Intracranial atheromatous disease treatment with the Wingspan stent system: evaluation of clinical, procedural outcome and restenosis rate in a single-center series of 21 consecutive patients with acute and mid-term results

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Aims and objectives

It has been reported that intracranial atherosclerosis may be the underlying pathology in up to 15% of patients with ischemic stroke, but may account for about 40% of strokes in some populations as african-americans, hispanics and asians\(^1\text{--}^7\). After a stroke or a transient ischemic attack determined by intracranial atherosclerosis, patients have a 12% annual risk of stroke recurrence while on medical therapy, mostly occurring in the first year.

Unlike for extracranial atherosclerotic stenosis, the safety and efficacy of antithrombotics in the treatment of intracranial atherosclerotic lesions has yet to be completely defined.\(^8\text{,}^9\) The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, in which patients with symptomatic 50% to 99% intracranial stenosis were randomized to warfarin or aspirin, showed a 1- and 2-year rates of stroke in the territory of the stenotic intracranial artery of 11% and 14% in both treatment arms combined. Among the WASID results, the most important baseline predictors of ipsilateral stroke in patients affected by intracranial atherosclerosis were the severity of stenosis and time from qualifying event to enrollement. The rate of stroke in the territory in patients with \#70 stenosis was 18% at 1 year (95% CI = 13% to 24%) vs 7% at 1 year (95% CI = 5% to 10%) in patients with <70% stenosis. Among patients with \#70% stenosis, patients who had their qualifying event within 30 days prior to enrollement had a 1 year rate of stroke in the territory of 23% (95% CI = 16% to 31%), whereas those with a qualifying event more than 30 days prior to enrollement had a lower 1 year rate of stroke in the territory (10%) (95% CI = 5% to 20%).\(^8\)

Other groups with the highest risk of recurrent stroke are those with recent symptoms onset, those with symptoms precipitated by hemodynamic maneuvers, and women. Moreover, a multicentric study suggests that patients with symptomatic atherosclerotic stenosis of the intracranial vertebrobasilar artery have poor prognosis.\(^9\)

High stroke rate in medically treated patients affected by 70% to 99% intracranial stenosis and recent cerebrovascular events, indicate that alternative therapies are needed for those patients. Intracranial angioplasty has largely been replaced because of the technical drawbacks associated with angioplasty including immediate elastic recoil of the artery, dissection, acute vessel closure, residual stenosis >50% following the procedure, and high restenosis rate\(^10\text{--}^{14}\).

Intracranial stenting emerged as an alternative option to intracranial angioplasty, initially with balloon-mounted coronaric stents, hardly vessel compliant and difficult to deliver in the tortous intracranial circulation\(^15\text{--}^{28}\).
In August 2005 the Food and Drug Administration (FDA) granted a humanitarian Device Exemption approval for a self-expanding nitinol intracranial stent (Wingspan, Boston Scientific, Freemont CA) for use in patients with #50% intracranial stenosis who have recurrent ischemic events while on antithrombotic therapy.

Published data since 2005 about the outcome after stenting with the Wingspan device in patients with 70% to 99% stenosis and recent TIA or stroke produced mixed results. Though an initial enthusiasm determined by the high stenting and procedural success, with acceptable morbidity and mortality rate and a low mid-term ipsilateral cerebrovascular rate, recent published data suggest that target lesion revascularization with wingspan stent system are not durable in 50% of patients and that aggressive medical therapy may be superior to intracranial stenting because of reported early stroke post-stenting rate and a lower than expected stroke rate in patients group receiving medical therapy.

The NIH registry on use of the Wingspan stent for symptomatic 70-99% intracranial arterial stenosis reported a difference in peri-procedural morbidity and mortality between low- and high-enrollement sites, being significantly higher among the first ones, suggesting that experience with the Wingspan stent system and careful selection of interventionalists may play an important role in the reduction of peri- and post-procedural cerebrovascular events.

