Target Lesion Revascularization After Wingspan
Assessment of Safety and Durability

David J. Fiorella, MD, PhD; Elad I. Levy, MD; Aquilla S. Turk, DO; Felipe C. Albuquerque, MD; G. Lee Pride, Jr, MD; Henry H. Woo, MD; Babu G. Welch, MD; David B. Niemann, MD; Phillip D. Purdy, MD; Beverly Aagaard-Kienitz, MD; Peter A. Rasmussen, MD; L. Nelson Hopkins, MD; Thomas J. Masaryk, MD; Cameron G. McDougall, MD

Background and Purpose—In-stent restenosis (ISR) occurs in approximately one-third of patients after the percutaneous transluminal angioplasty and stenting of intracranial atherosclerotic lesions with the Wingspan system. We review our experience with target lesion revascularization (TLR) for ISR after Wingspan treatment.

Methods—Clinical and angiographic follow-up results were recorded for all patients from 5 participating institutions in our US Wingspan Registry. ISR was defined as >50% stenosis within or immediately adjacent (within 5 mm) to the implanted stent and >20% absolute luminal loss.

Results—To date, 36 patients in the registry have experienced ISR after percutaneous transluminal angioplasty and stenting with Wingspan. Of these patients, 29 (80.6%) have undergone TLR with either angioplasty alone (n = 26) or angioplasty with restenting (n = 3). Restenting was performed for in-stent dissections that occurred after the initial angioplasty. Of the 29 patients undergoing TLR, 9 required ≥1 interventions for recurrent ISR, for a total of 42 interventions. One major complication, a postprocedural reperfusion hemorrhage, was encountered in the periprocedural period (2.4% per procedure; 3.5% per patient). Angiographic follow-up is available for 22 of 29 patients after TLR. Eleven of 22 (50%) demonstrated recurrent ISR at follow-up angiography. Nine patients have undergone multiple retreatments (2 retreatments, n = 6; 3 retreatments, n = 2; 4 retreatments, n = 1) for recurrent ISR. Nine of 11 recurrent ISR lesions were located within the anterior circulation. The mean age for patients with recurrent anterior circulation ISR was 57.9 years (vs 81 years for posterior circulation ISR).

Conclusions—TLR can be performed for the treatment of intracranial Wingspan ISR with a relatively high degree of safety. However, the TLR results are not durable in ≈50% of patients, and multiple revascularization procedures may be required in this subgroup. (Stroke. 2009;40:106-110.)

Key Words: intracranial atherosclerotic disease ■ poststenting in-stent restenosis ■ target lesion revascularization ■ Wingspan stent system

In-stent restenosis (ISR) after percutaneous transluminal angioplasty and stenting for intracranial atherosclerotic disease occurs in approximately one-third of patients treated with the Wingspan system. Target lesion revascularization (TLR) refers to any procedure performed to restore luminal patency after there has been late luminal loss attributable to ISR. There is an extensive body of literature characterizing TLR in the coronary circulation, but there are no data that specifically address intracranial TLR. We present the first series to our knowledge of intracranial TLR with attention to periprocedural safety and durability.

Patients and Methods

Patient and Institutional Enrollment
All patients with intracranial atherosclerotic disease undergoing attempted treatment with the Wingspan system were prospectively enrolled into a multicenter, intention-to-treat registry that included the Barrow Neurological Institute, Cleveland Clinic, State University of New York at Buffalo, University of Texas Southwestern, and University of Wisconsin. The institutional review board at each institution approved the use of Wingspan under a Humanitarian Device Exemption, as well as the collection and sharing of registry data among the participating centers.

