Angioplasty and Stenting of Extra-Cranial and Intra-Cranial Arteries

Number: 0276

**Policy**

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers percutaneous transluminal angioplasty of the extra-cranial carotid arteries, with or without stent implantation and embolic protection, medically necessary in symptomatic individuals with at least 50% stenosis of the carotid artery.

Aetna considers percutaneous transluminal angioplasty of the extra-cranial vertebral arteries, with or without stent implantation and embolic protection, medically necessary for persons with at least 50% stenosis of the vertebral artery who are symptomatic despite optimal medical treatment (e.g., antithrombotic agents, statins, and other risk factor modifications).

Aetna considers percutaneous transluminal angioplasty of the intracranial arteries medically necessary for the treatment of medically refractory symptomatic delayed cerebral ischemia (cerebral vasospasm) after aneurysmal subarachnoid hemorrhage.

**Policy History**

- **Last Review:** 05/18/2020
- **Effective:** 08/28/1998
- **Next Review:** 03/11/2021

**Review History**

**Definitions**

**Additional Information**

**Clinical Policy Bulletin**

**Notes**
Aetna considers prophylactic percutaneous transluminal angioplasty of intracranial arteries after aneurysmal subarachnoid hemorrhage experimental and investigational.

Aetna considers percutaneous transluminal angioplasty, with or without stenting, of the intra-cranial arteries experimental and investigational for the prophylaxis or treatment of atherosclerotic stenosis of intracranial arteries and for all other indications because its effectiveness for these indications has not been established:

Aetna considers endovascular repair of wide-necked intracranial aneurysms using stent assisted embolic coiling or flow diverting stents medically necessary for otherwise inoperable aneurysms.

Aetna considers extracranial-intracranial arterial bypass surgery medically necessary for ischemic moyamoya disease. Aetna considers extracranial-intracranial arterial bypass surgery for the treatment of other ischemic cerebrovascular disease of the carotid or middle cerebral arteries, which includes the treatment or prevention of stroke, experimental and investigational because the effectiveness of this approach has not been established for these other indications.

Aetna considers implantation of drug-eluting stents experimental and investigational for treatment of extra-cranial artery stenosis (e.g., carotid and vertebral arteries). See CPB 0621 - Drug-Eluting Stents (../600_699/0621.html).

Aetna considers trans-carotid artery revascularization (TCAR) for the treatment for carotid artery stenosis experimental and investigational because the effectiveness of this approach has not been established.
Background

Angioplasty and Stenting of Extra-Cranial Arteries

Angioplasty and stenting of carotid and vertebral lesions represents a promising therapeutic option in patients at increased risk for surgical endarterectomy. Endarterectomy has several limitations. Among them, patients with severe coronary artery disease show a 3-fold increase in morbidity and mortality due to cardiac complications of the procedure. Similarly, the risk of endarterectomy is increased in patients with carotid lesions that, due to their anatomic location, are difficult to approach surgically. In addition, the risk of endarterectomy is increased in patients having previous cervical radiotherapy, previous endarterectomy, or lesions located or extending distally in the internal carotid artery.

There has been a high level of interest in treating extra-cranial carotid and vertebral stenoses with either angioplasty or stents. The relative technical ease of performing such procedures has attracted considerable attention in the clinical community. Such procedures are being performed in several academic medical centers. A prospective, randomized, controlled, multicenter clinical trial designed to compare these endovascular interventions with the "gold standard" of surgical carotid endarterectomy is currently being conducted.

Although a recent study found that among patients with severe carotid artery stenosis and co-existing conditions (symptomatic carotid-artery stenosis of at least 50% of the luminal diameter or an asymptomatic stenosis of at least 80%), carotid stenting with the use of an emboli-protection device is not inferior to carotid endarterectomy (Yadav et al, 2004), the editorial accompanying this study stated that the small sample size and the study end points prevent conclusions regarding the relative roles of endarterectomy and carotid artery stenting in the treatment of carotid artery stenosis. Physicians, industry sponsors, and regulatory agencies should insist on large
scale, multi-center studies to ascertain the appropriate role of carotid artery stenting in patients in different clinical and anatomical subgroups.

Debette et al (2004) stated that carotid angioplasty and stenting is sometimes used as an alternative to surgery, despite the lack of evidence for its safety and effectiveness. These investigators concluded that carotid angioplasty and stenting cannot be considered as a routine procedure and should be restricted to high-risk patients unfit for surgery. Additionally, a recent Cochrane review (Coward et al, 2004) on percutaneous transluminal angioplasty and stenting for carotid artery stenosis concluded that: "Data from randomised trials comparing endovascular treatment for carotid artery stenosis with carotid endarterectomy suggest that the two treatments have similar early risks of death or stroke and similar long term benefits. However, the substantial heterogeneity renders the overall estimates of effect somewhat unreliable. Furthermore, two trials were stopped early because of safety concerns, so perhaps leading to an over-estimate of the risks of endovascular treatment. On the other hand, endovascular treatment appears to avoid completely the risk of cranial neuropathy. There is also uncertainty about the potential for re-stenosis to develop and cause recurrent stroke after endovascular treatment. The current evidence does not support a widespread change in clinical practice away from recommending carotid endarterectomy as the treatment of choice for suitable carotid artery stenosis. There is a strong case to continue recruitment in the current randomised trials comparing carotid stenting with endarterectomy".

In a study on indications for intervention of atherosclerotic occlusive extra-cranial vertebral artery disease, Wehman et al (2004) reported that symptomatic patients with a single, causative extra-cranial atherosclerotic vertebral artery lesion that measures more than 50 % stenosis by digital subtraction angiography receive treatment with angioplasty and stenting.
The Centers for Medicare and Medicaid Services (CMS) (2005) has determined that carotid artery stenting (CAS) with distal embolic protection is necessary for the following:

1. Patients who are at high risk for carotid endarterectomy and who also have symptomatic carotid artery stenosis greater than 70%. Medicare limits coverage to procedures performed using Food and Drug Administration (FDA)-approved CAS systems and embolic protection devices;

2. Patients who are at high risk for carotid endarterectomy and have symptomatic carotid artery stenosis between 50% and 70%, in accordance with the Category B Investigational Device Exemption (IDE) clinical trials regulation, as a routine cost under Medicare’s clinical trials policy, or in accordance with the National Coverage Determination on CAS post-approval studies;

3. Patients who are at high risk for carotid endarterectomy and have asymptomatic carotid artery stenosis greater than 80%, in accordance with the Category B IDE clinical trials regulation, as a routine cost under Medicare’s clinical trials policy, or in accordance with the National Coverage Determination on CAS post-approval studies.

The Centers for Medicare and Medicaid Services defines patients at high risk for carotid endarterectomy as having significant co-morbidities and/or anatomic risk factors (i.e., recurrent stenosis and/or previous radical neck dissection), and would be poor candidates for carotid endarterectomy (CEA) in the opinion of a surgeon. For purposes of Medicare policy, significant co-morbid conditions include but are not limited to:

1. Congestive heart failure (CHF) class III/IV;
2. Contralateral carotid occlusion;
3. Left ventricular ejection fraction (LVEF) less than 30%;
4. Other conditions that were used to determine patients at high risk for CEA in the prior carotid artery stenting trials and studies, such as ARCHER, CABERNET, SAPPHIRE, BEACH, and MAVERIC II;
5. Previous CEA with recurrent stenosis;
6. Prior radiation treatment to the neck;
7. Recent myocardial infarction (MI);
8. Unstable angina.

According to CMS, symptoms of carotid artery stenosis include carotid transient ischemic attack (distinct focal neurological dysfunction persisting less than 24 hours), focal cerebral ischemia producing a non-disabling stroke (modified Rankin scale less than 3 with symptoms for 24 hours or more), and transient monocular blindness (amaurosis fugax). The Centers for Medicare and Medicaid Services excludes patients who have had a disabling stroke (modified Rankin scale greater than 3) from eligibility for coverage of a carotid artery stent.

A CMS Decision Memorandum (2005) states that the degree of carotid artery stenosis should be measured by duplex Doppler ultrasound or carotid artery angiography and recorded in the patient medical records. If the stenosis is measured by ultrasound prior to the procedure, then the degree of stenosis must be confirmed by angiography at the start of the procedure. The Centers for Medicare and Medicaid Services states that if the stenosis is determined to be less than 70 % by angiography, then CAS should not proceed.

A CMS Decision Memorandum (2007) states that "for patients who are at high risk for CEA surgery with asymptomatic carotid artery stenosis greater than 80 %, several case series or registry reports and post-approval studies have been published since our prior decision which provided restricted coverage for these patients. The basis of our restricted coverage in the prior decision was the undocumented natural
history of asymptomatic stenosis on medical therapy (lack of a medical control group in past studies), the lack of long term data on CAS in these patients, and the lack of data on CAS performed outside the controlled trial setting. While the outcomes of asymptomatic carotid artery stenosis with optimal medical therapy remain unclear and unstudied, the published reports provide evidence regarding our other prior concerns. The observational studies by Halabi, Chaer, Park and Safian provided supporting evidence for CAS in patients with asymptomatic stenosis greater than 80%. The post-approval studies, CAPTURE and CASES-PMS, provided additional evidence on 30-day outcomes and some information on 1 year outcomes. The post-approval studies also showed that CAS outcomes were similar by provider volume (experience levels) and in settings outside clinical trials. Unlike the situation with symptomatic patients, there were no trials or studies that raised concerns about the safety of CAS in asymptomatic patients with stenosis greater than 80%. "With the published reports since our prior decision, CMS finds that the evidence is sufficient to conclude that PTA with carotid artery stenting improves health outcomes for patients who are at high risk for CEA surgery and have asymptomatic carotid artery stenosis > 80%. With this, CMS proposes to remove the requirement that these procedures only be performed in a clinical trial or post approval study, based largely on the findings from CAPTURE and CASES-PMS. As with the currently covered indications, facilities performing CAS for this patient group must meet the facility requirements outlined in this NCD. As discussed above, CAS is not covered in the absence of distal embolic protection including those instances in which technical difficulties prevented deployment."

The CMS Decision Memorandum (2007) also states that for patients who are greater than 80 years of age, there is mounting evidence that the rate of death, stroke and MI after CAS is higher than for patients less than 80 years. Stanziale and colleagues reported that octogenarians had a significantly higher rate of stroke, death or MI than nonoctogenarians (9.2
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% versus 3.4 %, respectively; p = 0.024). Safian and colleagues reported data that showed patients greater than 75 years had higher adverse outcomes than patients less than 75 (7.6 % versus 4.8 %). CAPTURE showed that patients greater than 80 years of age had significantly higher rates of death, stroke or MI at 30 days than patients less than 80 years (9.4 % versus 5.3 %, respectively; statistically significant, p < 0.0001). SPACE found that patients greater than 75 years of age had a significantly higher rate of ipsilateral ischemic stroke and death at 30 days compared to patients greater than 75 (11.01 % versus 5.92 %; exceeding the non-inferiority margin). Outcomes by age were not specifically reported by Chaer, Halabi, Mas and Park.

"The consistency of these findings across the trials and studies, observed in both symptomatic and asymptomatic patients, creates concerns for the safety of older patients undergoing CAS. This is also consistent with the recognition that patients > 80 years of age are at higher risk for CEA. These patients were specifically excluded from the NASCET and ACAS trials. This was also one of the high risk criteria in the SAPPHIRE trial for carotid revascularization in general. The higher incidence of adverse outcomes is particularly concerning for patients who have asymptomatic stenosis. In many of these patients, more harm than good would have come from the PTA and CAS procedure. Given the evidence, CMS proposes to continue the restriction that CAS for asymptomatic patients with stenosis > 80% and who are > 80 years of age be covered only in the setting of a clinical trial or post approval study for safety purposes. In addition, CMS proposes to expand this restriction to include symptomatic patients with stenosis > 70% and who are > 80 years of age".

Guidance from the National Institute for Health and Clinical Excellence (NICE, 2011) concludes that "current evidence on the safety of carotid artery stent placement for asymptomatic extracranial carotid stenosis shows well-documented risks, in particular
the risk of stroke. The evidence on efficacy is inadequate in quantity. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research."

Guidance from NICE (2011) concluded that "current evidence on the safety and efficacy of carotid artery stent placement for symptomatic extracranial carotid stenosis is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance and audit or research. During the consent process, clinicians should ensure that patients understand the risk of stroke and other complications associated with this procedure. Clinicians should also ensure that patients understand the reasons for advising carotid artery stent placement rather than endarterectomy in their particular case."

Gurm et al (2008) reported on the long-term (3 years) results of carotid stenting versus endarterectomy in high-risk patients. The trial evaluated carotid artery stenting with the use of an emboli-protection device as compared with endarterectomy in 334 patients at increased risk for complications from endarterectomy who had either a symptomatic carotid artery stenosis of at least 50 % of the luminal diameter or an asymptomatic stenosis of at least 80 %. The pre-specified major secondary endpoint at 3 years was a composite of death, stroke, or MI within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1080 days (3 years). At 3 years, data were available for 260 patients (77.8 %), including 85.6 % of patients in the stenting group and 70.1 % of those in the endarterectomy group. The pre-specified major secondary endpoint occurred in 41 patients in the stenting group (cumulative incidence, 24.6 %; Kaplan-Meier estimate, 26.2 %) and 45 patients in the endarterectomy group (cumulative incidence, 26.9 %; Kaplan-Meier estimate, 30.3 %) (absolute difference in cumulative incidence for the stenting group, -2.3 %; 95 % confidence interval [CI]: -11.8 to 7.0). There were 15 strokes in each of the 2 groups, of which 11 in
the stenting group and 9 in the endarterectomy group were ipsilateral. The authors concluded that in this trial of patients with severe carotid artery stenosis and increased surgical risk, no significant difference could be shown in long-term outcomes between patients who underwent carotid artery stenting with an emboli-protection device and those who underwent endarterectomy.

