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Intracranial Angioplasty and Stenting: Modern Approaches to Revascularization for Atherosclerotic Disease

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Atherosclerotic disease accounts for more deaths than any other disease process in the world. The United States is no exception: cardiovascular disease is the leading cause of death, and ischemic stroke is the third leading cause of death [1]. Furthermore, ischemic stroke is the primary cause of adult disability in the United States. The current incidence of combined stroke and transient ischemic attack (TIA) in the United States is approximately 1 million events per year [2,3]. Atherosclerotic disease of the intracranial arteries has been postulated as the cause of 5% to 10% of all intracranial ischemic events in the United States, approximately 50,000 to 100,000 vascular events per year [4–12]. Yet, the optimal treatment strategy for patients with this disease remains undetermined. Antiplatelet therapy, anticoagulation therapy, and interventional angioplasty with or without stenting have all been used in an effort to optimize the care of these patients. Enthusiasm regarding intracranial stent-assisted angioplasty, in particular, has increased considerably over the past decade. The efficacy of interventional therapy versus medical therapy for patients with symptomatic intracranial atherosclerosis has not been compared in a randomized prospective trial, however.

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Epidemiology of symptomatic intracranial atherosclerosis

A multitude of retrospective studies have been performed to quantify the incidence of intracranial atherosclerosis in patients who present after a stroke or TIA. Most of these studies indicate that atherosclerotic intracranial stenosis (ie, of the carotid siphon, M1 segment of the middle cerebral artery, vertebral artery, or basilar artery) accounts for between 5% and 10% of all ischemic strokes in the United States per year. Most of these studies defined radiologically significant intracranial lesions as stenoses of more than 50% maximum vessel caliber combined with an infarction in the parent vessel territory in the absence of an embolic source of stroke. It has previously been demonstrated that there are high levels of interobserver agreement regarding the degree of intracranial stenosis in a particular patient [13]. In patients who undergo an adequate medical workup after a stroke, large vessel intracranial stenosis is the third leading etiology of ischemic cerebral events after cardioembolic stroke and extracranial carotid artery stenosis [4,5]. The Centers for Disease Control and Prevention estimate a combined incidence of TIAs and stroke in the United States of 1 million events per year; as a result, intracranial atherosclerosis accounts for roughly 50,000 to 100,000 intracranial ischemic events per year [3]. Furthermore, multiple

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studies have indicated that black Americans, Asians, and Hispanics are more likely to have symptomatic intracranial stenosis than age-matched controls [9,11,14]. Men may be more likely than women to have symptomatic intracranial atherosclerotic disease, but the data are less clear on this issue [9,11,14].

The annual stroke risk for patients with significant large vessel intracranial stenosis may be particularly high. Retrospective trials have quoted a yearly stroke risk in these patients ranging from 5% to 30%, depending on location, symptomology, and severity of stenosis [12,15–23]. The only prospective trial to date regarding the incidence of ischemic stroke in such patients is the Extracranial-Intracranial (EC-IC) Bypass Study [24]. In the nonsurgical arm of this trial, 258 patients with middle cerebral artery stenosis or carotid siphon stenosis were randomized to receive a total of 1300 mg of aspirin per day as well as management of medical risk factors, such as hypertension and diabetes. This group of patients had a stroke rate of 8% to 10% per year. No such prospective data exist for stenotic disease of the posterior circulation, but retrospective data suggest an annual stroke rate of 2.5% to 5.5% in patients with asymptomatic angiographically proven stenosis exceeding 50% in the posterior circulation [18–20]. Symptomatic posterior circulation stenosis of this severity may be a far more treacherous problem: one retrospective study demonstrated an annual stroke rate of 22% in the territory of the affected vessel in 68 such patients [12]. Furthermore, these patients are at a particularly high risk of stroke recurrence after a previous ischemic event (somewhere between 7.1% and 7.9% within the first 30 days), and nearly 50% have repeat symptoms within 12 months [21,22,25]. Therefore, effective therapies for symptomatic intracranial atherosclerosis of the posterior circulation are in particularly high demand.

