Interventional Management of Intracranial Stenosis

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Abstract: Worldwide, intracranial atherosclerosis is the most common cause of ischemic stroke and is associated with a high risk of recurrence. Endovascular therapies including angioplasty and stent implantation may help in secondary stroke prevention due to intracranial stenosis, however rigorous appraisal of clinical efficacy is currently lacking. This review aims to introduce the basic concepts involved with endovascular treatment of intracranial stenosis, its strengths and limitations, and discuss the available data. The importance of patient selection, procedural risks, patient outcomes, and surveillance goals are also highlighted.

Keywords: Intracranial stenosis, stent, neurointerventional, angioplasty, intracranial atherosclerosis, angiography, secondary stroke prevention.

BACKGROUND

As more stroke patients undergo cerebral vascular imaging, intracranial atherosclerosis is becoming increasingly identified as a putative mechanism for ischemic stroke. Although found in approximately 10% of stroke patients in the US [1], it is even more common in Asia, accounting for 30-50% of strokes, making it the most common cause of stroke worldwide [2]. In the US, this translates to more than 70,000 strokes per year related to intracranial atherosclerosis. Our understanding of the pathophysiology and treatment options remains underdeveloped in this challenging disease. The recurrent risk of stroke remains staggeringly high despite standard medical therapy [3]. Furthermore, those with symptomatic intracranial stenosis ≥70% face a recurrent stroke risk of 23% in the first year [4]. While improving flow would appear to diminish this stroke risk, surgical bypass techniques have remained controversial and unproven [5]. Recent enthusiasm has emerged for endovascular treatment options that hold the promise for immediate and minimally invasive revascularization of stenotic intracranial vessels to improve flow and potentially reduce future stroke risk.

CURRENT ENDOVASCULAR APPROACHES

The goal of endovascular revascularization is to restore luminal patency with minimal vessel wall injury, reasonable safety, improved outcomes, and adequate durability. Initially developed in the coronary and peripheral vasculature, endovascular approaches have undergone modification to accommodate the tortuous and delicate intracranial anatomy. As catheter and guidewire flexibility have improved, stents have evolved to include self-expanding and drug-eluting designs. Likewise, techniques have changed with modifications to balloon sizing and inflation. Endovascular therapy for intracranial arterial stenosis includes percutaneous transluminal angioplasty (PTA) with or without stent placement.

PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

Angioplasty Mechanism and Device Design

Balloon catheters include a catheter tube and a distensible balloon at the distal end that is inflated with a mixture of contrast and saline solution to a desired diameter and subsequently deflated by withdrawal of the fluid. Balloons are noncompliant, being self-limited in size distending only to a specific diameter or volume, and are inflated to about 6 to 8 atmospheres of pressure. They may be used to restore vessel patency or expand stents for intra-arterial placement. The mechanism of angioplasty was initially thought to result from compression of atheromatous material; however, this has been shown to account for little improvement of lumen diameter. With a small amount of wall stress, arteries behave as truly elastic; however, further stretching of the vessel wall results in partial disruption of the intima and media resulting in a permanent arterial widening [6]. Axial redistribution of plaque material may also contribute to luminal diameter increase.

Evolution of Intracranial Angioplasty

Intracranial percutaneous transluminal angioplasty (PTA) was first described in 1980 with treatment of a basilar artery stenosis in two patients [7]. Successful intracranial angioplasty of a symptomatic, stenotic cavernous carotid artery was reported in 1984 [8], and additional case reports followed [9, 10]. Enthusiasm about treating intracranial atherosclerosis was tempered by a variety of complications including arterial dissection, vasospasm, perforator vessel compromise, and distal embolization [11]. Intraprocedural dissection rates, although largely asymptomatic, were reported in 40% to 50% of PTA cases [12, 13]. A series of 25 patients with 25 vertebral or basilar artery stenoses showed 40% reduction in stenosis by PTA; however, the procedures carried an overall 28% risk of stroke or death, and risk of disabling stroke or death was 16% [14]. A safer approach to intracranial angioplasty was demonstrated with slow balloon inflation, over minutes versus seconds, combined with balloon undersizing to minimize intimal damage, thrombus formation, and acute vessel occlusion.

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The authors reported a dissection rate of 14% (7/50) with the newer technique [13]. This technique has been adopted and reported in subsequent series with similar complication rates [15, 16].

