Advances in Interventional Neuroradiology

Ajay K. Wakhloo, MD, PhD; Michael J. Deleo, III, MD; Martin M. Brown, MD, FRCP

Abstract—In 2008 we witnessed a rapid advancement in stent technology, which is reflected in the high number of case reports, publications of case series, and randomized trials. Stents not only served for a combined intracranial and extracranial treatment of challenging aneurysms but also assisted the revascularization in acute and chronic ischemic conditions of the neurovascular system. Although a self-expanding nitinol semiopen cell stent is currently used for intracranial occlusive disease, a new retrievable closed-cell designed stent is widely used for aneurysms because of its easy delivery through a microcather in frequently tortuous head and neck as well as cerebrovascular circulation (Figure 1). However, despite numerous publications in the field, the widespread acceptance of the use of stents to routinely treat carotid stenosis awaits the results of the multicenter randomized clinical trials that should be available in 2009. The role of interventional neuroradiology in the treatment of acute ischemic stroke continues to expand and excite interest. (Stroke. 2009;40:e305-e312.)

Key Words: interventional neuroradiology ■ intracranial aneurysm ■ stroke management ■ carotid stenting ■ intracranial stenting

Stenting of carotid artery stenosis continues to remain a controversial procedure.1–5 An update was published on the 3-year results of the SAPPHIRE trial in 2008.6 The study evaluated carotid artery stenting (CAS) with the use of an emboli-protection device and compared it to carotid endarterectomy (CEA) in 334 patients at increased risk for complications from CEA who had either ≥50% symptomatic carotid artery stenosis or an asymptomatic stenosis of ≥80%. Follow-up data were available for 260 patients, 85.6% in CAS arm, and 70.1% in CEA arm. The prespecified major secondary end point at 3 years was a composite of death, stroke, or MI within 30 days after the procedure, or death or ipsilateral stroke between 31 days and 3 years. The prespecified major secondary end point occurred in 41 patients in the CAS group (cumulative incidence, 24.6%; Kaplan–Meier estimate, 26.2%) and 45 patients in CEA group (cumulative incidence, 26.9%; Kaplan–Meier estimate, 30.3%; absolute difference in cumulative incidence for CAS group, –2.3%; 95% CI, –11.8–7.0). There were 15 strokes in each of the 2 arms, a rate of 9% over 3 years in each group, of which 11 in CAS group and 9 in CEA group were ipsilateral. The authors concluded that no significant difference could be found in outcome between both groups.6 It is important to be aware of the fact that the majority of patients in SAPPHIRE were asymptomatic and both the CEA and CAS groups had a similar 30-day rate of stroke at 3 years at 9% to that recorded in the trials of CEA for asymptomatic patients in the medically treated patients (≈8%). Unfortunately, SAPPHIRE did not report data for symptomatic and asymptomatic patients separately. Moreover, follow-up data were only available at 3 years for 86% of the CAS group and 70% of the CEA group. The conclusions that can be drawn from the SAPPHIRE report are therefore limited.

