Treatment of Atherosclerotic Intracranial Arterial Stenosis

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Atherosclerotic stenosis of the major intracranial arteries (intracranial internal carotid artery, middle cerebral artery, vertebral artery, basilar artery) is probably the most common cause of stroke worldwide. Intracranial atherosclerosis causes 30% to 50% of strokes in Asia and 8% to 10% of strokes in North America. This review focuses on the medical and endovascular treatment of atherosclerotic intracranial arterial stenosis.

Antithrombotic Therapy

Initially, a retrospective study suggested that warfarin was superior to aspirin for stroke prevention in patients with symptomatic intracranial arterial stenosis. This retrospective data combined with a proposed pathophysiological rationale for anticoagulation made warfarin a common treatment choice for symptomatic intracranial stenosis. However, the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial showed that aspirin was safer and as effective as warfarin for stroke prevention in patients with symptomatic intracranial stenosis. WASID was stopped early after a mean follow-up of 1.8 years because of higher rates of death and major hemorrhage in the warfarin arm. The primary end point of ischemic stroke, brain hemorrhage or vascular death, occurred in 22.1% of patients assigned aspirin and 21.8% of those in the warfarin group. The rates of myocardial infarction or sudden death were also higher in the warfarin arm.

Certain high-risk subgroups of patients with intracranial stenosis were previously thought to benefit from anticoagulation, such as those with severe stenosis, vertebrobasilar disease, and those who have failed antithrombotic therapy. In WASID, however, patients with severe stenosis or those previously on antithrombotic therapy did not benefit from warfarin. Patients with basilar artery stenosis in WASID did appear to have a lower rate of the primary end point on warfarin, but there was no difference in the rate of stroke in the territory of the basilar artery between patients on aspirin versus warfarin. Neither patients with intracranial vertebral stenosis nor patients with posterior circulation stenosis (combined vertebral and basilar stenosis) had significantly lower rates of the primary end point or stroke in the territory on warfarin, suggesting there is no clear evidence of a benefit of warfarin over aspirin for patients with vertebropasilar stenosis.

Other antiplatelet agents (eg, clopidogrel and combination dipyridamole/aspirin) have been shown to have similar stroke recurrence rates in patients with various underlying causes of stroke and in a subset of patients with large artery atherosclerosis in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) Study. Other than aspirin, cilostazol is the only antiplatelet agent which has been studied in a multicenter, double-blinded controlled trial of secondary prevention in patients with symptomatic intracranial stenosis. In that study’s 6-month follow-up period, there were no strokes in either the cilostazol + aspirin or the placebo + aspirin arm. However, progression of the intracranial stenosis was less common in the cilostazol group (6.7% versus 28.8%; P=0.008). This finding has lead to an ongoing multicenter study of cilostazol + aspirin versus clopidogrel + aspirin in patients with symptomatic intracranial stenosis, the Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis II (TOSS-II) Trial (ClinicalTrials.gov identifier: NCT00130039).

Currently there are no published data establishing either the equivalence or superiority of other available antiplatelet agents over aspirin for secondary stroke prevention in patients with intracranial stenosis. A national survey of neurointerventionalists and neurologists completed after the publication of WASID showed that aspirin is now the preferred antiplatelet agent for stroke prevention in patients with intracranial stenosis.

This discussion of antithrombotic therapy focuses on secondary stroke prevention in intracranial stenosis. However, it is worthwhile to note that there has also been a randomized trial comparing low-molecular-weight heparin and aspirin in the acute stroke setting which included mostly patients with intracranial stenosis. This study did not show a significant benefit of anticoagulation over aspirin.

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Management of Risk Factors

Secondary prevention stroke trials in patients with various underlying causes of stroke have shown that treatment of risk factors such as elevated low-density lipoprotein (LDL)\textsuperscript{14} and blood pressure\textsuperscript{15} reduce the risk of recurrent stroke. WASID provides additional data supporting aggressive risk-factor control in patients with intracranial stenosis. In WASID, vascular risk factors were managed by the study neurologist and primary care physicians following national guidelines.\textsuperscript{7} However, in many patients risk-factor control was not optimal, and patients with poor control of risk factors had higher rates of recurrent vascular events.\textsuperscript{16,17}

In WASID, elevated blood pressure was significantly associated with an increased risk of ischemic stroke,\textsuperscript{17} stroke in the territory,\textsuperscript{17} and major vascular events.\textsuperscript{16} Patients perceived to be at higher risk of stroke with lower blood pressure, such as those with 70% to 99% stenosis and posterior circulation stenosis, also did not show an increased risk with maintaining blood pressure in the normal range.\textsuperscript{17} Although this study did not examine the effect of lowering blood pressure in acute, unstable patients, when analyzing patients with early events, normal blood pressure was not associated with increased risk of stroke.\textsuperscript{17} Therefore, these findings argue against the common practice of permissive hypertension to increase perfusion through a stenotic intracranial artery and suggest that patients with intracranial stenosis should not be excluded from the national guidelines for blood pressure control.

