Critical appraisal of medical devices in the management of cerebrovascular disease

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Abstract: Medical devices may revolutionize the management of acute ischemic stroke and prevention of recurrent events. By comparison with pharmaceuticals, the device approval process and subsequent application of these devices in stroke treatment is founded on a paucity of Class I evidence-based clinical trial data. Thromboembolectomy for acute stroke, stenting of cervical or cerebral arteries for stroke prevention, and percutaneous closure of patent foramen ovale for prevention or recurrent cerebral ischemia are being done with an ever-increasing frequency despite few, if any, randomized clinical trials to confirm the appropriateness of the interventions. The current basis, or lack thereof, for these interventions for cerebrovascular disease is therefore discussed. As such, a critical appraisal of the available clinical data does not support widespread use of medical devices at this time outside of well-designed clinical trials.

Keywords: medical devices, stroke, PFO closure, stents, clot retrieval devices, clinical trials

Introduction

The FDA approval process for medical devices is significantly different than the process for approval of new drugs or new indications for drug (Wright 2002; Devo 2004; Becker and Brott 2005; Furlan and Fisher 2005). For drugs, clinical efficacy and safety data are mandated and usually requires 2 randomized trials though in certain specific instances (ie, very robust or large studies) one randomized trial may be sufficient. However, approval of devices is typically governed by demonstration of 'substantial equivalence' to prior devices and only a very small percent of all new device submissions must undergo rigorous review and a randomized trial may still not be mandated by FDA for devices (Wright 2002; Devo 2004).

In the majority of instances "a device need only do technically what it claims and be reasonably safe" for approval to occur (Devo 2004). Wright highlights three areas where there are key differences in the product development process of devices versus drugs: the process of concept discovery, device classification, and iterative development (Wright 2002). Drugs are typically identified in a massive trial and error screening process with a defined clinical trial program whereas devices are designed to a particular specification and regulation is geared to safety of the design and manufacturing process. The iterative nature of the approval process is manifested when new devices are approved with the argument that the design or indication is merely an improvement or modification of an older technology or indication. Even when clinical trials are initiated for high-risk devices (such as the ones to be discussed below), the clinical trial data is focused on design safety and performance as opposed to clinical efficacy and rationale for the devices and randomized trials are very infrequently performed. As Furlan and Fisher point out, the end result is an approval process based on a mechanistic endpoint versus the "tougher" endpoint of clinical efficacy (Furlan and Fisher 2005). Thereafter, interventionalists are unlikely to enroll patients in clinical trials of devices versus medical controls when these interventionalists have a strong treatment (and possibly financial) imperative toward procedures.

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In the field of cerebrovascular disease, the differing standards for devices versus drug therapy was most recently highlighted with the approval of the Merci catheter for 'clot removal' in patients with stroke but the problem is also apparent in the use of other devices for stroke treatment and prevention (Becker and Brott 2005). Medical devices for the treatment of cerebrovascular disease are becoming rampant. Forecasts suggests almost quadruple growth in mechanical cerebral embolectomy over the next 10 years, a potential for up to 100,000 stroke patients potentially eligible for PFO closure and a future explosive growth for carotid stenting that is already manifested by increasing numbers of cardiologists and other interventionalists performing these procedures in both academic and community hospital settings (Sg2 Intelligence Reports 2006).

While these interventions have the potential to revolutionize our approach to cerebrovascular disease, the paradox is that this explosive growth in procedural interventions is not supported by the clinical trial data at this time. This review focuses on the lack of data to support widespread use of endovascular procedures in four areas of cerebrovascular disease and emphasizes the need for rigorous clinical trials to be completed prior to routine adoption of interventions for stroke.

Percutaneous closure of patent foramen ovale for prevention of recurrent stroke

Patent foramen ovale (PFO) is represented as the most frequent potential source of cardiac embolism in patients <60–65 years of age with no other obvious etiology for the stroke despite an extensive diagnostic evaluation ('cryptogenic stroke') (Horton and Bunch 2004; Wu et al 2004; Kizer and Deveruex 2005). Estimates are that 1/4 of all adults have a persistent PFO. The prevalence of PFO in cryptogenic stroke is particularly common but the relationship of a PFO to ischemic stroke is based mainly on associations seen in various case-control studies. In a meta-analysis of the risk of stroke related to PFO, the odds ratio was 5.01 (95% CI 3.24–7.75) among patients 55 or younger. There was no association of PFO and stroke among older persons with a reported odds ratio of 1.20 (95% CI 0.56–2.56). However, while anecdotal observation of clot passing from the right to left atrium is well-known, a causal etiology such as venous thrombosis with subsequent right-to-left cardiac shunt is rarely identified. Overall, the yearly risk of cryptogenic stroke in healthy persons with PFO has been estimated to be around 0.1 percent. However, once a PFO (with or without ASA) is identified in a younger patient with stroke, one must consider other causes of stroke including hypercoaguable and autoimmune states, occult arrhythmias, and any other anomalies of the cervico-cerebral vessels before attributing the stroke mechanism to a PFO. It is telling that neurological events recur in as may as twenty percent of patients who undergo surgical closure suggesting that alternate mechanisms may play a role in patients with presumed PFO-related strokes (Maisel and Laskey 2005).