The current study evaluates procedural safety, clinical outcome and restenosis rate of angioplasty and stent placement in 21 patients with atherosclerotic intracranial stenoses using the Wingspan self-expanding nitinol stent system.
Methods and materials

Before patient enrollment, the protocol for this study received approval by the ethical committee.

The primary end point were the technical success, the procedure success and the ipsilateral stroke/death at 30 days. Technical success was defined as adequate device performance, with a reduction in the stenosis degree to <50% immediately after implantation and valid distal flow. Procedure success was defined as technical success without stroke or death at discharge.

Secondary end points were late complications such as symptomatic restenosis, stent migration and neurological impairment at 6 and 12 months follow-up.

Clinical status at the 6-month and 12-month follow-up (ipsilateral stroke or death) was evaluated by a neurologist and a radiologist, which jointly evaluated clinical and imaging data. The degree or percent stenosis of the target lesion was determined from the formulas described by the WASID method, using CT- or MR- angiography, instead of angiographic evaluation.

Patients

From July 2008 to May 2011, 21 caucasoid patients were enrolled at the Stroke Unit of our institution. All patients provided signed, informed consent before enrollment. Target patients were affected by high-grade, symptomatic, intracranial atherosclerotic lesions and were considered at high stroke rate. Ten of the 21 patients enrolled were already under anti-thrombotic therapy at the time of enrollment. Enrollees were between 56 and 85 years of age, 12 were male and 9 were females; 2 octogenarians patients (one male 81 years old, one female 84 years old) were considered for intracranial stenting because of their overall healthy physiological condition and freedom from relevant comorbidities which may significantly reduce their life expectancy. Patient symptomatology consisted in 14 cases of stroke and in 7 cases of transient ischemic attack occurrence. Patients who suffered from stroke were considered for treatment at least a week after the symptomatology onset, after a MRI with T2 weighted -Fast Field Echo Sequences had excluded the eventuality of intraparenchimal hemorrhage.

Baseline evaluation included blood tests, physical examination, neurologic examination and stroke scales values assessment (modified Rankin Scale, national Institutes of Health Stroke Scale, Barthel Index). At the admission a baseline brain CAT-scan was acquired in order to exclude hemorrhagic stroke and CT-angiography or MR-angiography was performed in order to evaluate intra- and extra-cranial vessel patency. Patients presenting acute ischemic stroke with intracranial vessel or branches occlusion, patients
with a cardioembolic ischemic stroke etiology, patients presenting extracranial carotid artery stenosis are not considered in this study. Patients presenting intracranial vessel occlusion, with distal vessel patency, presenting 70% to 99% intracranial vessel stenosis, with stable life parameters and NIHSS score were considered suitable for endovascular intracranial stenting treatment. Target-lesion stenosis was determined by the WASID method using CT-angiography or MR-angiography instead of conventional angiography.

Each patient received oral clopidogrel (75 mg) and acetil-salicilic acid (100 mg), or clopidogrel (75 mg) and ticlopidin (250 mg) for at least two days before the procedure. Anesthesia was administered in accordance to each patient compliance. A sodic heparin bolus of 5000 UI was administered through an arterial access in order to maintain the activated clotting time at 2 to 3 times baseline throughout the procedure.

Procedure

Patients with no recent imaging evaluation underwent a CT-angiography or a MR-angiography of the aortic arch, thoracic and abdominal aorta and iliac-femoral arteries before the procedure, in order to rule out vessel stenoses, aneurysms or parietal thrombosis, which could contraindicate the procedure. In 19 patients a right 6 Fr common femoral access was acquired through Seldinger technique, in 2 patients a 7 Fr common femoral access was obtained for invasive blood pressure measurement.

A 5 Fr. A tetravasal angiography was obtained in every patient as an invasive pre-procedural evaluation.

