

# Intracranial Stenting: A Review of the Literature and Recommended Remedies

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## Abstract

Intracranial arterial stenosis (ICAS) is one of the main causes of ischemic stroke According to western epidemiological studies; 8-10% of ischemic strokes are attributable to intracranial stenosis. Three modalities of treatment considered for intracranial atherosclerotic disease include; aggressive medical therapy, endovascular revascularization with angioplasty and stent, and extracranial-intracranial bypass surgery. At present, medical management should be the first line of therapy for the most patients with symptomatic intracranial arterial stenosis. Angioplasty and stenting can be considered in some patients that are unstable or have multiple ischemic events in the territory despite aggressive medical management. [GMJ.2016;5(Supp.1):36-42]

**Keywords:** Cerebrovascular accident; Stroke; Ischemic; Intracranial arterial stenosis; Angioplasty; Stenting.

## Introduction

Intracranial arterial stenosis (ICAS) is one of the main causes of ischemic stroke According to western epidemiological studies, 8-10% of ischemic strokes are attributable to intracranial stenosis[1, 2].It seems that intracranial stenosis is more common in Asia[3]. Asian patients have a higher proportion of Middle carotid artery (MCA) stenosis and 33% of strokes in China are because of intracranial stenosis[4-6].Considering the population of Asia, intracranial stenosis is the most important cause of stroke in the world [7].

## Diagnosis

The diagnosis of ICAS may be made through several diagnostic procedures including conventional angiography, transcranial Doppler

ultrasound (TCD), magnetic resonance angiography (MRA) and computed tomography angiography (CTA). Conventional angiography is regarded as the gold standard with the advantages of accurate stenosis measurement, differentiation of occlusion from severe stenosis and collateral flow evaluation. Hence, non-invasive neuroimaging techniques may be useful as screening tests, but conventional angiography remains the gold standard for confirming the degree of stenosis [8].

## History

Its natural history is variable.It may progress, regress or remain stable during follow-up.The natural history depends on the location of stenosis and the extent of intracranial atherosclerosis.

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### Location

Distribution of intracranial stenosis, as shown by Comparison of warfarin and aspirin for symptomatic intracranial stenosis (WASID) study [9], is as below:

Internal carotid 20.3%, MCA 33.9%, Vertebral artery 19.6%, Basilar artery 20.3% and Multiple Artery 5.9%.

Patients with more than 70% stenosis are at more risk of developing a stroke in follow-up [10]. Moreover, the possibility of progression of stenosis in lesions of middle cerebral artery, anterior cerebral artery and posterior cerebral artery are more than intracranial internal carotid artery. The risk of annual stroke in symptomatic intracranial stenotic group is significantly more than patients with extracranial stenosis. Recurrent annual stroke rates are estimated at 4–12% per year with atherosclerosis of the intracranial anterior circulation and 2.5–15% per year with lesions of the posterior (vertebrobasilar) circulation.

### Racial and ethnic differences

In general, intracranial atherosclerosis occurs in the atherosclerosis settings widely. Asians, blacks and Hispanics are more likely to have intracranial atherosclerosis than whites [11]. Although ICAS is more prevalent in Asians than in Westerners, the reason for racial-ethnic differences is unknown. Possible explanations include inherited susceptibility to intracranial vessel atherosclerosis, acquired differences in risk factor prevalence and differential responses to the same risk factors. Because both Moyamoya disease (MMD) and ICAS are more prevalent in Asians than in Westerners [11, 12], the increased prevalence of ICAS may partly be caused by adult-onset MMD that is misclassified as ICAS.

MMD is a particular cerebrovascular disease which is characterized by progressive stenosis of the distal internal carotid artery (ICA) and a hazy network of basal collaterals called Moyamoya vessels. It was known that MMD mostly appears among Asian children, and worth mentioning that the hemorrhage rate is higher among adults than children. However, recent epidemiologic studies of Asians and Westerners illustrated that patients with MMD are older and more often ischemic or

asymptomatic than those revealed by previous studies [13-16] One regional, all-inclusive data set of newly registered patients with MMD in Hokkaido (Japan, 2002 to 2006) indicated that the percentage of patients aging less than 10 years old at onset was 15% (compared to 48% in previous studies), and the highest peak was observed at 45–49 years. The data also revealed that the percentage of cases with ischemia increased to 57.4%. Only 21% (previously 42%) of adult MMD patients were hemorrhagic [16].

### Risk factors

ICAS is also female predominance. In addition to sex, race and ethnical issues, risk factors associated with intracranial atherosclerosis including age, hypercholesterolemia, diabetes mellitus, cigarette smoking and hypertension are taken into consideration [1, 17, 18].

Risk factor control, aggressive medical management (including Statins) and stent placement (among the patients selected) are important to prevent stroke in patients with ICAS.

The pathophysiology of MMD is still unknown, and no medication can stop or reverse its progression. Several case series consistently showed that the role of stenting in MMD is highly questionable and is associated with a high rate of symptomatic re-stenosis/occlusion. Revascularization surgery remains the mainstay of treatment for MMD, whereas recent guidelines do not recommend bypass surgery for ICAS. Conclusively, differentiation of MMD from ICAS is of importance for treating patients with intracranial occlusive disease.