The management for preventing recurrent stroke in patients with cerebral ischemia attributed to a PFO includes anti-platelet drugs, anticoagulants and surgical or transcatheter closure. There are no randomized trials of anti-platelet versus anticoagulant therapy and no completed randomized trials of percutaneous PFO closure (Flachskampf and Daniel 2005; Maisel 2005). While many have advocated warfarin therapy as the preferred medical intervention for comparison with percutaneous closure, there is only limited data supporting the preferential use of warfarin for PFO related-stroke.

The largest observational study of medical therapy for PFO related stroke is the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), a sub-study of the Warfarin-Aspirin Recurrent Stroke Study (WARSS) (Homma et al 2002; Mohr et al 2001). In that study, of 630 patients who underwent TEE, there were only 98 patients with cryptogenic stroke and patent foramen ovale and only limited conclusions as to the relative benefit of anticoagulation could be made. In the PICSS cohort, there was a trend toward a benefit for warfarin compared to aspirin. However, this benefit was not specific to the PFO-related strokes but applied to all cryptogenic stroke patients in PICSS with or without PFO. Additionally, the cryptogenic stroke patients in PICSS were poorly characterized and the cohort was comprised of predominantly older stroke patients. In two subsequent smaller observational studies of approximately 50 patients with PFO associated stroke there was a trend to a benefit for warfarin but both of these studies were limited by a lack of random assignment of drug therapy (Cujec et al 1999; Schneck et al 2002). As such, current guidelines of the American Academy of Neurology guidelines regarding the management of PF-related stroke state that there is insufficient evidence at this time to support the use of warfarin preferentially as compared with aspirin (Messe et al 2004). Regardless of therapy used, the recurrence rate for PFO related stroke is fewer than 3 percent in several studies. Only one study reported a recurrence rate that was substantially higher and that was in the context of those patients with a combination of a PFO and ASA where the recurrence rate was 15.2% despite aspirin therapy (Mas et al 2001). This finding has not been confirmed in other observational studies however, and even in this study, the rate of PFO related stroke without ASA was less than 1 percent per year which would argue against warfarin use.

The recent introduction of percutaneous devices for closure of a PFO has led to widespread adoption of this approach, in place of medical therapy alone, for those patients at risk of recurrent stroke. The justification to support closure being superior to medical therapy is based on a meta-analysis of surgery versus anti-platelet therapy with an odds ratio of 0.36 but wide confidence intervals of 0.04 to 3.09. Certainly transcatheter closure seems to be an attractive option to patients, particularly as compared with surgery, since percutaneous closure has been touted as a 'permanent fix' that would obviate the need for anticoagulation though not concurrent anti-platelet therapy. In retrospective series, the one-year rates of recurrent cerebral ischemic events ranged from 0%–4.9% for closure and 3.8%–12% for medical therapy but complications of device implantation have been reported in upwards of 10% of patients (Maisel and Laskey 2005). Two devices, the Amplatzer PFO Occluder and the Cardioseal Septal Occlusion System are available in the United States but only on a Humanitarian Device Exemption (HDE) that limits closure to those patients who have had a recurrent cryptogenic stroke who have failed conventional drug therapy defined as oral anticoagulation with a therapeutic international normalized ratio (INR) (Flachskampf and Daniel 2005; Kizer and Deveruex 2005; Maisel and Laskey 2005). Otherwise, PFO closure is being done on an off-label basis as there is no data that clearly shows superiority of closure over medical therapy. Despite this lack of data supporting PFO closure, randomized studies to investigate medical therapy versus transcatheter PFO closure (such as CLOSURE, RESPECT, and the Cardia Star trials) have experienced very slow enrollment rates as off label use of devices has become rampant. The ready availability of PFO devices, however, cannot justify empiricism in the absence of clinical science (Flachskampf and Daniel 2005; Maisel and Laskey 2005). The Stroke Council of the American Heart Association and the American Academy of Neurology have issued guidelines that suggest patients with cryptogenic stroke and PFO should only undergo PFO closure in the context of randomized clinical trials; otherwise, medical therapy should be the preferred option at this time for patients with first-ever cryptogenic stroke and PFO (Messe et al 2004; Maisel and Laskey 2005).

Stenting for extracranial atherosclerotic carotid artery disease

Carotid endarterectomy for extracranial asymptomatic and symptomatic stenosis is a well established treatment option (Chaturvedi et al 2005). Large, prospective, randomized North American and European trials have confirmed the efficacy of carotid endarterectomy for patients with a prior history of stroke or TIA (symptomatic carotid stenosis) attributable to ipsilateral moderate to severe extra cranial carotid atherosclerosis who met otherwise well-defined study criteria (North American Symptomatic Carotid Endarterectomy Trial Collaborators 1991; ECST Investigators 1998; Ferguson et al 1999; Chaturvedi et al 2005). Similar results have been reported from European and North American randomized trials of highly selected patients with carotid stenosis and no prior history of cerebrovascular disease (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study 1995; Halliday et al 2004; Chaturvedi et al 2005).

