Aneurysms

Unruptured Aneurysms
The first report of the International Study of Unruptured Intracranial Aneurysms (ISUIA) cited very low rates of subarachnoid hemorrhage (SAH) for previously unruptured aneurysms. Data were collected retrospectively. It was difficult to reconcile these rates with those reported from prior studies, with the known sizes of ruptured aneurysms and with clinical experience. Prior reports including prospective studies suggested that unruptured aneurysms carried a 1% to 2% risk of hemorrhage per year. The second report from the ISUIA prospectively enrolled 4060 patients with unruptured aneurysms. Of these, 1692 had no intervention for their aneurysm, 1917 had open surgery, and 451 had endovascular procedures. The rupture rates were more in agreement with prior studies (Table). Risk factors for SAH were increasing aneurysm size and aneurysm location at the basilar apex or posterior communicating artery. The risk of surgical repair increased significantly with increasing patient age, posterior circulation location of the aneurysm, history of ischemic cerebrovascular disease, and presence of symptoms from the aneurysm. Thirty-day mortality occurred in 1.5%, morbidity in 3%, poor cognitive function plus morbidity (a Rankin score of 3 to 5) in 4%, and overall total morbidity and mortality in 13%. The data indicate that the decision to treat a ruptured aneurysm needs to include a careful analysis of the patient, their risk factors for poor outcome, and the features of the aneurysm. Endovascular treatment is an option, although overall complete obliteration rates were only about 50% in this study, and risk of treatment was similar to but lower than with surgery, although the groups were not randomized to treatment and are thus not comparable.

The findings of the initial results of ISUIA that were at variance with prior assumptions about unruptured aneurysms prompted an exhaustive review of the literature that suggested some explanations for the findings. Numerous assumptions and biases inherent in the retrospective design of the first study were cited. An important one is that selection bias could account for the finding that 10 mm seemed to be the cutoff for rupture, yet this is at odds with the fact that the average size of a ruptured aneurysm is 8 mm. The distribution of cases included in the initial cohort will strongly influence the size cutoff for rupture that is found. To take an extreme example, if one collects only aneurysms >10 mm in diameter, then one will necessarily conclude that the cutoff for rupture is some value >10 mm. The author recommended that unruptured aneurysms with clinical pathological profiles resembling those of ruptured lesions be considered for treatment at a smaller size than unruptured lesions with profiles typical of intact aneurysms. The question of whether and how to follow patients with unruptured aneurysms that are not treated is unanswered, but it was felt that periodic radiological imaging might be wise. Screening for aneurysms in asymptomatic patients is only recommended for patients with a strong family history of aneurysms or those with diseases associated with aneurysms such as autosomal dominant polycystic kidney disease. Although it is not proven that cessation of cigarette smoking will alter the natural history of an aneurysm, it would seem obvious to recommend stopping smoking in patients with aneurysms who do smoke.

Predicting which patients will suffer morbidity or mortality after surgery for unruptured aneurysms would be helpful. A single surgeon’s operative experience with 387 patients found that the risk of complications increased with increasing aneurysm size, broad neck, plaque or calcification at the neck of the aneurysm, temporary clipping, multiple aneurysms, need for repositioning of the clip, or multiple clips. Some of these factors cannot be predicted preoperatively of course, although it was suggested that surgeons carefully consider these factors preoperatively and consider obtaining high-resolution computed tomography (CT) through the aneurysm neck if there is suspicion about the condition of the neck, in addition to considering other factors previously identified to be associated with risk of complications such as aneurysm location and preexisting cerebrovascular disease.

What are the risk factors for development of a saccular cerebral aneurysm? Traditional factors include age, female sex, some rare inherited conditions, family history, heavy alcohol intake, and hypertension. A multivariable analysis of 312 patients with SAH and 618 controls determined that current cigarette smoking, history of hypertension, lower body mass index, family history of hemorrhagic stroke, caffeine in pharmaceutical products, lower educational achievement, and nicotine in pharmaceutical products were significant, independent risk factors for SAH. A literature review of 20 studies found that significant risk factors for SAH were smoking, hypertension, and drinking 150 g or more of alcohol per week.

