative Aneurysm Study. *J Neurosurg*. 1994;80:788–796.

412. Zabramski JM, Spetzler RF, Lee KS, Papadopoulos SM, Bovill E, Zimmerman RS, Bederson JB. Phase I trial of tissue plasminogen activator for the prevention of vasospasm in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 1991;75:189–196.

413. Suzuki J, Onuma T, Yoshimoto T. Results of early operations on cerebral aneurysms. *Surg Neurol*. 1979;11:407–412.

414. Kawamoto S, Tsutsumi K, Yoshikawa G, Shinozaki MH, Yako K, Nagata K, Ueki K. Effectiveness of the head-shaking method combined with cisternal irrigation with urokinase in preventing cerebral vasospasm after subarachnoid hemorrhage. *J Neurosurg*. 2004;100:236–243.

415. van den Bergh WM, for the MASH Study Group. Randomized controlled trial of acetylsalicylic acid in aneurysmal subarachnoid hemorrhage: the MASH Study. *Stroke*. 2006;37:2326–2330.

416. Hop JW, Rinkel GJ, Algra A, Berkelbach van der Sprenkel JW, van Gijn J. Randomized pilot trial of postoperative aspirin in subarachnoid hemorrhage. *Neurology*. 2000;54:872–878.

417. Wurm G, Tomancok B, Nussbaumer K, Adelwohrer C, Holl K. Reduction of ischemic sequelae following spontaneous subarachnoid hemorrhage: a double-blind, randomized comparison of enoxaparin versus placebo. *Clin Neurol Neurosurg*. 2004;106:97–103.

418. Siironen J, Juvela S, Varis J, Porras M, Poussa K, Ilveskero S, Hernesniemi J, Lassila R. No effect of enoxaparin on outcome of aneurysmal subarachnoid hemorrhage: a randomized, double-blind, placebo-controlled clinical trial. *J Neurosurg*. 2003;99:953–959.

419. Lanzino G, Kassell NF. Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage, part II: a cooperative study in North America. *J Neurosurg*. 1999;90:1018–1024.

420. Lanzino G, Kassell NF, Dorsch NW, Pasqualin A, Brandt L, Schmiedek P, Truskowski LL, Alves WM. Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage, part I: a cooperative study in Europe, Australia, New Zealand, and South Africa. *J Neurosurg*. 1999;90:1011–1017.

421. Haley EC Jr, Kassell NF, Apperson-Hansen C, Maile MH, Alves WM. A randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in North America. *J Neurosurg*. 1997;86:467–474.

422. Kassell NF, Haley EC Jr, Apperson-Hansen C, Alves WM. Randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in Europe, Australia, and New Zealand. *J Neurosurg*. 1996;84:221–228.

423. Saito I, Asano T, Sano K, Takakura K, Abe H, Yoshimoto T, Kikuchi H, Ohta T, Ishibashi S. Neuroprotective effect of an antioxidant, ebselen, in patients with delayed neurological deficits after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 1998;42:269–277.

424. Asano T, Takakura K, Sano K, Kikuchi H, Nagai H, Saito I, Tamura A, Ochiai C, Sasaki T. Effects of a hydroxyl radical scavenger on delayed ischemic neurological deficits following aneurysmal subarachnoid hemorrhage: results of a multicenter, placebo-controlled double-blind trial. *J Neurosurg*. 1996;84:792–803.

425. Vajkoczy P, Meyer B, Weidauer S, Raabe A, Thome C, Ringel F, Breu V, Schmiedek P. Clazosentan (AXV-034343), a selective endothelin A receptor antagonist, in the prevention of cerebral vasospasm following severe aneurysmal subarachnoid hemorrhage: results of a randomized, double-blind, placebo-controlled, multicenter phase IIa study. *J Neurosurg*. 2005;103:9–17.

