The treatment of symptomatic intracranial arterial stenosis (SIAS) aims to reduce the risk of occurrence or recurrence of ischemic stroke. However, even with a well-conducted medical management protocol and continuous administration of antiplatelet agents, secondary brain ischemia may occur. In the randomized study reported by Kasner et al. in 2005, as part of the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Trial, 19% of patients presented with recurrent events, most of them within the 1st year and in the same cerebral hemisphere. These recurrences appeared to be associated with the presence of diabetes or a high degree of stenosis severity ($\geq 70\%$).

The relative limitations of the standard medical treatment have encouraged the development of more aggressive strategies, such as endovascular treatment. The Wingspan stent and Gateway percutaneous transluminal angioplasty (PTA) balloon system (Boston Scien...
Treatment of intracranial stenosis with the Wingspan stent

tific Neurovascular) have been available on the market since 2005, as a self-expandable nitinol stent designed for the treatment of intracranial arterial stenosis. In the present study, we evaluate the efficacy and safety of Wingspan stents in a multicenter series of 60 consecutive patients presenting with refractory SIAS.

Methods

Patient Population

Information from medical files of all patients treated with Wingspan stents for refractory SIAS between September 2006 and August 2009 was retrieved from the databases of 5 French neurointerventional centers that shared the same management protocol for SIAS to constitute a common computerized database. Only patients presenting with recurrent symptoms despite adequate medical therapy were included. A retrospective review of their files allowed retrieval of the following population characteristics: primary diagnosis, sex, age at the time of treatment, cardiovascular risk factors, comorbidities, location and degree of the arterial stenosis, and length of follow-up. Patients with confirmed SIAS of at least 50% were included in this study. The decision to insert a stent was made collectively with the referring neurology team. As demonstrated in the WASID trial, the period of maximal risk of recurrence is the first 3 weeks. As a consequence, most of those who presented with transient ischemic attacks (TIAs) were treated as emergency cases, and all of them were treated within the first 48 hours. Patients presenting with a significant ischemic stroke could only be treated after a minimum period of 1 week had elapsed. Premature intracranial stent insertion would potentially have an increased risk of hemorrhagic transformation related to the mandatory use of double antiplatelet therapy. Any patient presenting with a contraindication for antiplatelet agents, a previous major disabling ipsilateral stroke, or needing an emergency revascularization for a complete arterial occlusion was excluded from the study.

Medical Management

Every patient was followed in parallel by 2 practitioners (a neurologist and a general practitioner) besides the interventional neuroradiology team for lifestyle changes and risk factor control (hypertension, obesity, diabetes, dyslipidemia). A written informed consent was obtained from the patient or his/her family for the intracranial angioplasty stent placement procedure. The day before the endovascular treatment, a neurological examination was performed and a modified Rankin Scale (mRS) score was recorded by a trained member of the neurology team (for both the first visit and follow-up). A loading dose of 300 mg of clopidogrel was then administered. At the beginning of the endovascular procedure, an aggregometry test was performed (Accumetrics) to assess the level of platelet inhibition achieved with aspirin and/or clopidogrel. In case of a low level of inhibition (< 30% for clopidogrel and > 530 Aspirin Reactive Units for aspirin), a second loading dose of 300 mg of clopidogrel was administered as soon as possible. Unfractionated heparin was infused during the endovascular procedure to obtain an activated clotting time of 250 seconds or longer, and an intravenous bolus of 250 mg of aspirin was delivered just after the angioplasty or stent placement. The anticoagulation therapy with heparin continued for at least 12 hours. At postoperative Day 1, this therapy was completely stopped and oral antiplatelets were restarted (75 mg of clopidogrel and 75 mg of aspirin). In case of perioperative intracranial arterial thrombosis, an intravenous bolus of a GPIIb/IIIa protein inhibitor (abciximab, 25 µg/kg) was administered, followed by an intravenous infusion of 125 µg/kg over 12 hours.

The target mean blood pressure during the procedure was 90 mm Hg to minimize the risk of hemodynamic ischemia. In the postoperative period, blood pressure should not exceed 140 mm Hg to minimize the risk of reperfusion lesion and hemorrhagic complications.

