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Intracranial Atherosclerosis: The Natural History and Management Strategies

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Abstract

Intracranial atherosclerotic disease (ICAD) represents a major cause of stroke and transient ischemic attacks. The prevalence and natural course of ICAD are closely related to race and ethnicity. The best treatment for ICAD is a crucial issue; data from recent trials indicate that aggressive medical management and life style modifications are better than endovascular treatments for prevention of recurrent stroke in high-risk patients with ICAD. Endovascular treatment is still an option for subgroup of patients who are not responded to optimal medical therapy.

Keywords

Intracranial Atherosclerosis, Medical Therapy, Endovascular Treatment

1. Introduction

Stroke is one of the global leading causes of death and disability as confirmed by many epidemiological studies [1]. Intracranial cerebral atherosclerosis accounts for approximately 8% - 10% of all ischemic strokes with a higher reported incidence in the Asian, African, and Hispanic descent populations [2]. Ethnicity accounts for significant variation in the incidence of the disease in symptomatic patients, but the effect of ethnicity in asymptomatic patients is not clear [3].

The risk factors for the development of intracranial atherosclerotic disease are broadly classified as non-modifiable (e.g. age, gender); modifiable—which are well documented—(e.g. hypertension, total serum cholesterol); and potentially modifiable factors—which are less well documented—(e.g. diabetes mellitus, metabolic syndrome) [4].

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Patients with intracranial atherosclerosis are classed as symptomatic or asymptomatic. The annual stroke risk in patients with intracranial atherosclerosis is estimated to be 3.6% - 13% annually, with a first year ischemic stroke rate in the pertinent vascular territory of at least 11% [5]. Patients who experience a stroke or transient ischaemic attack due to a stenosis of 50% - 99% have traditionally been treated with antithrombotic medication. Even with this treatment there remains a 12% - 14% risk of further stroke in the subsequent 2 years, increasing to 20% in at-risk individuals [4]. Trials comparing antithrombotic medications with anticoagulants for prevention of stroke or vascular events have not generated satisfactory results and, worse still, have been associated with high rates of bleeding [5].

Intracranial angioplasty (with or without a stent) was developed as a treatment option for patients with symptomatic intracranial atherosclerotic disease. Early intracranial angioplasty techniques used balloons, followed by balloon-mounted intracranial stents [6], but this was associated with high technical failure rates. In 2005, the Wingspan™ stent system with Gateway™ percutaneous transluminal angioplasty balloon was approved by the US Food and Drug Administration for the treatment of intracranial atherosclerotic disease with >50% stenosis [7].

Intracranial stent-assisted intervention is associated with several complications, including the formation of blood clots, thromboembolism, vascular rupture, dissection and re-narrowing in the long-term [8]. The reported risk of stroke and death during the procedure itself varies between 0% and 30%. These complications risk prompted this systematic review of the available literature to determine the effectiveness of intracranial angioplasty with stenting for treatment of intracranial atherosclerosis.

2. Intracranial Atherosclerotic Disease (ICAD)

2.1. Natural Course and Clinical Prognosis

The natural history of stenosis secondary to intracranial atherosclerosis has been angiographically studied by Akins *et al.* [9]. Over a follow-up period of more than 2 years, they found an increase in the degree of stenosis in the MCA-ACA-PCA group, whereas intracranial ICA stenoses remained stable with a 14% regression in intracranial ICA stenosis and a 28% regression in the MCA-ACA-PCA group. Accordingly, they concluded that intracranial lesions are dynamic and may progress or regress with time.

Many studies were conducted [10] [11] evaluating the effect of cilostazol and clopidogrel in intracranial atherosclerosis, a total of 14% of patients demonstrated lesion progression. The risk of future ischemic strokes depends on whether the vessel is asymptomatic or symptomatic. This difference has been well studied in the WASID trial (Warfarin vs. Aspirin for Symptomatic Intracranial Disease) [5], where patients recruited in the trial, though symptomatic, also had asymptomatic stenoses in other arteries. When these patients were followed up, the 1-year risk of developing a stroke in the territory of these asymptomatic vessels was 3.5% (CI 0.8% - 9%). In contrast to this, patients with ≥70% stenosis had a risk of 14% at one year for a stroke in the same territory and 19% for stroke in any vascular territory.