### Treatments

Three modalities of treatment considered for intracranial atherosclerotic disease include; medical therapy with Aspirin vs. Warfarin, endovascular revascularization with angioplasty and stent, and extracranial-intracranial bypass surgery.

1. Warfarin (anticoagulation) versus Aspirin (antiplatelet) for stroke prevention:

WASID trial indicated that Aspirin was as effective as and safer than Warfarin in order to

prevent stroke in patients with symptomatic intracranial stenosis. However, neither therapy was particularly effective, particularly in patients with more severe stenosis (70%-99%) and recent symptoms [9].

As shown by WASID study, the risk of recurrent ischemic stroke was still high in patients with intracranial artery stenosis even after Aspirin therapy and standard treatment of vascular risk factors. The overall rate of any stroke or death in 1 year was 22% in WASID for patients with 50–99% stenosis which can cause disability in nearly half of these patients. In particular, for patients with a high degree of stenosis ( $\geq 70$ –99%), the ischemic stroke recurrence rate in 1 year was 18% [9].

Warfarin-Aspirin Recurrent Stroke Study (WARSS) found that oral anticoagulation was no better than Aspirin for non-cardioembolic stroke [19]. Additional trials have demonstrated the added benefit of dual antiplatelet therapy over Aspirin alone [20]. These data strongly support the recommendation that patients with symptomatic ICAS should be treated with AMM (Aggressive Medical Management) consisting of antiplatelet therapy (with consideration of dual antiplatelet therapy for the first 90 days) and intensive risk factor management.

The WARSS and WASID trials showed the poor effectiveness of medical management of IAS. This is one of the reasons why transluminal angioplasty and vascular endoprosthesis arise as useful therapeutic tools.

## 2. Endovascular therapy for intracranial stenosis:

There are four options for endovascular revascularization: angioplasty alone, angioplasty followed by placement of a self-expanding stent, balloon expandable stents and balloon expandable drug-eluting stents.

Stenting and Aggressive Medical Management for Preventing Recurrent Stroke and Intracranial Stenosis (SAMMPRIS) trial, a randomized clinical trial comparing aggressive medical management to stenting with aggressive medical management for symptomatic intracranial stenosis, was prematurely halted when a high rate of periprocedural events was found in the stent arm [21].

Criticisms of SAMMPARIS soon followed. One particular concern involved technical aspects of the self-expanding stent used in this trial which required an over-the-wire exchange technique after balloon angioplasty, the balloon is removed over long exchanged wire and the stent advanced subsequently and deployed. In contrast, a balloon mounted stent requires crossing the lesion and a single time for simultaneous angioplasty and stent deployment. The stent system used in SAMMPARIS trial may increase the risk of hemorrhagic stroke theoretically from wire perforation during the exchange or ischemic stroke from crossing the lesion after angioplasty for stent deployment. Therefore, some authors have suggested these periprocedural risks could be lowered by delivering and deploying a balloon-mounted stent in a single-step procedure that leaves less residual stenosis.

Consequently, the first randomized trial to use balloon-mounted intracranial stent VISSIT (Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) which had similar eligibility criteria to SAMMPARIS including some sites in China and Europe was done but enrollment was stopped early after only 112 patients were randomized because of higher- than-expected rate of stroke in stenting group. The periprocedural stroke rate in VASSIT was 25.8% in 30 days (17.2%, ischemic stroke and 8.6% hemorrhagic stroke) [22].

The SAMMPRIS trial suggested that aggressive treatment was superior to endovascular stenting in patients with severe symptomatic intracranial atherosclerotic stenosis (ICAS) due to high complication rates in patients in the stenting group [21]. Given that 12.2% patients failed aggressive medical therapy in the SAMMPRIS study, it is imperative to perform a multicenter prospective registry study of stenting for patients with ICAS in China. The purpose of this study is to evaluate the safety and efficacy of endovascular stenting for patients with symptomatic intracranial artery stenosis and poor collaterals in China and to identify the characteristics of the population that would benefit the most from endovascular stenting in Chinese patients and reported the morbi-mortality about 11.5% which was similar to the last series published [23].

Based on these trials, there are some recommendations by AHA for the treatment of ICAS as follows:

- For patients with a stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, Aspirin is recommended as preferred to Warfarin (Class I; Level of Evidence B).

- Endovascular revascularization by intravascular balloon angioplasty and/or stenting may be considered for patients with symptomatic severe intracranial stenosis (70% luminal narrowing) despite optimal medical therapy (Class IIb, Level of Evidence C).

- For patients with stroke or TIA due to 70% to 99% stenosis of a major intracranial artery, extracranial-intracranial bypass surgery is not recommended (Class III; Level of Evidence B).

