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The Challenge of Stroke Prevention with Intracranial Arterial Stenosis

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Abstract

Patients with symptomatic intracranial atherosclerotic disease (ICAD) have a high risk of recurrent stroke and secondary prevention in these patients remains a challenge. Aggressive medical management of vascular risk factors is safe and effective for most high risk patients, but the role of endovascular and surgical therapies still remain uncertain. Future studies may identify novel therapeutic strategies for patients with ICAD, but aggressive risk factor control remains the mainstay of evidenced-based treatment at this time.

Keywords

intracranial atherosclerosis; intracranial arterial stenosis; medical management; risk factor control; intracranial stenting; stroke; prevention

Introduction

Intracranial atherosclerotic disease (ICAD) is an important cause of ischemic stroke and is probably the most common cause of stroke worldwide[1]. Over the past several decades, researchers have attempted to determine the optimal treatment for prevention of stroke in patients with ICAD, particularly those considered to be at highest risk (70–99% stenosis of a major intracranial artery)[2]. Initial studies focused on the choice of antithrombotic therapy. However, the recognition that traditional vascular risk factors have not been adequately addressed in prior trials and that uncontrolled risk factors are associated with higher risk of recurrent stroke in ICAD[3] has shifted the focus to more aggressive treatment of risk factors. More recently, endovascular treatments have also been evaluated in clinical trials, but have not shown any clear benefit for stroke prevention. This paper will focus on the evolution of medical, surgical or endovascular treatments of ICAD.

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Compliance with Ethics Guidelines

Conflict of Interest

Tanya N. Turan has been a consultant for Gore & Associates (REDUCE Trial - Clinical Events Committee), NIH- Veritas Study (Event Adjudication Committee), and BI 1356/BI 10773 (Clinical Trial Neurology Event Adjudication Committee).
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Marc I. Chimowitz has been a consultant for Gore & Associates (DSMB on PFO Closure Trial), Parexel/Merck (Stroke adjudicator in an osteoporosis Trial), and Medtronic (Stroke Adjudicator Committee). He has given expert testimony for non-corporate (Stroke Malpractice Case).

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Evolution of Medical Management of ICAD

Antithrombotics

The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial was the first clinical trial to compare antithrombotic agents for stroke prevention in patients with ICAD[4]. Patients with symptomatic intracranial stenosis (with stroke or transient ischemic attack (TIA) within the previous 90 days that was due to 50–99% intracranial stenosis) were randomized to either warfarin or aspirin and usual risk factor management. WASID showed that aspirin was safer and as effective as warfarin for stroke prevention in patients with symptomatic intracranial stenosis and led to a change in the typical antithrombotic management of patients with ICAD[5]. However, WASID also showed that patients with symptomatic intracranial atherosclerosis remained at high risk for recurrent stroke while taking aspirin or warfarin, with up to 18% having recurrent strokes in the territory of a 70–99% stenosis after 1 year.

While aspirin was shown to be as effective as warfarin but safer for stroke prevention in patients with ICAD in the WASID trial, newer antiplatelet agents were being used for stroke prevention in other causes of stroke. Combinations of antiplatelet agents (such as aspirin plus clopidogrel) were also being used for stroke prevention and studies to determine the safety and efficacy of dual antiplatelet therapy were performed. The MATCH trial compared dual antiplatelet therapy (aspirin and clopidogrel) vs. clopidogrel alone for prevention of major vascular events in high-risk patients with recent ischemic stroke or TIA and at least one vascular risk factor[6]. This study included patients with non-cardioembolic causes of ischemic stroke, but only about 1/3 had stroke due to large artery atherosclerosis (i.e. ICAD and extracranial carotid disease). There was no benefit for stroke prevention in the dual antiplatelet therapy group but the risk of major bleeding was higher with dual therapy beyond the 3rd month of treatment. Later, the CLAIR and CARESS studies suggested that the use of *short-term* dual anti-platelet therapy (aspirin and clopidogrel) may actually be effective at lowering the early risk of stroke recurrence in patients with stroke due to large artery atherosclerosis. In the Clopidogrel plus Aspirin for Infarction Reduction (CLAIR) study, patients with recently (≤7 days) symptomatic ICAD or extracranial carotid stenosis who were treated with dual antiplatelet agents (clopidogrel and aspirin) had significantly lower rates of microembolic signals detected by transcranial Doppler (TCD) on days 2 and 7 after randomization compared with patients treated with aspirin monotherapy[7]. In a weighted analysis, the recurrent stroke events of CLAIR combined with the events from the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) Trial (limited to patients with recently symptomatic > 50% extracranial carotid stenosis)[8], showed significantly more recurrent stroke events on aspirin alone compared with aspirin and clopidogrel combined[7]. These studies provided a rationale for including short-term dual antiplatelet (aspirin plus clopidogrel) use in future studies of ICAD.