Medical therapy for intracranial atherosclerosis

Several antiplatelet agents have been used in an attempt to treat patients with intracranial atherosclerotic disease, including aspirin, ticlopidine, clopidogrel, and combinations of these medications. The only drug in this group that has been studied prospectively is aspirin. As mentioned, the stroke rate among patients randomized to aspirin therapy in the EC-IC Bypass Study was 8% to 10% per year [24]. Patients randomized to the surgical arm of the study underwent bypass surgery, and no placebo arm was created. Therefore, no data exist regarding the absolute or relative stroke risk reduction associated with aspirin therapy in patients with known large vessel intracranial stenosis. Furthermore, the use of a radiographic standard instead of a physiologic standard (eg, stroke symptoms attributable to the stenotic vessel with insufficient blood flow demonstrated by radiographic studies) for the enrollment of patients into this trial creates uncertainty as to the applicability of the data to patients with symptomatic intracranial stenosis. Nonetheless, the high stroke rate among patients receiving aspirin in this study underscores the tremendous need for more effective treatments for this disease in general.

Several studies provide insight with respect to the relative efficacy of aspirin versus other antithrombotic agents in the prevention of stroke. In the Ticlopidine Aspirin Stroke Study, 3069 patients with extracranial and intracranial atherosclerotic disease were randomized to receive aspirin (1300 mg daily) or ticlopidine (500 mg daily; a platelet-aggregation inhibitor) after the occurrence of a noncardioembolic TIA [4,26]. The results showed that ticlopidine was more effective than aspirin in stroke prevention (21% relative risk reduction). Ticlopidine has been linked to multiple blood dyscrasias, however, most notably thrombocytopenia and neutropenia. As a result, clopidogrel, a platelet-aggregation inhibitor that is closely related to ticlopidine, gained increased popularity in stroke prevention. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial, more than 19,000 patients with documented cardiovascular, cerebrovascular, or other vascular disease were randomized to medical therapy with clopidogrel (75 mg daily) or aspirin (325 mg daily) [4,27]. Of these patients, 6431 were enrolled as the result of a stroke. In this group, the relative risk reduction for recurrent stroke was 8.7% in favor of clopidogrel.

Another important trial addressing medical therapy for the prevention of recurrent stroke among patients with multiple causes of stroke is the second European Stroke Prevention Study, in which a combination of extended-release dipyridamole (400 mg daily) and aspirin (50 mg daily) was compared with either drug alone and with placebo over a 2-year period [28]. The combination was found to be significantly more effective than either drug, providing a 37% relative stroke risk reduction versus 16% for dipyridamole alone and 18% for aspirin alone [4,28,29]. No specific comparison was made between

extended-release dipyridamole and aspirin in the management of primary atherosclerotic cerebrovascular disease, however. Although multiple studies have proven that other antiplatelet agents are superior to aspirin in the prevention of stroke recurrence, no study to date has demonstrated that any other antiplatelet agent is superior to aspirin alone in the prevention of primary or recurrent stroke secondary to atherosclerotic intracranial stenosis.

The major medical alternative to antiplatelet therapy is anticoagulation, typically with warfarin. Warfarin therapy is the current standard of care for the management of patients with cardioembolic stroke as well as for the prevention of cardioembolic stroke in patients with known atrial fibrillation [30]. This drug has never been shown to be superior to antiplatelet therapy in the prevention of noncardioembolic stroke, however. In a recent randomized, multicenter, double-blind trial, 2206 patients with a previous noncardioembolic ischemic stroke were assigned to receive warfarin (with a target international normalized ratio [INR] of 1.4–2.8) or aspirin (325 mg daily) [31]. At a 2-year follow-up interval, no significant differences were found in the rates of stroke, death, or major hemorrhage in the two groups. Another randomized, prospective, multicenter trial in which the effectiveness of aspirin and warfarin was compared with respect to noncardioembolic stroke was the Stroke Prevention in Reversible Ischemia Trial [32]. Patients with intracranial or extracranial arterial stenoses were included in this trial. A total of 1316 patients with a history of noncardioembolic TIA or minor ischemic stroke were randomized to receive aspirin (30 mg daily) or warfarin (target INR of 3–4.5). There was an excess of hemorrhagic complications in the warfarin group, and the trial was stopped at the first interim analysis. Critics of the study thought that a higher aspirin dose and a lower INR range would have been more reasonable in the comparison of the two medications.

