Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA): Study Results

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Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA)
Study Results

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Background and Purpose—Stroke rates in patients with symptomatic intracranial stenosis may be as high as 10% to 24% per year on medical therapy. This multicenter, nonrandomized, prospective feasibility study evaluated the NEUROLINK System for treatment of vertebral or intracranial artery stenosis.

Methods—Patients were 18 to 80 years old with symptoms attributed to a single target lesion of ≥50% stenosis. Patients received 5 neurological examinations before and in the year after the procedure, and another angiogram at 6 months.

Results—In 61 patients enrolled, 43 (70.5%) intracranial arteries (15 internal carotid, 5 middle cerebral, 1 posterior cerebral, 17 basilar, 5 vertebral) and 18 (29.5%) extracranial vertebral arteries (6 ostia, 12 proximal to the posterior inferior cerebellar artery [PICA]) were treated. In the first 30 days, 4 patients (6.6%) had strokes and no deaths occurred. Successful stent placement was achieved in 58/61 cases (95%). At 6 months, stenosis of >50% occurred in 12/37 (32.4%) intracranial arteries and 6/14 (42.9%) extracranial vertebrals, 4 in the vertebral ostia. Seven (39%) recurrent stenoses were symptomatic. Four of 55 patients (7.3%) had strokes later than 30 days, 1 of which was in the only patient not stented.

Conclusions—The NEUROLINK System is associated with a high rate of successful stent deployment. Strokes occurred in 6.6% of patients within 30 days and in 7.3% between 30 days and 1 year. Although restenoses occurred in 35% of patients, 61% were asymptomatic. Further trials involving the NEUROLINK System are warranted. (***Stroke***. 2004;35: 1388-1392.)

Key Words: intracranial pressure ■ stenosis ■ stents ■ stroke

Intracranial atherosclerotic disease is a high-risk cause of stroke that is potentially treatable. It is present in 8% to 10% of patients with cerebrovascular symptoms.[1–4] Higher rates are seen in Chinese, black, and Hispanic populations compared with whites[2,3,5] and in patients with cortical symptoms or signs.[4]

The risk of stroke of all causes in patients with intracranial stenosis may be as high as 10% to 24% per year.[6–9] Rates were 7% to 10% in the extracranial-to-intracranial bypass trial.[8] The Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) study retrospectively compared outcomes in patients with symptomatic intracranial large-artery stenosis treated with either warfarin or aspirin.[6] Seven percent of the warfarin-treated group and 24% of those treated with aspirin had an ischemic stroke during a median follow-up time of 14.7 and 19.3 months, respectively. Hemorrhagic complications in the warfarin group partially offset the benefit of anticoagulation in a subset with posterior circulation stenosis.[7] A prospective trial comparing high-dose aspirin to warfarin in symptomatic intracranial stenosis was stopped.

The risk of stroke and death appears to increase early and dramatically in patients for whom medical therapy is not successful. In a study with a stroke and death rate of 27.5% (mean follow-up 14.6 months), 29 of 52 (55.8%) patients had subsequent cerebral ischemic events while on an antithrombotic, and the median time to recurrent ischemic events or death was 36 days.[9] The Northern Manhattan Stroke Study found a 5.9% adjusted risk of recurrent stroke at 30 days in 57 patients relative to a nonatherosclerotic stroke group.[10]

There is a need for alternative treatment in this patient population at high risk for stroke. Because of issues of recoil and dissection seen with angioplasty alone, the use of stents has been proposed for the treatment of intracranial stenosis as an alternative to medical therapy.[11] The concern has been the availability of stents that can be tracked into the intracranial circulation, although flexible coronary stents have been used in reported cases.[12]

The primary purpose of this study was to evaluate the safety and procedural feasibility of the NEUROLINK System (Guidant Corporation) in patients with symptomatic atherosclerotic disease of the extracranial vertebral and intracranial arteries in a multicenter trial. The NEUROLINK System,