Risk factor management

During the WASID trial, risk factors were managed by the study neurologist in conjunction with the patient's primary care physician. Although national guidelines for treatment of risk factors were provided to the study neurologists, specific algorithms for risk factor control were not provided[9]. Many patients in WASID had uncontrolled risk factors during follow-up, suggesting that simply providing guidelines was not sufficient to achieve desired risk factor targets. Failure to achieve risk factor targets in WASID appeared to have important clinical consequences as post-hoc analyses showed that patients with poorly controlled blood pressure and elevated cholesterol during follow up had higher rates of recurrent stroke and other vascular events[3]. This raised the question whether aggressive management of

vascular risk factors might substantially reduce the risk of stroke in patients with intracranial atherosclerosis.

However, at that time, despite the fact that SPARCL[10] and PROGRESS[11] showed a benefit of risk factor control for stroke prevention, an aggressive approach to risk factor control in patients with stroke-related atherosclerosis was not being incorporated into clinical trials. For example, modern carotid revascularization studies[12, 13] placed little emphasis on risk factor control in their design and therefore had little impact on blood pressure and cholesterol measures at 1 year. On the other hand, the COURAGE trial demonstrated that among patients with stable coronary artery disease (CAD), intensive risk factor management alone was as good as endovascular intervention plus intensive medical management in preventing cardiac ischemic events, suggesting that a similar approach to patients with atherosclerotic stroke might be feasible[14]. So with the evidence from WASID that showed that poorly controlled vascular risk factors were associated with a higher risk of stroke and without a trial to date that had explored the use of a multimodal aggressive risk factor approach for stroke prevention as a primary treatment strategy, the stage was set for inclusion of aggressive management of vascular risk factors in the "Stenting and Aggressive Medical Management for Prevention of Stroke in Intracranial Stenosis (SAMMPRIS)" trial.

SAMMPRIS was a Phase III randomized, multicenter trial funded by NINDS in which eligible patients were randomized at 50 sites to aggressive medical therapy alone or percutaneous transluminal angioplasty and stenting (PTAS) using the Wingspan stent system plus aggressive medical therapy[15]. The main eligibility criteria included transient ischemic attack (TIA) or non-disabling stroke within 30 days prior to enrollment caused by 70–99% stenosis of a major intracranial artery. The primary outcome was stroke or death within 30 days after enrollment (or after a revascularization procedure for the qualifying lesion performed during the follow up period) or stroke in the territory of the qualifying artery beyond 30 days. Aggressive medical therapy included aspirin 325mg/day during the entire follow up period, clopidogrel 75mg/day for 90 days after enrollment, and aggressive risk factor management primarily targeting systolic blood pressure (SBP) ≤140mmHg (≤130mmgHg if diabetic) and low-density lipoprotein cholesterol (LDLc) <70mg/dL. The study neurologist and coordinator at each site implemented risk factor management for both primary and secondary targets (primary: LDLc, SBP; secondary: non-HDLc, hemoglobin A1c (HbA1c), smoking, weight management, physical activity) and were assisted by an evidence-based, educational, lifestyle modification program (INTERxVENT) that was administered at regularly scheduled times to all patients throughout the study[16].

SAMMPRIS began recruitment in November 2008, but the National Institute of Neurological Disorders and Stroke (NINDS) stopped SAMMPRIS enrollment early based on a recommendation by the independent Data Safety Monitoring Board on April 5, 2011 after 451 patients were enrolled. This decision was due to the higher than expected rate of periprocedural stroke and death risk in the stenting arm and the lower than expected stroke rate in the medical arm[15]. The 30-day rate of stroke or death was 14.7% in the PTAS group (nonfatal stroke, 12.5%; fatal stroke, 2.2%) and 5.8% in the medical-management group (nonfatal stroke, 5.3%; non–stroke-related death, 0.4%) (P=0.002). Beyond 30 days, stroke in the same territory occurred in 13 patients in each group. The probability of the occurrence of a primary end-point event over time differed significantly between the two treatment groups (P=0.009), with 1-year rates of the primary end point of 20.0% in the PTAS group and 12.2% in the medical-management group.