Despite the lack of benefit of warfarin in the treatment of patients with noncardioembolic stroke, the results of a few retrospective trials suggest the superiority of warfarin to aspirin in the management of patients with isolated symptomatic intracranial stenosis (extracranial carotid artery disease excluded). The most important of these trials is the retrospective Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study, a multicenter trial that assessed the outcomes of 151 patients receiving warfarin or aspirin for the treatment of symptomatic 50% to 99% intracranial stenosis [7]. In this study, warfarin provided a 46% relative risk reduction of a major vascular event compared with aspirin. The stroke rate among the aspirin-treated patients was approximately 10% per year.

Building on the findings of their retrospective study, the same group of physicians embarked on a prospective WASID study comparing the effectiveness of warfarin (target INR of 2–3) versus aspirin (1300 mg daily) for patients with symptomatic stenosis of an intracranial vessel [5,10,33]. Once complete, the prospective WASID study will be the most important study of its kind. This study is a prospective, randomized, double-blind multicenter trial for patients with symptomatic and significant (angiographically proven $\geq$50%) intracranial stenosis. Primary end points are stroke or other vascular death. Exclusion criteria include tandem stenoses, cardiac source of embolism, contraindications to medical therapy, severe neurologic deficit, and dementia. Inclusion criteria are listed in Box 1 [33]. The WASID trial will have substantial implications for neurosurgeons. Of primary importance, the results of this trial will

Box 1. Inclusion criteria for the Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) trial

- TIA or minor stroke (Rankin score $\leq$3) within 90 days before randomization
- Stenosis of 50% to 99% of a major intracranial artery (carotid artery, M1 branch of the middle cerebral artery, vertebral artery, or basilar artery) proven by conventional angiography within 90 days before randomization
- TIA or stroke attributed to high-grade intracranial stenosis
- Patient at least 40 years old
- Patient willing and able to follow an outpatient protocol of monthly blood tests and triennial clinic visits and available by telephone
- Patient provided informed consent

From WASID inclusion criteria. Emory University. Available at: www.sph.emory.edu/WASID. Accessed January 16, 2004.

provide an incidence of vascular events in general for patients receiving the best medical therapy; this incidence must be lower than the incidence of such events combined with complication rates associated with intracranial angioplasty with or without stenting for such interventions to be feasible as a primary treatment for symptomatic intracranial stenosis. In addition, the trial will identify which patients have an especially high incidence of vascular events and which vessels are less responsive to medical therapy; such data will help physicians to decide which patients should undergo endovascular interventions rather than medical therapy with aspirin or warfarin [5]. By using this information, a trial comparing the best medical therapy with intracranial angioplasty with or without stenting can then be performed. The original protocol of the WASID study involved the enrollment and randomization of 806 patients; however, the study was prematurely halted at approximately 600 patients. The results of the study are pending publication. Regardless of the outcome of the trial, the high stroke rate among patients with intracranial atherosclerosis who are receiving the best medical therapy necessitates a better treatment option for this disease.

Evolution of intracranial angioplasty and stenting

Intracranial angioplasty was born in 1980 with the performance of a successful basilar artery angioplasty on two patients by Sundt et al [34]. As more experience was gained with such procedures, the morbidity and mortality rates were thought to be too high to justify this procedure as a reasonable intervention at that time. The techniques of intracranial angioplasty and stenting have improved remarkably, however, particularly over the past 5 years, and the instrumentation is far more advanced as well. Microcatheters and balloons are more pliable and supple than they were during the early pilot studies. Furthermore, sizing of the catheters and balloons is now more appropriate to the intracerebral vasculature, which consists of a smaller caliber vascular bed with thinner vessels than the corresponding coronary vasculature. Nevertheless, intracranial angioplasty remains an uncommon procedure: only 42% of major medical centers in the United States are performing angioplasty of the cerebral vessels, and the mean number of intracranial stenoses treated at these centers per year is 12, or 1 per month [35].

Percutaneous transluminal angioplasty for intracranial atherosclerotic disease has been subject to a tremendous learning curve since its inception more than 20 years ago. The biggest change over this period is an increased understanding of the differences between the architecture of cerebral vessels compared with that of coronary vessels. This understanding developed as a result of a high incidence of vessel rupture and dissection; early complication rates ranged from 5% to as high as 50% in small retrospective studies [36–46]. A grouping of these studies, with their enrollment and complication data, is provided in Table 1.