In a phase II multi-center, randomized, clinical trial, Zwienenberg-Lee et al (2008) examined the effect of prophylactic transluminal balloon angioplasty (pTBA) on cerebral vasospasm and outcome in patients with Fisher grade III subarachnoid hemorrhage. A total of 170 patients were enrolled in the study. Of these, 85 patients were randomized to the treatment group and underwent pTBA within 96 hours after subarachnoid hemorrhage. Main endpoints of the study included the 3-month dichotomized Glasgow Outcome Score (GOS), development of delayed ischemic neurological deficit (DIND), occurrence of transcranial Doppler (TCD) vasospasm, and length of stay in the ICU and hospital. The incidence of DIND was lower in the pTBA group (p = 0.30) and fewer patients required therapeutic angioplasty to treat DIND (p = 0.03). Overall, pTBA resulted in an absolute risk reduction of 5.9 % and a relative risk reduction of 10.4 % unfavorable outcome (p = 0.54). Good grade patients had absolute and relative risk reductions of respectively 9.5 % and 29.4 % (p = 0.73). Length of stay in ICU and hospital was similar in both groups. Four patients had a procedure-related vessel perforation, of which 3 patients died. The authors concluded that while the trial is unsuccessful as defined by the primary endpoint (GOS), proof of concept is confirmed by these results. Fewer patients tend to develop vasospasm after treatment with pTBA and there is a statistically significantly decreased need for therapeutic angioplasty. Prophylactic TBA does not improve the poor outcome of patients with Fisher grade III subarachnoid hemorrhage.
van Haaften et al (2010) evaluated published evidence on therapeutic options for in-stent re-stenosis (ISR) following CAS placement. A total of 20 studies were found, describing 100 interventions after carotid ISR in 96 patients. The interventions most performed were repeat percutaneous transluminal angioplasty (PTA; n = 54), repeat CAS placement (n = 31), and carotid endarterectomy with stent removal (n = 9). No peri-procedural complications were identified in any of the studies evaluated. Recurrent re-stenosis after intervention for ISR occurred in 12 of 84 cases (14%). All 12 patients received tertiary treatment. Two patients developed a third recurrence and eventually disabling stroke, 1 of whom died. In the other 10 interventions, no further follow-up was described. The authors concluded that several treatment strategies for ISR after CAS placement have been reported, with acceptable short-term results. The quality of the currently available data is still limited by the variability of results and study designs. Thus, no recommendation can be made for any specific therapy. This argues for better study design and more consistency of reporting standards.

In a prospective, randomized, open-blinded clinical trial, Markus and associates (2017) compared in the Vertebral Artery Ischemia Stenting Trial (VIST) the risks and benefits of vertebral angioplasty and stenting with best medical treatment (BMT) alone for symptomatic vertebral artery stenosis. This study was performed in 14 hospitals in the United Kingdom. Participants with symptomatic vertebral stenosis greater than or equal to 50% were randomly assigned (1:1) to vertebral angioplasty/stenting plus BMT or to BMT alone with randomization stratified by site of stenosis (extra-cranial versus intra-cranial). Because of slow recruitment and cessation of funding, recruitment was stopped after 182 participants. Follow-up was a minimum of greater than or equal to 1 year for each participant; 3 patients did not contribute any follow-up data and were excluded, leaving 91 patients in the stent group and 88 in the medical group. Mean follow-up was 3.5 (inter-quartile range [IQR] 2.1 to 4.7) years.
Of 61 patients who were stented, stenosis was extra-cranial in 48 (78.7%) and intra-cranial in 13 (21.3%). No peri-procedural complications occurred with extra-cranial stenting; 2 strokes occurred during intra-cranial stenting. The primary end-point of fatal or non-fatal stroke occurred in 5 patients in the stent group versus 12 in the medical group (hazard ratio [HR] 0.40, 95% CI: 0.14 to 1.13, p = 0.08), with an absolute risk reduction of 25 strokes per 1,000 person-years. The HR for stroke or transient ischemic attack (TIA) was 0.50 (p = 0.05). The authors concluded that stenting in extra-cranial stenosis appeared safe with low complication rates. Moreover, they stated that large phase-III clinical trials are needed to determine whether stenting reduces stroke risk.

Hasani and colleagues (2018) stated that reducing the rate of post-operative stroke after cardiac surgery remains challenging, especially in patients with occlusive cerebrovascular disease. Angioplasty in all patients with high-grade carotid artery stenosis has not been shown to be effective in reducing the post-surgical stroke rate. In a single-center study, these investigators presented the initial results of a different approach using selective carotid angioplasty only in patients with poor intra-cranial collaterals. In this trial, the post-angioplasty complication rate of the study group was compared to that of patients who were scheduled for symptomatic carotid artery angioplasty. To determine the effectiveness of this procedure, the post-cardiac surgery complication rate of the study group was compared with that of the matched case controls. A total of 22 patients were treated with selective carotid angioplasty without developing persistent major neurological complications. All patients except 1 patient subsequently underwent surgery without developing persistent major neurological disabilities; 2 patients died of cardiogenic shock within 30 days. The authors concluded that selective carotid angioplasty prior to cardiac surgery in patients with a presumed high risk of stroke was relatively safe and effective in this study group. Although this strategy did not prevent stroke in these high-risk patients, data suggested that this
approach shifted the post-operative type of stroke from a severe hemodynamic stroke towards a minor embolic stroke with favorable neurological outcomes. Moreover, they stated that larger studies are needed to examine if this strategy can effectively eliminate the occurrence of hemodynamic stroke after cardiac surgery.

Angioplasty and Stenting of Intra-Cranial Arteries for the Treatment of Atherosclerotic Stenosis

Although atherosclerotic stenoses of the intra-cranial vessels are less frequent than those of the extra-cranial vessels, they are associated with a high risk for stroke that is the 3rd leading cause of death in the United States. Atherosclerotic stenosis of intra-cranial arteries is usually treated with medication (e.g., acetyl salicylic acid, clopidogrel, and ticlopidine). It has also been reported recently that cilostazol, a phosphodiesterase inhibitor, can prevent the progression of intra-cranial arterial stenosis (Kwon et al, 2005). When pharmacotherapies fail to improve symptoms, balloon angioplasty has been reported to be useful. However, this surgical procedure is associated with a significant risk of complications (e.g., acute occlusion or symptomatic dissection, re-stenosis, and stroke). It has also been reported that stenting could reduce the rate of re-stenosis following balloon angioplasty of intra-cranial arteries. However, the clinical benefit of balloon angioplasty, with or without stenting, has not been firmly established.

In a retrospective case series study, Lylyk et al (2005a) discussed their experience in the treatment of patients with symptomatic intra-cranial atherosclerotic stenoses that are refractory to medical therapy, and who underwent stent-assisted angioplasty (n = 104). Patient records were analyzed for location and degree of stenosis, regimen of anti-platelet agents, devices used, procedure-related complications and adverse events. Clinical (Modified Rankin Scale) and radiographical outcomes were obtained 24 hours, 1 month and 3 to 6 months after treatment. A total of 65 lesions (62.5%)
were located in the posterior circulation. Mean stenosis was 75.4%. In all patients, the angiographical degree of stenosis was reduced to less than 30%. One stent was implanted in 66 patients (63%), and 2 or more in 38 patients (37%). Modified Rankin Scale was 1 to 2 in 67.5% of the cases, 3 to 4 in 25.9%, 5 in 2.8%, and 6 in 3.8%. Procedural morbidity was 5.7%, while procedural mortality was 3.8%. Angiographical follow-up was available in 58 patients (55.7%) and the rate of re-stenosis was 12.5%. These investigators concluded that in selected patients, endovascular revascularization of intra-cranial arteries by means of stent-assisted angioplasty is technically feasible, effective and safe.

In an uncontrolled study, Yu and associates (2005) reported their findings on 18 patients who underwent stenting for symptomatic basilar artery stenosis. There were 3 major peri-procedural complications (16.7%) without fatality. At a mean follow-up of 26.7 months, 15 patients (83.3%) had an excellent long-term outcome. Only 1 patient (5.6%) had moderate disability from recurrent stroke, and 2 patients died of medical illness at 30 and 36 months after stenting. There were several limitations in this case series report: (i) it is a retrospective study in which patients were stented empirically without standard inclusion and exclusion criteria creating possible selection bias, (ii) not every patient received maximal medical therapy before stenting, and (iii) these are single-center data, and may not be generalizable for reasons of referral and selection bias, neurointerventional physicians’ expertise, and multi-disciplinary care. These authors stated that because of the poor prognosis of symptomatic basilar artery stenosis found in previous studies, prospective multi-center randomized controlled studies of endovascular basilar artery stenting are warranted despite the risk of major procedural complications.
In a retrospective study, Marks and colleagues (2005) assessed their findings on 36 patients with 37 symptomatic atherosclerotic intra-cranial stenoses who underwent primary balloon angioplasty. All patients had symptoms despite medical therapy. A total of 34 patients were available for follow-up (mean of 52.9 months, range of 6 to 128 months). Mean pretreatment stenosis was 84.2% before angioplasty and 43.3% after angioplasty. The peri-procedural death and stroke rate was 8.3% (2 deaths and 1 minor stroke). Two patients had strokes in the territory of angioplasty at 2 and 37 months following angioplasty. The annual stroke rate in the territory appropriate to the site of angioplasty was 3.36%, and for those patients with a residual stenosis of greater than or equal to 50% it was 4.5%. Patients with iatrogenic dissection (n = 11) did not have transient ischemic attacks or strokes after treatment. These investigators concluded that results of long-term follow-up suggest that intra-cranial angioplasty without stent placement reduces the risk of further stroke in symptomatic patients.

On the other hand, Hauth and colleagues (2004) found that angioplasty of intra-cranial arteries can be associated with life-threatening complications. These investigators ascertained the feasibility and safety of angioplasty or angioplasty and stenting of extra- and intra-cranial vertebral artery (VA) stenosis. In 16 consecutive patients (9 men, 7 women; mean age of 61 years, range of 49 to 74 years) 16 stenotic VAs were treated with angioplasty or angioplasty and stenting. Eleven stenoses were localized in V1 segment, 1 stenosis in V2 segment and 4 stenoses in V4 segment of VA. Fourteen VA stenoses were symptomatic, while 2 were asymptomatic. The etiology of the stenoses was atherosclerotic in all cases. Angioplasty was performed in 8/11 V1 and 2/4 V4 segments of the VA. In 3/11 V1 segments and 2/4 V4 segments of the VA, combined angioplasty with stenting were used. The procedures were successfully performed in 14/16 VAs (87%). Complications were asymptomatic vessel dissection resulting in vessel occlusion in 1/11 V1 segments and asymptomatic
vessel dissection in 2/4 V4 segments of the VA. One patient died in the 24-hr period after the procedure because of subarachnoid hemorrhage as a complication following vessel perforation of the treated V4 segment. These authors concluded that angioplasty or angioplasty in combination with stenting of extra-cranial VA stenoses can be performed with a high technical success rate and a low complication rate. However, in intra-cranial VA stenosis the procedure is technically feasible but complications can be life-threatening. The durability and procedural complication rates of primary stenting without using pre-dilation in extra- and intra-cranial VA stenosis should be defined in the future. Moreover, in a review on vertebrobasilar disease, Savitz and Caplan (2005) noted that preliminary results of angioplasty or stenting of occlusive VA lesion in the neck reveal that re-stenosis is more common than with carotid artery stenting. The small diameter and angulation of the VA origin complicate endovascular treatment. Intra-cranial vertebral and basilar artery angioplasty and stenting have produced mixed results. It is also interesting to note that Boulos and colleagues (2005) stated that placement of intra-cranial and extra-cranial drug-eluting stent appears to be a safe alternative to the medical management of atherosclerotic disease of the vertebrobasilar and carotid systems. Moreover, these researchers concluded that further randomized studies are needed to ascertain the safety and effectiveness of this procedure. These observations are in agreement with those of Gupta et al (2003), Doerfler et al (2004), Kim et al (2004), Komotar et al (2005), as well as Hartmann and Jensen (2005).

In a retrospective study (21 intra-cranial lesions in 18 patients), Gupta and associates (2003) reported that endovascular revascularization of intra-cranial vessels is technically feasible and may be performed successfully. However, peri-procedural complication and fatality rates in neurologically unstable patients are high. Endovascular re-vascularization was performed on 8 distal internal carotid artery lesions, 6 middle cerebral artery lesions, 4 intra-cranial VA lesions, and 3 basilar
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In a review on endovascular treatment of cerebrovascular disease, Doerfler et al (2004) stated that angioplasty and stenting of intra-cranial atherosclerotic disease is feasible but remains a high-risk procedure, indicated only in highly selected patients. These investigators noted that advances in endovascular therapy have occurred in all areas of cerebrovascular disease. They further stated that to obtain maximal patient benefit, endovascular treatment should be performed as an inter-disciplinary approach in high-volume centers; and concluded that long-term follow-up review is needed to clarify the overall role of endovascular treatment in the management of patients with cerebrovascular disease.

Furthermore, Kim and associates (2004) stated that although stent-assisted angioplasty is an effective treatment for coronary and peripheral arterial disease, its effectiveness in intra-cranial arteriosclerotic disease has not been verified. They evaluated the radiographical and clinical outcome of stent-assisted angioplasty for symptomatic middle cerebral artery (MCA) stenosis (n = 14). Patients had symptomatic high-grade stenosis (greater than 60 %) on the proximal portion of the MCA, and had experienced either recurrent TIAs resistant to medical therapy or one or more stroke attacks. Stent-assisted angioplasty was successfully performed in 8 of
14 patients without any serious complications and unsuccessful in 2 of 14 patients due to the tortuous curve of the internal carotid artery siphon. Four patients had complications: 2 had an arterial rupture (1 was rescued by an additional stent and balloon tamponade, the other patient died); the remaining 2 patients had thrombotic occlusion and distal thrombosis. Residual stenosis was less than 50% in diameter in all patients. All 8 patients who underwent follow-up cerebral angiography had no re-stenosis. Follow-up single photon emission computed tomography demonstrated improved perfusion in the affected MCA territory in all subjects with TIA and in 1 of 3 stroke patients. Using the Modified Rankin Scale at follow-up, 4 of 5 TIA patients and 5 of 6 stroke patients were deemed functionally improved or having a stable clinical status. These authors concluded that although the re-stenosis rate in stent-assisted angioplasty seems to be better than in primary balloon angioplasty as reported previously, the complication rate is still high. Elective stenting is an alternative therapeutic method for the prevention of secondary ischemic stroke in stroke patients with MCA stenosis, and seems to be a potentially effective but also hazardous therapeutic technique in patients with recurrent TIAs. These investigators concluded that the findings of this study indicate the need for randomized control studies of this intervention. In addition, long-term follow-up data and additional clinical experience are needed to determine the durability of this procedure.