Compared to similar patients treated with usual management of risk factors in the WASID trial, patients in the medical management group in SAMMPRIS had substantially better risk factor control and reduction in early stroke risk. In SAMMPRIS, within the first 30 days,

mean SBP decreased by over 5 mm Hg and mean LDL decreased by over 20 mg/dL, with both of these primary risk factor measures continuing to improve at 1 year[16]. Improvements in secondary risk factor targets were also seen, with significantly better control of non-HDL cholesterol and HbA1c, weight loss, improved exercise, and smoking cessation compared to baseline[16]. Among WASID patients who met the SAMMPRIS entry criteria and were treated with usual management of risk factors and aspirin or warfarin, the stroke and death rate was 10.7% at 30 days and the primary endpoint was 25% at 1 year, whereas the stroke and death rate in the aggressive medical management arm of SAMMPRIS was 5.8% at 30 days with a primary endpoint of 12.2% at 1 year[15]. Although historical comparisons between WASID and SAMMPRIS patients do not prove that the SAMMPRIS aggressive medical management strategy improved outcomes, these improvements in risk factor control very likely contributed to better-than-expected outcomes in the medical management arm of SAMMPRIS.

The SAMMPRIS aggressive medical management strategy has been criticized for not being 'real world'[17]. However, the primary and secondary risk factor targets used in SAMMPRIS are consistent with recommendations by National guidelines for stroke patients[18]. Furthermore, the medications recommended for risk factor control in SAMMPRIS (statins and antihypertensives) are commonly used and widely available and the medication-titration algorithms for the primary risk factors were largely implemented by the study coordinators. Additionally, the use of a lifestyle modification program in SAMMPRIS is similar to the use of cardiac rehabilitation programs by patients with CAD in "real-world" practice. Finally, a single-center study of 22 patients with an ischemic stroke or TIA secondary to 50–99% intracranial stenosis also showed that SAMMPRIS medical management could be implemented in a real practice [19].

Endovascular/Surgical Therapy

Given the high risk of recurrent stroke on medical therapy shown in WASID combined with the perceived successful prevention of recurrent events in patients with CAD who underwent endovascular and surgical treatments, endovascular and surgical therapies began to emerge as a treatment option for patients with ICAD. Initial reports of surgical treatment for intracranial stenosis or occlusion were described in the 1970s[20, 21] and endovascular treatment was reported in 1980[22].

Surgical therapy for stroke prevention in ICAD has been explored for both anterior and posterior arterial stenosis and occlusion. The potential efficacy of surgical bypass for carotid occlusive disease has been studied two large randomized trials. The EC/IC Bypass trial randomized 1377 patients with symptomatic extracranial carotid occlusion, distal carotid occlusive disease, or middle cerebral arteries (MCA) stenosis to best medical care (typically aspirin 325mg QID and blood pressure control) versus medical care plus extracranial-intracranial anastomosis surgery (attaching the superficial temporal artery and the middle cerebral artery)[23]. Stroke occurred earlier and more frequently in the surgery group during the mean follow-up of 55.8 months and patients with MCA stenosis actually did worse with the surgery than with medical therapy. The Carotid Occlusion Surgery Study (COSS) attempted to improve patient selection for EC/IC bypass by targeting patients with carotid occlusion and recent hemodynamic ischemic symptoms, but was terminated after enrollment of 195 patients due to futility[24]. The primary endpoint was any stroke or death within 30 days or ipsilateral stroke within 2 years, which occurred in 21.0% of patients in the surgical group and 22.7% in the non-surgical group. Regarding posterior circulation stenosis or occlusion, there are small case series and reports of surgical bypass for vertebrobasilar disease, but this approach has not been systematically studied[25–27].

While direct bypass of intracranial stenosis has been unsuccessful for stroke prevention, encephaloduroarteriosynangiosis (EDAS) is another surgical procedure designed to deliver flow beyond an intracranial stenosis. With EDAS, indirect revascularization is achieved by a network of collaterals forms between the donor artery and the adjacent brain vessels without a surgical anastomosis. In a small study of 13 patients with intracranial stenosis who had failed medical management, 85% of patients had complete resolution of ischemic symptoms over a median follow-up of 54 months[28].

Angioplasty alone has been reported in many retrospective studies, but the 30-day rate of stroke or death has varied widely (4% to 40%)[29], with restenosis rates after angioplasty between 24% to 50%[30–33]. A review in 2006 included 79 reports with at least 3 cases of angioplasty treatment for intracranial stenosis and found an overall periprocedural stroke or death rate of 9.5% (95% CI 7.0% to 12.0%)[34]. Another retrospective series of 4 centers and 74 patients showed a 30-day stroke and death rate of 5% (95% CI, 1.5% to 13%) and a 3 month stroke or death rate of 8.5% (95% CI, 3.1% to 17.5%)[35]. Angioplasty is technically easier to perform than stenting but disadvantages include high risks of acute intimal dissection, vessel rupture, immediate vessel recoil and poor post procedure residual stenosis[36].