The multicenter, single-arm BEACH, a nonrandomized CAS study with emboli-protection device for high-risk surgical patients, enrolled 480 patients with CAS.7 The primary end point (all stroke, death, or Q-wave MI through 30 days; non-Q-wave MI through 24 hours; and ipsilateral stroke or neurological death through 1 year) was compared with a proportionally weighted objective performance criterion of 12.6% for published CEA results in similar patients, plus a prespecified noninferiority margin of 4%. At 1 year, the composite primary end point occurred in 8.9%, with a repeat revascularization rate of 4.7% (upper 95% confidence limit of 11.5% for the primary composite end point). The results met the prespecified criteria for noninferiority relative to the calculated objective performance criterion plus noninferiority margin (16.6%) for historical surgical CEA outcomes in similar patients (P<0.0001 for noninferiority).7 A subgroup in BEACH of 78 patients (10.4%) underwent a contralateral procedure >30 days after the primary CAS. There were no statistically significant differences between the bilateral and the pivotal groups with regard to any of the components of the primary or secondary endpoints that were Q-wave MI within 24 hours, periprocedural (≤30 days) death, stroke, or Q-wave MI, and late ipsilateral stroke or death attributable to neurological events from 31 days up to 12 months.8 Proper patient selection for CAS seems to be important for a successful outcome.
A study from New York also aimed to evaluate whether patients at increased perioperative risk for CEA may be treated with CAS while maintaining equivalent outcomes. Two hundred thirty-one CAS were performed in patients with high surgical risk and compared with 647 CEA procedures. Factors associated with increased complications from standard CEA surgery were generally more prevalent in patients treated with CAS: neck irradiation (6.06% vs 1.24%; P<0.001), neck dissection for cancer therapy (7.8% vs 1.5%; P<0.001), previous ipsilateral CEA (15.2% vs 3.4%; P<0.001), contralateral carotid artery occlusion (12.1% vs 1.1%; P<0.001), modified Goldman Cardiac Risk II moderate risk (26.0% vs 11.3%; P<0.001), and modified Goldman Cardiac Risk III high risk (16.4% vs 2.1%; P<0.001) in patients treated with CAS and CEA, respectively. Perioperative outcomes did not differ between patients treated with CAS and CEA: MI (1.7% vs 2.6%; P=NS), stroke without residual symptoms (1.3% vs 1.2%; P=NS), stroke with residual symptoms (0.4% vs 0.8%, P=NS), mortality (0.4% vs 0.6%; P=NS), and total MI/stroke/mortality rate (3.9% vs 5.3%; P=NS). The results suggest that high-risk patients undergoing CAS had comparable outcomes to low-risk patients undergoing CEA.9

One specific factor associated with increased risk from CAS in many earlier studies has been older age. However, 1 recent study reported that in their experience in octogenarians, the neurological complications, death, and MI rate at 30 days associated with CAS were not higher than in younger patients.10 In another CAS study of elderly patients (mean patient age, 83.2 years), the 30-day stroke or death rate was 5.1% for symptomatic patients and 2.6% for asymptomatic patients,11 whereas in a third study, no deaths or major stroke events were reported with CAS at 30 days’ follow-up in 24 octogenarians and out of 178 patients treated, there was 1 non-Q wave MI (4.2%), 1 TIA, and 1 femoral occlusion in the symptomatic group.12

The best data to guide clinical decisions comes from randomized clinical trials. The 2-year results of the SPACE trial conducted in Germany and Austria, in which symptomatic patients were randomized between CAS and CEA, were reported in 2008.13 Overall, at 2 years’ follow up, the rate of recurrent ipsilateral stroke was similar in the 2 arms. However, the trial failed to prove equivalence of the 2 procedures because CAS was slightly riskier than CEA with the rate of ipsilateral ischemic stroke, plus any procedural stroke or death of 9.5% vs 8.8% (hazard ratio, 1.10; 95% CI, 0.75–1.61) in the intention to treat analysis and 9.4% vs 7.8% in the per protocol analysis (hazard ratio, 1.23; 95% CI, 0.82–1.83). The 2-year follow-up in the SPACE trial also showed a significantly higher rate of recurrent stenosis of ≥70% as measured by conventional ultrasound in the CAS group as compared with the CEA group, with a life table estimate of 11.1% vs 4.6% (P=0.0007), respectively. However, neurological symptoms were observed in only 2 patients with recurrent stenoses after carotid artery stenting.13 As suggested by others, ultrasound grading of carotid artery in-stent stenosis can be used as follow-up after CAS only if new customized velocity criteria are implemented by experienced operator according to specific protocol.14