Received May 13, 2008; accepted May 28, 2008.
From Departments of Neurosurgery and Neuroradiology (D.J.F., P.A.R., T.J.M.), Cleveland Clinic Foundation, Cleveland, Ohio; Departments of Neurosurgery and Radiology and Toshiba Stroke Research Center (E.L.L., L.N.H.), School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Millard Fillmore Gates Hospital, Kaleida Health, Buffalo, NY; Departments of Radiology and Neurosurgery (A.S.T.), Medical University of South Carolina, Charleston, SC; Department of Neurosurgery (F.C.A., C.G.M.), Barrow Neurological Institute, Phoenix, Ariz; Departments of Neurosurgery and Neuroradiology (L.P., B.G.W., P.D.P.), University of Texas Southwestern, Dallas, Tex; Departments of Neurological Surgery and Radiology (H.H.W.), University at Stony Brook, State University of New York, Stony Brook, NY; Departments of Neurosurgery and Neuroradiology (D.N., B.A.-K.), University of Wisconsin, Madison, Wisc.
Correspondence to David J. Fiorella, MD, PhD, Barrow Neurosurgical Associates, Ltd, Phoenix–Main Office, 2910 N. 3rd Avenue, Phoenix, AZ 85013. E-mail david.fiorella@bnaneuro.net
© 2008 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.108.525774
Data Collection
Clinical and angiographic data were collected at the time of the initial procedure and at 3 to 6 months and 12 to 15 months thereafter according to a standardized follow-up protocol. Clinical data were also collected at discharge and between 2 and 6 weeks after the original procedure. ISR was defined as >50% stenosis (using the technique established in the Warfarin-Aspirin Symptomatic Intracranial Disease study9), within or immediately adjacent (within 5 mm) to the implanted stent, and >20% absolute luminal loss (ie, >20% increase in posttreatment stenosis). For patients with ISR undergoing TLR, angiographic and clinical follow-up were performed at 3 to 6 months and 9 to 15 months after retreatment.

Original Stenting Technique
The original percutaneous transluminal angioplasty and stenting was performed using the Wingspan system as described previously.9 Patients were typically maintained on dual antiplatelet therapy through the time of their initial angiographic follow-up with the intention to discontinue clopidogrel if angiography showed no ISR. In patients with ISR, dual antiplatelet therapy was typically continued, in preparation either for reintervention or for stroke prophylaxis.2,10

Retreatments
Patients with late luminal loss meeting the registry definitions for ISR were considered candidates for lesion revascularization. No TLR procedures were performed in patients who did not meet ISR criteria. The decision to perform retreatment was based entirely on the opinion of the interventionist. There was no predetermined protocol that defined indications for reintervention in registry patients.

Access was typically achieved through the common femoral artery. All retreatment procedures were performed through a 6-Fr system. The targeted parent vessel was accessed with a 6-Fr guiding catheter (Envoy or Envoy XB, Cordis; or Neuron, Penumbra Inc). Heparinization was instituted to a targeted activated coagulation time of 250 to 300 seconds. In most cases, after conventional catheter-based angiography, an SL-10 (Boston Scientific), Prowler-10 (Cordis), or Echelon-10 (Micro Therapeutics/ev3) microcatheter was manipulated across the target lesion using a 0.014-inch Synchro Dis), or Echelon-10 (Micro Therapeutics/ev3) microcatheter was manipulated across the target lesion using a 0.014-inch Synchro (Boston Scientific) or Transcend EX Soft Tip (Boston Scientific) microwire. The microcatheter was then exchanged over a 0.014-inch Synchro (Boston Scientific) or Transcend EX Soft Tip (Boston Scientific) microwire and advanced into the distal parent artery. All retreatment procedures were performed under fluoroscopic control with a slow, graded inflation within the confines of the stented segment. Angioplasty was performed for in-stent dissections that occurred after the initial PTA (Figure 1). Among the retreated lesions, 23 were located within the anterior circulation (79.3%) vs 6 in the posterior circulation.

ISR lesions selected for retreatment were often either symptomatic (n=4), angiographically more severe (longer segment involved or greater percentage of stenosis) than the presenting stenosis (n=8), or both (n=9). In some cases (n=8), however, retreatment was performed in the absence of either of these factors. When symptomatic (n=13), approximately two-thirds of patients presented with transient ischemic attack (n=9) and one-third (n=4) presented with ipsilateral stroke.