The largest retrospective study of intracranial angioplasty to date is the series of 70 patients spanning a 9-year period reported by Connors and Wojak [47]. This study illustrates the learning curve involved in the application of intracranial angioplasty to the cerebral vasculature: because intracranial vessels are smaller and more friable than coronary vessels, angioplasty must be performed in a more gradual and less aggressive fashion to be successful. Over the course of the study, these authors' technique evolved, and their outcomes improved as a result (Table 2). Grouping of the patients in this study was determined by two variables: rate of balloon inflation and balloon size. After their relative success with group 1, these authors adopted a more aggressive technique that involved oversizing of the treated vessel (group 2). Unfortunately, this approach led to an increase in the dissection rate and even to abrupt vessel occlusion and death in 1 patient. As a result, they began to use an undersized balloon and an extremely slow inflation technique (group 3). This technical adjustment was of tremendous value: although 14% of patients suffered a dissection in the treated vessel, none of the patients suffered a stroke consequently [47]. Furthermore, microangioplasty balloon catheters and postprocedural abciximab therapy were technologic advances available to most patients in group 3 and likely contributed to the improved outcomes [47]. Although these authors did not provide long-term follow-up data on recurrent stenosis rates, their data were promising because, despite a larger patient population, their complication rates were lower than those in most contemporary intracranial angioplasty studies.

Connors and Wojak [47] noted the implications of a less aggressive approach in achieving adequate intracranial flow. According to Poiseuille's law, flow is directly proportional to the

Table 1
Retrospective studies of angioplasty alone for intracranial atherosclerotic disease with associated complication rates

Study	Intracranial vessels treated	Initial success rate (%)	Immediate complication rate (%)
Alazzaz et al, 2000 [36]	16	75	13
Callahan and Berger, 1997 [37]	15	100	13
Clark et al, 1995 [38]	22	82	12
Higashida et al, 1993 [39]	8	75	38
Marks et al, 1999 [40]	23	91	9
McKenzie et al, 1996 [41]	12	92	8
Mori et al, 1997 [42]	35	77	9
Nahser et al, 2000 [43]	20	95	5
Takis et al, 1997 [44]	10	80	40
Terada et al, 1996 [45]	12	67	33
Touho, 1995 [46]	19	68	N/A

Abbreviation: N/A, not available.

Success rate is defined as the percentage of patients with decreased stenosis of the treated vessel immediately after angioplasty who did not develop an acute complication. Complication rate includes the occurrence of stroke attributed to the treated vessel, vessel rupture, and periprocedural death. Asymptomatic dissections and TIAs are not included. Complication rate is listed per vessel treated. Restenosis rates are not included because of the variance in follow-up intervals and criteria.

fourth power of the radius of the vessel lumen in a laminar flow system:

$$\text{Flow} = \Delta P \pi r^4 / 8(\text{Viscosity})(\text{Vessel length})$$

Multiple aspects of this law are manipulated in the clinical setting in an attempt to improve cerebral blood flow in patients with atherosclerotic intracranial cerebrovascular disease. For example, vasopressor therapy and volume expansion help to improve the pressure differential, and mild hemodilution therapy helps to decrease blood viscosity. None of these therapies has been shown to be as effective as an increase in vessel lumen caliber, however; in fact, a small change in vessel caliber yields a tremendous relative increase in flow. For example, a 10 mm vessel with 75% stenosis (on conventional angiography) has a lumen radius of only 1.25 mm. Achieving a partial resolution of this stenosis to only 50% provides a lumen radius of 2.5 mm. As a result of this change, vessel flow increases by a factor of 16.

Another important principle illustrated by the experience of Connors and Wojak [47] is that intracranial vessels are less resistant to dilation than coronary vessels or even extracranial cerebral vessels. Intracranial vessels lack the external

Table 2
Patient groups and outcomes for intracranial angioplasty in a retrospective study from Connors and Wojak

Patient group	1	2	3
Patients	8	12	50
Balloon size	Approximate to vessel diameter but always smaller than treated vessel	Equal to vessel diameter, with oversizing up to 0.25 mm allowed	Always undersized by 0.2–0.7 mm
Inflation period	15–30 seconds	A few seconds	Several minutes
Patient dissection rate (%)	50	75	14
Patient stroke rate (%)[a]	0	8	0
Patient death rate (%)	0	8	2

[a] Stroke rate refers to infarctions within the territory of the treated vessel.