426. Shaw MD, Vermeulen M, Murray GD, Pickard JD, Bell BA, Teasdale GM. Efficacy and safety of the endothelin, receptor antagonist TAK-044 in treating subarachnoid hemorrhage: a report by the Steering Committee on behalf of the UK/Netherlands/Eire TAK-044 Subarachnoid Haemorrhage Study Group. *J Neurosurg*. 2000;93:992–997.

427. Reinert M, Wiest R, Barth L, Andres R, Ozdoba C, Seiler R. Transdermal nitroglycerin in patients with subarachnoid hemorrhage. *Neurol Res*. 2004;26:435–439.

428. Lynch JR, Wang H, McGirt MJ, Floyd J, Friedman AH, Coon AL, Blessing R, Alexander MJ, Graffagnino C, Warner DS, Laskowitz DT. Simvastatin reduces vasospasm after aneurysmal subarachnoid hemorrhage: results of a pilot randomized clinical trial. *Stroke*. 2005;36:2024–2026.

429. Tseng MY, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ. Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: a phase II randomized placebo-controlled trial. *Stroke*. 2005;36:1627–1632.

430. Zubkov YN, Nikiforov BM, Shustin VA. Balloon catheter technique for dilatation of constricted cerebral arteries after aneurysmal SAH. *Acta Neurochir (Wien)*. 1984;70:65–79.

431. Eskridge JM, Song JK. A practical approach to the treatment of vasospasm. *AJNR Am J Neuroradiol*. 1997;18:1653–1660.

432. Eskridge JM, Newell DW, Winn HR. Endovascular treatment of vasospasm. *Neurosurg Clin N Am*. 1994;5:437–447.

433. Higashida RT, Halbach VV, Cahan LD, Brant-Zawadzki M, Barnwell S, Dowd C, Hieshima GB. Transluminal angioplasty for treatment of intracranial arterial vasospasm. *J Neurosurg*. 1989;71(pt 1):648–653.

434. Higashida RT, Halbach VV, Dowd CF, Dormandy B, Bell J, Hieshima GB. Intravascular balloon dilatation therapy for intracranial arterial vasospasm: patient selection, technique, and clinical results. *Neurosurg Rev*. 1992;15:89–95.

435. Terada T, Nakamura Y, Yoshida N, Kuriyama T, Isozaki S, Nakai K, Itakura T, Hayashi S, Komai N. Percutaneous transluminal angioplasty for the M2 portion vasospasm following SAH: development of the new microballoon and report of cases. *Surg Neurol*. 1993;39:13–17.

436. Newell DW, Eskridge JM, Mayberg MR, Grady MS, Winn HR. Angioplasty for the treatment of symptomatic vasospasm following subarachnoid hemorrhage. *J Neurosurg*. 1989;71(pt 1):654–660.

437. Polin RS, Coenen VA, Hansen CA, Shin P, Baskaya MK, Nanda A, Kassell NF. Efficacy of transluminal angioplasty for the management of symptomatic cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2000;92:284–290.

438. Rosenwasser RH, Armonda RA, Thomas JE, Benitez RP, Gannon PM, Harrop J. Therapeutic modalities for the management of cerebral vasospasm: timing of endovascular options. *Neurosurgery*. 1999;44:975–979.

439. Mathis JM, Jensen ME, Dion JE. Technical considerations on intra-arterial papaverine hydrochloride for cerebral vasospasm. *Neuroradiology*. 1997;39:90–98.

440. McAuliffe W, Townsend M, Eskridge JM, Newell DW, Grady MS, Winn HR. Intracranial pressure changes induced during papaverine infusion for treatment of vasospasm. *J Neurosurg*. 1995;83:430–434.

441. Milburn JM, Moran CJ, Cross DT 3rd, Diringer MN, Pilgram TK, Dacey RG Jr. Effect of intraarterial papaverine on cerebral circulation time. *AJNR Am J Neuroradiol*. 1997;18:1081–1085.