Genes definitively associated with intracranial aneurysms have not been identified. One study in a Japanese cohort identified a locus associated with intracranial aneurysms on...
A polymorphism of the endoglin gene also was associated with intracranial aneurysms in Japanese subjects. Endoglin is a protein in the transforming growth factor-β receptor complex that is expressed predominately on the surface of endothelial cells. A study of 121 white patients with intracranial aneurysms, 124 healthy white subjects, and 15 Japanese volunteers found that this endoglin polymorphism was more frequent in Japanese individuals but that it was not significantly associated with aneurysms in white individuals. Other investigators also could not confirm an association between endoglin gene polymorphisms and aneurysms among Japanese. Khurana et al examined endothelial nitric oxide synthase (eNOS) T-786C single nucleotide polymorphisms among patients with small and large aneurysms. All 13 patients with large aneurysms were heterozygous for the polymorphism, whereas 9 of 22 patients with small aneurysms were homozygous (P = 0.019). More patients rebled after endovascular treatment than surgery but the risk of delayed cerebral ischemia was more common after surgery. This trial randomized a subset of patients in whom both coiling and surgery were judged to be possible (about one quarter of cases); in the rest, the treating physicians thought surgery or coiling was preferable. The aneurysms were located on the anterior circulation in 97% of cases and 92% were >11 mm in diameter. The fact that results of trials of drugs for SAH and of the timing of surgery for aneurysms were quite different in North America compared with other continents has, among other reasons, fueled the controversy about the generalizability of the results of this study to other geographic areas.

Ruptured Aneurysms

Endovascular treatment of ruptured aneurysms with detachable coils is becoming increasingly popular. The International Subarachnoid Aneurysm Trial (ISAT) compared endovascular coiling to surgery in a randomized, multicenter trial conducted mainly in the United Kingdom and Europe. A total of 2143 patients were randomized to surgery (n = 1070) or endovascular treatment (n = 1073). Dependence (modified Rankin scale score of 3 to 6) or death at 1 year occurred in 24% of patients treated endovascularly and 31% of those undergoing surgery (P = 0.0019). More patients rebled after endovascular treatment than surgery but the risk of delayed cerebral ischemia was more common after surgery. This trial randomized a subset of patients in whom both coiling and surgery were judged to be possible (about one quarter of cases); in the rest, the treating physicians thought surgery or coiling was preferable. The aneurysms were located on the anterior circulation in 97% of cases and 92% were >11 mm in diameter. The fact that results of trials of drugs for SAH and of the timing of surgery for aneurysms were quite different in North America compared with other continents has, among other reasons, fueled the controversy about the generalizability of the results of this study to other geographic areas.

Prediction of outcome after aneurysmal SAH remains inexact. The search for biological markers that influence outcome has included the apolipoprotein E (ApoE) isoforms. ApoE genotype is important in susceptibility to Alzheimer’s disease and is associated with outcome after traumatic brain injury. A study of 126 patients with aneurysmal SAH found a significantly higher risk of poor outcome in patients with
the ApoE 4 allele, which is the allele associated with poor outcome in the other diseases mentioned above. ApoE and S100B, a marker of brain injury, were measured in the cerebrospinal fluid (CSF) of SAH patients. Concentrations of S100B increased but those of ApoE decreased, suggesting that ApoE is retained in the brain after injury in response to injury and leading the authors to speculate that this is a protective mechanism. Other compounds examined for their ability to predict outcome after SAH include C-type natriuretic peptide (CNP). Measurement of CNP in plasma and CSF of 26 patients with SAH showed that CNP in CSF or plasma did not vary according to outcome or whether or not vasospasm developed.