Data from Connors JJ III, Wojak JC. Percutaneous transluminal angioplasty for intracranial atherosclerotic lesions: evolution of technique and short-term results. J Neurosurg 1999;91(3):415–23.

elastic lamina and the extensive adventitia of the extracranial carotid and vertebral arteries. Furthermore, the muscular tunica media of the coronary vessels is essentially absent in the intracranial vessels. As a result, aggressive dilation of intracranial vessels via excessive balloon size or rapid balloon inflation often leads to dissection and thrombosis or, even worse, rupture and hemorrhage [47].

Early lessons learned about the anatomy of intracranial vessels and plaques are recapitulated by the work of Mori et al [48], who developed a classification system of intracranial plaques on the basis of plaque length, stenosis degree, and lesion eccentricity (Table 3). This histopathologic classification scheme is predictive of periprocedural complication rates and subsequent restenosis rates. Using this system, Mori et al [48] found that type A lesions had a 92% immediate success rate and a 0% restenosis rate at 1 year of follow-up. Type B lesions had an 86% immediate success rate and a 33% restenosis rate at 1 year of follow-up. Type C lesions had a 33% immediate success rate and a 56% restenosis rate at 1 year of follow-up. On the basis of these data, this group recommended percutaneous transluminal angioplasty only for type A and B lesions of the posterior circulation in patients experiencing crescendo TIAs [48]. Most patients with symptomatic intracranial atherosclerotic disease do not harbor Mori type A intravascular lesions, however, and their symptoms are more likely to be refractory to medical management. Mori type C lesions are associated with an 87% combined risk of stroke or death versus an 8% combined risk of stroke or death with Mori type A lesions [48,49]. Clearly, technologic refinements of intracranial angioplasty were required for the benefit of those patients in greatest need. Furthermore, the risk of major complications, such as vessel dissection, distal embolization, and arterial rupture, underscored the need for an adjunct technology to improve outcomes. Finally, some reports of angioplasty alone for intracranial atherosclerosis have demonstrated more than 40% postprocedural stenosis [38,40]. The emerging solution to these challenges is intracranial stenting, a technique that has appeared only in the past 5 years. The concept is relatively simple: a permanent device is placed in the vessel to maintain lumen patency after angioplasty, helping to decrease restenosis rates as well as to increase short-term lumen patency rates by preventing vessel recoil. Like intracranial angioplasty, stenting is a technique originally pioneered by interventional cardiologists and subsequently applied to the intracranial circulation. Stents have been proven to decrease dissection risk and improve long-term patency rates in coronary vessels and the extracranial carotid vessels in multiple studies [50,51].

Table 3
Classification of intracranial atherosclerotic plaques

Lesion type	Length	Stenosis	Eccentricity
A	<5 mm	Not totally occluded	Concentric or moderately eccentric
B	5–10 mm	If occluded, for <3 months	Very eccentric or totally occluded
C	>10 mm	Occluded for >3 months	Angulated >90° with excessive proximal segment tortuosity or totally occluded

Data from Mori T, Fukuoka M, Kazita K, Mori K. Follow-up study after intracranial percutaneous transluminal cerebral balloon angioplasty. AJNR Am J Neuroradiol 1998;19(8):1525–33.

Most reports of intracranial angioplasty with stenting include even fewer patients than do reports of angioplasty alone. Nevertheless, they provide promising data for the treatment of patients with symptoms caused by medically refractory intracranial stenosis, particularly of the posterior circulation. In 1999, Phatouros et al [52] successfully treated a thrombotic occlusion of the basilar artery via angioplasty with stenting. In 2000, Rasmussen et al [53] published the results of stent-assisted angioplasty of the intracranial vertebral or basilar artery in eight patients with medically refractory posterior circulation TIAs. Successful vessel revascularization with a mean residual stenosis of 17% was achieved in all patients. One patient died of a subarachnoid hemorrhage that occurred the evening of the procedure, however, for a mortality rate of 12.5% [53].