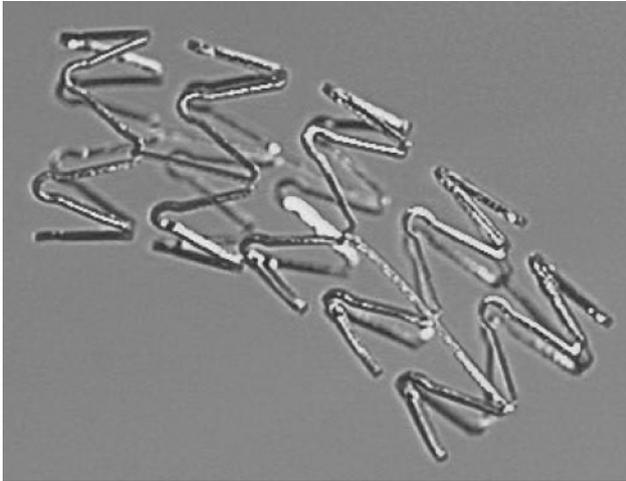**DOI: 10.1161/01.STR.0000128708.86762.d6**

Figure 1. The NEUROLINK stent.

designed for the cerebral vasculature, comprises a balloon dilatation catheter and a stent and delivery catheter. The stent is made of 316L stainless steel, with diameters of 2.5 to 4.5 mm and length of 8 mm (Figure 1). Only a few links connect the rings, rendering the stent flexible enough to navigate tortuous intracranial vessels. Because the struts do not lift as the stent negotiates a turn, the likelihood of vessel wall injury is lessened.

Materials and Methods

Endpoints

The SSYLVIA study was a prospective, nonrandomized, international trial. The primary endpoints assessed the rate of: (1) death or stroke within 30 days of the procedure and (2) stent success, resulting in <50% stenosis and covering an area no longer than the original lesion. Procedure success was defined as stent success with no stroke or death before discharge.

Secondary endpoints included angiographic evaluation of the treated segment at 6 months, target lesion-related stroke at 12 months, and access site events that required treatment. An independent angiographic core laboratory analyzed available angiograms and a Clinical Events Adjudication Committee adjudicated all major adverse events that might qualify as endpoints, including stroke, death, and access site events. A major stroke was defined as one that led to a National Institutes of Health Stroke Scale (NIHSS) score of ≥15, a modified Rankin scale (mRS) score of ≥4, or a Barthel Index (BI) of ≥60 30 days after the stroke.

Study Population

Patients were 19 to 80 years old with transient ischemic attack (TIA) or stroke attributed to a single atherosclerotic stenosis of $\geq50\%$ of an extracranial vertebral or intracranial artery by angiography. They were at least 7 days after stroke and free of TIAs for 24 hours before study enrollment. Patients had an mRS of ≤3 and could take 2 antiplatelet agents. Women of childbearing potential had a negative pregnancy test. The institutional review board at each institution approved the study and each subject gave informed consent.

Patients were excluded if they had had an intracranial hemorrhage or hemorrhagic stroke within 30 days or a stroke within 6 weeks of the procedure that involved one third of the vascular territory on imaging and was in the same hemisphere as the target lesion. Intracranial tumors, cerebral arteriovenous malformations, or aneurysms (except unruptured aneurysms ≤5 mm in diameter and in a different circulation than the target lesion) were excluded, as was any neurological illness that could confound the diagnosis of TIA or

stroke. Patients were excluded if they could not cooperate with the study procedures or provide informed consent.

Candidates were ineligible if they had known contraindication to heparin, stainless steel, anesthesia, or x-ray contrast; Hgb <10 g/dL, platelet count <100 000; international normalized ratio >1.5 (irreversible), received thrombolytic agents within 24 hours, or had noniatrogenic uncontrolled bleeding diathesis. Patients were excluded if they had a potential source of cardiac embolism; known symptomatic epicardial stenosis >50% that potentially required revascularization; a major surgical intervention within the past 30 days or a scheduled major surgical intervention within 90 days; life expectancy <1 year because of other medical conditions; a condition precluding proper angiographic assessment; or previous treatment of the target lesion with a stent.

