Emerging Endovascular Therapies for Symptomatic Intracranial Atherosclerotic Disease

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Over the past 2 decades there has been an exponential growth in the scope of disease processes amenable to neuroendovascular treatment. The number and sophistication of the available devices and correspondingly the number of patients undergoing treatment has expanded accordingly. The development and implementation of these new procedures has in some cases outpaced our ability to carefully assess their merits. In comparison to peripheral and coronary vascular disease, neurovascular lesions are less common and far more heterogeneous, ranging from acquired cerebrovascular ischemic disease to hemorrhagic congenital arteriovenous malformations. Each individual disease process (e.g., cerebral aneurysm) is composed of a myriad of lesions with different anatomical and pathophysiological characteristics. The natural history of these lesions and their subtypes are likewise poorly defined. For these reasons, personal bias, institutional custom, and anecdotal experience rather than scientific evidence have played a dominant role in guiding therapy. We must move toward collaborative multi-center efforts, prospective data collection and well designed randomized controlled trials to mature as a field over the coming decades.

In some ways, symptomatic intracranial atherosclerotic disease (SxICAD) represents an optimal disease process with which to establish this progress toward evidenced based treatment. SxICAD is considerably less heterogeneous than other cerebrovascular disease processes and is arguably best suited as a paradigm for study.

In the current article we have attempted to review the available evidence describing the natural history of medically treated SxICAD to determine those patients best suited for invasive treatment strategies. We will also discuss the available treatment modalities which may represent viable options to medical therapy. These data form the basis for the design of future prospective multicenter studies to evaluate the relative merits of interventional treatment.

Symptomatic ICAD: Rationale for Invasive Treatment Strategies

Any invasive treatment strategy for symptomatic intracranial atherosclerosis must satisfy two criteria to establish viability as a reasonable alternative to medical therapy. First, the treatment must be performed with a rate of periprocedural morbidity and mortality which compares favorably to the natural history of the disease process treated with medical therapy. Second, the successfully executed invasive strategy must have efficacy with respect to the reduction of stroke and neurological death in the years following treatment.

Who to Treat?

In the WASID study, more than one-fifth of patients with a symptomatic intracranial stenosis of greater than 50% went on to ischemic stroke, brain hemorrhage, or other vascular death during the 1.8 years of follow-up. Twenty-three percent (23%) of patients with high grade (>70%) intracranial stenosis presenting with stroke as their qualifying event went on to experience another ipsilateral ischemic stroke over the next year despite medical therapy. Currently there are no data to support the treatment of asymptomatic patients with intracranial stenoses, regardless of whether or not they had failed medical therapy at the time of their qualifying event. Much lower rates of ipsilateral stroke were noted in patients with less than 70% stenosis (<10%). Currently there are no data to support the treatment of asymptomatic patients with intracranial stenoses, regardless of the severity of the stenosis or findings on perfusion imaging studies. Thus, as a first pass, those patients with greater than 70% symptomatic intracranial stenoses are most likely to benefit from invasive treatment strategies.

When to Treat?

The risk for stroke in patients with symptomatic ICAD is not constant over time. Similar to those patients with symptomatic carotid stenosis, the available data indicate that patients are at the highest risk for additional ischemic events soon...
after their qualifying event. For this reason, patients are likely to benefit most from early treatment, preferably within days after their qualifying event. Although there is some concern for hemorrhagic conversion of new ischemic injury after treatment, the existing data would indicate that this is probably unlikely. In most cases, patients who are candidates for treatment will have suffered only small strokes which are unlikely to undergo hemorrhagic conversion. Patients presenting with large strokes as their qualifying event are unlikely to benefit from revascularization and are not likely to be candidates for treatment.

