Long term clinical and angiographic outcomes with the Wingspan stent for treatment of symptomatic 50–99% intracranial atherosclerosis: single center experience in 51 cases

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ABSTRACT
Background and aim: Two independent post-approval registries have reported favorable periprocedural and short term outcomes with the use of the Wingspan stent for treatment of intracranial arterial stenosis. Data on long term clinical and imaging outcomes after Wingspan stent placement are limited.

Methods: All patients treated with the Wingspan stent in a single academic center from January 2006 to February 2008 were identified. Data on stenting indication, severity of stenosis, technical success, re-stenosis and clinical outcome were collected.

Results: 51 patients were treated with the Wingspan stent system for a symptomatic intracranial atherosclerotic stenosis of 50–99%. The technical success rate was 98%. The mean pre- and post-stent stenoses were 73 (11)% and 21 (7)%. Any stroke or death within 24 h of the procedure occurred in 1/51 (2%). The frequency of any stroke or death within 30 days or ipsilateral stroke beyond 30 days was 5/51 (10.0%) at a mean follow-up time of 14.6 months (range 8–30). The frequency of $\geq$ 50% re-stenosis on follow-up imaging was 7/29 (24%) at 8.6 (4.4) months (range 3–20); all were detected on the initial imaging within 3–6 months, and only one was symptomatic.

Conclusion: The use of the Wingspan stent in patients with $\geq$50% symptomatic intracranial stenosis is associated with good long term clinical outcome. One stroke occurred after the first 30 days, suggesting a significant stabilization of the adverse event rate after the first month.

Intracranial atherosclerotic disease is increasingly recognized as the cause of ischemic stroke in approximately 8–10% of patients.1-7 The Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial randomized patients with symptomatic intracranial stenosis between 50% and 99% to medical therapy with either warfarin or aspirin, and found no difference in the rates of stroke between the two groups. The overall rates of stroke in the territory of the stenotic intracranial artery at 1 and 2 years were 11% and 14%, respectively.6 Moreover, in WASID, patients with $\geq$70% stenosis who had their qualifying event within 17 days prior to enrollment had a 1 year rate of stroke in the territory of the stenotic artery of 25% (95% CI 16% to 31%).9-10 The high rate of neurological events on medical therapy has lead to an renewed interest in intracranial stenting as an alternative therapeutic option.11-22 Since the FDA Humanitarian Device Exemption (HDE) approval of the Wingspan intracranial stent in August 2005,23 several publications have emerged in the literature reporting immediate periprocedural complication rates of 4.5–6.2% and re-stenosis rates of between 7% and 30% at 6 months.24-28 Two of the series also reported on clinical outcomes followed-up to 6 months, with combined rates of periprocedural stroke and death and ipsilateral stroke after 30 days of 7–14%.25 28 Currently, there are no published post-approval data on the long term clinical follow-up (greater than 6 months) after Wingspan stent placement. The aim of this study was to obtain preliminary data on the long term clinical and imaging outcomes of patients treated with the Wingspan stent for symptomatic intracranial arterial stenosis.

METHODS
Patients
Institutional review board (IRB) approval was obtained for the HDE protocol and for clinical and imaging data collection, performed in accordance with the Health Insurance Portability and Accountability Privacy Act.

All patients undergoing stenting with Wingspan under the HDE criteria (patients with 50–99% stenosis of a major intracranial artery with a cerebral ischemic event on antithrombotic therapy) between January 2006 and February 2008 were potential candidates for this study. Patients with any of the following criteria were excluded: those $<45 years of age, angiographic and clinical characteristics suggestive of moyamoya disease, vasculitis or non-atherosclerotic vasculopathy, and use of the Wingspan stent to treat an acute ischemic stroke, cerebral aneurysm or carotid–cavernous fistula. The first 18 patients in the current study were also enrolled and published previously in the NIH Wingspan registry.28