Angiographic inclusions required a discrete lesion occupying 50% to 99% of the target artery diameter with a reference vessel diameter between 2.5 to 4.5 mm and lesion length ≤5 mm.

Angiographic exclusions were an untreated stenosis ($\geq50\%$) proximal or distal to the target lesion; visual evidence of severe calcium at the target lesion that the investigator believed would be resistant to dilatation; visual evidence of intramural thrombus; evidence of diffuse disease or poor outflow distal to the target lesion; or acute arterial dissection, vasculitis, moyamoya disease, radiation-induced vasculopathy, or fibromuscular dysplasia.

Clinical Follow-up

Examinations with the mRS, NIHSS, and BI were conducted by a nonoperator study neurologist before the procedure, at 30 days, and at 3, 6, and 12 months. Telephone contact was made at 9 months. Diagnostic angiography was performed after the stent procedure and again at 6 months.

Procedure

Aspirin (minimum 100 mg, twice daily) and clopidogrel (minimum 75 mg twice daily) were given at least 48 hours before the procedure. After the procedure, aspirin (minimum 100 mg daily) was prescribed for a minimum of 1 year and clopidogrel (75 mg daily) for at least 4 weeks. Heparin was administered to maintain an activated clotting time of 200 to 300 seconds throughout the procedure. Either local or general anesthesia was used. Adjunctive drugs such as IIb/IIIa inhibitors were only allowed in patients at high risk for subsequent thromboembolic complications.

The lesion was first predilated at the discretion of the interventionalist using the NEUROLINK balloon dilatation catheter only. The stent size was matched to the vessel diameter proximal or distal to the lesion, whichever was smaller. The system was delivered over a 0.014-inch guidewire until the markers straddled the lesion, and the stent was then deployed with the inflation device. If the stent was not optimally deployed, leaving >30% residual stenosis, for example, then the lesion could be redilated at the option of the interventionalist. Before treating the first patient under the protocol, each interventionalist took part in a didactic and practical training program. The core laboratory determined all angiographic measurements, using the WASID criteria for intracranial lesions and the North American Symptomatic Carotid Endarterectomy Trial criteria for extracranial lesions.[13,14]

Statistical Methods

The primarily descriptive data were analyzed according to intent-to-treat methodology, including those patients not implanted with a stent. The literature was used to derive an acceptable 30-day stroke and death rate set at <21%. A stopping rule was determined prospectively to ensure that the occurrence of stroke and death did not present safety risk to the study population.

Results

Patient Characteristics

Sixty-one patients were enrolled from November 9, 2000, through November 19, 2001. Their mean age was 63.6 years

TABLE.   Lesion Locations in Treated Patients and Resultant Strokes by 1 Year

Primary Lesion Location	Patients, N (n=61)	% of Total	Strokes, N (n=8) (% at Location)
Intracranial			
Internal carotid petrous	2	3.3%	0 (0)
Internal carotid cavernous	7	11.5%	1 (14)
Internal carotid supraclinoid	6	9.8%	1 (17)
Middle cerebral	5	8.2%	1 (20)
Intracranial vertebral post-PICA	5	8.2%	1 (20)
Basilar proximal	11	18.0%	1 (9)
Basilar mid	6	9.8%	1 (17)
Posterior cerebral	1	1.6%	0 (0)
Total intracranial	43	70.5%	6 (14)
Extracranial			
Extracranial vertebral pre-PICA	12	19.7%	0 (0)
Extracranial vertebral ostium	6	9.8%	2 (33)
Total extracranial	18	29.5%	2 (11)

PICA indicates posterior inferior cerebellar artery.