Limited data for long-term follow up of PTA are available. Smaller series have suggested an annual stroke rate of 1.8% to 3.2% [17], and intracranial re-stenosis of 8% to 27.4% during variable follow-up times within one year [13, 15]. A recent large series included 120 patients with 124 lesions of greater than 50% stenosis treated by primary angioplasty. The authors described a peri-procedural stroke and death rate of 5.8% and an annual stroke rate of 3.2% [16]. This study represents the largest series to date on primary angioplasty alone and shows a remarkably low annual stroke rate after treatment. It must be cautioned that these data are limited by selection bias and retrospective analysis. A common limitation of the series and others studying follow-up of intracranial atherosclerosis is that the severity of concurrent atherosclerotic vascular disease

**Fig. (1).** Depiction of intracranial stent implantation using the Wingspan stent system. Severe focal narrowing due to atherosclerosis is depicted (A). First, a Gateway balloon catheter is advanced over a guidewire to cross the lesion and slowly inflated to perform submaximal angioplasty (B). After removal of the balloon catheter, the stent delivery catheter is advanced and positioned symmetrically across the dilated lesion (C). The stent delivery catheter is withdrawn, unsheathing the self-expanding stent (D, E). The implanted stent (F) spans the entire lesion and exerts an outward radial force (arrows). Adapted image courtesy of Boston Scientific, Inc. All rights reserved.
elsewhere in the body likely also contributes to future stroke risk, independent of a specific cerebral vascular stenosis. Therefore, extrapolation of these future stroke rates to clinical scenarios must also include an evaluation to see if baseline demographics are also similar. Nevertheless, the major limitations of angioplasty alone include the risk of vessel dissection, and the high rate of restenosis and questionable long-term durability.

**INTRACRANIAL STENTS**

**Stent Mechanism and Device Design**

Intracranial stents range in diameter from about 2.5 mm to 5 mm and are intended to maintain vessel lumen patency after angioplasty. The goal in stent design is to achieve biocompatibility, corrosion resistance, flexibility, minimal thrombogenicity, and adequate fluoroscopic visualization in a device that can be technically implanted safely and consistently. Older stent materials included stainless steel and cobalt-based alloys, which have been limited in performance by restricted elastic deformation properties, super-elasticity and shape memory characteristics that make it favorable for use in intracranial revascularization. The super-elasticity allows the nitinol stent to be constrained in a low profile catheter with the flexibility to accommodate navigation through tortuous anatomy. Upon deployment, the stent self-expands to its original size and shape (Fig. 1). After expanding to the size of the vessel, it exerts a low continuous outward radial force (less than 0.1 atm for the Wingspan stent) that is thought to assist with maintaining long-term lumen patency [19]. Fluoroscopic visibility decreases due to the small stent profile, which requires electroplating of radiopaque markers on the distal and proximal borders (Fig. 2) [18].

Self-expanding stents do not necessitate delivery over balloons, therefore they can be delivered within microcatheters alone, improving navigation within small intracranial arteries. Stent geometry varies widely, however common intracranial stent designs have included closed-cell and open-cell sequential ring construction. In open-cell construction, some or all of the internal inflection points of the structural members are not connected by bridging elements allowing for improved longitudinal flexibility [20]. Flexibility is important for the ability of the stent to conform to curved and tapered vessels of the cerebrovasculature.

Newer technology includes drug-eluting stents (DES) which offer local delivery of a pharmacologic agent to the vessel wall to suppress neointimal proliferation. The desired drug is adherent to the stent by a polymer coating that allows sustained release. DES have been widely adopted in periprocedural complication rate at 30 days [26]. Outcome data from the use of the Wingspan stent in a more select, high risk group (70% to 99% intracranial stenosis), was reported on a total of 129 patients [27]. The frequency of any stroke, intracerebral hemorrhage, or death within 30 days or ipsilateral stroke beyond 30 days was 14% at 6 months and 25% had > 50% restenosis on follow-up angiography. Longer-term outcome data on the Wingspan system was only recently reported from a single center where 51 patients had an overall 10% rate of stroke or death at a mean follow up time of up to 14.6 months [28].

Angioplasty and implantation of intracranial stents has been demonstrated to be technically possible with success rates of ≥ 95% in most reports, while reduction of residual luminal stenosis to below 50% is commonly reported [25-33]. However, these are largely self-reported results. Stent success has been defined as adequate device performance based on an investigator rating system and a reduction in the degree of stenosis to < 50% immediately after implantation [25].

