

## Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage

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

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

*Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons; and by the Society of NeuroInterventional Surgery*

E. Sander Connolly, Jr, MD, FAHA, Chair; Alejandro A. Rabinstein, MD, Vice Chair; J. Ricardo Carhuapoma, MD, FAHA; Colin P. Derdeyn, MD, FAHA; Jacques Dion, MD, FRCPC; Randall T. Higashida, MD, FAHA; Brian L. Hoh, MD, FAHA; Catherine J. Kirkness, PhD, RN; Andrew M. Naidech, MD, MSPH; Christopher S. Ogilvy, MD; Aman B. Patel, MD; B. Gregory Thompson, MD; Paul Vespa, MD, FAAN; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Council on Cardiovascular Surgery and Anesthesia, and Council on Clinical Cardiology

**Purpose**—The aim of this guideline is to present current and comprehensive recommendations for the diagnosis and treatment of aneurysmal subarachnoid hemorrhage (aSAH).

**Methods**—A formal literature search of MEDLINE (November 1, 2006, through May 1, 2010) was performed. Data were synthesized with the use of evidence tables. Writing group members met by teleconference to discuss data-derived recommendations. The American Heart Association Stroke Council's Levels of Evidence grading algorithm was used to grade each recommendation. The guideline draft was reviewed by 7 expert peer reviewers and by the members of the Stroke Council Leadership and Manuscript Oversight Committees. It is intended that this guideline be fully updated every 3 years.

**Results**—Evidence-based guidelines are presented for the care of patients presenting with aSAH. The focus of the guideline was subdivided into incidence, risk factors, prevention, natural history and outcome, diagnosis, prevention of rebleeding, surgical and endovascular repair of ruptured aneurysms, systems of care, anesthetic management during repair, management of vasospasm and delayed cerebral ischemia, management of hydrocephalus, management of seizures, and management of medical complications.

**Conclusions**—aSAH is a serious medical condition in which outcome can be dramatically impacted by early, aggressive, expert care. The guidelines offer a framework for goal-directed treatment of the patient with aSAH. (*Stroke*. 2012;43:00-00.)

**Key Words:** AHA Scientific Statements ■ aneurysm ■ delayed cerebral ischemia ■ diagnosis ■ subarachnoid hemorrhage ■ treatment ■ vasospasm

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

The American Heart Association requests that this document be cited as follows: Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, Patel AB, Thompson BG, Vespa P; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Council on Cardiovascular Surgery and Anesthesia, and Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:000-000.

Expert peer review of AHA Scientific Statements is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit <http://my.americanheart.org/statements> and select the "Policies and Development" link.

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at [http://www.heart.org/HEARTORG/General/Copyright-Permission-Guidelines\\_UCM\\_300404\\_Article.jsp](http://www.heart.org/HEARTORG/General/Copyright-Permission-Guidelines_UCM_300404_Article.jsp). A link to the "Copyright Permissions Request Form" appears on the right side of the page.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on January 30, 2012. A copy of the document is available at <http://my.americanheart.org/statements> by selecting either the "By Topic" link or the "By Publication Date" link. To purchase additional reprints, call 843-216-2533 or e-mail [kelle.ramsay@wolterskluwer.com](mailto:kelle.ramsay@wolterskluwer.com).

© 2012 American Heart Association, Inc.

*Stroke* is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STR.0b013e3182587839

To respond to the growing call for more evidenced-based medicine, the American Heart Association (AHA) commissions guidelines on various clinical topics and endeavors to keep them as current as possible. The prior aneurysmal subarachnoid hemorrhage (aSAH) guidelines, sponsored by the AHA Stroke Council, were previously issued in 1994<sup>1</sup> and 2009.<sup>2</sup> The 2009 guidelines covered literature through November 1, 2006.<sup>2</sup> The present guidelines primarily cover literature published between November 1, 2006, and May 1, 2010, but the writing group has strived to place these data in the greater context of the prior publications and recommendations. In cases in which new data covered in this review have resulted in a change in a prior recommendation, this is explicitly noted.

aSAH is a significant cause of morbidity and mortality throughout the world. Although the incidence of aSAH varies widely among populations, perhaps because of genetic differences, competing burden of disease, and issues of case ascertainment, at the very least, a quarter of patients with aSAH die, and roughly half of survivors are left with some persistent neurological deficit. That said, case-fatality rates appear to be falling, and increasing data suggest that early aneurysm repair, together with aggressive management of complications such as hydrocephalus and delayed cerebral ischemia (DCI), is leading to improved functional outcomes. These improvements underscore the need to continually reassess which interventions provide the greatest benefit to patients.

Although large, multicenter, randomized trial data confirming effectiveness are usually lacking for many of the interventions discussed, the writing group did its best to summarize the strength of the existing data and make practical recommendations that clinicians will find useful in the day-to-day management of aSAH. This review does not discuss the multitude of ongoing studies. Many of these can be found at <http://www.strokecenter.org/trials/>. The mechanism of reviewing the literature, compiling and analyzing the data, and determining the final recommendations to be made is identical to the 2009 version of this guideline.<sup>2</sup>

The members of the writing group were selected by the AHA to represent the breadth of healthcare professionals who must manage these patients. Experts in each field were screened for important conflicts of interest and then met by telephone to determine subcategories to evaluate. These subcategories included incidence, risk factors, prevention, natural history and outcome, diagnosis, prevention of rebleeding, surgical and endovascular repair of ruptured aneurysms, systems of care, anesthetic management during repair, management of vasospasm and DCI, management of hydrocephalus, management of seizures, and management of medical complications. Together, these categories were thought to encompass all of the major areas of disease management, including prevention, diagnosis, and treatment. Each subcategory was led by 1 author, with 1 or 2 additional coauthors who made contributions. Full MEDLINE searches were conducted independently by each author and coauthor of all English-language papers on treatment of relevant human disease. Drafts of summaries and recommendations were circulated to the entire writing group for feedback. A confer-

ence call was held to discuss controversial issues. Sections were revised and merged by the writing group chair. The resulting draft was sent to the entire writing group for comment. Comments were incorporated into the draft by the writing group chair and vice chair, and the entire writing group was asked to approve the final draft. The chair and vice chair revised the document in response to peer review, and the document was again sent to the entire writing group for additional suggestions and approval.

The recommendations follow the AHA Stroke Council's methods of classifying the level of certainty of the treatment effect and the class of evidence (Tables 1 and 2). All Class I recommendations are listed in Table 3. All new or revised recommendations are listed in Table 4.

### Incidence and Prevalence of aSAH

Considerable variation in the annual incidence of aSAH exists in different regions of the world. A World Health Organization study found a 10-fold variation in the age-adjusted annual incidence in countries in Europe and Asia, from 2.0 cases per 100 000 population in China to 22.5 cases per 100 000 in Finland.<sup>3</sup> A later systematic review supported a high incidence of aSAH in Finland and Japan, a low incidence in South and Central America, and an intermediate incidence of 9.1 per 100 000 population in other regions.<sup>4</sup> In a more recent systematic review of population-based studies, the incidence of aSAH ranged from 2 to 16 per 100 000.<sup>5</sup> In that review, the pooled age-adjusted incidence rate of aSAH in low- to middle-income countries was found to be almost double that of high-income countries.<sup>5</sup> Although some reports have suggested the incidence of aSAH in the United States to be 9.7 per 100 000,<sup>6</sup> the 2003 Nationwide Inpatient Sample provided an annual estimate of 14.5 discharges for aSAH per 100 000 adults.<sup>7</sup> Because death resulting from aSAH often occurs before hospital admission (an estimated 12% to 15% of cases),<sup>8,9</sup> the true incidence of aSAH might be even higher. Although a number of population-based studies have indicated that the incidence of aSAH has remained relatively stable over the past 4 decades,<sup>5,10–16</sup> a recent review that adjusted for age and sex suggested a slight decrease in incidence between 1950 and 2005 for regions other than Japan, South and Central America, and Finland.<sup>4</sup> These data are consistent with studies that show that the incidence of aSAH increases with age, with a typical average age of onset in adults  $\geq 50$  years of age.<sup>3,7,17,18</sup> aSAH is relatively uncommon in children; incidence rates increase as children get older, with incidence ranging from 0.18 to 2.0 per 100 000.<sup>4,19</sup> The majority of studies also indicate a higher incidence of aSAH in women than in men.<sup>7,11–13,20–22</sup> Most recent pooled figures report the incidence in women to be 1.24 (95% confidence interval, 1.09–1.42) times higher than in men.<sup>4</sup> This is lower than a previous estimate of 1.6 (95% confidence interval, 1.1–2.3) for the years 1960 to 1994.<sup>23</sup> Evidence of a sex-age effect on aSAH incidence has emerged from pooled study data, with a higher incidence reported in younger men (25–45 years of age), women between 55 and 85 years of age, and men  $>85$  years of age.<sup>4</sup> Differences in incidence of aSAH by race and ethnicity appear to exist.

Table 1. Applying Classification of Recommendation and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT				
	CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/ administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> <i>Additional studies with focused objectives needed</i> <b>IT IS REASONABLE</b> to per- form procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i>  Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>	
				Procedure/ Test	Treatment
				COR III: No benefit	No Proven Benefit
				COR III: Harm	Excess Cost w/o Benefit or Harmful
<b>LEVEL A</b> Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	
<b>LEVEL B</b> Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	
<b>LEVEL C</b> Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit  is not recommended is not indicated should not be performed/ administered/ other is not useful/ beneficial/ effective	COR III: Harm  potentially harmful causes harm associated with excess morbidity/mortality should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B			

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

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

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

Blacks and Hispanics have a higher incidence of aSAH than white Americans.<sup>6,24,25</sup>

### Risk Factors for and Prevention of aSAH

Behavioral risk factors for aSAH include hypertension, smoking, alcohol abuse, and the use of sympathomimetic drugs (eg, cocaine). In addition to female sex (above), the risk of aSAH is increased by the presence of an unruptured cerebral aneurysm (particularly those that are symptomatic, larger in size, and located either on the posterior communicating artery or the vertebrobasilar system), a history of previous aSAH (with or without a residual untreated aneurysm), a history of

familial aneurysms (at least 1 first-degree family member with an intracranial aneurysm, and especially if ≥2 first-degree relatives are affected) and family history of aSAH,<sup>26,27</sup> and certain genetic syndromes, such as autosomal dominant polycystic kidney disease and type IV Ehlers-Danlos syndrome.<sup>28,29</sup> Novel findings reported since publication of the previous version of these guidelines include the following: (1) Aneurysms in the anterior circulation appear to be more prone to rupture in patients <55 years of age, whereas posterior communicating aneurysms ruptured more frequently in men, and basilar artery aneurysm rupture is associated with lack of use of alcohol.<sup>30</sup> (2) The size at which



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

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment.
Class IIb	Usefulness/efficacy is less well established by evidence or opinion.
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study, or $\geq 1$ case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

aneurysms rupture appears to be smaller in those patients with the combination of hypertension and smoking than in those with either risk factor alone.<sup>31</sup> (3) Significant life events such as financial or legal problems within the past month may increase the risk of aSAH.<sup>32</sup> (4) Aneurysm size  $>7$  mm has been shown to be a risk factor for rupture.<sup>33</sup> (5) There does not appear to be an increased risk of aSAH in pregnancy, delivery, and puerperium.<sup>34,35</sup>

Inflammation appears to play an important role in the pathogenesis and growth of intracranial aneurysms.<sup>36</sup> Prominent mediators include the nuclear factor  $\kappa$ -light-chain enhancer of activated B cells (NF- $\kappa$ B),<sup>37</sup> tumor necrosis factor, macrophages, and reactive oxygen species. Although there are no controlled studies in humans, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statin)<sup>38</sup> and calcium channel blockers may retard aneurysm formation through the inhibition of NF- $\kappa$ B and other pathways. Among the risk factors for aSAH, clearly attributable and modifiable risks are very low body mass index, smoking, and high alcohol consumption.<sup>31,39,40</sup> Yet, despite marked improvements in the treatment of hypertension and hyperlipidemia and the decrease in rates of smoking over time, the incidence of aSAH has not changed appreciably in 30 years.<sup>16</sup>

It is possible that diet increases the risk of stroke in general and aSAH in particular. In an epidemiological study of Finnish smokers who were monitored for  $>13$  years, increased consumption of yogurt (but not all dairy products) was associated with a higher risk of aSAH.<sup>41</sup> Greater vegetable consumption is associated with a lower risk of stroke and aSAH.<sup>42</sup> Higher coffee and tea consumption<sup>43</sup> and higher magnesium consumption<sup>44</sup> were associated with reduced risk of stroke overall but did not change the risk of aSAH.

Predicting the growth of an individual intracranial aneurysm and its potential for rupture in a given patient remains problematic. When followed up on magnetic resonance imaging, larger aneurysms ( $\geq 8$  mm in diameter) tended to grow more over time,<sup>45</sup> which implies a higher risk of rupture. Several characteristics of aneurysm morphology (such as a bottleneck shape<sup>46</sup> and the ratio of size of aneurysm to parent vessel<sup>47,48</sup>) have been associated with rupture status, but how these might be applied to individual patients to predict future aneurysmal rupture is still unclear.<sup>33</sup> Variability within each patient is unpredictable at this time, but such intraindividual variability markedly changes the risk of aneurysm detection and rupture and may attenuate the benefits of routine screening in high-risk patients.<sup>49</sup>

Given such uncertainties, younger age, longer life expectancy, and higher rate of rupture all make treatment of unruptured aneurysms more likely to be cost-effective and reduce morbidity and mortality.<sup>50</sup> Two large observational studies of familial aneurysms suggest that screening these patients may also be cost-effective in preventing aSAH and improving quality of life.<sup>26,27</sup> Smaller studies have suggested that screening of those with 1 first-degree relative with aSAH may be justified as well, but it is far less clear whether patients who underwent treatment for a previous aSAH require ongoing screening.<sup>51,52</sup> In the Cerebral Aneurysm Rerupture After Treatment (CARAT) study, recurrent aSAH was predicted by incomplete obliteration of the aneurysm and occurred a median of 3 days after treatment but rarely after 1 year.<sup>53</sup> Repeated noninvasive screening at later times may not be cost-effective, increase life expectancy, or improve quality of life in unselected patients.<sup>54</sup> Patients with adequately obliterated aneurysms after aSAH have a low risk of recurrent aSAH for at least 5 years,<sup>55,56</sup> although some coiled aneurysms require retreatment.<sup>57</sup>

### **Risk Factors for and Prevention of aSAH: Recommendations**

1. **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. **Hypertension should be treated, and such treatment may reduce the risk of aSAH (Class I; Level of Evidence B).**
3. **Tobacco use and alcohol misuse should be avoided to reduce the risk of aSAH (Class I; Level of Evidence B).**

**Table 3. Class I Recommendations**

Level of Evidence	Recommendation
A	1. Treatment of high blood pressure with antihypertensive medication is recommended to prevent ischemic stroke, intracerebral hemorrhage, and cardiac, renal, and other end-organ injury.
A	2. Oral nimodipine should be administered to all patients with aSAH. (It should be noted that this agent has been shown to improve neurological outcomes but not cerebral vasospasm. The value of other calcium antagonists, whether administered orally or intravenously, remains uncertain.)
B	1. Hypertension should be treated, and such treatment may reduce the risk of aSAH
B	2. Tobacco use and alcohol misuse should be avoided to reduce the risk of aSAH.
B*	3. After any aneurysm repair, immediate cerebrovascular imaging is generally recommended to identify remnants or recurrence of the aneurysm that may require treatment.
B	4. The initial clinical severity of aSAH should be determined rapidly by use of simple validated scales (eg, Hunt and Hess, World Federation of Neurological Surgeons), because it is the most useful indicator of outcome after aSAH.
B	5. The risk of early aneurysm rebleeding is high and is associated with very poor outcomes. Therefore, urgent evaluation and treatment of patients with suspected aSAH is recommended.
B	6. aSAH is a medical emergency that is frequently misdiagnosed. A high level of suspicion for aSAH should exist in patients with acute onset of severe headache.
B	7. Acute diagnostic workup should include noncontrast head CT, which, if nondiagnostic, should be followed by lumbar puncture.
B*	8. DSA with 3-dimensional rotational angiography is indicated for detection of aneurysm in patients with aSAH (except when the aneurysm was previously diagnosed by a noninvasive angiogram) and for planning treatment (to determine whether an aneurysm is amenable to coiling or to expedite microsurgery).
B*	9. Between the time of aSAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure.
B	10. Surgical clipping or endovascular coiling of the ruptured aneurysm should be performed as early as feasible in the majority of patients to reduce the rate of rebleeding after aSAH.
B	11. Complete obliteration of the aneurysm is recommended whenever possible.
B†	12. For patients with ruptured aneurysms judged to be technically amenable to both endovascular coiling and neurosurgical clipping, endovascular coiling should be considered.
B*	13. In the absence of a compelling contraindication, patients who undergo coiling or clipping of a ruptured aneurysm should have delayed follow-up vascular imaging (timing and modality to be individualized), and strong consideration should be given to retreatment, either by repeat coiling or microsurgical clipping, if there is a clinically significant (eg, growing) remnant.
B†	14. Low-volume hospitals (eg, <10 aSAH cases per year) should consider early transfer of patients with aSAH to high-volume centers (eg, >35 aSAH cases per year) with experienced cerebrovascular surgeons, endovascular specialists, and multidisciplinary neuro-intensive care services.
B†	15. Maintenance of euolemia and normal circulating blood volume is recommended to prevent DCI.
B†	16. Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it.
B†	17. aSAH-associated acute symptomatic hydrocephalus should be managed by cerebrospinal fluid diversion (EVD or lumbar drainage, depending on the clinical scenario).
B*	18. Heparin-induced thrombocytopenia and deep venous thrombosis, although infrequent, are not uncommon occurrences after aSAH. Early identification and targeted treatment are recommended, but further research is needed to identify the ideal screening paradigms.
C†	1. Determination of aneurysm treatment, as judged by both experienced cerebrovascular surgeons and endovascular specialists, should be a multidisciplinary decision based on characteristics of the patient and the aneurysm.
C†	2. aSAH-associated chronic symptomatic hydrocephalus should be treated with permanent cerebrospinal fluid diversion.

aSAH indicates aneurysmal subarachnoid hemorrhage; CT, computed tomography; DSA, digital subtraction angiography; DCI, delayed cerebral ischemia; and EVD, external ventricular drainage.

\*A new recommendation.

†A change in either level of evidence or strength of the recommendation from previous guidelines.