Intracranial stenting technique
Details of the technique have been described previously.28 In our institution, all neuro-interventionalists performed the procedure under general anesthesia via a transarterial femoral or brachial approach, by placing a 6 French guide catheter into the target parent vessel proximally. Diameter measurements were performed according to the WASID technique.29 The Gateway balloon, which is used for pre-dilatation of the lesion prior to inserting the Wingspan stent, was sized to approximate the...
length of the lesion, and the diameter was estimated at 80% of the normal vessel size. The stent diameter was sized to be equal to or the next size up from the largest vessel diameter (eg, a 4.0 mm stent should be placed in a 4.0 mm vessel size but for a vessel measuring 4.1 mm, a 4.5 mm stent should be placed). Stent length was estimated according to the length of the lesion plus 6 mm, to allow a 3 mm overlap on either side of the lesion.

All patients were treated with aspirin (81–325 mg daily) and clopidogrel 75 mg daily at least 7 days prior to the procedure or loaded with 300 mg of clopidogrel and 81–325 mg aspirin within 24 h of the procedure. Intraprocedure un-fractionated heparin was administered as an intravenous bolus to achieve an activated clotting time of 250–300 s. Heparin was not reversed post-procedure. Patients were admitted to a neurointensive care unit for stenting.

The following clinical outcomes were evaluated: any stroke or death within 24 h of the procedure, any stroke or death within 30 days of the procedure and ischemic stroke in the territory of the stented artery beyond 30 days. Stroke was defined as any hemorrhagic or ischemic event associated with a neurological deficit lasting longer than 24 h. Other procedural related complications such as arterial dissection, vasospasm, vessel perforation, groin hematoma and pseudoaneurysm were also documented. Technical success of the procedure was defined as performing the balloon angioplasty and placing the stent across the target lesion with less than 50% immediate residual stenosis.

Follow-up angiography and imaging data, performed at the discretion of the interventionalist, were collected to estimate the rate of re-stenosis, usually within 3–6 months after the procedure. A proportion of patients had their non-invasive testing within 4–8 weeks of the procedure and subsequently had an early follow-up diagnostic angiogram. All baseline, immediate post-procedure and follow-up measurements of stenosis were made by the site interventionalist. Re-stenosis was defined as ≥50% luminal narrowing within the stent or contiguous to the proximal or distal ends of the stent. A lesion that begins >2 mm from the stent margin was not considered in-stent re-stenosis.

Follow-up information was obtained on each patient from their medical records, personal interview or telephone contact. Patients were followed to the date of a stroke or death or last contact. The last follow-up visit occurred on August 2008. Adjudications of all strokes, including whether the strokes were in the territory of the stented artery, and all other complications of stenting, were performed by the study investigators only (interventional neurologists and vascular neurologists).

Analysis
Results are presented as means (SD) and as percentages. A univariate analysis was performed with Fisher and $\chi^2$ tests to compare the age, gender, ethnicity and lesion location between the group with and without re-stenosis.

RESULTS
Demographic features, stent indication (Table 1)
The mean age of the 51 patients enrolled in this study was 63 (11.4) years; 74% were white, 24% were black and 2% were of other races/ethnicity. Men comprised 59%. The indication for stenting was minor or major stroke in 78%, transient ischemic attack (TIA) in 18% and other cerebral ischemic event in 4% (eg, vertebrobasilar insufficiency).

Technical results
The stented arteries were the intracranial vertebral artery in 55%, intracranial carotid in 27%, basilar artery in 18%, middle cerebral artery (MCA) in 16%, vertebrobasilar junction in 2% and posterior cerebral artery (PCA) in 2%. The technical success rate was 98% (50 of 51 procedures). The inability to deploy one stent across a stenotic M2 segment was possibly due to the leading nose cone of the stabilizer being larger in diameter than the distal M2/M3 branch; therefore, this stenosis was treated with angioplasty alone. Mean pre-stenting stenosis was 75 (11)% (range 50–99%) and the immediate mean post-stenting residual stenosis was 21 (7.3)% (range 0–40%).