442. Milburn JM, Moran CJ, Cross DT 3rd, Diringer MN, Pilgram TK, Dacey RG Jr. Increase in diameters of vasospastic intracranial arteries by intraarterial papaverine administration. *J Neurosurg*. 1998;88:38–42.

443. Cross DT 3rd, Moran CJ, Angtuaco EE, Milburn JM, Diringer MN, Dacey RG Jr. Intracranial pressure monitoring during intraarterial papaverine infusion for cerebral vasospasm. *AJNR Am J Neuroradiol*. 1998;19:1319–1323.

444. Clyde BL, Firlik AD, Kaufmann AM, Spearman MP, Yonas H. Paradoxical aggravation of vasospasm with papaverine infusion following aneurysmal subarachnoid hemorrhage: case report. *J Neurosurg*. 1996;84:690–695.

445. Clouston JE, Numaguchi Y, Zoarski GH, Aldrich EF, Simard JM, Zitnay KM. Intraarterial papaverine infusion for cerebral vasospasm after subarachnoid hemorrhage. *AJNR Am J Neuroradiol*. 1995;16:27–38.

446. Kassell NF, Helm G, Simmons N, Phillips CD, Cail WS. Treatment of cerebral vasospasm with intra-arterial papaverine. *J Neurosurg*. 1992;77:848–852.

447. Feng L, Fitzsimmons BF, Young WL, Berman MF, Lin E, Aagaard BD, Duong H, Pile-Spellman J. Intraarterially administered verapamil as adjunct therapy for cerebral vasospasm: safety and 2-year experience. *AJNR Am J Neuroradiol*. 2002;23:1284–1290.

448. Badjatia N, Topcuoglu MA, Pryor JC, Rabinov JD, Ogilvy CS, Carter BS, Rordorf GA. Preliminary experience with intra-arterial nicardipine as a treatment for cerebral vasospasm. *AJNR Am J Neuroradiol*. 2004;25:819–826.

449. Biondi A, Ricciardi GK, Puybasset L, Abdennour L, Longo M, Chiras J, Van Effenterre R. Intra-arterial nimodipine for the treatment of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage: preliminary results. *AJNR Am J Neuroradiol*. 2004;25:1067–1076.

450. Elliott JP, Newell DW, Lam DJ, Eskridge JM, Douville CM, Le Roux PD, Lewis DH, Mayberg MR, Grady MS, Winn HR. Comparison of balloon angioplasty and papaverine infusion for the treatment of vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 1998;88:277–284.

451. Bejjani GK, Bank WO, Olan WJ, Sekhar LN. The efficacy and safety of angioplasty for cerebral vasospasm after subarachnoid hemorrhage. *Neurosurgery*. 1998;42:979–986.

452. Mehta V, Holness RO, Connolly K, Walling S, Hall R. Acute hydrocephalus following aneurysmal subarachnoid hemorrhage. *Can J Neurol Sci*. 1996;23:40–45.

453. Suarez-Rivera O. Acute hydrocephalus after subarachnoid hemorrhage. *Surg Neurol*. 1998;49:563–565.

454. Lin CL, Kwan AL, Howng SL. Acute hydrocephalus and chronic hydrocephalus with the need of postoperative shunting after aneurysmal subarachnoid hemorrhage. *Kaohsiung J Med Sci*. 1999;15:137–145.

455. Sheehan JP, Polin RS, Sheehan JM, Baskaya MK, Kassell NF. Factors associated with hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 1999;45:1120–1127.

456. Rajshekhar V, Harbaugh RE. Results of routine ventriculostomy with external ventricular drainage for acute hydrocephalus following subarachnoid haemorrhage. *Acta Neurochir (Wien)*. 1992;115:8–14.

457. Hasan D, Vermeulen M, Wijdicks EF, Hijdra A, van Gijn J. Management problems in acute hydrocephalus after subarachnoid hemorrhage. *Stroke*. 1989;20:747–753.