A dual antiplatelet regimen was maintained until the first follow-up angiogram (digital subtraction [DS] angiography or CT angiography) at 6 months. If no in-stent restenosis (ISR) was observed, clopidogrel (75 mg daily) was generally discontinued, but the patient continued to receive permanent aspirin therapy.

Endovascular Therapy

Every procedure was performed via a femoral approach after induction of general anesthesia. A 6 Fr guiding catheter was introduced through a femoral sheath into the carotid artery or vertebral artery (VA) upstream to the site of stenosis, and an angiographic examination of the target vessel was performed using a biplane angiographic system. Then, the degree of stenosis was evaluated according to the measurement criteria established in the WASID trial, by using DS angiography images.

Prior to the stent delivery, dilation of the target vessel was accomplished with the Gateway PTA balloon. The size of the balloon (from 2 to 4 mm) was chosen not to exceed 80% of the diameter of the artery, and the length (9, 15, or 20 mm) should be as close as possible to the length of the stenosis. The Wingspan stent should ensure complete coverage of the stenotic lesion and at least 3 mm beyond its proximal and distal ends. The diameter (from 2.5 to 4.5 mm) was chosen according to the proximal, nonstenotic artery. Slight oversize was permitted for stabilization purposes. The aim of the procedure was to obtain a residual stenosis of < 50%.

Follow-Up Protocol

A new DS angiography study was performed at the end of the procedure, after stent placement. After extubation, a neurological examination was performed. A new mRS score was recorded on postoperative Day 1. In case of clinical worsening, an MR imaging examination was immediately performed, as well as a complete neurological examination and a National Institutes of Health Stroke Scale (NIHSS) score.

One month after the endovascular treatment, patients were asked to answer a questionnaire via a telephone interview or a medical appointment, and a new mRS score was obtained. The questionnaire pertained to their neurological symptoms and quality of life. In case of wors-
ening, the patient was scheduled for urgent MR imaging and neurological examinations. An angiogram (CT or DS angiography) and a neurological examination were also scheduled at 6 months and then yearly thereafter. If ISR was suspected on CT angiography, a DS angiography study was systematically obtained. The ISR rates were assessed by the practitioner in charge of treating the patient and then reviewed by an independent neuroradiologist (V.C.) for the purpose of this study. In case of disagreement, a second assessment was performed by another observer (I.L.M.) to adjudicate it. As proposed by Albuquerque et al.,* ISR was defined as a lesion fulfilling the following criteria: stenosis > 50% and > 20% of absolute luminal loss in comparison with the immediate postoperative angiogram.

The occurrence of any of the following outcomes was recorded: periprocedural complications of any type, such as arterial dissection, subarachnoid hemorrhage (SAH), hemorrhagic transformation, intracranial hematoma, thromboembolism, vessel occlusion, or failure of stent delivery; residual stenosis; TIA; ischemic or hemorrhagic stroke; stent occlusion; ISR; delayed cerebral thromboembolism; neurological worsening (with the corresponding mRS and NIHSS scores); and death due to any cause.

Statistical Analysis

Statistical analyses were performed using the SAS version 8.2 software. Frequencies and percentages were calculated for categorical variables, and the means ± SDs and ranges were determined for continuous variables. When a single patient was treated for two stenotic lesions, each one was categorized and analyzed independently. Survival rates were calculated from the date of the endovascular treatment. The restenosis-free survival rate was estimated using the Kaplan-Meier method, taking into consideration the occurrence of restenosis or death by any cause.

Results

Patient Population

Sixty individuals with a mean age of 65.35 ± 9 years (range 50–85 years), harboring a total of 63 SIASs, were treated with Wingspan stents between September 2006 and August 2009: there were 40 male patients (66.7%) and 20 were female (33.3%). The clinical events that preceeded the decision to perform an endovascular treatment were recorded: periprocedural complications of any type, such as arterial dissection, subarachnoid hemorrhage (SAH), hemorrhagic transformation, intracranial hematoma, thromboembolism, vessel occlusion, or failure of stent delivery; residual stenosis; TIA; ischemic or hemorrhagic stroke; stent occlusion; ISR; delayed cerebral thromboembolism; neurological worsening (with the corresponding mRS and NIHSS scores); and death due to any cause.