A total of 29 patients (56%) had follow-up cerebral angiography at a mean of 8.6 (4.4) months after stenting (range 3–20 months). Some patients refused follow-up angiography and others were not certified by their insurance company for an outpatient elective angiography. Re-stenosis (≥50%) was found in 7/29 patients (24%) (two had 50–69% and five had 70–100%). No significant difference was found between the anterior and posterior circulation, although four of those lesions were in the anterior circulation (two MCA and two internal carotid artery (ICA)) and three in the posterior circulation (intracranial vertebral artery). One of the posterior circulation re-stenosis was an asymptomatic complete in-stent occlusion of the vertebral artery. Of the seven patients with re-stenosis, one had recurrent symptoms with TIAs and three were retreated: the patient with recurrent symptoms (recurrent amaurosis fugax) had an intracranial ICA stenosis that was retreated with angioplasty and restenting, and two other patients had posterior circulation lesions with severe >90% re-stenosis and were retreated with angioplasty alone. All cases of re-stenosis were found on the initial follow-up angiogram performed within 3–6 months, and patients who did not have an initial re-stenosis did not develop one on subsequent imaging. There was no difference in age, ethnicity, gender or vessel location between the re-stenosis and no re-stenosis groups.

Peri-procedural complications
Any stroke (ischemic or hemorrhagic with neurological deficit lasting >24 h) or death occurred in 1/51 (2%) patients within 24 h of the stenting procedure. One additional patient had basilar artery stenosis with worsening dysarthria and dysphagia that resolved within 24 h. Other complications that occurred in the periprocedural period included one case of femoral artery pseudoaneurysm requiring thrombin injection and one case of large groin hematoma requiring surgical de-compression.

One month clinical outcome
Three additional events occurred between days 2 and 30. Two patients who initially presented with brainstem infarcts due to basilar stenosis died; one died as a result of sepsis following feeding tube placement on day 28 and one died after family withdrawal of life support measures on day 3. A third patient developed a hyperperfusion syndrome on day 3 following stenting of a >95% right MCA stenosis, with vasogenic cerebral edema, seizures and worsening neurological examination that resolved over 2 weeks with blood pressure control and anti-epileptic medications. The event rate for any stroke or death within 50 days (including first 24 h) was 4/51 (8%).
Midterm events

The mean time from stenting to stroke or death within 30 days, stroke in the territory of the stented artery after 30 days or last clinical follow-up was 14.6 (9) months (range 8–30 months). One additional ischemic stroke in the territory of the stented artery occurred beyond 30 days (at 2 months). The stroke was a lacunar stroke in the territory of the stented right middle cerebral artery despite dual antiplatelet agents with pure left-sided motor weakness. The rate of any stroke or death within 30 days or stroke in the territory of the stented artery beyond 30 days was 5/51 (10.0%) at a mean follow-up of 14.6 months. Technical and clinical outcome is summarized in table 2.

**DISCUSSION**

Limited data are available on the long term clinical outcomes of patients treated with the Wingspan stent for symptomatic intracranial atherosclerosis. The initial Wingspan HDE study followed patients for up to 6 months and reported a 7.0% rate of ipsilateral stroke or death during that period. The only other study to report clinical outcomes at 6 months from treatment was the post-marketing NIH registry which reported a combined rate of any stroke or death within 30 days and ipsilateral stroke beyond 30 days of 14.6 (9) months (range 8–30 months). The lower rate of stroke in the initial HDE study might be partially explained by the inclusion of patients with less severe stenosis in the HDE study (50–99%) compared with the NIH registry which required at least 70% stenosis for enrollment.

