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The NIH registry on use of the Wingspan stent for symptomatic 70–99% intracranial arterial stenosis

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Abstract

Background—The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial showed that patients with symptomatic 70% to 99% intracranial arterial stenosis are at particularly high risk of ipsilateral stroke on medical therapy: 18% at 1 year (95% CI = 3% to 24%). The Wingspan intracranial stent is another therapeutic option but there are limited data on the technical success of stenting and outcome of patients with 70% to 99% stenosis treated with a Wingspan stent.

Methods—Sixteen medical centers enrolled consecutive patients treated with a Wingspan stent in this registry between November 2005 and October 2006. Data on stenting indication, severity of stenosis, technical success (stent placement across the target lesion with <50% residual stenosis), follow-up angiography, and outcome were collected.

Results—A total of 129 patients with symptomatic 70% to 99% intracranial stenosis were enrolled. The technical success rate was 96.7%. The mean pre and post-stent stenoses were 82% and 20%. The frequency of any stroke, intracerebral hemorrhage, or death within 30 days or ipsilateral stroke beyond 30 days was 14.0% at 6 months (95% CI = 8.7% to 22.1%). The frequency of 50% restenosis on follow-up angiography was 13/52 (25%).

Conclusion—The use of a Wingspan stent in patients with severe intracranial stenosis is relatively safe with high rate of technical success with moderately high rate of restenosis. Comparison of the event rates in high-risk patients in Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) vs this registry do not rule out either that stenting could be associated with a substantial relative risk reduction (e.g., 50%) or has no advantage compared with medical therapy. A randomized trial comparing stenting with medical therapy is needed.

Intracranial stenosis is responsible for 8% to 10% of ischemic strokes in the United States.^{1–7} 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 no difference in the rates of stroke between the aspirin and warfarin arms, and the 1-

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and 2-year rates of stroke in the territory of the stenotic intracranial artery were 11% and 14% in both treatment arms combined.⁸

In WASID the most important baseline predictors of stroke in the territory were severity of stenosis and time from qualifying event to enrollment. 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. In patients with 70% stenosis, those who had their qualifying event within 30 days prior to enrollment 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 enrollment had a 1 year rate of stroke in the territory of 10% (95% CI = 5% to 20%).^{9,10}

The high rate of stroke in medically treated patients with 70% to 99% stenosis and recent events indicate that alternative therapies are needed for these patients. Intracranial angioplasty is an option, however, it has largely been replaced by stenting 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 rates.^{11–15} Intracranial stenting has emerged as the preferred technique by most interventionalists and is increasingly being used in the United States and other countries.^{16–29} Most of the experience with intracranial stenting has been with balloon mounted coronary stents but these stents are difficult to deliver in the tortuous intracranial circulation. In August 2005, the Food and Drug Administration (FDA) granted a Humanitarian Device Exemption (HDE) approval for a self-expanding nitinol intracranial stent (the Wingspan stent, Boston Scientific, Fremont, CA) for use in patients with 50% intracranial stenosis who have recurrent ischemic events while on antithrombotic therapy.²⁸

Since FDA approval of the Wingspan stent, over 100 neurointerventionalists have been trained to use it and over 1,500 stenting procedures have been performed in the United States (personal communication, Boston Scientific). Currently, there are no published data on the outcome after stenting with the Wingspan device in patients with 70% to 99% stenosis and recent TIA or stroke. The aims of this study were to obtain preliminary data on the technical success of stenting and outcome of high-risk patients with symptomatic intracranial arterial stenosis treated with the Wingspan stent.

METHODS

Participating sites and patient entrance criteria

Sites interested in participating in a planned randomized clinical trial comparing stenting with medical therapy in patients with severe intracranial stenosis were invited to participate in this National Institute of Health funded stenting registry. Site criteria for participating were completion of a 2-day Boston Scientific training program by the interventionalists at each site. The patients treated during this training program were included in this registry.

Each participating site was required to obtain institutional review board approval for the registry data collection, performed in accordance with the Health Insurance Portability & Accountability Privacy Act. Sixteen sites met all these criteria and participated in the registry (appendix).