(range 37 to 80) and 82% were male. The patients had a mean baseline mRS of 1.1 (range 0 to 5), BI of 94.5 (range 12 to 100), and an NIHSS score of 1.2 (range 0 to 8). The qualifying event was a stroke in 37 (60.7%) patients and a TIA in 24 (39.3%), 12 of whom had had a stroke in the past. The mean duration between the qualifying event and procedure was 72.8 days (median 28.5, range 1 to 959 days). The most prevalent risk factors included hypertension (63.9%, 39/61), hypercholesterolemia (54.1%, 33/61), smoking (52.5%, 32/61), and diabetes (32.8%, 20/61). Hereditary (family history of stroke) or racial risk (black, Asian, or Hispanic ethnicity) was seen in 18% (11/61). Forty-one percent of patients (25/61) had been on anticoagulation before enrollment, whereas 56% (34/61) were on antiplatelet agents alone, and 3% (2/61) were not on any antithrombotic. The treated vessels were intracranial in 43 patients (70.5%) and extracranial in 18 (29.5%), 6 (9.8%) of which were in the vertebral ostium (Table). The mean baseline stenosis was 69.9%±SD of 12.41 and median was 70.2% (range 42% to 100%).

Primary Endpoints

At 30 days, no deaths had occurred. Four (6.6%) strokes were seen, 3 of them major and ipsilateral. Two ischemic strokes occurred during the procedure. One was noted on awakening from anesthesia, thought to be caused by a slow flow state developing during vertebral stenting distal to the posterior inferior cerebellar artery (PICA) and treated with heparin. The other, in a patient with a midbasilar lesion, was believed to be caused by occlusion of perforators by plaque during balloon inflation and not further treated. A third stroke occurred later in a patient with a proximal basilar artery lesion, whereas the fourth was a subarachnoid hemorrhage that resolved without residual deficits.

The stent was successfully placed in 58 of 61 (95%) cases. Figure 2 shows 1 such case. Procedure success was seen in 54
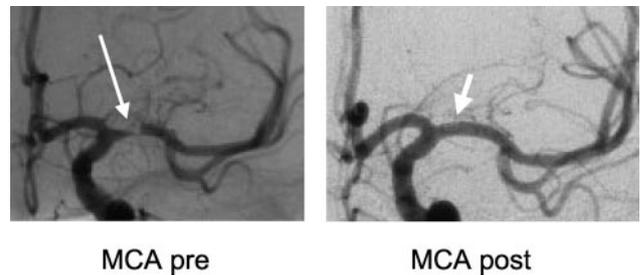

MCA pre   MCA post

Figure 2. Middle cerebral artery (MCA) showing 64% stenosis by core laboratory reading before treatment and no residual stenosis after stent placement.

of 61 patients (88.5%). Two patients (3%) were lost to follow-up after the discharge visit.

Secondary Endpoints

Investigator measurements were provided for follow-up angiography without core laboratory interpretations, including occlusions. Stenosis of >50% at 6 months was seen in 12 of 37 (32.4%) (30 read by the core laboratory, 7 by the investigator) intracranial stents and 6 of 14 (42.9%) extracranial vertebral stents (including 3 occlusions read by the investigator only). Of these extracranial stenoses, 67% (4/6) occurred in vertebral ostium lesions. Figure 3 provides the cumulative frequency distribution of the percent stenosis at baseline, immediately after the procedure and at 6 months. Figure 4 shows an example of a vessel with restenosis.