In a review on endovascular treatment options for intra-cranial carotid artery atherosclerosis, Komotar et al (2005) stated that novel stent technology represents the beginning of innovative methods that will be employed by endovascular neurosurgeons to treat intra-cranial atherosclerosis. However, more clinical trials, especially those that compare stenting with the best medical management available are needed to ascertain the effectiveness and appropriateness of this technique. These investigators concluded that "angioplasty with stent placement carries risks along with a significant rate of restenosis; however, advancements in technology and
methodology have begun to address these issues. In short, endovascular methods have revolutionized the treatment of this disease. With continued experience and a multidisciplinary approach in the evaluation of these patients, favorable outcomes may be achieved.

In a review on conventional, direct, and staged stenting for high-grade stenoses involving the posterior intra-cranial circulation, Levy and associates (2005) stated that for patients with high-grade posterior circulation intra-cranial stenoses involving the perforator-rich zones of the basilar artery, staged stenting may reduce procedure-related morbidity. A staged approach allows for plaque stabilization resulting from post-angioplasty fibrosis, which may protect patients from "snow-plowing," embolic shower of debris, or dissection. The authors noted that further clinical, in vivo, and histological investigation is warranted. In a review on recent advances in angioplasty and stenting of intra-cranial atherosclerotic stenosis, Hartmann and Jansen (2005) stated that "intracranial angioplasty with or without stenting is a promising treatment option. Patient selection, careful periprocedural medical management, and a highly skilled neuroendovascular surgeon are all required to perform the procedure with an acceptable risk. If stenting is to be shown to be a safe therapeutic alternative, prospective trials comparing stenting with optimal medical treatment need to be performed". Furthermore, a recent Cochrane review (Coward et al, 2005) concluded that there is currently inadequate evidence to evaluate the effectiveness of percutaneous transluminal angioplasty, with or without stenting, or primary stenting for the treatment of VA stenosis.

Through Humanitarian Device Exemptions (HDEs), the FDA approved 2 intra-cranial stent systems: (i) the Neurolink System (Guidant Corporation) in August 2002, and (ii) the Wingspan Stent System with Gateway PTA Balloon Catheter (Boston Scientific Corporation) in August 2005. The former is indicated for the treatment of patients with recurrent intra-
cranial stroke caused by atherosclerotic disease refractory to pharmacotherapies, in intra-cranial vessels ranging from 2.5 to 4.5 mm in diameter with greater than or equal to 50% stenosis that are accessible to the stent system. The latter is indicated for improving cerebral artery lumen diameter in patients with intra-cranial atherosclerotic disease, refractory to pharmacotherapies, in intra-cranial vessels with greater than or equal to 50% stenosis that are accessible to the system.

Although approved by the FDA, the clinical effectiveness of these two intra-cranial stent systems has not been clearly established. In a multi-center, non-randomized, prospective feasibility study, the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSLYVIA) Study group (2004) assessed the Neurolink System for the treatment of patients with vertebral or intra-cranial artery stenosis. In 61 patients enrolled in this study, 43 (70.5%) intra-cranial arteries (15 internal carotid, 5 middle cerebral, 1 posterior cerebral, 17 basilar, 5 vertebral) and 18 (29.5%) extra-cranial VAs (6 ostia, 12 proximal to the posterior inferior cerebellar artery [PICA]) were treated. In the first 30 days, 4 patients (6.6%) had strokes and no deaths occurred. Successful stent placement was achieved in 58/61 cases (95%). At 6 months, stenosis of greater than 50% occurred in 12/37 (32.4%) intra-cranial arteries and 6/14 (42.9%) extra-cranial VAs, 4 in the vertebral ostia. Seven (39%) recurrent stenoses were symptomatic. Four of 55 patients (7.3%) had strokes later than 30 days, 1 of which was in the only patient not stented. These investigators concluded that the Neurolink System is associated with a high rate of successful stent deployment. Strokes occurred in 6.6% of patients within 30 days and in 7.3% between 30 days and 1 year. Although re-stenoses occurred in 35% of patients, 61% were asymptomatic, the authors stated that more studies involving the Neurolink System are warranted.
The FDA’s approval of the Wingspan Stent System was based on an international safety study of 45 patients who had a stroke caused by an intra-cranial lesion and for whom medical treatment failed to prevent another stroke. The device had a stent success rate of 100 %, a procedural success rate of 97.7 %, and a 4.4 % incidence of death or stroke in the ipsilateral hemisphere of the brain as the lesion at 30 days post-procedure. The incidence of death or same hemisphere stroke at 6-month follow-up was 7.0 % (Kofol and Donovan, 2005). This encouraging preliminary finding needs to be validated by further randomized controlled trials.

In March 2005, the FDA also granted a HDE to the CoAxia NeuroFlo catheter for the treatment of cerebral ischemia caused by symptomatic vasospasm following aneurysmal subarachnoid hemorrhage (SAH). The NeuroFlo catheter is a multi-lumen device with 2 balloons mounted near the tip. The balloons can be inflated or deflated independently for controlled partial obstruction of aortic blood flow. It is assumed that the obstruction created by the inflated balloons will reduce blood flow to the lower part of the body while increasing blood volume to the upper part of the body, including the brain, without significant increase in pressure. The increase in cerebral blood volume presumably drives blood flow into the penumbra, restoring circulation and improving chances of recovery. This procedure has not exhibited significant cardiac, cerebral, or renal complications in clinical trials. The NeuroFlo catheter is inserted through an introducer sheath through the femoral artery, and balloons are placed on either side of the renal arteries. The infra-renal (IR) balloon is inflated first to 70 % occlusion. It is recommended that the supra-renal (SR) balloon be inflated to 70 % occlusion about 5 minutes later. Inflation of both balloons should be maintained for 40 minutes. Balloon inflation may be modified over this period, based on the patient’s blood pressure. The balloons should be sequentially deflated, SR then IR, and removed. Treatment with the NeuroFlo catheter is recommended only after patients have failed or are ineligible for medical therapy.
Lylyk et al (2005b) reported the findings of 24 selected patients with symptomatic vasospasm due to aneurysmal SAH treated by partial and transitory aortic obstruction with a novel device (NeuroFlo, CoAxia, MN). Aneurysms were secured by coils prior to the procedure. These researchers studied the adverse effects related to the aorta-obstructing device, and changes in cerebral blood flow (CBF) and neurological outcome. Mean flow velocity increased in both middle cerebral arteries over 15%, and the score in the NIH Stroke Scale decreased greater than or equal to 2 point in 20 patients (83%). During the procedure, 3 patients developed symptoms that were controlled. At 30 days follow-up, 3 patients had 6 points (unrelated death), 3 had 3 points, 6 had 1 point, and 12 had 0 points, in the modified Rankin scale. The authors concluded that partial aortic obstruction was safe, the CBF increased without inducing significant hypertension and the neurological defects improved in most of the patients. They stated that efficacy with a better level of evidence will be determined by a randomized study.

In an interim report of the Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke (SENTIS) trial, Uflacker et al (2008) concluded that the NeuroFlo system so far proved to be safe enough for clinical use and seems to be promising in improving survival in the acute stroke population. However, this article was later retracted (2009).

In a Cochrane review on angioplasty for intra-cranial artery stenosis, Cruz-Flores and Diamond (2006) concluded that there is currently insufficient evidence to recommend angioplasty with or without stent placement in routine practice for the prevention of stroke in patients with intra-cranial artery stenosis. The descriptive studies showed that the procedure is feasible although it carries a significant morbidity and mortality risk. Evidence from randomized controlled trials is needed to evaluate the safety and effectiveness of angioplasty in preventing recurrent stroke. This is in agreement with the observation of Higashida and Meyers (2006) who stated that
"at this time, patients with significant intracranial stenosis should receive counseling on the benefits and risks of revascularization therapy. Ultimately, determination of which patients should undergo revascularization procedures will require carefully planned, randomized clinical trials".

An assessment by the National Institute for Health and Clinical Excellence (NICE, 2007) concluded: "The evidence on clinical efficacy of endovascular stent insertion for intracranial atherosclerotic disease is currently inadequate and the procedure poses potentially serious safety concerns. Therefore, clinicians should collaborate to organise randomised studies of adequate size to compare endovascular stent insertion for intracranial atherosclerotic disease against best medical management. These studies should clearly define patient selection and be designed to provide outcome data based on follow-up of at least 2 years." The Specialist Advisors to NICE considered this procedure to be of uncertain safety with potential adverse effects including death, stroke, arterial dissection, vessel occlusion, vessel rupture, hemorrhage, restenosis and stent thrombosis.

The Centers for Medicare & Medicaid Services (CMS, 2008) reconsidered their prior decision on intracranial PTA and stenting in November 2006, and announced their decision to maintain their position that this is a promising but unproven therapy. The Centers for Medicare & Medicaid Services reviewed 5 studies (Bose et al, 2007; Fiorella et al, 2007; Levy et al, 2007; Layton et al, 2008; Zaidat et al, 2008) published since their last review that presented data using the Wingspan stent system. The Centers for Medicare & Medicaid Services noted that the study by Bose et al (2007) presented data that was submitted to the FDA, and was considered in CMS' prior decision memorandum.

The Centers for Medicare & Medicaid Services observed that 3 of the new studies report on registry data; CMS noted that, as with all case series type studies, these studies are difficult to
interpret without additional studies that reduce the possibility of inherent biases and substantiate the clinical findings. The studies by Fiorella et al (2007) and Levy et al (2007) presented data from the Wingspan registry of 78 patients. Zaidat and colleagues (2008) reported on the National Institutes of Health (NIH) Wingspan registry of 129 patients. The Centers for Medicare & Medicaid Services stated that various biases may have been factors in the observed differences in the registry data compared to the initial Wingspan study presented by Bose et al (2007). Levy and colleagues (2007) reported: “The ISR (in-stent restenosis) rate with the Wingspan stent is higher in our series than previously reported, occurring in 29.7 % of patients.” The Centers for Medicare & Medicaid Services found, in addition, that the lack of control groups and long term follow-up add to the uncertainty of clinical benefit. The CMS decision memorandum also expressed concern that Levy et al (2007) considers in-stent dissections to be “clinically silent,” particularly in view of their treatment with a second stent. The CMS decision memorandum also pointed out that concerns were also noted by Kallmes and Cloft (2008) who reported: “The overall restenosis rate in the study by Levy et al was 31 %, even though they excluded 4 cases of complete occlusion. Including those cases of complete occlusion would have increased the reported rate of restenosis by approximately 4 %.” The CMS decision memorandum also found that a higher restenosis rate (25 %) and adverse outcome rate (14 %) were also seen in the analysis by Zaidat and colleagues (2008), although the patients enrolled in the NIH registry had greater stenosis (70 to 99 %) compared to the other registry.

The Centers for Medicare & Medicaid Services concluded that "given the invasive nature of this treatment and the severe risks, as noted by Fiorella and colleagues, a well designed, well conducted randomized controlled trial is needed." In supporting the need for a clinical trial, the CMS decision memorandum cited Derdeyn and Chimowitz (2007) who stated: "At present, however, there is no level 1 evidence to support angioplasty and stenting for patients who have
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.” The CMS decision memorandum also cited Kallmes and Cloft (2008), who wrote: “We, the community of physicians, really have to continue to ponder what the real value of Wingspan is, and we must demand more data about safety and efficacy relative to other treatment options.”

The Centers for Medicare & Medicaid Services concluded that it "believes the evidence is promising and strongly encourages the development and completion of randomized controlled trials and currently covers PTA and stenting for the treatment of intracranial artery stenosis greater than or equal to 50 percent in patients with atherosclerotic disease when furnished in accordance with the FDA-approved protocols governing Category B IDE clinical trials." The CMS decision memorandum noted that there is a newly funded clinical trial titled “Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)” designed to determine health outcomes comparing optimal medical therapy to stenting and includes a 2-year mean follow-up. The Centers for Medicare & Medicaid Services stated that this randomized trial "is expected to provide solid evidence on this intervention."

Chimowitz et al (2011) stated that atherosclerotic intra-cranial arterial stenosis is an important cause of stroke that is increasingly being treated with percutaneous transluminal angioplasty and stenting (PTAS) to prevent recurrent stroke. However, PTAS has not been compared with medical management in a randomized trial. These investigators randomly assigned patients who had a recent TIA or stroke attributed to stenosis of 70 to 99 % of the diameter of a major intra-cranial artery to aggressive medical management alone or aggressive medical management plus PTAS with the use of
the Wingspan stent system. The primary end-point was stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period or stroke in the territory of the qualifying artery beyond 30 days. Enrollment was stopped after 451 patients underwent randomization, because the 30-day rate of stroke or death was 14.7 % in the PTAS group (non-fatal stroke, 12.5 %; fatal stroke, 2.2 %) and 5.8 % in the medical-management group (non-fatal stroke, 5.3 %; non-stroke-related death, 0.4 %) (p = 0.002). Beyond 30 days, stroke in the same territory occurred in 13 patients in each group. Currently, the mean duration of follow-up, which is ongoing, is 11.9 months. The probability of the occurrence of a primary end-point event over time differed significantly between the two treatment groups (p = 0.009), with 1-year rates of the primary end-point of 20.0 % in the PTAS group and 12.2 % in the medical-management group. The authors concluded that in patients with intra-cranial arterial stenosis, aggressive medical management was superior to PTAS with the use of the Wingspan stent system, both because the risk of early stroke after PTAS was high and because the risk of stroke with aggressive medical therapy alone was lower than expected.