458. Rinkel GJ, Wijdicks EF, Vermeulen M, Tans JT, Hasan D, van Gijn J. Acute hydrocephalus in nonaneurysmal perimesencephalic hemorrhage: evidence of CSF block at the tentorial hiatus. *Neurology*. 1992;42:1805–1807.

459. Milhorat TH. Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 1987;20:15–20.

460. Gruber A, Reinprecht A, Bavinzski G, Czech T, Richling B. Chronic shunt-dependent hydrocephalus after early surgical and early endovascular treatment of ruptured intracranial aneurysms. *Neurosurgery*. 1999;44:503–509.

461. Sethi H, Moore A, Dervin J, Clifton A, MacSweeney JE. Hydrocephalus: comparison of clipping and embolization in aneurysm treatment. *J Neurosurg*. 2000;92:991–994.

462. Dorai Z, Hynan LS, Kopitnik TA, Samson D. Factors related to hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2003;52:763–769.

463. Widenka DC, Wolf S, Schurer L, Plev DV, Lumenta CB. Factors leading to hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurol Neurochir Pol*. 2000;34(suppl):56–60.

464. Schmieder K, Koch R, Lucke S, Harders A. Factors influencing shunt dependency after aneurysmal subarachnoid haemorrhage. *Zentralbl Neurochir*. 1999;60:133–140.

465. Yoshioka H, Inagawa T, Tokuda Y, Inokuchi F. Chronic hydrocephalus in elderly patients following subarachnoid hemorrhage. *Surg Neurol*. 2000;53:119–124.

466. Komotar RJ, Olivi A, Rigamonti D, Tamargo RJ. Microsurgical fenestration of the lamina terminalis reduces the incidence of shunt-dependent hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2002;51:1403–1412.

467. Black PM. Hydrocephalus and vasospasm after subarachnoid hemorrhage from ruptured intracranial aneurysms. *Neurosurgery*. 1986;18:12–16.

468. van Gijn J, Hijdra A, Wijdicks EF, Vermeulen M, van Crevel H. Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 1985;63:355–362.

469. Klopfenstein JD, Kim LJ, Feiz-Erfan I, Hott JS, Goslar P, Zabramski JM, Spetzler RF. Comparison of rapid and gradual weaning from external ventricular drainage in patients with aneurysmal subarachnoid hemorrhage: a prospective randomized trial. *J Neurosurg*. 2004;100:225–229.

470. Hart RG, Byer JA, Slaughter JR, Hewett JE, Easton JD. Occurrence and implications of seizures in subarachnoid hemorrhage due to ruptured intracranial aneurysms. *Neurosurgery*. 1981;8:417–421.

471. Deutschman CS, Haines SJ. Anticonvulsant prophylaxis in neurological surgery. *Neurosurgery*. 1985;17:510–517.

472. Butzkueven H, Evans AH, Pitman A, Leopold C, Jolley DJ, Kaye AH, Kilpatrick CJ, Davis SM. Onset seizures independently predict poor outcome after subarachnoid hemorrhage. *Neurology*. 2000;55:1315–1320.

473. Rhoney DH, Tipps LB, Murry KR, Basham MC, Michael DB, Coplin WM. Anticonvulsant prophylaxis and timing of seizures after aneurysmal subarachnoid hemorrhage. *Neurology*. 2000;55:258–265.

474. Lin CL, Dumont AS, Lieu AS, Yen CP, Hwang SL, Kwan AL, Kassell NF, Howng SL. Characterization of perioperative seizures and epilepsy following aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2003;99:978–985.

475. Claassen J, Peery S, Kreiter KT, Hirsch LJ, Du EY, Connolly ES, Mayer SA. Predictors and clinical impact of epilepsy after subarachnoid hemorrhage. *Neurology*. 2003;60:208–214.

476. Carhuapoma JR, Qureshi AI, Tamargo RJ, Mathis JM, Hanley DF. Intra-arterial papaverine-induced seizures: case report and review of the literature. *Surg Neurol*. 2001;56:159–163.