Raised LDL was also strongly associated with poor outcome in patients in WASID, because 25.0% of patients with LDL ≥115 mg/dL (the median LDL) had the primary end point compared with 18.5% of patients with a mean LDL <115 mg/dL.\textsuperscript{16} When applying the current recommended LDL target to the WASID population, among the mere 10% of patients with mean LDL <70 mg/dL only 7% had a primary end point compared to 23% of the patients with LDL ≥70 mg/dL (P=0.09). Although this difference was not statistically significant (likely due to low power from the small number of subjects in the LDL <70 group), this analysis suggests that aggressive lowering of LDL may decrease the risk of vascular events substantially. Despite previous concern that lowering LDL might be harmful in stroke patients, recent studies have shown no relationship between LDL levels and hemorrhagic risk\textsuperscript{18} and that the benefits of statins in patients with ischemic stroke outweigh the risk of hemorrhage\textsuperscript{19} suggesting that patients with intracranial stenosis should have aggressive lowering of their LDL.

The results of recent studies of risk factor control in stroke patients overall and the results of these post hoc analyses in WASID suggest that targeting lowering blood pressure and LDL may reduce major vascular events in patients with intracranial stenosis. Furthermore, aggressive risk factor management in patients with coronary artery disease has also been shown to be as effective as endovascular intervention for preventing cardiac ischemic events in patients with stable coronary artery disease,\textsuperscript{20} suggesting that aggressive risk factor management in stroke patients with intracranial stenosis might obviate the need for endovascular treatment as well.

Endovascular Therapies

Angioplasty and stenting have emerged as therapeutic options for symptomatic intracranial stenosis over the past few decades. Initially, intracranial angioplasty experience had a high risk of complications and the procedure was abandoned.\textsuperscript{21} Since that time, advances in microcatheter and balloon technology, the high risk of recurrent stroke in patients with intracranial stenosis despite medical management in WASID, and the success of endovascular treatments for coronary artery disease have led to renewed interest in intracranial angioplasty and stenting.

Angioplasty

There are no prospective studies of the safety or performance of angioplasty for the treatment of symptomatic intracranial stenosis. Retrospective angioplasty studies report high technical success rates (reduction of stenosis to <50%), but the 30-day rate of stroke or death has varied widely (4% to 40%).\textsuperscript{22} Restenosis rates after angioplasty have been reported between 24% to 50%.\textsuperscript{23-26} There are limited data on the long-term prognosis after intracranial angioplasty. A retrospective review of 120 patients who underwent intracranial angioplasty at 4 sites reported a 1-year stroke rate of 4.4% (3.2% in the territory of stenosis),\textsuperscript{24} but the limitations of this study include the retrospective design and the lack of systematic evaluation of these patients by a neurologist after angioplasty.

Overall, available data on intracranial angioplasty suggest that it can be performed relatively safely in stable patients, but the long-term outcome after angioplasty has not been prospectively studied. Moreover, there are numerous technical drawbacks to angioplasty including immediate elastic recoil of the artery, dissection, acute vessel closure, residual stenosis after the procedure, and high restenosis rates.

Stenting

Initially, studies on intracranial stenting suffered from the same design flaws as the angioplasty studies (ie, single-center, retrospective, or lack of systematic evaluation by a neurologist).\textsuperscript{27} A more detailed review of these single-center studies is provided elsewhere.\textsuperscript{27} Overall, these studies suggested that intracranial stenting could be performed safely and with high technical success (91% to 98%). Subsequently multicenter, prospective data on intracranial stenting has emerged. Stenting of Symptomatic atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA)\textsuperscript{28} was the first multicenter Phase I trial of a bare metal stent (Neurolink, Guidant Corp) for intracranial stenosis. SSYLVIA included 61 patients with either symptomatic intracranial stenosis (43 patients) or extracranial vertebral stenosis (18 patients).\textsuperscript{28} The technical success of stenting was 95% and the 30-day stroke rate was 7.2% with no deaths. The 1-year stroke rate was 10.9% with all of the strokes within the territory of the stented artery. Recurrent stenosis (≥50%) at 6 months was documented by angiography in 35% of patients.\textsuperscript{28}

In 2005, the Wingspan Stenting System (Boston Scientific) was approved by the FDA for use under an HDE (humanitarian device exemption) in patients with symptomatic intracranial stenosis who are refractory to medical therapy. Wing-
span is a flexible, self-expanding, microcatheter deployed stent designed specifically for the intracranial arteries. The first Wingspan study was a prospective multicenter international Phase I trial which included 45 patients with symptomatic 50% to 99% intracranial stenosis who had recurrent stroke on antithrombotic therapy.29 The technical success rate was 97.7% and the 30-day stroke or death rate was 4.5%. The 1-year rate of ipsilateral stroke was 9.3%. The restenosis rate was 7.5% at 6 months and none were symptomatic.29