The Wingspan Stent system was designed for the treatment of intracranial atherosclerotic stenoses. The stent system comprises a self-expanding nitinol stent preloaded in a delivery catheter and a separately packaged Gateway PTA balloon catheted. The balloon catheter is used for a sub-maximal angioplasty of the stenotic lesion, or predilation. The stent is then released across the lesion, further remodeling the target vessel to maintain luminal patency.

The stent delivery catheter is a 3.5 Fr, coaxial, over-the-wire catheter with segments of varying stiffness and a nominal working length of 135 mm. The outer body of the delivery catheter is hydrophilically coated, and the distal end of the inner shaft has a soft, atraumatic tip for trackability. An integrated rotating hemostasis valve permanently attached to the proximal end of the outer body allows continuous heparinized saline flush and provided a hemostatic seal around the inner body. The stent was constrained by the outer body shaft before deployment.

Gateway balloon diameter was chosen to be 80% of the native vessel diameter at the nominal inflation pressure of 6 atm, to determine an undersized PTA balloon in order to restrict the barotrauma to the plaque and minimize the intimal damage to the vessel (Fig
Size selection was based on the native diameter of the target vessel (fully expanded stent diameter is 0.5 to 1.0 mm greater than the labeled diameter) and length of the stenotic lesion (deployed stent to extend at least 3 mm on either side of the lesion).

**Postprocedure Evaluation and Medical Therapy**

After angioplasty and subsequent stent placement, each patient was evaluated by digital subtraction angiography. After manual hemostasis of the puncture site, patient underwent a 48-hours minitorization of life parameters and NIHSS stroke scale. A baseline brain CAT scan was performed 6 hours after each procedure to rule out asymptomatic cerebrovascular events. Patients medium hospital post-procedural stay length resulted 4.3 days (range 3 to 7). Patients were discharged receiving oral clopidogrel (75 mg) for 6 months and ASA (100 mg) or Ticlopidin (250 mg) *quoad vitam*.

**Follow-up**

Each patient was evaluated at 30 days, 3, 6 and 12 months with a neurologic examination (including stroke scales). All patients underwent a MRI scan, with diffusion-weighted and T2 weighted FLAIR sequences, integrated with MR-angiography acquired through the Time of Flight technique, at 30 days and 6 months. Stent patency and angiographic evaluation were obtained at 30 days, 6 and 12 months through CTA in all patients (Figure 2). The 1-year clinical and instrumental follow-up was completed for each patient. Patient with a longer than 12 months follow-up underwent annual CTA evaluation.

**Statistical Methods**

Analysis of the data gathered from this retrospective study was descriptive. Simple descriptive statistics (n, mean, median, SD, minimum and maximum for continuous variables, and n and percentage for discrete variables), graphs, and patient listings were used to evaluate and summarize the data.
Results

Patient Characteristics

Twenty-one patients were enrolled in the study and treated with the Wingspan stent system.

Medium patient hospital post-procedural hospitalization length resulted 4.3 days (range 3 to 7 days). All patients were caucasoid, 12 were male and 9 were females. Mean age at enrollment was 70.5 years (range 56 to 85 years). Patient symptomatology consisted in stroke as a qualifying event in 14 cases (66.6%) and in transient ischemic attack in 7 cases (33.3%). The most common reported risk factors were hypertension (16 - 76.2%), diabetes (12 - 57.1%), hypercholesterolemia/dyslipidemia (14 - 66.7%), coronary artery disease (8 - 38%) and smoking habit (12 - 57.1%). Ten of the 21 patients enrolled were already under antithrombotic therapy at the time of enrollment. Of these, 6 (28.6%) patients were taking combined antiplatelet therapy (acetilsalicilic acid, clopidogrel, ticlopidin), 3 (14.3%) were taking anticoagulants (heparin of warfarin) and one was taking combined anticoagulant-antiplatelet therapy.