SPACE was notable because many of the German neuro-radiologists did not use protection devices, but in the trial there was no significant difference in procedural stroke rates in those stented with and without a protection device. One possible explanation is that protection devices are beneficial at preventing stroke in patients at high risk for stroke (eg, the elderly), and harmful in those at lower risk (eg, younger patients) because they cause a small number of strokes. A recent study from 3 centers in Germany examined this hypothesis using MRI before and after CAS, but did not confirm the suggestion.15 The number of patients with new ipsilateral diffusion-weighted imaging lesions were significantly smaller after protected vs unprotected CAS (52% vs 68%), both in symptomatic patients (56% vs 74%) and in patients younger than age 75 years (46% vs 67%; all P<0.05). However, for asymptomatic patients the results for CAS with or without emboli protection devices were not significantly different (48% vs 52%; P=0.8) or for patients older than age 75 years (73% vs 69%; P=0.7).15 In another study examining cognitive function, patients with a unilateral stenosis of mean 80% a significant improvement of the extended mental status examination and the cognitive function was found after CAS, whereas no change was found in the Mini-Mental State Examination.16

Another randomized trial of CAS vs CEA in symptomatic carotid stenosis patients, EVA-3S, performed in France, also reported the results of medium term follow-up in 2008.17 The results strongly favored CEA with a cumulative probability of ipsilateral stroke, plus periprocedural stroke or death, after 4 years of follow up of 6.2% for CEA vs 11.1% for CAS (hazard ratio, 1.97; 95% CI, 1.06–3.67; P=0.03). However, this difference was largely accounted for by the higher periprocedural stroke rate within 30 days of CAS, and after the periprocedural period, the risk of ipsilateral stroke was low and similar in both groups. The authors concluded that the safety of CAS needs to be improved before it can be used as an alternative to CEA in symptomatic patients.

The controversy relating to the selection of patients who appear suitable for both CEA or CAS is unlikely to be resolved until the results of the 2 other large randomized
Intracranial Disease

Symptomatic intracranial arterial stenosis is associated with a high rate of recurrent stroke when treated medically, but because of the high incidence of in-stent stenosis, the wide spread use of the self-expanding nitinol Wingspan stent (Boston Scientific) for intracranial disease is controversial. In-stent stenosis >50% occurred in 45.2% (14/31) of the younger group (<55 years) and 24.2% (15/62) in the older group (OR, 2.6; 95% CI, 1.03–6.5). Of notice is that in all ages, supraclinoid placed devices had much higher rates of both in-stent stenosis (66.6% vs 24.4%) and symptomatic in-stent stenosis (40% vs 3.9%) in comparison with all other locations. In-stent stenosis was focal in 61.0% of the patients; in more than half of the cases the stenosis was more extensive than the original lesion treated in terms of lesion length or stenosis severity. The number of cases performed at each site seems to affect the periprocedural complications and the rate of stroke and death within 30 days (low-volume centers vs high-volume centers, 29.3% vs 4.2%; P<0.00005) and after 30 days at 6 months (24.1% vs 10.7%; P<0.058). An NIH-funded trial with the self-expanding Wingspan stent is currently underway. Other investigators studied balloon-expandable coronary stents for intracranial disease. The technical success was reported in 99% of the patients. The overall death and stroke rate was 10%. In-stent stenosis at 6 months and 12 months was reported in 0% and 7.5% of the cases, respectively. VITESS is an industry-sponsored multicenter randomized trial (MicroEndovascular) launched this year to evaluate a balloon-expandable carbide-coated stent in patient with symptomatic intracranial disease that remains nonresponsive to standard medical treatment. The results of randomized trials are urgently needed to establish the place of stenting for intracranial stenosis.