**4. In addition to the size and location of the aneurysm and the patient's age and health status, it might be reasonable to consider morphological and hemodynamic characteristics of the aneurysm when discussing the risk of aneurysm rupture (Class IIb; Level of Evidence B).** (New recommendation)

**5. Consumption of a diet rich in vegetables may lower the risk of aSAH (Class IIb; Level of Evidence B).** (New recommendation)

**6. It may be reasonable to offer noninvasive screening to patients with familial (at least 1 first-degree relative) aSAH and/or a history of aSAH to evaluate**

**Table 4. New or Revised Recommendations**

New or Revised	Recommendation	Class of Recommendation/ Level of Evidence
New	1. In addition to the size and location of the aneurysm and the patient's age and health status, it might be reasonable to consider morphological and hemodynamic characteristics of the aneurysm when discussing the risk of aneurysm rupture.	Class IIb, Level B
New	2. Consumption of a diet rich in vegetables may lower the risk of aSAH.	Class IIb, Level B
New	3. After any aneurysm repair, immediate cerebrovascular imaging is generally recommended to identify remnants or recurrence of the aneurysm that may require treatment.	Class I, Level B
New	4. After discharge, it is reasonable to refer patients with aSAH for a comprehensive evaluation, including cognitive, behavioral, and psychosocial assessments.	Class IIa, Level B
New	5. CTA may be considered in the workup of aSAH. If an aneurysm is detected by CTA, this study may help guide the decision for the type of aneurysm repair, but if CTA is inconclusive, DSA is still recommended (except possibly in the instance of classic perimesencephalic SAH).	Class IIb, Level C
New	6. Magnetic resonance imaging (fluid-attenuated inversion recovery, proton density, diffusion-weighted imaging, and gradient echo sequences) may be reasonable for the diagnosis of SAH in patients with a nondiagnostic CT scan, although a negative result does not obviate the need for cerebrospinal fluid analysis.	Class IIb, Level C
New	7. DSA with 3-dimensional rotational angiography is indicated for detection of aneurysm in patients with aSAH (except when the aneurysm was previously diagnosed by a noninvasive angiogram) and for planning treatment (to determine whether an aneurysm is amenable to coiling or to expedite microsurgery).	Class I, Level B
New	8. Between the time of aSAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure.	Class I, Level B
New	9. The magnitude of blood pressure control to reduce the risk of rebleeding has not been established, but a decrease in systolic blood pressure to <160 mm Hg is reasonable.	Class IIa, Level C
New	10. In the absence of a compelling contraindication, patients who undergo coiling or clipping of a ruptured aneurysm should have delayed follow-up vascular imaging (timing and modality to be individualized), and strong consideration should be given to retreatment, either by repeat coiling or microsurgical clipping, if there is a clinically significant (eg, growing) remnant.	Class I, Level B
New	11. Microsurgical clipping may receive increased consideration in patients presenting with large (>50 mL) intraparenchymal hematomas and middle cerebral artery aneurysms. Endovascular coiling may receive increased consideration in the elderly (>70 y of age), in those presenting with poor-grade WFNS classification (IV/V) aSAH, and in those with aneurysms of the basilar apex.	Class IIb, Level C
New	12. Stenting of a ruptured aneurysm is associated with increased morbidity and mortality.	Class III, Level C
New	13. Annual monitoring of complication rates for surgical and interventional procedures is reasonable.	Class IIa, Level C
New	14. A hospital credentialing process to ensure that proper training standards have been met by individual physicians treating brain aneurysms is reasonable.	Class IIa, Level C
New	15. Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended.	Class III, Level B
New	16. Transcranial Doppler is reasonable to monitor for the development of arterial vasospasm.	Class IIa, Level B
New	17. Perfusion imaging with CT or magnetic resonance can be useful to identify regions of potential brain ischemia.	Class IIa, Level B
New	18. Weaning EVD over >24 hours does not appear to be effective in reducing the need for ventricular shunting.	Class III, Level B
New	19. Routine fenestration of the lamina terminalis is not useful for reducing the rate of shunt-dependent hydrocephalus and therefore should not be routinely performed.	Class III, Level B
New	20. Aggressive control of fever to a target of normothermia by use of standard or advanced temperature modulating systems is reasonable in the acute phase of aSAH.	Class IIa, Level B
New	21. The use of packed red blood cell transfusion to treat anemia might be reasonable in patients with aSAH who are at risk of cerebral ischemia. The optimal hemoglobin goal is still to be determined.	Class IIb, Level B
New	22. Heparin-induced thrombocytopenia and deep venous thrombosis are relatively frequent complications after aSAH. Early identification and targeted treatment are recommended, but further research is needed to identify the ideal screening paradigms.	Class I, Level B
Revised	1. For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, short-term (<72 hours) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding.	Class IIa, Level B
Revised	2. Determination of aneurysm treatment, as judged by both experienced cerebrovascular surgeons and endovascular specialists, should be a multidisciplinary decision based on characteristics of the patient and the aneurysm.	Class I, Level C

(Continued)

Table 4. Continued

New or Revised	Recommendation	Class of Recommendation/ Level of Evidence
Revised	3. For patients with ruptured aneurysms judged to be technically amenable to both endovascular coiling and neurosurgical clipping, endovascular coiling should be considered.	Class I, Level B
Revised	4. Low-volume hospitals (eg, <10 aSAH cases per year) should consider early transfer of patients with aSAH to high-volume centers (eg, >35 aSAH cases per year) with experienced cerebrovascular surgeons, endovascular specialists, and multidisciplinary neuro-intensive care services.	Class I, Level B
Revised	5. Maintenance of euolemia and normal circulating blood volume is recommended to prevent DCI.	Class I, Level B
Revised	6. Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it.	Class I, Level B
Revised	7. Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy.	Class IIa, Level B
Revised	8. aSAH-associated acute symptomatic hydrocephalus should be managed by cerebrospinal fluid diversion (EVD or lumbar drainage, depending on the clinical scenario).	Class I, Level B
Revised	9. aSAH-associated chronic symptomatic hydrocephalus should be treated with permanent cerebrospinal fluid diversion.	Class I, Level C

aSAH indicates aneurysmal subarachnoid hemorrhage; CTA, computed tomography angiography; DSA, digital subtraction angiography; CT, computed tomography; DSA, digital subtraction angiography; EVD, external ventricular drainage; DCI, delayed cerebral ischemia; and WFNS, World Federation of Neurological Surgeons.

**for de novo aneurysms or late regrowth of a treated aneurysm, but the risks and benefits of this screening require further study (Class IIb; Level of Evidence B).**

- 7. After any aneurysm repair, immediate cerebrovascular imaging is generally recommended to identify remnants or recurrence of the aneurysm that may require treatment (Class I; Level of Evidence B).** (New recommendation)

### Natural History and Outcome of aSAH

Although the case fatality of aSAH remains high worldwide,<sup>5</sup> mortality rates from aSAH appear to have declined in industrialized nations over the past 25 years.<sup>9,11,15,58,59</sup> One study in the United States reported a decrease of  $\approx 1\%$  per year from 1979 to 1994.<sup>60</sup> Others have shown that case fatality rates decreased from 57% in the mid-1970s to 42% in the mid-1980s,<sup>11</sup> whereas rates from the mid-1980s to 2002 are reported to be anywhere from 26% to 36%.<sup>6,12,13,18,20,61,62</sup> Mortality rates vary widely across published epidemiological studies, ranging from 8% to 67%.<sup>59</sup> Regional variations become apparent when numbers from different studies are compared. The median mortality rate in epidemiological studies from the United States has been 32% versus 43% to 44% in Europe and 27% in Japan.<sup>59</sup> These numbers are based on studies that did not always fully account for cases of prehospital death. This is an important consideration because the observed decrease in case fatality is related to improvements in survival among hospitalized patients with aSAH.

The mean age of patients presenting with aSAH is increasing, which has been noted to have a negative impact on survival rates.<sup>59</sup> Sex and racial variations in survival may also play a role in the variable rates, with some studies suggesting higher mortality in women than in men<sup>9,11,60</sup> and higher

mortality in blacks, American Indians/Alaskan Natives, and Asians/Pacific Islanders than in whites.<sup>63</sup>

Available population-based studies offer much less information about the functional outcome of survivors. Rates of persistent dependence of between 8% and 20% have been reported when the modified Rankin Scale is used.<sup>59</sup> Although not population based, trial data show a similar picture, with 12% of patients in the International Subarachnoid Aneurysm Trial (ISAT) showing significant lifestyle restrictions (modified Rankin Scale 3) and 6.5% being functionally dependent (modified Rankin Scale score of 4–5) 1 year after aSAH. Furthermore, scales that are relatively insensitive to cognitive impairment, behavioral changes, social readjustment, and energy level may substantially underestimate the effect of aSAH on the function and quality of life of surviving patients. Multiple studies using diverse designs have consistently demonstrated that intellectual impairment is very prevalent after aSAH. Although cognitive function tends to improve over the first year,<sup>64</sup> global cognitive impairment is still present in  $\approx 20\%$  of aSAH patients and is associated with poorer functional recovery and lower quality of life.<sup>65</sup> Cognitive deficits and functional decline are often compounded by mood disorders (anxiety, depression), fatigue, and sleep disturbances.<sup>66</sup> Therefore, scales assessing well-being and quality of life can be particularly useful in the integral assessment of patients with aSAH, even among those who regain functional independence.<sup>67,68</sup> Behavioral and psychosocial difficulties, as well as poor physical and mental endurance, are some of the most commonly encountered factors accounting for the inability of otherwise independent patients to return to their previous occupations.<sup>66,68</sup>

Much remains to be learned about the causes of cognitive and functional deficits after aSAH and the best methods to assess intellectual outcome and functional recovery in these patients. The severity of clinical presentation is the strongest prognostic indicator in aSAH. Initial clinical severity can be



reliably categorized by use of simple validated scales, such as the Hunt and Hess and World Federation of Neurological Surgeons scales.<sup>69,70</sup> Aneurysm rebleeding is another major predictor of poor outcome, as discussed in a later section. Other factors predictive of poor prognosis include older age, preexisting severe medical illness, global cerebral edema on computed tomography (CT) scan, intraventricular and intracerebral hemorrhage, symptomatic vasospasm, delayed cerebral infarction (especially if multiple), hyperglycemia, fever, anemia, and other systemic complications such as pneumonia and sepsis.<sup>71–77</sup> Certain aneurysm factors, such as size, location, and complex configuration, may increase the risk of periprocedural complications and affect overall prognosis.<sup>78</sup> Treatment in high-volume centers with availability of neurosurgical and endovascular services may be associated with better outcomes.<sup>79–81</sup>

### Natural History and Outcome of aSAH: Recommendations

1. **The initial clinical severity of aSAH should be determined rapidly by use of simple validated scales (eg, Hunt and Hess, World Federation of Neurological Surgeons), because it is the most useful indicator of outcome after aSAH (Class I; Level of Evidence B).**
2. **The risk of early aneurysm rebleeding is high, and rebleeding is associated with very poor outcomes. Therefore, urgent evaluation and treatment of patients with suspected aSAH is recommended (Class I; Level of Evidence B).**
3. **After discharge, it is reasonable to refer patients with aSAH for a comprehensive evaluation, including cognitive, behavioral, and psychosocial assessments (Class IIa; Level of Evidence B).** (New recommendation)

### Clinical Manifestations and Diagnosis of aSAH

The clinical presentation of aSAH is one of the most distinctive in medicine. The hallmark of aSAH in a patient who is awake is the complaint “the worst headache of my life,” which is described by  $\approx 80\%$  of patients who can give a history.<sup>82</sup> This headache is characterized as being extremely sudden and immediately reaching maximal intensity (thunderclap headache). A warning or sentinel headache that precedes the aSAH-associated ictus is also reported by 10% to 43% of patients.<sup>83,84</sup> This sentinel headache increases the odds of early rebleeding 10-fold.<sup>85</sup> Most intracranial aneurysms remain asymptomatic until they rupture. aSAH can occur during physical exertion or stress.<sup>86</sup> Nevertheless, in a review of 513 patients with aSAH, the highest incidence of rupture occurred while patients were engaged in their daily routines, in the absence of strenuous physical activity.<sup>87</sup> The onset of headache may be associated with  $\geq 1$  additional signs and symptoms, including nausea and/or vomiting, stiff neck, photophobia, brief loss of consciousness, or focal neurological deficits (including cranial nerve palsies). In a retrospective study of 109 patients with proven aSAH, headache was present in 74%, nausea or vomiting in 77%, loss of con-

sciousness in 53%, and nuchal rigidity in 35%.<sup>88</sup> As many as 12% of patients die before receiving medical attention.

Despite the classic presentation of aSAH, individual findings occur inconsistently, and because the type of headache from aSAH is sufficiently variable, misdiagnosis or delayed diagnosis is common. Before 1985, misdiagnosis of aSAH occurred in as many as 64% of cases, with more recent data suggesting a misdiagnosis rate of  $\approx 12\%$ .<sup>89,90</sup> 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.<sup>89</sup> The most common diagnostic error is failure to obtain a noncontrast head CT scan.<sup>89,91–93</sup> In a small subset of patients, a high degree of suspicion based on clinical presentation will lead to the correct diagnosis despite normal head CT and cerebrospinal fluid test results, as shown in a recent study in which 1.4% of patients were diagnosed with aSAH only after vascular imaging techniques were used.<sup>94</sup>

Patients may report symptoms consistent with a minor hemorrhage before a major rupture, which has been called a sentinel bleed or warning leak.<sup>83,84</sup> The majority of these minor hemorrhages occur within 2 to 8 weeks before overt aSAH. The headache associated with a warning leak is usually milder than that associated with a major rupture, but it may last a few days.<sup>95,96</sup> Nausea and vomiting may occur, but meningismus is uncommon after a sentinel hemorrhage. Among 1752 patients with aneurysm rupture from 3 series, 340 (19.4%; range, 15%–37%) had a history of a sudden severe headache before the event that led to admission.<sup>82,95,97</sup> The importance of recognizing a warning leak cannot be overemphasized. Headache is a common presenting chief complaint in the emergency department, and aSAH accounts for only 1% of all headaches evaluated in the emergency department.<sup>92</sup> Therefore, a high index of suspicion is warranted, because diagnosis of the warning leak or sentinel hemorrhage before a catastrophic rupture may be lifesaving.<sup>93</sup> Seizures may occur in up to 20% of patients after aSAH, most commonly in the first 24 hours and more commonly in aSAH associated with intracerebral hemorrhage, hypertension, and middle cerebral and anterior communicating artery aneurysms.<sup>98,99</sup>

Noncontrast head CT remains the cornerstone of diagnosis of aSAH; since publication of the previous version of these guidelines,<sup>1,2</sup> there have been only minor changes in imaging technology for this condition. The sensitivity of CT in the first 3 days after aSAH remains very high (close to 100%), after which it decreases moderately during the next few days.<sup>2,100</sup> After 5 to 7 days, the rate of negative CT increases sharply, and lumbar puncture is often required to show xanthochromia. However, advances in magnetic resonance imaging of the brain, particularly the use of fluid-attenuated inversion recovery, proton density, diffusion-weighted imaging, and gradient echo sequences,<sup>101–103</sup> can often allow the diagnosis of aSAH to be made when a head CT scan is negative and there is clinical suspicion of aSAH, possibly avoiding the need for lumbar puncture. The role of magnetic resonance imaging in perimesencephalic aSAH is controversial.<sup>104</sup> Indications for magnetic resonance angiography in aSAH are still few because of limitations with routine



availability, logistics (including difficulty in scanning acutely ill patients), predisposition to motion artifact, patient compliance, longer study time, and cost. Aneurysms <3 mm in size continue to be unreliably demonstrated on computed tomographic angiography (CTA),<sup>105,106</sup> and this generates continued controversy in the case of CTA-negative aSAH.<sup>107</sup> In cases of perimesencephalic subarachnoid hemorrhage (SAH), some authors claim that a negative CTA result is sufficient to rule out aneurysmal hemorrhage and that cerebral angiography is not required, but this is controversial. In 1 study, the overall interobserver and intraobserver agreement for nonaneurysmal perimesencephalic hemorrhage was good, but there was still a level of disagreement among observers, which suggests that clinicians should be cautious when deciding whether to pursue follow-up imaging.<sup>108</sup> In another study,<sup>109</sup> a negative CTA result reliably excluded aneurysms when head CT showed the classic perimesencephalic SAH pattern or no blood. Digital subtraction angiography (DSA) was indicated if there was a diffuse aneurysmal pattern of aSAH, and repeat delayed DSA was required if the initial DSA findings were negative, which led to the detection of a small aneurysm in 14% of cases. When the blood is located in the sulci, CTA should be scrutinized for vasculitis, and DSA is recommended for confirmation.<sup>109</sup> Others have shown that CTA may not reveal small aneurysms and that 2- and 3-dimensional cerebral angiography should be performed, especially when the hemorrhage is accompanied by loss of consciousness.<sup>110</sup> In cases of diffuse aSAH pattern, most agree that negative CTA should be followed by 2- and 3-dimensional cerebral angiography. In older patients with degenerative vascular diseases, CTA can replace catheter cerebral angiography in most cases if the image quality is excellent and analysis is performed carefully.<sup>111</sup> Overlying bone can be problematic with CTA, especially at the skull base. A new technique, CTA-MMBE (multisection CTA combined with matched mask bone elimination), is accurate in detecting intracranial aneurysms in any projection without superimposed bone.<sup>112</sup> CTA-MMBE has limited sensitivity in detecting very small aneurysms. The data suggest that DSA and 3-dimensional rotational angiography can be limited to the vessel harboring the ruptured aneurysm before endovascular treatment after detection of a ruptured aneurysm with CTA. Another new technique, dual-energy CTA, has diagnostic image quality at a lower radiation dose than digital subtraction CTA and high diagnostic accuracy compared with 3-dimensional DSA (but not 2-dimensional DSA) in the detection of intracranial aneurysms.<sup>113</sup>

Cerebral angiography is still widely used in the investigation of aSAH and the characterization of ruptured cerebral aneurysms. Although CTA is sometimes considered sufficient on its own when an aneurysm will be treated with surgical clipping,<sup>114</sup> substantial controversy remains about the ability of CTA to determine whether or not an aneurysm is amenable to endovascular therapy.<sup>115–120</sup> In 1 series,<sup>115</sup> 95.7% of patients with aSAH were referred for treatment on the basis of CTA. In 4.4% of patients, CTA did not provide enough information to determine the best treatment, and those patients required DSA; 61.4% of patients were referred to endovascular treatment on the basis of CTA; and successful

coiling was achieved in 92.6%. The authors concluded that CTA with a 64-slice scanner is an accurate tool for detecting and characterizing aneurysms in acute aSAH and that CTA is useful in deciding whether to coil or clip an aneurysm.<sup>115</sup> Partial volume averaging phenomena may artificially widen the aneurysmal neck and may lead to the erroneous conclusion that an aneurysm cannot be treated by endovascular coiling. This controversy is likely caused by the different technological specifications (16- versus 64-detector rows), slice thickness, and data processing algorithms of various CT systems, which have different spatial resolutions. Three-dimensional cerebral angiography is more sensitive for detecting aneurysms than 2-dimensional angiography.<sup>121,122</sup> The combination of 3- and 2-dimensional cerebral angiography usually provides the best morphological depiction of aneurysm anatomy with high spatial resolution, and it is, of course, always used in preparation for endovascular therapy.

Flat-panel volumetric CT is a relatively recent development that allows the generation of CT-like images from a rotational 3-dimensional spin of the x-ray gantry in the angiography room. For the moment, it has no substantial role in the initial diagnosis of aSAH because its spatial and contrast resolutions are not high enough<sup>123</sup>; however, this technology can be used intraprocedurally during embolizations to rule out hydrocephalus.<sup>124</sup> Recently, radiation dose has emerged as an important and worrisome consideration for patients with SAH.<sup>125,126</sup> The combination of noncontrast head CT for the diagnosis of aSAH, confirmation of ventriculostomy placement, investigation of neurological changes, CTA for aneurysmal diagnosis, CTA and CT perfusion for recognition of vasospasm, and catheter cerebral angiography for aneurysm embolization and then for endovascular therapy of vasospasm can result in substantial radiation doses to the head, with possible risk of radiation injury, such as scalp erythema and alopecia. Although some or all of these radiological examinations are often necessary, efforts need to be made to reduce the amount of radiation exposure in patients with aSAH whenever possible.

