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Angioplasty and Stenting for Atherosclerotic Intracranial Stenosis: Rationale for a Randomized Clinical Trial

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Synopsis

Atherosclerotic disease of the major intracranial arteries is a frequent cause of stroke. In addition, many patients with symptomatic intracranial stenosis are at very high risk for recurrent stroke. A recently completed medical treatment trial, the Warfarin versus Aspirin for Symptomatic Intracranial Stenosis (WASID) trial, showed that aspirin was as effective and safer than warfarin for preventing stroke or vascular death in these patients, and that patients with 70%-99% intracranial stenosis are at particularly high risk of stroke despite antithrombotic therapy and usual management of vascular risk factors. Preliminary studies suggest that angioplasty and stenting may reduce the risk of stroke in patients with severe stenosis of intracranial arteries. However, data for angioplasty and stenting consists of case series: no randomized studies have been completed to date. These data will be reviewed and the rationale for a randomized trial of angioplasty and stenting versus best medical management for patients with symptomatic intracranial stenosis will be discussed.

Introduction

Atherosclerotic stenosis affecting the major intracranial arterial is a common cause of stroke in North America, particularly in some minority populations [1-3]. Patients presenting with transient ischemic attack (TIA) or stroke and severe (>70% diameter reduction) stenosis are at a very high risk for future stroke [4]. The mechanism of stroke in these patients may be related to thromboembolism owing to biologic plaque factors, hemodynamic factors owing to flow reduction beyond the stenosis, or synergistic effects of the two [5, 6]. Angioplasty and stenting offers the potential to address both mechanisms and to substantially reduce stroke risk. Angioplasty and stent technology has improved dramatically over recent years. There are accumulating data on the technical success and safety of these procedures but the long term stroke risk reduction remains undetermined. At present, only one device, the Wingspan self-expanding stent, is approved by the Food and Drug Administration (FDA) for use in patients with symptomatic atherosclerotic stenosis (50%-99%) of intracranial arteries.

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In this review, we will discuss the outcome of medically treated patients with intracranial stenosis, drawing heavily from the recently reported Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) study [4, 7, 8]. Following this, we will review the published data for intracranial angioplasty, with and without stenting. Finally, we will discuss the rationale for a randomized trial of angioplasty and stenting for symptomatic intracranial atherosclerotic stenosis.

Epidemiology

Atherosclerotic stenosis of large intracranial arteries accounts for approximately 10% of ischemic strokes that occur in North America. There is racial and ethnic variance in this disease. Intracranial arterial stenosis is responsible for 6% - 10% of ischemic strokes in Whites, 6% – 29% of ischemic strokes in Blacks, 11% of ischemic strokes in Hispanics, and 22% -26% of ischemic strokes in Asians [1-3, 9]. This projects to approximately 70,000 strokes per year in the United States [10] compared to the 140,000 and 70,000 strokes caused by extracranial carotid stenosis and non-valvular atrial fibrillation [11, 12].

Pathophysiology

The mechanisms of ischemic stroke related to intracranial atherosclerotic disease include thromboembolic factors, such as in situ thrombosis and distal embolism, as well as hemodynamic factors owing to flow reduction and lack of adequate sources of collateral flow [13-15]. As discussed in a prior chapter, both mechanisms are commonly involved in most patients and are likely synergistic. Lee, et al., reviewed diffusion-weighted MR imaging in 63 acute ischemic stroke patients who had ipsilateral MCA disease, 32 of whom showed multiple lesions [15]. Most patients had perforating artery infarcts, either solitary or accompanied by pial or border-zone territory infarcts. Their data suggests that local branch occlusion and simultaneous distal embolization is a common stroke mechanism in patients with MCA disease. We measured hemodynamics in 10 patients with symptomatic middle cerebral artery occlusion or stenosis, using positron emission tomography [13]. Four of the five patients with stenosis had normal measurements of blood flow and oxygen extraction. These data suggest that most patients with symptomatic intracranial stenosis are symptomatic owing to thromboembolic factors.

Nevertheless, hemodynamic impairment is a risk factor for stroke in patients with intracranial occlusive disease, just as in those with extracranial carotid artery occlusive disease [16]. Amin-Hanjani and colleagues measured quantitative bulk flow in the basilar artery and its branches in 50 patients with symptomatic vertebrobasilar disease. Forty seven of the 50 patients were followed for a mean of 28 months, although those with low flow were offered intervention. None of the 31 patients with normal distal flow had a recurrent event. Several of the 16 patients with low flow suffered recurrent strokes prior to intervention.