Preoperative neurological examinations revealed the following most common presenting symptoms: hemiparesis (7 - 33.3%), transient neurological deficit (18 - 85.7%), focal neurological deficit (6 - 28.6%), and ataxia (2 - 9.5%). Stroke scale evaluations were consistent with the presenting neurologic symptoms. The majority of the patients had mild to moderate residual neurologic and functional deficits (mRS # 3, National Institutes of Health Stroke Scale # 8, Barthel Index # 55) from before or ongoing cerebral ischemia associated with intracranial atherosclerosis.

Nineteen (90.5%) of the lesions were located in the anterior circulation, and 2 (9.5%) were located in the posterior circulation. The mean degree of stenosis before the stent procedure was 84%, all of them being >50% at baseline.

Table 1 summarizes lesion locations and dimensions as determined by preoperative angiography.

Treatment results

Primary End Points

No technical complications such as arterial dissections, vasospasm, or in-stent thrombosis were observed. One patient had a ipsilateral transient ischemic attack, solved 4 hours after the procedure. In another patient, free from symptomatology after a middle cerebral artery stenting procedure, an ipsilateral temporal area of diffusion restriction was
shown in a post-procedural MRI examination. No stroke or death were observed at 30 days follow-up.

The mean percent of stenosis was reduced from 84% (range 76% to 93%) to 17% (range 15% to 22%) after stent placement.

Table 2 summarizes preprocedure and postprocedure angiographic results. The mean percent of stenosis was reduced from 84% (range 76% to 93%) to 17% (range 15% to 22%) after stent placement. Technical success resulted 100%, with all target lesions being reduced to <50% stenosis) and procedure success resulted 100%, with no post-procedural major stroke or death and no stroke or death at the 30 days follow-up.

**Secondary End Points**

Medium follow-up was 19.5 months (range 6 to 36 months). No stroke or death occurred in any patient. A complete MR examination (also including diffusion-weighted, T2-FLAIR, Fast-Field-Echo and Time-Of-Flight angiographic sequences) didn't show occurrence of new ischemic lesions at the 6 month follow-up. Angiographic evaluation obtained through CTA or MRA, was aimed to compare treated vessel stent patency with the post-procedural angiographic patency rate. None of the patients presented a <50% patency rate at follow-up.

None of the enrolled patients experienced puncture site adverse events or required further treatment for procedure related complications.
Conclusion

In the United States, ischemic stroke affects 88% of the about 700,000 patients who experience new or recurrent stroke and about 15% are determined by atherosclerosis\(^1\)\(^-\)\(^3\). Depending on the stenosis degree and other conditions, patients affected by intracranial atherosclerosis have a cerebrovascular event rate of 10% to 50% per year. \(^1\)^5\(^\text{8}^\text{,9}\).

The WASID trial investigators observed an ipsilateral ischemic stroke rate at 1 year of about 11% in patients with intracranial\(^8\). Patients with a history of TIA and stroke in the territory of a 70-99% stenosis, while on antithrombotic therapy, were found to have a stroke rate of 18% at 1 year\(^35\). A matched comparison between patients on medical therapy enrolled in the WASID trial and patients treated with the Wingspan system in the National Institute of Health Intracranial Stent Registry, concluded that stent placement might offer the highest benefit in patients presenting 70-99% stenosis\(^36\).

Initial endovascular experience in the treatment of intracranial atheromatous disease by angioplasty alone or balloon-mounted coronary stents provided mixed results, generally characterized by an unsatisfying morbidity and mortality rate. Most series regarding angioplasty alone as treatment option for intracranial stenosis report unsatisfying procedure success rate. Marks et al., for instance, report a 40.7% of patients having residual stenosis >50% after angioplasty and 12.9% patients requiring stent placement after angioplasty because of "unchanged or worse" stenosis rate compared to the pre-procedural\(^13\). Currently, however, sub-maximal angioplasty and stent placement has not definitely proved to be superior to angioplasty alone\(^37\). Most series describing the outcomes of patients undergoing treatment with balloon mounted coronary stents report periprocedural complication rates in the range of 15% to 30%\(^38\)\(^-\)\(^42\).