### Clinical Manifestations and Diagnosis of aSAH: Recommendations

1. aSAH is a medical emergency that is frequently misdiagnosed. A high level of suspicion for aSAH should exist in patients with acute onset of severe headache (*Class I; Level of Evidence B*).
2. Acute diagnostic workup should include noncontrast head CT, which, if nondiagnostic, should be followed by lumbar puncture (*Class I; Level of Evidence B*).
3. CTA may be considered in the workup of aSAH. If an aneurysm is detected by CTA, this study may help guide the decision for type of aneurysm repair, but if CTA is inconclusive, DSA is still recommended (except possibly in the instance of classic perimesencephalic aSAH) (*Class IIb; Level of Evidence C*). (New recommendation)
4. Magnetic resonance imaging (fluid-attenuated inversion recovery, proton density, diffusion-weighted imaging, and gradient echo sequences) may be reasonable for the diagnosis of aSAH in patients with a nondiagnostic CT scan, although a negative result

does not obviate the need for cerebrospinal fluid analysis (*Class IIb; Level of Evidence C*). (New recommendation)

5. DSA with 3-dimensional rotational angiography is indicated for detection of aneurysm in patients with aSAH (except when the aneurysm was previously diagnosed by a noninvasive angiogram) and for planning treatment (to determine whether an aneurysm is amenable to coiling or to expedite microsurgery) (*Class I; Level of Evidence B*). (New recommendation)

### Medical Measures to Prevent Rebleeding After aSAH

Aneurysm rebleeding is associated with very high mortality and poor prognosis for functional recovery in survivors. The risk of rebleeding is maximal in the first 2 to 12 hours, with reported rates of occurrence between 4% and 13.6% within the first 24 hours.<sup>127–130</sup> In fact, more than one third of rebleeds occur within 3 hours and nearly half within 6 hours of symptom onset,<sup>131</sup> and early rebleeding is associated with worse outcome than later rebleeding.<sup>132</sup> Factors associated with aneurysm rebleeding include longer time to aneurysm treatment, worse neurological status on admission, initial loss of consciousness, previous sentinel headaches (severe headaches lasting >1 hour that do not lead to the diagnosis of aSAH), larger aneurysm size, and possibly systolic blood pressure >160 mm Hg.<sup>87,129,130</sup> Genetic factors, although related to the occurrence of intracranial aneurysms, do not appear to be related to an increased incidence of rebleeding.<sup>133</sup> Early treatment of the ruptured aneurysm can reduce the risk of rebleeding.<sup>71</sup> Among patients who present in a delayed manner and during the vasospasm window, delayed obliteration of aneurysm is associated with a higher risk of rebleeding than early obliteration of aneurysm.<sup>134</sup>

There is general agreement that acute hypertension should be controlled after aSAH and until aneurysm obliteration, but parameters for blood pressure control have not been defined. A variety of titratable medications are available. Nicardipine may give smoother blood pressure control than labetalol<sup>135</sup> and sodium nitroprusside,<sup>136</sup> although data showing different clinical outcomes are lacking. Although lowering cerebral perfusion pressure may lead to cerebral ischemia, a cohort study of neurologically critically ill patients did not find an association between use of nicardipine and reduced brain oxygen tension.<sup>137</sup> Clevidipine, a very short-acting calcium channel blocker, is another option for acute control of hypertension, but data for aSAH are lacking at this time.

Antifibrinolytic therapy has been shown to reduce the incidence of aneurysm rebleeding when there is a delay in aneurysm obliteration. One referral center instituted a policy of short-term use of aminocaproic acid to prevent rebleeding during patient transfer. Such use led to a decreased incidence in rebleeding without increasing the risk of DCI, but 3-month clinical outcomes were not affected.<sup>138</sup> There was an increased risk of deep venous thrombosis but not pulmonary embolism. Neither aminocaproic acid nor tranexamic acid is approved by the US Food and Drug Administration for prevention of aneurysm rebleeding.

### Medical Measures to Prevent Rebleeding After aSAH: Recommendations

1. Between the time of aSAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure (*Class I; Level of Evidence B*). (New recommendation)
2. The magnitude of blood pressure control to reduce the risk of rebleeding has not been established, but a decrease in systolic blood pressure to <160 mm Hg is reasonable (*Class IIa; Level of Evidence C*). (New recommendation)
3. For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, short-term (<72 hours) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding (*Class IIa; Level of Evidence B*). (Revised recommendation from previous guidelines)

### Surgical and Endovascular Methods for Treatment of Ruptured Cerebral Aneurysms

Microsurgical clip obliteration of intracranial aneurysms was the primary modality of treatment before 1991, when Guglielmi first described occlusion of an aneurysm by an endovascular approach with electrolytically detachable coils.<sup>139</sup> With advancements in both microsurgical and endovascular approaches, algorithms to determine the proper patient population and aneurysmal characteristics for each treatment are continually undergoing refinement. The only multicenter randomized trial comparing microsurgical and endovascular repair, ISAT, randomized 2143 of 9559 screened patients with aSAH across 42 neurosurgical centers.<sup>140</sup> For a patient to be considered eligible for the trial, neurosurgeons and interventionalists had to agree that the aneurysm was comparably suitable for treatment with either modality. Primary outcomes included death or dependent living, and secondary outcomes included risk of seizures and risk of rebleeding. Initial 1-year outcomes revealed a reduction in death and disability from 31% in the microsurgery arm to 24% in the endovascular arm (relative risk reduction, 24%).<sup>141</sup> This difference was mainly driven by a decrease in the rate of disability among survivors 16% in the endovascular arm and 22% in the craniotomy arm) and was likely attributable at least in part to the greater incidence of technical complications in the clipping (19%) versus the coiling (8%) arms and the longer time needed to secure the aneurysm.<sup>142,143</sup> The risk of epilepsy and significant cognitive decline was also reduced in the endovascular group, but the incidence of late rebleeding (2.9% after endovascular repair versus 0.9% after open surgery) was higher in the endovascular arm, and only 58% of coiled aneurysms were completely obliterated compared with 81% of clipped aneurysms.<sup>140</sup> A large retrospective analysis found that the rate of incomplete occlusion and subsequent aneurysm recurrence depended critically on neck diameter and dome size.<sup>139</sup> It can also be difficult to achieve complete obliteration in very small aneurysms (<3 mm), with 1 study

reporting no coils deployed in 5% of cases, residual dome filling or a neck remnant in 30%, and a higher procedural complication rate than in larger aneurysms.<sup>144</sup>

Although the complete obliteration rate can be increased by the addition of a high-porosity stent, this has been associated with an increased risk of complications, especially in patients with SAH, in large part because of the need for periprocedural dual-antiplatelet therapy to prevent arterial thromboembolism.<sup>145</sup> Whether low-porosity flow-diverting stents with or without coils represent a better option for many or most of those presenting with SAH from saccular aneurysms remains to be studied, but these stents make more conceptual sense for use in the patient with a dissecting aneurysm, in whom vessel sacrifice is not an option and microsurgical solutions carry higher risk.

Another approach to increasing complete obliteration rates involves the deployment of biologically active rather than pure platinum coils.<sup>146</sup> Although uncontrolled studies suggest a potential reduction in the risk of recurrence, these data are preliminary and have yet to be confirmed in prospective controlled trials.<sup>147,148</sup> Thus, although the short-term efficacy of endovascular coil obliteration is well established compared with microsurgical approaches, close long-term surveillance continues to be warranted, because durability remains a significant concern.<sup>149</sup>

Given this delicate balance between safety and durability, there have been multiple efforts to identify subgroups of patients who might be best treated with endovascular or microsurgical techniques. Although the quality of the data is modest, most agree that with current endovascular technology, middle cerebral artery aneurysms can be difficult to treat with coil embolization, and in this location, surgical treatment has tended to yield more favorable results.<sup>146,150–152</sup> Although some have suggested that older patients are ideal candidates for coiling rather than clipping, data on this population are sparse and at times conflicting.<sup>141,153,154</sup> Although patients presenting with an intraparenchymal hematoma >50 mL have a higher incidence of unfavorable outcome, hematoma evacuation within <3.5 hours has been shown to improve outcome in this subgroup and argues in favor of microsurgery for most patients with large parenchymal clots.<sup>155</sup> By contrast, patients presenting during the vasospasm period, especially those with confirmed vasospasm, may be better treated with endovascular techniques, depending on the anatomy of the aneurysm and its relationship to the spasm.<sup>150</sup> Patients presenting with poor clinical grade appear to benefit more from endovascular coiling, especially if they are also elderly, because advanced age renders long-term durability less important.<sup>156</sup> Still, it is critical that patients with poor clinical grade be treated in centers where both modalities are available.<sup>157</sup>

Endovascular treatment of posterior circulation aneurysms has been gaining widespread acceptance based on several observational studies. A meta-analysis revealed that the mortality from coiling of a basilar bifurcation aneurysm was 0.9%, and the risk of permanent complications was 5.4%.<sup>158</sup> More recently, with regard to treatment of posterior circulation aneurysms, the mortality and morbidity in 112 ruptured aneurysms was 3.7% and 9.4%, respectively.<sup>159</sup> These data have led to an increasing tendency toward coiling ruptured

posterior circulation aneurysms. One study that compared clipping versus coiling of basilar apex aneurysm (44 patients in each treatment arm) found a poor outcome rate of 11% in the endovascular treatment group versus 30% in the surgical group. In that study, the main difference was the rate of ischemia and hemorrhage during the surgical intervention. The rates of recurrent hemorrhage and delayed ischemia were actually similar in both groups.<sup>159</sup>

Incomplete aneurysm occlusion and recurrent aneurysm filling from progressive coil compaction are particularly difficult challenges encountered with endovascular treatment of basilar artery aneurysms. In a study of 41 posterior circulation aneurysms, 35 (85%) had complete or near-complete immediate angiographic occlusion. The follow-up time frame for this study was 17 months, and of the 29 patients for whom follow-up was obtained, those with completely occluded aneurysms did not reveal any compaction. In the remaining patients who had near-complete occlusion, 47% had experienced recanalization, with 1 patient experiencing a rehemorrhage.<sup>160</sup> On the basis of these findings, closer follow-up with sequential DSA is needed in patients who undergo coiling of posterior circulation aneurysms, particularly those who do not exhibit complete occlusion on immediate follow-up angiography.

### **Surgical and Endovascular Methods of Treatment of Ruptured Cerebral Aneurysms: Recommendations**

- 1. Surgical clipping or endovascular coiling of the ruptured aneurysm should be performed as early as feasible in the majority of patients to reduce the rate of rebleeding after aSAH (Class I; Level of Evidence B).**
- 2. Complete obliteration of the aneurysm is recommended whenever possible (Class I; Level of Evidence B).**
- 3. Determination of aneurysm treatment, as judged by both experienced cerebrovascular surgeons and endovascular specialists, should be a multidisciplinary decision based on characteristics of the patient and the aneurysm (Class I; Level of Evidence C).** (Revised recommendation from previous guidelines)
- 4. For patients with ruptured aneurysms judged to be technically amenable to both endovascular coiling and neurosurgical clipping, endovascular coiling should be considered (Class I; Level of Evidence B).** (Revised recommendation from previous guidelines)
- 5. In the absence of a compelling contraindication, patients who undergo coiling or clipping of a ruptured aneurysm should have delayed follow-up vascular imaging (timing and modality to be individualized), and strong consideration should be given to retreatment, either by repeat coiling or microsurgical clipping, if there is a clinically significant (eg, growing) remnant (Class I; Level of Evidence B).** (New recommendation)
- 6. Microsurgical clipping may receive increased consideration in patients presenting with large (>50 mL) intraparenchymal hematomas and middle cerebral artery aneurysms. Endovascular coiling may receive increased consideration in the elderly (>70 years of age), in those presenting with poor-grade**



(World Federation of Neurological Surgeons classification IV/V) aSAH, and in those with aneurysms of the basilar apex (*Class IIB; Level of Evidence C*). (New recommendation)

7. **Stenting of a ruptured aneurysm is associated with increased morbidity and mortality, and should only be considered when less risky options have been excluded (*Class III; Level of Evidence C*).** (New recommendation)

### Hospital Characteristics and Systems of Care

In a US study of 31 476 nontraumatic cases of aSAH from 2003, definitive aneurysm repair was delivered in fewer than one third of cases. That said, the adjusted odds of definitive repair were significantly higher in urban teaching hospitals than in urban nonteaching hospitals (odds ratio, 1.62) or rural hospitals (odds ratio, 3.08).<sup>7</sup> In another study from 1993 to 2003, teaching status and larger hospital size were associated with higher charges and longer stay but also with better outcomes ( $P<0.05$ ) and lower mortality rates ( $P<0.05$ ), especially in patients who underwent aneurysm clipping ( $P<0.01$ ). Endovascular treatment, which was more often used in the elderly, was also associated with significantly higher mortality rates in smaller hospitals ( $P<0.001$ ) and steadily increasing morbidity rates (45%). Large academic centers were associated with better results, particularly for surgical clip placement.<sup>161</sup> Prior studies have also indicated that 82% of US hospitals admitted  $<19$  patients with aSAH annually, and the 30-day mortality rate was significantly higher in hospitals that admitted  $<10$  patients with aSAH versus  $>35$  patients with aSAH (39% versus 27%; odds ratio, 1.4).<sup>80</sup>

Two factors associated with better outcomes were greater use of endovascular services and a higher percentage of patients transferred from other hospitals.<sup>79–81</sup> Institutions that used endovascular coil embolization more frequently had lower in-hospital mortality rates, a 9% reduction in risk for every 10% of cases treated. In addition, there was a 16% reduction in risk of in-hospital death at institutions that used interventional therapies such as balloon angioplasty to treat arterial vasospasm.<sup>2,81,162</sup> Therefore, hospital treatment volumes and availability of both endovascular and neurological intensive care services at hospitals are important determinants of improved outcomes in aSAH.<sup>163</sup> In addition, a cost-utility analysis estimated that transferring a patient with aSAH from a low- to a high-volume hospital would result in a gain of 1.6 quality-adjusted life-years at a cost of \$10 548.<sup>162,163</sup>

Although 1 study suggested that care was uniformly delivered within an institution when weekend and weekday admissions were compared,<sup>164</sup> others have shown that intensive care specialists followed evidence-based recommendations very inconsistently, and these variations in practice did not depend on the quality of the supporting data.<sup>165</sup> Significant practice differences were noted between respondents from North America and Europe and between those working in high- and low-volume centers. Thus, the study demonstrated that the practices of intensive care unit physicians treating aSAH are heterogeneous and often at variance with available evidence.<sup>165</sup>

One recent effort to increase the uniformity of care is the development of an Accreditation Council on Graduate Medical Education–approved fellowship training program for endovascular surgical neuroradiology.<sup>166</sup> Another effort is legislation or regulation in  $>10$  states that defines elements of comprehensive stroke centers and their role in networks and stroke systems of care. The Brain Attack Coalition paper that proposed the establishment of these centers included management of aSAH in its scope.<sup>167</sup> From the endovascular perspective, this expertise includes the ability to treat patients with intracranial aneurysms, SAH-induced vasospasm, brain arteriovenous malformations, and ischemic stroke. Other important required elements of these centers are vascular neurosurgical expertise, dedicated intensive care units, and 24/7 access to advanced neuroimaging. The rationale for comprehensive stroke centers is based on the success of similar models for trauma.

### Hospital Characteristics and Systems of Care: Recommendations

1. **Low-volume hospitals (eg,  $<10$  aSAH cases per year) should consider early transfer of patients with aSAH to high-volume centers (eg,  $>35$  aSAH cases per year) with experienced cerebrovascular surgeons, endovascular specialists, and multidisciplinary neuro-intensive care services (*Class I; Level of Evidence B*).** (Revised recommendation from previous guidelines)
2. **Annual monitoring of complication rates for surgical and interventional procedures is reasonable (*Class IIA; Level of Evidence C*).** (New recommendation)
3. **A hospital credentialing process to ensure that proper training standards have been met by individual physicians treating brain aneurysms is reasonable (*Class IIA; Level of Evidence C*).** (New recommendation)

### Anesthetic Management During Surgical and Endovascular Treatment

The general goals of anesthetic management involve hemodynamic control to minimize the risk of aneurysm rerupture and strategies to protect the brain against ischemic injury. Although induced hypotension has been used in the past to prevent aneurysm rupture, data suggest that there could be potential harm, with an increased risk of early and delayed neurological deficits.<sup>168,169</sup> A retrospective study suggests that a decrease in mean arterial pressure of  $>50\%$  is associated with poor outcome; however, after adjustment for age, this association was no longer statistically significant.<sup>170</sup> In patients undergoing cerebral aneurysm surgery, intraoperative hyperglycemia has been associated with long-term decline in cognition and gross neurological function.<sup>171</sup> These associations are seen at levels of hyperglycemia commonly encountered in practice, with increased risk of alterations in cognition with glucose concentrations  $>129$  mg/dL and neurological deficits with glucose concentrations  $>152$  mg/dL.<sup>171</sup> Numerous pharmacological agents have been used to promote cerebral protection during cerebral aneurysm sur-

gery,<sup>172–181</sup> but none have been clearly shown to improve outcome.

Systemic hypothermia has been used in several clinical settings, including head injury, ischemic stroke, and circulatory arrest, to protect the brain against ischemic injury.<sup>182–188</sup> Use of hypothermia during craniotomy for the treatment of ruptured cerebral aneurysm was evaluated in a multicenter randomized, controlled trial. The study showed that hypothermia was relatively safe but was not associated with a beneficial effect in mortality or neurological outcome among patients with good-grade aSAH.<sup>189</sup> In addition, intraoperative hypothermia had no beneficial effect on neuropsychological function after SAH.<sup>190</sup> Of note, the power of these 2 studies was not sufficient to detect more modest benefits from hypothermia, and there were some trends in favor of hypothermia for secondary end points.

Temporary clipping is frequently used to improve surgical conditions and prevent intraoperative rupture during the surgical dissection of aneurysms. In a retrospective study, outcome was not affected by temporary vascular occlusion.<sup>191</sup> Induced hypertension can be considered when the duration of temporary clipping is expected to be >120 seconds, but the value of this strategy has not been well studied in aneurysm surgery. In selected patients with giant aneurysms, deep hypothermia with circulatory arrest under cardiopulmonary extracorporeal circulation has been shown to be a feasible and possibly useful technique, but outcome data are lacking.<sup>192–196</sup> Transient cardiac pause induced by adenosine has been used to control bleeding from intraoperative aneurysm rupture or to decompress large aneurysms and facilitate aneurysm clip application<sup>197,198</sup>; however, controlled studies are needed to validate this intervention.

There is little information in the literature about anesthetic management of patients undergoing endovascular treatment of ruptured cerebral aneurysms.<sup>199–201</sup> Generally, the anesthetic principles that apply to open surgical treatment of ruptured cerebral aneurysms also apply to endovascular treatment. The choice of anesthetic technique varies depending on the institution, with the most common techniques being conscious sedation and general anesthesia.<sup>202–204</sup> There have been no studies comparing these 2 techniques. One of the main goals of the anesthetic technique is keeping the patient motionless to optimize the quality of the images used to perform the endovascular procedure; hence, general anesthesia with endotracheal intubation is often preferred for these procedures.