Further analysis of the NIH registry data also suggested that clinical outcomes were strongly associated with the volume of Wingspan procedures performed. For low volume centers, the rate of any stroke or death within 30 days and ipsilateral stroke beyond 30 days was 25% versus 9% for the higher volume centers. Our current series of 51 patients treated by two neurointerventionists at a high volume center supports this observation, with a combined rate of any stroke or death within 30 days and ipsilateral stroke beyond 30 days of 10% at a mean follow-up of 14.6 months.

The technical success rate in our series was very high (98%), and was similar to previously reported series of Wingspan treated patients (96.7–98.3%). We had only one major peri-procedural neurological complication (2%), less than in previously reported series (6.1–6.2%), which may support a diminishing rate of procedural complications with increasing Wingspan experience.

The rate of re-stenosis in our series was 24% at a mean follow-up of 8.6 months. This rate is similar to the rates of re-stenosis published in the other post-marketing series (25–29.7% at 6 months) and remains significantly higher than the initial Wingspan HDE trial (7.5% at 6 months). The reason for the higher re-stenosis rates in the post-marketing experience is uncertain but the consistency of the rates now demonstrated in multiple series suggests that the initial HDE study significantly underestimated the true rate of re-stenosis with Wingspan. However, it is also possible that the post-marketing re-stenosis rates may overestimate the true rate as selection bias may have influenced the selection of patients for re-imaging as only 56% of our patients in this series underwent follow-up angiography.

Re-stenosis after stenting of coronary and peripheral atherosclerotic disease often occurs within 3–6 months of treatment. This observation is consistent with our data for intracranial atherosclerosis where in our series all re-stenosis was detected on angiography within 3–6 months. Similarly, arteries with no re-stenosis on initial follow-up imaging did not develop re-stenosis during the follow-up period.

The risk of stroke associated with re-stenosis of an intracranial artery has not been well described. In our series, only one of the seven patients with angiographically proven re-stenosis was symptomatic (TIA). The risk of stroke associated with re-stenosis after extracranial carotid stenting appears to be low, possibly related to the fact that re-stenosis within the first 6 months of stenting is usually due to neointimal hyperplasia rather than recurrent atherosclerosis. This observation may be

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**Table 1** Clinical and imaging features of the study cohort (51 patients)

<table>
<thead>
<tr>
<th>Age (years) (mean (SD))</th>
<th>63 (11.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity (n (%))</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>38 (74)</td>
</tr>
<tr>
<td>Black</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Gender, male (n (%))</td>
<td>30 (59)</td>
</tr>
<tr>
<td>Stenting indication (n (%))</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>40 (78)</td>
</tr>
<tr>
<td>TIA</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (4)</td>
</tr>
<tr>
<td>Stented arteries (n (%))</td>
<td></td>
</tr>
<tr>
<td>Intracranial vertebral</td>
<td>18 (35)</td>
</tr>
<tr>
<td>Intracranial carotid</td>
<td>14 (27)</td>
</tr>
<tr>
<td>MCA</td>
<td>9 (18)</td>
</tr>
<tr>
<td>BA</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Vertebrobasilar junction</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

**Table 2** Technical and clinical outcome following intracranial stenting

**Technical outcome**

- Technical success (deploying the stent across the lesion with < 50% stenosis)
  - 98%
- Post-stent stenosis (% (mean (SD, range))
  - 73 (11, 50–99)
- Post-stent imaging follow-up time (months (mean (SD, range))
  - 9 (4, 3–20)
- No of patients with follow-up imaging (n (%))
  - 29 (56)
  - Vertebral
  - 10
  - MCA
  - 7
  - BA
  - 6
  - ICA
  - 5
  - PCA
  - 1

**Patient re-stenosis: ≥50% in-stent stenosis (n (%))**

- 7/29 (24)
- 50–69% 2
- 70–99% 4
- Occlusion, vertebral 1
- Symptomatic (TIA, ICA with amaurosis) 1