Due to considerable stent re-stenosis rates with nitinol stents, interest has developed for the possible benefit of drug-eluting stents (DES) in maintaining long-term vessel patency. Drug-eluting stents target cellular proliferation by local delivery of drug while minimizing systemic toxicity. Sirolimus-eluting stents in coronary arteries have been shown to significantly reduce restenosis [34]. The use of DES for intracranial stenosis has not been well-studied. Small series of patients receiving either sirolimus or
paclitaxel-coated stents have reported a 0 to 14% restenosis rate at variable follow-up times over one year and major stroke or death rate of up to 11% [35-37]. The largest series using drug-eluting stents included 62 lesions (59 patients) which were both intracranial (26) and extracranial (36) [33]. Fifty vessels were evaluated with angiography at a median 4-month follow-up period and showed greater than 50% stenosis in 7% of the extracranial stents and 5% of the intracranial stents. Post-implantation dual antiplatelet therapy varied from 3-6 months duration. Although early restenosis rates seem improved, the long-term durability of coronary artery DES is uncertain. Reports of late thrombosis have suggested a possible hypersensitivity reaction to a stent polymer [38], and late endothelialization [39]. Furthermore, the risk of neural toxicity from DES has been a target of inquiry. Data from the use of sirolimus-eluting stents used in canine cerebral arteries shows no toxicity [40]. Another major concern with DES for intracranial circulation will be navigating a rigid stent into the brain and technical success of stent delivery and placement for a wide variety of lesions and locations.

**ANGIOPLASTY ALONE VERSUS ANGIOPLASTY WITH STENTING**

Superiority of either angioplasty alone or angioplasty with stenting has not been clearly demonstrated. PTA was compared with stent placement in 24 patients with petrous or cavernous internal carotid artery stenosis and revealed greater immediate decrease in stenosis ratio in those treated with stent placement compared to those with only PTA (stenosis decrease by 73.4% versus 42.5%, respectively) [12]. Additionally, there was greater than 50% re-stenosis in four patients who underwent PTA and no re-stenosis in those who received stent placement. A non-randomized comparison of angioplasty versus drug-eluting stent placement showed no significant difference between major stroke or death between the two cohorts at 12 month evaluation [41]. A report on treatment of 69 lesions over a 7-year period with angioplasty alone or with stent implantation (76.8%, 53/69) showed an overall restenosis rate of 15.9% (with 18.2% being symptomatic [2/11]). The restenosis rate was 50% (8/16) for angioplasty and 7.5% (4/53) for stenting [32]. These data suggest durability of luminal dilation may be enhanced by stent placement.

**SAFETY OF ENDOVASCULAR THERAPY**

Concerns and Risks

Endovascular procedures involve intracranial manipulation of guide wires and catheters as well as balloon inflation and stent implantation, each of which carries the risk of vessel injury or embolic events. The intracranial arteries have a thin adventitial layer and are surrounded only by the cerebrospinal fluid filled subarachnoid space. Injury with balloon dilation or catheter and guide-wire manipulation may result in perforation, dissection, and life-threatening subarachnoid hemorrhage. The risk of adverse cerebral hemorrhagic events is exacerbated by the concurrent use of dual antiplatelets if stent placement is anticipated. Operator and institution experience may influence outcomes as has been suggested by the increased risk of adverse events in patients treated at low volume sites [42]. Development in device technology, and improved technique will likely reduce these complications, however peri-procedure complication rates remain an important consideration. Plaque manipulation in cerebral vessels carries the unique risk of perforator vessel occlusion, particularly in the first segment of the middle cerebral artery or the basilar artery, which may lead to infarcts of cerebral tissue that have little inherent collateral reserve. The risks of endovascular therapy extend beyond those inherent to the catheter procedure and include risk of general anesthesia. General anesthesia is frequently used for intracranial stent implantation and therefore may limit stent therapy to those patients without significant co-morbid conditions [43].