In an editorial that accompanied the afore-mentioned study, Broderick (2011) noted that this is not the first trial that failed to show a benefit for intra-cranial re-vascularization. These failed trials provide some key lessons: (i) the challenges of intra-cranial re-vascularization are greater than those of extra-cranial re-vascularization, (ii) aggressive and attentive medical therapy is an effective approach to prevent stroke in high-risk patients, and (iii) the FDA and the Centers for Medicare and Medicaid Services (CMS) play critical roles in the advancement of cost-effective medicine. Moreover, they stated that new technology for preventing and treating stroke should be tested in trials that address clinical effectiveness and incorporate the best current medical management of stroke.
A systematic literature review of the Wingspan stent from the U.S. Food and Drug Administration (2012) concluded:
"Currently available data demonstrate that with the use of the Stryker Wingspan stent system a decrease in stenosis levels can be achieved immediately and technical success of placement is generally high. However, in the only available randomized controlled trial (RCT) to date, use of the Stryker Wingspan stent system presented a 30-day and 1-year risk of stroke or death which is about twice as high as that observed with aggressive medical care for the treatment of intracranial arterial stenosis. Across studies, immediate improvement in stenosis may not be maintained and ISR can occur. There is an array of acute complications (<72 hours post-procedure).
In conclusion, we find evidence that the Stryker Wingspan stent system can be deployed successfully and can decrease stenosis levels following the procedure. However, data from randomized clinical trials demonstrating its ability to be used safely and effectively to decrease the risk of stroke or death are not available".

Malik et al (2011) noted that acute ischemic stroke due to tandem occlusions of the extra-cranial internal carotid artery and intra-cranial arteries has a poor natural history. These investigators evaluated their single-center experience with endovascular treatment of this unique stroke population. Consecutive patients with tandem occlusions of the internal carotid artery origin and an intra-cranial artery (i.e., internal carotid artery terminus, M1 middle cerebral artery, or M2 middle cerebral artery) were studied retrospectively. Treatment consisted of proximal re-vascularization with angioplasty and stenting followed by intra-cranial intervention. End-points were re-canalization of both extra-cranial and intra-cranial vessels (Thrombolysis In Myocardial Ischemia greater than or equal to 2), parenchymal hematoma, and good clinical outcome (modified Rankin Scale less than or equal to 2) at 3 months. These researchers identified 77 patients with tandem occlusions. Re-canalization occurred in 58 cases (75.3 %) and parenchymal hematoma occurred in 8 cases (10.4 %).
Distal embolization occurred in 3 cases (3.9%). In 18 of 77 patients (23.4%), distal (i.e., intra-cranial) re-canalization was observed after proximal re-canalization, obviating the need for distal intervention. Good clinical outcomes were achieved in 32 patients (41.6%). In multi-variave analysis, Thrombolysis In Myocardial Ischemia greater than or equal to 2 re-canalization, baseline National Institutes of Health Stroke Scale score, baseline Alberta Stroke Programme Early CT score, and age were significantly associated with good outcome. The authors concluded that endovascular therapy of tandem occlusions using extra-cranial internal carotid artery re-vascularization as the first step is technically feasible, has a high re-canalization rate, and results in an acceptable rate of good clinical outcome. They stated that future randomized, prospective studies should clarify the role of this approach.

Jiang et al (2011) stated that there were limited data on the long-term outcome of patients with symptomatic intra-cranial atherosclerotic stenosis greater than or equal to 70 % after Wingspan stenting. Using these researchers' Wingspan cohort data and the data from the Warfarin and Aspirin for Symptomatic Intracranial Atherosclerotic Disease (WASID) as a historical control, they tested the hypothesis that stenting provided no benefit over anti-thrombotic therapy alone for these high-risk patients. Between January 2007 and February 2009, 100 consecutive patients with intra-cranial atherosclerotic stenosis greater than or equal to 70 % and symptoms within 90 days were enrolled into this prospective single-center Wingspan cohort study and followed-up until the end of February 2010. Stenosis was measured per the WASID criteria. One-year risk of primary end point (any stroke or death within 30 days and ipsilateral ischemic stroke afterward) was compared with that of ipsilateral ischemic stroke in the WASID patients with greater than or equal to 70% stenosis. The stent placement success rate was 99 %. All patients but 1 had clinical follow-up of greater than or equal to 12 months. During a mean follow-up of 1.8 years, 9 patients developed primary end point events (5 within 30 days and 4
The 1-year risk of the outcome events was lower than that in similar WASID patients: 7.3 % (95 % CI: 2.0 % to 12.5 %) versus 18 % (95 % CI: 13 % to 24 %; p < 0.05). The authors concluded that the clinical outcome of Wingspan stenting for high-risk intra-cranial atherosclerotic stenosis patients in this high-volume center study compares favorably with that of anti-thrombotic therapy alone. They stated that a randomized trial comparing medical therapy alone with medical therapy plus Wingspan stenting, conducted at high-volume centers, is needed to confirm the stenting benefit.

Qureshi et al (2012) noted that the results of prematurely terminated stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) due to excessively high rate of stroke and death in patients randomized to intra-cranial stent placement is expected to affect the practice of endovascular therapy for intra-cranial atherosclerotic disease. These investigators reviewed the components of the designs and methods SAMMPRIS trial and described the influence of those components on the interpretation of trial results. A critical review of the patient population included in SAMMPRIS was conducted with emphasis on "generalizability of results" and "bias due to cherry picking phenomenon". The technical aspects of endovascular treatment protocol consisting of intra-cranial angioplasty and stent placement using the Gateway balloon and Wingspan self-expanding nitinol stent and credentialing criteria of trial interventionalists were reviewed. The influence of each component is estimated based on previous literature including multi-center clinical trials reporting on intra-cranial angioplasty and stent placement. The inclusion criteria used in the trial ensured that patients with adverse clinical or angiographic characteristics were excluded. Self-expanding stent as the sole stent, technique of pre-stent angioplasty, peri-procedural anti-platelet treatment, and intra-procedural anti-coagulation are unlikely to adversely influence the results of intra-cranial stent placement. A more permissive policy toward primary angioplasty as an acceptable
treatment option may have reduced the overall peri-procedural complication rates by providing a safer option in technically challenging lesions. The expected impact of a more rigorous credentialing process on peri-procedural stroke and/or death rate following intra-cranial stent placement in SAMMPRIS such as the one used in carotid re-vascularization endarterectomy versus stenting trial remains unknown. The authors concluded that the need for developing new and effective treatments for patients with symptomatic intra-cranial stenosis can not be undermined. The data support modification but not discontinuation of the approach to intra-cranial angioplasty and/or stent placement for intra-cranial stenosis. There are potential patients in whom angioplasty and/or stent placement might be the best approach, and a new trial with appropriate modifications in patient selection and design may be warranted.

In summary, although there is preliminary evidence that balloon angioplasty, with or without stenting, may be effective in treating symptomatic patients with intra-cranial stenoses, available data are mainly from retrospective case series. Randomized controlled studies are needed to ascertain the effectiveness of this technology compared to best medical care in preventing stroke in patients with intra-cranial stenosis that is symptomatic or asymptomatic. Other parameters that need to be addressed are: (i) the frequency of peri-procedural stroke (disabling and non-disabling), death, and the combination of stroke and death, (ii) the frequency of other major peri-procedural complications that require additional therapy, prolonged hospital stay or death as well as minor complications (e.g., hematoma, wound infection, and nerve palsy), (iii) the frequency of stroke in the territory of the stenosed vessels, (iv) the frequency of re-stenosis in the involved vessels, and (v) the frequency of hospital resource use, including length of stay and frequency of re-admission.
Derdeyn et al (2014) noted that early results of the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial showed that, by 30 days, 33 (14.7 %) of 224 patients in the stenting group and 13 (5.8 %) of 227 patients in the medical group had died or had a stroke (percentages are product limit estimates), but provided insufficient data to establish whether stenting offered any longer-term benefit. In this study, these researchers reported the long-term outcome of patients. They randomly assigned (1:1, stratified by center with randomly permuted block sizes) 451 patients with recent transient ischemic attack or stroke related to 70 to 99 % stenosis of a major intracranial artery to aggressive medical management (anti-platelet therapy, intensive management of vascular risk factors, and a lifestyle-modification program) or aggressive medical management plus stenting with the Wingspan stent. The primary end-point was any of the following: stroke or death within 30 days after enrolment, ischemic stroke in the territory of the qualifying artery beyond 30 days of enrolment, or stroke or death within 30 days after a re-vascularization procedure of the qualifying lesion during follow-up. Primary end-point analysis of between-group differences with log-rank test was by intention-to-treat. During a median follow-up of 32.4 months, 34 (15 %) of 227 patients in the medical group and 52 (23 %) of 224 patients in the stenting group had a primary end-point event. The cumulative probability of the primary end-points was smaller in the medical group versus the PTAS group (p = 0.0252). Beyond 30 days, 21 (10 %) of 210 patients in the medical group and 19 (10 %) of 191 patients in the stenting group had a primary end-point. The absolute differences in the primary end-point rates between the 2 groups were 7.1 % at year 1 (95 % CI: 0.2 to 13.8 %; p = 0.0428), 6.5 % at year 2 (-0.5 to 13.5 %; p = 0.07) and 9.0 % at year 3 (1.5 to 16.5 %; p = 0.0193). The occurrence of the following adverse events was higher in the PTAS group than in the medical group: any stroke (59 [26 %] of 224 patients versus 42 [19 %] of 227 patients; p = 0.0468) and major hemorrhage (29 [13 %] of 224 patients versus 10 [4 %] of 227
patients; $p = 0.0009$). The authors concluded that the early benefit of aggressive medical management over stenting with the Wingspan stent for high-risk patients with intracranial stenosis persists over extended follow-up. They stated that these findings provided support to the use of aggressive medical management rather than PTAS with the Wingspan system in high-risk patients with atherosclerotic intracranial arterial stenosis.

Abuzinadah et al (2016) conducted a systematic review and meta-analysis of studies reporting the rates of stroke recurrence or death (the primary outcome) in symptomatic intracranial vertebro-basilar stenosis with medical or endovascular treatment over a minimum follow-up period of 6 months. These researchers included all studies in any language indexed in MEDLINE or EMBASE, supplemented by bibliography searches and by contacting the authors. The secondary end-points were stroke recurrence, and basilar artery and vertebral artery stroke recurrence rates. A total of 23 studies (592 medical treatment patients and 480 endovascular treatment patients) were included. The risk of combined stroke recurrence or death was 14.8 per 100 person-years (95% CI: 9.5 to 20.1) in the medical group compared with 8.9 per 100 person-years (95% CI: 6.9 to 11.0) in the endovascular group. The incidence rate ratio was 1.3 (95% CI: 1.0 to 1.7). The stroke recurrence rate was 9.6 per 100 person-years (95% CI: 5.1 to 14.1) in the medical group compared with 7.2 per 100 person-years (95% CI: 5.5 to 9.0) in the endovascular group. The authors concluded that these findings showed that the risk of stroke recurrence or death or the risk of stroke recurrence alone was comparable between the medical and endovascular therapy groups. A small preventive effect of endovascular therapy may exist, particularly if the 30 day post-procedural risk is reduced.

Wabnitz and Chimowitz (2017) noted that although there is an intuitive appeal to treat symptomatic stenotic intra-cranial arteries with endovascular therapies such as angioplasty and
stenting, current data from randomized trials showed intensive medical therapy is far superior for preventing stroke. This is in large part due to the high risk of peri-procedural stroke from angioplasty and stenting. If angioplasty and stenting is to emerge as a proven treatment for intra-cranial stenosis, endovascular techniques will need to become much safer, identification of patients with intra-cranial stenosis who are at particularly high risk of stroke despite intensive medical therapy will need to be targeted, and well-designed randomized trials will be necessary to show endovascular therapy is superior to medical therapy in these high-risk patients.

Derdeyn and co-workers (2017) examined the frequency of symptomatic in-stent restenosis (ISR) and its contribution to non-procedural symptomatic infarction in the SAMMPRIS trial (Stenting and Aggressive Medical Management for the Prevention of Recurrent Stroke in Intracranial Stenosis). Patients without a peri-procedural primary end-point were followed-up to determine the occurrence of any of the following events: ischemic stroke, cerebral infarct with temporary signs, or TIA in the territory of the stented artery. Vascular imaging performed after these events was reviewed for ISR. Annual rates for symptomatic ISR were calculated using Kaplan-Meier estimates. Of 183 patients in the stenting group without a peri-procedural primary end-point, 27 (14.8 %) had a symptomatic infarction (stroke or cerebral infarct with temporary signs) and 16 (8.7 %) had TIA alone in the territory during a median follow-up of 35.0 months. Of the 27 patients with infarctions, 17 (9.3 %) had an ischemic stroke and 10 (5.5 %) had a cerebral infarct with temporary signs alone. Adequate vascular imaging to evaluate ISR was available in 24 patients with infarctions (showing ISR in 16 [66.7 %]) and in 10 patients with TIA alone (showing ISR in 8 [80 %]). The 1-, 2-, and 3-year rates (with 95 % CIs) for symptomatic ISR in the SAMMPRIS stent cohort were 9.6 % (6.1 % to 14.9 %), 11.3 % (7.5 % to 17.0 %), and 14.0 % (9.6 % to 20.2 %), respectively. The authors concluded that symptomatic ISR occurred in at
least 1 in 7 patients during a median follow-up of 35 months in SAMMPRIS and was associated with the majority of symptomatic infarcts in the territory of the stented artery beyond the peri-procedural period. Taken together with the peri-procedural outcomes in SAMMPRIS, these data showed that it will be necessary to substantially lower both the rate of peri-procedural stroke and the rate of symptomatic ISR for stenting to have a role in the treatment of intra-cranial stenosis.