Of the 29 patients undergoing primary TLR, 9 required ≥1 interventions for recurrent ISR, for a total of 42 TLR interventions. Only 1 major complication, a postprocedural reperfusion hemorrhage, was encountered during TLR (complication rates: 2.4% per procedure; 3.5% per patient). This patient had poorly controlled hypertension in the immediate periprocedural period.

Angiographic follow-up is available for 129 treated lesions (75 anterior circulation, 54 posterior circulation) in the present series. Thirty-six of 129 (27.9%) patients with treated lesions with imaging follow-up experienced ISR. Of these 36, 29 (80.6%) underwent TLR with either angioplasty alone (n=26) or angioplasty with restenting (n=3). Restenting was performed for in-stent dissections that occurred after the initial PTA (Figure 1). Among the retreated lesions, 23 were located within the anterior circulation (79.3%) vs 6 in the posterior circulation.

ISR lesions selected for retreatment were often either symptomatic (n=4), angiographically more severe (longer segment involved or greater percentage of stenosis) than the presenting stenosis (n=8), or both (n=9). In some cases (n=8), however, retreatment was performed in the absence of either of these factors. When symptomatic (n=13), approximately two-thirds of patients presented with transient ischemic attack (n=9) and one-third (n=4) presented with ipsilateral stroke.

Figure 1. A 53-year-old man initially underwent percutaneous transluminal angioplasty and stenting with Wingspan for a right supracalvinal internal carotid artery stenosis symptomatic with stroke while administered clopidogrel. The 3-month follow-up angiogram demonstrates focal ISR (a). After angioplasty, control angiography demonstrates an in-stent dissection flap at the angioplasty site (b, arrow). This in-stent dissection was secured with a second Wingspan stent (c, arrow).

Class I: Focal. Lesions involving less than half of the length of the stented segment and either involving the end of the stent (IA), the body of the stent (IB), or multiple foci (IC).

Class II: Diffuse intrastent lesion. Lesions involving more than half of the length of the stented segment but contained within the confines of the stented segment.

Class III: Proliferative group. Lesions involving more than half of the length of the stented segment, extending beyond the confines of the stented segment.

Class IV: Complete stent occlusion.

All imaging was reviewed by a single neuroradiologist (D.F.) who determined percentage of stenosis and modified Mehran classification.

Results
Imaging follow-up was available for 129 treated lesions (75 anterior circulation, 54 posterior circulation) in the present series. Thirty-six of 129 (27.9%) patients with treated lesions with imaging follow-up experienced ISR. Of these 36, 29 (80.6%) underwent TLR with either angioplasty alone (n=26) or angioplasty with restenting (n=3). Restenting was performed for in-stent dissections that occurred after the initial PTA (Figure 1). Among the retreated lesions, 23 were located within the anterior circulation (79.3%) vs 6 in the posterior circulation.

ISR lesions selected for retreatment were often either symptomatic (n=4), angiographically more severe (longer segment involved or greater percentage of stenosis) than the presenting stenosis (n=8), or both (n=9). In some cases (n=8), however, retreatment was performed in the absence of either of these factors. When symptomatic (n=13), approximately two-thirds of patients presented with transient ischemic attack (n=9) and one-third (n=4) presented with ipsilateral stroke.

Of the 29 patients undergoing primary TLR, 9 required ≥1 interventions for recurrent ISR, for a total of 42 TLR interventions. Only 1 major complication, a postprocedural reperfusion hemorrhage, was encountered during TLR (complication rates: 2.4% per procedure; 3.5% per patient). This patient had poorly controlled hypertension in the immediate periprocedural period.

