

## JOURNAL CLUB CRITIQUE

# Stenting versus aggressive medical therapy for intracranial arterial stenosis: more harm than good

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### Expanded abstract

#### Citation

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#### Background

Atherosclerotic intracranial arterial stenosis is an important cause of stroke that is increasingly being treated with percutaneous transluminal angioplasty and stenting (PTAS) to prevent recurrent stroke. However, PTAS has not been compared with medical management in a randomized trial.

#### Methods

**Objective:** To determine whether intracranial stenting (using the Wingspan self-expanding nitinol stent, Boston Scientific) and intensive medical therapy is superior to intensive medical therapy alone for preventing stroke in recently symptomatic patients with severe intracranial atherosclerotic stenosis.

**Design:** Phase III, multi-center, randomized, open label, clinical trial.

**Setting:** 50 sites in the US

**Subjects:** Patients who had a recent transient ischemic attack or stroke attributed to stenosis of 70 to 99% of the diameter of a major intracranial artery.

**Intervention:** Eligible patients were randomized to receive either aggressive medical management alone or aggressive medical management plus PTAS with the use of the Wingspan stent system.

**Outcomes:** The primary end point was stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period or stroke in the territory of the qualifying artery beyond 30 days. Patients in the medical arm who undergo angioplasty for recurrent TIAs (*i.e.* cross-overs) and who have a stroke or death within 30 days will also meet this endpoint.

#### Results

Of the 451 patients who underwent randomization, 227 were assigned to the medical management group and 224 to the PTAS group. 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.

#### Conclusions

In patients with intracranial arterial stenosis, aggressive medical management was superior to PTAS with the use of the Wingspan stent system, both because the risk of early stroke after PTAS was high and because the risk of stroke with aggressive medical therapy alone was lower than expected.

#### Commentary

Stroke is a major public health problem as it is a leading cause of death and long-term disability in the United States. There are approximately 795,000 incident strokes each year, resulting in more than 140,000 deaths annually [1]. In 2010, the cost of stroke care was estimated at \$74 billion, with a mean lifetime cost of \$140,000 per patient [2]. Atherosclerotic disease of the major intracranial arteries is a frequent cause of ischemic stroke with annual risk as high as 24% [3]. Patients with severe intracranial

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arterial stenosis (70% to 99%) are at high risk of stroke in the territory of the stenotic artery [4], which is potentially amenable to intracranial angioplasty or stenting.

Current primary prevention strategies include a combination of life style modification (smoking cessation, dietary intervention, weight loss, and exercise), anti-hypertensive medications, antithrombotic therapy, and statins [5]. Recommended secondary prevention includes a combination of medical therapy and revascularization [6]. Tremendous advances have been made in cerebral revascularization techniques in recent years, which include percutaneous transluminal angioplasty (PTA) alone, PTA with stenting (PTAS) using balloon-mounted coronary stents, and extracranial-intracranial surgical bypass. However, unlike extracranial carotid disease, the long term efficacy and safety of revascularization strategies of intracranial atherosclerotic disease have not been well established.

Several retrospective case series suggest that PTA alone is a safe and effective treatment strategy for intracranial atherosclerotic disease [7]. However, PTA has several technical drawbacks including immediate elastic recoil of the artery and high restenosis rates [8]. Surgical bypass was shown to be inferior to medical therapy for middle cerebral artery stenosis [9]. While some studies reported that PTAS with balloon-mounted coronary stents was safe and effective [10], others showed high rates of periprocedural morbidity (23%) and mortality (5%) [11].

The Wingspan, a flexible, self-expanding, is the first stent designed specifically for the treatment of symptomatic intracranial atherosclerotic disease. The high flexibility of these stents makes them suitable for treatment of lesions of the distal internal carotid artery and middle cerebral artery that are either inaccessible or difficult to reach with a balloon-mounted coronary stent.

The Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial is the first prospective randomized trial in patients' with symptomatic intracranial atherosclerotic disease to compare the Wingspan stent and aggressive medical therapy with aggressive medical therapy alone. Aggressive medical therapy included aspirin 325 mg per day for entire follow-up, clopidogrel 75 mg per day for 90 days after enrollment, and aggressive risk factor management primarily targeting blood pressure <140/90 mmHg (<130/80 if diabetic) and LDL <70 mg/dl. However, the Data Safety Monitoring Board halted the trial after enrollment of 451 (59%) of the planned 764 participants because of the significant stroke and mortality rates observed in the stent arm.

The SAMMPRIS is a well-conducted, multicenter, controlled trial that has provided strong scientific evidence of the superiority of medical therapy to PTAS. The two-fold increased risk of stroke with stent clearly indicates

that stenting should not be used for stroke prevention in high-risk individuals. Of particular concern is the significant number of periprocedural intracranial hemorrhages. Unlike coronary vasculature, intracranial vessels are more challenging to stent because they are difficult to navigate due to their very tortuous course and sharp angles, and those vessels are delicate and more susceptible to injury due to lack of supporting connective tissue.

Based on the current study, the authors recommend adding clopidogrel to aspirin for the first 90 days following stroke in patients with high grade intracranial stenosis. However, it has to be pointed out that the control arm does not represent the current standard of care for stroke prevention as addition of clopidogrel to aspirin has been shown to increase the risk of hemorrhage [12]. The main reason for adding clopidogrel to aspirin in the control arm of SAMMPRIS trial was to balance the antithrombotic regimen in order to establish the superiority of the stent. The study did not include an aspirin monotherapy arm to compare the result of aspirin monotherapy with dual antiplatelet (aspirin and clopidogrel) therapy. Therefore it is unclear whether a combination of aspirin and clopidogrel is superior to aspirin monotherapy, combination of aspirin and extended-release dipyridamole, and clopidogrel monotherapy, all of which are acceptable options for secondary prevention after ischemic stroke or TIA [6].

Two ongoing trials, Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT), which is comparing the use of the balloon-mounted stents to aspirin and clopidogrel, and Interventional Management of Stroke III (IMS III) trial, which is evaluating different revascularization strategies including clot retrieval devices, should hopefully provide more insight towards optimal strategy for stroke prevention.

## Recommendation

Treatment with the Wingspan stent system for patients with intracranial stenosis carries substantial risk of death and stroke and should be abandoned.

## Competing interests

The authors declare that they have no competing interests.

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