A recent meta-analysis by Taylor et al\(^9\) on eleven series reported that the self-expanding Wingspan stent provides the highest technical success rates (97-99%) and an acceptable 30-day stroke/death rates (4.5%-9.3%). Initial studies reported only 7.5% of patients having stenosis of 50% or greater on mid-term angiographic follow-up, but subsequent studies have shown higher 50% or higher restenosis rates (34.5%-36.2%) after Wingspan stent placement\(^43\)\(^,44\). Fiorella et al. reported that in 50% of patients stent placement results are not durable, requiring multiple revascularization procedures\(^31\).

Substantial reduction in periprocedural complications with the Wingspan has generally been attributed to both the device design and the recommended treatment strategy. The conservative angioplasty has been considered responsible for the reduction of complications such as target-vessel perforation or downstream embolization of atheromatous debris caused by plaque disruption. Moreover the stent design, its low
profile and high flexibility, together with the possibility to be advanced over a floppy guidewire, granted a high navigability through tortuous intracranial vascular anatomy and a higher navigability across an intracranial target lesion, avoiding complications such as vasospasms and vessel traumas, vessel perforation, dissecation or injury.

Recently, results of the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial on a high-risk group of 451 patients with a recent transient ischemic attack or stroke that was attributed to a 70% to 99% intracranial stenosis, randomly assigned to receive aggressive medical management with or without the addition of intracranial angioplasty and stenting using the Wingspan system, were published. The investigators reported that the 30 days rate of stroke or death resulted significantly higher in patients receiving intracranial angioplasty and stenting compared both to one of patients receiving aggressive medical management, and resulted also significantly higher than the ones reported in previous studies, such as "The Wingspan study" (14.7% vs. average 5.8%) 32. Results were interpreted by the investigator as determined by a higher than expected rate of early stroke after angioplasty and stenting, and by a lower than expected stroke rate in patients receiving aggressive medical therapy alone. Similar results were reported by a similar cohort study by Samaniego et al. 46, in which a similar combined ischemic event rate for the occurrence of TIA, stroke and vascular death between patients receiving medical treatment and those receiving endovascular stent placement was observed (24% vs 28.3%).

The results of our series are far more compatible with previous series as the Wingspan study 29, and the high enrolling sites arm results of the NIH registry on use of the Wingspan stent for symptomatic 70-99% intracranial arterial stenosis 33, and results similar to those provided by some authors such as those by Tang et al. 45 and Fiorella et al. 31, except for the 30-days >50% in-stent restenosis percentage of the latter one, which resulted significantly lower in our data (0%).

Though providing results similar to earlier studies, a significant discrepancy between our results and the larger SAMMPRIS trial results can't be ignored. Tough we cannot rule out that this discrepancy may be mostly attributable to the small number of treated patients in our series, we believe that other factors have to be taken into account. All the patients presented in this series were treated by two highly skilled interventional radiologists, with at least 25 years of experience in the carotid artery stenting field and at least 10 years of experience in the treatment of intracranial aneurysms. A non-negligible factor is the availability of diagnostic tools such a 64-row CT and a high-field 3 Tesla MR, which may allow a more accurate preprocedural diagnostic evaluation and a strict choice of the balloon and stent sizes. A lesson learned from decades of carotid stenting is the key role of the pre- and post-stenting medical therapy and its standardization in this series, above all the 6-months post-procedural therapy with clopidogrel, may be one of the reasons of the low rate of in-stent thrombosis. There are currently no studies evaluating
the pseudoendothelization of intracranial arteries after stenting, so we don’t actually
know how much it differs from the carotid one; we, thus, strongly believe a longer post-
procedural administration of clopidogrel should be mandatory until further autopic studies
are provided. At last, in this consecutive each enrolled patient underwent a scrupulous
joint radiological and neurological evaluation, with each indication to treatment decided
after an overall risk/benefit evaluation; we believe this approach, though producing less
scientifical evidence compared with a randomized trial, may have eliminated the side
effects of a too rigid randomization. Many patients are, indeed, poor candidates to
intracranial stenting due to conditions which are not perforce considered as exclusion
factors, such a tortuous anatomy, a risky location of the atherosclerotic plaque or, more
simply, the need to suspend the post-procedural antiplatelet therapy before the time
because of not postponable surgical interventions; though this approach, as stated
before, is not perfectly applicable to randomized trials, it is essential, in our opinion, for
a good outcome of each procedure, particularly of intracranial endovascular ones.