American Academy of Neurology guidelines for carotid endarterectomy (CEA) were based on these well-designed randomized trials that demonstrated CEA is beneficial for stroke risk reduction, as compared with medical therapy, for patients with moderate to severe carotid stenosis (Chaturvedi et al 2005). The recommendations specifically state that the peri-operative stroke/death rate should be less than 6 percent for symptomatic disease and less than 3 percent for asymptomatic disease. Patients with high grade stenosis and recent TIA or minor stroke should undergo CEA within two weeks of the event. The guidelines also state that patients being considered for CEA should haven at least 5 year life expectancy. Furthermore, the data regarding CEA for asymptomatic disease is proven only for patients 40–75 years with very well-defined clinical characteristics and women with either asymptomatic or moderate (50–69 percent) symptomatic derive a less clear benefits from CEA as opposed to men. A key point of the guidelines is that whereas CEA can provide a reasonable reduction in stroke risk, careful patient selection and well-defined diagnostic and surgical parameters are paramount. The advent and widespread use of angioplasty and stenting technology in coronary arteries has been extended to the extra cranial carotid, vertebral and intracranial arteries with tremendous enthusiasm and hype. .Carotid artery stenting (CAS) is now being adopted as a less-invasive and presumably equally effective treatment for to CEA for the management of carotid stenosis. Carotid angioplasty and stenting (CAS) may obviate the need for surgery and advocates argue that this approach is associated with fewer strokes, cardiac events and other complications particularly including postoperative hematoma and cranial nerve injury. However, whereas, the clinical efficacy of carotid endarterectomy as compared with medical therapy has been well established based on well-designed randomized clinical trials only recently has there been evidence suggesting CAS is a reasonable alternative to CEA outside of observational studies.

Case selection is clearly paramount regardless whether CAS or CEA is the procedure of choice. CEA trials revealed a benefit/risk ratio for patients with asymptomatic or moderate grade symptomatic stenosis that was much smaller compared to the benefit/risk for patient with high grade carotid artery stenosis patients (Chaturvedi 2003; Chaturvedi et al 2005). The current consensus for a minimal standard for CEA is a major complication rate of less than 3 percent (stroke, MI, and death) derived from the asymptomatic trial data (Lanska and Kryscio 1997). Furthermore, in the CEA trials, the comparison was made of medical therapy versus surgery with angiographic confirmation of lesions along with follow-up by neurologists with expertise in stroke presumably providing independent verification of stroke event rates. However, while the reliance on non-invasive imaging to assess degree of stenosis is problematic as regards to accuracy of stenosis current surgical practice is to eliminate the use of preoperative angiography for estimation of the degree of stenosis because, in the ACAS study, a full 1 percent of complications in the surgical arm were directly related to angiography (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study 1995; Johnston and Goldstein 2001). With this approach, surgeons have been reporting 30 day complication rates of 2 percent or less in their current series for CEA and this is the benchmark which CAS must achieve in randomized studies with CEA (LaMuraliga et al 2004).

A meta-analysis of the five available randomized trials, totaling 1154 patients (577 patients in each arm), showed that the composite endpoint for CAS versus CEA was not different at the one month stroke/death endpoint (Qureshi et al 2005). The one month stroke rate and disabling stroke rate was also similar. The major difference was that the one month MI rate in the 814 total patients for whom data was available was lower for CAS (RR 0.03; 95% CI 0.1–0.9) and the cranial nerve injury rate for CAS was also lower in the 918 analyzed patients (RR 0.05; 95% CI 0.01–0.3). At one year, no significant differences in the rate of ipsilateral stroke was observed in the 814 patients analyzed (RR 0.8; 95% CI 0.5–1.2) (Qureshi 2005). In the included series, however, four of the five studies were restricted to symptomatic carotid disease. The results from SAPPHIRE, the most recent trial, are in conflict with the other early trials where there were worse outcomes for CAS. Whether experience of the interventionalists with the early devices or different patient populations explains the dichotomy is somewhat less clear. Major criticism of two early studies focused on both sample size inadequacies and procedural/recruitment difficulties (Alberts et al 1997; Naylor et al 1998). In the CAVATAS study, significant carotid artery restenosis (>70%) was also greater for CAS versus CEA (18.5% versus 5.2%, $p = 0.0001$) (Dominick et al 2005). However, it should be recognized that most of the endovascular procedures in CAVATAS were angioplasties without stenting. A subsequent meta-analysis of 34 studies noted cumulative restenosis rates after 1 and 2 years of 6% and 7.5% in those studies, using a lower restenosis threshold of 50%–70% and 4% in the first 2 years after CAS for a restenosis threshold of 70%–80% (Gröschel et al 2005). These authors noted that the early restenosis rates after CAS compare well with those reported for CEA. However, this analysis of the peer-reviewed literature also indicates that the early restenosis rates after CAS might be higher than previously suggested in observational surveys (Gröschel et al 2005).