Endovascular treatment of aneurysms with Guglielmi detachable or other types of coils has revolutionized the care of patients with cerebral aneurysms. Advances in endovascular techniques and technology are ongoing and are beginning to meld coils and inorganic materials with biological therapies. These have been the subject of a prior review. Surgery remains, however, a critical aspect of treatment since, among other reasons, coiling is judged to be reasonable in only some patients with aneurysms. Recent publications have suggested that better results can be achieved when teams of physicians with expertise in both endovascular and surgical aspects of treatment can evaluate and treat such patients. Furthermore, each treatment can compliment the other and allow optimal treatment of complex aneurysms. Periprocedural outcome of treatment of anterior communicating aneurysms was lower when endovascular treatment was added to the management. In this study, the results were compared with historical controls so it also is possible that the improvement was due to better neurosurgical intensive care, earlier treatment of the aneurysm, and better management of vasospasm. The findings are consistent with other reports, however, that document that outcome for patients with ruptured or unruptured aneurysms is better as the number of patients treated at the hospital increase and when endovascular services are available.

**Other Aspects of Aneurysm Surgery**

The surgical care of patients with aneurysms can be simplified by avoiding catheter angiography in some cases. CT angiography (CTA) has been receiving more attention than magnetic resonance angiography, particularly for investigation of patients with SAH. One third of 67 patients in one series and almost 70% in another underwent surgery based on CTA alone. The advantage is obvious avoidance of the risk of catheter angiography, but there remains a risk of missing a ruptured aneurysm or of an aneurysm near a ruptured one that could have been clipped during a craniotomy for the ruptured aneurysm. A tentative algorithm was proposed in which patients with SAH could be operated on when an aneurysm was found on CTA that was consistent with the SAH appearance. Negative CTA in the setting of SAH would mandate catheter angiography and the probability of finding a sizable aneurysm in patients without SAH in whom CTA is negative would be small. Titanium and titanium alloy clips for aneurysms have been developed and used extensively. They have the advantages of producing less clip artifact on follow-up imaging studies and no risk of movement in the MRI magnetic field that is a theoretical risk in 1.5-T magnets with the more common iron-cobalt-chromium Phynox alloy clips.

**Intensive Care and Vasospasm**

There remains interest in methods for bedside monitoring of cerebral blood flow and of other parameters such as brain tissue oxygenation, particularly in poor-grade SAH patients in whom clinical detection of ischemia is difficult. One promising technique is insertion of thermodilution probes into the brain for measurement of cerebral blood flow. Preliminary experience in 14 poor-grade SAH patients found that thermodilution probes inserted into white matter regions of vascular territories judged to be at risk for delayed ischemia from vasospasm could reliably predict development of vasospasm compared with the gold-standard tests of xenon-computed tomographic blood flow measurement and catheter angiography.

Administration of intrathecal fibrinolytic drugs to clear subarachnoid clot and prevent vasospasm is used by some neurosurgeons in selected patients with thick SAH on admission CT. Whether this is safe or not after aneurysm coiling was addressed by Hamada et al: 110 patients with aneurysmal SAH had their aneurysms coiled and were randomly assigned to receive intrathecal urokinase or not. Symptomatic vasospasm occurred in significantly fewer patients receiving urokinase (9% versus 30%) and importantly, there were no serious bleeding complications in patients injected with urokinase.

Transcranial Doppler ultrasound (TCD) is used to detect vasospasm after SAH, but reports of its value vary widely. A comprehensive review of the literature found 26 reports comparing TCD with angiography. Among 5 evaluable studies, sensitivity was 67%, specificity was 99%, positive predictive value was 97%, and negative predictive value was 78% for the middle cerebral artery. Therefore, for the middle cerebral artery, the high specificity makes it unlikely for TCD to diagnose spasm when there is none, and TCD may be used to identify patients with vasospasm. No such statements could be made for other arteries and situations.