Intraprocedural aneurysm rupture during endovascular treatment presents a major challenge unlike that encountered with open craniotomy. There may be a sudden and massive rise in blood pressure with or without bradycardia attributable to an elevation in intracranial pressure. Hyperventilation and osmotic diuresis may be required to control the intracranial hypertension. Aggressive treatment of surges in blood pressure may induce ischemia; therefore, antihypertensive therapy should be reserved for patients with extreme elevations in blood pressure.

Endovascular procedures differ from open procedures in that anticoagulation with heparin is frequently administered during the embolization of aneurysms. Patients who have

undergone anticoagulation require rapid reversal with protamine if intraprocedural aneurysm rupture occurs. With the increasing use of intravascular stents, the administration of antiplatelet agents (aspirin, clopidogrel, and glycoprotein IIb/IIIa receptor antagonists) during these procedures has become more common. In case of intraprocedural rupture, rapid reversal of antiplatelet activity can be attempted by platelet transfusion.

### Anesthetic Management During Surgical and Endovascular Treatment: Recommendations

1. **Minimization of the degree and duration of intraoperative hypotension during aneurysm surgery is probably indicated (Class IIa; Level of Evidence B).**
2. **There are insufficient data on pharmacological strategies and induced hypertension during temporary vessel occlusion to make specific recommendations, but there are instances when their use may be considered reasonable (Class IIb; Level of Evidence C).**
3. **Induced hypothermia during aneurysm surgery is not routinely recommended but may be a reasonable option in selected cases (Class III; Level of Evidence B).**
4. **Prevention of intraoperative hyperglycemia during aneurysm surgery is probably indicated (Class IIa; Level of Evidence B).**
5. **The use of general anesthesia during endovascular treatment of ruptured cerebral aneurysms can be beneficial in selected patients (Class IIa; Level of Evidence C).**

### Management of Cerebral Vasospasm and DCI After aSAH

Narrowing (vasospasm) of the angiographically visible cerebral arteries after aSAH is common, occurring most frequently 7 to 10 days after aneurysm rupture and resolving spontaneously after 21 days. The cascade of events culminating in arterial narrowing is initiated when oxyhemoglobin comes in contact with the abluminal side of the vessel.<sup>205</sup> The pathways leading to arterial narrowing have been the focus of extensive basic research, but no effective preventive therapy has been developed to date. Part of the reason for this lack of success likely stems from the fact that vasospasm occurs at multiple levels in the arterial and arteriolar circulation. Large artery narrowing seen in angiographically visible vessels only results in ischemic neurological symptoms in 50% of cases, and although there is a correlation between the severity of large artery spasm and symptomatic ischemia, there are patients with severe large artery spasm who never become symptomatic and others with quite modest spasm who not only develop symptoms but go on to develop infarction.<sup>206</sup> Probably many factors contribute to the development of ischemia and infarction, including but not limited to distal microcirculatory failure, poor collateral anatomy, and genetic or physiological variations in cellular ischemic tolerance.<sup>207,208</sup>

DCI, especially that associated with arterial vasospasm, remains a major cause of death and disability in patients with aSAH. The management of aSAH-induced vasospasm is complex. Many significant advances in the understanding of aSAH-induced vasospasm and DCI have been made since

publication of the previous version of these guidelines, which focused on prevention with oral nimodipine and maintenance of euvolemia, as well as treatment with triple-H therapy (hemodynamic augmentation therapy) and/or endovascular therapy with vasodilators and angioplasty balloons. First, the case for nimodipine is even stronger, with a recent comprehensive meta-analysis confirming improved neurological outcomes by preventing processes other than large-vessel narrowing.<sup>209,210</sup> Although there have been sparse new important data on the lack of benefit for prophylactic hypervolemia compared with maintenance of euvolemia, new data show that both prophylactic angioplasty of the basal cerebral arteries and antiplatelet prophylaxis are ineffective in reducing morbidity.<sup>211–213</sup> Similarly, the only supportive data for the use of lumbar drainage come from a single case-control study,<sup>214</sup> although there is ongoing investigation on the value of this intervention to reduce arterial spasm and DCI.<sup>214</sup>

The data are a bit better for intrathecal thrombolytic infusions, with a recent meta-analysis of 5 randomized, controlled trials suggesting a benefit despite some methodological weaknesses.<sup>215,216</sup> There are also emerging data for several novel methods to reduce the incidence and ischemic consequences of aSAH-induced vasospasm. These new approaches are based on robust experimental data that indicate a critical role for endothelial dysfunction, particularly at the microcirculatory level.<sup>217</sup>

Several recent clinical trials have investigated the utility of statins, endothelin-1 antagonists, and magnesium sulfate.<sup>218</sup> Statin agents have been studied in several small, single-center randomized trials with variable results. Although a recent meta-analysis reported no evidence for clinical benefit,<sup>219</sup> a larger phase 3 trial (SimvasTatin in Aneurysmal Subarachnoid Hemorrhage [STASH]) is in progress. Clazosentan, an endothelin-1 receptor antagonist, had been shown to be associated with a dose-dependent reduction in the incidence of angiographic vasospasm in a phase IIb trial (Clazosentan to Overcome Neurological iSChemia and Infarct OccUrring after Subarachnoid hemorrhage [CONSCIOUS-1]).<sup>220</sup> A benefit for clinical outcomes was not initially apparent but then was judged present when a stricter definition of vasospasm-related stroke was used. However, a subsequent trial (CONSCIOUS-2) that tested the drug in patients treated with aneurysm clipping found no improvement in clinical outcome in the clazosentan group.<sup>221</sup> A similar study in patients treated with coiling (CONSCIOUS-3) was then stopped before completion. Magnesium sulfate has been studied in several pilot trials. Although there is some suggestion of reduction in delayed ischemic deficits associated with magnesium infusion, a benefit has not been conclusively shown in a meta-analysis.<sup>222</sup> A phase 3 trial (Intravenous Magnesium sulfate for Aneurysmal Subarachnoid Hemorrhage [IMASH]) did not support any clinical benefit from magnesium infusion over placebo in aSAH.<sup>223</sup> A larger randomized trial is under way.

With regard to the diagnosis of DCI, which can often be problematic, it is increasingly clear that although serial neurological examinations are important, they are of limited sensitivity in patients with poor clinical grade. Therefore, the diagnostic approach needs to be tailored to the clinical situation. Various diagnostic tools are commonly used to

identify (1) arterial narrowing and/or (2) perfusion abnormalities or reduced brain oxygenation. These different tools have advantages and disadvantages. Although comparative studies of diagnostic accuracy for large arterial narrowing have been performed for some modalities, no randomized trials have compared the impact of the use of different diagnostic methods on patient outcomes. That said, there are emerging data that perfusion imaging, demonstrating regions of hypoperfusion, may be more accurate for identification of DCI than anatomic imaging of arterial narrowing or changes in blood flow velocity by transcranial Doppler, for which the data are best for the middle cerebral artery territory.<sup>224–226</sup> Perfusion CT is a promising technology, although repeat measurements are limited by the risks of dye load and radiation exposure.<sup>226</sup>

When DCI is diagnosed, the initial treatment is the induction of hemodynamic augmentation to improve cerebral perfusion. No randomized trials of this intervention have been performed, but the rapid improvement of many patients with this therapy and their worsening when it is stopped prematurely are convincing proof of efficacy. The exact mechanism of benefit is unclear. In some patients, increased mean arterial pressures may increase cerebral blood flow in the setting of autoregulatory dysfunction. In others, there may be some direct transluminal pressure effect that leads to arterial dilation.<sup>227</sup> Traditionally, hemodynamic augmentation has consisted of hemodilution (a common occurrence in this population), hypervolemia, and hypertensive therapy. Accumulating literature has shifted the focus from this triple-H therapy to the maintenance of euvolemia and induced hypertension.<sup>228</sup>

One novel method of hemodynamic augmentation under investigation is an aortic balloon device, approved under a humanitarian device exemption.<sup>229</sup> Endovascular intervention is often used in patients who do not improve with hemodynamic augmentation and those with sudden focal neurological deficits and focal lesions on angiography referable to their symptoms.<sup>230</sup> Interventions generally consist of balloon angioplasty for accessible lesions and vasodilator infusion for more distal vessels. Many different vasodilators are in use. In general, these are calcium channel blockers, but nitric oxide donors have been used in small series as well.<sup>231</sup> Papaverine is used less frequently because it can produce neurotoxicity.<sup>232</sup> The primary limitation of vasodilator therapy is the short duration of benefit. As with hemodynamic augmentation, there have been no randomized trials of these interventions, but large case series have demonstrated angiographic and clinical improvement.<sup>233</sup>

## Management of Cerebral Vasospasm and DCI After aSAH: Recommendations

1. **Oral nimodipine should be administered to all patients with aSAH (Class I; Level of Evidence A).** (It should be noted that this agent has been shown to improve neurological outcomes but not cerebral vasospasm. The value of other calcium antagonists, whether administered orally or intravenously, remains uncertain.)
2. **Maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI (Class**



- I; Level of Evidence B*). (Revised recommendation from previous guidelines)
3. **Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended (Class III; Level of Evidence B).** (New recommendation)
  4. **Transcranial Doppler is reasonable to monitor for the development of arterial vasospasm (Class IIa; Level of Evidence B).** (New recommendation)
  5. **Perfusion imaging with CT or magnetic resonance can be useful to identify regions of potential brain ischemia (Class IIa; Level of Evidence B).** (New recommendation)
  6. **Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it (Class I; Level of Evidence B).** (Revised recommendation from previous guidelines)
  7. **Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy (Class IIa; Level of Evidence B).** (Revised recommendation from previous guidelines)

### Management of Hydrocephalus Associated With aSAH

Acute hydrocephalus occurs in 15% to 87% of patients with aSAH.<sup>234–240</sup> Chronic shunt-dependent hydrocephalus, on the other hand, occurs in 8.9% to 48% of patients with aSAH.<sup>234–238,240–244</sup> There is only 1 randomized, controlled trial pertaining to the management of hydrocephalus associated with aSAH<sup>245</sup> and 2 meta-analyses<sup>236,243</sup>; the rest of the literature consists of nonrandomized case-control, case series, or case reports. Acute hydrocephalus associated with aSAH is usually managed by external ventricular drainage (EVD) or lumbar drainage. EVD for patients with aSAH-associated hydrocephalus is generally associated with neurological improvement.<sup>246–249</sup> The risk of aneurysm rebleeding with EVD has been studied in 3 retrospective case series, 1 of which found a higher risk of rebleeding with EVD,<sup>250</sup> whereas the other 2 studies found no increased risk.<sup>239,251</sup>

Lumbar drainage for the treatment of aSAH-associated hydrocephalus has been reported to be safe (no increase in the risk of rebleeding), but it has only been examined in retrospective series,<sup>214,252–255</sup> 1 of which specifically evaluated intraoperative lumbar drainage for brain relaxation.<sup>256</sup> The theoretical risk of tissue shift after placement of a lumbar drain in patients with severe intracranial hypertension should be considered when deciding what method of cerebrospinal fluid diversion to use, particularly in patients with associated intraparenchymal hematomas. When obstructive hydrocephalus is suspected, an EVD should be preferred. Preliminary data have suggested that lumbar drainage is associated with reduced incidence of vasospasm.<sup>214,255</sup> Serial lumbar punctures to manage acute aSAH-associated hydrocephalus have been described as safe, but this strategy has only been assessed in small retrospective series.<sup>239,257</sup>

Chronic hydrocephalus associated with aSAH is usually treated with ventricular shunt placement. Only a proportion of patients with aSAH-associated acute hydrocephalus develop

shunt-dependent chronic hydrocephalus. The method of determining which patients require ventricular shunt placement was studied in a single-center, prospective, randomized, controlled trial in which 41 patients were randomized to rapid weaning of EVD (wean period <24 hours) and 40 patients were randomized to gradual EVD weaning (wean period 96 hours).<sup>245</sup> There was no difference in the rate of shunt placement (63.4% rapid versus 62.5% gradual), but the gradual wean group had 2.8 more days in the intensive care unit ( $P=0.0002$ ) and 2.4 more days in the hospital ( $P=0.0314$ ).<sup>245</sup>

A number of retrospective series have attempted to identify factors predictive of aSAH-associated shunt-dependent chronic hydrocephalus.<sup>235,236,240,242</sup> A meta-analysis<sup>236</sup> of 5 nonrandomized studies<sup>236,258–261</sup> with 1718 pooled patients (1336 who underwent clipping, 382 who underwent coiling) found a lower risk of shunt dependency in the clipping group (relative risk, 0.74; 95% confidence interval, 0.58–0.94) than in the coiling group ( $P=0.01$ ); however, only 1 of the 5 studies showed an independent significant difference.<sup>258</sup> Three other nonrandomized series not included in the meta-analysis showed no significant difference between clipping and coiling in shunt-dependent chronic hydrocephalus.<sup>237,244,262</sup> Fenestration of the lamina terminalis has been suggested to reduce the incidence of shunt-dependent chronic hydrocephalus, yet a meta-analysis<sup>243</sup> of 11 nonrandomized studies<sup>234,260,263–271</sup> pooled 1973 patients (975 who had undergone fenestration and 998 who had not) and found no significant difference in shunt-dependent hydrocephalus between patients who had undergone fenestration of the lamina terminalis and those who had not (10% in the fenestrated cohort versus 14% in the nonfenestrated cohort;  $P=0.09$ ). A nonrandomized study not included in the meta-analysis compared 95 patients who underwent aneurysm clipping, cisternal blood evacuation, and lamina terminalis fenestration with 28 comparable, non-blood-cleansed, endovascular therapy-treated patients and found that shunt-dependent hydrocephalus occurred in 17% of surgical patients versus 33% of patients treated with endovascular therapy (statistical significance not reported).<sup>237</sup>

### Management of Hydrocephalus Associated With aSAH: Recommendations

1. **aSAH-associated acute symptomatic hydrocephalus should be managed by cerebrospinal fluid diversion (EVD or lumbar drainage, depending on the clinical scenario) (Class I; Level of Evidence B).** (Revised recommendation from previous guidelines)
2. **aSAH-associated chronic symptomatic hydrocephalus should be treated with permanent cerebrospinal fluid diversion (Class I; Level of Evidence C).** (Revised recommendation from previous guidelines)
3. **Weaning EVD over >24 hours does not appear to be effective in reducing the need for ventricular shunting (Class III; Level of Evidence B).** (New recommendation)
4. **Routine fenestration of the lamina terminalis is not useful for reducing the rate of shunt-dependent hydrocephalus and therefore should not be routinely**

performed. (*Class III; Level of Evidence B*). (New recommendation)

### Management of Seizures Associated With aSAH

The incidence, future implications, and management of seizures associated with aSAH are controversial. At present, no randomized, controlled trials are available to guide decisions on prophylaxis or treatment of seizures.<sup>2,272</sup> A relatively high percentage of aSAH patients (as many as 26%) experience seizure-like episodes,<sup>99,272,273</sup> but it remains unclear whether these episodes are verifiably epileptic in origin.<sup>99,274</sup> More recent retrospective reviews suggest a lower seizure incidence of 6% to 18%,<sup>275–278</sup> and 2 of these studies<sup>276,278</sup> found that the majority of such patients reported onset of seizure occurring before medical evaluation. Delayed seizures occurred in 3% to 7% of patients.<sup>276,278</sup> Retrospective studies have identified several risk factors for the development of early seizures associated with aSAH, including aneurysm in the middle cerebral artery,<sup>279</sup> thickness of aSAH clot,<sup>276</sup> associated intracerebral hematoma,<sup>280–282</sup> rebleeding,<sup>276</sup> infarction,<sup>283</sup> poor neurological grade,<sup>276</sup> and history of hypertension.<sup>98</sup>

The mode of treatment for patients with ruptured aneurysms also appears to influence the subsequent development of seizures. One study of patients treated by endovascular means reported no periprocedural seizures and a delayed seizure rate of 3%.<sup>284</sup> Moreover, extended follow-up of patients enrolled in the ISAT demonstrated a significantly lower incidence of seizures in patients treated with endovascular coiling.<sup>140</sup> The association between seizures and functional outcome remains unclear. Some studies have reported no impact on outcome,<sup>276,278</sup> whereas others found seizures to be independently associated with worse outcome.<sup>275</sup> Two recent large, retrospective, single-institution studies of patients with aSAH found that nonconvulsive status epilepticus is a very strong predictor of a poor outcome.<sup>285,286</sup> Although high-quality evidence for routine anticonvulsant use in aSAH is lacking, short-term prophylactic antiepileptic therapy is still commonly used in patients with aSAH,<sup>274,276,278</sup> based on the argument that seizures in acutely ill patients with aSAH could lead to additional injury or rebleeding from an unsecured aneurysm. Evidence from a few relatively small non-randomized studies of craniotomy patients supports this position,<sup>281,282,287</sup> but the efficacy of routine use of anticonvulsants in patients with aSAH managed with microsurgical techniques remains unproven.<sup>288–290</sup>

Any purported benefit of routine anticonvulsant use in aSAH must be tempered by a consideration of the potential risks of such use. In 1 large single-institution study in which anticonvulsants were used routinely, adverse drug effects were seen in 23% of patients.<sup>276</sup> Another single-center retrospective study found that the use of prophylactic phenytoin was independently associated with a worse cognitive outcome at 3 months after aSAH.<sup>291</sup> Data pooled from trials of the impact of other therapies also suggest a worse outcome in those treated with anticonvulsants, but use of anticonvulsants was also associated with vasospasm, DCI, and fever, which suggests that there may have been bias in who was treated with antiepileptic drugs.<sup>292</sup> Although retrospective studies

have not demonstrated a benefit for use of prophylactic anticonvulsants after aSAH,<sup>273,288</sup> the studies were small and hampered by limitations (eg, anticonvulsant levels were not routinely monitored).<sup>2,273,288</sup>

### Management of Seizures Associated With aSAH: Recommendations

1. The use 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 known risk factors for delayed seizure disorder, such as prior seizure, intracerebral hematoma, intractable hypertension, infarction, or aneurysm at the middle cerebral artery (*Class IIb; Level of Evidence B*).