Correspondingly, patients who are asymptomatic for months after an initial qualifying event are unlikely to benefit from revascularization, as the majority of their “time at risk” has passed. This phenomenon is most striking when evaluating the WASID subset analysis for patients with 70% stenosis. Over 1 year, the risk of a new stroke was 22.5%. When these patients were followed for an additional year, the overall cumulative risk rose to only 24.6%—correlating to an accrued risk of only 2.1% during this second year. This decline in risk after the qualifying event is evident quite early. Patients enrolled in WASID at 17 days or less after their qualifying event experienced a significantly greater risk of reaching a primary end point than those enrolled later. This precipitous drop in stroke risk with time makes it difficult to justify the risks of intervention in patients who have been asymptomatic for months after their qualifying event on medical therapy.

Strategies for the Revascularization

Surgical Treatment

Extracranial to intracranial bypass has been applied as a treatment for both anterior and posterior circulation cerebrovascular ischemic disease. The EC-IC bypass trial represents the largest and best data set describing the efficacy of this procedure for anterior circulation disease. In this study, the subset of patients with severe middle cerebral artery stenosis did worse than any other patient subset within the trial after bypass—with a risk of stroke nearly 2 times higher after surgical bypass compared with medical therapy. Smaller series of posterior circulation bypass procedures also yielded suboptimal results with significant complications encountered in 55% of patients despite excellent technical results and high patency rates for the bypasses.

On the basis of these data, it can be stated that surgical bypass therapy does not represent a reasonable therapeutic option for the vast majority of patients with symptomatic intracranial stenosis.

Endovascular Treatment

The rapid development, widespread success, and general acceptance of angioplasty and stenting for the treatment of peripheral and coronary atheromatous disease have predictably spurred a gradual adaptation of these techniques for the treatment of symptomatic intracranial atheromatous lesions. In the past, the application of these techniques has been limited by the inability of the existing devices to navigate the tortuous cerebrovasculature. However, these barriers are gradually being overcome as lower profile and more flexible devices are being developed for the coronary circulation and in some cases specifically for neurovascular applications.

Percutaneous Transluminal Balloon Angioplasty

Balloon angioplasty was the first endovascular technique applied to the treatment of intracranial atherostenoses, first reported by Sundt et al in 1980. Several groups subsequently reported technically successful intracranial percutaneous transluminal balloon angioplasty (PTA) in small series of patients. Gress et al reviewed the UCSF experience with posterior circulation PTA in a series of 25 patients treated between 1986 and 1999. In these patients, PTA was technically successful, albeit at a relatively high cost in terms of periprocedural morbidity and mortality with 28% of patients experiencing periprocedural stroke or death.

However, as the devices and techniques evolved, the procedure became safer and better. Connors and Wojak systematically analyzed the angioplasty technique and determined that if the angioplasty balloon is undersized with respect to the diameter of the targeted blood vessel and the lesion is subsequently dilated with a very slow inflation (over several minutes), that their complications could be reduced substantially. In addition, the routine incorporation of periprocedural dual antiplatelet agents and the availability of the IIb/IIIa inhibitors for selected applications also reduced the thromboembolic complications associated with these procedures.

Using these “modern” PTA techniques in conjunction with dual antiplatelet therapy, several larger retrospective studies have suggested that PTA alone represents a viable treatment strategy. Marks et al presented retrospective data for a series of 120 patients treated at multiple institutions, reporting a 5.8% rate of periprocedural stroke and death and a total yearly event rate of 3.2% (ipsilateral stroke or neurological death) for 116 patients in the series with long term follow-up which averaged more than 40 months.

Despite these impressive results, PTA alone suffers several shortcomings which are of debatable clinical significance. First, acute vessel recoil after angioplasty frequently results in a residual postprocedure stenosis of 50% or more, a finding observed in 40.3% of the patients in the Marks et al series. In most series, the average posttreatment residual stenosis is in the 40% range. Air angiographically evident vessel dissection with a visualized intimal flap occurs in more than 20% of cases which may necessitate either subsequent stent placement or more aggressive postprocedural anticoagulation. However, with appropriate management, these angiographic phenomena are rarely manifest as clinical events. Finally, some data suggest that the durability of the technique is lacking, with approximately 20% of patients eventually requiring retreatment (either re-PTA or PTAS).