Apart from severity of stenosis, recent symptoms and female gender also predicted risk of stroke recurrence in this study [12]. A similar risk rate of 14% was reported from the GESICA (Grouped' Etude des Sténoses Intra-Crâniennes Athéromateusessymptomatiques) study [13]. A WASID sub study [14] has identified that the presence of collaterals is a strong predictor of subsequent stroke in case of moderate-to-severe stenosis, but milder stenoses are more unstable.

2.2. Pathophysiology, Clinical and Radiological Presentation of ICAD

2.2.1. Intracranial Arterial Steno-Occlusion

Intracranial atherosclerotic disease could be asymptomatic or presents with ischemic strokes and transient ischaemic attacks (TIA). Several proposed mechanisms could be behind this ischemia which includes artery-to-artery embolism, local branch occlusion, hemodynamic compromise resulting from progressive arterial narrowing, or a combination of these factors [15]. The radiological presentations of these strokes include cortical infarctions, watershed infarctions [16] and lacunes [17].

Progressive reduction in flow due to progressive narrowing of the large atherosclerotic arteries leads to gradual formation of leptomeningeal collaterals. When the compromise reaches a stage when these collaterals are insufficient to maintain perfusion to the terminal areas, infarctions develop in border zone territories [18]. Both internal and cortical border zone infarctions of the MCA territory are reported in literature to result from ICAD [19].

Reduction of regional cerebral blood flow is identified in the presence of high-grade stenosis and contributes both to the occurrence and magnitude of ischaemic injury [20].

Lacunar infarctions identified in 10% - 19% of patients are most often located in the pons followed by the corona radiata or centrum semiovale regions [21].

Clinical presentation includes cortical function impairments such as aphasia, neglect, and hemianopsia in almost half of patients with cortical and large subcortical infarctions. In the remaining patients, signs of isolated motor or sensory deficits predominate, in association with lacunar and small subcortical infarctions [22].

2.2.2. Intracranial Arterial Dolichoectasia (IADE): The Hidden Convict

Symptomatic intracranial atherosclerosis, not only could cause stroke via different mechanisms related to the steno-occlusive pathology but it could be associated with stroke related to intracranial arterial dolichoectasia (IADE); the other ICAD fingerprint as well. Approximately one patient in eight who has brain imaging has some increase in the length and diameter of intracranial arteries [23].

IADE has been found in 12% of stroke patients [24]. IADE may be asymptomatic, or it may be associated with clinical manifestations such as stroke, subarachnoid hemorrhage, cranial nerve palsy, compression of the midbrain, or obstructive hydrocephalus [25].

Regarding IADE haemodynamic changes; the process of marked elongation, widening, and tortuosity of arteries is termed dilatativearteriopathywhere intracranial vertebral and basilar arteries are preferentially affected. This type of angiopathy is characterized by an abnormally enlargement of the external diameter and thinning of the arterial wall, with degeneration of the internal elastic lamina leading to multiple gaps in the internal elastica, and thinning of the media secondary to reticular fiber deficiency, and smooth muscle atrophy [26].

Bidirectional flow changes in dilated arteries can reduce the antegrade flow and can results in thrombus formation. Additionally, elongation and angulations of arteries can impair blood flow especially in the penetrating branches due to stretching and distortion of the orifices of the arterial branches [26].

The prognosis for patients with dolichoectasia is highly variable, ranging from benign to malignant. In one study, dolichoectasia progressed in 43% of patients, and occurred more frequently in younger patients and those with anterior circulation involvement. Overall, there is a high frequency of recurrent events. One study of 93 patients over 11 years found that 60% had at least one clinical event, of which ischemic strokes comprised 80% [26].

2.3. Counting the Facts for ICAD Management from Reviewing of Current Studies

2.3.1. Review of Medical Therapy

1) Medical treatment for intracranial arterial steno-occlussion

Patients with symptomatic intracranial large artery stenosis >50% treated either with aspirin or warfarin were evaluated for success of medical therapy in the first WASID trial in a retrospective manner [5]. Where during a mean follow-up of 14.7 months in the warfarin-treated group, there was an 8.4% stroke or death rate, and in the aspirin treated group there was an 18.1% rate of major stroke or death, with 9% stroke in the same vascular territory.

Based upon these data, a second pivotal trial was subsequently performed. The multi-center, randomized, double-blind NIH-sponsored WASID trial was performed from 1998-2003 where the trial was prematurely halted due to concerns about the safety of the patients who had been assigned to receive warfarin [5].