Immediate Postoperative Outcome

There were no perioperative deaths. Also, no signifi-

cant peripheral bleeding requiring urgent blood transfusion or femoral hematomas necessitating surgical treatment were recorded. Procedural success was defined as an immediate postoperative residual stenosis < 50%, which was achieved in 95.2% of cases. There was 1 case of technical failure of the stent delivery, characterized by incomplete opening inside the ICA. In 2 cases, immediate in-stent balloon inflation was performed for treatment of a significant residual stenosis. Perioperative complications (Table 1) were recorded in 13 (20.6%) of 63 procedures. In 3 of them (4.8%) a permanent neurological morbidity and worsening of the mRS score was observed. These adverse events are detailed below.

Perforator Artery Occlusion. There were 4 cases of perforator artery occlusion (6.3%), 2 of them asymptomatic. Three cases were observed during stent placement in the middle third of the BA; the remaining case occurred during the treatment of a stenosis of the M1 segment of the MCA. In 2 patients, stent insertion in the BA caused a paramedian infarction of the pons. The mRS score worsened from 0 to 1 in one case and from 0 to 2 in the other. The final NIHSS scores were 5 and 7, respectively.

Focal SAH. There were 3 cases of focal SAH (4.8%). All of these patients presented with unusual persistent postoperative headaches, and the hemorrhage was centered on the stent-treated artery: 1 MCA, 1 VA, and 1 BA. A small temporal hematoma was detected in the case in which the MCA stent was placed (Fig. 1), and a localized SAH without hematoma was found in the other two. There was no neurological worsening.

Distal Embolic Occlusion. There was 1 case of distal embolic occlusion (1.6%); occlusion of the left posterior cerebral artery (P1 segment) occurred during the treatment of a BA stenosis. The patient received an immediate intravenous bolus of a GPIIb/IIIa inhibitor, with no significant angiographically confirmed effect. No clinical worsening occurred, and the postoperative NIHSS score was 0. On the CT angiography control study, the left P1 segment was still occluded by a calcified fragment, which may explain the ineffectiveness of the GPIIb/IIIa inhibitor.

<table>
<thead>
<tr>
<th>Category</th>
<th>Immediate Comps</th>
<th>1-Mo Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Treated SIAS Cases</td>
<td>No. of Op Comps</td>
</tr>
<tr>
<td>autoexpanisible Wingspan stent</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>asymptomatic comp</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>symptomatic comp</td>
<td>NA</td>
<td>3</td>
</tr>
</tbody>
</table>

* Comps = complications; NA = not applicable; Pts = patients.
Acute In-Stent Thrombosis. There were 2 cases of acute in-stent thrombosis (3.2%). In 1 patient, an MCA thrombosis occurred 48 hours after the stent delivery. The patient worsened clinically. The mRS score increased from 2 to 4, and the final NIHSS score was 16. There was extension of the previous ischemic lesions in the putamen and corona radiata. In the remaining patient, a perioperative VA occlusion was treated with a GPIIb/IIIa inhibitor, and immediate recanalization was obtained. These 2 patients had presented with a platelet inhibition rate <30% on the day of the endovascular procedure, and they received a complementary loading dose of clopidogrel after extubation.

Minor Hemorrhagic Transformation. There was 1 case of minor hemorrhagic transformation (1.6%). This patient had suffered a recent stroke in the MCA territory and presented with persistent unusual postoperative headaches. The antiplatelet regimen was reduced to a single agent. The patient was discharged at postoperative Day 8.

Asymptomatic Intracranial Dissection. There were 2 cases of asymptomatic intracranial dissection (3.2%); one of the BA and the other of the MCA, with no associated acute ischemic event.

Early (1-Month) Results

At this follow-up interval, 1 patient had died of a pulmonary embolism; this patient had an advanced prostatic neoplasm. Data from 7 other patients (11.6%) were not available due to the following reasons: 5 patients moved and were lost to follow-up, and 2 could not be contacted despite multiple attempts. One delayed stroke was recorded: a minor cerebellopontine infarction in a patient who underwent stent placement for a BA stenosis and presented with transient ataxia at Day 17. The final NIHSS score was 0, and there was no change in mRS score.