Outcome of Patients Treated Medically

The best estimates of the outcome of medically treated patients with symptomatic intracranial atherosclerotic disease were generated by the Warfarin Versus Aspirin for Symptomatic Intracranial Disease (WASID) trial [4, 7, 8]. In this section we will review the data from this study in detail, including secondary analyses identifying particularly high-risk patients. We will also review the current data for risk factor management in this population. These data are important, as angioplasty and stenting should target the patients at the highest risk for stroke with medical therapy. In addition, most of these patients will have vascular risk factors that should be treated as well.

Warfarin Versus Aspirin for Symptomatic Intracranial Disease (WASID) trial

WASID was a randomized, double-blinded, multi-center controlled study designed to determine the relative efficacy of aspirin (1300 mg po qd) versus anticoagulation with warfarin (target international normalized ratio (INR) 2.0 to 3.0) in patients with angiographically proven 50 to 99% stenosis of a major intracranial artery and recent TIA or minor stroke [4].

At total of 569 patients were enrolled between 1999 and 2003. The median time from qualifying event to randomization was 17 days. Mean follow up was 1.8 years. Baseline clinical characteristics between the two groups were similar. These baseline characteristics were also very similar to prior clinical trials in patients with atherosclerotic extracranial carotid stenosis or occlusion [5, 17, 18]. The majority of patients had a history of hypertension or smoking. A large minority had diabetes or prior coronary artery disease. Subjects could be screened by transcranial Doppler, magnetic resonance angiography, or computed tomographic angiography. Enrollment required confirmation of 50 to 99% stenosis with catheter angiography [19]. Study drug was discontinued in more warfarin patients than aspirin patients (28.4% versus 16.4%, $p < 0.001$). The mean INR was 2.5. The percentage of maintenance time at target INR was 23% ≤ 2.0, 63% 2.1 to 3.0, 13% 3.1 to 4.0, and 1% > 4.0.

The primary endpoint was any ischemic stroke, brain hemorrhage, or death from non-stroke vascular cause. The primary endpoint was reached in 22.1% of the aspirin group and 21.8% of the Warfarin group. The probability of ischemic stroke in the territory of the stenotic artery at 1 year was 12% in the aspirin group and 11% in the Warfarin group. At two years, the probabilities of ipsilateral ischemic stroke were 15% and 13% respectively. Warfarin was associated with a higher rate of non-vascular death (1.1% versus 3.8%, $p = 0.05$) and major hemorrhage (3.2% versus 8.3%, $p = 0.02$). Data were nearly identical when analyzed by on-treatment analysis. It should be noted that the study was halted at the recommendation of the Data Safety and Monitoring Board owing to excess mortality in the warfarin arm. The conclusion of WASID was that aspirin should be preferred over warfarin for the treatment of symptomatic intracranial disease, owing to the lack of evidence for benefit with warfarin and lower risks of death and major bleeding with aspirin.

Subgroup analyses in WASID

Prior retrospective studies had reported that certain subgroups of patients with intracranial arterial stenosis are at particularly high risk of stroke. These subgroups include patients with severe stenosis [20], vertebrobasilar disease [21], and patients who fail anti-thrombotic therapy [22]. The WASID trial provided a unique opportunity to determine prospectively whether these and other risk factors are associated with an increased risk of stroke in the territory of a stenotic intracranial artery. In a pooled analysis of all 569 patients in WASID, ischemic stroke in any vascular territory occurred in 106 patients (19.0%), of which 77 (73%) were in the territory of the stenotic artery [7]. In univariate analyses, severity of stenosis (≥70% vs. <70%), time from qualifying event to enrollment (≤17 days vs. >17 days), female gender, NIH stroke scale (>1 vs. ≤1), and history of diabetes mellitus were significantly associated ($P \leq 0.05$) with stroke in the territory of the stenotic artery while body mass index (BMI) was of borderline significance ($P = 0.068$). Age, race, location of stenosis (i.e., vertebrobasilar disease vs. carotid –MCA disease), length of stenosis, other vascular risk factors, comorbidities, and treatment with antithrombotic agents at the time of the qualifying event (so called “medical failures”) were not significantly associated with an increased risk of stroke in the territory of the stenotic artery. Multivariate analysis showed that the only significant predictors of stroke in the territory were severity of stenosis (≥70% vs. <70%), time from qualifying event to enrollment (≤17 days vs. >17 days), NIH stroke scale (>1 vs. ≤1), and female gender.