In this trial because of the higher adverse event rates (stroke and death), higher symptomatic hemorrhage rate for patients treated with warfarin, and lack of therapeutic benefit of warfarin over aspirin for prevention of ischemic stroke secondary to intracranial stenosis, it was concluded that aspirin should be used in preference to warfarin for patients with intracranial arterial stenosis. However, the most important message was neither therapy offered acceptable protection from stroke.

The WASID authors concluded that "these data indicate that intracranial stenosis is a high-risk disease for which alternative therapies are needed" [5].

After results of the SAMPRIS trial; the aggressive medical therapy (AMT) is considered as the first choice, beside life style modifications, for treatment of symptomatic ICAD. The trial adopted the following strategy, Aggressive medical treatment consisted of aspirin 325 mg daily plus clopidogrel 75 mg daily for 90 days, intensive management of vascular risk factors (primarily targeting systolic blood pressure <140 mmHg and <130 mmHg if diabetic, as well as LDL (<70 mg/dl), and provision of a lifestyle modification program [58].

2) Medical treatment for intracranial arterial dolichoectasia (IADE)

Treatment of dolichoectasia remains uncertain. Antiplatelet or anticoagulant treatments have limited effectiveness, perhaps due to multiple stroke mechanisms other than atherosclerosis. In one prospective study, patients who initially presented with ischemia or other symptoms due to vertebrobasilar dolichoectasia and who were treated with antiplatelets or anticoagulants had a higher incidence of hemorrhage [27]. Further study is needed to assess the risks and benefits of antiplatelet or anticoagulation treatment for vertebrobasilar dolichoectasia. Caution is advised in giving antiplatelets or anticoagulants to vertebrobasilar dolichoectasia patients who present with symptoms other than ischemia (e.g., hemifacial spasm or cranial nerve deficits).

2.3.2. Intracranial Angioplasty and Stenting (Endovascular Treatment of ICAD)

1) Primary Intracranial Angioplasty

The earliest reports of angioplasty for intracranial atherosclerosis using coronary balloon were reported, a large number of individual series of cases were consequently published in literature with technical success rates exceeding 90%, with clinical complication rates ranging from 0% - 20% [28]-[32].

Sundt *et al.* [33] first reported angioplasty for treatment of symptomatic intracranial stenosis. Early studies reported a 33% complication rate in the form of intraprocedural vessel rapture, vasospasm, dissection or death [34]. Subsequent studies have reported less than 50% residual stenosis with few complication rates in retrospective case series [35].

Marks *et al.* reported 23 patients with symptomatic ICAD treated by Percutaneous Transluminal Angioplasty (PTA) which resulted in reduced stenosis in 21 of 23 patients. In one patient crossing of the lesion failed and the other patient died as a result of vessel rupture from ballondilation. Three years follow-up after the procedures showed annual stroke rate of 3.2% [35].

Conners and Wojak reported overall good angiographic and clinical outcomes in 98% of transluminal angioplasty procedures performed upon 70 patients with ICAD along a period of 9 years [36].

Callahan and Berger conducted a study on 15 patients with ICAD related stroke who had failed warfarin therapy. Dilation was successful in all vessels with residual stenosis averaging <30% however, one patient died secondary to vessel rupture and another patient suffered pontinestroke secondary to perforator compromise and another diedfrom ICH after perforation by the guidewire [34].

Nahser *et al.* reported 20 patients with vertebrobasilar stenosis treated with PTA with success rate was 86%.One patient had an ischemic stroke during the procedure [37]. Within 3 - 18 months follow-up a 14% rate of restenosis was encountered.

Marks *et al.* reported retrospectively on their experience of treating a cohort of patients all had neurological symptoms on medical therapy with 37 symptomatic atherosclerotic intracranial stenotic lesions by PTA [38]. They achieved a decline in the mean stenosis from 84.2% to 43.3% after treatment with periprocedural stroke and death rate 8.3%. The annual stroke rate in the territory of the treated lesion was 3.4% and in the subset of patients with >50% residual stenosis, it was 4.5%.

The long-term clinical benefit of endovascular therapy for intracranial atherosclerosis is studied by Wojak *et al.* [36]. The authors performed Angioplasty alone in 62 procedures, while 22 procedures involved intracranial stenting with overall complication-free procedural success rate of 90.5%. The periprocedural stroke or death rate was 4.8%. Angiographic restenosis occurred in 23 lesions at a mean of 4.6 months; 13 were re-treated without complication. The annualized stroke rate in the treated vascular territory was 1.8%, and the annualized stroke and death rate was 3.0%.