A total of 93.6% of the 63 mRS scores recorded were stable or improved during the 1st month. Among the 12 patients (20%) who improved, the change in mRS score was between 1 and 3 points (mean 1.6 points). A 57-year-old man presenting with a BA stenosis of 80% and a previous ischemic stroke (initial mRS Score 3) died during the same hospitalization at postoperative Day 21 after a technically uneventful endovascular procedure. As a consequence, at the end of the 1st month of follow-up, a worsening of the mRS score in comparison with the initial score was observed in a total of 4 patients (6.3%).

Six-Month Assessment

Six months after the procedure, clinical evaluations and angiograms were available for 50 patients. One patient had died (see above), 5 had moved, and 4 had not yet reached the 6-month follow-up term at the time of this report.

Between the 1st and 6th month after the endovascular treatment, all patients presented with stable or improved mRS scores. One patient had a new TIA in a vascular territory different from the target lesion. Nine occurrences (14.3%) of ISR or occlusion were recorded at the 6-month follow-up interval (Tables 2 and 3): 7 in the posterior and 2 in the anterior circulation; 8 of them were asymptomatic. Those events are detailed as follows.

Asymptomatic ISR. There were 2 cases of asymptomatic ISR in the anterior circulation. In one case, there was a stenosis of 60% of the MCA. In the other (Fig. 2), there was a reduction of 70% of the ICA lumen (which remained stable, as demonstrated by the second angiogram performed 1 year later).

In-Stent Restenosis of the BA. There were 6 cases of ISR of the BA (Fig. 3), 5 of them asymptomatic. In 1 case, a restenosis of the BA was responsible for recurrent TIAa of the posterior circulation. This patient was treated again at 6 months with a balloon angioplasty, without complications.

Silent ISR of the VA. There was 1 case of silent in-stent occlusion of a VA.

Follow-Up Findings at 1 Year

At the time of this report, 33 patients had completed the 1-year-interval clinical and radiological evaluations. There were no new neurological events in the territory.
of the treated lesions between the 6- and 12-month follow-up intervals. One asymptomatic restenosis recorded at the 6-month follow-up visit progressed to silent stent occlusion. Two additional asymptomatic ISRs were recorded, increasing the overall ISR rate to 17.4% among the successful stent placement procedures. In the patient in whom an incomplete opening of the stent was observed in the ICA, the residual stenosis increased from 60% to 75% (Fig. 4). In another one, a restenosis of 50% of the MCA was observed. A follow-up angiogram performed 12 months later showed stability the lesion.

The survival without restenosis for the whole series is illustrated by the curve in Fig. 5. It corresponded to 79.4% at the end of the 1st year of follow-up.

**Discussion**

As previously reported, the endovascular treatment of SIAS seems to be associated with a significant risk of perioperative complications and a moderate risk of neurological morbidity.\(^1\)\(^-\)\(^8\)\(^,\)\(^9\)\(^,\)\(^10\)\(^,\)\(^12\)\(^,\)\(^13\)\(^,\)\(^15\)\(^,\)\(^19\)\(^,\)\(^21\) These figures may still be advantageous, given the considerable morbidity and mortality levels that are related to the natural history of the disease itself. In 2006, high rates of ipsilateral ischemic recurrence (38.2%) and vascular death (8.8%) were reported in the Groupe d’Etude des Sténoses Intracrâniennes Athéromateuses Symptomatiques (GESICA) study.\(^1\)\(^4\)

There is no clear-cut guideline for the management of intracranial stenosis with endovascular techniques. In 2005, the American Societies of NeuroInterventional Surgery, Interventional Radiology, and Neuroradiology published a position statement in which it was said that the endovascular treatment for patients with SIAS > 50% should be considered for those in whom medical therapy has failed.\(^7\) The last consensus reference on intracranial atherosclerotic disease\(^1\)\(^8\) also considered that endovascular therapy with stent placement may offer benefit. Moreover, the WASID investigators have recently observed that patients in whom antithrombotic therapy initially succeeded may not be at lower risk in comparison with the others.\(^22\) In this regard, we have been perceiving an increasing interest in the development of endovascular treatment possibilities, as well as of new trials that will compare intracranial stent insertion to aggressive medical management. The Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study, an NIH-funded multicenter clinical trial, will compare the effectiveness and safety of intensive medical therapy plus stent placement versus intensive medical therapy alone to prevent stroke, heart attack, or death.