**Procedure Complications**

Rates of complications from endovascular procedures vary widely from 4.5% to 50% among reports of varying interventional modalities including PTA, balloon-mounted stents, and self-expanding stents [12, 13, 16, 24-27, 44]. These peri-procedural complications are commonly reported as adverse events within the first 30 days post-procedure. The types of reported complications vary and frequently include ischemic stroke, dissection, intracranial hemorrhage, and death. A retrospective review to evaluate procedure-related cerebrovascular complications reported on 169 patients (181 lesions) who underwent stent placement for intracranial stenosis >50% found a 11.8% complication rate at 30 days which included intracranial hemorrhage, target-lesion thrombosis, perforator stroke, embolic stroke, TIA, and vessel dissection [45]. Perforator stroke has been reported in higher frequency after stenting stenoses that have adjacent preoperative perforator infarct [46]. A Cochrane database review in March of 2006 identified 79 reports that included 1999 cases comparing best medical care plus angioplasty with or without stent placement, with best medical care alone [47]. The overall perioperative rate of stroke was 7.9% (95% confidence intervals (CI) 5.5% to 10.4%), perioperative rate of death was 3.4% (95% CI 2.0% to 4.8%), and perioperative rate of stroke or death was 9.5% (95% CI 7.0% to 12.0%).

**Event Rate**

Rates of ischemic stroke or death also vary widely among reports, ranging from 3.2% to 10% [16, 24, 25, 28, 48]. Interpretation of these rates is further complicated by the inconsistent mean follow-up times that range from 6 to 14 months. An interesting comparison has been made regarding complication and event rates between balloon-mounted and self-expanding stents. The higher rate of peri-procedural complication with balloon-mounted stents (7-10%) with a lower rate of long-term recurrent events at follow-up (2.9-3.7%) when compared to self-expanding stents (6.4% peri-procedural complication and 10.3% long-term event rates) may suggest an increased risk of peri-procedural events in balloon-mounted stents but decreased delayed events compared to self-expanding stents [49].

**In-Stent Restenosis**

An important limitation to the long-term success of endovascular therapy for intracranial stenosis is restenosis. Following angioplasty, elastic recoil accounts for acute lumen restenosis, which is followed by negative remodeling and neointimal hyperplasia over the ensuing six months [50].
Balloon injury to the vessel results in a cascade of events including an inflammatory response that largely involves leukocyte migration, and results in neointimal formation [51]. Stent implantation reduces the element of elastic recoil and negative remodeling; however current stent technology is overcome by the potent inflammatory response to the stent and proliferative events that lead to neointimal hyperplasia. In-stent restenosis may be decreased with antiplatelet therapy and use of drug-eluting stents, while angioplasty may be used for re-dilation of a stenosed vessel. Identifying those patients who will be at risk for re-stenosis is challenging; however, factors associated with restenosis include small vessel size (< 2.5 mm), interventions performed in the setting of an acute stroke [32], location of stenosis at the supraclinoid segment, and older age [52]. The reported rate of restenosis has been high, up to 25% for the Wingspan stent at 6 months, though the majority of cases have been asymptomatic [32]. Although a 1-year rate of restenosis was reported to be 15.9% (11/69), only 18.2% of those (2/11) were symptomatic [32]. This series included both angioplasty alone and with stenting and some of the stents used were drug-eluting. The reported restenosis rates are also likely subject to compliance with post-procedure antiplatelet regimens and whether drug-eluting stents have been used, methods which vary widely among reported cases.

**Management**

**Patient Selection**

Besides identifying patient characteristics of those at highest risk of recurrent stroke (see Chapter 3), the lesion characteristics likely influence the technical success of endovascular therapy. In addition to degree of stenosis (≥70%), location of the target lesion in relation to perforator vessels and branches is a consideration as is technical accessibility of the lesion in predicting the success of effective angioplasty and stent placement. Morphology of the lesion is also related to risk of complications and restenosis [31]. Because of these associations, a classification of lesions based on location, morphology, and access was proposed (LMA classification) suggesting importance of individual lesion characteristics in deciding therapy [31]. Integration of a classification system such as this may assist in identifying those patients who would benefit most from endovascular therapy. Prospective data suggests there is not a greater risk of stroke in either an anterior or posterior circulation stenosis [4]. However, periprocedural complications have been higher in the posterior circulation compared to anterior circulation [42, 53]. Therefore, greater caution may be appropriate in the decision to pursue a posterior circulation stenosis with endovascular therapy. Angiographic appearance of the stenotic lesion may offer additional information to facilitate patient selection. In a series of 42 hemodynamically significant intracranial lesions of greater than 70% stenosis treated with PTA, angiographic characteristics of the lesion including length, concentric or eccentric lesion, and tortuosity were assessed [54]. These data suggested that PTA for “simple” intracranial lesions in symptomatic patients produces a more favorable clinical outcome, while angulated lesions with tortuous access were associated with higher complications.