### Management of Medical Complications Associated With aSAH

Both hyponatremia and hyponatremia are frequently observed in the acute phase after aSAH.<sup>293,294</sup> The reported incidence of hyponatremia in this disease ranges from 10% to 30%. Hyponatremia has been chronologically associated with the onset of sonographic and clinical vasospasm.<sup>295,296</sup> Hyponatremia can develop from different mechanisms after aSAH. The syndrome *cerebral salt wasting* is produced by excessive secretion of natriuretic peptides and causes hyponatremia from excessive natriuresis, which may also provoke volume contraction.<sup>297</sup> The diagnosis of cerebral salt wasting is more common in patients with poor clinical grade, ruptured anterior communicating artery aneurysms, and hydrocephalus, and it may be an independent risk factor for poor outcome.<sup>298–300</sup> Uncontrolled studies using crystalloid or colloid agents suggest that aggressive volume resuscitation can ameliorate the effect of cerebral salt wasting on the risk of cerebral ischemia after aSAH.<sup>301,302</sup> One retrospective study has suggested that 3% saline solution is effective in correcting hyponatremia in this setting.<sup>303</sup> In addition, use of hypertonic saline solution appears to increase regional cerebral blood flow, brain tissue oxygen, and pH in patients with high-grade aSAH.<sup>304</sup>

Two randomized, controlled trials have been performed to evaluate fludrocortisone to correct hyponatremia and fluid balance. One trial found that it helped to correct the negative sodium balance, and the other reported a reduced need for fluids and improved sodium levels using this mineralocorticoid.<sup>305,306</sup> A similar randomized, placebo-controlled trial showed reduced natriuresis and a lower rate of hyponatremia in aSAH patients treated with hydrocortisone.<sup>307</sup> The value of albumin as an efficient volume expander during the vasospasm phase in aSAH has been suggested in uncontrolled studies, but there is no clear evidence of its superiority over crystalloids in patients with aSAH.<sup>308</sup>

Fever is the most common medical complication in aSAH.<sup>309</sup> The presence of fever of noninfectious (central) origin has been associated with severity of injury, amount of hemorrhage, and development of vasospasm, and it may represent a marker of a systemic inflammatory state triggered

by blood and its byproducts.<sup>310–312</sup> Analysis of data from a prospectively collected registry of aSAH indicated that fever was independently associated with worse cognitive outcome in survivors of aSAH.<sup>313,314</sup> Improved functional outcome with effective control of fever has been reported.<sup>315</sup>

Both animal studies and human case series have demonstrated an association between elevated blood glucose concentration and poor outcome after ischemic brain injury.<sup>316–323</sup> The mechanisms explaining such an association in human beings are unclear. Data obtained from consecutive patients with aSAH using historical controls to compare aggressive versus standard management of hyperglycemia suggest that effective glucose control after aSAH can significantly reduce the risk of poor outcome in these patients.<sup>324</sup> Nevertheless, even serum glucose levels within the normal range may be associated with brain energy metabolic crisis and lactate-pyruvate ratio elevation in patients with poor-grade aSAH.<sup>325</sup>

Anemia is common after aSAH and may compromise brain oxygen delivery.<sup>326</sup> Transfusion of red blood cells in anemic patients with aSAH results in a significant rise in cerebral oxygen delivery and a reduction in oxygen extraction ratio.<sup>327</sup> Data obtained from prospective registries of patients with aSAH suggest that higher hemoglobin values are associated with improved outcomes after aSAH.<sup>328,329</sup> Nevertheless, thresholds for blood transfusion have been dictated in a nonsystematic manner and have therefore varied widely. Furthermore, red blood cell transfusions, as used in daily practice, have been associated with worse outcomes in aSAH in some series.<sup>330,331</sup> Recently, a prospective randomized trial has shown the safety and feasibility of keeping a higher hemoglobin goal in patients with aSAH who are at high risk of vasospasm.<sup>332</sup> The optimal hemoglobin goal after aSAH is not yet known, however.

Two additional medical complications are heparin-induced thrombocytopenia<sup>333–335</sup> and deep venous thrombosis. With regard to the former, the incidence, based on 3 single-center series, is likely  $\approx 5\%$  and does not appear to be related to the use of heparin for deep venous thrombosis prophylaxis, but rather to the number of angiographic procedures performed. Patients with heparin-induced thrombocytopenia type II appear to have higher rates of thrombotic complications and symptomatic vasospasm/DCI, more deaths, and significantly less favorable outcomes. It is currently unclear whether there is a practical means of preventing heparin-induced thrombocytopenia, given the need for heparin in many angiographic procedures, but it is clearly important to recognize this complication to avoid further heparin exposure and to use instead a nonheparin alternative under the guidance of a hematologist.<sup>336</sup> By comparison, deep venous thrombosis has long been recognized as a relatively frequent occurrence after aSAH, especially in patients immobilized because of poor mental status.<sup>337,338</sup> Nevertheless, in examining cohorts in which routine prophylaxis (subcutaneous

heparinoids and external pneumatic compression sleeves) was used, recent data suggest that although screening protocols may identify additional cases of asymptomatic thrombosis, there is no significant difference in the incidence of pulmonary embolism between those screened and those not screened.

### Management of Medical Complications Associated With aSAH: Recommendations

1. **Administration of large volumes of hypotonic fluids and intravascular volume contraction is not recommended after aSAH (Class III; Level of Evidence B).**
2. **Monitoring volume status in certain patients with recent aSAH by some combination of central venous pressure, pulmonary wedge pressure, and fluid balance is reasonable, as is treatment of volume contraction with crystalloid or colloid fluids (Class IIa; Level of Evidence B).**
3. **Aggressive control of fever to a target of normothermia by use of standard or advanced temperature modulating systems is reasonable in the acute phase of aSAH (Class IIa; Level of Evidence B).** (New recommendation)
4. **Careful glucose management with strict avoidance of hypoglycemia may be considered as part of the general critical care management of patients with aSAH (Class IIb; Level of Evidence B).**
5. **The use of packed red blood cell transfusion to treat anemia might be reasonable in patients with aSAH who are at risk of cerebral ischemia. The optimal hemoglobin goal is still to be determined (Class IIb; Level of Evidence B).** (New recommendation)
6. **The use of fludrocortisone acetate and hypertonic saline solution is reasonable for preventing and correcting hyponatremia (Class IIa; Level of Evidence B).**
7. **Heparin-induced thrombocytopenia and deep venous thrombosis are relatively frequent complications after aSAH. Early identification and targeted treatment are recommended, but further research is needed to identify the ideal screening paradigms (Class I; Level of Evidence B).** (New recommendation)

### Summary and Conclusions

The management of aSAH is a complex undertaking, and the current state of knowledge is in rapid evolution. This update, which is based on a mere 42 months of publications, identified 22 new recommendations (Table 4), 5 of which were Class I recommendations. There were also 9 changes in prior recommendations. In total, there are now 22 Class I recommendations (Table 3). Although these data show that frequent revision of these guidelines is clearly needed, the data presented here only begin to scratch the surface of the burgeoning knowledge in this fast-developing field. Those faced with managing these patients will thus do well to use these guidelines as merely the starting point for doing everything possible to improve the outcomes of patients with aSAH.



## Disclosures

## Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
E. Sander Connolly, Jr.	Columbia University	None	None	None	None	None	None	None
Alejandro A. Rabinstein	Mayo Clinic	None	None	None	None	None	None	None
J. Ricardo Carhuapoma	Johns Hopkins Hospital	None	None	None	None	None	None	None
Colin P. Derdeyn	Washington University School of Medicine (St. Louis)	NIH†	None	None	Witness for plaintiff*	Nfocus*	None	None
Jacques Dion	Emory University Hospital	None	None	None	None	NeuroVasx*; Nfocus Neuromedical*; Sequent Medical*	MicroVention/Terumo*	None
Randall T. Higashida	University of California at San Francisco Medical Center	None	None	None	None	None	None	None
Brian L. Hoh	University of Florida	Brain Aneurysm Foundation†; Micrus Endovascular*; NIH†; Thomas H. Maren Foundation†	None	None	None	None	Actelion Pharmaceuticals*; Codman Neurovascular*	None
Catherine J. Kirkness	University of Washington	NIH*	None	None	None	None	None	None
Andrew M. Naidech	Northwestern University/FDA	Astellas Pharma*; Gaymar, Inc*	None	None	None	None	Journal Watch Neurology*	None
Christopher S. Ogilvy	Massachusetts General Hospital	Actelion Pharmaceuticals†; NIH†	None	None	None	None	Mizuho America, Inc*	None
Aman B. Patel	Mount Sinai Medical Center	None	None	None	None	None	Cordis/Codman Neurovascular*; Penumbra*	None
B. Gregory Thompson	University of Michigan	None	None	None	None	None	None	None
Paul Vespa	University of California at Los Angeles	NIH†	None	None	None	InTouch Health*	EDGE Therapeutics*	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 writing group members 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
Opeolu Adeoye	University of Cincinnati	None	None	None	None	None	None	None
Sepideh Amin-Hanjani	University of Illinois at Chicago	None	None	None	None	None	Micrus Endovascular, >1 y ago, served as DSMB Chair*	None
Kevin M. Cockroft	Penn State Hershey Medical Center	None	None	None	None	None	eV3 Neurovascular†	None
Gary Ross Duckwiler	UCLA	None	None	None	None	None	None	Boston Scientific, patent royalties†
J. Claude Hemphill 3rd	University of California, San Francisco	None	None	None	Raphaelson law firm*	None	None	None
Stephan Mayer	Columbia University	None	None	None	None	None	Edge Therapeutics*; Actelion Pharmaceuticals†	None
Gene Sung	University of Southern California	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

- Mayberg MR, Batjer HH, Dacey R, Diringer M, Haley EC, Heros RC, Sternau LL, Torner J, Adams HP Jr, Feinberg W, Thies 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. *Circulation*. 1994;90:2592–2605.
- Bederson JB, Connolly ES Jr, Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner JE Jr, Harbaugh RE, Patel AB, Rosenwasser RH. 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 [published correction appears in *Stroke*. 2009;40:e518]. *Stroke*. 2009;40:994–1025.
- 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.
- de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry*. 2007;78:1365–1372.
- Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol*. 2009;8:355–369.
- Labovitz DL, Halim AX, Brent B, Boden-Albala B, Hauser WA, Sacco RL. Subarachnoid hemorrhage incidence among Whites, Blacks and Caribbean Hispanics: the Northern Manhattan Study. *Neuroepidemiology*. 2006;26:147–150.
- Shea AM, Reed SD, Curtis LH, Alexander MJ, Villani JJ, Schulman KA. Characteristics of nontraumatic subarachnoid hemorrhage in the United States in 2003. *Neurosurgery*. 2007;61:1131–1137.
- Schievink WI, Wijedicks EF, Parisi JE, Piegras DG, Whisnant JP. Sudden death from aneurysmal subarachnoid hemorrhage. *Neurology*. 1995;45:871–874.
- 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.
- Harmen 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.
- Ingall TJ, Whisnant JP, Wiebers DO, O'Fallon WM. Has there been a decline in subarachnoid hemorrhage mortality? *Stroke*. 1989;20:718–724.
- Kozak N, Hayashi M. Trends in the incidence of subarachnoid hemorrhage in Akita Prefecture, Japan. *J Neurosurg*. 2007;106:234–238.
- Sacco S, Totaro R, Toni D, Marini C, Cerone D, Carolei A. Incidence, case-fatality and 10-year survival of subarachnoid hemorrhage in a population-based registry. *Eur Neurol*. 2009;62:155–160.
- Kita Y, Turin TC, Ichikawa M, Sugihara H, Morita Y, Tomioka N, Rumana N, Okayama A, Nakamura Y, Abbott RD, Ueshima H. Trend of stroke incidence in a Japanese population: Takashima stroke registry, 1990–2001. *Int J Stroke*. 2009;4:241–249.
- Vemmos KN, Bots ML, Tsibouris PK, Zis VP, Grobbee DE, Stranjalis GS, Stamatiopoulos S. Stroke incidence and case fatality in southern Greece: the Arcadia stroke registry. *Stroke*. 1999;30:363–370.
- Lovelock CE, Rinkel GJ, Rothwell PM. Time trends in outcome of subarachnoid hemorrhage: population-based study and systematic review. *Neurology*. 2010;74:1494–1501.
- Mahindu A, Koivisto T, Ronkainen A, Rinne J, Assaad N, Morgan MK. Similarities and differences in aneurysmal subarachnoid haemorrhage between eastern Finland and northern Sydney. *J Clin Neurosci*. 2008;15:617–621.
- Vadikolias K, Tsivgoulis G, Heliopoulos I, Papaioakim M, Aggelopoulou C, Serdari A, Biribilis T, Piperidou C. Incidence and case fatality of subarachnoid haemorrhage in Northern Greece: the Evros Registry of Subarachnoid Haemorrhage. *Int J Stroke*. 2009;4:322–327.
- Jordan LC, Johnston SC, Wu YW, Sidney S, Fullerton HJ. The importance of cerebral aneurysms in childhood hemorrhagic stroke: a population-based study. *Stroke*. 2009;40:400–405.
- Koffijberg H, Buskens E, Granath F, Adami J, Ekblom A, Rinkel GJ, Blomqvist P. Subarachnoid haemorrhage in Sweden 1987–2002: regional incidence and case fatality rates. *J Neurol Neurosurg Psychiatry*. 2008;79:294–299.

21. van Munster CE, von und zu Fraunberg M, Rinkel GJ, Rinne J, Koivisto T, Ronkainen A. Differences in aneurysm and patient characteristics between cohorts of Finnish and Dutch patients with subarachnoid hemorrhage: time trends between 1986 and 2005. *Stroke*. 2008;39:3166–3171.
22. Ostbye T, Levy AR, Mayo NE. Hospitalization and case-fatality rates for subarachnoid hemorrhage in Canada from 1982 through 1991: the Canadian Collaborative Study Group of Stroke Hospitalizations. *Stroke*. 1997;28:793–798.
23. Linn FH, Rinkel GJ, Algra A, van Gijn J. Incidence of subarachnoid hemorrhage: role of region, year, and rate of computed tomography: a meta-analysis. *Stroke*. 1996;27:625–629.
24. 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.
25. Eden SV, Meurer WJ, Sanchez BN, Lisabeth LD, Smith MA, Brown DL, Morgenstern LB. Gender and ethnic differences in subarachnoid hemorrhage. *Neurology*. 2008;71:731–735.
26. Bor AS, Koffijberg H, Wermer MJ, Rinkel GJ. Optimal screening strategy for familial intracranial aneurysms: a cost-effectiveness analysis. *Neurology*. 2010;74:1671–1679.
27. Broderick JP, Brown RD Jr, Sauerbeck L, Hornung R, Huston J 3rd, Woo D, Anderson C, Rouleau G, Kleindorfer D, Flaherty ML, Meissner I, Foroud T, Moomaw EC, Connolly ES, FIA Study Investigators. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. *Stroke*. 2009;40:1952–1957.
28. Adams HP Jr, Putman SF, Kassell NF, Torner JC. Prevalence of diabetes mellitus among patients with subarachnoid hemorrhage. *Arch Neurol*. 1984;41:1033–1035.
29. 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; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;362:103–110.
30. Lindner SH, Bor AS, Rinkel GJ. Differences in risk factors according to the site of intracranial aneurysms. *J Neurol Neurosurg Psychiatry*. 2010;81:116–118.
31. Etminan N, Beseoglu K, Steiger HJ, Hänggi D. The impact of hypertension and nicotine on the size of ruptured intracranial aneurysms. *J Neurol Neurosurg Psychiatry*. 2011;82:4–7.
32. Shiue I, Arima H, Anderson CS; ACROSS Group. Life events and risk of subarachnoid hemorrhage: the Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS). *Stroke*. 2010;41:1304–1306.
33. Lall RR, Eddleman CS, Bendok BR, Batjer HH. Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: sifting through the sands of data. *Neurosurg Focus*. 2009;26:E2.
34. Hirsch KG, Froehler MT, Huang J, Ziai WC. Occurrence of perimesencephalic subarachnoid hemorrhage during pregnancy. *Neurocrit Care*. 2009;10:339–343.
35. Tiel Groenestege AT, Rinkel GJ, van der Bom JG, Algra A, Klijn CJ. The risk of aneurysmal subarachnoid hemorrhage during pregnancy, delivery, and the puerperium in the Utrecht population: case-cross-over study and standardized incidence ratio estimation. *Stroke*. 2009;40:1148–1151.
36. Aoki T, Nishimura M. Targeting chronic inflammation in cerebral aneurysms: focusing on NF-kappaB as a putative target of medical therapy. *Expert Opin Ther Targets*. 2010;14:265–273.
37. Aoki T, Kataoka H, Shimamura M, Nakagami H, Wakayama K, Moriwaki T, Ishibashi R, Nozaki K, Morishita R, Hashimoto N. NF-kappaB is a key mediator of cerebral aneurysm formation. *Circulation*. 2007;116:2830–2840.
38. Aoki T, Kataoka H, Ishibashi R, Nozaki K, Hashimoto N. Simvastatin suppresses the progression of experimentally induced cerebral aneurysms in rats. *Stroke*. 2008;39:1276–1285.
39. Clarke M. Systematic review of reviews of risk factors for intracranial aneurysms. *Neuroradiology*. 2008;50:653–664.
40. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, Anderson CS. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke*. 2005;36:2773–2780.
41. Larsson SC, Mannisto S, Virtanen MJ, Kontto J, Albanes D, Virtamo J. Dairy foods and risk of stroke. *Epidemiology*. 2009;20:355–360.
42. Larsson SC, Mannisto S, Virtanen MJ, Kontto J, Albanes D, Virtamo J. Dietary fiber and fiber-rich food intake in relation to risk of stroke in male smokers. *Eur J Clin Nutr*. 2009;63:1016–1024.
43. Larsson SC, Männistö S, Virtanen MJ, Kontto J, Albanes D, Virtamo J. Coffee and tea consumption and risk of stroke subtypes in male smokers. *Stroke*. 2008;39:1681–1687.
44. Larsson SC, Virtanen MJ, Mars M, Männistö S, Pietinen P, Albanes D, Virtamo J. Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. *Arch Intern Med*. 2008;168:459–465.
45. Burns JD, Huston J 3rd, Layton KF, Piepgras DG, Brown RD Jr. Intracranial aneurysm enlargement on serial magnetic resonance angiography: frequency and risk factors. *Stroke*. 2009;40:406–411.
46. Hoh BL, Siström CL, Firmont CS, Fauthere GL, Velat GJ, Whiting JH, Reavey-Cantwell JF, Lewis SB. Bottleneck factor and height-width ratio: association with ruptured aneurysms in patients with multiple cerebral aneurysms. *Neurosurgery*. 2007;61:716–722.
47. Dhar SBE, Tremmel M, Mocco J, Kim M, Yamamoto J, Siddiqui AH, Hopkins LNM, Meng H. Morphology parameters for intracranial aneurysm rupture risk assessment. *Neurosurgery*. 2008;63:185–197.
48. Rahman M, Smietana J, Hauck E, Hoh B, Hopkins N, Siddiqui A, Levy EI, Meng H, Mocco J. Size ratio correlates with intracranial aneurysm rupture status: a prospective study. *Stroke*. 2010;41:916–920.
49. Koffijberg H, Rinkel G, Buskens E. Do intraindividual variation in disease progression and the ensuing tight window of opportunity affect estimation of screening benefits? *Med Decis Making*. 2009;29:82–90.
50. Greving JP, Rinkel GJ, Buskens E, Algra A. Cost-effectiveness of preventive treatment of intracranial aneurysms: new data and uncertainties. *Neurology*. 2009;73:258–265.
51. Miller TD, White PM, Davenport RJ, Al-Shahi Salman R. Screening patients with a family history of subarachnoid haemorrhage for intracranial aneurysms: screening uptake, patient characteristics and outcome. *J Neurol Neurosurg Psychiatry*. 2011;83:86–88.
52. Brown RD Jr, Huston J, Hornung R, Foroud T, Kallmes DF, Kleindorfer D, Meissner I, Woo D, Sauerbeck L, Broderick J. Screening for brain aneurysm in the Familial Intracranial Aneurysm study: frequency and predictors of lesion detection. *J Neurosurg*. 2008;108:1132–1138.
53. Johnston SC, Dowd CF, Higashida RT, Lawton MT, Duckwiler GR, Gress DR; CARAT Investigators. Predictors of rehemorrhage after treatment of ruptured intracranial aneurysms: the Cerebral Aneurysm Rerupture After Treatment (CARAT) study. *Stroke*. 2008;39:120–125.
54. Wermer MJH, Koffijberg H, van der Schaaf IC; ASTRA Study Group. Effectiveness and costs of screening for aneurysms every 5 years after subarachnoid hemorrhage. *Neurology*. 2008;70:2053–2062.
55. Schaafsma JD, Sprengers ME, van Rooij WJ, Sluzewski M, Majoie CB, Wermer MJ, Rinkel GJ. Long-term recurrent subarachnoid hemorrhage after adequate coiling versus clipping of ruptured intracranial aneurysms. *Stroke*. 2009;40:1758–1763.
56. Molyneux AJ, Kerr RS, Birks J, Ramzi N, Yarnold J, Sneade M, Rischmiller J; ISAT Collaborators. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *Lancet Neurol*. 2009;8:427–433.
57. Willinsky RA, Peltz J, da Costa L, Agid R, Farb RI, terBrugge KG. Clinical and angiographic follow-up of ruptured intracranial aneurysms treated with endovascular embolization. *AJNR Am J Neuroradiol*. 2009;30:1035–1040.
58. 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.
59. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. *Lancet Neurol*. 2009;8:635–642.
60. Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. *Neurology*. 1998;50:1413–1418.
61. The ACROSS Group. 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.