The short time to recurrence is an argument for aggressive therapeutic strategies.\(^1\)\(^4\) An MR imaging examination performed after the initial stroke may detect clinically silent ipsilateral infarctions in patients receiving double antiplatelet therapy. In such a case, the neuroimaging may be a supporting element for discussion of a rapid endovascular treatment with the neurological team, with the aim of minimizing the risk of symptomatic recurrences.

**Antiplatelet Regimen**

Preventive antiplatelet agents and anticoagulation therapy are important issues in the perioperative period of intracranial stent treatment. In 2008, Müller-Schunk et al.\(^1\)\(^6\) observed a strong association between insufficient platelet inhibition and perioperative thromboembolic complications in a mixed series of extracranial and intracranial stent placement procedures. In the present study, 2 cases of in-stent thrombosis were recorded. Because the endovascular treatment of intracranial arterial stenosis was proposed to patients who were symptomatic even though receiving appropriate medical therapy, it is possible that we were more frequently faced with the phenomenon of individual resistance to antiplatelet agents and, as a consequence, a higher risk for thromboembolic complications.

---

**TABLE 2:** Incidence of ISR in 60 patients treated using the Wingspan stent and Gateway PTA balloon system for 63 cases of SIAS*

<table>
<thead>
<tr>
<th>Category</th>
<th>6-Mo Findings</th>
<th>12-Mo Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Pts Followed</td>
<td>No. w/ Restenosis</td>
</tr>
<tr>
<td>autoexpandable Wingspan stent</td>
<td>50</td>
<td>9</td>
</tr>
<tr>
<td>asymptomatic ISR</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>symptomatic ISR</td>
<td>NA</td>
<td>1</td>
</tr>
</tbody>
</table>

* NA = not applicable.

**TABLE 3:** Characteristics of patients with and without restenosis in 52 cases of intracranial arterial stenosis treated using the Wingspan stent and Gateway PTA balloon system*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Stenotic Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>w/ Restenosis</td>
</tr>
<tr>
<td>no. of cases</td>
<td>11</td>
</tr>
<tr>
<td>sex</td>
<td>F</td>
</tr>
<tr>
<td>mean age (yrs)</td>
<td>63.9</td>
</tr>
<tr>
<td>mean initial stenosis</td>
<td>80.2%</td>
</tr>
<tr>
<td>periop comps</td>
<td>6 (54.5%)†</td>
</tr>
<tr>
<td>location of stenosis</td>
<td>BA</td>
</tr>
<tr>
<td>mean</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td>range</td>
<td>12 (29.3%)</td>
</tr>
</tbody>
</table>

* Includes patients for whom follow-up angiograms were available until the end of the study.
† p < 0.05.
Resistance to antiplatelet agents is not completely understood. The effect of aspirin or clopidogrel can currently be tested by impedance aggregometry. Even though this method provides quantification of the inhibition of the platelet function, its usefulness in daily clinical practice has not been fully determined. In our center, a point-of-care analysis using the VerifyNow system (Accumetrics) has been used to screen for nonresponding patients.

To minimize the risk of acute stent thrombosis, when a patient presented with an inhibition rate of < 30%, a bolus of intravenous aspirin (250–500 mg) was administered during the endovascular procedure, and a second oral loading dose of clopidogrel (300 mg) just after it. This was the case for the 2 patients who presented with acute perioperative in-stent thrombosis. We may also hypothesize that other factors influence the risk of perioperative in-stent thrombosis, such as a lower flow through the target artery during general anesthesia. Rigorous hemodynamic control may also be an important issue during the endovascular treatment.