Bare Metal Balloon Mounted (Coronary) Stents

Experience in the peripheral and coronary circulation indicated that the shortcomings of angioplasty (acute recoil, acute occlusion, dissection, and recurrent stenosis) could be largely overcome with angioplasty and stenting. These data were extrapolated to the intracranial circulation, and several case reports and small series of intracranial stenting were subsequently reported. The rigidity of the available balloon...
mounted coronary stents greatly limited the access of these devices to the tortuous cerebrovascular and considerably increased the technical difficulty of the procedure in comparison to PTA alone. The reported periprocedural complication rates (0% to 36%) for intracranial PTAS vary widely, but in general, trend higher than those reported for PTA alone. These higher rates of periprocedural complications are accepted in return for superior postprocedure angiographic results with residual immediate postprocedure stenoses typically reported to be less than 10% after successful PTAS—versus 40% for PTA alone—because of the efficacy of the stent to resist early lesion recoil and essentially eliminate the issue of target vessel dissection.

In SSYLVIA, a balloon-mounted stent (Neurolink) designed specifically for cerebrovascular applications was used to treat 43 intracranial lesions and an additional 18 extracranial vertebral artery lesions. These investigators reported a 6.6% periprocedural stroke rate and an additional 7.3% stroke rate at delayed (30 days to 1 year) follow-up. If only the intracranial lesions are considered (n=43), the cumulative overall stroke rate, including periprocedural events (n=4) and 1 year follow-up (n=2), was 14% (6/43). These data indicate that with the Neurolink device, PTAS represents a potentially viable alternative to medical therapy for selected patients. Unfortunately, the Neurolink is no longer commercially available.

Levy et al demonstrated that the periprocedural complications associated with primary PTAS using balloon mounted coronary stents could be reduced by adopting a staged technique in which an initial angioplasty was performed during the first procedure, followed several weeks later by PTAS. Staged PTA-first technique avoids the primary traversal of a high-grade atherostenosis with the more rigid high-profile stent and also allows an interval period of healing with remodeling, intimal proliferation, and luminal scarring which may make subsequent stent delivery and deployment safer.

More recently, Jiang et al published their single-center 4-year experience using balloon-mounted stents, and reported a very low complication rate of approximately 5% in 203 patients. In addition, these authors did not identify any increased risk of complications associated with the treatment of high grade (>70%) in comparison with lower grade (50% to 69%) stenoses.

Although stenting produces better immediate angiographic results than PTA alone, it does not overcome the problem of late luminal loss or obviate the requirement for the retreatment of some lesions. Although late luminal loss is common after PTA, occurring in 20% to 30% of patients, a similar percentage of patients undergoing PTAS also demonstrate late luminal loss as a result of in-stent restenosis (ISR). ISR produced greater than 50% luminal compromise in 32.4% of patients with intracranial stents during the SSYLVIA trial. Although ISR was relatively common, only one-third of the patients became symptomatic, and those who were symptomatic very rarely presented with stroke. Jiang et al observed a 19.2% rate (n=19) of ISR in a series of 99 patients with angiographic follow-up. Of these patients, only 6 were symptomatic and only 2 were symptomatic with stroke.

These data suggest that newer generation devices (such as the Apollo stent used by Jiang et al, and previously the Neurolink stent) and evolving techniques, such as a staged treatment strategy, may facilitate a significant reduction in the periprocedural complications associated with PTAS using balloon mounted coronary stents. More data will be required to determine whether PTAS with the newer generation balloon-mounted stents will represent a potentially viable alternative to medical therapy.

Self-Expanding Intracranial Stents

In 2002 the first dedicated self-expanding intracranial stent (Neuroform) was developed to support the treatment of wide-necked intracranial aneurysms. Neuroform differed from its predecessor balloon mounted coronary stents in that the device was composed of Nitinol and thereby very flexible and of low profile with delivery accomplished via a standard microcatheter. These properties markedly augmented the ability to atraumatically deliver and deploy stents within almost any location throughout the tortuous cerebrovasculature. This device significantly expanded the number and complexity of cerebral aneurysms amenable to endovascular therapy.