The appropriate timing for endovascular intervention is unknown [55]. A short duration of angina has been correlated with increased distensibility of atheroma in the coronary arteries, suggesting that the early stage of development of an intimal plaque involves largely atheromatous material, whereas subsequent fibrous proliferation and intimal calcification may limit effectiveness of intervention [56]. Time since the qualifying event was an independent predictor of risk for stroke recurrence in the WASID trial with the highest risk occurring if enrolled within 17 days after a symptomatic event [4]. Although chronic severe intra-arterial occlusion has been treated with angioplasty and stent placement [57], early revascularization has been emphasized given the predominant risk of recurrent stroke in the early post-event period. However, acute revascularization of intracranial vessels may confer higher periprocedural complications. A report of 18 neurologically unstable patients with 21 lesions who underwent urgent (6 patients had acute stroke within 3 days of procedure, 2 patients had 2 days of progressive neurologic deficit, and 10 patients had recurrent TIA) revascularization with angioplasty or stent-assisted angioplasty revealed major periprocedural complications in 50% (9/18) [43]. The appropriate procedure timing may be within the sub-acute period following the qualifying event. Nevertheless, it appears that if able to be performed safely, the greatest benefit is derived within days of the initial event.

**Post-Treatment Management**

**Antiplatelet Therapy**

To reduce the risk of stent thrombosis, long-term management with antiplatelet therapy has been routinely used. In patients with acute coronary syndrome undergoing percutaneous coronary intervention, pretreatment with clopidogrel and aspirin was shown to be beneficial in reducing 30-day post-procedure major ischemic events [58]. The American Heart Association guidelines recommend dual antiplatelet therapy for 1 month for bare metal stents and up to 6 to 12 months for drug eluting stents [59]. Adjunctive antiplatelet therapy has also been employed in management of stent implantation for intracranial stenosis. In the SSYLVIA trial, pre-procedure aspirin and clopidogrel were used followed by 4 weeks of clopidogrel and one year of aspirin therapy for placement of a bare-metal stent [24]. A similar regimen was used in the Wingspan study with pre-procedure aspirin and clopidogrel treatment, followed by daily clopidogrel for one month and aspirin thereafter for life [25]. Dual antiplatelet therapy for an extended period has become common practice following drug-eluting stent implantation due to a possible increased risk of delayed in-stent thrombosis. The practice of antiplatelet pre-medication for intracranial drug-eluting stent placement with 5-7 days of aspirin (325 mg/d) and clopidogrel (75 mg/d) followed by clopidogrel (75 mg/d) for 6 to 12 months and lifelong aspirin (325 mg/d) is commonly used [35, 37, 60].

Antiplatelet resistance is a recently recognized challenge in the management of patients who undergo cerebrovascular stent placement. Clopidogrel resistance occurred in about half of patients undergoing cerebrovascular stent placement in one study [61]. Additionally, the authors reported that older patients and those with diabetes mellitus may be poor
responders to clopidogrel. A similar study found that 21% of
patients premedicated with aspirin and clopidogrel were non-
responders to aspirin [60]. Furthermore, a greater percentage
of inadequate platelet inhibition was noted in patients
premedicated with clopidogrel when compared to aspirin
(66% versus 13%) and same-day antiplatelet loading may be
insufficient [62].

An additional challenge in antiplatelet therapy is
compliance. Perioperative non-compliance with antiplatelet
therapy was found to be significantly associated with target-
lesion thrombosis [45]. Given the consequences of
restenosis, the ideal antiplatelet agent, dosing, duration of
therapy, responsiveness to treatment, and compliance are as
critical an aspect to prevent further ischemic events as the
technical success of the stent implantation.

**Surveillance Imaging**

Catheter angiography remains the ideal modality for
surveillance imaging (Fig. 3). Following a standardized
method of measurement with angiography, the degree of
intracranial stenosis can be reliably evaluated [63]. Although
neurologic complications of catheter angiography are rare
(0.34%) [64], non-invasive evaluation would further
minimize risk. The conventional computerized tomography
(CT) imaging algorithm fails when reconstructing an image
of an interface between an unusually dense structure (a stent)
and surrounding soft tissue, resulting in beam-hardening
artifact. CT angiography of endovascular stents is subject to
an exaggerated thickening or blooming of the stent struts
causing artificial lumen narrowing [65]. In general, CT
angiography overestimates the degree of in-stent stenosis
[66]. These factors limit the usefulness of CT angiography in
surveillance imaging. A recent report of rotational
acquisition of a c-arm mounted flat-panel detector CT has
shown promise as a non-invasive method for follow-up [67].