Percutaneous Angioplasty and Stenting was initially performed using stents designed for the coronary vasculature and used off-label to treat intracranial atherosclerosis. The first multicenter, non-randomized prospective trial using a balloon expanding bare metal stent, Neurolink, was Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (**SSYLVIA**). Of the 61 patients enrolled, 43 had ICAD. In the first 30 days, 4 patients (6.6%) had strokes and no deaths occurred. Beyond 30 days to 1 year, the stroke rate was 7.3%. There was a restenosis rate of 35% and 39% of those patients with restenosis were symptomatic.[37]

More recently, the Vitesse Intracranial Stent Study for Ischemic Therapy for Symptomatic Intracranial Stenosis Trial (VISSIT) explored the use of a balloon-mounted stent for preventing stroke in patients with high-grade symptomatic stenosis (≥70%)[38]. The investigators evaluated the safety and efficacy of the Pharos Vitesse stent plus medical therapy versus medical therapy alone. Medical therapy included clopidogrel 75mg for 90 days after enrollment and aspirin 81mg or 325mg/day for the duration of the study. The medical therapy included statin therapy to achieve an LDLc ≤ 100mg/dL, antihypertensive medication, smoking cessation and diet modification. Clinical follow-up was performed at 30 days, 90 days, 180 days, and 1 year. The stenting group was also required to undergo a 1-year follow up digital subtraction single vessel angiography to assess for in-stent restenosis. Primary endpoints of the study were stroke in the same territory as the presenting event within 12 months of randomization and “hard TIA” in the same territory as the presenting event from day 2 through 12 months post randomization. Secondary endpoints included technical success, in-stent restenosis and comparison of NIHSS and mRS between the treatment arms. Enrollment in VISSIT was stopped early but final results are still pending.

The only FDA approved stent for ICAD is the Wingspan self-expanding Nitinol stent. The Gateway balloon-Wingspan stent system was designed specifically for the cerebral vasculature and became commercially available in 2005 after its approval under a humanitarian use device exemption (HDE) for “treatment resistant intracranial atherosclerotic disease” with ≥ 50% narrowing in the intracranial arteries. A HDE is intended to treat or diagnose a disease or condition that affects fewer than 4000 people in the United States per year[39]. The initial study that led to FDA approval was a study of 45 patients with 50–99% stenosis. The technical success rate was 98.8% and the 30-day stroke

and death rate was 4.5%. The 6 month stroke rate was 9.7% and all-cause mortality was 2.3%[40].

After FDA approval, 2 large registries, the US Wingspan Registry[41] and the NIH Wingspan Registry[42] reported data on the use of this stent in the US. The US Wingspan Registry initially tracked patients at 4 US centers that received percutaneous transluminal angioplasty (PTAS) and stenting with the Gateway-Wingspan system for the treatment of symptomatic stenosis due to 50–99% intracranial stenosis. Of the 82 lesions treated, there were 5 (6.1%) major periprocedural neurological complications, 4 of which ultimately led to patient death within 30 days of the procedure[41]. As follow-up continued and more patients were added to the registry, the restenosis rate increased to almost 30%, although most patients had asymptomatic restenosis [43]. The NIH Wingspan registry limited collection of data to patients with 70–99% symptomatic intracranial stenosis. Sixteen centers participated and compiled data on 129 patients. The frequency of any stroke, intracerebral hemorrhage, or death within 30 days or ipsilateral stroke beyond 30 days was 14.0% at 6 months (95% CI = 8.7% to 22.1%). The restenosis rate on follow-up angiography was 13/52 (25%)[42]. These registries suggested that the compared to patients with 70–99% stenosis treated with usual medical therapy in WASID, PTAS with Wingspan might be a safe, more effective option for stroke prevention. However a randomized trial was needed to compare PTAS to medical management which led to initiation of the SAMMPRIS trial.

The early results of SAMMPRIS have been discussed above. At the time enrollment was stopped, stroke or death within 30 days occurred in 33 patients in the stenting group and in 13 patients in the medical therapy group (14.7% vs 5.8%, p=0.002). The number of events in both arms of the trial beyond 30 days was similar but follow-up in SAMMPRIS continued until April 2013 and the final outcome analyses are expected later this year.