Thus, up until, the SAPPHIRE study, there was little data to support preferential use of CAS versus CEA. As opposed to the other randomized studies, SAPPHIRE was a study of CAS (with deployment of a distal protection device to minimize emboli from the site of the plaque) as compared to CEA for patients otherwise defined as high risk for surgery (Yadav et al 2004). SAPPHIRE was a study of 747 patients of which 413 patients were treated as part of a registry (406 were treated by CAS and 7 underwent CEA). 334 cases were randomized to either CEA or CAS of which 310 were treated; there were 159 casers in the CAS arm and 151 cases in the CEA arm. The inclusion criteria included a definition of the high risk patient: congestive heart failure, positive stress test, need for cardiac surgery, severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, recurrent carotid stenosis from prior CEA, age >80 years, previous radical neck surgery or radiation therapy to the neck. Symptomatic patients were enrolled with >50 percent stenosis and asymptomatic patients were enrolled with >80 percent stenosis. The CAS procedural success rate was 91.2%.

The 30 day event rate showed a significant difference between CAS and CEA of 5.8 percent for the combined endpoint of stroke, MI, or death versus 12.6 $p < 0.047$ but these results were driven by non-Q-wave myocardial infarctions (MI). One goal of the study was to demonstrate equivalence of CAS and CEA and this was achieved by the study. Furthermore, while the differences were not statistically significant ($p = 0.17$), the trend favored a better outcome for CAS for the combined endpoint. The intention to treat analysis thirty day outcomes included a death rate of 1.2%, stroke rate of 3.6% and MI rate of 2.4% (all non-q wave MI) for the CAS

and a death rate of 2.5%, stroke rate of 3.1% and MI rate of 6.1% (1.2% q-wave MI) for the CEA arm. The combined endpoint of stroke, death and/or MI was 4.8% for CAS and 9.8% for CEA. The major ipsilateral stroke rate was 0.6% for CAS and 1.2% for CEA whereas the minor ipsilateral rate was 2.4% for CAS and 0.6% for CEA. The one year analysis was also reported. At one year, the outcomes included a death rate of 7.4%, stroke rate of 6.3% and combined endpoint of stroke, death and 30 day MI rate of 12.2% for the CAS arm and a death rate of 13.5%, stroke rate of 7.9% and combined endpoint of stroke, death at one-year and/or 30 day MI rate of 20.1% for the CEA arm with a p-value for the combined endpoint of 0.05 favoring CAS. While major stroke was less common for CAS in the randomized arm (0.6%) versus surgery (3.0%), major ipsilateral stroke was as common in the CAS registry (3.2%) as compared with CEA and minor stroke was less common for CEA (1.8%) as opposed to CAS in either the randomized CAS (3.6%) or registry CAS arms (3.9%).

Subsequent claims have been made that CAS has now been established as the treatment of choice for high risk individuals and other patients (Roubin et al 2006). Recently, an FDA advisory recommended approval of CAS along with a distal protection system for patients with symptomatic carotid artery stenosis who are otherwise at high surgical risk This approval was based on data from the SAPPHIRE study (Yadav et al 2004). However, the data from the SAPPHIRE study and other single-arm studies, while favorable to CAS versus CEA raise many questions about generalizability such that the widespread adoption of CAS for management of both symptomatic and asymptomatic disease should be approached with caution.

When the analysis of SAPPHIRE data was presented by asymptomatic versus symptomatic carotid artery disease, the cumulative incidence of the combined primary endpoint was 16.8 percent for those who underwent CAS versus 16.5 percent for those who underwent CEA though the results at 30 days for the symptomatic patients and at one year were 2.1 vs 9.3 ($p = 0.18$) and 16.5 versus 16.8 CAS ($p = 0.5$). The data were driven by the MI population. For patients with asymptomatic carotid artery stenosis, the rate was 9.9% for those who received a stent and 21.5% for those who underwent CEA and the 30 day combined stroke/death and/or MI rate for the asymptomatic patients who underwent CAS was 5.4% versus 10.2% for CEA ($p = 0.20$).