Angiographic follow-up is available for 22 of 29 patients after primary TLR. Eleven of 22 (50%) patients demonstrated recurrent ISR at follow-up angiography. Subsequently, 9 of these patients have undergone multiple retreatments (2 retreatments, n=6; 3 retreatments, n=2; 4 retreatments, n=1) for recurrent ISR (Figures 2 and 3).
Nine of 11 (81.8%) recurrent ISR lesions were located within the anterior circulation. These lesions involved the supraclinoid internal carotid artery (n=3), cavernous internal carotid artery (n=2), petrous internal carotid artery (n=1), and middle cerebral artery (n=3). Both posterior circulation lesions involved the basilar artery (n=2). Nine of 17 (52.9%) anterior circulation ISR lesions that were retreated demonstrated recurrent ISR vs 2 of 5 (40%) posterior circulation lesions. The mean age for patients with recurrent anterior circulation ISR was 57.9 years (n=9) vs 81 years for posterior circulation ISR (n=2).

The angiographic pattern of ISR did not seem to influence the risk of recurrence after TLR. Of patients with a durable result after TLR, 8 lesions were focal and 3 were diffuse, vs those with recurrent ISR, of which 7 were focal and 4 were diffuse (Table).

**Discussion**

The most important findings of this study are: (1) TLR of ISR after Wingspan percutaneous transluminal angioplasty and stenting of intracranial atherosclerotic vessels is relatively safe, with a major complication rate of <3% per lesion treated; (2) the results of TLR are often not durable, with 50% of patients demonstrating recurrent ISR at follow up; and (3) a small subset of patients have lesions that seem refractory to retreatment with angioplasty, often undergoing 1 additional retreatments for recurrent ISR (Figure 2).

ISR occurs in ~30% of patients after percutaneous transluminal angioplasty and stenting with Wingspan.1,2 Similar rates of ISR have reported for balloon-expandable stents used to treat atherostenosis of the intracranial12 as well as the coronary circulation. Numerous strategies for TLR after late-luminal loss attributable to ISR have been devised, including balloon angioplasty, restenting, mechanical debulking, brachytherapy, implantation of drug-eluting stents, and, more recently, reangioplasty with drug-eluting balloons.3,6,7,14–19 Balloon angioplasty remains the first-line treatment option for recurrent ISR in coronary vessels; however, recurrence rates are typically >40%.4 To this point,
no study has addressed the safety or durability of reangioplasty for intracranial ISR.

Reintervention for ISR appeared to be as safe, if not safer than, the initial treatment. We encountered only 1 significant complication in the context of 42 retreatments. That complication was a reperfusion hemorrhage that occurred hours after the procedure in the setting of suboptimal postprocedural blood pressure control and as such was potentially avoidable. Although there was only a single clinically evident neurological complication, lesion retreatment could be technically challenging. We encountered 4 in-stent dissections after angioplasty; however, all were clinically silent. In addition, gaining access across the in situ stents to perform angioplasty was, at times, challenging.1

The results of TLR were durable in only half of the patients treated. The other half demonstrated recurrent ISR at follow-up, often prompting ≥1 additional retreatments. In this small subset of “refractory patients,” retreatment has been followed by recurrent symptomatic restenoses at intervals of 2 to 3 months (Figure 2). For these patients, most of whom have anterior circulation disease, we have begun to explore other retreatment options, including drug-eluting stents and repeat angioplasty with a drug-eluting balloon.15–17 Although surgical bypass represents an option, patients with intracranial middle cerebral artery stenosis represented the worst subgroup for surgical therapy, with an event rate nearly double that for the medical therapy arm in the extracranial–intracranial arterial bypass trial.20 In patients with internal carotid artery stenosis, no benefit over medical therapy was evident.20

In our registry patients, ISR occurred with greater frequency after the treatment of anterior circulation lesions.2 Similarly, anterior circulation stenoses accounted for the majority of lesions both in which TLR was performed (~80%) and in which recurrent ISR developed after primary TLR (~80%). Although the number of patients with posterior circulation ISR undergoing recanalization in our series was quite small (n = 6), the incidence of recurrent ISR in the anterior circulation (52.9%) trended slightly higher than in the posterior circulation (40%). In addition, the average age of patients with recurrent ISR after TLR in the anterior circulation (57.9 years) trended lower than for posterior circulation patients (81 years). These observations suggest that younger patients with anterior circulation stenosis may be predisposed not only to ISR but also to recurrent ISR after retreatment. No trend was evident with respect to the angiographic pattern of ISR at presentation and the subsequent durability of retreatment.