Acute Ischemic Stroke

There is increasing interest in the use of interventional radiology techniques to treat hyperacute ischemic stroke with intracranial vessel occlusion, as an adjunct or alternative to intravenous thrombolyis. An update was reported on the IMS II study that used reduced-dose intravenous recombinant tissue plasminogen activator followed by additional intra-arterial recombinant tissue plasminogen activator and low-energy sonography via the EKOS Primo Micro-Infusion Catheter at the occlusion site in selected patients with ischemic stroke treated within 3 hours of onset. A complete recanalization at 60 minutes was observed in 41.4% of the treated patients. At 2 hours, or at procedure end, 68.9% of treated patients showed a complete recanalization. A final thrombolysis in cerebral infarction two-thirds reperfusion was demonstrated in 62.0% of ultrasound-treated patients. Follow-up angiograms at 15-minute intervals showed some recanalization in 69 of 145 (46.7%) of patients treated with combined sonography microcatheter system as compared with 39 of 111 (35.1%) in IMS I-treated patients, with 23 subjects having reliable 15-minute angiograms (P<0.046). Pooled IMS I-II data demonstrated that partial or complete recanalization occurred in 56 of 75 (74.6%) and good reperfusion (thrombolysis in cerebral infarction two-thirds) occurred in 46/75 (61.3%) of internal carotid artery T and M1 occlusions. Revascularization correlated with good outcome for thrombolysis in cerebral infarction two-thirds reperfusion (P<0.0004), thrombolysis in cerebral infarction two-thirds reperfusion (P<0.0002), and arterial occlusive lesion two-thirds recanalization (P<0.03). Reperfusion using mechanical devices is a promising approach for patients unresponsive to thrombolyis. A report on mechanical clot aspiration in acute ischemic stroke using the Penumbra system showed in the preliminary study a high-safety profile of the device and a recanalization rate of 100%. Patients presented with a mean NIHSS score of 21 and a mean modified Rankin scale score of 4.6. At 30-day follow-up, 45% had a 4-point or more NIHSS improvement; 70% of the patients presented either with a basilar occlusion or a NIHSS score >20. A second penumbra trial in 24 centers (noncontrolled, technical efficacy study; n=125; baseline NIHSS score 17.6) showed recanalization in 82% patients (internal carotid artery occlusion in 18%; vertebralbasilar occlusion in 9%). Procedural but not device related complications were seen in 3.2%. However, a good clinical outcome (modified Rankin Scale score ≤2) at 90 days was seen in only 25% of the treated patients. An image-guided industry-funded multicenter registry (PICS; Penumbra) is currently collecting data to study penumbra-imaging guided intervention with the Penumbra clot suction system. The final results of the Multi-Merci Trial showed that with technical improvement of the Merci clot remover, a higher recanalization of up to 57.3% of treated arteries could be achieved but were not significant as compared to the earlier iteration of the device. The recanalization rate with adjunctive therapy was 69.5%. Favorable outcome (modified Rankin Scale score ≤2) was seen in 36% of the patients, whereas mortality was 34%. Procedural related complications were reported in 5.5%. An NIH-funded MRI-guided trial (MR-Rescue) with the Merci clot removal device is underway. Distal emboli during clot manipulation remains a short coming with most of the currently used mechanical clot busters. Retrievable stents are being evaluated for acute revascularization of thrombo-embolic occlusions in acute ischemic stroke. Stents either serve in conjunction with thrombolytics for immediate reperfusion and are retrieved at the end of the procedure or are permanently deployed. A novel tubular mesh designed device was tested in vitro and in vivo on its feasibility and safety to reroute cardioembolic material for stroke prevention. It is too early to be clear about the role of these promising interventional techniques for acute ischemic stroke, but the field is rapidly expanding and the time is approaching when large, randomized, clinical trials are required.