62. Inagawa T. Trends in incidence and case fatality rates of aneurysmal subarachnoid hemorrhage in Izumo City, Japan, between 1980–1989 and 1990–1998. *Stroke*. 2001;32:1499–1507.
63. 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.
64. Samra SK, Giordani B, Caveney AF, Clarke WR, Scott PA, Anderson S, Thompson BG, Todd MM. Recovery of cognitive function after surgery for aneurysmal subarachnoid hemorrhage. *Stroke*. 2007;38:1864–1872.
65. Springer MV, Schmidt JM, Wartenberg KE, Frontera JA, Badjatia N, Mayer SA. Predictors of global cognitive impairment 1 year after subarachnoid hemorrhage. *Neurosurgery*. 2009;65:1043–1050.
66. Al-Khindi T, Macdonald RL, Schweizer TA. Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. *Stroke*. 2010;41:e519–e536.
67. Scharbrodt W, Stein M, Schreiber V, Böker DK, Oertel MF. The prediction of long-term outcome after subarachnoid hemorrhage as measured by the Short Form-36 Health Survey. *J Clin Neurosci*. 2009;16:1409–1413.
68. Wermer MJ, Kool H, Albrecht KW, Rinkel GJ; Aneurysm Screening after Treatment for Ruptured Aneurysms Study Group. Subarachnoid hemorrhage treated with clipping: long-term effects on employment, relationships, personality, and mood. *Neurosurgery*. 2007;60:91–97.
69. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg*. 1968;28:14–20.
70. Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. *J Neurosurg*. 1988;68:985–986.
71. Kassell NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL. The International Cooperative Study on the Timing of Aneurysm Surgery, part 1: overall management results. *J Neurosurg*. 1990;73:18–36.
72. Lanzino G, Kassell NF, Germanson TP, Kongable GL, Truskowski LL, Torner JC, Jane JA. Age and outcome after aneurysmal subarachnoid hemorrhage: why do older patients fare worse? *J Neurosurg*. 1996;85:410–418.
73. Claassen J, Carhuapoma JR, Kreiter KT, Du EY, Connolly ES, Mayer SA. Global cerebral edema after subarachnoid hemorrhage: frequency, predictors, and impact on outcome. *Stroke*. 2002;33:1225–1232.
74. Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke*. 2007;38:2315–2321.
75. Rabinstein AA, Weigand S, Atkinson JL, Wijedicks EF. Patterns of cerebral infarction in aneurysmal subarachnoid hemorrhage. *Stroke*. 2005;36:992–997.
76. Wartenberg KE, Schmidt JM, Claassen J, Temes RE, Frontera JA, Ostapovich N, Parra A, Connolly ES, Mayer SA. Impact of medical complications on outcome after subarachnoid hemorrhage. *Crit Care Med*. 2006;34:617–623.
77. Solenski NJ, Haley EC Jr, Kassell NF, Kongable G, Germanson T, Truskowski L, Torner JC. Medical complications of aneurysmal subarachnoid hemorrhage: a report of the Multicenter, Cooperative Aneurysm Study: participants of the Multicenter Cooperative Aneurysm Study. *Crit Care Med*. 1995;23:1007–1017.
78. Pierot L, Cognard C, Anxionnat R, Ricolfi F; CLARITY Investigators. Ruptured intracranial aneurysms: factors affecting the rate and outcome of endovascular treatment complications in a series of 782 patients (CLARITY study). *Radiology*. 2010;256:916–923.
79. 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.
80. 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.
81. Johnston SC. Effect of endovascular services and hospital volume on cerebral aneurysm treatment outcomes. *Stroke*. 2000;31:111–117.
82. 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.
83. de Falco FA. Sentinel headache. *Neurol Sci*. 2004;25(suppl 3):S215–S217.
84. Polmear A. Sentinel headaches in aneurysmal subarachnoid haemorrhage: what is the true incidence? A systematic review. *Cephalalgia*. 2003;23:935–941.
85. Beck J, Raabe A, Szelenyi A, Berkefeld J, Gerlach R, Setzer M, Seifert V. Sentinel headache and the risk of rebleeding after aneurysmal subarachnoid hemorrhage. *Stroke*. 2006;37:2733–2737.
86. Brisman JL, Song JK, Newell DW. Cerebral aneurysms. *N Engl J Med*. 2006;355:928–939.
87. Matsuda M, Watanabe K, Saito A, Matsumura K, Ichikawa M. Circumstances, activities, and events precipitating aneurysmal subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis*. 2007;16:25–29.
88. Fontanarosa PB. Recognition of subarachnoid hemorrhage. *Ann Emerg Med*. 1989;18:1199–1205.
89. Kowalski RG, Claassen J, Kreiter KT, Bates JE, Ostapovich ND, Connolly ES, Mayer SA. Initial misdiagnosis and outcome after subarachnoid hemorrhage. *JAMA*. 2004;291:866–869.
90. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet*. 2007;369:306–318.
91. Edlow JA. Diagnosis of subarachnoid hemorrhage. *Neurocrit Care*. 2005;2:99–109.
92. Edlow JA. Diagnosing headache in the emergency department: what is more important? Being right, or not being wrong? *Eur J Neurol*. 2008;15:1257–1258.
93. Jakobsson KE, Säveland 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.
94. Eggers C, Liu W, Brinker G, Fink GR, Burghaus L. Do negative CCT and CSF findings exclude a subarachnoid haemorrhage? A retrospective analysis of 220 patients with subarachnoid haemorrhage. *Eur J Neurol*. 2011;18:300–305.
95. Juvela S. Minor leak before rupture of an intracranial aneurysm and subarachnoid hemorrhage of unknown etiology. *Neurosurgery*. 1992;30:7–11.
96. Leblanc R. The minor leak preceding subarachnoid hemorrhage. *J Neurosurg*. 1987;66:35–39.
97. Hauerberg J, Andersen BB, Eskesen V, Rosenørn 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.
98. Ohman J. Hypertens as a risk factor for epilepsy after aneurysmal subarachnoid hemorrhage and surgery. *Neurosurgery*. 1990;27:578–581.
99. Sundaram MB, Chow F. Seizures associated with spontaneous subarachnoid hemorrhage. *Can J Neurol Sci*. 1986;13:229–231.
100. Cortum S, Sørensen P, Jørgensen J. Determining the sensitivity of computed tomography scanning in early detection of subarachnoid hemorrhage. *Neurosurgery*. 2010;66:900–902.
101. Fiebach JB, Schellinger PD, Geletnek K, Wilde P, Meyer M, Hacke W, Sartor K. MRI in acute subarachnoid haemorrhage: findings with a standardised stroke protocol. *Neuroradiology*. 2004;46:44–48.
102. Kidwell C, Wintermark M. Imaging of intracranial haemorrhage. *Lancet Neurol*. 2008;7:256–267.
103. Shimoda M, Hoshikawa K, Shiramizu H, Oda S, Matsumae M. Problems with diagnosis by fluid-attenuated inversion recovery magnetic resonance imaging in patients with acute aneurysmal subarachnoid hemorrhage. *Neurol Med Chir (Tokyo)*. 2010;50:530–537.
104. Maslehaty H, Petridis AK, Barth H, Mehdorn HM. Diagnostic value of magnetic resonance imaging in perimesencephalic and nonperimesencephalic subarachnoid hemorrhage of unknown origin. *J Neurosurg*. 2011;114:1003–1007.
105. Donmez H, Serifov E, Kahrman G, Mavili E, Durak AC, Menkü A. Comparison of 16-row multislice CT angiography with conventional angiography for detection and evaluation of intracranial aneurysms. *Eur J Radiol*. 2011;80:455–461.
106. McKinney AM, Palmer CS, Truwit CL, Karagulle A, Teksam M. Detection of aneurysms by 64-section multidetector CT angiography in patients acutely suspected of having an intracranial aneurysm and comparison with digital subtraction and 3D rotational angiography. *AJNR Am J Neuroradiol*. 2008;29:594–602.
107. McCormack RF, Hutson A. Can computed tomography angiography of the brain replace lumbar puncture in the evaluation of acute-onset headache after a negative noncontrast cranial computed tomography scan? *Acad Emerg Med*. 2010;17:444–451.
108. Brinjikji W, Kallmes DF, White JB, Lanzino G, Morris JM, Cloft HJ. Inter- and intraobserver agreement in CT characterization of non-

- aneurysmal perimesencephalic subarachnoid hemorrhage. *AJNR Am J Neuroradiol.* 2010;31:1103–1105.
109. Agid R, Andersson T, Almqvist H, Willinsky RA, Lee SK, terBrugge KG, Farb RI, Söderman M. Negative CT angiography findings in patients with spontaneous subarachnoid hemorrhage: when is digital subtraction angiography still needed? *AJNR Am J Neuroradiol.* 2010;31:696–705.
  110. Dupont SA, Lanzino G, Wijidicks EF, Rabinstein AA. The use of clinical and routine imaging data to differentiate between aneurysmal and non-aneurysmal subarachnoid hemorrhage prior to angiography: clinical article. *J Neurosurg.* 2010;113:790–794.
  111. Pechlivanis I, Harders A, Tutenberg J, Barth M, Schulte-Altdorneburg G, Schmieder K. Computed tomographic angiography: diagnostic procedure of choice in the management of subarachnoid hemorrhage in the elderly patient? *Cerebrovasc Dis.* 2009;28:481–489.
  112. Romijn M, Gratama van Andel HA, van Walderveen MA, Sprengers ME, van Rijn JC, van Rooij WJ, Venema HW, Grimbergen CA, den Heeten GJ, Majoie CB. Diagnostic accuracy of CT angiography with matched mask bone elimination for detection of intracranial aneurysms: comparison with digital subtraction angiography and 3D rotational angiography. *AJNR Am J Neuroradiol.* 2008;29:134–139.
  113. Zhang LJ, Wu SY, Niu JB, Zhang ZL, Wang HZ, Zhao YE, Chai X, Zhou CS, Lu GM. Dual-energy CT angiography in the evaluation of intracranial aneurysms: image quality, radiation dose, and comparison with 3D rotational digital subtraction angiography. *AJR Am J Roentgenol.* 2010;194:23–30.
  114. Nagai M, Watanabe E. Benefits of clipping surgery based on three-dimensional computed tomography angiography. *Neurol Med Chir (Tokyo).* 2010;50:630–637.
  115. Agid R, Lee SK, Willinsky RA, Farb RI, terBrugge KG. Acute subarachnoid hemorrhage: using 64-slice multidetector CT angiography to “triage” patients’ treatment. *Neuroradiology.* 2006;48:787–794.
  116. Lubicz B, Levivier M, François O, Thoma P, Sadeghi N, Collignon L, Balériaux D. Sixty-four-row multisection CT angiography for detection and evaluation of ruptured intracranial aneurysms: interobserver and intertechnique reproducibility. *AJNR Am J Neuroradiol.* 2007;28:1949–1955.
  117. Miley JT, Taylor RA, Janardhan V, Tummala R, Lanzino G, Qureshi AI. The value of computed tomography angiography in determining treatment allocation for aneurysmal subarachnoid hemorrhage. *Neurocrit Care.* 2008;9:300–306.
  118. Nijjar S, Patel B, McGinn G, West M. Computed tomographic angiography as the primary diagnostic study in spontaneous subarachnoid hemorrhage. *J Neuroimaging.* 2007;17:295–299.
  119. Westerlaan HE, Gravendeel J, Fiore D, Metzmaekers JD, Groen RJ, Mooij JJ, Oudkerk M. Multislice CT angiography in the selection of patients with ruptured intracranial aneurysms suitable for clipping or coiling. *Neuroradiology.* 2007;49:997–1007.
  120. Westerlaan HE, van Dijk JM, Jansen-van der Weide MC, de Groot JC, Groen RJ, Mooij JJ, Oudkerk M. Intracranial aneurysms in patients with subarachnoid hemorrhage: CT angiography as a primary examination tool for diagnosis: systematic review and meta-analysis. *Radiology.* 2011;258:134–145.
  121. Ishihara H, Kato S, Akimura T, Suehiro E, Oku T, Suzuki M. Angiogram-negative subarachnoid hemorrhage in the era of three dimensional rotational angiography. *J Clin Neurosci.* 2007;14:252–255.
  122. van Rooij WJ, Peluso JP, Sluzewski M, Beute GN. Additional value of 3D rotational angiography in angiographically negative aneurysmal subarachnoid hemorrhage: how negative is negative? *AJNR Am J Neuroradiol.* 2008;29:962–966.
  123. Struffert T, Eyupoglu IY, Huttner HB, Engelhorn T, Doelken M, Saake M, Ganslandt O, Doerfler A. Clinical evaluation of flat-panel detector compared with multislice computed tomography in 65 patients with acute intracranial hemorrhage: initial results: clinical article. *J Neurosurg.* 2010;113:901–907.
  124. Doelken M, Struffert T, Richter G, Engelhorn T, Nimsky C, Ganslandt O, Hammen T, Doerfler A. Flat-panel detector volumetric CT for visualization of subarachnoid hemorrhage and ventricles: preliminary results compared to conventional CT. *Neuroradiology.* 2008;50:517–523.
  125. Gelfand AA, Josephson SA. Substantial radiation exposure for patients with subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis.* 2011;20:131–133.
  126. Mamourian AC, Young H, Stiefel MF. Cumulative radiation dose in patients admitted with subarachnoid hemorrhage: a prospective study using a self-developing film badge. *AJNR Am J Neuroradiol.* 2010;31:1787–1790.
  127. 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.
  128. Kassell NF, Torner JC. Aneurysmal rebleeding: a preliminary report from the Cooperative Aneurysm Study. *Neurosurgery.* 1983;13:479–481.
  129. 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.
  130. Ohkuma H, Tsurutani H, Suzuki S. Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management. *Stroke.* 2001;32:1176–1180.
  131. Tanno Y, Homma M, Oinuma M, Kodama N, Yamamoto T. Rebleeding from ruptured intracranial aneurysms in North Eastern Province of Japan: a cooperative study. *J Neurol Sci.* 2007;258:11–16.
  132. Cha KC, Kim JH, Kang HI, Moon BG, Lee SJ, Kim JS. Aneurysmal rebleeding: factors associated with clinical outcome in the rebleeding patients. *J Korean Neurosurg Soc.* 2010;47:119–123.
  133. Ruigrok YM, Slooter AJ, Rinkel GJ, Wijmenga C, Rosendaal FR. Genes influencing coagulation and the risk of aneurysmal subarachnoid hemorrhage, and subsequent complications of secondary cerebral ischemia and rebleeding. *Acta Neurochir (Wien).* 2010;152:257–262.
  134. Tong Y, Gu J, Fan WJ, Yu JB, Pan JW, Wan S, Zhou YQ, Zheng XJ, Zhan RY. Patients with supratentorial aneurysmal subarachnoid hemorrhage during the intermediate period: waiting or actively treating. *Int J Neurosci.* 2009;119:1494–1506.
  135. Liu-Deryke X, Janisse J, Coplin WM, Parker DJ, Norris G, Rhoney DH. A comparison of nicardipine and labetalol for acute hypertension management following stroke. *Neurocrit Care.* 2008;9:167–176.
  136. Roitberg BZ, Hardman J, Urbaniak K, Merchant A, Mangubat EZ, Alaraj A, Mlinarevich N, Watson KS, Ruland SMD. Prospective randomized comparison of safety and efficacy of nicardipine and nitroprusside drip for control of hypertension in the neurosurgical intensive care unit. *Neurosurgery.* 2008;63:115–121.
  137. Narotam PK, Puri V, Roberts JM, Taylon C, Vora Y, Nathoo N. Management of hypertensive emergencies in acute brain disease: evaluation of the treatment effects of intravenous nicardipine on cerebral oxygenation. *J Neurosurg.* 2008;109:1065–1074.
  138. Starke RM, Kim GH, Fernandez A, Komotar RJ, Hickman ZL, Otten ML, Ducruet AF, Kellner CP, Hahn DK, Chwajol M, Mayer SA, Connolly ES Jr. Impact of a protocol for acute antifibrinolytic therapy on aneurysm rebleeding after subarachnoid hemorrhage. *Stroke.* 2008;39:2617–2621.
  139. 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.
  140. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, Sandercock P; 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.
  141. Karamanakos PN, Koivisto T, Vanninen R, Khallaf M, Ronkainen A, Parviainen I, Manninen H, von und zu Fraunberg M, Morgan MK, Jaaskelainen JE, Hernesniemi J, Rinne J. The impact of endovascular management on the outcome of aneurysmal subarachnoid hemorrhage in the elderly in Eastern Finland. *Acta Neurochir (Wien).* 2010;152:1493–1502.
  142. Bakker NA, Metzmaekers JD, Groen RJ, Mooij JJ, Van Dijk JM. International Subarachnoid Aneurysm Trial 2009: endovascular coiling of ruptured intracranial aneurysms has no significant advantage over neurosurgical clipping. *Neurosurgery.* 2010;66:961–962.
  143. Risselada R, Lingsma HF, Bauer-Mehren A, Friedrich CM, Molyneux AJ, Kerr RS, Yarnold J, Sneade M, Steyerberg EW, Sturkenboom MC. Prediction of 60 day case-fatality after aneurysmal subarachnoid haemorrhage: results from the International Subarachnoid Aneurysm Trial (ISAT). *Eur J Epidemiol.* 2010;25:261–266.
  144. Ioannidis I, Lalloo S, Corkill R, Kukur W, Byrne JV. Endovascular treatment of very small intracranial aneurysms. *J Neurosurg.* 2010;112:551–556.