A number of issues need to be considered as we analyze CAS versus CEA in the SAPPHIRE trial. For one thing, there is no medical arm in this and other stent studies. This is important as the nature of medical therapy for the treatment of carotid artery disease has changed over time with more aggressive anti-platelet therapy, more widespread use of statins and more aggressive blood pressure control. In the past decade since the completion of the various CEA trials, best medical therapy has gotten better. To therefore state that medical therapy was not believed to be suitable for the patients enrolled into SAPPHIRE based on preferences of the referring physicians or the SAPPHIRE investigators is disingenuous. The trial is also biased to asymptomatic disease with 70 percent of the cases being asymptomatic; SAPPHIRE included 96 symptomatic and 219 asymptomatic patients though there was relative balance between the CAS and CEA groups regarding symptomatic versus asymptomatic disease. (Alberts et al 1997). Additionally 30 percent of the cases were redo procedures for which the management is different than de novo carotid atherosclerotic disease. Finally, of 747 cases, only 334 were randomized whereas of the 413 registry patients, 306 underwent CAS and 7 had CEA. The SAPPHIRE conclusion for the worse outcome rates in both the CAS and CEA arms as compared with the older randomized CEA studies is that the SAPPHIRE is different from the previous CEA trials in that these patients were higher risk patients. Based on the worse outcomes, seen in even the CAS arms, a logical rejoinder is that high-risk patients should be left alone and treated medically and the current stroke guidelines do not support routine use of CAS pending more definitive data (Sacco et al 2006). This is particular critical to the assessment of patients with asymptomatic carotid artery stenosis. While one could argue that the benefit outweighs the risk for symptomatic patients for whom the cross-over point for benefit from CEA (and perhaps by extension CAS) occurs at around 3 months, the benefit for CEA for asymptomatic disease is not achieved till close to one year and a statistically significant was not seen till after two and one-half years. While the asymptomatic CEA randomized trials may have been "robust", those results do not translate over to the SAPPHIRE population (Yadav et al 2005). Chaturvedi and colleagues have further argued that more aggressive use of statin therapy and other modalities for stroke risk reduction may reduce the absolute benefit for any revascularization procedures (Chaturvedi 2003; Betancourt et al 2004). It is worth noting here that while registry data presents an even rosier picture of CAS, the argument for CAS remains unsupported as compared with CEA from the randomized studies or medical therapy. The most recent registry, CAPTURE, sought to determine whether CAS can be performed safely by physicians with

varying levels of experience who underwent a Guidant, Inc. mandated training program; only 1/3 of cases could come from hospitals with high levels of CAS experience (Gray et al 2006). 2500 patients were enrolled in this post-marketing study of which 23.8 percent were above the age of 80 and only 9.3 percent had symptomatic carotid stenosis. In CAPTURE, the rate of stroke or death was 5.1 percent and the rate of stroke, death and MI was 5.7 percent. For asymptomatic patients the rate was 4.4% and 4.9% respectively. For the symptomatic patients the stroke and death rate was 12 percent and the stroke/death/MI rate at 30 days was 14.2 percent.

By comparison, in a CEA registry, Mozes et al (2004) reported the Mayo Clinic experience from 1998 to 2002 in light of the SAPHHIRE data with high versus low risk CEA. Of 776 CEAs, 42 percent were considered high risk by SAPPHIRE criteria. The overall stroke risk in the Mayo Clinic series was 1.4% (2.9% symptomatic and 0.9% in the asymptomatic patients and the overall mortality was 0.3 percent (symptomatic 0% and asymptomatic 0.2%. The only difference was that non-Q wave MI was more frequent in the high-risk group (3.1 versus 0.9 $p < 0.05$) and the composite endpoint was more frequent in the symptomatic (9.3 versus 1.6% $p < 0.005$) but not the asymptomatic high risk groups. A critique of this paper by Ouriel (2004) argued that any comparisons of high risk versus low risk surgical patients was irrelevant and that the only validity was a randomized trial of high-risk CEA versus CAS. This argument is appropriate and only by direct comparison between the two modalities can allow us to understand the best procedural option. It is still telling however, that the overall event rate for stroke and death was lower in the Mayo Clinic experience as compared to the SAPPHIRE trial data, raising questions about the generalizability of the SAPPHIRE data (Ouriel 2004).

As an aside, age is a particularly important factor. While patients in the older NASCET CEA subgroup (age 75–80) seemed to have a greater risk stroke reduction following surgery as compared to medical therapy, the lead-in phase component of the CREST study and the CAPTURE registry noted that age greater than 80 was an independent risk factor for a worse 30 day stroke or death rate. For CREST the rate was 5.3% for patients age 70–79 and 12.1 percent in CREST for patients >age 80. In CAPTURE, octogenarians also fared less well with a combined endpoint at 30 days of 8.2 for those above age 80 and 4.9 percent below the age of 80. For stroke, the rate was 6.6% for those above age 80 and 3.5% below the age of 80.

Recently, the SPACE and EVA-3S 30 day results became available. SPACE was a non-inferiority trial of 1200 German, Swiss and Austrian patients with retinal or hemispheric TIA or ischemic stroke and ipsilateral carotid stenosis greater than 70% by ultrasound (corresponding to ≥50% by NASCET and ≥70% by ECST criteria) (SPACE Collaborative Group 2006). The patients were randomized to either CEA or CAS with a primary endpoint of ipsilateral ischemic stroke or death from randomization up to 30 days post-procedure. Surgeons and interventionalists in SPACE were required to have at least 25 successful procedures to participate in the study. EVA-3S was a French study of symptomatic patients with symptomatic carotid artery stenosis of ≥60% by NASCET criteria that was stopped prematurely after enrollment of 527 patients (Mas et al 2006). One critical difference between SPACE and EVA-3S was that the interventional physician had to perform fewer CAS (12) to be a study participant as opposed to the surgeons (25 CEAs) in EVA-3S. By contrast to SAPPHIRE, non-atherosclerotic carotid artery disease and patients with recurrent stenosis were excluded in both SPACE and EVA-3S. Furthermore, in SPACE, embolic protection devices were optional and EVA-3S did not employ emboli protection devices in the initial phase of the study. Additionally myocardial ischemia was not a specified endpoint for the SPACE study.