Magnetic resonance angiography (MRA) is an alternative
non-invasive method of imaging intracranial stents, although
similar challenges with image artifact exist. The paramagnetic
nature of a metallic stent causes a localized
distortion of the magnetic fields resulting in loss of signal
and artifact. MR imaging at field strengths of up to 3 Tesla
in patients with implanted nitinol stents has been previously
demonstrated as safe [68]. Stainless-steel stents impart
extensive signal loss at the level of the stented area, whereas
nitinol stents are associated with less distortion allowing for
improved MRA vessel imaging, which can be enhanced with
contrast [69]. Quantitative MRA (QMRA) has been used in
evaluation of an extracranial vertebral artery stent [70], and
more recently as a screening tool for detecting intracranial
in-stent stenosis [71]. The latter study reviewed 13 cases of
stent-assisted coiling and 1 case of stent placement for
atherosclerosis and found that time-of-flight MRA was non-
diagnostic in detecting in-stent stenosis due to coil or stent
artifact. However, a greater than 20% reduction in blood
flow on QMRA was associated with the presence of greater
than 50% in-stent stenosis. Quantitative MRA may have a
role in screening for in-stent restenosis.

The optimal timing and modality for surveillance
imaging following endovascular therapy for intracranial
stenosis is unresolved. Additionally, long-term data on
restenosis rates are not available. Follow-up with
conventional angiography at three months has been proposed
[72].

Fig. (2) Depiction of the Wingspan stent in an artery showing various components. Radiopaque markers placed on the ends of the stent allow for visualization during and after stent implantation. Struts form the stent framework and are either joined or open at each vertex. Depicted in this image is an open-cell design which offers greater flexibility than a closed-cell design. Adapted image courtesy of Boston Scientific, Inc. All rights reserved.
SUMMARY

Whether endovascular therapy can improve the natural history risk of hemodynamically significant intracranial stenosis remains unknown. The management of intracranial stenosis is challenging and optimal therapy is unclear at this time. Data from the WASID trial showed that with best medical therapy, there was an 11% to 14% chance of recurrent stroke in the first and second years following the initial event. Furthermore, those with stenosis of ≥70% had up to 23% risk of recurrent stroke at one year. The high rate of stroke recurrence among those with high grade intracranial atherosclerotic stenosis presents an appropriate opportunity for the investigation of endovascular therapies to reduce this risk.

Interpretation of data from reports of endovascular therapy for intracranial stenosis is challenging with widely heterogeneous groups represented by varying degrees of stenosis, type of treatment (angioplasty alone, angioplasty with stent), type of stent (balloon-mounted, self-expanding, drug-eluting), lesion location, follow-up duration, and post-procedure antiplatelet therapy (Table 1). This is compounded by an overall lack of randomized controlled trial data, which is of particular importance because of the wide spectrum of atherosclerotic disease severity. The available data suggest that endovascular therapy carries a peri-procedural risk of about 5-10% at 30 days and a 5% stroke or death risk in the first year after 30 days. These cumulative risks approach the recurrent stroke risk observed in patients treated with medical therapy alone. Therefore, it seems reasonable that with further experience, improved technique, and advances in device technology, endovascular therapy may have a substantial role in treating this challenging disease.

Fig. (3). Anteroposterior digital subtraction angiogram demonstrating 70% stenosis (arrow) of the left proximal middle cerebral artery (A), and postangioplasty and stent implantation study demonstrating recanalization (arrow) after stent placement (B). Anteroposterior digital subtraction angiogram demonstrating 90% stenosis (arrow) of the right vertebral artery (C), and postangioplasty and stent implantation study demonstrating recanalization (arrow) after stent placement in the right vertebral artery (D).
Table 1. Major Studies of Intracranial Stenosis Treatment

