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

Poster No.: C-0873
Congress: ECR 2012
Type: Scientific Exhibit
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Keywords: Ischaemia / Infarction, Embolism / Thrombosis, Arteriosclerosis, Stents, Arterial access, Angioplasty, MR-Diffusion/Perfusion, CT-Angiography, Catheter arteriography, Neuroradiology brain, Interventional vascular, Head and neck
DOI: 10.1594/ecr2012/C-0873

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Purpose

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.

The primary end points were the evaluation of ipsilateral stroke/death at 30 days, technical success and procedure success. 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.

The secondary end points were the angiographic identification of events as vessel dissecation, symptomatic restenosis, stent migration, access-site complications, and the evaluation of clinical outcomes at 6 and 12 months follow-up.
Methods and Materials

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

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Clinical status at the 6-month and 12-month follow-up (ipsilateral stroke or death) was evaluated by specialists in the areas of neurology, radiology and interventional radiology, which evaluated and monitored 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. (34).

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, were on antithrombotic therapy and were considered at high stroke rate. Enrollees were between 56 and 85 years of age, 12 were male and 9 were females. 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 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 1). 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 60 days 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.

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.
Fig. 1: Figure 1 A case of a 75 y.o. male presenting a right M1 middle cerebral artery stenosis. (a) Preprocedural angiography

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Fig. 2: Figure 1 A case of a 75 y.o. male presenting a right M1 middle cerebral artery stenosis. (b) a Transend guidewire is advanced into the M3 segment of the middle cerebral artery

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**Fig. 3:** Figure 1 A case of a 75 y.o. male presenting a right M1 middle cerebral artery stenosis. (c) An under-sized Gateway balloon is advanced over the guidewire under fluoroscopic guide, using its marker as reference

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**Fig. 4:** Figure 1 A case of a 75 y.o. male presenting a right M1 middle cerebral artery stenosis. (d) 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.

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**Fig. 5:** Figure 1 A case of a 75 y.o. male presenting a right M1 middle cerebral artery stenosis. (e) 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

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**Fig. 6:** Figure 1 A case of a 75 y.o. male presenting a right M1 middle cerebral artery stenosis. (f) 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.

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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%), hypercholesterolemia/hyperlipidemia (14 - 66.7%), smoking habit (12 - 57.1%), diabetes (12 - 57.1%), and coronary artery disease (8 - 38%). Eighteen of the 21 patients enrolled were 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 1 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.

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.

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. MR examination didn’t show occurrence of asymptomatic 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.

Discussion

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 (1,2,3). Depending on the stenosis degree and other conditions, patients affected by intracranial atherosclerosis have a cerebrovascular event rate of 10% to 50% per year. (1-5,8,9).

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 coronaric 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. (32)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%). (29) 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. (13 di 8), 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 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 stenosis degree evaluation through WASID method, all patients were asymptomatic at 6 months and 1-year follow up and no new ischemic lesions were observed at MRI or CT examination. Though providing similar results to earlier studies, a significant discrepancy between our results and the larger SAMMPRIS trial results can't be ignored.
Fig. 7: Figure 2. Same case shown in figure 1. (A) Preprocedural MRA. Time-of-flight acquisition 3D-MIP reformatting, axial plane, showing high-grade right M2 stenosis.

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**Fig. 8:** Figure 2. Same case shown in figure 1. (b) Six-month follow-up CTA, axial MIP reformatting, showing regular stent patency.

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**Fig. 9:** Figure 2. Same case shown in figure 1. (c) Six-month follow-up CTA, coronal MIP reformatting, showing regular stent patency.

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<table>
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<tr>
<th>Location</th>
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<th>Percent</th>
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<tr>
<td>Middle Cerebral Artery (M1)</td>
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<td>71.43%</td>
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<td>Middle Cerebral Artery (M2)</td>
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<tr>
<td>Posterior circulation</td>
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<tr>
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<td>9.5%</td>
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**Lesion Dimensions**

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<tr>
<th>Lesion Length, mm</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tr>
<td>Reference vessel diameter</td>
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<tr>
<td>Minimum lumen diameter</td>
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<tr>
<td>Percent stenosis*</td>
<td>84</td>
<td>76.0 - 93.0</td>
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**Table 1:** Lesion locations and baseline characteristics. *The degree (%) of stenosis was determined by the WASID method using preprocedural angiography. (34)
Table 2: Angiographic evaluation of intracranial vessel treatment results with the Wingspan Stent System. * 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)
Conclusion

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.
References