Although the present study provides some insight into the safety and durability of TLR, very little is known to this point regarding the long-term natural history of this disease process on medical therapy. It is equally unclear what represents “optimal” medical therapy for these patients and exactly what the threshold should be for reintervention (particularly in asymptomatic patients). We expect that additional data may become available during the upcoming Stent Placement vs Aggressive Medical Management for the Prevention of Recurrent Stroke in Intracranial Stenosis study and associated substudies to better elucidate these issues.

Limitations
The present study has several important limitations. First, despite the overall large size of the US Wingspan registry series, we were studying a relatively small subset of the overall group. As such, our ability to perform multivariate analyses to identify specific factors that may predispose these patients to recurrent restenosis after TLR was limited. Second, the rationale on the part of the operators governing their decisions whether (or not) to retreat asymptomatic patients with ISR was not prospectively collected. Although unlikely, it is possible that unknown factors influencing these treatment decisions could have introduced a selection bias into the data.

Summary
TLR of intracranial ISR with angioplasty alone is relatively safe. However, half of patients demonstrate recurrent ISR after retreatment. A small subset of these patients has lesions that are “refractory” to angioplasty alone and demonstrate multiple instances of recurrent ISR, which are typically symptomatic and require numerous retreatments.

Acknowledgment
The authors thank Paul H. Dressel, BFA, for preparation of the illustrations.

Sources of Funding
The US Wingspan registry is supported by a research grant from Boston Scientific.

Disclosures
Aagaard-Kienitz received a research grant (> $10 000) from Micrus Endovascular and is a Consultant and member of the Advisory Board (< $10 000 each) for Micrus Endovascular and MicroVention/Terumo. Albuquerque received Honoraria (< $10 000 each) from ev3 and Micrus. Fiorella received grant support (> $10 000 each) from Boston Scientific and NIH-SAMMPRIS, is a member of the Speakers’ Bureau (< $10 000 each) for Boston Scientific, Cordis, MicroVention, and Micrus. Hopkins received a research grant (> $10 000 each) from Boston Scientific, Cordis, MicroVention, and Micrus, has ownership interest (> $10 000) in Revasc Inc (purchased by Micrus), and is a Consultant and member of the Advisory Board for Micrus (< $10 000). Levy received a research grant (< $10 000 each) from Cordis Scientific, Cordis, Micrus, and Cordis, received Honoraria (< $10 000 each) from Abbott, Boston Scientific, and Cordis, has ownership interest (< $10 000 each) in AccessClosure, Boston Scientific, Micrus, Square One Inc, and is a Consultant and member of the Advisory Board (< $10 000 each) for Abbott, Bard, Boston Scientific, Cordis, and Micrus. Niemann received a research grant (< $10 000 each) from Cordis Scientific, ev3, and Cordis, received other research support (> $10 000 each) from Boston Scientific and Wingspan devices, received an Honorarium (> $10 000 each) from Boston Scientific, is a Consultant and member of the Advisory Board (> $10 000 each) for Cordis Neurovascular and Micrus Endovascular, and has received carotid stent training fees from Abbott Vascular and ev3 for carotid stent training (> $10 000 each). Pride is employed by (< $10 000 each) ev3 Neurovascular. Purdy received an Honorarium (< $10 000 each) from Cordis Corporation (J&J) and received royalties (> $10 000 each) from Cordis Corporation (J&J), Rasmussen
received an Honorarium (<$10 000) from Boston Scientific. Turk is a Consultant and member of the Advisory Board (<$10 000) for Boston Scientific. Welch received a research grant (<$10 000) from Boston Scientific. Woo received an Honorarium (<$10 000) from Micrus Endovascular and is a Consultant and member of the Advisory Board (>=$10 000) for Micrus Endovascular.

References


Target Lesion Revascularization After Wingspan: Assessment of Safety and Durability

Stroke. 2009;40:106-110; originally published online October 16, 2008; doi: 10.1161/STROKEAHA.108.525774

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/1/106

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/