Feasibility of the procedure was confirmed in many in the above mentioned descriptive studies though it carries a significant morbidity and mortality risk in the form of periprocedural complications such as vessel occlusion, immediate elastic recoil, dissection of the artery, and higher restenosis rates.

Additionally, extrapolating the vast amount of data from the coronary literature has rendered balloon angioplasty alone may be inferior compared to angioplasty with stenting. However, that being said the two modalities have not been compared head to head prospectively. Evidence could be extracted from randomized controlled trials assessing the safety and effectiveness of both procedures in preventing recurrent stroke.

2) Intracranial Angioplasty and Stent Placement

Three types of stents are available and already experienced in a lot of ICAD treatment trials; balloon expandable bare metal stents (BEBMS), drug-eluting balloon expandable stents, and self-expanding stents. From the technical point; these stentscould be divided into those primarily designed for the coronary vasculature or those that have

been designed for intracranial one.

Frequent dissection complicating Primary angioplasty without stent placement was recorded in initial series [39]-[44]. However, many of the coronary BEBMS stents were rigid making them difficult to navigate into the intracranial circulation. They were the only available stents at that time to be used in an acute vessel dissection after angioplasty of an ICAD lesion [45].

For fairness, some of them were found to be flexible enough to track into the intracranial vasculature like; Gianturco-Rubin-2 stent [46], Palmaz-Schatz stent [45], and the Arterial Vascular Engineering stent series which included the AVE S670 stent and Guidant Tetra multilink stent. However, with highly flexible BEBMS, some difficulties of navigation could hinder the success achievement of the procedure like in series published by Mori *et al*. [47].

Yu *et al*. reported the outcomes of stenting for symptomatic basilar artery stenosis (79.6% ± 11.7%) over a 4-year period [48]. There were 11.1% neurological complications but no deaths. At a mean follow-up of 26.7 months, 83.3% had excellent long-term functional outcome with 55.6% being asymptomatic, although 27.8% experienced several minor episodic symptoms without disability.

Gomez *et al*. reported near similar results upon 12 patients undergoing elective stenting for symptomatic basilar artery stenosis, with a 100% technical success [49].

Mazighi *et al*. treated 69 intracranial arterial lesions with coronary BEMBS [50] in retrospectively reexamined 53 consecutive symptomatic patients. A success rate of 98.6% was achieved, with a reduction of the median percent stenosis from 85 to 0%. Stents were used in 76.8%. Death or stroke rate was 10.1% with one death during theperiod of follow-up of 30 days.

In SSYLVIA study (The stenting of symptomatic atherosclerotic lesion in the vertebral or intracranial arteries) the NEUROLINK System (Guidant Corporation)—specifically designed for navigating intracranial vasculature —was used in forty-three patients with intracranial arteries and 18 patients with extracranial vertebral arteries. 6.6% was the rate of occurrence of ischemic strokes while no deaths during the first 30 days follow up. While after 30 days, 7.3% of patients had recurrent strokes [51].

The NEUROLINK system was not marketed even past the trial. However, this trial provided valuable data about the safety of stenting in the treatment of ICAD. Since The NEUROLINK system discontinuation until very recently there were no other BEBMS for ICAD. However, most recently, Micrus Corporation® (San Jose, CA, USA) has designed the Pharos Vitesse Chrome Cobalt BEMS that is under study in Europe [52].

3) Drug-Eluting Stents (DES)

DES is designed to have a coating of antiproliferative drug that inhibits neointimal hyperplasia like in the coronary vasculature some centers have employed its use to treat ICAD. Pacilitaxel-coated stents were used to treat series of cases with symptomatic posterior circulation stenosis with 7.7% periprocedural stroke. The study reported 69.2% free in-stent stenosis during a mean period of follow up of about 6 months [53]. Qureshi *et al.* by using DES in treating series of symptomatic ICAD patients (≥70% or failed medical management), he achieved a major stroke-free survival of 86%, with only 5.5% symptomatic angiographic restenosis during the follow-up period of 12 months [54]. Similarly Abou-Chebl *et al*. [55] and Gupta *et al*. [56] showed feasibility and safety by treating symptomatic lesions with DES with lesser in-stent restenosis during the period of follow-up. The previous DES studies used first generation stents with sirolimus or paclitaxel.