After reviewing the available safety information and trials, the FDA approved Wingspan only for patients who are between 22 and 80 years old who meet ALL of the following criteria [24,25]:

- have had two or more strokes despite aggressive medical management,
- Most recent stroke occurred more than seven days prior to planned treatment with Wingspan,
- have 70-99 percent stenosis due to atherosclerosis of the intracranial artery related to the recurrent strokes, and
- have made good recovery from previous stroke and have a modified Rankin score of 3 or less prior to Wingspan treatment. The Rankin scale is applied to measure the degree of disability in stroke patients. Lower scores indicate less disability.

#### 2.1. Patient selection:

Due to intracranial artery morphology which has thin media without robust adventitia, nearly absent external elastic lamina and vasa vasorum any interventional procedure to overcome the stenosis has own special risks. Therefore, case selection is an important aspect for treatment strategy in these groups of arterial stenotic disease.

So, for determining the efficacy of endovascular treatment, two important factors should be considered:

1. Patient's related factor
2. Endovascular feasibility

Regarding the first issue, endovascular treatment is recommended only for patients with more than 70% stenosis of major intracranial vessels and refractory to medical therapy, previous stroke or TIA, neurologic symptoms referable to the target lesion, presence of symptoms during the 6 months prior to treatment and minimum vessel diameter of 2 mm.

Endovascular feasibility depends on a few factors including stenotic lesion character which is classified by Mori into three types [26,27]:

1. Type A: <5mm in concentric or moderately eccentric, smooth stenosis
2. Type B: 5mm to 10mm in length, extremely eccentric or angulated (>45°), or irregular stenosis, or total occlusion (<3 months old)
3. Type C: >10mm in length, extremely angulated (>90°) stenosis, or total occlusion (>3 months old), or lesion with a number of neovasculatures all around.

Other important factors considering endovascular treatment are vascular access which also has its own classification [28]:

Type I: mild-to-moderate tortuosity and smooth access

Type II: severe tortuosity and/or irregular arterial wall

Type III: excessively severe tortuosity

Therefore, patient selection according to above criteria is very important in endovascular cerebral revascularization with stent and angioplasty.

#### 2.2. Procedural protocol:

Accepted procedure consists of percutaneous transluminal balloon angioplasty with gateway balloon and deployment of wingspan stent which is self-expandable stent with low radial force. Balloon should be 0.5-1mm smaller than vessel diameter and stent should be 0.5-1mm larger [29]. Cautions should be taken during balloon angioplasty due to vessel dissection that may occur in 20%, acute occlusion, acute vessel recoil and post residual stenosis. So, for better outcome, deployment of stent is advisable which has some advantages including avoiding plaque dislodgement, avoiding intimal dissection, avoiding elastic vessel recoil, avoiding plaque re-growth and avoiding late re-stenosis.

Recently, cerebral revascularization with bal-

loon expandable stents is also tried in many cases with good results [30, 31]. This includes using stents that are equal to or slightly less than diameter of the adjacent distal normal vessel. The length of stent should be slightly more (1-2mm) than the length of lesion. The balloon is then inflated gradually at 6 to 9 atm depending on the type of stent and its location. After technical success was achieved, defined as  $\leq 20\%$  of residual stenosis, the balloon is withdrawn and the micro-guide wire is left in the original site for a 30-minute observation until general anesthesia is discontinued. After ensuring angiographical patency and evaluating the National Institutes of Health Stroke Scale (NIHSS) score [32], the micro-guide wire and guiding catheter will be withdrawn. Residual stenosis at the end of procedure defined as more than 20% stenosis is due to balloon sub-expansion and elastic recoil.

#### Possible complications

Early detection of complication could be life-saving. These complications include:

Ischemic stroke, intracerebral hemorrhage, hyperperfusion syndrome, snow plow effect and re-stenosis [33, 34].

Timing of ischemic complication could lead us to determining the cause and mechanism of this type of complication. Acute intra-operative strokes that manifest immediately after stent placement may be the result of a "snow plowing" effect, thromboembolism, acute occlusion of perforator ostia by stent struts or in situ thrombus. Early delayed strokes that develop within the first few days after stent placement may be related to in-stent thrombus, occlusion of perforator ostia or thromboembolism. Late delayed strokes ( $\geq 2$  weeks after stent placement) may be related to all of

the above factors in addition to another potential mechanism caused by intimal hyperplasia within and around perforator ostia [35].

#### Conclusion

At present, medical management should be the first line of therapy for the most patients with symptomatic ICAS. Angioplasty and stenting can be considered in some patients that are unstable or have multiple ischemic events in the territory despite AMM.

Further studies have shown that lesions less than 5mm in length may have significantly less peri-procedural risk as well as restenosis following angioplasty, and patients who fail AMM with these shorter lesions may be more amenable to stenting.

It is reasonable to consider percutaneous transluminal angioplasty and stenting (PTAS) for unstable patients or those with recurrent events despite AMM, although there is no good evidence that PTAS provides a benefit. Future studies of PTAS for ICAS are needed to address the following issues:

- (1) Identify high-risk subgroup of patients likely to benefit from PTAS using non-invasive imaging
- (2) Identify and overcome the mechanisms behind reperfusion hemorrhage
- (3) Identify and overcome the mechanisms for procedural ischemic stroke
- (4) Overcome significant problem of delayed symptomatic stent restenosis.

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