The most effective method for prevention of aneurysm rebleeding remains surgical clipping, with coil occlusion a close second. In some cases, however, these procedures cannot be performed immediately. Antifibrinolytic drugs have been tested in numerous trials in order to reduce the risk of rebleeding. A recent meta-analysis examined randomized trials comparing antifibrinolytic drugs (tranexamic acid, epsilon amino-caproic acid, or an equivalent) with control in patients with SAH. Antifibrinolytic therapy did not decrease the risk of poor outcome or death. The risk of rebleeding was reduced but that of ischemia was increased. These findings are well known, but the suggestion has been made that with modern treatment of ischemia and vasospasm, antifibrinolytics might be of benefit, especially if given for only a few days after SAH until the aneurysm is treated, since rebleeding could be reduced without increasing the risk of ischemia. A recent trial from Sweden that was designed to test this idea, however, did not show any difference in outcome at 6
months.\(^4^7\) Therefore, at this point, routine use of antifibrinolytic drugs cannot be recommended.

Vasospasm remains a significant factor contributing to poor outcome after SAH. Progress in terms of treatment may come via local administration of higher doses of calcium channel antagonists. There is good experimental evidence to suggest that dysfunction of potassium channels in cerebrovascular smooth muscle contributes to vasospasm, and that if this is the case, then antagonists of voltage-gated calcium channels should prevent vasospasm.\(^4^8\) Indeed, the intrathecal delivery of nicardipine using prolonged release pellets in 20 patients with SAH found that there was no angiographic vasospasm 7 to 12 days after SAH in arteries that were in or near the pellets.\(^4^9\)

**Extracranial Vascular Disease**

Carotid endarterectomy continues to be compared with emerging noninvasive therapies such as angioplasty with or without stenting. Two published trials have had conflicting results, with one study showing no difference in periprocedural stroke and death between angioplasty alone and endarterectomy\(^5^0\) and the other study showing a higher risk with angioplasty and stenting.\(^5^1\) The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) is under way, and results should be known within the next several years.\(^5^2\) The SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) study showed a significant improvement in the composite primary end point among patients undergoing angioplasty and stenting compared with endarterectomy.\(^5^3\) There was, however, no significant difference in the rate of stroke and death, the addition of myocardial infarction leading to the significance (6% versus 13% overall, 4% versus 8%). Carotid endarterectomy remains a durable, safe, and effective treatment for carotid stenosis. The long-term outcome after angioplasty with or without stenting is not known and will not be for some time due to continual development of new stents and noninvasive methods. However, until such time as these data become available, carotid endarterectomy remains the major therapeutic modality for treatment of extracranial carotid artery stenosis.

The randomized trials prove that carotid endarterectomy reduces the risk of stroke and, in some cases, death from carotid stenosis in both symptomatic and asymptomatic patients. The benefit is very dependent on the risk of surgery, and there is great interest in being able to predict the risk of surgery based on preoperative factors. A systematic review of the published trials showed that risk of surgery is lowest for patients with no symptoms, highest for those with hemispheric symptoms, and intermediate for those with ocular ischemia.\(^5^4\) There is a higher risk during the acute phase of cerebral ischemia so that surgery generally should be delayed for some time in these cases.

**Cerebral Ischemia**

New techniques for bypass and reconstruction of cerebral arteries are being reported. Newell et al used a microanastomotic device to reconstruct the middle cerebral artery in 2 patients with fusiform aneurysms.\(^5^5\) The occlusion times necessary to complete the reconstructions (10 and 15 minutes) were short and the method is very promising for appropriate types of anastomoses. While difficult to quantify, the combination of improvements in neuroanesthesia, surgical techniques, patient selection, and intensive care likely will make contemporary results of various cerebral revascularization procedures better than in the past.