Severity of stenosis was the most powerful predictor of stroke in the territory which increased linearly (p-value for trend = 0.0026) with greater percent stenosis. The rates of stroke in the territory of the stenotic artery in patients with TIA or stroke and ≥ 70% stenosis were 18% at 1 year (95% CI 13% - 24%) and 19 % at 2 years (95% CI 14% -25%), whereas the rates of stroke in the territory of the stenotic artery in patients with TIA or stroke and < 70% stenosis were 6% at 1 year (95% CI 4%-10%) and 10% at 2 years (95% CI 7%-14%). Notably, two of the variables that had previously been associated with increased risk of stroke in retrospective studies, vertebrobasilar disease and "failure" of anti-thrombotic therapy, had no association with an increased risk for ipsilateral stroke. The current indication for the Wingspan device (Boston Scientific, Natick, MA) which is approved by the FDA under a Humanitarian Device Exemption (HDE) for the treatment of intracranial stenosis, is for patients with 50-99% stenosis who have cerebral ischemic events while on antithrombotic therapy. This requirement to fail antithrombotic therapy before using Wingspan is not supported by the WASID data.

Another important finding in WASID was that the majority of strokes in the territory of the stenotic artery occurred within 1 year of enrollment: of 77 strokes in the territory, 60 (78%) occurred within 1 year. The magnitude of stroke risk and the temporal pattern of risk are nearly identical to data reported for the medical treatment arms of clinical trials for symptomatic extracranial carotid stenosis and occlusion [17, 18]. Whether the decrease in stroke risk after one year reflects improvement in hemodynamic, embolic, or both factors over time is unclear.

A second subgroup analysis compared the outcomes between warfarin and aspirin in different subgroups of patients [8]. These subgroups included time from qualifying event, age, gender, race, smoking, hypertension, diabetes, coronary artery disease, site of symptomatic lesion (middle cerebral, anterior cerebral, internal carotid, vertebral and basilar arteries), anterior versus posterior circulation, % stenosis, length of stenosis, and antithrombotic therapy at the time of qualifying event. No definite differences between aspirin and warfarin in the risk of stroke or vascular death were observed in any of these subgroups but the power of the study to detect differences in these subgroups was low.

In summary, angioplasty and stenting cannot be justified in patients with < 70% stenosis, given the low risk of stroke in the territory of a stenotic artery (6 % at 1 year) and the inherent risk of angioplasty and stenting (30-day rate of stroke and death in 4-7% range – see next section). Furthermore, the concept of medical treatment failure should not be used as an indication for angioplasty and stenting. Patients in whom this procedure should be considered are those with severe stenosis, recent ischemic symptoms, and an NIH stroke scale score of greater than 1.

Medical management

Risk factor management in WASID was performed by the study neurologist and primary care physicians, according to published national guidelines on hypertension [23], hyperlipidemia [24], and diabetes (ADA) [25]. Despite these recommendations, many vascular risk factors were poorly controlled. Poorly controlled blood pressure and elevated LDL were the most important risk factors for stroke, vascular death, or MI during follow-up in WASID. During a mean of 1.8 years of follow-up, 30.7% of patients with mean systolic BP ≥ 140 mm Hg had a stroke, vascular death, or MI compared with 18.3% of patients with mean systolic BP < 140 mm Hg (P<0.0005). Over the same period, 25.0% of patients with LDL ≥ 115 mg / dl (the median LDL) had a stroke, vascular death, or MI compared with 18.6% of patients with a mean LDL < 115 mg / dl (p=0.03). Considering an LDL target of < 70 mg / dl, 22.5% of patients with mean LDL above this target had a stroke, MI, or vascular death compared with 7.4% with mean LDL below this target (HR 3.13 95% CI 0.77 – 12.67). Poorly controlled blood pressure and elevated LDL were also important risk factors for ischemic stroke alone in WASID. The risk of any ischemic stroke was found to increase with increasing mean systolic BP and diastolic BP (p<0.0001 and <0.0001, respectively) using a log-rank trend test. Elevated systolic BP and

diastolic BP were also associated with increased risk of ischemic stroke in the territory of the stenotic artery (p= 0.0065 and <0.0001, respectively) (in press, Circulation). LDL ≥ 115 mg / dl (the median value) was highly correlated with ischemic stroke (HR 1.82 95% CI 1.17-2.83, p=0.0072) (presented at Joint World Congress of Stroke, 2006).