In the SPACE study, the stroke/death rate was 6.84% for CAS and 6.34% for CEA. Other than death at 30 days (4 in the CAS arm and 5 in the CEA arm) and intracerebral hemorrhage (1 in the CAS arm and 5 in the CEA arm), there was a trend to better outcomes for the CEA group in all other parameters including procedural failure, ipsilateral stroke, any stroke, and disabling stroke. As seen in previous studies, the risk of complications in SPACE was higher for women and older patients. The EVA-3S study was actually stopped early because of an excess of stroke or death in the CAS arm (9.6%) versus the cEA arm (3.9%) with a relative risk of 2.5 (95% CI 1.2–5.1); there no significant difference in the 30-day incidence rates of myocardial infarction. There were more systemic complications (mainly pulmonary) after CEA and more local complications after CAS but the differences were not significant. As in SAPPHIRE, cranial nerve injury was more common after CEA compared with CAS (7.7% versus 1.1%; $p < 0.001$)As the stroke rates were noted to be high in the initial phase of EVA-3S, emboli protection devices were then employed in this study and yet the incidence of stroke was still higher for CAS (7.9%) as compared with CEA. As, the results did not meet the prespecified non-inferiority margin for CAS, the conclusion of the SPACE investigators

was that, widespread use of CAS is not justified, at least based on the initial short-term 30 day results. The EVA-3S investigators further noted the low rates of CEA in their study may reflect a decrease in risk of surgery since the earlier surgical trials reflecting improved surgical technique and perioperative management over time.

These recent trials therefore set the bar much higher for those who would advocate widespread adoption of CAS for carotid artery disease. While the United States Center for Medicare and Medicaid Services (CMMS) reimburses treatment for patients at high risk for carotid endarterectomy who have symptomatic carotid stenosis, who are participants in an investigational device (IDE) study, or are participants in an FDA mandated post-approval study such as the CAPTURE study, we should therefore be ultra-cautious to in our case selection of patients for CAS until completion of further randomized studies. Significantly, the pace of enrollment in SAPPHIRE slowed in early 2002 because of several non-randomized carotid stenosis registries that began around that time and so SAPPHIRE was therefore terminated early because of slow enrollment of patients. Whenever possible, physicians should preferentially refer patients for randomized comparison studies rather than falling prey to a stenting imperative. There remain a number of available options worldwide. CREST (Carotid Revascularization Endarterectomy versus Stent) is a randomized trial of CEA and CAS for nominally low surgical risk patients. Initially the trial was designed for symptomatic patients with >50 percent carotid stenosis only nut has recently included to expanded to include asymptomatic patients with >60 carotid artery stenosis (70% by ultrasound) as well. While enrollment had lagged in this study, gradually randomization is increasing and as of 2005, 600 persons had been enrolled in the study. A follow-up study to CAVATAS is also underway, the International Carotid Stenting Study (ICSS) with 600 patients accrued to date.

Intracranial stenting

Stenting of the intracranial circulation, by comparison with CAS, is still very much in its infancy. The frequency of intracranial stenosis related ischemic stroke may be as large as the frequency of stroke attributable to extracranial large vessel atherosclerotic disease (Chimowitz et al 1995; Sacco et al 1995; Wityk et al 1996). Randomized clinical trial data, from the WASID investigators, of medical therapy for symptomatic intracranial atherosclerosis patients followed for an average of 1.8 years, showed that aspirin (1300 mg daily) has fewer adverse events and equal benefit to warfarin (INR 2–3) (Chimowitz et al 2005). In this population, the primary endpoint of ischemic or hemorrhage stroke or vascular death occurred in 22 percent of patients in either group. However, the rate of death, major hemorrhage and myocardial infarction or sudden death was higher in the warfarin group. As a pre-specified secondary endpoint, the rate of ischemic stroke in the territory of the stenotic artery was 15 percent for the aspirin treated patients and 12.1 percent for the warfarin treated group but this was not a statistically significant observation. Therefore, in light of the high stroke and complication rates for those patients treated medically (ie, WASID); there has been an understandable groundswell of interest in intracranial stenting. However, this procedure is associated with great risk and variable restenosis rates have been reported with limited long term follow-up of patients; complication rates range from 9%–38% post-stent have been reported (Jiang et al 2004; Abou-Chebl et al 2005; Kessler et al 2005; Lee et al 2005; Lylyk et al 2005; Qureshi et al 2005; Strabue et al 2005). One author has observed that "stent-assisted intracranial procedures are becoming a routine clinical practice" despite the limited evidence to support that conclusion (Kessler et al 2005). To date, there are only two, non-randomized multicenter feasibility trials of small numbers of patients (Higashida et al 2005).