Gomez et al [54] reported the treatment of medically refractory basilar stenosis via angioplasty and stenting in 12 patients. The mean degree of stenosis in these patients changed from 71.4% before the procedure to 10.3% after the procedure. At a mean follow-up of 6 months, there were no deaths, restenoses, or strokes. Angiographic follow-up was available for only 2 patients, however. The same group also reported

a single middle cerebral artery stenosis successfully treated with angioplasty and stenting [55]. Over a similar period, Levy et al [56] described 11 patients with medically refractory intracranial basilar or vertebral artery stenosis treated with transluminal angioplasty and stenting. Four (36%) of 11 patients died. The stented vessel was patent in only 5 (71%) of the 7 surviving patients at the time of angiographic follow-up. These findings emphasize the potentially devastating complications of this procedure, particularly in the posterior circulation. Lylyk et al [57] treated 34 successive patients with more than 50% intracranial stenosis secondary to atherosclerosis or dissection via a combination of direct stenting (ie, stenting without prior balloon dilation on a separate catheter) and conventional stent placement (ie, stenting after prior balloon dilation of the treated vessel). Successful stent deployment occurred in all but 2 patients, and 2 patients died as a result of the procedure, but the remaining results were favorable. Mori et al [58] successfully treated 8 of 10 patients with vertebrobasilar or distal internal carotid artery stenosis via flexible coronary stents. Fifteen patients with intracranial carotid or vertebrobasilar stenosis were treated via conventional angioplasty with or without stenting by Ramee et al [49]. The 5 patients who received stents had no complications, although 1 patient for whom stent placement was intended had an extremely tortuous carotid siphon that the authors were unable to traverse with the stent. In addition, multiple case series of successful stent-assisted angioplasty with 3 or fewer patients each have been reported [59–61]. A summary of these studies is delineated in Table 4.

To date, the only prospective clinical trial regarding the safety and efficacy of stenting for intracranial atherosclerosis is the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) trial [62]. Unlike the previous stenting trials discussed in this review, the results of direct (or primary) stenting performed in 43 patients with intracranial arterial stenosis and 18 patients with extracranial vertebral artery stenosis were evaluated in this trial. Although the SSYLVIA trial was a prospective multicenter trial, the study patients were not randomized. Nevertheless, this trial provides an assessment of the usefulness of a stent system specifically designed for intracranial atherosclerosis (NEUROLINK; Guidant Corporation, Menlo Park, California). All patients were enrolled within 7 days of a stroke or a TIA, and none developed new symptoms within 24 hours of the procedure. The stroke or TIA had to be ascribed to the stenotic vessel, and the degree of vessel stenosis had to be at least 50% to be considered adequate for treatment. Initial stent deployment was successful in 95% of patients, and the stroke rate in the territory of the treated vessel at 1 year of follow-up was 13.2%. Unfortunately, these results are an amalgamation of data for extracranial and intracranial lesions, which precludes an assessment of the effectiveness of direct stenting for intracranial arterial stenosis alone. Of greater concern are the angiographic follow-up data: 49 patients have undergone follow-up angiography 6 months after the intervention, and 18 (37%) of these patients demonstrated more than 50% restenosis of the treated vessel at that time. The high restenosis rate implies that bare metal stents are not the definitive answer in the long-term maintenance of vessel patency after intracranial angioplasty, and it underscores the need for more effective stents.

Future directions

Recent advances in the evolution of stent-assisted angioplasty for intracranial atherosclerosis are staged stenting and drug-coated stents. Staged stenting involves angioplasty followed by repeat angioplasty and stent placement at a later time (Fig. 1). The technique was originally developed to improve the treatment of eccentric high-grade (Mori type C) stenoses. In 2002, Levy et al [63] performed a retrospective review of a consecutive series of eight patients treated for medically refractory intracranial vertebrobasilar stenosis. All patients had eccentric high-grade stenoses. The procedure planned for these patients was angioplasty followed by repeat angioplasty and stent placement 1 month or more after the original procedure. The time interval was chosen because experimental data in animal models suggest that the process of remodeling in an atherosclerotic vessel injured by balloon angioplasty lasts for up to 1 month and that the healing lesion is particularly fragile during this period [64,65]. One patient suffered a periprocedural dissection requiring immediate stent placement [63]. The vessel was too tortuous to navigate in one patient, and it was widely patent at follow-up after angioplasty alone in another patient. Stent placement was accomplished successfully in the remaining patients. No deaths or permanent neurologic morbidity occurred.