These risk factor data suggest that optimal outcome for patients with intracranial atherosclerotic disease, including those that undergo angioplasty and stenting, will require careful and intensive adjunctive risk factor management. Further support for the importance of risk factor management in patients with intracranial stenosis is provided by recent secondary prevention stroke trials that have shown treatment of elevated low density lipoproteins (LDL) [26] and blood pressure [27] reduce the risk of recurrent stroke. Additionally, intensive risk factor management in patients with coronary artery disease (CAD) has been shown to reduce major cardiac events and stroke [28, 29], and has been shown to be as good as endovascular intervention and usual or aggressive medical management for preventing cardiac ischemic events in patients with stable angina and severe atherosclerotic coronary artery disease [30, 31].

There are little data regarding the optimal antiplatelet regimen in this population. WASID tested high-dose aspirin (1300 mg/day) and found it to be equivalent to warfarin for stroke risk reduction. There are no data on the effectiveness or safety of other antiplatelet agents specifically in patients with intracranial stenosis. In other stroke populations with heterogeneous causes of stroke, combination aspirin and clopidigrel therapy has been found to be equivalent for stroke risk reduction in two secondary prevention studies when compared to monotherapy [32] and combination low dose aspirin and dypiridamole has been shown to be more effective than low dose aspirin for stroke prevention [33, 34].

Angioplasty / Stenting as a Treatment for Symptomatic Intracranial Stenosis

Over the past decade, angioplasty and stenting have emerged as therapeutic options for symptomatic intracranial arterial stenosis. The first report of angioplasty for intracranial atherosclerotic disease was in 1980 [35]. Since then there have been dramatic improvements in balloon and stent technology, as well as in the imaging systems that provide the guidance for these procedures.

Angioplasty Alone

There have been no prospective studies of intracranial angioplasty without stent placement. Technical success (defined as reduction of stenosis to < 50%) can be achieved in over 80% of patients and the rate of stroke or death within 30 days of angioplasty has varied between 4% and 40% in several retrospective angioplasty studies [36-46]. One reason for the wide variation in complication rates may be variability in the acuity of patients being treated. Procedures that were largely elective were associated with lower complication rates (4% to 6%) [41, 42, 44]. Restenosis rates following angioplasty alone range from 24% - 40% [41, 42]. There are limited data on the long term outcome after intracranial angioplasty alone. Marks and colleagues reported an annual stroke rate of 4.4% (3.2% in the territory of stenosis) in a recent retrospective review of 120 patients who underwent intracranial angioplasty at four sites [41]. The actual stroke rate is uncertain given the retrospective nature of the study and the lack of adjudication of events by neurologists. While some practitioners strongly advocate the use of this procedure alone, i.e., without a stent, most favor the use of stents. This can be attributed to several technical drawbacks to angioplasty including immediate elastic recoil of the artery, dissection, acute vessel closure, residual stenosis > 50% following the procedure, and high restenosis rates. These limitations, coupled with the success of stenting in the coronary circulation, have led to the emergence of stenting as the preferred interventional technique for treating intracranial stenosis.

Stenting

Until recently, most data on the safety and efficacy of intracranial stenting have been limited to single center series [47-57]. The largest of these studies are summarized in table 1. These data suggest that intracranial stenting can be performed relatively safely and with high technical success. The larger, more recent studies suggest that the rate of stroke after stenting in patients with 70%-99% stenosis may be substantially lower than the rate of stroke in WASID patients with 70-99% stenosis. Data exists for three categories of stents: bare-metal balloon expandable, drug-eluting balloon expandable, self-expanding stents.

Balloon-expandable bare-metal stents

An industry sponsored multicenter Phase 1 trial of a balloon expandable bare metal stent (Neurolink, Guidant Corporation) for intracranial stenosis provided encouraging data on the safety and potential efficacy of stenting for intracranial arterial stenosis. The Stenting of Symptomatic atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) trial was a non-randomized, multi-center study that evaluated the safety and performance of primary stenting in 61 patients with intracranial arterial stenosis (43 patients), vertebral pre-PICA stenosis (12 patients) or vertebral ostium stenosis (6 patients) ≥ 50% [58]. Deployment of the stent was successful in 58 of 61 (95%) patients. In the first 30 days after stenting, 4 / 55 patients with intracranial or pre-PICA stenosis (defined as intracranial in WASID) had a stroke (30 day rate:7.2%; 95% CI 2.0% - 17.6%) and there were no deaths. The frequency of stroke within 1 year (including the 30 day rate) was 6 / 55 (10.9%; 95% CI 4.1% - 22.3%). All strokes were in the territory of the treated artery. Recurrent stenosis (≥ 50%) at 6 months was documented by angiography in 18 of 51 (35%; 95% CI 22.2% - 48.4%) patients (intracranial, pre-PICA, and vertebral ostial lesions combined - data not provided to separate out the vertebral ostial lesions).