Aneurysm

 Advances in the dynamic field of endovascular aneurysm treatment included analysis of long-term follow-up results after coil embolization, early follow-up of modified platinum...
coils, development of new device technologies, improvements in periprocedural patient management, and further characterization of the molecular, genetic, and mechanical features of aneurysms. Long-term durability of aneurysm occlusion and low rebleeding rates are critical for the efficacy and safety of coil embolization, respectively. These aspects were studied in 1810 patient-years, the longest follow-up period published thus far. A 2.2% periprocedural morbidity rate and a 0.2% rate of bleeding were found.37 The rebleeding rate is in line with those from the Cerebral Aneurysm Rerupture After Treatment trial, which reported a 2.2% rerupture rate in the first year after the coil embolization, 0.2% rate in the second year, and 0% thereafter.38 This study also suggests that an initial degree of aneurysm occlusion was a strong predictor of risk for reruptures after coil embolization. However, other investigators come to the conclusion that an angiographic stability of neck remnants over time is more important than the presence of neck remnants themselves.37 Additional data continue to emerge from the International Subarachnoid Aneurysm Trial, including subgroup analysis in the elderly and a study suggesting that age at onset of aneurysm rupture may be a key factor in determining superiority of coil embolization vs clip placement.39–40 A further analysis of the International Subarachnoid Aneurysm Trial data found no significant difference in costs involved either in endovascular or in surgical treatment at 12 or 24 months.41

Stent technology has improved with the introduction of the retrievable Enterprise stent (Codman Neurovascular), which has facilitated the endovascular treatment of complex, wide-necked, and fusiform/dissecting aneurysms with promising preliminary results (Figure 2).42–44 The largest series to date (142 aneurysms) reports 2.8% morbidity and 2% mortality associated with use of Enterprise.45 As we await mid-term and long-term follow-up results, diligent surveillance in this group is emphasized as reports of delayed recanalization and stent migration emerge.46 Thromboembolic events and in-stent thrombosis remain critical especially in light of reports of clopidogrel resistance in patients undergoing cerebrovascular stent placement.47 Point-of care testing of platelet function may be feasible so that antiplatelet regimens may be modified.48

Inconsistent data on the use of modified coils with no clear evidence emphasizes the need for prospective, randomized trials to evaluate the safety and efficacy of new devices as they enter the market.49–54 This year has seen patient enrollment into the industry-sponsored Cerecyte Coil Trial, HydroCoil Endovascular Aneurysm Occlusion and Packing Study trial, and the Matrix and Platinum Science trial. The Pipeline braided stent (Chestnut Medical), the braided Leo stent (Balt), and other stent-like devices and stent grafts have potential to represent a paradigm shift in the treatment of intracranial aneurysms away from coil embolization and toward parent vessel reconstruction and flow diversion, as well as vessel-preserving strategy for vascular wall lesions. Published preliminary results in human aneurysms and fistulae are encouraging.55–58

Intracranial aneurysm pathogenesis and progression continue to attract significant attention. Recent studies have identified aneurysm formation at areas of low wall shear
stress, and the molecular and genetic factors associated with aneurysm progression are being further delineated.59–65 Although the controversy over the management of unruptured intracranial aneurysms continues, additional studies on the natural history and endovascular treatment outcomes in small unruptured aneurysms prove valuable.66–67 Six-hundred forty-nine patients with a total of 1100 aneurysms were treated endovascularly in 27 Canadian and French neurointerventional centers.68 Aneurysms were treated with coils alone in 54.5% of the cases, in 37.3% and 7.8% of the cases a temporary balloon-assistance or stenting was required, respectively. Endovascular treatment failed in 4.3% of the cases. Thromboembolic complications were encountered in 7.1% per procedure, intraoperative rupture occurred in 2.6% per procedure, and device-related problems were observed in 2.9% per procedure. Adverse events associated with transient or permanent neurological deficit or death were encountered in 5.4% of cases. Thirty-day morbidity and mortality rates were 1.7% and 1.4%, respectively.

**Vasospasm**

Whereas angioplasty remains the primary endovascular treatment option for subarachnoid hemorrhage-associated vasospasm, a continuous intra-arterial infusion of nimodipine at 1 mg per hour and a high-dose intra-arterial infusion of nicardipine up to 25 mg have been reported to improve perfusion by proximal and distal vasodilation with no major periprocedural morbidity.66–70 The role of angioplasty remains uncertain and it may well be unjustified. A randomized trial has recently started in the UK and will help to address this issue.