Table 4
Outcomes and complications associated with stent-assisted angioplasty for intracranial atherosclerotic stenosis

Study	Intracranial vessels treated	Initial success rate (% of patients)	Major complication rate (% of patients)
Gomez et al, 2000 [55] (middle cerebral artery only)	1	100	0
Gomez et al, 2000 [54] (basilar artery only)	12	100	0
Levy et al, 2001 [56]	11	64	36
Lylyk et al, 2002 [57] (these patients had dissections as well as atherosclerotic lesions)	34	100	6
Mori et al, 1999 [59]	1	100	0
Mori et al, 2000 [58]	12	83	0
Morris et al, 1999 [60]	3	100	0
Nakahara et al, 2002 [61]	2	100	0
Ramee et al, 2001 [49] (10 additional patients were treated with angioplasty alone)	5	100	0
Rasmussen et al, 2000 [53]	8	88	13

Success is defined as decreased stenosis of the treated vessel immediately after angioplasty and stenting without the development of an acute complication. Major complications include stroke attributed to the treated vessel, vessel rupture, and periprocedural death. Asymptomatic dissection and TIA are not included. Complication rate is listed per vessel treated. Restenosis rates are not included because of the variance in follow-up intervals and criteria.

Early successes with intracranial stenting led many physicians to question whether angioplasty was necessary before stenting of stenotic vessels. The SSYLVIA trial and a few retrospective intracranial studies had demonstrated success with intracranial stenting [49,57,62]; furthermore, multiple prospective studies of coronary stenting demonstrated that direct stenting was equally safe and more cost-effective than conventional stent-assisted angioplasty [66–68]. Levy et al [69] evaluated this approach in patients with medically refractory basilar artery stenosis. Four patients were treated with direct stent placement; two of these patients developed pontine infarctions manifested by dense postprocedural quadriparesis. The authors thought that an "embolic shower" was probably responsible for the events, and they suggested the avoidance of direct stent placement into the basilar artery. Unlike the coronary circulation, which can be forgiving of small embolic infarctions, the cerebral circulation is extremely sensitive to perforator infarctions, particularly in the posterior circulation; thus, direct stenting is unlikely to be the safest approach in this vascular bed.

An increasing number of randomized prospective trials have demonstrated the efficacy of drug-coated stents in the coronary circulation. Antiproliferative and immunosuppressive agents have been used. For example, the sirolimus-eluting stent was compared with a standard stent in 1058 patients with newly diagnosed coronary stenosis; at a 270-day follow-up interval, the stent failure rate in the target vessel was 21% for bare metal stents versus 8.6% for the sirolimus stent [70]. Furthermore, the results of the Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL) showed that sirolimus-eluting stents prevent neointimal proliferation, regardless of vessel diameter [71]. Neither of these trials demonstrated any adverse effects of the sirolimus-eluting stent [70,71]. Another stent that has been studied is the polymer-based paclitaxel-eluting stent. In a prospective, randomized, multicenter trial of 536 patients, paclitaxel-eluting stents reduced neointimal propagation as well as restenosis rates at 6 months of follow-up [72]. Other agents that have been used for stent coating or elution include QP-2, rapamycin, actinomycin D, dexamethasone, tacrolimus, and everolimus [73]. Although the active agents differ, the message is clear: drug-coated stents yield lower restenosis rates than bare metal stents.

Because coronary vessels are generally of larger caliber than cerebral vessels and their vessel wall histology is different, there is a tremendous need for a randomized clinical trial of the efficacy