All patients undergoing stenting with the Wingspan device under the HDE criteria (patients with 50% to 99% stenosis of a major intracranial artery with a cerebral ischemic event on antithrombotic therapy) at 16 participating sites between November 2005 and October 2006 were potential candidates for this study. Patients with any of the following criteria were

excluded: <70% stenosis, concurrent treatment with two stents for tandem intracranial stenoses, use of the Wingspan stent to treat an acute ischemic stroke.

Stenting procedure description

All sites had been trained by Boston Scientific proctors to use the following stenting protocol. The procedure was performed under general anesthesia, via transarterial femoral or brachial approach by placing a 6-French Guide Catheter or 6-French Long Sheath into the parent target vessel proximally. Diameter measurements were performed at the site of highest stenosis and the normal artery to estimate percent stenosis according to the WASID measurement technique.³⁰ 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, e.g., 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. The stent length was estimated according to the length of the lesion plus 3 mm on either side of the lesion.

Via the base catheter, a microcatheter was used to cross the lesion over a micro-guide wire (0.010" or 0.014") and placed distal to the lesion allowing a reasonable purchase of microwire. An exchange length floppy tip microwire (0.014") was placed via the microcatheter, and the latter was removed.

Over the exchange length microwire the Gateway balloon was placed, centered across the lesion, and inflated slowly at 6 to 10 atmospheric pressure with a 50 to 70% mixture of iodinated contrast and saline. Slow inflation and deflation, over 60 to 120 seconds, was performed to allow the contrast to migrate in and out of the balloon lumen to minimize recoil and intimal injury.

The balloon was deflated and another angiogram was performed. After reviewing the images, the balloon was completely removed and the Wingspan over-the-wire self-expandable stent system was placed over the exchange length microwire, centered across the lesion, and deployed slowly by fixing the stabilizer and unsheathing the stent. Repeat imaging of the stented artery and measurements of the residual stenosis were performed.

All patients were treated with aspirin (81 to 325 mg daily) and clopidogrel 75 mg daily at least 3 days prior to the procedure or loaded with 300 mg of clopidogrel and 81 to 325 mg aspirin within 24 hours of the procedure. Intraprocedure unfractionated heparin was administered at approximately 70 units/kg as an IV bolus to achieve an activated clotting time of 250 to 300 seconds. The heparin was not reversed post procedure. Patients were admitted to a neurointensive or general critical care unit for 24 hours for hemodynamic and neurologic monitoring. Aspirin 81 to 325 mg was recommended throughout follow-up and clopidogrel 75 mg daily was recommended for 4 to 12 weeks after stenting.

Evaluation of outcomes

The following clinical outcomes were evaluated: any stroke or death within 24 hours and 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 neurologic deficit lasting longer than 24 hours. 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 data, performed at the discretion of the local investigator, were collected to estimate the rate of restenosis. All baseline, immediate post procedure, and follow-up measurements of stenosis were made by the site interventionalist. Restenosis was defined as 50% luminal narrowing.

Follow-up information was obtained on each patient from the 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 April 4, 2007. 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 local study investigators only (neurologist or interventionalist).

Statistical analysis

Retrospective and prospective data collection occurred via a data collection form. Completed data forms were submitted to the Data Management Center at Emory University for analysis. Results are presented as means ($\pm$ SD) and as percentages, with 95% CIs for binary clinical outcomes calculated using the exact binomial method. The cumulative probability of an event (any stroke or death within 30 days or stroke in the territory after 30 days) over time was estimated using the Kaplan-Meier (product limit) method with pointwise CIs calculated using the log cumulative hazard transformation. Strokes and deaths occurring between days 1 and 30 were considered to have occurred on day 15 since exact dates for events in this time frame were not collected. The log-rank test was used to compare the time to this outcome between patients at low enrolling and high enrolling sites with a hazard ratio and 95% CI determined using Cox proportional hazards regression.

RESULTS

Demographic features, qualifying events

The mean age of the 129 patients enrolled in this registry was 64.2 ± 12.4 years, 81% were white, 13% were black, and 6% were of other races/ethnicity. Men comprised 55%. The indication for stenting was stroke in 61%, TIA in 29%, and other cerebral ischemic event in 10% (e.g., vertebrobasilar insufficiency). Median time from qualifying event to stenting was 12 days (quartiles 4 to 36 days).