By oversizing the Neuroform device relative to the diameter of the target vessel, the outward radial force could be significantly augmented. Because of the improved deliverability of the device, some investigators chose to use Neuroform for the treatment of selected intracranial aneurysms which were not accessible to standard coronary stents. In 2005, the Wingspan stent, a modified version of Neuroform, was released in the US under a Humanitarian Device Exemption (HDE) for the treatment of symptomatic intracranial stenoses (>50%) which were refractory to medical therapy. The Wingspan stent incorporated thicker struts and additional interconnects which augmented its outward radial force to better counteract the acute recoil of aneurysms after PTAS. The Wingspan device is implemented in the context of a treatment strategy which combines aspects of the PTA alone strategy and the stenting strategy. The lesion is initially dilated with a PTA balloon sized to 80% of the “normal” vessel diameter using the slow inflation technique advocated by Connors and Wojak. After the initial PTA, the stent delivery system is exchanged over a 0.014” microwire and the self-expanding stent is deployed across the lesion. Proliferation of the stent after implementation is discouraged by the manufacturer. At the conclusion of the procedure, the typical residual stenosis (~30%) is less than that observed after PTA alone (~40%) but considerably more than what is accepted after balloon-mounted stent deployment (~10%). Correspondingly, Wingspan represents an entirely new treatment paradigm which is essentially a hybrid between the PTA and stenting strategies that seeks to capitalize on the advantages of both techniques. For this reason, it is difficult to extrapolate the existing experiences with either of the predicate techniques to predict the results with this device.

Preliminary results with Wingspan have been very favorable. The initial study performed in Europe and Asia Fiorella and Woo Emerging Endovascular Therapies for SxICAD 2393
demonstrated very low rates of periprocedural morbidity and mortality (4.4%) in a series of 45 patients undergoing treatment. Recent data from a multicenter US registry also reported relatively low rates of periprocedural complications (6.1%) and very high rates of successful deployment (>98%).34 Six-month follow-up data from the Eurasian study, available in 43 patients, yielded an overall rate of ipsilateral stroke or death of 9.3% from the time of treatment to last clinical follow-up. Angiographic follow-up at 6 months revealed a remarkably low rate (7.5%) of ISR. In fact, follow-up angiography overall demonstrated a slight non-statistically significant (3%) average late luminal gain, which was attributed to the chronic outward radial force of the self-expanding Nitinol stent.39 This represents a critical point, given that late luminal loss, occurring in 32.4% of patients in the SSYLVIA trial and in at least 20% to 30% of patients after PTA alone, is a major potential downfall of the predicate technologies which might only be otherwise overcome with the implementation of drug eluting stents (see below). Unfortunately, as more data become available, it does not appear that the rates of ISR occurring after PTAS with Wingspan are any less than those observed after PTA or PTAS with other devices. In a prospective series of patients treated with Wingspan, ISR was observed at a rate of 28.8% in a group of 68 patients with 3 to 6 month imaging follow-up. Two additional patients in this series presented with complete stent occlusion at follow-up.36 Moreover, very few compelling individual examples of late luminal gain have been observed. As more data become available over the next year, the merits and limitations of the Wingspan treatment strategy will be better elucidated.