While recently Natarajan *et al*. reported their experience in treating symptomatic ICAD using a second generation DES that has greater deliverability [57]. In this study, The Xience V everolimus-eluting stent (Abbott Vascular) was placed in six patients with >70% stenosis with average stenosis reduction from 83% to 6%, one periprocedural ICH (Intracerebral haemorrahge) was reported and 83.3% of the cases followed up for about 6 months without in-stent restenosis.

More studies are required to confirm the safety and effectiveness of DES in the intracranial vasculature. The ongoing concerns with DES are the need for prolonged use of dual antiplatelet therapy with aspirin and clopidrogel which may increase the risk of hemorrhage especially in the brain and late restenosis.

4) Self-Expanding Intracranial Stents

The year of 2011 was disappointing forneuro-interventionists interested in cerebral revascularization to prevent stroke from intracranial atherosclerotic steno-occlusive disease. Specially after the results of the Stenting and Aggressive Medical Therapy for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study [58].

High recurrent stroke risks in patients with symptomatic intracranial stenosis were the driving force for device

development for treatment [59]. Wingspan (Boston Scientific, Natick, MSA, USA), a self-expandable stent, was developed for this purpose with improved flexibility and trackability with a reasonable safety profile [60] [61].

SAMMPRIS was an investigator-initiated randomized, controlled, blindly adjudicated multi-center clinical trial to test whether early angioplasty and stenting can reduce subsequent ischemic stroke risk in patients with symptomatic severe stenosis of a major intracranial artery.

Aggressive medical management in both arms consisted of aspirin 325 mg daily for the entire follow-up, clopidogrel 75 mg daily for 90 days, intensive management of vascular risk factors (primarily targeting systolic blood pressure <140 mmHg and <130 mmHg if diabetic, as well as LDL <70 mg/dl), and provision of a lifestyle modification program.

The target sample size was 372. Enrolment within 30 days of symptoms was intended to maximize possible stroke reduction during the high-stroke-risk period. SAMMPRIS recruitment was halted in April 2011 by the United States National Institute of Neurological Disorders and Stroke (NINDS) for the significantly higher 30-day rate of stroke or death in the stenting arm as compared to the aggressive medical management alone arm (14% vs. 6%) [62] [63].

The 30-day rate of stroke or death in the aggressive medical management alone arm was lower than historical controls, while the 30-day rate of stroke or death in the stenting arm was higher than previous registry data [34]. The subsequent stroke risks were similar at last follow-up [63]. Higher 30-day rate of stroke or death in the stenting arm was thought to be related technical aspects of the Wingspan stent system (WS System) and lack of an angioplasty with stent placement, in addition, the inappropriate selection of patients, may have led to early termination of the study. Future randomized trials with different devices and modified patient selection criteria are warranted. Another similar single-center trial is ongoing with a target sample size of 200 in Hong Kong [64].

2.3.3. Surgical Revascularization—EC/IC Bypass Trial

Researches into hemodynamic factors have shed light on the pathogenesis of the strokes caused by haemodynamicischaemia identified different stages of cerebral hemodynamic failure.

Stage I refers to autoregulatory vasodilatation which maintains a constant cerebral blood flow but with reduced responsiveness of cerebral blood flow to a vasodilatory stimulussuch as hypercapnia or acetazolamide. Stage II is indicated by increases in regional oxygen perfusion, which is also known as misery perfusion. Stage II hemodynamic failure correlates withmarkedly elevated stroke risk and formed the basis to further evaluate surgical revascularization in new randomized trials targetingthis patient subgroup [65]. The year 2011 carried more disappointing news for neurosurgeons who are interested in revascularization of steno-occlusive pathology. After the results of the COSS (Carotid Occlusion Surgery Study) [66], where Extracranial-intracranial (EC-IC) bypass for intracranial atherosclerotic steno-occlusive diseases and its indications have undergoneintense scrutiny and re-evaluation after the negative results of the initial EC-IC Bypass Study published in the New England Journal of Medicine in 1985 [67]. Subsequent efforts have focused on identifying patients at high risk of subsequent stroke after carotid occlusion, withthe hypothesis that stroke risk reduction in patients with highstroke risk will outweigh the procedural risks of EC-IC bypass.