Strokes in the distribution of the target lesion occurring after 30 days but by 12 months were seen in 4 of 55 patients (7.3%), 2 in posterior circulation cases and 2 in the anterior circulation. One of these occurred in the only patient not stented, who had a left supraclinoid ICA stenosis. In the patients who had strokes between 30 days and 12 months, the mean stenosis was 66.5% (range 58% to 76%). Of the 18 patients with stenosis of >50% at 6 months, 7 (39%) were symptomatic with a stroke or TIA and were treated at the discretion of the investigator. Of the 5 patients who had symptoms in the distribution of the stented vessel, 2 received no reported change in treatment, whereas treatment in the others included a subclavian to vertebral bypass, in-stent angioplasty, or warfarin. Two patients with asymptom-
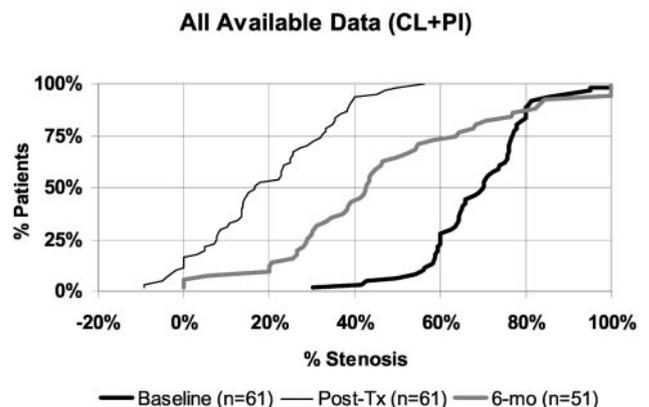
All Available Data (CL+PI)

Figure 3. Cumulative frequency distribution of degree of stenosis at baseline, after treatment, and at 6 months using core laboratory (CL) and principal investigator (PI) data for those cases without core laboratory interpretations.
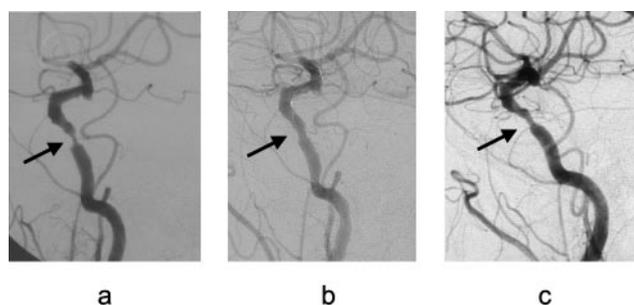
Figure 4. Right cavernous internal carotid artery showing (a) 65% stenosis before treatment; (b) 39% after stent placement; and (c) 54% at 6 months.

atic restenosis also had in-stent angioplasty. The composite 1-year stroke rate was 13.1% (8/61) (Table).

At 6 months, only 5 patients (8%) were known to be on anticoagulants, although antithrombotic information was not available for 9 of 61 (15%) patients. Forty-seven of the 61 patients (77%) were known to be using 1 or more antiplatelet agents at 6 months.

The rate of occurrence of critical events met the acceptance criteria and did not invoke the stopping rule at any time during the study enrollment period. One access site infection was seen that required treatment. No unanticipated safety concerns were identified.

An exploratory analysis was performed to determine which variables best predicted the presence of stenosis at 6 months. The list of potential variables queried with a stepwise linear regression included diabetes, hypertension, hypercholesterolemia, tobacco use, gender (male), index stenosis in the posterior circulation, ostial stenosis location, postprocedure stenosis of $\geq$30% (each of these either present or absent for the attribute), and pretreatment vessel diameter, pretreatment minimum lumen diameter, pretreatment lesion length, pretreatment percent stenosis, posttreatment lesion length, posttreatment percent stenosis, and age. For the 51 patients with 6-month angiography data, the resulting regression model showed that diabetes, ostial stenosis location, the postprocedure percent stenosis, pretreatment vessel diameter, and age contributed significantly to the prediction of stenosis at 6 months, higher pretreatment vessel diameter, and age lessening the likelihood of stenosis. When the analysis was limited to the 37 patients with intracranial stenoses and 6-month angiography, only diabetes, postprocedure percent stenosis of $\geq$30%, and pretreatment vessel diameter contributed significantly to the prediction of stenosis at 6 months and were included in the model.

In 1 patient, a stenosed vertebral stent was explanted during a right subclavian to right vertebral artery bypass procedure. Pathologic examination showed neointimal hyperplasia.

Discussion

The SSYLVIA trial showed that the NEUROLINK System is safe and feasible for the treatment of atherosclerotic lesions of the extracranial vertebrals and intracranial vessels. The stent was deployed with a high rate (95%) of success. There were no deaths and patients had relatively low rates of stroke at 30 days (6.6%). Four strokes occurred between 30 days and 1 year, one of which was fatal.