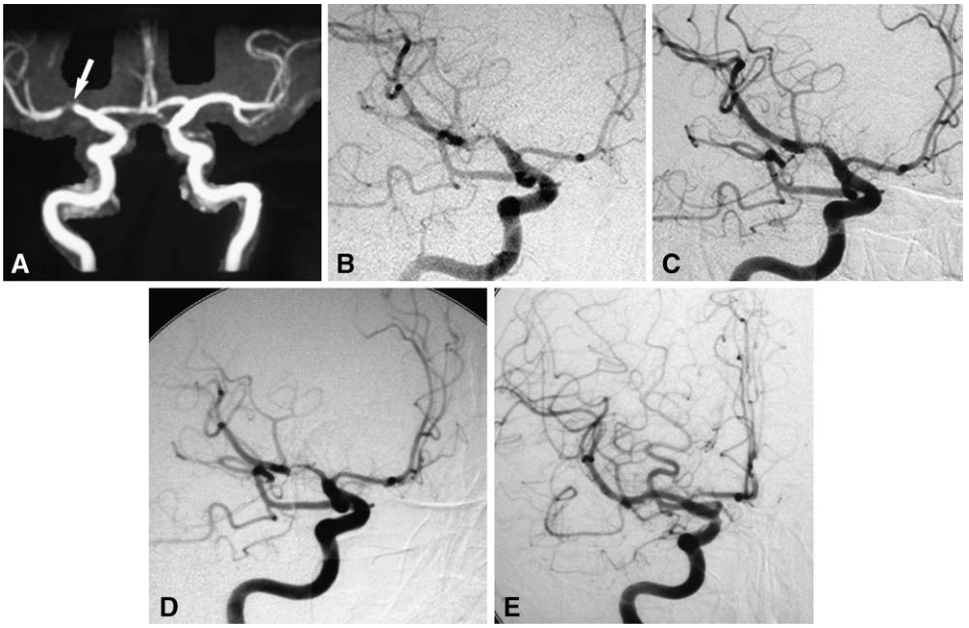

Fig. 1. (*A*) Magnetic resonance angiogram of the intracranial circulation in a 64-year-old woman with recurring transient ischemic attacks demonstrating focal, high-grade, middle cerebral artery (MCA) stenosis. (*B*) Digital subtraction angiogram (DSA) in the same patient demonstrating the focal stenosis in the MCA proximal to the bifurcation. (*C*) DSA after the initial angioplasty. This angioplasty is suboptimal, as evidenced by the residual stenosis. (*D*) DSA 6 weeks after the initial angioplasty. The residual stenosis is now more prominent, but the healed lesion is theoretically more stable than in the period immediately after the initial angioplasty. This lesion was then treated with repeat angioplasty and stent placement. (*E*) DSA 3 months after the original angiogram demonstrates continued complete resolution of the stenosis.

of drug-coated stents within the intracranial circulation. The purpose of the Stenting in Small Coronary Arteries trial was to assess the effects of stenting in smaller vessels [74]. A total of 145 patients were randomized to receive angioplasty alone or angioplasty combined with a heparin-coated stent. Among the heparin-coated stent group, not only was the event-free survival rate higher, but the 6-month angiographic results were superior. This study confirms the finding of the RAVEL study that small-caliber vessels respond favorably to drug-coated stents [71].

No drug-coated stents are currently approved by the US Food and Drug Administration for intracranial use; however, many seem to be on the way. Experimental data indicate that such stents may yield lower rates of long-term restenosis than bare metal stents: a recent study using heparin-coated stents versus bare metal stents in a canine basilar artery model demonstrated an average of 12% luminal stenosis in the drug-coated stents at 12 weeks of follow-up versus 22% in the bare metal stent group [75]. Further study is needed to determine the safety, efficacy, ideal dosing parameters, and durability of these devices. Nonetheless, it is essential that a safe and effective drug-coated stent be developed to maintain the patency of intracranial arteries after angioplasty.

The future of evidence-based treatment of intracranial atherosclerotic disease will involve the conclusion of the WASID trial and the initiation of other clinical trials to evaluate the safety and efficacy of drug-coated stents in the cerebral vasculature. Finally, a randomized multicenter trial comparing angioplasty and stenting with medical management alone must be performed. Until the results of such a trial are published, it may be reasonable to recommend intracranial angioplasty and stenting only for patients with symptomatic intracranial stenosis who have symptoms that are refractory to medical therapy. A therapy superior to antithrombotic medications is sorely needed for the many patients with medically refractory intracranial stenosis.

Summary

The tremendous importance of intracranial atherosclerotic disease cannot be overestimated. Traditionally, patients with this condition have been managed by neurologists and internists. As the inadequacy of medical therapy has come to light, neurosurgeons and neurointerventionists have begun to pay more attention to this highly prevalent problem. The newfound interest in this disease is well justified: intracranial atherosclerotic stenosis is more prevalent and more dangerous than unruptured cerebral aneurysms and arteriovenous malformations put together [15]. It is essential that we maintain our focus regarding the relative frequency and importance of the diseases that we treat as physicians so as to deliver the best therapies to the largest number of patients. Over the next few years, a rigorous assessment of the efficacy of coated stents compared with medical therapy for the treatment of intracranial atherosclerotic disease will provide another step toward the goal of adequately managing this difficult problem.

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