Factors that were significantly associated with restenosis were diabetes, post-procedure diameter stenosis > 30%, and small vessel diameter. These features have also been associated with higher restenosis rates after coronary stenting. Of the 55 patients with intracranial stenosis in SSYLVIA, 33 had 70%-99% stenosis. Of these 33 patients, 1 patient had a stroke within 30 days and 2 patients had an ischemic stroke between day 31 and 1 year (personal communication Marcia Wachna, Guidant Corporation). The SSYLVIA trial provides important preliminary pilot data suggesting that: 1. intracranial stenting can be performed relatively safely – the point estimate of the 30-day stroke and death rate was similar to the 30-day stroke and death rate after carotid endarterectomy in NASCET [17]; 2. risk of stroke at 1 year after stenting in patients with 70%-99% stenosis may be lower than the rate of stroke in similar patients in WASID suggesting a possible benefit of stenting in these high-risk patients. Based on these findings, Guidant Corporation applied to the FDA for approval of the Neurolink device for use in patients who fail medical therapy, and a HDE (Human Device Exemption) was approved. However, Guidant Corporation has disbanded their Neurovascular Unit and is no longer manufacturing the stent.

Another recent study by Jiang et al. also suggests that the rate of stroke or symptomatic brain hemorrhage at 1 year after stenting in patients with ≥ 70% intracranial stenosis may be as low as 7.2% [59]. This is substantially lower than the 1 year rate of stroke in WASID patients with ≥ 70% stenosis. The stent used in this study was a balloon expandable stent that is not available in the USA.

Drug-eluting balloon expandable stents

Following the lead from cardiology, some investigators have treated patients with intracranial stenosis with coronary drug-eluting stents which are not approved for the cerebral circulation and have not been shown to be safe in this population. The number of patients treated with

drug-eluting stents for intracranial stenosis is too small to provide reliable data on the performance, safety, and potential efficacy of these stents in the cerebral circulation [60, 61]. Preliminary experience indicates that these inflexible stents are difficult to deliver in the tortuous cerebral circulation, particularly to the middle cerebral arteries, a common location of intracranial atherosclerosis. Additionally, it is likely that the future development of intracranial drug-eluting stents will be impeded by recent reports that coronary drug-eluting stents increase the risk of late-stent thrombosis and subsequent MI or death [62], and that prolonged use of aspirin and clopidogrel is required with drug-eluting stents. This could increase the risk of major hemorrhage, particularly intracerebral hemorrhage [32].

Self-expanding Stents

The bare metal self-expanding Wingspan stent (Boston Scientific) designed specifically to treat intracranial stenosis was approved by the FDA on August 3, 2005 for use under an HDE (humanitarian device exemption) for patients with intracranial stenosis "who are refractory to medical therapy**".** This approval was based on a European / Asian study of 45 patients with symptomatic 50%-99% stenosis who had recurrent stroke on antithrombotic therapy. The main results of the study were that the stent was successfully deployed in 44 of 45 (98%) patients (95% CI 88.2% - 99.9%), the 30-day rate of stroke or death was 4.4% (95% CI 0.5% - 15.2%), and the 12-month rate of ipsilateral stroke or death was 9.3% (4/43) (95% CI 2.6 – 22.1). Only 3 of 40 patients (7.5%) (95% CI 1.6% - 20.4%) had restenosis at 6 months and none were symptomatic (www.fda.gov/cdrh/pdf5/h050001b.pdf). Of the 45 patients enrolled in the European / Asian Wingspan study, 29 had 70% - 99% stenosis. Of these 29 patients, 3 (10.3%) had a stroke in the territory or died with 1 year (95% CI 2.2% - 27.4%) (unpublished data presented at International Stroke Conference 2006, Orlando, Florida).

More recently, Fiorella and colleagues described their experience at 4 US sites with the wingspan device [63, 64]. Seventy eight patients with symptomatic intracranial atherosclerotic stenosis were treated over a 9 month period. A total of 82 lesions were treated, of which 54 had ≥ >70% stenosis. Lesions treated involved the internal carotid (n=32; 8 petrous, 10 cavernous, 11 supraclinoid segment, 3 terminus), vertebral (n=14; V4 segment), basilar (n=14), and middle cerebral (n=22) arteries. The technical success rate was 98.8% and the mean pretreatment stenosis was 74.6% and the mean post-stent stenosis was 27.2%. There were 5 major periprocedural neurological complications (2 vessel perforations, both fatal; 2 ischemic strokes, both fatal; 1 non-fatal reperfusion hemorrhage) for an overall major periprocedural complication rate of 6.1%.