Angioplasty and Stenting of Intra-Cranial Arteries for the Treatment of Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage

Aneurysmal subarachnoid hemorrhage is a common form of stroke. Frequently, a significant number of patients with this condition develop angiographical or clinical vasospasm with devastating consequences. The pathogenesis of cerebral vasospasm following SAH remains unclear despite extensive research. Due to the lack of a clear etiology, medical treatment is still largely limited to hypertensive-hypervolemic-hemodilution (triple-H) therapy, and calcium channel blockers (e.g., nimodipine). Cerebral vasospasm that has become refractory to maximal medical therapy can be treated with intra-arterial infusion of vasodilators (e.g. papaverine). Moreover, recent advent in the field of interventional neurology and the development of minimally invasive techniques has resulted in expansion of potential therapeutic approaches for cerebral vasospasm secondary to aneurysmal SAH (Kosty, 2005). Balloon angioplasty is being investigated as a treatment option in patients with vasospasm following aneurysmal SAH; however its effectiveness for this indication has yet to be established.

In a case reports study, Murayama et al (2003) assessed the safety and effectiveness of combined Guglielmi detachable coil (GDC) embolization and balloon angioplasty in a single session for the treatment of ruptured aneurysms associated
with symptomatic vasospasm (n = 12). Patients underwent GDC aneurysm occlusion and balloon angioplasty (n = 6), intra-arterial papaverine infusion (n = 2), or both (n = 4) in a single session. In 9 patients, aneurysm coil occlusion was performed first. Complete GDC occlusion was achieved in 8 patients, a small neck remnant persisted in 3, and embolization was incomplete in 1 patient. In all subjects, angiographical improvement of cerebral vasospasm was obtained. In 1 subject, a thromboembolic complication occurred and was treated with urokinase. Clinical outcomes at discharge were good recovery in 6, moderate disability in 2, severe disability in 3, and death in 1. These researchers concluded that endovascular treatment can be the first therapeutic option for ruptured aneurysms associated with severe vasospasm on admission. It offers some advantages over surgery in this setting, but these are balanced by the risk of thromboembolism. This is in agreement with the observation of Wijdicks et al (2005) who noted in their review that balloon angioplasty is a durable means of alleviating arterial narrowing and preventing stroke in patients with symptomatic vasospasm following aneurysmal SAH. However, the procedure has risks, especially in inexperienced hands. Additionally, the timing of endovascular intubation and use of inotropes in patients with cardiac dysfunction are unresolved issues.

In a review on cerebral vasospasm after SAH, Janjua and Mayer (2003) stated that the care management of this condition has evolved significantly over the past 10 years, with many new diagnostic modalities and promising treatments (e.g., balloon angioplasty) now available. These researchers concluded that clinical trials are needed to assess the effectiveness of these new techniques and to further define the optimal management of this often devastating complication following SAH. This is in agreement with the observation of Rabinstein and colleagues (2004). These investigators reviewed 81 consecutive patients with symptomatic cerebral vasospasm from aneurysmal SAH treated with percutaneous
balloon angioplasty or selective intra-arterial papaverine infusion (105 procedures). Mean patient age was 54 years (range of 29 to 88 years). Twenty-nine patients (36 %) presented with poor-grade (World Federation of Neurologic Surgeons [WFNS] grade IV or V) SAH. Clinical deficits were global in 55 patients (70 %), and angiographic vasospasm was diffuse in 53 (65 %). Endovascular treatment consisted of transluminal angioplasty alone (18 procedures, 17 %), intra-arterial papaverine infusion (65 procedures, 62 %), or both (22 procedures, 21 %). Unequivocal arterial dilatation was achieved in all but 2 patients, and major complications occurred in 2 % of the procedures. Ten patients (12 %) died in the hospital, and 36 (44 %) recovered poorly. Permanent deficits attributable to cerebral vasospasm were present in 37 patients (52 % of survivors). On multi-variate logistic regression analysis, advanced age and poor WFNS grade at presentation were predictive of poor clinical outcome. These authors stated that balloon angioplasty and intra-arterial papaverine are promising treatments for severe symptomatic vasospasm following SAH. They also noted that advanced age and poor clinical status (WFNS grade IV or V) at the time of SAH onset are predictive of poor clinical outcome despite endovascular treatment with balloon angioplasty or intra-arterial papaverine in patients with symptomatic vasospasm.

In a retrospective study, Turowski et al (2005) reported that in experienced hands, intra-cranial angioplasty is a feasible and safe option in a selected group of patients with severe (over 50 % stenosis) symptomatic vasospasm following SAH. Cerebral circulation time is a surrogate parameter closely linked to cerebral perfusion. This study showed that not only stenosis but also changes in circulation time were obtained by angioplasty. A total of 20 angioplasties of 1 or 2 vessel segments were performed over 2 years in 18 consecutive patients with post-hemorrhagic vasospasm. In all patients, degree of stenosis and circulation time could be reduced by angioplasty. Clinical results were ranked according to Glasgow Outcome Scale. Imaging after 15/20 angioplasties
showed no additional infarction. In 4/20 cases, computed
tomography (CT) showed demarcation of infarction after
angioplasty. In 1/20 cases of posterior circulation angioplasty,
CT is not sensitive enough to exclude smaller infarctions.

In a clinical trial, Murai and associates (2005) examined the
long-term effects of transluminal balloon angioplasty (TBA) on
cerebral blood flow (CBF) and the functional properties of the
arterial wall after aneurysmal SAH. A total of 12 patients
underwent unilateral TBA. Xenon-enhanced CT was
performed for an average of 18 days after TBA to measure
CBF and cerebrovascular reactivity (CVR). Cerebral blood
flow and CVR were compared between the side of TBA and
the contralateral side. A total of 19 vascular territories were
treated successfully with TBA in the subjects. Angiographical
improvement of vasospasm was demonstrated in all 12
patients, and 9 (75 %) patients showed neurological
improvement. After TBA, global CBF was 35.1 +/- 8.2 mL/100
g per minute, with CBF on the side with TBA (37.8 +/- 10.3
mL/100 g per minute) being essentially the same as that on
the other side (p = 0.0671, paired Student t test). Likewise,
reactivity to acetazolamide did not differ significantly between
sides (p = 0.0817). These investigators concluded that TBA
increased proximal vessel diameters but showed no significant
influence on CBF or CVR 3 weeks later. Benefits presumably
were short-term, but the procedure was clinically safe.

Balloon angioplasty is also being used prophylactically for
patients with cerebral vasospasm following SAH (Janjua and
Mayer, 2003; Wu et al, 2004). A phase II clinical trial is
ongoing at 5 centers comparing the outcomes of transluminal
balloon prophylaxis with those of conventional medical
management in patients with aneurysmal SAH who are at high
risk for vasospasm (the Internet Stroke Center, 2004).

Velat et al (2011) reviewed RCTs and meta-analyses in the
literature regarding the treatment and prevention of cerebral
vasospasm following aneurysmal SAH. A literature search of
MEDLINE, the Cochrane Controlled Trials Registry, and the National Institutes of Health/National Library of Medicine clinical trials registry was performed in January 2010 using predefined search terms. These trials were critically reviewed and categorized based on therapeutic modality. A total of 44 RCTs and 9 meta-analyses met the search criteria. Significant findings from these trials were analyzed. The results of this study were as follows: nimodipine demonstrated benefit following aneurysmal SAH; other calcium channel blockers, including nicardipine, do not provide unequivocal benefit; triple-H therapy, fasudil, transluminal balloon angioplasty, thrombolytics, endothelin receptor antagonists, magnesium, statins, and miscellaneous therapies such as free radical scavengers and anti-fibrinolytics require additional study. Tirilazad is ineffective. The authors concluded that there are many possible successful treatment options for preventing vasospasm, delayed ischemic neurologic deficits, and poor neurologic outcome following aneurysmal SAH; however, further multi-center RCTs are needed to determine if there is a significant benefit from their use. Nimodipine is the only treatment that provided a significant benefit across multiple studies.

An UpToDate review on "Treatment of aneurysmal subarachnoid hemorrhage" (Singer et al, 2013) states that "Angioplasty -- While balloon angioplasty of the basal cerebral blood vessels appears to be an effective treatment for treatment of cerebral vasospasm, it has not as yet been found to be a useful prophylactic approach. A phase II randomized trial of 85 patients found that prophylactic angioplasty was not associated with significant reductions in the incidence of delayed ischemia or vasospasm, nor with improved outcomes .... Balloon angioplasty has become the mainstay of treatment at many centers for symptomatic focal vasospasm of the larger cerebral arteries which is refractory to hemodynamic augmentation, again despite an absence of clinical trial data .... Clinical vasospasm that persists despite hyperdynamic therapy may be treated by percutaneous intraarterial
angioplasty or intraarterial administration of vasodilators. There is limited data suggesting that their use improves clinical outcomes.

Guidelines from the American Academy of Neurology on subarachnoid hemorrhage (Connolly, et al., 2012) state: "Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy (Class IIa; Level of Evidence B).". The guidelines explain: Endovascular intervention is often used in patients who do not improve with hemodynamic augmentation and those with sudden focal neurological deficits and focal lesions on angiography referable to their symptoms. Interventions generally consist of balloon angioplasty for accessible lesions and vasodilator infusion for more distal vessels. Many different vasodilators are in use. In general, these are calcium channel blockers, but nitric oxide donors have been used in small series as well. Papaverine is used less frequently because it can produce neurotoxicity. The primary limitation of vasodilator therapy is the short duration of benefit. As with hemodynamic augmentation, there have been no randomized trials of these interventions, but large case series have demonstrated angiographic and clinical improvement." The guidelines recommend against stenting, stating that "Stenting of a ruptured aneurysm is associated with increased morbidity and mortality, and should only be considered when less risky options have been excluded (Class III; Level of Evidence C)."

Guidelines from the Neurocritical Care Society (Diringer, et al., 2011) state: "Endovascular treatment using intra-arterial vasodilators and/or angioplasty may be considered for vasospasm-related DCI [delayed cerebral ischemia] (moderate quality evidence-strong recommendation)." The guidelines state that "the timing and triggers of endovascular treatment of vasospasm remains unclear, but generally rescue therapy for ischemic symptoms that remain refractory to medical treatment..."
should be considered. The exact timing is a complex decision which should consider the aggressiveness of the hemodynamic intervention, the patients' ability to tolerate it, prior evidence of large artery narrowing, and the availability of and the willingness to perform angioplasty or infusion of intra-arterial agents (moderate quality evidence—strong recommendation)." The guidelines, however, recommend against prophylactic endovascular treatment. "The use of routine prophylactic cerebral angioplasty is not recommended (High quality Evidence—Strong Recommendation)." The guidelines explain: "Most studies are retrospective case series or comparison studies, with few prospective studies. Hence, the literature has demonstrated the feasibility, durability, and safety profile of intra-arterial vasodilator therapy and angioplasty, and the combination of the two, but has not demonstrated this for newer methods. The literature has not provided sufficient information regarding timing of the endovascular rescue therapy nor the optimum number of repeat treatments necessary. However, the single randomized controlled trial of prophylactic angioplasty, done early after SAH without the presence of angiographic arterial narrowing, suggested a lower risk of DCI, albeit at a risk of vessel rupture and death from the procedure and ultimately no difference in outcome [citing Zwienenberg-Lee, et al., 2008]. There are presently insufficient data to determine if intraarterial vasodilator therapy alone, or angioplasty alone, or a combination of treatments is superior to one another or superior to medical treatment alone."

By contrast, international guidelines from the European Stroke Organization on management of intracranial aneurysms and subarachnoid hemorrhage (Steiner et al, 2013) have no recommendations for angioplasty or intra-arterial vasodilators.

Veldeman et al (2016) stated that the leading cause of morbidity and mortality after surviving the rupture of an intracranial aneurysm is delayed cerebral ischemia (DCI). These investigators presented an update of recent literature
on the current status of prevention and treatment strategies for DCI after aneurysmal subarachnoid hemorrhage. They performed a systematic literature search of 3 databases (PubMed, ISI Web of Science, and Embase). Human clinical trials assessing treatment strategies, published in the last 5 years, were included based on full-text analysis. Study data were extracted using tables depicting study type, sample size, and outcome variables. These researchers identified 49 studies meeting the inclusion criteria. Clazosentan, magnesium, and simvastatin have been tested in large high-quality trials but failed to show a beneficial effect. Cilostazol, eicosapentaenoic acid, erythropoietin, heparin, and methylprednisolone yielded promising results in smaller, non-randomized or retrospective studies and warrant further investigation. Topical application of nicardipine via implants after clipping has been shown to reduce clinical and angiographic vasospasm. Methods to improve subarachnoid blood clearance have been established, but their effect on outcome remains unclear. Hemodynamic management of DCI is evolving towards euvoletic hypertension. Endovascular rescue therapies, such as percutaneous transluminal balloon angioplasty and intra-arterial spasmolysis, are able to resolve angiographic vasospasm, but their effect on outcome needs to be proved. Many novel therapies for preventing and treating DCI after aneurysmal subarachnoid hemorrhage have been assessed, with variable results. Limitations of the study designs often preclude definite statements. Current evidence does not support prophylactic use of clazosentan, magnesium, or simvastatin. Many strategies remain to be tested in larger RCTs.

In summary, while there is some preliminary evidence from retrospective case series studies that balloon angioplasty may be beneficial in treating cerebral vasospasm following aneurysmal SAH, its effectiveness in the prevention and treatment of this condition need to be verified by prospective, randomized, controlled trials.
Extracranial-Intracranial Arterial Bypass Surgery

The Centers for Medicare & Medicaid Services’ National Coverage Determination for “Extracranial-Intracranial (EC-IC) Arterial Bypass Surgery” (CMS, 1991) stated that “EC-IC arterial bypass surgery is not a covered procedure when it is performed as a treatment for ischemic cerebrovascular disease of the carotid or middle cerebral arteries, which includes the treatment or prevention of strokes. The premise that this procedure which bypasses narrowed arterial segments improves the blood supply to the brain and reduces the risk of having a stroke has not been demonstrated to be any more effective than no surgical intervention. Accordingly, EC-IC arterial bypass surgery is not considered reasonable and necessary within the meaning of §1862(a)(1) of the Act when it is performed as a treatment for ischemic cerebrovascular disease of the carotid or middle cerebral arteries”.