477. Dennis LJ, Claassen J, Hirsch LJ, Emerson RG, Connolly ES, Mayer SA. Nonconvulsive status epilepticus after subarachnoid hemorrhage. *Neurosurgery*. 2002;51:1136–1143.

478. O'Laoire SA. Epilepsy following neurosurgical intervention. *Acta Neurochir Suppl (Wien)*. 1990;50:52–54.

479. Sbeih I, Tamas LB, O'Laoire SA. Epilepsy after operation for aneurysms. *Neurosurgery*. 1986;19:784–788.

480. Shaw MD. Post-operative epilepsy and the efficacy of anticonvulsant therapy. *Acta Neurochir Suppl (Wien)*. 1990;50:55–57.

481. Kvam DA, Loftus CM, Copeland B, Quest DO. Seizures during the immediate postoperative period. *Neurosurgery*. 1983;12:14–17.

482. Matthew E, Sherwin AL, Welner SA, Odusote K, Stratford JG. Seizures following intracranial surgery: incidence in the first post-operative week. *Can J Neurol Sci*. 1980;7:285–290.

483. North JB, Penhall RK, Hanieh A, Frewin DB, Taylor WB. Phenytoin and postoperative epilepsy: a double-blind study. *J Neurosurg*. 1983;58:672–677.

484. Byrne JV, Boardman P, Ioannidis I, Adcock J, Traill Z. Seizures after aneurysmal subarachnoid hemorrhage treated with coil embolization. *Neurosurgery*. 2003;52:545–552.

485. Rose FC, Sarner M. Epilepsy after ruptured intracranial aneurysm. *BMJ*. 1965;5426:18–21.

486. Ukkola V, Heikkinen ER. Epilepsy after operative treatment of ruptured cerebral aneurysms. *Acta Neurochir (Wien)*. 1990;106:115–118.

487. Cabral RJ, King TT, Scott DF. Epilepsy after two different neurosurgical approaches to the treatment of ruptured intracranial aneurysm. *J Neurol Neurosurg Psychiatry*. 1976;39:1052–1056.

488. Kotila M, Waltimo O. Epilepsy after stroke. *Epilepsia*. 1992;33:495–498.

489. Naidech AM, Kreiter KT, Janjua N, Ostapkovich N, Parra A, Commichau C, Connolly ES, Mayer SA, Fitzsimmons BF. Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. *Stroke*. 2005;36:583–587.

490. Brouwers PJ, Dippel DW, Vermeulen M, Lindsay KW, Hasan D, van Gijn J. Amount of blood on computed tomography as an independent predictor after aneurysm rupture. *Stroke*. 1993;24:809–814.

491. Sayama T, Inamura T, Matsushima T, Inoha S, Inoue T, Fukui M. High incidence of hyponatremia in patients with ruptured anterior communicating artery aneurysms. *Neurol Res*. 2000;22:151–155.

492. Qureshi AI, Suri MF, Sung GY, Straw RN, Yahia AM, Saad M, Guterman LR, Hopkins LN. Prognostic significance of hypernatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2002;50:749–755.

493. Diringer MN, Wu KC, Verbalis JG, Hanley DF. Hypervolemic therapy prevents volume contraction but not hyponatremia following subarachnoid hemorrhage. *Ann Neurol*. 1992;31:543–550.

494. Solomon RA, Post KD, McMurtry JG 3rd. Depression of circulating blood volume in patients after subarachnoid hemorrhage: implications for the management of symptomatic vasospasm. *Neurosurgery*. 1984;15:354–361.

495. Hasan D, Lindsay KW, Wijdicks EF, Murray GD, Brouwers PJ, Bakker WH, van Gijn J, Vermeulen M. Effect of fludrocortisone acetate in patients with subarachnoid hemorrhage. *Stroke*. 1989;20:1156–1161.