Priority for a Trial

The stage is optimally set for a randomized trial comparing stenting with medical therapy because a series of events have converged: 1. completion of WASID has enabled identification of patients at high risk of stroke despite usual medical management, 2. completion of two Phase I trials have established preliminary safety and feasibility of intracranial stenting for patients with intracranial stenosis, 3. FDA approval of the Wingspan intracranial stent under an HDE for treating patients who have failed antithrombotic therapy, 4. training of over 50 sites in the USA by Boston Scientific Corporation to use the Wingspan stent and delivery system, 5. accumulating experience with Wingspan in clinical practice, and 6. the results of antihypertensive and recent lipid lowering therapy trials that mandate an evaluation of the role of aggressive risk factor management in patients with intracranial stenosis, a particularly high-risk subtype of cerebrovascular disease. Since Wingspan is the only FDA approved stent for intracranial atherosclerotic stenosis and is likely to remain so for the next several years given the length of of time it takes to develop and test new stents and receive FDA approval, it is incumbent on us now to determine the efficacy of stenting with Wingspan before it becomes established as standard but unproven therapy for intracranial stenosis.

Summary

Symptomatic atherosclerotic intracranial stenosis is a high-risk condition. The recently completed WASID trial has provided excellent estimates of the outcome of these patients on aspirin or warfarin and usual management of risk factors. Angioplasty and stenting cannot be justified in patients with < 70% stenosis, given the low risk of stroke in the territory of a stenotic artery (6 % at 1 year) and the inherent risk of current technology. Furthermore, the concept of medical treatment failure should not be required to perform angioplasty and stenting. Patients with severe stenosis, recent ischemic symptoms and an NIH stroke scale score of > 1, and females are at the highest risk for stroke, and therefore have the greatest likelihood of benefiting from angioplasty and stenting. The linear relationship between the degree of stenosis and stroke risk with medical therapy also supports a mechanical approach to revascularization. At present, however, there is no level 1 evidence to support angioplasty and stenting for patients with symptomatic intracranial atherosclerotic disease. Case series suggest that the safety and stroke risk reduction of this procedure may provide a benefit, particularly with self-expanding stent technology. A randomized controlled trial is needed to prove the efficacy of this therapy. In should also be noted that these patients as a group have frequent vascular risk factors and will require aggressive medical management. In addition, rates of restenosis and the clinical consequences of restenosis will need to be closely monitored in future studies. Advances in stent design may be required if self expanding bare stents are associated with a high risk of stroke associated with restenosis in clinical trials.

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TABLE 1

Author	N	Vessel	Technical Success	Major Peri- Procedural Complications	Follow-up Period and Events
Jiang 2003 [55]	42	ICA, MCA, VA, B	40/42 (95%)	4/42 (10%) "complication and death"	Median 8 months, 39 free of ischemic symptoms restenosis 0/7 at 6 months, 0/4 at 12 months
Zhang 2003 [54]	48	ICA, MCA VA, B	46/48 (96%)	4/48 (8%) – 2 vessel rupture, 1 acute stent thrombosis, 1 perforate vessel occlusion	"short term follow-up showed good clinical improvement"
Liu 2004 [53]	46	ICA, MCA VA,B	49/50 (98%)	1/46 (2%) SAH 1 (2%) extracranial carotid dissection requiring a stent	37/37 patients followed for a mean of 8.5 months were free of TIAs
de Rochemont 2004 [52]	18	ICA, MCA VA, B	18 /20 (90%) stenoses	30 day combined stroke and death = 6%	0 recurrent events in 6 months
Jiang 2004 [56]	40	MCA	41/42 (98%)	3/40 (8%) – 3 SAH (1 fatal), 1acute occlusion Rx with lytics without sequelae	Median 10 months: 0/38 had TIA or stroke, restenosis in 1/8 vessels
Lylyk 2005 [57]	106	ICA, MCA VA, B	104/106 (98%)	30 day stroke (6/104; 5.7%) and death (4/104; 3.7%)	Restenosis in 7/58 (12%)

VA = vertebral artery; B = basilar artery; ICA = internal carotid artery; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage, * data yet to be published