A study by the EC/IC Bypass Study Group (1985) failed to confirm the hypothesis that extracranial-intracranial anastomosis is effective in preventing cerebral ischemia in patients with atherosclerotic arterial disease in the carotid and middle cerebral arteries. To determine whether bypass surgery would benefit patients with symptomatic atherosclerotic disease of the internal carotid artery, the investigators studied 1377 patients with recent hemisphere strokes, retinal infarction, or transient ischemic attacks who had atherosclerotic narrowing or occlusion of the ipsilateral internal carotid or middle cerebral artery. Of these, 714 were randomly assigned to the best medical care, and 663 to the same regimen with the addition of bypass surgery joining the superficial temporal artery and the middle cerebral artery. The patients were followed for an average of 55.8 months. Thirty-day surgical mortality and major stroke morbidity rates were 0.6 and 2.5 per cent, respectively. The postoperative bypass patency rate was 96 per cent. Nonfatal and fatal stroke occurred both more frequently and earlier in the patients...
operated on. Secondary survival analyses comparing the two groups for major strokes and all deaths, for all strokes and all deaths, and for ipsilateral ischemic strokes demonstrated a similar lack of benefit from surgery. Separate analyses in patients with different angiographic lesions did not identify a subgroup with any benefit from surgery. Two important subgroups of patients fared substantially worse in the surgical group: those with severe middle-cerebral-artery stenosis (n = 109, Mantel-Haenszel chi-square = 4.74), and those with persistence of ischemic symptoms after an internal-carotid-artery occlusion had been demonstrated (n = 287, chi-square = 4.04).

Rodriguez-Hernandez et al (2011) stated that although most ischemic strokes are thrombo-embolic in origin and their management is endovascular or medical, some are hemodynamic in origin and their management may be surgical. Extracranial-intracranial bypass with superficial temporal artery-to-middle cerebral artery (MCA) bypass, high-flow interposition grafts, and reconstructive techniques have been developed. Clinical indications and efficacy are controversial, and these researchers examined current practices. Bypass surgery is indicated for patients with athero-occlusive disease that results in chronic, low cerebral blood flow accompanied by episodes of ischemic symptoms. Specific diagnoses include: (i) internal carotid artery occlusion; (ii) MCA occlusion and, rarely, high-grade MCA stenosis; (iii) vertebra-basilar atherosclerotic steno-occlusive disease; (iv) vasculitis resulting in severe occlusive disease; and (v) moyamoya disease. Discouraging results from the Extracranial-Intracranial Bypass Trial demonstrated the importance of selecting surgical patients based on objective measures of hemodynamic insufficiency. Two such tests are xenon-enhanced computed tomography with acetazolamide challenge and positron emission tomography with measurement of oxygen extraction fraction. Perfusion computed tomography may be another, more practical test.
Surgical series, systematic reviews of the literature, and 2 new RCTs that use these diagnostic techniques reveal contradictory results. Although they demonstrated that bypass surgery has a morbidity rate of less than 5% and a patency rate of more than 95%, they have not proven a clear benefit.

Powers et al (2011) tested the hypothesis that EC-IC bypass surgery, added to best medical therapy, reduces subsequent ipsilateral ischemic stroke in patients with recently symptomatic atherosclerotic internal carotid artery occlusion (AICAO) and hemodynamic cerebral ischemia. Patients with arteriographically confirmed AICAO causing hemispheric symptoms within 120 days and hemodynamic cerebral ischemia identified by ipsilateral increased oxygen extraction fraction measured by PET were included in this analysis. Of 195 patients who were randomized, 97 were randomized to receive surgery and 98 to no surgery. Follow-up for the primary end point until occurrence, 2 years, or termination of trial was 99% complete. No participant withdrew because of adverse events. Anastomosis of superficial temporal artery branch to a MCA cortical branch for the surgical group was carried out. Antithrombotic therapy and risk factor intervention were recommended for all participants. Main outcome measures included: for all participants who were assigned to surgery and received surgery, the combination of (i) all stroke and death from surgery through 30 days after surgery, and (ii) ipsilateral ischemic stroke within 2 years of randomization; for the non-surgical group and participants assigned to surgery who did not receive surgery, the combination of (i) all stroke and death from randomization to randomization plus 30 days, and (ii) ipsilateral ischemic stroke within 2 years of randomization. The trial was terminated early for futility. Two-year rates for the primary end point were 21.0% (95% CI: 12.8% to 29.2%; 20 events) for the surgical group and 22.7% (95% CI: 13.9% to 31.6%; 20 events) for the non-surgical group (p = 0.78, Z test), a difference of 1.7% (95% CI: -10.4% to 13.8%). Thirty-day
rates for ipsilateral ischemic stroke were 14.4% (14/97) in the surgical group and 2.0% (2/98) in the non-surgical group, a difference of 12.4% (95% CI: 4.9% to 19.9%). The authors concluded that among participants with recently symptomatic AICA0 and hemodynamic cerebral ischemia, EC-IC bypass surgery plus medical therapy compared with medical therapy alone did not reduce the risk of recurrent ipsilateral ischemic stroke at 2 years.

Jacobs and Nichols (2014) stated that vascular cognitive impairment may be related to clinically apparent stroke, silent smaller strokes, or perhaps zones of incomplete infarction related to cerebral hypoperfusion. Flow limiting carotid stenosis or complete occlusion is associated with hemodynamic failure and poorer cognition. Improving CBF in such patients via re-vascularization procedures such as carotid endarterectomy, carotid stenting, EC-IC bypass surgery has inconsistently been associated with improved cognition.

Guidelines from the National Institute for Health and Care Excellence (NICE, 2017) concluded: "Current evidence on the safety and efficacy of extracranial to intracranial bypass for intracranial atherosclerosis shows that there is no benefit to the patient from the intervention. There are major concerns around its safety, therefore this procedure should not be used to treat this condition."

**Drug-Eluting Stent for the Intra-Cranial Atherosclerotic Disease**

Ye and colleagues (2019) stated that drug-eluting stent (DES) is a potential endovascular treatment for patients with symptomatic intra-cranial atherosclerotic disease (sICAD). However, evidence regarding the treatment of ICAD with DES is lacking. These investigators systematically searched PubMed, Embase, Cochrane database (before December 21, 2017) for literature reporting the application of DES in the
treatment of sICAD. The main outcomes were as follows: the incidence of any stroke or death within 30 days (peri-operative complications), ischemic stroke in the territory of the qualifying artery beyond 30 days (long-term complications), ISR and symptomatic ISR during follow-up. Those studies with mean stenosis rate greater than 70% and less than 70% were defined as severe and moderate stenosis group, respectively. The random effect model was used to pool the data. Of 518 articles, 13 studies were eligible and included in this analysis (n = 336 patients with 364 lesions). After the implantation of DES, peri-operative complications (mortality = 0) occurred in 6.0% (95% CI: 2.0% to 11.9%), long-term complications occurred in 2.2% (95% CI: 0.7% to 4.5%), ISR rate was 4.1% (95% CI: 1.6% to 7.7%) and the symptomatic ISR rate was only 0.5% (95% CI: 0 to 2.2%). In addition, subgroup analysis showed that the peri-operative complication rate in severe stenosis group [10.6% (95% CI: 6.5% to 15.7%)] was significantly (p < 0.01) higher than that in moderate stenosis group [1.0% (95% CI: 0.3% to 3.5%)]. The authors concluded that endovascular DES implantation is a relatively safe and effective method compared with stents or medical management group in SAMMPRIS and VISSIT trials. However, a higher pre-operative stenosis rate may imply a higher risk of peri-operative complications; further studies are needed.

Flow-Diverting Stent in the Treatment of Cervical Carotid Dissection and Pseudo-Aneurysm

For patients with extracranial carotid or vertebral arterial dissection who have definite recurrent ischemic events despite adequate antithrombotic therapy, the 2014 American Heart Association/American Stroke Association guidelines conclude that stenting may be considered (Kernan, et al., 2014).

Baptista-Sincos and colleagues (2018) stated that the endovascular technique has been recommended over the past few years to extra-cranial carotid dissection and pseudo-
aneurysm with promising results, especially after medical therapy failure. Flow-diverting stents are an alternative for complex cases. These stents have proven to be effective treatment devices for intra-cranial aneurysms. The reference list of Pham’s systematic review, published in 2011, and Seward’s literature review, published in 2015, was considered, as well as all new articles with eligible features. Search was conducted on specific databases: Medline and Literatura Latino-Americana e do Caribe em Ciências da Saúde. For carotid dissection and pseudo-aneurysm, this review yielded 3 published articles including 12 patients. The technical success rate of flow-diverting stent was 100% with no procedural complication described. Mean clinical follow-up was 27.2 months (range of 5 to 48), and in 5 months’ angiographic follow-up, all lesions had healed. No new neurological events were reported during the clinical follow-up. The authors concluded that flow diverter stent use on intra-cranial and peripheral vascular surgery demonstrated satisfactory initial results, but it is still under investigation. There are very few cases treated until now and the initial results with flow-diverting stents to cervical carotid dissection are promising. These researchers stated that in well-selected cases, where simple embolization or conventional stent is not appropriate, this technic may be considered.

Flow-Diverting Stent / Willis Intra-Cranial Covered Stent in the Treatment of Blood Blister-Like Aneurysms

Currently, the treatment of blood blister-like aneurysms (BBAs) of the internal carotid artery (ICA) utilizes many therapeutic methods, including direct clipping and suturing, clipping after wrapping, clipping after suturing, coil embolization, stent-assisted coil embolization, multiple overlapping stents, flow-diverting stents, covered stents, and trapping with or without bypass. In these therapeutic approaches, the optimal treatment method for BBAs has not yet been defined based on the current understanding of BBAs of the supraclinoid ICA (Ji, et al., 2017).
Yang and colleagues (2017) stated that blood blister aneurysms (BBAs) are small sessile lesions that typically occur at non-branching sites of the dorsal surface of the supraclinoid internal carotid artery. These aneurysms are rare, contributing to less than 2% of all intra-cranial aneurysms. Nonetheless, these account for 2.2% of all SAH from a ruptured internal carotid artery aneurysm. If left untreated, once ruptured, these demonstrated poor clinical outcomes. Histologically, BBAs are associated with dissections, focal arterial wall loss of the internal elastic lamina and media, with a thin layer of fibrous tissue and/or thrombus covering the defect. Essentially, such lesions behave as pseudo-aneurysms. These researchers performed a single-center evaluation and quick literature review of the effectiveness of primary flow-diverter (FD) treatment of ruptured BBAs, with additional relevance of adjunctive coiling. Patients presenting with SAH due to ruptured BBAs and subsequently treated with FDs were retrospectively selected from June 2010 to January 2017. Treatment techniques, angiographic data on occlusion rates and procedural success as well as clinical outcomes using the modified Rankin Scale (mRS) were collated. Cross-reference of results were made with available literature. A total of 13 patients harboring 14 BBAs were recruited. Of the 14 aneurysms, 5 (35.7%) showed immediate complete occlusion after the procedure (4 of these 5 patients had adjunctive coiling). All of the aneurysms showed complete occlusion by the 6- to 9-month control diagnostic angiogram. No re-bleed or re-treatment was experienced; 12 of 13 (92%) patients had an mRS score of 0 to 1 at the last clinical follow-up. From the pooled data of the literature review, eventual aneurysm occlusion was achieved in 48/56 patients, with 5 patients requiring further endovascular treatment. In the clinical follow-up period, an mRS of 0 to 2 was recorded for 83.3% (45/54) of patients. The authors concluded that endovascular reconstruction of BBAs using FD treatment was an effective method with good final clinical outcomes. Adjunctive use of coiling achieved higher incidence of immediate complete occlusion of BBAs. These researchers
stated that they have also illustrated the significant challenges in managing patients requiring invasive intra-cranial procedures post-commencement of dual-antiplatelet therapy, highlighting the need for relevant guidelines and future research.

Fang and associates (2017) examined the safety and feasibility of endovascular treatment of BBAs with the Willis covered stent. A total of 13 patients (7 men and 6 women, age range of 28 to 68 years) who presented with ruptured BBAs and were treated with the Willis covered stent were retrospectively reviewed. Results of the procedures and treatment-related complications were recorded. Angiographic and clinical follow-ups were performed 4 to 6 months after the procedure. Placement of the covered stent was successful in all patients. Immediate angiography showed complete aneurysm occlusion in 12 patients while 1 patient showed a mild endoleak. This high rate of aneurysm exclusion ensured the security of post-operative anti-platelet treatment.

Occlusion of the ophthalmic artery occurred in 2 patients and occlusion of the anterior choroidal artery occurred in 1 patient; however, none of them showed acute or delayed clinical symptoms. Thrombosis, aneurysm rupture, and other complications did not develop in any case. Angiographic follow-up showed complete aneurysm exclusion without aneurysm recurrence in any patients. Only 2 patients showed asymptomatic mild-to-moderate in-stent stenosis. All patients had satisfactory clinical outcomes (mRS score of less than or equal to 1). The authors concluded that the Willis covered stent implementation may be safe and feasible for BBAs; this strategy might be a promising option for this high-risk type of aneurysm.