496. Mori T, Katayama Y, Kawamata T, Hirayama T. Improved efficiency of hypervolemic therapy with inhibition of natriuresis by fludrocortisone in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 1999;91:947–952.

497. Suarez JI, Qureshi AI, Parekh PD, Razumovsky A, Tamargo RJ, Bhardwaj A, Ulatowski JA. Administration of hypertonic (3%) sodium chloride/acetate in hyponatremic patients with symptomatic vasospasm following subarachnoid hemorrhage. *J Neurosurg Anesthesiol*. 1999;11:178–184.

498. Sakowitz OW, Raabe A, Vucak D, Kiening KL, Unterberg AW. Contemporary management of aneurysmal subarachnoid hemorrhage in Germany: results of a survey among 100 neurosurgical departments. *Neurosurgery*. 2006;58:137–145.

499. Schmid-Elsaesser R, Kunz M, Zausinger S, Prueckner S, Briegel J, Steiger HJ. Intravenous magnesium versus nimodipine in the treatment

of patients with aneurysmal subarachnoid hemorrhage: a randomized study. *Neurosurgery.* 2006;58:1054–1065.

500. Veyna RS, Seyfried D, Burke DG, Zimmerman C, Mlynarek M, Nichols V, Marrocco A, Thomas AJ, Mitsias PD, Malik GM. Magnesium sulfate therapy after aneurysmal subarachnoid hemorrhage. *J Neurosurg.* 2002; 96:510–514.

501. Vanninen R, Koivisto T, Saari T, Hernesniemi J, Vapalahti M. Ruptured intracranial aneurysms: acute endovascular treatment with electrolytically detachable coils: a prospective randomized study. *Radiology.* 1999;211:325–336.

502. Anderson SW, Todd MM, Hindman BJ, Clarke WR, Torner JC, Tranel D, Yoo B, Weeks J, Manzel KW, Samra S; IHAST Investigators. Effects of intraoperative hypothermia on neuropsychological outcomes after intracranial aneurysm surgery. *Ann Neurol.* 2006;60:518–527.

503. Karibe H, Sato K, Shimizu H, Tominaga T, Koshu K, Yoshimoto T. Intraoperative mild hypothermia ameliorates postoperative cerebral blood flow impairment in patients with aneurysmal subarachnoid hemorrhage. *Neurosurgery.* 2000;47:594–601.

504. Hindman BJ, Todd MM, Gelb AW, Loftus CM, Craen RA, Schubert A, Mahla ME, Torner JC. Mild hypothermia as a protective therapy during intracranial aneurysm surgery: a randomized prospective pilot trial. *Neurosurgery.* 1999;44:23–33.

505. Diringer MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. *Crit Care Med.* 2004;32:1489–1495.

506. Moro N, Katayama Y, Kojima J, Mori T, Kawamata T. Prophylactic management of excessive natriuresis with hydrocortisone for efficient hypervolemic therapy after subarachnoid hemorrhage. *Stroke.* 2003;34: 2807–2811.

507. Hamada J, Kai Y, Morioka M, Yano S, Mizuno T, Hirano T, Kazekawa K, Ushio Y. Effect on cerebral vasospasm of coil embolization followed by microcatheter intrathecal urokinase infusion into the cisterna magna: a prospective randomized study. *Stroke.* 2003;34:2549–2554.

508. Findlay JM, Kassell NF, Weir BK, Haley EC Jr, Kongable G, Germanson T, Truskowski L, Alves WM, Holness RO, Knuckey NW. A randomized trial of intraoperative, intracisternal tissue plasminogen activator for the prevention of vasospasm. *Neurosurgery.* 1995;37:168–178.

509. Roos YB, Rinkel GJ, Vermeulen M, Algra A, van Gijn J. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev.* 2000:CD001245.

KEY WORDS: AHA Scientific Statements ■ aneurysm ■ angiography ■ cerebrovascular disorders ■ hemorrhage ■ stroke ■ surgery ■ vasospasm