**Brain Arteriovenous Malformation and Dural Arteriovenous Fistula**

The choice of treatment options for arteriovenous malformations continues to be a difficult decision in many cases, because of the lack of comparative series or randomized trials. More data are available on the recently introduced liquid embolic agent Onyx in embolization of brain arteriovenous malformation and dural arteriovenous fistulae. Whereas cure of dural arteriovenous fistulae is reported in most of the treated patients with no major periprocedural morbidity, the treatment of brain arteriovenous malformation remains challenging.71–73 The goal to cure brain arteriovenous malformation with use of Onyx is achieved in 2% to 28% of the patients with permanent morbidity and mortality of 3% to 11%. Whereas increased cure rates are achieved, the periprocedural complications are higher as compared with other liquid embolic agents used in the past.73,74 The ARUBA Study has started randomizing patients with unruptured brain arteriovenous malformations between conservative management and active intervention, which can include interventional radiology. The results will be of major importance, but will not be available for several years.

**Antiplatelet Agents**

With increased use of antiplatelet drugs such as aspirin and clopidogrel to prevent thromboembolic events associated with intracranial stenting and coiling, there is a better understanding of these agents in the neurovascular field. Using a new point-of-care platelet function test (VerifyNow assay), Clopidogrel 300 mg of loading dose followed by 75 mg daily per mouth, showed in 28% to 51.9% of treated patients a poor
platelet inhibition whereas nonresponders in aspirin group were rare (<5%). However, the extent to which these in vitro tests correlate with clinical effectiveness is uncertain.

Imaging
A meeting in Advanced Neuroimaging for Acute Stroke Treatment held on September 7 and 8, 2007, in Washington DC, involving different disciplines in medicine, the NIH, the FDA, and the industry resulted in recommendations for standardization of penumbra imaging, clinical utility of imaging markers of the ischemic penumbra, and validation of the imaging biomarkers for clinical outcomes. In a retrospective data analysis, the Alberta Stroke Program Early CT Score during the first 3 hours of a middle cerebral artery stroke was most accurately determined on the CT perfusion cerebral blood volume maps. Introduction of flat panel detectors to the angiography unit has enabled to use the system as cone beam CT to detect brain hemorrhage during endovascular treatment, developing hydrocephalus, details of vascular structure in conjunction with the surrounding brain tissue, and also temporary or permanent implants with high resolution (Figure 3). However, many issues, such as the optimal method to select patients with penumbra for reperfusion therapy, remain unresolved.

Radiation
With rapid increase in neuroendovascular procedures and associated fluoroscopy time with interventions such as Onyx infusion, awareness in calculating skin dose has grown to avoid skin injuries and damage to the lens. In a study, the surface doses recorded during endovascular procedures were comparable to the mean dose of 1.5 Gy, which, as suggested, may increase the relative risk of inducing meningiomas, gliomas, and nerve sheath tumors.

Conclusions
Neuroradiology has an increasing role to play in the diagnosis and treatment of ischemic stroke and the structural lesions causing cerebral hemorrhage. Technological advances are occurring more rapidly than can be tested in clinical trials. Nevertheless, randomized clinical trials play an important role in determining the role of established interventional techniques and many more are needed. Undoubtedly, we shall see further advances, and perhaps setbacks, in the next year.

Disclosures
None.

References
24. Nahab F, Zaidat AO, Lynn M, Chimowitz MI, for the NIH Multi-Center Wingspan Intracranial Stent Registry Study Group. Relationship of site


Advances in Interventional Neuroradiology
Ajay K. Wakhloo, Michael J. Deleo III and Martin M. Brown

Stroke. 2009;40:e305-e312; originally published online April 9, 2009;
doi: 10.1161/STROKEAHA.108.548438
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/40/5/e305

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/