The low restenosis rate provided in our series may be questioned because of the choice to
use CTA or MRA instead of the gold standard angiography for the evaluation of restenosis
degree. Currently only one study comparing MRA and CTA with angiography in the in
the intracranial in-stent restenosis detection is available; this study concludes that CTA
and MRA are not comparable with angiography for the evaluation of in-stent restenosis.
Though we knew the limits of both MRA and CTA, in particular for the evaluation of
the proximal and distal edges of the stent where the thicker radio-opaque markers
are located, we decide to avoid the embolic risks of a further cerebral angiography,
which are higher in elder patients which usually present aortic arch and common carotid
artery thrombo-atheromatosis. We decided in the beginning to perform an angiography
in patients symptomatic to follow-up, or in patients with an unclear CTA or MR result;
however, all patients were asymptomatic at the 6 months and 1-year follow up and no
new ischemic lesions were observed at the MR or CT examination, so no follow-up
angiographies were performed.

Conclusions

The short-term results and follow up analysis reported herein provide evidence
demonstrating the safety of the Wingspan stent system when used as endovascular
therapy in high-risk patient population. Due to concerns regarding long-term stent patency
and ischemic events occurrence such as ipsilateral stroke and death emerged from
clinical trials such as the SAMMPRIS, intracranial conservative predilation and stent
placement with the Wingspan self-expandable stent should, however, be considered
only in high risk patients refractory to aggressive medical therapy in which it may be
considered the only viable therapeutic option.
Fig. 1: A case of a 75 y.o. male presenting a right M1 middle cerebral artery stenosis. Preprocedural angiography (a); angiogram performed after conservative angioplasty (predilation) showing reduction of the stenosis degree (b); a slightly oversized Wingspan stent system is advanced over the guidewire over the stenotic M1 middle cerebral artery segment under fluoroscopic guide, using the radio-opaque markers as positioning reference (c); the post-procedural angiography shows correct positioning of the Wingspan stent system, significant increment of vessel diameter and patency, valid flow through the stent and distal branches perfusion in absence of intra-procedural complications (d).
Fig. 2: Same patient shown in figure 1. Preprocedural MRA. Time-of-flight acquisition 3D-MIP reformatting, axial plane, showing high-grade right M2 stenosis (a). Six-month follow-up CTA, axial (b) and coronal (c) MIP reformatting, showing regular stent patency.

* The degree (%) of stenosis was determined by the WASID method using preprocedural angiography for baseline and after stenting measurements, using CTA for 6 months and 12 months follow-up measurements. 30-days MRA-based measurements are not considered in this table (34)
Fig. 3: Adapted from: Arani B, Hartmann M, Henkes H et al. A Novel, self-expanding, Nitinol Stent in Medically refractory intracranial atherosclerotic stenoses: the wingspan Study. Stroke. 2007;38:1531-1537. * The degree (%) of stenosis was determined by the WASID method using preprocedural angiography. (34).
**Fig. 4:** Adapted from: Arani B, Hartmann M, Henkes H et al. A Novel, self-expanding, Nitinol Stent in Medically refractory intracranial atherosclerotic stenoses: the wingspan Study. Stroke. 2007;38:1531-1537. * The degree (%) of stenosis was determined by the WASID method using preprocedural angiography for baseline and after stenting measurements, using CTA for 6 months and 12 months follow-up measurements. 30-days MRA-based measurements are not considered in this table (34).

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