Technical and angiographic results

The stented intracranial arteries were the MCA in 33%, carotid 26%, vertebral artery 24%, and basilar artery 17%. The technical success rate was 96.7% (95% CI = 91.8% to 99.1%). Mean pre-stenting diameter stenosis was $82\% \pm 9\%$ (median 80%, quartiles 75% and 90%) and the immediate mean post stenting residual stenosis was $20\% \pm 16\%$ (median 20%, quartiles 10% and 30%). A total of 52 patients (40%) had follow-up cerebral angiography at a mean of 4.8 ± 2.1 months after stenting (quartiles 3.4 and 6.3 months). The mean residual stenosis on repeat angiography rate was $29\% \pm 28\%$ (median 20%, quartiles 10% and 48%). Restenosis ($\geq 50\%$) was found in 13/52 patients (25%) (6 had 50 to 69% and 7 had 70 to 100%). Of the 13 patients with restenosis, 2/13 had a stroke (both attributed to stent occlusion): one patient, who had a stroke at 2 months, had been taken off aspirin and clopidogrel 5 weeks after stenting for a surgical procedure and only aspirin was restarted; the other patient had been on aspirin and clopidogrel for 30 days after stenting then aspirin alone at the time of recurrent stroke and follow-up angiogram. Figure 1 shows the technical outcome in one patient at 4 months.

Periprocedural event rates

Any stroke (ischemic or hemorrhagic) or death occurred in 8 patients within 24 hours of the stenting procedure for an event rate of 6.2% (95% CI = 3.2% to 12.0%, figure 2). Table 1 shows the causes of stroke or death in these 8 patients. Other neurologic complications that occurred in the periprocedural period included four cases of stent thrombosis that were successfully treated with IIb/IIIa agents in three cases and the treatment was not specified in the other case, two patients had a cerebral infarct on MRI with neurologic signs lasting less than 24 hours, two patients had TIA, one patient was somnolent for 3 days after the procedure but had no infarct on MRI, two patients had asymptomatic vessel dissection, and two patients experienced transient vasospasm.

Clinical events during follow-up

Two additional ischemic strokes occurred during days 2 to 30. One was in the territory and one out of the territory of the stented artery. Two additional deaths occurred during days 2 to 30, one due to an intracerebral hemorrhage (ICH) and one of unknown cause (table 2). The event rate for any stroke or death within 30 days was 9.6% (95% CI = 5.6% to 16.3%, figure 2).

Four additional ischemic strokes in the territory of the stented artery occurred beyond 30 days, one just beyond 1 month, one at 2 months, one at 4 months, and one at 6 months. 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 5.8 months (range of 1 day to 15.6 months). The rate of any stroke or death within 30 days or stroke in the territory of the stented artery beyond 30 days was 14.0% at 6 months (95% CI = 8.7% to 22.1%, figure 2).

Event rates at high vs low enrolling sites

Of the 16 centers, 10 centers enrolled 1 to 8 patients (a total of 35 patients) and 6 centers enrolled 14 to 19 patients (a total of 94 patients). Among low enrolling sites, 8 patients (23%) had a stroke or died within 30 days or had a stroke in the territory after 30 days. Among high enrolling sites, 8 patients (9%) had this outcome. The Kaplan-Meier curves for the two groups were significantly different ($p = 0.022$, hazard ratio = 2.9 [95% CI = 1.1 to 7.8]). For low enrolling sites, the rate of this outcome was 14.3% (95% CI = 6.2% to 31.0%) at 24 hours, 17.2% (95% CI = 8.1% to 34.4%) at 30 days, and 26.9% (95% CI = 13.8% to 48.5%) at 6 months. For high enrolling sites, the rate of this outcome was 3.2% (95% CI = 1.0% to 9.6%) at 24 hours, 6.8% (95% CI = 3.1% to 14.5%) at 30 days, and 9.5% (95% CI = 4.9% to 18.3%) at 6 months.

Among the characteristics compared between patients at high vs low enrolling sites (age, gender, race, reason for stenting, time from last symptom to stenting, artery stented, and percent stenosis), mean percent stenosis was the only factor that was significantly different between the two groups (high recruiting: $80\% \pm 8\%$; low recruiting: $86\% \pm 10\%$; $p = 0.004$). A Cox regression model including high vs low enrolling sites ($p = 0.088$) and percent stenosis ($p = 0.21$) showed that type of site was the more important factor.