145. Piotin M, Blanc R, Spelle L, Mounayer C, Piantino R, Schmidt PJ, Moret J. Stent-assisted coiling of intracranial aneurysms: clinical and angiographic results in 216 consecutive aneurysms. *Stroke*. 2010;41:110–115.
146. Deng J, Zhao Z, Gao G. Periprocedural complications associated with endovascular embolisation of intracranial ruptured aneurysms with matrix coils. *Singapore Med J*. 2007;48:429–433.
147. Brisman JL, Niimi Y, Song JK, Berenstein A. Aneurysmal rupture during coiling: low incidence and good outcomes at a single large volume center. *Neurosurgery*. 2005;57:1103–1109.
148. Ishii A, Murayama Y, Nien YL, Yuki I, Adapon PH, Kim R, Jahan R, Duckwiler G, Viñuela F. Immediate and midterm outcomes of patients with cerebral aneurysms treated with Matrix1 and Matrix2 coils: a comparative analysis based on a single-center experience in 250 consecutive cases. *Neurosurgery*. 2008;63:1071–1077.
149. Hoh BL, Topcuoglu MA, Singhal AB, Pryor JC, Rabinov JD, Rordorf GA, Carter BS, Ogilvy CS. Effect of clipping, craniotomy, or intravascular coiling on cerebral vasospasm and patient outcome after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2004;55:779–786.
150. Bracard S, Lebedinsky A, Anxionnat R, Neto JM, Audibert G, Long Y, Picard L. Endovascular treatment of Hunt and Hess grade IV and V aneurysms. *AJNR Am J Neuroradiol*. 2002;23:953–957.
151. 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.
152. Suzuki J, Yoshimoto T, Kayama T. Surgical treatment of middle cerebral artery aneurysms. *J Neurosurg*. 1984;61:17–23.
153. Cai Y, Spelle L, Wang H, Piotin M, Mounayer C, Vanzin JR, Moret J. Endovascular treatment of intracranial aneurysms in the elderly: single-center experience in 63 consecutive patients. *Neurosurgery*. 2005;57:1096–1102.
154. 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.
155. 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.
156. Proust F, G  rardin E, Derrey S, Lesv  que S, Ramos S, Langlois O, Tollard E, B  nichou J, Chassagne P, Clavier E, Fr  ger P. Interdisciplinary treatment of ruptured cerebral aneurysms in elderly patients. *J Neurosurg*. 2010;112:1200–1207.
157. Taylor CJ, Robertson F, Brealey D, O'shea F, Stephen T, Brew S, Grieve JP, Smith M, Appleby I. Outcome in poor grade subarachnoid hemorrhage patients treated with acute endovascular coiling of aneurysms and aggressive intensive care. *Neurocrit Care*. 2011;14:341–347.
158. Brilstra EH, Rinkel GJ, van der Graaf Y, van Rooij WJ, Algra A. Treatment of intracranial aneurysms by embolization with coils: a systematic review. *Stroke*. 1999;30:470–476.
159. L  sneveld E, Brilstra EH, Nijssen PC, van Rooij WJ, Sluzewski M, Tullock CA, Wijnalda D, Schellens RL, van der Graaf Y, Rinkel GJ. Endovascular coiling versus neurosurgical clipping in patients with a ruptured basilar tip aneurysm. *J Neurol Neurosurg Psychiatry*. 2002;73:591–593.
160. Uda K, Murayama Y, Gobin YP, Duckwiler GR, Vi  uela F. Endovascular treatment of basilar artery trunk aneurysms with Guglielmi detachable coils: clinical experience with 41 aneurysms in 39 patients. *J Neurosurg*. 2001;95:624–632.
161. Andal  z N, Zuccarello M. Recent trends in the treatment of cerebral aneurysms: analysis of a nationwide inpatient database. *J Neurosurg*. 2008;108:1163–1169.
162. 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.
163. Varelas PN, Schultz L, Conti M, Spanaki M, Genarrelli T, Haccin-Bey L. The impact of a neuro-intensivist on patients with stroke admitted to a neurosciences intensive care unit. *Neurocrit Care*. 2008;9:293–299.
164. Crowley RW, Yeoh HK, Stukenborg GJ, Ionescu AA, Kassell NF, Dumont AS. Influence of weekend versus weekday hospital admission on mortality following subarachnoid hemorrhage: clinical article. *J Neurosurg*. 2009;111:60–66.
165. Stevens RD, Naval NS, Mirski MA, Citerio G, Andrews PJ. Intensive care of aneurysmal subarachnoid hemorrhage: an international survey. *Intensive Care Med*. 2009;35:1556–1566.
166. Accreditation Council on Graduate Medical Education. ACGME program requirements for fellowship education in endovascular surgical neuroradiology. [http://www.acgme.org/acWebsite/RRC\\_160/160\\_prIndex.asp](http://www.acgme.org/acWebsite/RRC_160/160_prIndex.asp). Accessed October 26, 2010.
167. Alberts MJ, Latchaw RE, Selman WR, Shephard T, Hadley MN, Brass LM, Koroshetz W, Marler JR, Booss J, Zorowitz RD, Croft JB, Magnis E, Mulligan D, Jagoda A, O'Connor R, Cawley CM, Connors JJ, Rose-DeRenzy JA, Emr M, Warren M, Walker MD; Brain Attack Coalition. Recommendations for comprehensive stroke centers: a consensus statement from the Brain Attack Coalition. *Stroke*. 2005;36:1597–1616.
168. 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.
169. 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.
170. Hoff RG, Van Dijk GW, Mettes S, Verweij BH, Algra A, Rinkel GJ, Kalkman CJ. Hypotension in anaesthetized patients during aneurysm clipping: not as bad as expected? *Acta Anaesthesiol Scand*. 2008;52:1006–1011.
171. Pasternak JJ, McGregor DG, Schroeder DR, Lanier WL, Shi Q, Hindman BJ, Clarke WR, Torner JC, Weeks JB, Todd MM; IHAIST Investigators. Hyperglycemia in patients undergoing cerebral aneurysm surgery: its association with long-term gross neurologic and neuropsychological function. *Mayo Clin Proc*. 2008;83:406–417.
172. 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.
173. Bendtsen AO, Cold GE, Astrup J, Rosen  rn J. Thiopental loading during controlled hypotension for intracranial aneurysm surgery. *Acta Anaesthesiol Scand*. 1984;28:473–477.
174. Chen L, Gong Q, Xiao C. Effects of propofol, midazolam and thiopental sodium on outcome and amino acids accumulation in focal cerebral ischemia-reperfusion in rats. *Chin Med J (Engl)*. 2003;116:292–296.
175. Cheng MA, Theard MA, Tempelhoff R. Intravenous agents and intraoperative neuroprotection: beyond barbiturates. *Crit Care Clin*. 1997;13:185–199.
176. Lei B, Popp S, Cottrell JE, Kass IS. Effects of midazolam on brain injury after transient focal cerebral ischemia in rats\*. *J Neurosurg Anesthesiol*. 2009;21:131–139.
177. McDermott MW, Durity FA, Borozny M, Mountain MA. Temporary vessel occlusion and barbiturate protection in cerebral aneurysm surgery. *Neurosurgery*. 1989;25:54–61.
178. McGregor DG, Lanier WL, Pasternak JJ, Rusy DA, Hogan K, Samra S, Hindman B, Todd MM, Schroeder DR, Bayman EO, Clarke W, Torner J, Weeks J; Intraoperative Hypothermia for Aneurysm Surgery Trial Investigators. Effect of nitrous oxide on neurologic and neuropsychological function after intracranial aneurysm surgery. *Anesthesiology*. 2008;108:568–579.
179. Obradovi   DI, Savi   MM, Andjelkovi   DS, Ugresi   ND, Bokoni   DR. The influence of midazolam and flumazenil on rat brain slices oxygen consumption. *Pharmacol Res*. 2003;47:127–131.
180. 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.
181. 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.
182. Clifton GL, Drever P, Valadka A, Zygun D, Okonkwo D. Multicenter trial of early hypothermia in severe brain injury. *J Neurotrauma*. 2009;26:393–397.
183. Cronberg T, Lilja G, Rundgren M, Friberg H, Widner H. Long-term neurological outcome after cardiac arrest and therapeutic hypothermia. *Resuscitation*. 2009;80:1119–1123.
184. Friberg H, Nielsen N. Hypothermia after cardiac arrest: lessons learned from national registries. *J Neurotrauma*. 2009;26:365–369.
185. Hemmen TM, Lyden PD. Hypothermia after acute ischemic stroke. *J Neurotrauma*. 2009;26:387–391.
186. Hemmen TM, Lyden PD. Multimodal neuroprotective therapy with induced hypothermia after ischemic stroke. *Stroke*. 2009;40(suppl):S126–S128.



187. MacLellan CL, Clark DL, Silasi G, Colbourne F. Use of prolonged hypothermia to treat ischemic and hemorrhagic stroke. *J Neurotrauma*. 2009;26:313–323.
188. Tang XN, Liu L, Yenari MA. Combination therapy with hypothermia for treatment of cerebral ischemia. *J Neurotrauma*. 2009;26:325–331.
189. Todd MM, Hindman BJ, Clarke WR, Torner JC: Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) Investigators. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med*. 2005;352:135–145.
190. 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.
191. Jabre A, Symon L. Temporary vascular occlusion during aneurysm surgery. *Surg Neurol*. 1987;27:47–63.
192. Levati A, Tommasino C, Moretti MP, Paino R, D'Aliberti G, Santoro F, Meregalli S, Vesconi S, Collice M. Giant intracranial aneurysms treated with deep hypothermia and circulatory arrest. *J Neurosurg Anesthesiol*. 2007;19:25–30.
193. Mack WJ, Ducruet AF, Angevine PD, Komotar RJ, Shrebnick DB, Edwards NM, Smith CR, Heyer EJ, Monyero L, Connolly ES Jr, Solomon RA. Deep hypothermic circulatory arrest for complex cerebral aneurysms: lessons learned. *Neurosurgery*. 2008;62:1311–1323.
194. Schebesch KM, Proescholdt M, Ullrich OW, Camboni D, Moritz S, Wiesenack C, Brawanski A. Circulatory arrest and deep hypothermia for the treatment of complex intracranial aneurysms—results from a single European center. *Acta Neurochir (Wien)*. 2010;152:783–792.
195. 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.
196. 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.
197. Bebawy JF, Gupta DK, Bendok BR, Hemmer LB, Zeeni C, Avram MJ, Batjer HH, Koht A. Adenosine-induced flow arrest to facilitate intracranial aneurysm clip ligation: dose-response data and safety profile. *Anesth Analg*. 2010;110:1406–1411.
198. Guinn NR, McDonagh DL, Borel CO, Wright DR, Zomorodi AR, Powers CJ, Warner DS, Lam AM, Britz GW. Adenosine-induced transient asystole for intracranial aneurysm surgery: a retrospective review. *J Neurosurg Anesthesiol*. 2011;23:35–40.
199. Jones M, Leslie K, Mitchell P. Anaesthesia for endovascular treatment of cerebral aneurysms. *J Clin Neurosci*. 2004;11:468–470.
200. Lakhani S, Guha A, Nahser HC. Anaesthesia for endovascular management of cerebral aneurysms. *Eur J Anaesthesiol*. 2006;23:902–913.
201. Varma MK, Price K, Jayakrishnan V, Manickam B, Kessell G. Anaesthetic considerations for interventional neuroradiology. *Br J Anaesth*. 2007;99:75–85.
202. Manninen PH, Chan AS, Papworth D. Conscious sedation for interventional neuroradiology: a comparison of midazolam and propofol infusion. *Can J Anaesth*. 1997;44:26–30.
203. Qureshi AI, Suri MF, Khan J, Kim SH, Fessler RD, Ringer AJ, Guterman LR, Hopkins LN. Endovascular treatment of intracranial aneurysms by using Guglielmi detachable coils in awake patients: safety and feasibility. *J Neurosurg*. 2001;94:880–885.
204. Young WL, Pile-Spellman J. Anesthetic considerations for interventional neuroradiology. *Anesthesiology*. 1994;80:427–456.
205. Weir B. *Subarachnoid Hemorrhage: Causes and Cures*. New York, NY: Oxford University Press; 1998.
206. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, Mendelow AD, Juvela S, Yonas H, Terbrugge KG, Macdonald RL, Diringer MN, Broderick JP, Dreier JP, Roos YB. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke*. 2010;41:2391–2395.
207. Yundt KD, Grubb RL Jr, Diringer MN, Powers WJ. Autoregulatory vasodilation of parenchymal vessels is impaired during cerebral vasospasm. *J Cereb Blood Flow Metab*. 1998;18:419–424.
208. Takeuchi H, Handa Y, Kobayashi H, Kawano H, Hayashi M. Impairment of cerebral autoregulation during the development of chronic cerebral vasospasm after subarachnoid hemorrhage in primates. *Neurosurgery*. 1991;28:41–48.
209. Dorhout Mees SM, Rinkel GJ, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, van Gijn J. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2007;(3):CD000277.
210. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, 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.
211. 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.
212. Zwienenberg-Lee M, Hartman J, Rudisill N, Madden LK, Smith K, Eskridge J, Newell D, Verweij B, Bullock MR, Baker A, Coplin W, Mericle R, Dai J, Rocke D, Muizelaar JP; Balloon Prophylaxis for Aneurysmal Vasospasm (BPAV) Study Group. Effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III subarachnoid hemorrhage: results of a phase II multicenter, randomized, clinical trial. *Stroke*. 2008;39:1759–1765.
213. Dorhout Mees SM, van den Bergh WM, Algra A, Rinkel GJ. Antiplatelet therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2007;(4):CD006184.
214. 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.
215. Kramer AH, Fletcher JJ. Locally-administered intrathecal thrombolytics following aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. *Neurocrit Care*. 2011;14:489–499.
216. 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.
217. Macdonald RL, Pluta RM, Zhang JH. Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution. *Nat Clin Pract Neurol*. 2007;3:256–263.
218. Rabinstein AA, Lanzino G, Wijdicks EF. Multidisciplinary management and emerging therapeutic strategies in aneurysmal subarachnoid haemorrhage. *Lancet Neurol*. 2010;9:504–519.
219. Vergouwen MD, Meijers JC, Geskus RB, Coert BA, Horn J, Stroes ES, van der Poll T, Vermeulen M, Roos YB. Biologic effects of simvastatin in patients with aneurysmal subarachnoid hemorrhage: a double-blind, placebo-controlled randomized trial. *J Cereb Blood Flow Metab*. 2009;29:1444–1453.
220. Macdonald RL, Kassell NF, Mayer S, Ruefenacht D, Schmiedek P, Weidauer S, Frey A, Roux S, Pasqualin A; CONSCIOUS-1 Investigators. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. *Stroke*. 2008;39:3015–3021.
221. Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, Vajkoczy P, Wanke I, Bach D, Frey A, Marr A, Roux S, Kassell N. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). *Lancet Neurol*. 2011;10:618–625.
222. Zhao XD, Zhou YT, Zhang X, Zhuang Z, Shi JX. A meta analysis of treating subarachnoid hemorrhage with magnesium sulfate. *J Clin Neurosci*. 2009;16:1394–1397.
223. Wong GK, Poon WS, Chan MT, Boet R, Gin T, Ng SC, Zee BC; IMASH Investigators. Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage (IMASH): a randomized, double-blinded, placebo-controlled, multicenter phase III trial. *Stroke*. 2010;41:921–926.
224. Jost SC, Diringer MN, Zazulia AR, Videon TO, Aiyagari V, Grubb RL, Powers WJ. Effect of normal saline bolus on cerebral blood flow in regions with low baseline flow in patients with vasospasm following subarachnoid hemorrhage. *J Neurosurg*. 2005;103:25–30.
225. Dankbaar JW, de Rooij NK, Velthuis BK, Frijns CJ, Rinkel GJ, van der Schaaf IC. Diagnosing delayed cerebral ischemia with different CT modalities in patients with subarachnoid hemorrhage with clinical deterioration. *Stroke*. 2009;40:3493–3498.