Assessment and Management of ISR

A definition for ISR has been proposed recently by Albuquerque et al.: a residual stenosis > 50% and a luminal loss > 20% from baseline. This definition is angiographic and cannot be transferred from DS to CT angiography, in which stent artifacts (especially around the stent markers) limit the ability of the operator to establish the actual lumen of the vessel. Even though no systematic follow-up angiography was performed in the present study, it was proposed in cases in which CT angiography was judged to be insufficient, or in the case of strong suspicion of ISR. When contrast medium was seen filling all stent cross-sections on multiplanar views, no extra DS angiography study was obtained.

It is worth noting that artifacts on CT angiography
are mainly due to the distal markers of the stent, and that 2 different types were observed in this series, depending on the vessel orientation. Markers from devices inserted in the BA or supraclinoidal ICA are distinguishable from those of MCA stents. In instances in which the x-ray beam is parallel to the distal markers, such as in MCA cases, the artifacts penetrate widely inside the stent lumen. In the BA and in the C1 segment of the ICA, the x-ray beam, being mostly orthogonal, produces fewer intrastent artifacts, which are limited to the distal end. New imaging strategies such as CT angiography performed with new-generation flat-panel detectors in angiography suites might be a solution for noninvasive follow-up examination of intracranial stents.

The ISR rate may be as high as 32.3%. An overall incidence of ISR of 17.4% is reported in the present series. This series includes a small number of patients younger than 55 years old, which may be a factor responsible for this lower rate of ISR as opposed to that reported in North American series. This influence of age has been suggested by preview studies published by Albuquerque et al. and Turk et al. in 2008.

No correlation between stent location and the frequency of ISR was observed. Interestingly, the ISR group was also the group of patients with stenotic lesions in which postoperative complications were more likely to be observed (Table 3). All cases of ISR except 1 were asymptomatic. We hypothesize that the progressive nature of ISR allows the development of collateral blood supply by means of leptomeningeal anastomoses and progressive adaptation of the circle of Willis. An important benefit of intracranial stent placement besides arterial lumen recovery may be stabilization of the atheromatous plaque, maybe resulting from a synergy with maximal medical treatment and lifestyle changes. The endothelial proliferation that contributes to ISR is not systematically responsible for new ischemic events. If the patient is completely asymptomatic, surveillance may be an acceptable option.

**Limitations of the Study**

The present study has some important limitations. First, although this is a relatively large case series, the absolute number of lesions included is still relatively small in comparison with similar studies of coronary stenosis, and the cases are heterogeneous in terms of the location of the arterial lesion. Therefore, the statistical power is not sufficient to perform detailed subset analyses. Second, follow-up was not available for all patients. Therefore, the evolution of the various patterns of ISR (and the response of these lesions to retreatment) remains unknown for the moment.

**Conclusions**

In this French multicenter series, the endovascular treatment of patients with SIAS with the Wingspan stent and Gateway PTA balloon system resulted in a moderate risk for neurological complications. Nevertheless, considering the critical natural history of severe refractory lesions, stent placement may be considered the first alternative in cases of failed medical therapy. Technical failure, residual stenosis, or ISR did not lead to systematic recurrent stroke in this series, which suggests the importance of plaque stabilization and neoendothelialization. The management of ISR is still a challenge for interventionists, and further investigation is needed.

**Disclosure**

Alain Bonafé, M.D., Ph.D., is a consultant for Boston Scientific.
Treatment of intracranial stenosis with the Wingspan stent

The other authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Maldonado, Costalat, Bonafé. Acquisition of data: Costalat, Arteaga, Turjman, Desal, Sedat. Analysis and interpretation of data: Maldonado, Costalat, Bonafé. Drafting the article: Maldonado, Costalat, Bonafé. Critically revising the article: Maldonado, Costalat, Bonafé. Statistical analysis: Maldonado, Costalat. Administrative/technical/material support: Vendrell, Riquelme, Bonafé. Study supervision: Bonafé. Patient care: all authors. Follow-up: Riquelme, Machi, Arteaga, Turjman, Desal, Sedat, Bonafé.

References


Please include this information when citing this paper: published online July 8, 2011; DOI: 10.3171/2011.5.JNS101583.