In the SSYLVIA study restenosis occurred in at least 1/3 of all patients with close to 39.1 percent of the recurrent stenoses being symptomatic (SSYLVIA investigators 2004). SSYLIVA study employed the NEUROLINK device in 61 patients with intracranial or extra-cranial vertebral stenosis. Restenosis occurred in 12/37 (32.4%) of intracranial cases and 6/14 (42%) of extra-cranial vertebral stenosis. Strokes occurred in 4/55 (7.3%) of patients beyond 30 days. In a report of the multicenter experience with the WINGSPAN self-expanding system, 45 patients were described who underwent WINGSPAN device placement for recurrent symptoms despite medical therapy (Higashida et al 2005; Hartmann 2006). The average pre-stent stenosis was 72 percent and immediately after stent placement, the degree of stenosis was 52 percent with the stroke/death rate reported as 4.4% within 30 days and 7.1% at six months. Both of these devices have subsequently been approved in the United States under an FDA Humanitarian Device Exemption (HDE) and an interventional society position paper has declared that this procedure should be offered to patients who "fail medical therapy" with third party reimbursement (Higashida et al 2005).

Otherwise, the role of both coated and uncoated stents in the intracranial circulation is poorly defined and only case

series exist at this time with variable reports of morbidity, mortality and restenosis (Abou-Chebl and Yadav 2005; Boulos et al 2005). While, deployment of drug eluting stents has been proposed as one solution to the high rate of intracranial restenosis, by analogy to coronary artery disease, this concept should also be called into question in light of recent questions about the strength of the evidence for these stents in the management of coronary restenosis (Tung et al 2006). Chatervedi and Caplan emphasize that, given the lack of randomized studies, variable reported short and long-term complication rates, limited neurological follow-up, and an absence of randomized clinical trial data, intracranial stenting is a procedure that must be reserved only or those patients with symptomatic intracranial atherosclerotic vascular disease who have had recurrent events despite *aggressive maximalmedical therapy* who have a presumed annual stroke rate >10%–15% (Chaturvedi and Caplan 2003). These patients should also be treated with under formal investigation review board (IRB) oversight and continued long-term vascular neurology follow-up for assessment of complications and recurrent events should be mandatory (Benesch and Chimowitz 2000; Chaturvedi and Caplan 2003).

Mechanical thromboembolectomy for acute ischemic stroke

At present, intravenous tPA is the only FDA approved therapy for acute ischemic stroke. However, this therapy can only be administered to those patients treated within three hours of acute symptom onset and the treatment is also limited to patients at low risk of systemic hemorrhagic complications such that patients on anticoagulants or who have undergone recent surgical procedures are ineligible for tPA. Furthermore, the benefit of intravenous tPA is thought to be less effective for patients with large strokes typically the result of large proximal cervico-cerebral arterial occlusions (Kasner 2004; Ng et al 2004). Intra-arterial mechanical and/or pharmacologic thrombolysis has been adopted as an alternate strategy for appropriate patients either as a substitute or in addition to intravenous TPA. The rationale for this approach is based on the seminal PROACT studies (Furlan et al 1999; Kasner 2004).

PROACT II was a double-blind randomized trial of intra-arterial pro-urokinase of 180 patients with proximal middle cerebral artery occlusion who were randomized to IA pro-urokinase plus heparin versus heparin alone (Furlan et al 1999). In the study, there was a recanalization rate of 66% with the study drug and only 18 percent for the control group ($p < 0.001$). Forty percent of the pro-urokinase treated patients but only 25 percent of control patients had a good outcome defined as modified Rankin score of less than or equal to 2. The intracranial hemorrhage rate was 10% for the pro-urokinase arm and 2% for the control arm. Because of the study size and lack of a robust finding for the primary outcome, the FDA did not approved IA pro-urokinase for acute ischemic stroke.

However, the PROACT studies served as a proof of concept for intra-arterial thrombolysis and many centers have utilized this therapy on an unapproved off-label basis while clinical trials using combinations of intravenous and intra-arterial TPA for acute stroke are currently underway (Broderick 2004; Kasner 2004). The argument has been that IV TPA does not open larger vessels such as the internal carotid artery or the proximal middle cerebral artery as well as more distal arterial occlusive lesions (ASITN et al 2001; Ng et al 2004). Furthermore, patients with large strokes (NIHSS > 20) have a much lower chance of improving to NIHSS 0 or 1. Fifty two percent of patients with NIHSS < 10 had little or no deficit as compared to 8% of patients with NIHSS > 20 in the NINDS tPA studies (ASITN et al 2001; Ng et al 2004). An interventional society position statement thereby suggested that IA thrombolysis was appropriate in selected patients despite lack of randomized data and that criteria such as the location of the arterial occlusive lesion, magnitude of the neurologic deficit and time to treatment were potential criteria that might determine which patients should go directly for intra-arterial thrombolysis in place of FDA-approved intravenous TPA for acute stroke (ASITN et al 2001). Anecdotal evidence suggests that this approach is being widely adopted nationwide in both academic and community medical centers. Caution about this assumption is however warranted. A meta-analysis of IA thrombolysis (344 cases) versus IV thrombolysis (76 cases)for basilar artery occlusion, for which the assumption has been that IA thrombolysis is the preferred modality, did show that recanalization was more common with IA versus IV thrombolysis (Lindsbert and Mattle 2006). But death and dependency was equal for both IA and IV thrombolysis. Thus, while centers with experienced interventionalists might still opt for IA thrombolysis for basilar ischemia, intravenous thrombolysis is still a very reasonable alternative particularly in those centers where an interventionalist is not readily available.