226. van der Schaaf I, Wermer MJ, van der Graaf Y, Hoff RG, Rinkel GJ, Velthuis BK. CT after subarachnoid hemorrhage: relation of cerebral perfusion to delayed cerebral ischemia. *Neurology*. 2006;66:1533–1538.
227. Ray WZ, Moran CJ, Derdeyn CP, Diringer MN, Dacey RG Jr, Zipfel GJ. Near-complete resolution of angiographic cerebral vasospasm after extreme elevation of mean arterial pressure: case report. *Surg Neurol*. 2009;72:347–353.
228. Dankbaar JW, Slooter AJ, Rinkel GJ, Schaaf IC. Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: a systematic review. *Crit Care*. 2010;14:R23.
229. Appelboom G, Strozzyk D, Hwang BY, Prowda J, Badjatia N, Helbok R, Meyers PM. Bedside use of a dual aortic balloon occlusion for the treatment of cerebral vasospasm. *Neurocrit Care*. 2010;13:385–388.
230. Jun P, Ko NU, English JD, Dowd CF, Halbach VV, Higashida RT, Lawton MT, Hetts SW. Endovascular treatment of medically refractory cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *AJNR Am J Neuroradiol*. 2010;31:1911–1916.
231. Shankar JJ, dos Santos MP, Deus-Silva L, Lum C. Angiographic evaluation of the effect of intra-arterial milrinone therapy in patients with vasospasm from aneurysmal subarachnoid hemorrhage. *Neuroradiology*. 2011;53:123–128.
232. Smith WS, Dowd CF, Johnston SC, Ko NU, DeArmond SJ, Dillon WP, Setty D, Lawton MT, Young WL, Higashida RT, Halbach VV. Neurotoxicity of intra-arterial papaverine preserved with chlorobutanol used for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke*. 2004;35:2518–2522.
233. Terry A, Zipfel G, Milner E, Cross DT 3rd, Moran CJ, Diringer MN, Dacey RG Jr, Derdeyn CP. Safety and technical efficacy of over-the-wire balloons for the treatment of subarachnoid hemorrhage-induced cerebral vasospasm. *Neurosurg Focus*. 2006;21:E14.
234. Komotar RJ, Hahn DK, Kim GH, Khandji J, Mocco J, Mayer SA, Connolly ES Jr. The impact of microsurgical fenestration of the lamina terminalis on shunt-dependent hydrocephalus and vasospasm after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2008;62:123–132.
235. Little AS, Zabramski JM, Peterson M, Goslar PW, Wait SD, Albuquerque FC, McDougall CG, Spetzler RF. Ventriculoperitoneal shunting after aneurysmal subarachnoid hemorrhage: analysis of the indications, complications, and outcome with a focus on patients with borderline ventriculomegaly. *Neurosurgery*. 2008;62:618–627.
236. de Oliveira JG, Beck J, Setzer M, Gerlach R, Vatter H, Seifert V, Raabe A. Risk of shunt-dependent hydrocephalus after occlusion of ruptured intracranial aneurysms by surgical clipping or endovascular coiling: a single-institution series and meta-analysis. *Neurosurgery*. 2007;61:924–933.
237. Mura J, Rojas-Zalazar D, Ruíz A, Vintimilla LC, Marengo JJ. Improved outcome in high-grade aneurysmal subarachnoid hemorrhage by enhancement of endogenous clearance of cisternal blood clots: a prospective study that demonstrates the role of lamina terminalis fenestration combined with modern microsurgical cisternal blood evacuation. *Minim Invasive Neurosurg*. 2007;50:355–362.
238. Kwon JH, Sung SK, Song YJ, Choi HJ, Huh JT, Kim HD. Predisposing factors related to shunt-dependent chronic hydrocephalus after aneurysmal subarachnoid hemorrhage. *J Korean Neurosurg Soc*. 2008;43:177–181.
239. Hellingman CA, van den Bergh WM, Beijer IS, van Dijk GW, Algra A, van Gijn J, Rinkel GJ. Risk of rebleeding after treatment of acute hydrocephalus in patients with aneurysmal subarachnoid hemorrhage. *Stroke*. 2007;38:96–99.
240. Rincon F, Gordon E, Starke RM, Buitrago MM, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Frontera J, Seder DB, Palestrant D, Connolly ES, Lee K, Mayer SA, Badjatia N. Predictors of long-term shunt-dependent hydrocephalus after aneurysmal subarachnoid hemorrhage: clinical article. *J Neurosurg*. 2010;113:774–780.
241. Chan M, Alaraj A, Calderon M, Herrera SR, Gao W, Ruland S, Roitberg BZ. Prediction of ventriculoperitoneal shunt dependency in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2009;110:44–49.
242. O'Kelly CJ, Kulkarni AV, Austin PC, Urbach D, Wallace MC. Shunt-dependent hydrocephalus after aneurysmal subarachnoid hemorrhage: incidence, predictors, and revision rates: clinical article. *J Neurosurg*. 2009;111:1029–1035.
243. Komotar RJ, Hahn DK, Kim GH, Starke RM, Garrett MC, Merkow MB, Otten ML, Sciacca RR, Connolly ES Jr. Efficacy of lamina terminalis fenestration in reducing shunt-dependent hydrocephalus following aneurysmal subarachnoid hemorrhage: a systematic review: clinical article. *J Neurosurg*. 2009;111:147–154.
244. Jartti P, Karttunen A, Isokangas JM, Jartti A, Koskelainen T, Tervonen O. Chronic hydrocephalus after neurosurgical and endovascular treatment of ruptured intracranial aneurysms. *Acta Radiol*. 2008;49:680–686.
245. Klopfeinstein 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.
246. Rajshekhar V, Harbaugh RE. Results of routine ventriculostomy with external ventricular drainage for acute hydrocephalus following subarachnoid hemorrhage. *Acta Neurochir (Wien)*. 1992;115:8–14.
247. Ransom ER, Mocco J, Komotar RJ, Sahni D, Chang J, Hahn DK, Kim GH, Schmidt JM, Sciacca RR, Mayer SA, Connolly ES. External ventricular drainage response in poor grade aneurysmal subarachnoid hemorrhage: effect on preoperative grading and prognosis. *Neurocrit Care*. 2007;6:174–180.
248. Milhorat TH. Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 1987;20:15–20.
249. Hasan D, Vermeulen M, Wijdevicks EF, Hijdra A, van Gijn J. Management problems in acute hydrocephalus after subarachnoid hemorrhage. *Stroke*. 1989;20:747–753.
250. Paré L, Delfino R, Leblanc R. The relationship of ventricular drainage to aneurysmal rebleeding. *J Neurosurg*. 1992;76:422–427.
251. McIver JJ, Friedman JA, Wijdevicks 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.
252. Hoekema D, Schmidt RH, Ross I. Lumbar drainage for subarachnoid hemorrhage: technical considerations and safety analysis. *Neurocrit Care*. 2007;7:3–9.
253. Ochiai H, Yamakawa Y. Continuous lumbar drainage for the preoperative management of patients with aneurysmal subarachnoid hemorrhage. *Neurol Med Chir (Tokyo)*. 2001;41:576–580.
254. Ruijs AC, Dirven CM, Algra A, Beijer J, Vandertop WP, Rinkel G. The risk of rebleeding after external lumbar drainage in patients with untreated ruptured cerebral aneurysms. *Acta Neurochir (Wien)*. 2005;147:1157–1161.
255. Kwon OY, Kim YJ, Cho CS, Lee SK, Cho MK. The utility and benefits of external lumbar CSF drainage after endovascular coiling on aneurysmal subarachnoid hemorrhage. *J Korean Neurosurg Soc*. 2008;43:281–287.
256. Connolly ES Jr, Kader AA, Frazzini VI, Winfree CJ, Solomon RA. The safety of intraoperative lumbar subarachnoid drainage for acutely ruptured intracranial aneurysm: technical note. *Surg Neurol*. 1997;48:338–342.
257. Hasan D, Lindsay KW, Vermeulen M. Treatment of acute hydrocephalus after subarachnoid hemorrhage with serial lumbar puncture. *Stroke*. 1991;22:190–194.
258. Dorai Z, Hynan LS, Kopitnik TA, Samson D. Factors related to hydrocephalus after aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2003;52:763–769.
259. Varelas P, Helms A, Sinson G, Spanaki M, Hachein-Bey L. Clipping or coiling of ruptured cerebral aneurysms and shunt-dependent hydrocephalus. *Neurocrit Care*. 2006;4:223–228.
260. Dehdashti AR, Rilliet B, Rufenacht DA, de Tribolet N. Shunt-dependent hydrocephalus after rupture of intracranial aneurysms: a prospective study of the influence of treatment modality. *J Neurosurg*. 2004;101:402–407.
261. Gruber A, Reinprecht A, Bavinszki 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.
262. 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.
263. Sindou M. Favourable influence of opening the lamina terminalis and Lilliequist's membrane on the outcome of ruptured intracranial aneurysms: a study of 197 consecutive cases. *Acta Neurochir (Wien)*. 1994;127:15–16.
264. 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.

265. Yonekawa Y, Imhof HG, Ogata N, Bernays R, Kaku Y, Fandino J, Taub E. Aneurysm surgery in the acute stage: results of structured treatment. *Neurol Med Chir (Tokyo)*. 1998;38(suppl):45–49.
266. Andaluz N, Van Loveren HR, Keller JT, Zuccarello M. Anatomic and clinical study of the orbitopterional approach to anterior communicating artery aneurysms. *Neurosurgery*. 2003;52:1140–1148.
267. Andaluz N, Zuccarello M. Fenestration of the lamina terminalis as a valuable adjunct in aneurysm surgery. *Neurosurgery*. 2004;55:1050–1059.
268. Schmieder K, Koch R, Lucke S, Harders A. Factors influencing shunt dependency after aneurysmal subarachnoid haemorrhage. *Zentralbl Neurochir*. 1999;60:133–140.
269. Akyuz M, Tuncer R. The effects of fenestration of the interpeduncular cistern membrane aroused to the opening of lamina terminalis in patients with ruptured ACoA aneurysms: a prospective, comparative study. *Acta Neurochir (Wien)*. 2006;148:725–723.
270. Kim JM, Jeon JY, Kim JH, Cheong JH, Bak KH, Kim CH, Yi HJ, Kim KM. Influence of lamina terminalis fenestration on the occurrence of the shunt-dependent hydrocephalus in anterior communicating artery aneurysmal subarachnoid hemorrhage. *J Korean Med Sci*. 2006;21:113–118.
271. 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.
272. Gilmore E, Choi HA, Hirsch LJ, Claassen J. Seizures and CNS hemorrhage: spontaneous intracerebral and aneurysmal subarachnoid hemorrhage. *Neurologist*. 2010;16:165–175.
273. 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.
274. Deutschman CS, Haines SJ. Anticonvulsant prophylaxis in neurological surgery. *Neurosurgery*. 1985;17:510–517.
275. 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.
276. Choi KS, Chun HJ, Yi HJ, Ko Y, Kim YS, Kim JM. Seizures and epilepsy following aneurysmal subarachnoid hemorrhage: incidence and risk factors. *J Korean Neurosurg Soc*. 2009;46:93–98.
277. Lin CL, Dumont AS, Lieu AS, Yen CP, Hwang SL, Kwan AL, Kassell NF, Hwang SL. Characterization of perioperative seizures and epilepsy following aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2003;99:978–985.
278. 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.
279. Ukkola V, Heikkinen ER. Epilepsy after operative treatment of ruptured cerebral aneurysms. *Acta Neurochir (Wien)*. 1990;106:115–118.
280. Cabral NL, Gonçalves AR, Longo AL, Moro CH, Costa G, Amaral CH, Fonseca LA, Eluf-Neto J. Incidence of stroke subtypes, prognosis and prevalence of risk factors in Joinville, Brazil: a 2 year community based study. *J Neurol Neurosurg Psychiatry*. 2009;80:755–761.
281. Kvam DA, Loftus CM, Copeland B, Quest DO. Seizures during the immediate postoperative period. *Neurosurgery*. 1983;12:14–17.
282. 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.
283. Kotila M, Waltimo O. Epilepsy after stroke. *Epilepsia*. 1992;33:495–498.
284. Byrne JV, Boardman P, Ioannidis I, Adcock J, Traill Z. Seizures after aneurysmal subarachnoid hemorrhage treated with coil embolization. *Neurosurgery*. 2003;52:545–552.
285. Dennis LJ, Claassen J, Hirsch LJ, Emerson RG, Connolly ES, Mayer SA. Nonconvulsive status epilepticus after subarachnoid hemorrhage. *Neurosurgery*. 2002;51:1136–1143.
286. Little AS, Kerrigan JF, McDougall CG, Zabramski JM, Albuquerque FC, Nakaji P, Spetzler RF. Nonconvulsive status epilepticus in patients suffering spontaneous subarachnoid hemorrhage. *J Neurosurg*. 2007;106:805–811.
287. North JB, Penhall RK, Hanieh A, Frewin DB, Taylor WB. Phenytoin and postoperative epilepsy: a double-blind study. *J Neurosurg*. 1983;58:672–677.
288. O’Laoire SA. Epilepsy following neurosurgical intervention. *Acta Neurochir Suppl (Wien)*. 1990;50:52–54.
289. Sbeih I, Tamas LB, O’Laoire SA. Epilepsy after operation for aneurysms. *Neurosurgery*. 1986;19:784–788.
290. Shaw MD. Post-operative epilepsy and the efficacy of anticonvulsant therapy. *Acta Neurochir Suppl (Wien)*. 1990;50:55–57.
291. Naidech AM, Kreiter KT, Janjua N, Ostapovich N, Parra A, Com-michau C, Connolly ES, Mayer SA, Fitzsimmons BF. Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. *Stroke*. 2005;36:583–587.
292. Rosengart AJ, Huo JD, Tolentino J, Novakovic RL, Frank JJ, Gold-enberg FD, Macdonald RL. Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. *J Neurosurg*. 2007;107:253–260.
293. Disney L, Weir B, Grace M, Roberts P. Trends in blood pressure, osmolality and electrolytes after subarachnoid hemorrhage from aneurysms. *Can J Neurol Sci*. 1989;16:299–304.
294. James IM. Electrolyte changes in patients with subarachnoid haemorrhage. *Clin Sci*. 1972;42:179–187.
295. Chandy D, Sy R, Aronow WS, Lee WN, Maguire G, Murali R. Hyponatremia and cerebrovascular spasm in aneurysmal subarachnoid hemorrhage. *Neurol India*. 2006;54:273–275.
296. Nakagawa I, Kurokawa S, Takayama K, Wada T, Nakase H. Increased urinary sodium excretion in the early phase of aneurysmal subarachnoid hemorrhage as a predictor of cerebral salt wasting syndrome [in Japanese]. *Brain Nerve*. 2009;61:1419–1423.
297. Rahman M, Friedman WA. Hyponatremia in neurosurgical patients: clinical guidelines development. *Neurosurgery*. 2009;65:925–935.
298. 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.
299. Qureshi AI, Suri MF, Sung GY, Straw RN, Yahia AM, Saad M, Guterman LR, Hopkins LN. Prognostic significance of hyponatremia and hyponatremia among patients with aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2002;50:749–755.
300. 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.
301. Harrigan MR. Cerebral salt wasting syndrome. *Crit Care Clin*. 2001;17:125–138.
302. Naval NS, Stevens RD, Mirski MA, Bhardwaj A. Controversies in the management of aneurysmal subarachnoid hemorrhage. *Crit Care Med*. 2006;34:511–524.
303. Suarez JJ, 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.
304. Al-Rawi PG, Tseng MY, Richards HK, Nortje J, Timofeev I, Matta BF, Hutchinson PJ, Kirkpatrick PJ. Hypertonic saline in patients with poor-grade subarachnoid hemorrhage improves cerebral blood flow, brain tissue oxygen, and pH. *Stroke*. 2010;41:122–128.
305. 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.
306. 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.
307. Katayama Y, Haraoka J, Hirabayashi H, Kawamata T, Kawamoto K, Kitahara T, Kojima J, Kuroiwa T, Mori T, Moro N, Nagata I, Ogawa A, Ohno K, Seiki Y, Shiokawa Y, Teramoto A, Tominaga T, Yoshimine T. A randomized controlled trial of hydrocortisone against hyponatremia in patients with aneurysmal subarachnoid hemorrhage. *Stroke*. 2007;38:2373–2375.
308. 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.
309. Kilpatrick MM, Lowry DW, Firlik AD, Yonas H, Marion DW. Hyperthermia in the neurosurgical intensive care unit. *Neurosurgery*. 2000;47:850–855.
310. Dorhout Mees SM, Luitse MJ, van den Bergh WM, Rinkel GJ. Fever after aneurysmal subarachnoid hemorrhage: relation with extent of hydrocephalus and amount of extravasated blood. *Stroke*. 2008;39:2141–2143.



311. Stevens RD, Nyquist PA. The systemic implications of aneurysmal subarachnoid hemorrhage. *J Neurol Sci.* 2007;261:143–156.
312. Rabinstein AA, Sandhu K. Non-infectious fever in the neurological intensive care unit: incidence, causes and predictors. *J Neurol Neurosurg Psychiatry.* 2007;78:1278–1280.
313. Fernandez A, Schmidt JM, Claassen J, Pavlicova M, Huddleston D, Kreiter KT, Ostapkovich ND, Kowalski RG, Parra A, Connolly ES, Mayer SA. Fever after subarachnoid hemorrhage: risk factors and impact on outcome. *Neurology.* 2007;68:1013–1019.
314. Zhang G, Zhang JH, Qin X. Fever increased in-hospital mortality after subarachnoid hemorrhage. *Acta Neurochir Suppl.* 2011;110:239–243.
315. Badjatia N, Fernandez L, Schmidt JM, Lee K, Claassen J, Connolly ES, Mayer SA. Impact of induced normothermia on outcome after subarachnoid hemorrhage: a case-control study. *Neurosurgery.* 2010;66:696–700.
316. Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, Lyden PD, Broderick JP, Kwiatkowski TG, Fineberg SE; NINDS rt-PA Stroke Study Group. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology.* 2002;59:669–674.
317. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients [published correction appears in *Mayo Clin Proc.* 2005;80:1101]. *Mayo Clin Proc.* 2004;79:992–1000.
318. Lanier WL, Stangland KJ, Scheithauer BW, Milde JH, Michenfelder JD. The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: examination of a model. *Anesthesiology.* 1987;66:39–48.
319. Longstreth WT Jr, Diehr P, Inui TS. Prediction of awakening after out-of-hospital cardiac arrest. *N Engl J Med.* 1983;308:1378–1382.
320. Longstreth WT Jr, Inui TS. High blood glucose level on hospital admission and poor neurological recovery after cardiac arrest. *Ann Neurol.* 1984;15:59–63.
321. Wass CT, Lanier WL. Glucose modulation of ischemic brain injury: review and clinical recommendations. *Mayo Clin Proc.* 1996;71:801–812.
322. Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. *BMJ.* 1997;314:1303–1306.
323. Young B, Ott L, Dempsey R, Haack D, Tibbs P. Relationship between admission hyperglycemia and neurologic outcome of severely brain-injured patients. *Ann Surg.* 1989;210:466–472.
324. Schlenk F, Vajkoczy P, Sarrafzadeh A. Inpatient hyperglycemia following aneurysmal subarachnoid hemorrhage: relation to cerebral metabolism and outcome. *Neurocrit Care.* 2009;11:56–63.
325. Helbok R, Schmidt JM, Kurtz P, Hanafy KA, Fernandez L, Stuart RM, Presciutti M, Ostapkovich ND, Connolly ES, Lee K, Badjatia N, Mayer SA, Claassen J. Systemic glucose and brain energy metabolism after subarachnoid hemorrhage. *Neurocrit Care.* 2010;12:317–323.
326. Giller CA, Wills MJ, Giller AM, Samson D. Distribution of hematocrit values after aneurysmal subarachnoid hemorrhage. *J Neuroimaging.* 1998;8:169–170.
327. Dhar R, Zazulia AR, Videen TO, Zipfel GJ, Derdeyn CP, Diringner MN. Red blood cell transfusion increases cerebral oxygen delivery in anemic patients with subarachnoid hemorrhage. *Stroke.* 2009;40:3039–3044.
328. Naidech AM, Drescher J, Ault ML, Shaibani A, Batjer HH, Alberts MJ. Higher hemoglobin is associated with less cerebral infarction, poor outcome, and death after subarachnoid hemorrhage. *Neurosurgery.* 2006;59:775–779.
329. Naidech AM, Jovanovic B, Wartenberg KE, Parra A, Ostapkovich N, Connolly ES, Mayer SA, Commichau C. Higher hemoglobin is associated with improved outcome after subarachnoid hemorrhage. *Crit Care Med.* 2007;35:2383–2389.
330. Kramer AH, Gurka MJ, Nathan B, Dumont AS, Kassell NF, Bleck TP. Complications associated with anemia and blood transfusion in patients with aneurysmal subarachnoid hemorrhage. *Crit Care Med.* 2008;36:2070–2075.
331. 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.
332. Naidech AM, Shaibani A, Garg RK, Duran IM, Liebling SM, Bassin SL, Bendok BR, Bernstein RA, Batjer HH, Alberts MJ. Prospective, randomized trial of higher goal hemoglobin after subarachnoid hemorrhage. *Neurocrit Care.* 2010;13:313–320.
333. Alaraj A, Wallace A, Mander N, Aletich V, Charbel FT, Amin-Hanjani S. Risk factors for heparin-induced thrombocytopenia type II in aneurysmal subarachnoid hemorrhage. *Neurosurgery.* 2011;69:1030–1036.
334. Kim GH, Hahn DK, Kellner CP, Komotar RJ, Starke R, Garrett MC, Yao J, Cleveland J, Mayer SA, Connolly ES. The incidence of heparin-induced thrombocytopenia type II in patients with subarachnoid hemorrhage treated with heparin versus enoxaparin. *J Neurosurg.* 2009;110:50–57.
335. Hoh BL, Aghi M, Pryor JC, Ogilvy CS. Heparin-induced thrombocytopenia type II in subarachnoid hemorrhage patients: incidence and complications. *Neurosurgery.* 2005;57:243–248.
336. Lassila R, Antovic JP, Armstrong E, Baghaei F, Dalsgaard-Nielsen J, Hillarp A, Holme PA, Holmstrom M, Johnsson H, Joutsu-Korhonen L, Sandset PM. Practical viewpoints on the diagnosis and management of heparin-induced thrombocytopenia. *Semin Thromb Hemost.* 2011;37:328–336.
337. Ray WZ, Strom RG, Blackburn SL, Ashley WW, Sicard GA, Rich KM. Incidence of deep venous thrombosis after subarachnoid hemorrhage. *J Neurosurg.* 2009;110:1010–1014.
338. Mack WJ, Ducruet AF, Hickman ZL, Kalyvas JT, Cleveland JR, Mocco J, Schmidt M, Mayer SA, Connolly ES Jr. Doppler ultrasonography screening of poor-grade subarachnoid hemorrhage patients increases the diagnosis of deep venous thrombosis. *Neurol Res.* 2008;30:889–892.