COSS was a randomized, controlled, blindly adjudicated multi-center clinical trial designed to determine whether surgical revascularization can reduce subsequent ischemic stroke in high-stroke-risk patients with symptomatic internal carotid artery occlusion (SICAO) with corresponding stage II cerebral hemodynamic failure. Surgical revascularization is achieved by anastomosis of the superficial temporal artery to the middle cerebral artery. Their target sample size was 372. The results were presented in February 2011 [42] [68]. COSS recruitment was stopped by the Data Safety Monitoring Board in June 2010 as the pre-defined boundary for declaring futility was crossed. One hundred ninety-five subjects were randomized.

Analysis of the 142 subjects who had been followed for two years confirmed that the two-year stroke recurrence rates were 21% and 23% for the surgical group and the medical therapy alone group respectively ($p = 0.88$, log-rank test).Graft patency rate at last follow-up was 96% [68]. The lack of benefit is attributed to better stroke prevention in the medical group as compared to historical controls.

The COSS study with no doubt is definitely an important landmark study in cerebral revascularization. A pivotal question has been answered without the shadow of any bias the study has showed that in spite of hemodynamic improvement and excellent graft patency in patients treated with extracranial-intracranial arterial bypass, there was no benefit in reducing new stroke events when compared with the patients randomized to best medical treatment alone. However a number of questions need to be clarified for neurovascular specialists involved in

the management of symptomatic internal carotid artery occlusion (SICAO).

1) What would be the best treatment option for patients who in spite of maximal medical treatment continue to have symptoms in the form of TIAs or recurrent strokes?

2) What is the underlying mechanism in patient with SICAO shows a clinical perfusion mismatch but continue having symptoms despite restoration of good hemodynamic status following bypass surgery.

3) The study does not address the issue of cognitive impairment either pre or postoperatively in patients with SICAO and whether medical treatment or bypass surgery had a differential impact on improvement or deterioration in patients with such impairment.

4) PET although a very elegant method of determining the cerebral metabolic rate by quantifying regional oxygen consumption, however, using the oxygen ligand for PET still remains expensive and impractical for use as a routine method of investigating patients with SICAO. Further studies need to identify more economical and practical method to stratify patient with SICAO.

3. How the Reading of the Above Mentioned Studies Could Update the Current Position Statement Regarding Intracranial Stenting in ICAD

1) The health care authorities should invest more in preventive strategy by aggressive medical control which of course needs more finances to change both physician and patient orientation.

2) The prevention strategies should involve life style modifications beside "best medical therapy" in patients with intracranial atherosclerotic steno-occlusive diseases.

3) For symptomatic patients with a >50% intracranial stenosis who have failed medical therapy, balloon angioplasty with or without stenting should be considered.

4) Proper selection of patients suitable for surgery or neurointervention is with lower procedural risk. Patients with symptomatic steno-occlusive disease should be differentiated into subcategorical groups according to the pathological mechanisms:

    a) Focal short segment atherosclerotic steno-occlusive disease benefits from balloon angioplasty and/or stenting, if best medical treatment fails.

    b) Patients with perforator syndrome due to branch ostial stenosis harbor higher procedural stroke risk due to plaque shifting into the ostia of the perforators, completing the infarct, thus may derive minimal benefit in terms of future stroke risk reduction, in spite of restoration of flow to the asymptomatic distal territory.

    c) Patients with carotid occlusion with persistent fluctuating symptoms and severe hemodynamic insufficiency should still be considered for the benefit of surgery.

5) Patients with asymptomatic intracranial arterial stenosis should first be counseled regarding the nature and extent of their disease, and then regarding optimizing medical therapy and the impact of controlling risk factors as in SAMPRIS-Fashion on the clinical outcome. They should be monitored for any neurological symptoms, and have periodic non-invasive imaging at regular intervals using transcranial Doppler, magnetic resonance angiography or computed tomographic angiography initially, and then by cerebral angiography if warranted. At a minimum, optimal prophylactic medical therapy should be instituted, which might include antiplatelet and/or statin therapy.

6) Continued evaluation and improvements in both pharmacological and catheter-based therapies, in parallel not competing manner are needed to reduce the stroke burden from intracranial atherosclerosis. Up till now, there is insufficient evidence to make definitive recommendations regarding endovascular therapy in asymptomatic patients with severe intracranial atherosclerosis.

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