The 3 ischemic strokes that occurred within the first 30 days were all in posterior circulation vessels. Because the natural history of vertebrobasilar stenosis has been characterized by especially high stroke rates,[7,15] the apparently higher risk of periprocedural stroke in the posterior circulation may be warranted.

A unique contribution of the SSYLVIA trial was a multicenter assessment of restenosis rates and their potential associations with clinical symptoms and risks. Certain of the factors generated by the exploratory analysis, specifically diabetes, greater postprocedure stenosis, and smaller pretreatment vessel size, have also been described in the cardiac literature.[16,17] The analysis also identified lesion location in the vertebral ostium as a risk for restenosis. Restenosis occurred in 67% of vertebral ostium lesions, compared with only 25% of pre-PICA vertebral and 32% of intracranial lesions, suggesting that ostial recoil may require a more robust stent. The majority, 61%, of patients with stenosis at 6 months remained asymptomatic. Stenosis caused by neointimal proliferation likely carries a lower thromboembolic risk than atherosclerosis.[18]

Although the cardiac literature supports rates of restenosis in untreated stents that are close to those of the SSYLVIA trial, $\approx$20% to 30%,[19,20] the rates reported in subgroups of stented cerebral stenoses have been lower. In 2 studies of intracranial lesions, zero of 8 and of 9 patients (0%) with angiographic follow-up had restenosis >50% at means of 3 and 5 months, respectively.[12,21] Gomez recently reported restenosis in 3 of 28 (10.7%) intracranial cases and 6 of 72 (8.3%) extracranial vertebral cases.[22,23] The differences between larger trial and single institution results may partially be explained by patient selection, including risk factors,[16] angiography timing, and the use of core laboratories in the larger trials.

Although 30-day stroke and death rates were 5.3% and 3.2% in the Gomez series[22,23] and 0% and 36% in the earlier studies,[12,21] none reported strokes during later follow-up. In the current study, nonprocedural strokes occurred in patients with restenosis. Although angiograms were not reviewed to determine whether stent struts crossed perforators in these cases, another small series found this had no association with stroke.[24]

The retrospective WASID study suggested a benefit for warfarin compared with aspirin in patients with a symptomatic intracranial stenosis.[6] Although antithrombotic information was not known for 9 patients at 6 months in the SSYLVIA trial, even if all 9 were on anticoagulation, there were still fewer patients overall treated with anticoagulants needing monitoring than there were at study entry.

Further clinical trials with the NEUROLINK System are warranted, perhaps with a treated stent. Future trials would ideally compare stenting to the best medical therapy, to be determined by the WASID trial, because currently there is no proven benefit of this procedure relative to medical therapy. The probable benefit-to-risk ratio of the NEUROLINK System has led to a Humanitarian Device Exemption designation for this device from the Food and Drug Administration for use in patients who have had events despite medical therapy. Although it was not the population studied in this trial, patients with intracranial stenosis in whom medical therapy has failed may be at the highest risk for stroke.[9]

Acknowledgments

Appendix

The SSYLVIA Study Investigators are: Helmi L. Lutsep, Stanley Barnwell, Oregon Health and Science University; Michel Mawad, David Chiu, Baylor College of Medicine, the Methodist Hospital; Marius Hartmann, Werner Hacke, Universitäts Klinike Heidelberg; Jürgen Reul, Robert Janker Klinik, Bonn; Rolf Biniek, Rheinische Kliniken, Bonn; Lee Guterman, Abutaher Yahia, Millard Fillmore Hospital, SUNY Buffalo; Cornelius Weiller, Hermann Zeumer, Universitäts Krankenhaus Eppendorf; Serge Bracard, Xavier Ducrocq, Hopital Neurologique; Jacques Dion, Owen Samuels, Emory University; Camilo R. Gomez, Alabama Neurological Institute; and Peter King, University of Alabama.

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