**Distribution of re-stenosis according to vessel location**

- Posterior circulation (carotid 3/10, BA 0/6, PCA 0/1)
  - 3/16 (19%); p = 0.24
- Anterior circulation (carotid 2/5, MCA 2/7)
  - 4/13 (31%); p = 0.24

**Re-treatment for >90% re-stenosis**

- 3/7

**Angioplasty with drug eluting stent, ICA**

- 1

**Angioplasty alone, vertebral**

- 2

**Clinical outcome**

- Mean clinical follow up time (months (mean (SD))
  - 14.6 (8, 8–30)
- 24 h any stroke or death (n (%))
  - 1 (2)
- Site related events (pseuodaneurysm, hematoma) (n (%))
  - 2 (4)
- 30 days stroke or death (including 24 h events) (n (%))
  - 8
  - Long term events (ipsilateral stroke or death beyond 30 days, and stroke or death within 30 days) (n (%))
  - 5 (10)

**Table headers**

- **Clinical follow-up was 14.6 (9) months (range 8–30 months).**
- **Further analysis of the NIH registry data also suggested that clinical outcomes were strongly associated with the volume of Wingspan procedures performed.**
- **Our current series of 51 patients treated by two neurointerventionists at a high volume center supports this observation, with a combined rate of any stroke or death within 30 days and ipsilateral stroke beyond 30 days of 10% at a mean follow-up of 14.6 months.**
- **The technical success rate in our series was very high (98%), and was similar to previously reported series of Wingspan treated patients (96.7–98.3%). We had only one major peri-procedural neurological complication (2%), less than in previously reported series (6.1–6.2%), which may support a diminishing rate of procedural complications with increasing Wingspan experience.**
- **The rate of re-stenosis in our series was 24% at a mean follow-up of 8.6 months. This rate is similar to the rates of re-stenosis published in the other post-marketing series (25–29.7% at 6 months) and remains significantly higher than the initial Wingspan HDE trial (7.5% at 6 months). The reason for the higher re-stenosis rates in the post-marketing experience is uncertain but the consistency of the rates now demonstrated in multiple series suggests that the initial HDE study significantly underestimated the true rate of re-stenosis with Wingspan. However, it is also possible that the post-marketing re-stenosis rates may overestimate the true rate as selection bias may have influenced the selection of patients for re-imaging as only 56% of our patients in this series underwent follow-up angiography.**

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similar for intracranial re-stenosis but larger series with good long term follow-up are needed to answer this question.

The data presented in this series had several limitations. Unlike a well designed clinical trial, it lacks several features that add rigor to the data collection and generalizability to the results, such as a prespecified procedural protocol, central adjudication of events and angiograms, and independent neurological evaluations pre- and post-procedure. Given that complications were assessed and reported by the primary operators, it is possible that peri-procedural morbidity could have been underestimated. However, significant clinical events that occurred during the long-term follow-up period would not likely be missed given the cooperation of multiple medical personal in the long term care of patients with significant vascular disease.

Despite these limitations, the current series with a mean clinical follow-up of >1 year provides the longest clinical follow-up to date of patients treated with the Wingspan stent for symptomatic intracranial atherosclerotic disease. The 10% combined rate of any stroke or death within 50 days or ipsilateral stroke after 50 days in our series may not be superior to the 11% rate of ipsilateral stroke reported in WASID at 1 year with medical therapy alone.1 However, our study population is different than the WASID population. In our study, we did not exclude patients with progressive basilar syndrome or with a modified Rankin scale ≥5.

Moreover, our data are encouraging in that only one of the five adverse events occurred after the first 50 days, suggesting significant stabilization of the adverse event rate after the first month. This finding adds hope to the possibility that intracranial stenting may eventually be proven superior to medical therapy for the treatment of intracranial atherosclerotic disease in a randomized clinical trial performed over a longer follow-up period.

Ethics approval: The study was approved by the institutional review board.

Competing interests: None.

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