Event rates in patients with 70 to 99% and recent TIA or stroke in this registry vs WASID

A comparison of the outcome of patients with 70% to 99% stenosis and TIA or stroke within 30 days prior to stenting in this registry ($n = 86$) vs patients in WASID with 70% to 99% stenosis and TIA or stroke within 30 days prior to enrollment ($n = 122$) is shown in the Kaplan-Meier curves in figure 3. These curves indicate that the observed rates of any stroke or death within 30 days or stroke in the territory beyond 30 days are similar in the two groups up to 3 months but diverge afterwards (lower in the stented patients). However, given the small sample size in this registry, the 95% CI for the stented patients are wide and

the upper 95% CI curve for the stented patients is higher than the observed curve in the WASID high-risk patients.

DISCUSSION

This study provides preliminary postmarketing multicenter data on the experience with the Wingspan stent in patients with 70% to 99% symptomatic intracranial stenosis. Compared to the Wingspan Phase I study of patients with 50% to 99% stenosis,³¹ the use of the Wingspan stent in this registry was associated with a similar high rate of technical success but higher rates of restenosis and stroke or death within 30 days of stenting.

The high technical success rate (96.7%) in this study, even in arteries that have been challenging to stent previously (e.g., the MCA), is probably related to the very flexible design of the Wingspan stent and the fact that the Wingspan system is an iteration of the Neuroform stent (BSC, Fremont, CA) which most neurointerventionalists have experience with in treating cerebral aneurysms.³² Other studies involving experienced neurointerventionalists have also shown similar high technical success rates associated with the use of the Wingspan stent.^{29,31,33} These high rates of technical success may not be reproducible by less experienced interventionalists with little Neuroform or cerebral microcatheterization experience.

The deliverability of Wingspan, a flexible self-expanding stent, is in contrast to the deliverability of coronary balloon-mounted stents which have been used off-label in the intracranial circulation.^{16,17,19–25,27} In a report of 59 patients treated with drug-eluting balloon-mounted coronary stents, 50% of the patients had lesions in the extracranial vertebral artery, 8% were in the intracranial internal carotid artery, and none were in middle cerebral artery, reflecting the difficulty in tracking the coronary stents into the intracranial circulation.³⁴

The rate of restenosis in this study is higher than the rate in the Wingspan Phase I study (7.5% at 6 months). The reasons for the higher rate in this registry are uncertain but it is possible that our restenosis rate may be an overestimate of the true rate since selection bias may have influenced who underwent reimaging (<50% of our patients underwent reimaging). However, it is also possible that the Phase I study may have underestimated the true rate of restenosis associated with the Wingspan stent.

Intraprocedure technical factors (size and location of stented artery, residual stenosis poststenting) and postprocedure medical factors (e.g., control of vascular risk factors, duration of combined anti-platelet therapy with aspirin and clopidogrel) will need to be monitored and correlated with the risk of restenosis, especially symptomatic restenosis, in future stenting trials. The risk of stroke associated with restenosis after stenting of an intracranial artery has not been well studied, however, the risk of stroke associated with restenosis after extracranial carotid stenting appears to be low.³⁵ This is probably related to the fact that restenosis within the first 6 months of stenting is usually due to neointimal proliferation rather than recurrent atherosclerosis. Neointimal proliferation results in a smooth endothelial surface which is less likely to ulcerate or produce turbulent flow and distal embolization than atherosclerotic stenosis.^{35,36}

The rate of stroke or death within 24 hours in this study of patients with 70% to 99% stenosis was 6.2% and is similar to the periprocedural rates of stroke or death in two other Wingspan series of symptomatic patients with 50% to 99% stenosis (6.1% to 6.7%).^{29,33} At 30 days, the rate of stroke or death in patients in this registry was 9.6% which is higher than the 30-day rate of stroke or death in patients with 50% to 99% stenosis treated in the Wingspan Phase I trial (4.4%). Based on the lower 30-day rate of stroke and death at our

high enrolling sites vs low enrolling sites, we anticipate that the overall 30-day rate of stroke or death will diminish as more experience with the Wingspan stent accumulates. Additionally, with careful selection of interventionalists in future trials and the use of aggressive statin therapy before stenting, which has been associated with a lower periprocedural risk of stenting in patients with extracranial carotid stenosis,³⁷ a lower 30-day rate of stroke or death after stenting with Wingspan in patients with 70% to 99% stenosis is possibly achievable in future studies.