Liu and colleagues (2019) presented their initial experience with the use and feasibility of the intra-cranial Willis covered stent (WCS) in the treatment of BBAs and performed a systematic review of the reported data on the treatment of BBAs with covered stents. A total of 14 consecutive patients
with BBAs had been treated with WCSs at West China Hospital from January 2015 to August 2017. The patient medical records, angiographic findings, and endovascular treatment reports were reviewed by interventional neuroradiologists and neurosurgeons to obtain relevant clinical and angiographic information. These investigators conducted a systematic review of all reports of BBAs treated with covered stents. They searched the reported data using PubMed, Embase, China National Knowledge Infrastructure, and Wanfang databases and commercial Internet search engines; and included BBAs located at non-branching portions of the internal carotid artery. The present study included 9 men and 5 women, with a mean age of 54.5 years (range of 30 to 79). All patients had complete occlusion found on immediate post-operative angiography. The ophthalmic artery was occluded in 2 patients (14.3 %). No mortality or morbidity had occurred during the procedure; 2 patients (14.3 %) experienced a mild recurrence; 1 patient (7.1 %) had developed mild in-stent stenosis. The clinical follow-up period was 6 to 15 months for all the patients. Of the 14 patients, 11 (78.6 %) had a mRS score of 0, and 1 (7.1 %) had a mRS score of 1 during the follow-up period; 1 patient (7.1 %) experienced SAH at 7 days post-operatively and had died 10 days after surgery. None of the patients experienced visual defects. Of the 14 patients, 13 (92.9 %) survived, as determined by out-patient department visits or telephone interviews. A total of 8 reports, including 38 patients, met the inclusion criteria. Of these 38 patients, 37 (97.3 %) had successful delivery to the diseased internal carotid artery, and 34 (89.5 %) had experienced complete occlusion during follow-up. The overall rate of complete occlusion was 83.0 % (95 % CI: 68 % to 91 %). The authors concluded that patients with ruptured BBAs treated with WCSs could achieve satisfactory clinical results. Thus, for BBAs, the implementation of the WCS could be safe and feasible; this strategy could be a promising option for this type of high-risk aneurysm. However, patients with tortuous ICAs or aneurysms close to essential branch arteries should be carefully evaluated before the WCS is used.
Willis Intra-Cranial Covered Stent in the Treatment of Carotid Siphon Aneurysms

In a retrospective analysis, Ma and colleagues (2018) reported the clinical results and initial clinical experience of endovascular isolation with the Willis covered stent for carotid siphon aneurysms. Between November 2013 and December 2016, a total of 57 patients who presented with carotid siphon aneurysms were treated with the Willis covered stent. Results of the procedures, technical events, and complications were recorded. Clinical and imaging follow-ups were performed at 3 months following the endovascular procedures. Placement of the Willis covered stent was successful in all patients. Immediate angiography revealed complete exclusion of aneurysms in 48 patients (84 %), while endoleak occurred in 9 patients (16 %). Procedure-related complications occurred in 3 cases, including displacement of the covered stent in 1 patient, acute in-stent thrombosis in 1 patient, and microwire-related intra-cranial hemorrhage in 1 patient. Angiographic follow-ups were done in 49 patients, with complete exclusion of aneurysms in 47 patients. Endoleak was present in 2 patients. No aneurysm recurrence occurred; 44 patients showed good parent artery patency, while the other 5 patients showed mild-to-moderate asymptomatic in-stent stenosis.

During the follow-up period, no ischemic or hemorrhagic event occurred. The mRS scores at follow-up were 0 to 2 in 56 patients and greater than 2 in 1 patient. The authors concluded that the treatment of siphon aneurysms with Willis covered stent implantation resulted in satisfactory clinical outcomes. The Willis covered stent appeared safe and feasible for the treatment of siphon aneurysms, which still needs to be confirmed by longer follow-up periods and controlled studies with larger samples.

Encephaloduroarterio-synangiosis (EDAS) and Other Cerebrovascular Procedures for the Treatment of Moyamoya Disease
Direct revascularization (superficial temporal artery - middle cerebral artery (STA-MCA) bypass) and indirect revascularization (encephaloduroarteriosynangiosis (EDAS), encephalomyosynangiosis (EMS), encephaloduroarteriomyosynangiosis (EDAMS)) procedures are standard options for treatment of symptomatic moyamoya and certain asymptomatic moyamoya cases. Surgery is regarded as helpful for preventing stroke and transient ischemic attack, but is unproven with regard to reducing risk of cerebral hemorrhage. Revascularization should be performed when the patient is stable (i.e., not during treatment for acute hemorrhage). Direct revascularization is generally considered superior to indirect revascularization, but is not always feasible because the vessel sizes may not match.

Suwanwela (2019) explained that the goal of surgical treatment for moyamoya disease is to reduce the risk of ischemic stroke by improving the cerebral circulation. Thus, surgical procedures are used most often for patients with ischemic-type moyamoya who have cognitive decline or progressive symptoms. Surgical techniques for moyamoya disease can be divided into direct and indirect revascularization procedures and their combinations. Direct revascularization is used by many centers, and it is thought to improve the angiographic and cerebral blood flow abnormalities, as well as the prognosis associated with moyamoya. Superficial temporal artery to middle cerebral artery (MCA) bypass or middle meningeal artery to MCA bypass are the most common direct techniques. Direct methods are technically difficult to perform in children because of the small size of donor and/or recipient vessels. Suwanwela (2019) stated that indirect revascularization is preferred at other centers, particularly in cases where the cortical recipient artery is not available for anastomosis. The technique aims to promote the development of a new vascular network over time. In general, indirect revascularization requires less operation time and has lower procedure-related complications than direct revascularization. Indirect techniques include the...
following: encephaloduroarteriosynangiosis and a modification called pial synangiosis; encephalomyosynangiosis; encephaloarteriosynangiosis; encephalodurogaleosynangiosis; omentum transplantation; craniotomy with inversion of the dura; multiple burr holes without vessel synangiosis; and cervical sympathectomy. Combined revascularization involving direct revascularization (to immediately augment cerebral blood flow) plus indirect revascularization (to promote improved flow over time), has also been used. Suwanwela (2019) found that most of the evidence supporting the effectiveness of surgical treatment for moyamoya comes from retrospective case series and case reports, as there is a paucity of randomized controlled trials.

Tsujimura et al (2011) noted that MR angiography (MRA) for pediatric moyamoya disease is important as a non-invasive examination to diagnose blood flow in the brain. Generally, the conventional 3D-TOF MRA is used for moyamoya disease. However, retrobulbar and subcutaneous fat of the head show high intensity signals. These investigators found that using the conventional MRA to diagnose the details of brain blood flow is difficult and that it cannot differentiate moyamoya vessels and fat. It similarly obscured the ophthalmic artery and superficial temporal artery that overlap with fat in the direction of the maximum intensity projection (MIP). Thus, these researchers devised an MRA technique with fat suppression to diagnose blood flow in moyamoya disease patients: MRA with the principle of selective excitation technique (PROSET). The scan time does not need to be increased. They studied the TOF effect in constant and pulsatile flows and the water selective excitation method with the binominal pulse (PROSET) for the fat suppression effect for moyamoya disease. The results showed that PROSET-MRA achieved better image results than conventional MRA. The development of collaterals of the superficial temporal artery and occipital artery in pre- and post-operation moyamoya disease could be clearly visualized and evaluated. The authors concluded that the PROSET-MRA method is useful for
evaluating pre- and post-operation (encephalo-duro-arterio-
syngangiosis [EDAS], encephalo-myo-syngangiosis [EMS]) blood
flow reconstruction for patients who have moyamoya disease.

Liu et al (2016) described the clinical, angiographic
characteristics, and long-term surgical outcome of
hemorrhagic moyamoya disease in children. These
researchers retrospectively collected 374 consecutive children
with moyamoya disease (hemorrhagic 30 and ischemic 344)
between 2004 and 2012 in their hospital. The clinical and
radiological characteristics of the hemorrhagic patients were
retrospectively described and analyzed. All the hemorrhagic
patients underwent EDAS procedure. Digital subtraction
angiography was performed to evaluate the efficacy of
vascularization. Clinical follow-up outcomes were obtained
through clinical visits, telephone, or letter interview. In this
study, the ratio of female to male patients in the hemorrhagic
group was significantly higher than the ischemic group (2:1
versus 0.9:1; p < 0.05). The most frequent hemorrhagic
location was intra-ventricular hemorrhage (n = 22, 73 %). In
addition, significantly greater dilatation of the anterior choroidal
artery and the posterior communicating artery were observed
in the hemorrhagic group (p < 0.05). Good or fair
vascularization were observed in all the 15 children with digital
subtraction angiography follow-up. Clinical outcomes showed
that 25 of 30 (83 %) patients had no disability (modified Rankin
scale [mRS] score, 0 and 1); 1 patient (3.3 %) died of recurrent
hemorrhagic stroke. The authors concluded that the presence
of anterior choroidal artery and posterior communicating artery
dilation may be associated with the bleeding episode in the
children with hemorrhagic moyamoya disease. The EDAS
surgery can effectively increase the cerebral blood flow in
children, which may decrease the incidence of recurrent
hemorrhage.

Trans-Carotid Artery Revascularization (TCAR)
Liang and colleagues (2019) stated that trans-femoral carotid stenting has struggled to become a suitable alternative to carotid endarterectomy for the treatment of carotid disease because of higher peri-operative stroke risks, even with use of embolic protection devices. To reduce the peri-operative stroke rates associated with carotid stenting, several advancements in stent design, embolic protection systems, and technical approaches have been developed. Trans-carotid artery revascularization (TCAR) was also recently introduced as a novel carotid artery stenting option that circumvents several of the high embolic-risk maneuvers found in trans-femoral carotid stenting and employs a flow reversal system that provides continuous embolic protection throughout the procedure. Early results from this technique have shown low stroke/death rates comparable to CEA while maintaining the minimally invasive benefits of carotid stenting. The authors concluded that TCAR has a strong potential to become the preferred method of carotid stenting in the near future and may challenge CEA as the preferred carotid artery revascularization method.

Kashyap and associates (2019) noted that TCAR is a novel approach to carotid intervention that uses a direct carotid cut-down approach coupled with CBF reversal to minimize embolic potential. The initial positive data with TCAR indicated that it may be an attractive alternative to trans-femoral carotid artery stenting and possibly CEA for high-risk patients. In a retrospective study, these researchers presented 30-day and 1-year outcomes following treatment by TCAR and compared these outcomes against a matched control group undergoing CEA at the same institutions. All patients who underwent TCAR at 4 institutions between 2013 and 2017 were evaluated regarding the use of the ENROUTE Transcarotid Neuroprotection System (Silk Road Medical, Inc, Sunnyvale, CA). TCAR patients had high-risk factors and were either enrolled in prospective trials or treated with a commercially available TCAR device. Contemporaneous patients undergoing CEA at each institution were also reviewed.
Patients were propensity matched in a 1:1 (CEA:TCAR) fashion with respect to pre-operative co-morbidities. Data were analyzed using statistical models with a p value of less than 0.05 considered significant. Individual and composite stroke, MI, and death at 30 days and 1 year post-operatively were assessed. Consecutive patients undergoing TCAR or CEA were identified (n = 663) and compared. Patients undergoing the TCAR procedure (n = 292) had higher rates of diabetes (p = 0.01), hyperlipidemia (p = 0.02), coronary artery disease (p < 0.01), and renal insufficiency (p < 0.01) compared with unmatched CEA patients (n = 371). Stroke rates were similar at 30 days (1.0 % TCAR versus 1.1 % CEA) and 1 year (2.8 % TCAR versus 3.0 % CEA) in the unmatched groups.

After propensity matching by baseline characteristics including gender, age, symptom status (36.3 %, 35.3 %) and diabetes, 292 TCAR patients were compared with 292 CEA patients. TCAR patients were more likely to be treated pre-operatively and post-operatively with clopidogrel (pre-operatively, 82.2 % versus 39.4 % [p < 0.01]; post-operatively, 98.3 % versus 36.0 % [p < 0.01]) and statins (pre-operatively, 88.0 % versus 75.0 % [p < 0.01]; post-operatively, 97.8 % versus 78.8 % [p < 0.01]). Stroke (1.0 % TCAR versus 0.3 % CEA; p = 0.62) and death (0.3 % TCAR versus 0.7 % CEA; p = NS) rates were similar at 30 days and comparable at 1 year (stroke, 2.8 % versus 2.2 % [p = 0.79]; death 1.8 % versus 4.5 % [p = 0.09]). The composite end-point of stroke/death/MI at 1 month post-operatively was 2.1 % versus 1.7 % (p = NS). TCAR was associated with a decreased rate of cranial nerve injury (0.3 % versus 3.8 %; p = 0.01). The authors concluded that these early data suggested that patients undergoing TCAR, even those with high-risk co-morbidities, achieved broadly similar outcomes compared with patients undergoing CEA while mitigating cranial nerve injury. These researchers stated that further comparative studies are needed.

Luk and co-workers (2019) stated that carotid artery stenosis is a significant cause of ischemic stroke, and studies have shown that trans-femoral carotid artery stenting is associated
with a higher peri-operative stroke risk than open endarterectomy. Trans-carotid artery revascularization is a novel technique in carotid stenting via direct trans-cervical carotid access without the risk of arch manipulation, offers a smaller wound compared with endarterectomy, and employs flow reversal to decrease the risk of antegrade embolic stroke. These researchers examined contemporary evidence on the safety and efficacy of TCAR. They carried out a systematic literature review on TCAR from January 2009 to August 2019 in PubMed and Embase databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. Clinical studies on TCAR with flow reversal with clinical outcomes of stroke, MI, and death were included. Initial search of the literature yielded 161 articles, of which 8 studies were included comprising of 5 single-arm studies and 3 comparative studies. Studies demonstrated high technical success rates of TCAR from 90.6% to 100%, with low peri-operative stroke, MI, and mortality rates of 0 to 4%, 0 to 0.7% and 0 to 2.7%, respectively. TCAR was significantly associated with a lower in-hospital stroke/TIA rate when compared to trans-femoral carotid stenting. There was no significant difference in peri-operative stroke/MI/death when compared to endarterectomy although TCAR had a significantly lower risk of cranial nerve injury. The authors concluded that TCAR with flow reversal is a promising therapeutic option for carotid occlusive disease; clinical trials are currently underway to provide a better report on outcomes of TCAR and for further comparison between TCAR and CEA.