A new extracranial-intracranial artery bypass study is under way (Carotid Occlusion Surgery Study, COSS). In contrast to the prior study,\(^5^6\) COSS will randomize patients with recent symptomatic unilateral internal carotid occlusion who have increased oxygen extraction fraction on positron-emission tomography since prior studies suggested that this subgroup of patients is at substantial stroke risk compared with similar patients with normal oxygen extraction fraction.\(^5^7\)

Decompressive craniectomy has been performed for years to reduce intracranial pressure and brain shift in patients with SAH and middle cerebral artery territory infarction. A Cochrane review concluded that only a few patients have been reported in the literature and that they were compared with historical or poorly matched controls.\(^5^8\) This is being addressed in randomized, controlled trials, one of which (HEADDFIRST) is completed and publication is awaited.

**Arteriovenous and Other Vascular Malformations**

Han and colleagues presented an intention to treat analysis of a consecutive series of 73 Spetzler-Martin grade 4 and 5 arteriovenous malformations (AVM).\(^5^9\) Partial treatment of the AVM had been performed previously in 14 cases. The risk of hemorrhage was 1.5% per year in those patients who had not had their AVM treated, whereas it was 10.4% per year among the patients with partially treated AVMs. Some prior studies have suggested that partial treatment of AVMs does not reduce the risk of hemorrhage and that only complete obliteration—by surgery, radiosurgery, embolization, or a combination of these methods—is the only useful goal of treatment. The authors concluded that partial treatment was not effective or to be recommended for these types of AVMs and, furthermore, that it may even alter the natural history unfavorably. Risks of treatment for these higher-grade AVMs remain substantial and are in the vicinity of 15% morbidity for grade 4 and 33% for grade 5 AVMs.

Thus far 3 chromosome loci have been identified as harboring mutations associated with cavernous malformations.\(^6^0\) These include the KRIT1 (Krev Interaction Trapped 1) gene on chromosome 7q21, the CCM2 locus on chromosome 7p, and CCM3 on 3q. Mutations of these 3 sites have been identified in familial cavernous malformations. Most Hispanic-American families with CMs have mutations in KRIT1, usually a 2105C to T that inserts a stop codon in exon 14 (Q455X). This mutation is a recent founder mutation among Hispanic-Americans because analysis of families with cavernous malformations from Mexico did not disclose the mutation. On the other hand, at least 88 other mutations have been identified in KRIT1 among other familial cases of cavernous malformations, and mutations in KRIT1 were found in about 30% of non-Hispanic families with 2 or more cavernous malformations. In addition, most Hispanic-Americans with apparently sporadic cavernous malforma-
tions also have mutations in KRIT1, although not the Q455X mutation.

**Spontaneous Intracranial Hemorrhage**

Surgery for evacuation of spontaneous intracerebral hemorrhage remains controversial with wide variation in clinical practice in different geographic areas. A premise of clot removal would be that ongoing damage can be prevented. Recent evidence, however, has found it extremely difficult to confirm that there is any penumbral area of reduced cerebral blood flow around intracerebral hemorrhages, meaning that other secondary injury mechanisms need to be important and preventable for surgery to be of benefit. A Cochrane review of 4 trials comparing medical management to evacuation of intracerebral hemorrhage by craniotomy or endoscopy were included. The etiology of the hemorrhage in these trials generally is hypertension, and no trial has had blinded outcome assessment. There was a nonsignificant trend toward increased odds of death and dependency among survivors undergoing craniotomy (odds ratio 2.0, 99% confidence interval 0.9 to 4.3) and no trend for endoscopic evacuation. The conclusion was essentially that more trials are needed in which modern management techniques are used. A new randomized trial comparing surgical evacuation to medical treatment is ongoing (STICH trial). In the STICH trial, the method of hematoma evacuation is up to the surgeon. Some investigators are using stereotactic and endoscopic methods to remove the clot with the goal being to reduce potential brain injury due to surgery and thereby maximize the beneficial effects of surgery. Whether or not this will be an improvement on craniotomy awaits definitive study.

**References**