Since the initial Wingspan HDE study, additional data on the safety and success of Wingspan have been reported in 2 multicenter registries. The first report included data from 5 centers on 78 patients with 82 symptomatic intracranial stenoses (50% to 99%) and demonstrated a technical success rate of 98.8% and a periprocedural rate of major neurological complications of 6.1%.30

Because patients with 70% to 99% stenosis are at highest risk on medical therapy34 and the stenting complication rates are similar between patients with moderate and severe stenosis,32 the benefit of stenting is likely to be greater in the severe stenosis group. Therefore, the National Institutes of Health (NIH) multicenter Wingspan registry focused on this higher risk group. This registry of 129 patients with 70% to 99% symptomatic intracranial stenosis at 16 centers showed the technical success rate was 96.7% and the frequency of any stroke, intracerebral hemorrhage, or death within 30 days or ipsilateral stroke beyond 30 days was 14.0% at 6 months.33

Since the initial reports of the Wingspan registries, additional follow-up data have become available. Restenosis rates in these registries (≥50% on follow-up angiogram) have been reported between 25% to 32%33,34 and appear to be higher in younger patients, especially those with supraclinoid carotid stenosis.35 However, the restenosis is usually asymptomatic.33,36

Bare metal balloon-mounted (coronary) stents and drug-eluting stents have also been used to treat symptomatic intracranial stenosis. However, reports of their use have been limited to case reports and small series. In addition to the lack of multicenter prospective data, bare metal balloon-mounted stents are limited by their rigidity, making delivery to intracranial lesions technically difficult. Drug-eluting stents are limited by the lack of long-term safety data and risk of in-stent thrombosis.

Recently, data on 2 new balloon-mounted stents designed to treat intracranial stenoses have been reported. The Apollo stent (MicroPort Medical) was studied in a small single-center series of 46 patients and found to have a technical success rate of 91.7%, but delivery of the stent was limited by vessel tortuosity and the restenosis rate was 28%.38 In addition, the Pharos intracranial stent (Micrus) was used to treat 21 patients with acute or chronic intracranial stenoses.39 Among the 14 patients treated nonemergently the technical success was 85.7% and the procedure-related complication rate was 28.5%.

Comparative studies of primary angioplasty and stent placement have also been recently reported.25,26,40 Overall, these reports suggest patients undergoing angioplasty alone may have higher rates of restenosis26,40 and possibly worse 2-year clinical outcomes25 than stented patients. However, these studies were all limited by their retrospective design and low power to detect differences between the stented and angioplasty groups.

The Wingspan system is currently the only FDA-approved device for treating symptomatic intracranial stenosis. Wingspan is also the most well studied of the available devices, and the existing data have indicated high rates of technical success and reasonable levels of periprocedural adverse events, but long-term efficacy for stroke prevention has not yet been adequately assessed and further studies are needed. For these reasons, Wingspan has been selected as the stent to be evaluated in an upcoming investigator-initiated, NIH-funded multicenter randomized trial to evaluate the safety and efficacy of intracranial stenting in patients with symptomatic severe intracranial stenosis.

The Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) Trial (ClinicalTrials.gov Identifier: NCT00576693) is an NIH-sponsored, randomized trial at 60 US sites designed to determine whether angioplasty and stenting plus aggressive medical management is superior to aggressive medical management alone for the prevention of recurrent stroke in patients with 70% to 99% stenosis of a major intracranial artery. Patients with transient ischemic attack or nonsevere stroke within 30 days will be randomized 1:1 to either arm. Aggressive medical management in SAMMPRIS will consist of dual antiplatelet therapy (aspirin + clopidogrel) for 90 days in all patients, followed by aspirin monotherapy for the remainder of the study. All patients will also receive protocol-driven risk factor management targeting a LDL <70 mg/dL and systolic blood pressure <140 mm Hg (<130 if diabetic) and a comprehensive lifestyle modification program to assist with weight reduction, exercise, smoking cessation, and nutrition.

Despite the global health impact of intracranial atherosclerosis, relatively few clinical trials have been undertaken to evaluate treatments for this disease, perhaps because accurate diagnosis still requires catheter angiography given the poor positive predictive value of noninvasive tests.41 Nevertheless, the poor prognosis and current lack of proven therapies (either medical or endovascular) emphasizes the need to refer all eligible patients for possible participation in ongoing clinical trials.

**Summary**

Symptomatic intracranial stenosis is associated with a high risk of recurrent stroke. WASID showed that aspirin is safer and as effective as warfarin for preventing recurrent stroke and provided strong evidence that aggressive management of vascular risk factors (particularly systolic blood pressure and LDL) may lower the risk of stroke. Patients with 70% to 99% stenosis and recent symptoms are at the highest risk of recurrent stroke on medical therapy. These high-risk patients represent the cohort who stands to gain the most from endovascular intervention and represent an optimal target population for further therapeutic trials. Although intracranial stenting appears to be a promising therapy, a randomized trial of intracranial stenting and aggressive medical therapy versus aggressive medical therapy alone is needed to determine the clinical benefits.
whether stenting offers additional benefit for patients with severe symptomatic intracranial stenosis.

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References


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