In an effort to understand the high periprocedural stroke and death rate in SAMMPRIS, analyses of these early events in the PTAS arm have been performed. The majority of periprocedural ischemic strokes were perforator occlusions and the symptomatic hemorrhages were a roughly equal mix of ICH and SAH[44]. Similar to previous retrospective reports[45, 46], perforator occlusions in the PTAS arm in SAMMPRIS were seen more commonly in the treated basilar arteries[47]. Multivariate analyses showed that factors associated with periprocedural hemorrhagic stroke were a higher percent stenosis, lower modified Rankin score, and clopidogrel load associated with an activated clotting time above the target range, whereas, factors associated with ischemic stroke were nonsmoking, basilar artery stenosis, diabetes, and older age[44]. Operator inexperience or inadequate credentialing of interventionists was not associated with an increased risk of periprocedural complications, as interventionists with more experience (i.e. more than 10 Wingspan cases submitted for credentialing prior to study entry) tended to have higher rates of 30 day events (19.0% vs 9.9%) than those with less experience (less than 10 Wingspan cases submitted for credentialing) [48]. However, higher enrolling sites in SAMMPRIS tended to have lower rates of hemorrhagic stroke (9.8% at sites enrolling <12 patients vs 2.7% at sites enrolling >12 patients).

While some have argued that the periprocedural complication rate in SAMMPRIS was unexpectedly high, several non-randomized case series and registries using the Wingspan stent have been reported since the SAMMPRIS trial started in 2008 and have also shown periprocedural complication rates similar to the 14.7% rate in SAMMPRIS. A small series of 27 patients treated with Wingspan reported in 2009 had a complication rate of 14.8%[49], a series of 17 patients treated with Wingspan reported a 30 day stroke and death rate of 17.6% in 2010[50], another series of 30 patients with vertebrobasilar disease treated with Wingspan had a 30 day complication rate of 10% reported in 2011 [51], and finally another study of 63

intracranial stenoses treated with Wingspan reported a procedural complication rate of 20% in 2011 [52]. These studies suggest that the periprocedural complication rate seen in SAMMPRIS was well within the range of other contemporary reports of periprocedural complications from Wingspan.

In March 2012 the FDA convened an advisory panel to discuss continuation of the HDE for the Wingspan stenting system in light of the SAMMPRIS results. Additional restrictions for the use of Wingspan under the HDE were implemented by the FDA, which include limiting use to patients with 70–99% stenosis and "a very specific group of patients with severe intracranial stenosis and recurrent stroke despite continued medical management [who] may benefit from use of the device," although the definition of "despite continued medical management" is not clearly defined. Moreover, the concept of "failure of medical therapy", or recurrent stroke or TIA while on an antiplatelet agent or antithrombotic agent, has not been shown to confer a higher risk of recurrent stroke and may therefore not be a good criteria for selecting patients for the procedure. A WASID analysis compared the recurrent stroke risk between patients who were on antithrombotic agents at the time of their stroke or TIA that qualified them for enrollment vs. those who were not on antithrombotic agents and found no difference in the recurrent stroke risk [53]. A similar preliminary analysis in SAMMPRIS showed the same result[54].

Given that there are multiple mechanisms of stroke due to ICAD (e.g. atherosclerotic plaque extension over the ostia of a perforating artery (branch atheromatous disease)[55], thrombus formation at the site of stenosis with distal embolization (artery-to-artery embolization), or hypoperfusion to areas supplied by the stenotic artery with poor collateral flow), it is tempting to argue that the optimal treatment for stroke prevention in patients with ICAD should focus on the mechanism of stroke. For example, one could argue that stroke due to artery-to-artery embolization from plaque rupture may be best treated with antiplatelet agents and statins, whereas stroke due to hypoperfusion may be best treated with revascularization. However, predicting the mechanism of the potential recurrent stroke from the prior stroke is not always clear-cut. A WASID post-hoc analysis showed that compared to patients who presented with non-lacunar strokes at study entry, patients who presented with lacunar strokes were not more likely to have lacunar strokes during follow-up[56]. This suggests that the mechanism of the index stroke does not necessarily predict the mechanism of a subsequent stroke. However, more studies are needed to better understand the pathophysiology of ICAD and potential to design prevention strategies specifically to each patient.

Conclusion

In summary, patients with symptomatic ICAD still have a relatively high risk of recurrent stroke compared to other causes of stroke. However, aggressive medical management can safely and effectively reduce the risk of recurrent stroke in the vast majority of patients. Further studies are needed to determine subgroups of patients that may do poorly despite aggressive medical management and to explore novel treatments for these high-risk patients.

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