Schermerhorn and colleagues (2019) noted that several trials have observed higher rates of peri-operative stroke following trans-femoral carotid artery stenting compared with CEA; and TCAR with flow reversal was recently introduced for carotid stenting. This technique was developed to decrease stroke risk observed with the trans-femoral approach; however, its outcomes, compared with transfemoral carotid artery stenting, are not well characterized. These researchers compared outcomes associated with TCAR and trans-femoral carotid...
They carried out an exploratory propensity score-matched analysis of prospectively collected data from the Vascular Quality Initiative Transcarotid Artery Surveillance Project and Carotid Stent Registry of asymptomatic and symptomatic patients in the U.S. and Canada undergoing TCAR and trans-femoral carotid artery stenting for carotid artery stenosis, from September 2016 to April 2019. The final date for follow-up was May 29, 2019. Outcomes included a composite end-point of in-hospital stroke or death, stroke, death, MI, as well as ipsilateral stroke or death at 1 year. In-hospital stroke was defined as ipsilateral or contralateral, cortical or vertebra-basilar, and ischemic or hemorrhagic stroke. Death was all-cause mortality. During the study period, a total of 5,251 patients underwent TCAR and 6,640 patients underwent trans-femoral carotid artery stenting. After matching, 3,286 pairs of patients who underwent TCAR or trans-femoral carotid artery stenting were identified (trans-carotid approach: mean [SD] age, 71.7 [9.8] years; 35.7 % women; trans-femoral approach: mean [SD] age, 71.6 [9.3] years; 35.1 % women). TCAR was associated with a lower risk of in-hospital stroke or death (1.6 % versus 3.1 %; absolute difference, -1.52 % [95 % CI: -2.29 % to -0.75 %]; relative risk [RR], 0.51 [95 % CI: 0.37 to 0.72]; p < 0.001), stroke (1.3 % versus 2.4 %; absolute difference, -1.10 % [95 % CI: -1.79 % to -0.41 %]; RR, 0.54 [95 % CI: 0.38 to 0.79]; p = 0.01), and death (0.4 % versus 1.0 %; absolute difference, -0.55 % [95 % CI: -0.98 % to -0.11 %]; RR, 0.44 [95 % CI: 0.23 to 0.82]; p = 0.008). There was no statistically significant difference in the risk of peri-operative MI between the 2 cohorts (0.2 % for trans-carotid versus 0.3 % for the trans-femoral approach; absolute difference, -0.09 % [95 % CI: -0.37 % to 0.19 %]; RR, 0.70 [95 % CI: 0.27 to 1.84]; p = 0.47). At 1 year using Kaplan-Meier life-table estimation, the trans-carotid approach was associated with a lower risk of ipsilateral stroke or death (5.1 % versus 9.6 %; HR, 0.52 [95 % CI: 0.41 to 0.66]; p < 0.001). TCAR was associated with higher risk of access site complication resulting in interventional treatment (1.3 % versus 0.8 %; absolute difference, 0.52 % [95 % CI:
-0.01% to 1.04%]; RR, 1.63 [95% CI: 1.02 to 2.61]; p = 0.04), whereas trans-femoral carotid artery stenting was associated with more radiation (median fluoroscopy time, 5 mins [IQR, 3 to 7] versus 16 mins [IQR, 11 to 23]; p < 0.001) and more contrast (median contrast used, 30 ml [IQR, 20 to 45] versus 80 ml [IQR, 55 to 122]; p < 0.001). The authors concluded that among patients undergoing treatment for carotid stenosis, TCAR, compared with trans-femoral carotid artery stenting, was significantly associated with a lower risk of stroke or death.

The authors stated that this study had several drawbacks. First, therapeutic options were not randomized, but were selected by the treating physician, thereby, introducing the possibility of confounding by indication. Second, because of the study’s observational design, causal inferences could not be made. Third, because the end-point of stroke was determined clinically by peri-operative neurological symptoms and there was no requirement for formalized neurologic testing or imaging, this study was subject to ascertainment bias. Fourth, clinical registries are subject to selection bias since not all U.S. hospitals participate. Although not all patients undergoing carotid stenting nationally are captured in this study, based on industry reporting, 95.4% of all trans-carotid procedures utilizing flow reversal performed in the U.S. were recorded in this registry. Fifth, while this registry contains multiple pre-defined anatomic and medical variables specific to carotid disease, unmeasured confounding may still be present. Sixth, this study’s definition of TIA was based on focal neurological symptoms lasting less than 24 hours and did not reflect the current definition of TIA set forth by the American Heart Association and American Stroke Association. Seventh, there were no details captured to differentiate between ischemic versus hemorrhagic strokes nor guidance provided regarding classifying location of sub-cortical anterior circulation and occipital cortex strokes. Eighth, 1-year follow-up was not complete for all patients in the study. However, this was accounted for with Kaplan-Meier censoring,
and multiple randomized trials have demonstrated no statistically significant difference in stroke or death occurring beyond the peri-operative period between stenting and endarterectomy, so there was no reason to suspect that adverse events (AEs) past this study period would be different for trans-carotid versus trans-femoral stents.

Furthermore, an UpToDate review on "Carotid artery stenting and its complications" (Fairman, 2020) states that "Retrograde flow devices typically deploy occlusion balloons in the external carotid artery and common carotid artery, which results in cessation or reversal of flow in the internal carotid artery depending upon the specific device design. Following stent insertion, the proximal internal carotid artery is suctioned to remove debris prior to deflating the occlusion balloon. Balloon-type retrograde flow devices are typically passed antegrade via the femoral sheath that will be used to place the stent. Novel devices place a sheath directly into the ipsilateral common carotid artery to create a dynamic flow reversal circuit between it and the femoral sheath (trans-carotid artery revascularization)."

Pipeline Embolization Device for Posterior Circulation Aneurysms

Liang and colleagues (2019) noted that the use of the Pipeline embolization device (PED) for posterior circulation aneurysms is controversial. In a meta-analysis, these researchers examined the safety and efficacy of PED for these aneurysms; meta-regression was used to identify predictors for incomplete aneurysm occlusion and procedure-related complications. PubMed, Web of Science, and OVID databases were searched to identify all published references evaluating the treatment effect of PED for posterior circulation aneurysms. Only studies written in English that reported original data and included greater than 10 cases were considered for inclusion. Patient demographics, aneurysm characteristics, angiographic outcomes, and clinical outcomes were
extracted. A random-effects model was adopted to pool the obliteration rates and complication rates across selected studies. Finally, these investigators conducted meta-regression analysis to identify predictors of angiographic outcomes. A total of 12 studies including 358 patients with 365 aneurysms were included. The pooled complete aneurysm obliteration rate was 82% (95% CI: 73% to 90%), and pooled procedure-related complication rate was 18% (95% CI 14% to 22%). Increasing age predicted incomplete obliteration of aneurysms after PED treatment in these patients (p = 0.01). The authors concluded that PED is an alternative to treat intra-cranial aneurysms of the posterior circulation, achieving high complete occlusion rates, but it is less effective in elderly patients. The risk of procedure-related complications is not negligible. These researchers stated that further larger, long-term follow-up studies are needed before definitive conclusions can be drawn.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0075T</td>
<td>Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous; initial vessel</td>
</tr>
<tr>
<td>+ 0076T</td>
<td>each additional vessel (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>36100</td>
<td>Introduction of needle or intracatheter, carotid or vertebral artery</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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</tr>
<tr>
<td>37215</td>
<td>Transcatheter placement of intravascular stent(s), cervical carotid artery, open or percutaneous, including angioplasty, when performed, and radiological supervision and interpretation; with distal embolic protection</td>
</tr>
<tr>
<td>37216</td>
<td>without distal embolic protection</td>
</tr>
<tr>
<td>37217</td>
<td>Transcatheter placement of intravascular stent(s), intrathoracic common carotid artery or innominate artery by retrograde treatment, open ipsilateral cervical carotid artery exposure, including angioplasty, when performed, and radiological supervision and interpretation</td>
</tr>
<tr>
<td>37218</td>
<td>Transcatheter placement of intravascular stent(s), intrathoracic common carotid artery or innominate artery, open or percutaneous antegrade approach, including angioplasty, when performed, and radiological supervision and interpretation</td>
</tr>
<tr>
<td>37246 -</td>
<td>Transluminal balloon angioplasty (except lower extremity artery(ies) for occlusive disease, intracranial, coronary, pulmonary, or dialysis circuit), open or percutaneous, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty within the same artery</td>
</tr>
<tr>
<td>37247</td>
<td>37248 - Transluminal balloon angioplasty (except dialysis circuit), open or percutaneous, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty within the same vein</td>
</tr>
<tr>
<td>37249</td>
<td>37248 - Transluminal balloon angioplasty (except dialysis circuit), open or percutaneous, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty within the same vein</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>61630</td>
<td>Balloon angioplasty, intracranial (eg, atherosclerotic stenosis), percutaneous [not covered for prophylactic percutaneous transluminal angioplasty of intracranial arteries after aneurysmal subarachnoid hemorrhage] [dual diagnosis needed- subarachnoid hemorrhage and ischemia]</td>
</tr>
<tr>
<td>61635</td>
<td>Transcatheter placement of intravascular stent(s), intracranial (eg, atherosclerotic stenosis), including balloon angioplasty, if performed [not covered for prophylactic percutaneous transluminal angioplasty of intracranial arteries after aneurysmal subarachnoid hemorrhage] [dual diagnosis needed- subarachnoid hemorrhage and ischemia]</td>
</tr>
<tr>
<td>61640</td>
<td>Balloon dilatation of intracranial vasospasm, percutaneous; initial vessel [not covered for prophylactic percutaneous transluminal angioplasty of intracranial arteries after aneurysmal subarachnoid hemorrhage][dual diagnosis needed- subarachnoid hemorrhage and ischemia]</td>
</tr>
<tr>
<td>+61641</td>
<td>each additional vessel in same vascular family (List separately in addition to code for primary procedure) [not covered for prophylactic percutaneous transluminal angioplasty of intracranial arteries after aneurysmal subarachnoid hemorrhage][dual diagnosis needed- subarachnoid hemorrhage and ischemia]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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</tr>
<tr>
<td>+61642</td>
<td>each additional vessel in different vascular family (List separately in addition to code for primary procedure) [not covered for prophylactic percutaneous transluminal angioplasty of intracranial arteries after aneurysmal subarachnoid hemorrhage] [dual diagnosis needed- subarachnoid hemorrhage and ischemia]</td>
</tr>
</tbody>
</table>

**CPT codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>61711</td>
<td>Anastomosis, arterial, extracranial-intracranial (eg, middle cerebral/cortical) arteries</td>
</tr>
</tbody>
</table>

**Other HCPCS codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1725</td>
<td>Catheter, transluminal angioplasty, non-laser (may include guidance, infusion/perfusion capability)</td>
</tr>
<tr>
<td>C1726</td>
<td>Catheter, balloon dilation, non-vascular</td>
</tr>
<tr>
<td>C1727</td>
<td>Catheter, balloon tissue dissector, non-vascular (insertable)</td>
</tr>
<tr>
<td>C1874</td>
<td>Stent, coated/covered, with delivery system [not covered for drug-eluting stents]</td>
</tr>
<tr>
<td>C1875</td>
<td>Stent, coated/covered, without delivery system [not covered for drug-eluting stents]</td>
</tr>
<tr>
<td>C1876</td>
<td>Stent, non-coated/non-covered, with delivery system</td>
</tr>
<tr>
<td>C1877</td>
<td>Stent, non-coated/non-covered, without delivery system</td>
</tr>
<tr>
<td>C1884</td>
<td>Embolization protective system</td>
</tr>
<tr>
<td>C1885</td>
<td>Catheter, transluminal angioplasty, laser</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>C2617</td>
<td>Stent, non-coronary, temporary, without delivery system</td>
</tr>
<tr>
<td>C2625</td>
<td>Stent, non-coronary, temporary, with delivery system</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

- G45.0, G45.2, G45.8, G45.9: Transient cerebral ischemic attacks
- I63.031, I63.039: Occlusion and stenosis of carotid artery with or without mention of cerebral infarction
- I63.131, I63.139, I63.231, I63.239, I65.21, I65.29
- I63.011, I63.019: Occlusion and stenosis of vertebral artery with or without mention of cerebral infarction
- I63.111, I63.119, I63.211, I63.219, I65.01, I65.09
- I67.1: Cerebral aneurysm, nonruptured
- I67.5: Moyamoya disease
- I67.82: Cerebral ischemia [medically refractory symptomatic delayed cerebral ischemia (cerebral vasospasm)]
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I67.841 - I67.848</td>
<td>Cerebral vasospasm and vasoconstriction [medically refractory symptomatic delayed cerebral ischemia (cerebral vasospasm)]</td>
</tr>
<tr>
<td>Q28.0 - Q28.3</td>
<td>Arteriovenous malformation of precerebral vessels and cerebral vessels</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I66.01 - I66.9</td>
<td>Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

**Angioplasty/Stenting of Extra-Cranial Arteries**


23. Ederle J, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid


41. Menon D, Stafinski T. Cerebral protection devices for use during carotid artery angioplasty with stenting: A


Atherosclerotic Stenosis of Intra-Cranial Arteries


Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage


Angioplasty and Stenting of Extra-Cranial and Intra-Cranial Arteries


9. Macdonald RL, Pluta RM, Zhang JH. Cerebral vasospasm after subarachnoid hemorrhage: The
Angioplasty and Stenting of Extra-Cranial and Intra-Cranial Arteries - Medical Clinical... Page 81 of 85


17. Velat GJ, Kimball MM, Mocco JD, Hoh BL. Vasospasm after aneurysmal subarachnoid hemorrhage: Review


Extracranial-Intracranial Arterial Bypass Surgery


Moyamoya Surgery

2. Suwanwela NC. Moyamoya disease: Treatment and prognosis. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed August 2019.

Trans-Carotid Artery Revascularization (TCAR)


Amendment to
Aetna Clinical Policy Bulletin Number: 0276 Angioplasty and Stenting of Extra-Cranial and Intra-Cranial Arteries

There are no amendments for Medicaid.