Drug-Eluting Stents
Balloon-mounted coronary stents coated with sirolimus (antiproliferative, antiinflammatory, and immunosuppressive agent) and paclitaxel (antiproliferative agent) have tremendously reduced coronary ISR from the greater than 30% rate observed with bare metal stents to less than 10%.40 Several groups have used these devices to treat intracranial atherosclerotic lesions in small series of patients—data have been reported for only 57 patients to date.41-43 From the small number of patients treated and the limited available follow-up, it is difficult to ascertain the safety profile or efficacy of this approach. Although the avoidance of ISR is clearly desirable, there are potential drawbacks of intracranial drug-eluting stents (DES) implantation. The concerns that intracranial drug elution could result in neurotoxicity have not been borne out in controlled animal studies44 or in any of the small human series. A more important issue is that DESs require significantly longer time to endothelialize than bare metal stents and are associated with incomplete intimal healing after implantation. In the BASKET-LATE study, this phenomenon resulted in a 2-fold increase in documented late stent thrombosis and related death/target vessel MI in patients treated with DES versus those with bare metal stents.45 In a metaanalysis of 14 randomized trials of DES, a 4- to 5-fold increase in late stent thrombosis was observed with DES, with an incidence of very late (>1 year postprocedure) thrombosis of 0.5% with DES versus 0% with bare metal stents.46 With sirolimus eluting stents, the incidence of stent thrombosis remained constant up to 4 years after implantation. These observations led the authors to conclude that the original recommended duration of dual antiplatelet therapy (3 months for sirolimus eluting and 6 months for paclitaxel eluting stents) was inadequate and that caution should be given to interrupting dual antiplatelet therapy even several years after DES implantation. Thus, the decision to place a DES within one of the relatively small target vessels within the intracranial circulation likely consigns the recipient to prolonged (>1 year), possibly lifelong, dual antiplatelet therapy because of the risk of late stent thrombosis. The precise etiology of delayed thrombosis with DES remains incompletely understood. Investigators have suggested that the defects in the drug containing polymer,47 the mechanisms of action of the various drugs,48 the ultimate distribution of the drugs within the vessel wall and the actual structure of the stent may contribute to this risk.49 It is possible that modifications in the engineering of these devices, the drugs they elute, and the elution polymers themselves may significantly reduce this risk in the future.

When considering DES for intracranial use, the relative risk and implications of late stent thrombosis and the potential complications and costs of prolonged dual antiplatelet therapy must be weighed against the risk of ISR which is often asymptomatic and may be treated (if necessary) with a relatively high safety margin.

Conclusions
The current overview indicates that although our understanding of the natural history of symptomatic ICAD has progressed quite significantly with the results of the WASID trial, our understanding of those procedures available for the treatment of the disease has lagged behind. Whereas surgical revascularization is clearly not efficacious, the available endovascular strategies may have merit in the appropriate patients—particularly those with high grade (>70%) symptomatic intracranial stenosis presenting early after their qualifying event.

Unfortunately very little reliable data exist about the individual treatment strategies. Each strategy has its advantages and drawbacks; however, many of these remain theoretical. PTA alone may have a relatively low rate of periprocedural complications, and existing data suggest that the long-erm efficacy may be good; however, the procedure is perceived as limited because of poor immediate angiographic results in up to half of the cases, the relatively common phenomenon of angiographically evident dissection, the relatively frequent need for retreatment, and the bias related to the dominance of stenting over PTA alone in peripheral vascular distributions. The balloon mounted stenting approach overcomes these angiographically evident and theoretical limitations, but at the cost of the increased technical difficulty involved with negotiating a more rigid, higher profile device through the cerebrovasculature, slightly higher procedural complication rates, and ultimately the potential for delayed ISR. Wingspan represents a new hybrid strategy extrapolated from these 2, relatively poorly understood, predicate techniques. As such, many important details regard-
ing the optimal application of the Wingspan strategy and its role among the other endovascular treatment options remains unknown. Similarly, although DES provide the potential to overcome ISR—one of the major limitations of intracranial stenting—the cost with respect to late stent thrombosis and the complications associated with long-term, possibly life-long, dual antiplatelet therapy represent important considerations.

Although each treatment strategy has its enthusiasts, it is critical that neurointerventionalists move toward organized, prospective, and (when possible) independently adjudicated data collection such that the myriad of available endovascular treatments for this disease process can be better understood, optimized, and applied. This understanding can then form the basis for a randomized trial of one or more of these treatment modalities versus medical therapy.

Disclosures

D.F. received significant research support from Boston Scientific.

References


**Key Words:** angioplasty, drug eluting stent, intracranial atherosclerosis, stent, wingspan stent.
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*Stroke*. 2007;38:2391-2396; originally published online June 21, 2007;
doi: 10.1161/STROKEAHA.107.482752

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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