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Stent</th>
<th>Type</th>
<th>Lesions, n (Patients)</th>
<th>Inclusion Stenosis</th>
<th>Mean Stenosis, % (Pre-Post-Treatment)</th>
<th>Restenosis Rate (&gt;50%)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolfe TJ et al.</td>
<td>Wingspan</td>
<td>Self-expanding</td>
<td>51 (51)</td>
<td>50-99%</td>
<td>73 → 21%</td>
<td>24% at mean 8.6 months</td>
<td>8% at 30 days (stroke or death)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>10% at mean 14.6 month follow-up.</td>
<td></td>
</tr>
<tr>
<td>Samaniego et al.</td>
<td>Wingspan,</td>
<td>Self-expanding and balloon</td>
<td>53</td>
<td>&gt;= 50%</td>
<td>Unreported</td>
<td>Unreported</td>
<td>5.6% at 24 hours periprocedural complication rate</td>
</tr>
<tr>
<td></td>
<td>Neuroform,</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>28% TIA, stroke, or death, at average 14 months</td>
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<tr>
<td></td>
<td>Various</td>
<td>balloon mounted</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Zaidat et al.</td>
<td>Wingspan</td>
<td>Self-expanding</td>
<td>129</td>
<td>70-99%</td>
<td>82 → 20%</td>
<td>25% (13/52) at unreported time</td>
<td>14% at 6 months</td>
</tr>
<tr>
<td>Mazighi et al.</td>
<td>Various</td>
<td>PTA w/o balloon-mounted</td>
<td>69 (53)</td>
<td>&gt;=70%</td>
<td>85 → 0%</td>
<td>16% (11/69) at 1 year (symptomatic in 18%)</td>
<td>10% at 30 d (stroke/death)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>5.8% at 2 yr (TIA or stroke)</td>
</tr>
<tr>
<td>Suh et al.</td>
<td>Various</td>
<td>Balloon-mounted</td>
<td>100 (100)</td>
<td>&gt;=70%</td>
<td>70 → 25%</td>
<td>0% (0/59) at 6 months</td>
<td>10% at 6 months (minor stroke, major stroke, death)</td>
</tr>
<tr>
<td>Bose et al.</td>
<td>Wingspan</td>
<td>Self-expanding</td>
<td>45</td>
<td>50-99%</td>
<td>75 → 32%</td>
<td>7.5% at 6 months</td>
<td>4.5% (stroke or death at 30 days)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>7% (stroke or death at 6 months)</td>
</tr>
<tr>
<td>Jiang et al.</td>
<td>Various</td>
<td>Balloon-mounted</td>
<td>181 (169)</td>
<td>&gt;50%</td>
<td>Unreported</td>
<td>Unreported</td>
<td>11.8% (20/169) overall</td>
</tr>
<tr>
<td>Fiorella et al.</td>
<td>Wingspan</td>
<td>Self-expanding</td>
<td>82 (78)</td>
<td>&gt;= 50%</td>
<td>75 → 27%</td>
<td>Unreported</td>
<td>6.1% (30 day major complication)</td>
</tr>
<tr>
<td>Steinfort et al.</td>
<td>Paclitaxel</td>
<td>DES</td>
<td>13</td>
<td>&gt;= 60%</td>
<td>67 → 8%</td>
<td>0 (9 patients had followup at 5.4 months)</td>
<td>8% (1/12 had stroke at mean 10 month followup)</td>
</tr>
<tr>
<td>Marks et al.</td>
<td>None</td>
<td>PTA</td>
<td>124 (120)</td>
<td>50-95%</td>
<td>82 → 36%</td>
<td>Unreported</td>
<td>5.8% stroke and death at 30 days</td>
</tr>
<tr>
<td>Wojack et al.</td>
<td>Various</td>
<td>PTA and stent</td>
<td>84 (71)</td>
<td>&gt;=70%</td>
<td>Unreported</td>
<td>27.4% at a mean of 4.6 months (23/84)</td>
<td>3.2% annual stroke rate</td>
</tr>
<tr>
<td>Gupta et al.</td>
<td>Sirolimus and paclitaxel</td>
<td>DES</td>
<td>62 (59)</td>
<td>90% of patients had 70% or greater stenosis</td>
<td>83 → 12%</td>
<td>6% total (3/50) at median 4 months</td>
<td>3% at median 4 months</td>
</tr>
<tr>
<td>Qureshi et al.</td>
<td>Sirolimus and paclitaxel</td>
<td>DES</td>
<td>18</td>
<td>&gt;=70%</td>
<td>68 → 14%</td>
<td>14% (1/7 at 6 months)</td>
<td>5% (30 day stroke)</td>
</tr>
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<td></td>
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<td></td>
<td>11% 1-year major stroke or death rate</td>
</tr>
<tr>
<td>Abou-Chebl et al.</td>
<td>Sirolimus and paclitaxel</td>
<td>DES</td>
<td>8</td>
<td>&gt;=70%</td>
<td>84 → 2.5%</td>
<td>0/8</td>
<td>1 intraprocedural retinal embolism</td>
</tr>
<tr>
<td>Henkes H et al.</td>
<td>Wingspan</td>
<td>Self-expanding</td>
<td>15</td>
<td>&gt;50%</td>
<td>72-38%</td>
<td>0</td>
<td>7% (1/15 had transient periprocedural symptom) 0 at 4 weeks</td>
</tr>
<tr>
<td>Jiang WJ et al.</td>
<td>Various</td>
<td>Balloon-mounted</td>
<td>42 (40)</td>
<td>&gt;= 50%</td>
<td>Unreported</td>
<td>12.5% at 10 months (1/8), only 8 vessels had follow up.</td>
<td>10% total complication</td>
</tr>
<tr>
<td>SSYLVIA investigators</td>
<td>Neurolink</td>
<td>Balloon-mounted</td>
<td>61</td>
<td>&gt;=50%</td>
<td>Unreported</td>
<td>32% at 6 months</td>
<td>6.6% (4/61 had stroke at 30 days)</td>
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<td>7.3% (4/55 had stroke after 30 days)</td>
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<td>10.9% (stroke at 1 year)</td>
</tr>
</tbody>
</table>