The rate of any stroke or death within 30 days or stroke in the territory beyond 30 days (the anticipated primary endpoint in a randomized trial of stenting vs medical therapy) was 14.0% at 6 months which is similar to the 6-month rate of this endpoint in WASID patients with 70% to 99% stenosis.⁹ However, at high enrolling sites in this registry, the primary endpoint rate at 6 months was 9.5%. This rate is similar to the rate of stroke in a study of patients with 70% to 99% stenosis treated with intracranial stenting at a high-volume center in China.¹⁹

Since patients with 70% to 99% stenosis and TIA or stroke within the previous 30 days are at highest risk of stroke, they stand to gain the most from stenting. Therefore, in the randomized trial of stenting vs medical therapy we are planning, these are the patients who will be targeted for enrollment. Comparison of the Kaplan-Meier curves (figure 3) for the patients in WASID vs the patients in this registry with these high-risk features suggests that the curves are similar in the first 90 days and then diverge in favor of stenting beyond 90 days. However, the wide CIs around the primary endpoint rate in the stenting arm do not rule out that stenting could lower the risk of the primary endpoint by as much as 50% or may have no benefit over medical therapy.

This study has several limitations. It was not designed as a prospective clinical trial and therefore does not have many of the rigorous design features of such a trial, e.g., prospective collection of data in all patients, rigorous data auditing, a protocol specified evaluation by a neurologist before and after the procedure, central adjudication of events and angiogram readings, more rigorous inclusion and exclusion criteria, and a prespecified protocol for the stenting procedure and concomitant medical therapy. Additionally, the small number of patients followed beyond 6 months makes the estimation of event rates 6 to 12 months after stenting imprecise.

Despite these limitations, this study provides important preliminary data on the technical success of stenting and outcome of patients with 70% to 99% intracranial stenosis treated with the Wingspan stent. Whether stenting with Wingspan provides any benefit compared with medical therapy in these patients can only be established in a randomized trial which we are planning.

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GLOSSARY

FDA	Food and Drug Administration
HDE	Humanitarian Device Exemption
ICH	intracerebral hemorrhage
WASID	Warfarin-Aspirin Symptomatic Intracranial Disease

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APPENDIX

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Figure 1. Symptomatic proximal basilar artery stenosis

Symptomatic proximal basilar artery stenosis with 80% stenosis and 35% residual stenosis on the immediate post stenting result, and 40% on 4 months angiographic follow-up.

The dotted lines show the 95% CIs.

Figure 2.

A Kaplan-Meier curve for the outcome stroke or death within 30 days or stroke in the territory after 30 days among Wingspan registry patients with 70% stenosis prior to stenting

Figure 3. Kaplan-Meier curves

Kaplan-Meier curves showing a comparison of Warfarin-Aspirin Symptomatic Intracranial Disease patients (n = 122) with Wingspan registry patients (n = 86) with the high-risk entrance criteria of 70% to 99% stenosis and TIA or stroke within 30 days prior to study entry for the outcome stroke or death within 30 days or stroke in the territory after 30 days.

Table 1

Major neurologic events within 24 hours

Events	No.
Non-fatal ischemic stroke	3
In territory of stented artery	2
In and out of territory of stented artery	1
Non-fatal ischemic stroke in the territory and ICH or SAH	2
Non-fatal ICH alone	1
Death	2
Ischemic pontine stroke	1
Pontine hemorrhage	1
Any ischemic or hemorrhagic stroke or death	8

Table 2

Major neurologic events within 30 days (including events within 24 hours)

Events	No.
Non-fatal ischemic stroke	5
In territory of stented artery	3
In and out of territory of stented artery	1
Out of territory of stented artery	1
Non-fatal ischemic stroke in the territory and ICH or SAH	2
Non-fatal ICH alone	1
Death	4
ICH	2
Ischemic stroke	1
Unknown	1
Any ischemic or hemorrhagic stroke or death at 30 days	12