Recently the MERCI retriever was approved through the 510 K process. Becker and Brott reviewed the 510 K approval process used for this device that based on the predicate device

of the Concentric retriever, approved in May 2001 for "use in the retrieval of foreign bodies in the peripheral coronary and neuro-vasculature" (Becker and Brott 2005). The advantages of the catheter based on the MERCI trial (Mechanical Embolus Removal in Cerebral Ischemia) patient selection criteria included extension of the window of opportunity to 8 hours for treatment of intracranial vertebral, basilar, intracranial ICA or M1 division MCA occlusions; patients with INR up to 3.0 or platelet count less than 30,000/uL could be treated as well. The MERCI trial presented to the FDA was a single arm prospective non-randomized trial of patients treated within 8 hours of symptom onset (Smith et al 2005). The primary endpoint was revascularization of the target vessel with a low rate of serious adverse events (vessel perforation, vascular dissection and distal clot embolization). The MERCI investigators compared their data to the placebo control arm of PROACT II. As described above, the PROACT-II was a study limited to proximal MCA occlusions whereas the intracranial vessels involved in the MERCI trial were more heterogeneous. 141 patients were treated (151 in the intention to treat analysis) using the MERCI retriever with a recanalization rate of 68/141 compared to the historical PROACT-II placebo control rate of 18 percent recanalization. A clinically significant device event-related complication rate of 10/147 (7%) was reported in the MERCI trial and the symptomatic intracranial hemorrhages rate was reported as 11/141 (7.8%). Clinical neurological outcome was only a secondary endpoint in the MERCI trial. The overall mortality rate was 43.5% at 90 days (n = 138) and, when embolectomy was unsuccessful, the mortality was 54.2%. Mortality dropped to 31.8%, however, for those who for whom embolectomy resulted in recanalization. In patients with MCA stroke in MERCI, mortality was 39% at 90 days compared with 27% in the historical control PROACT II placebo arm. Good outcome (modified Rankin less than or equal to 2) was similar for both the PROACT II placebo arm and the MERCI trial. In the Merci trial, there was an overall mortality rate of 27.7% at 90 days. For patients in MERCI who were PROACT-II eligible, the mortality rate was 33% compared with a rate of 27% in the PROACT-II control arm. For those successfully revascularized, a good outcome was seen in 46% of patients and for non-revascularized patients, the rate of good outcome was 10.4% at 90 days. The authors explained these differences by noting that the clinical severity of the MERCI trial patients was more severe (NIHSS 19 for MERCI versus NIHSS = 17 for PROACT-II) and the vessels treated in the MERCI trial were more heterogeneous. The problem of this approval process, however, was highlighted by Becker and Brott who note that while a clinical trial is underway to confirm efficacy via the MR RESCUE study (Magnetic Resonance and Recanalization of Stroke Clots Using Embolectomy) at the same time, a new and improved version of the MERCI catheter is being evaluated for approval using the same 501K process via a similar non-randomized trial (Multi-MERCI) (Becker and Brott 2005). While recanalization is an appropriate surrogate endpoint for a Phase II trial, clinical outcomes are the desirable measure for intra-arterial therapy (Wechsler 2006).

Conclusions

The four examples described above reflect the increasing interest in procedures to treat acute stroke, promote stroke recovery and prevent stroke recurrence. The technological imperative in medicine has led to the widespread adoption of medical devices and the field of cerebrovascular disease has not been shielded from this explosion in device utilization. The issue of efficacy versus safety remains unclear however. We have seen the limitations of observational studies in many pharmaceutical areas. The recent controversy over postmenopausal hormone replacement whereby a large randomized study failed to confirm benefit seen in older cohort and cross-section studies and the failure of vitamin E supplements to demonstrate benefit in trials of cardiovascular disease or cancer are just two examples of the limits of registry type data in drug studies (Pham and Plakogeniannis 2005; Hsia 2006). Medical devices should be subjected to the same standards of safety and efficacy as pharmaceuticals. The future offers a major opportunity to successfully prevent stroke through multi-modality and interdisciplinary approaches. However, "just because an attractive procedure is available does not mean it should be recommended" (Thomas 2005). There are some circumstances where off-label use of medical devices in cerebrovascular disease is appropriate. However, we should encourage enrollment of patients in randomized studies of these devices prior to widespread and routine adoption of a procedural approach to cerebrovascular disease. If the device approval process continues to not require randomized trials, clinical investigators should 'step up to the plate' and insist that the necessary studies be performed regardless of the current approval requirements.

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