DES: drug eluting stent; PTA: percutaneous transluminal angioplasty.
Some authors caution that a judgment on the effectiveness of intracranial endovascular angioplasty and stenting therapy may be premature when the field is only in its infancy, and that further device development, technique, and experience are needed to truly understand its safety and efficacy [73]. The evolving variables in endovascular treatment of intracranial stenosis include technique, the growing technology of balloons and stents, post-procedure antiplatelet management, and surveillance imaging.

Rigorous scientific evaluation of endovascular therapy remains to be completed. The ongoing phase III clinical trial, Stenting and Aggressive Medical Management for Preventing Stroke in Intracranial Stenosis (SAMMPRIS), will compare maximum medical therapy alone with maximum medical therapy and adjunctive intracranial angioplasty and stenting in patients with symptomatic intracranial stenosis greater than or equal to 70% [74].

CONCLUSIONS

The current data suggest that endovascular therapy has promise in the treatment of intracranial stenosis ≥70% in patients who remain symptomatic despite medical therapy. A recent publication of the American Heart Association guidelines on neurointerventional procedures has advised that endovascular therapy may be considered for patients with symptomatic severe intracranial stenosis (≥70% luminal narrowing) despite optimal medical therapy [75]. This practice is becoming widely adopted with the increasing skill of interventionalists and advancing device technology in the setting of a complex and challenging disease that carries a strikingly high risk of future stroke. The use of endovascular therapy for intracranial stenosis however currently lacks rigorous appraisal of its ability in conferring additional benefit over and above optimal medical therapy alone. The ongoing SAMMPRIS trial aims to provide this data; however, clinical application of these results will be challenging with the rapidly changing field of neuroendovascular therapy. Significant advances have been made in the arena of neuroendovascular therapy over the past two decades and accelerated growth is anticipated. Device technology is quickly developing, endovascular technique will continue to progress, and the experience of interventionalists with the use of these tools will increase. Aggressive medical treatment of risk factors such as hypertension, diabetes, and hypercholesterolemia is fundamental in prevention of stroke from intracranial artery narrowing. Improved patient selection with better understanding of risk factors and predictors of outcomes will allow us to better select patients who will truly benefit from interventional approaches to intracranial atherosclerosis.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>PTA</td>
<td>Percutaneous transluminal angioplasty</td>
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<tr>
<td>DES</td>
<td>Drug-eluting stent</td>
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<tr>
<td>WASID</td>
<td>Warfarin-Aspirin Symptomatic Intracranial Disease Study</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized tomography</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>rCBF</td>
<td>Regional cerebral blood flow</td>
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<tr>
<td>MRA</td>
<td>Magnetic resonance angiography</td>
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<tr>
<td>QMRA</td>
<td>Quantitative magnetic resonance angiography</td>
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<tr>
<td>SSYLVIA</td>
<td>Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries</td>
</tr>
<tr>
<td>SAMMPRIS</td>
<td>Stenting and Aggressive Medical Management for Preventing Stroke in Intracranial Stenosis</td>
</tr>
</tbody>
</table>

REFERENCES

Interventional Management of Intracranial Stenosis

The Open Atherosclerosis & Thrombosis Journal, 2010, Volume 3


[74] Chimowitz MI. Stenting vs aggressive medical management for preventing recurrent stroke in intracranial stenosis (Sammpris), 2009.
