



BlueCross BlueShield of Louisiana

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Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

Policy # 00198

Original Effective Date: 02/23/2006

Current Effective Date: 04/23/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider intracranial stent placement to be **eligible for coverage** as part of the endovascular treatment of intracranial aneurysms for patients when surgical treatment is not appropriate and standard endovascular techniques do not allow for complete isolation of the aneurysm, e.g., wide-neck aneurysm (4 mm or more) or sack-to-neck ratio less than 2:1.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers intracranial stent placement in the treatment of intracranial aneurysms, except as noted above, to be **investigational**.*

Based on review of available data, the Company considers intracranial percutaneous transluminal angioplasty with or without stenting in the treatment of atherosclerotic cerebrovascular disease to be **investigational**.*

Based on review of available data, the Company considers endovascular interventions (mechanical embolectomy, angioplasty, stenting) in the treatment of acute stroke to be **investigational**.*

Background/Overview

Intracranial arterial disease includes thromboembolic events, vascular stenoses, and aneurysms. Endovascular techniques have been investigated for treatment of intracranial arterial disease, as an alternative to intravenous tissue plasminogen activator (tPA) and supportive care for acute stenosis and as an alternative to risk factor modification for chronic stenosis. For cerebral aneurysms, stent-assisted coiling has been evaluated as an alternative to endovascular coiling in patients whose anatomy is not amenable to simple coiling.

Cerebrovascular diseases include a range of processes affecting the cerebral vascular system, including arterial thromboembolism, arterial stenosis, and arterial aneurysms, all of which can lead to restrictions in cerebral blood flow due to ischemia or hemorrhage. Endovascular techniques, including endovascular pharmacologic thrombolysis, endovascular mechanical embolectomy; using one of several types of devices,



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endovascular deployment of several types of stents, and angioplasty with or without stenting, have been investigated for treatment of cerebrovascular diseases.

Acute Stroke

Acute stroke is the third leading cause of death in the U.S., Canada, Europe and Japan and is the leading cause of adult disability in the U.S. The acute brain injury of stroke has 2 major types: ischemic and hemorrhagic. Of patients with stroke presenting to the emergency department, approximately 80% will be diagnosed with ischemic brain injury. Distinguishing between these types of stroke is important because the established treatments for each are significantly different. The focus of treatment in ischemic stroke is reperfusion of hypoxic brain tissue, while the focus in hemorrhagic stroke is correction of the condition which led to bleeding. If the underlying cause of ischemia is systemic hypotension, this must be corrected. Far more commonly, however, a clot occluding an intracranial vessel is the cause of ischemic stroke. Recanalization of the vessel, particularly in the first few hours after occlusion, has been shown to reduce rates of disability and death.

While spontaneous thrombolysis does occur, treatment of ischemic stroke has focused on the use of intravenous tPA to promote dissolution of the clot and subsequent restoration of blood flow to the ischemic area of the brain. The use of intravenous tPA within 3 hours of stroke onset for selected patients is the standard of care for ischemic stroke treatment. Despite its benefits, widespread implementation of intravenous tPA is challenging. Reperfusion benefits decrease over time; infarcted brain tissue will not recover. In most states, fewer than 10% of ischemic stroke patients arrive in the hospital in time for intravenous tPA within the 3-hour window for its use. Because tPA is associated with an increased risk of intracranial bleeding, it is contraindicated in hemorrhagic stroke and in some ischemic stroke patients in which the risk of bleeding outweighs potential benefit, such as those with mild or resolving symptoms, hypocoagulable state, or advanced age.

There are several ways in which endovascular interventions may be used as a treatment for acute stroke. For patients who present with acute stroke within the time window for thrombolysis and meet other clinical criteria for intravenous tPA, endovascular interventions may be used in combination with thrombolysis. For patients who are not candidates for thrombolysis (eg, who present past the time window for thrombolysis), endovascular interventions can be considered as an alternative to standard conservative medical therapy.

Intravenous tPA has improved outcomes for many, but not all, ischemic stroke patients. Researchers have studied intra-arterial tPA, transcranial ultrasound energy, and mechanical clot destruction or clot removal as an alternative, or second line, to the established intravenous tPA therapy. Clots can be defined as located in large or small vessels. Large intracranial arteries include the internal carotid, Circle of Willis and the first 2 branches of the anterior (A1 and A2), middle (M1 and M2), and posterior (P1 and P2) cerebral arteries. These can be accessed with a catheter; further branches of the cerebral circulation are defined as small vessels and are too tortuous to be mechanically accessed with available technology.

Several types of endovascular treatments for ischemic strokes have been considered:

1. Intra-arterial fibrinolytic therapy (ie, intra-arterial tPA). Although tPA only has approval from the U.S. Food and Drug Association (FDA) for its intravenous route of delivery, intra-arterial tPA has been



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considered for patients who fail to present within the window of treatment for intravenous tPA or who have failed to show benefit from intravenous tPA. It is also frequently used in conjunction with other endovascular devices.

2. Acute angioplasty and/or stent deployment. Balloon angioplasty and balloon-expandable stents have been investigated for acute stroke. Given concern for higher risks of complications in the cerebral vasculature with the use of balloon-expandable stents, self-expanding stents have gained more attention. At present, no balloon- or self-expandable stent has FDA approval for treatment of acute stroke.
3. Endovascular mechanical embolectomy. Endovascular embolectomy devices remove or disrupt clots by a number of mechanisms. Four devices are considered here (see "Regulatory Status"), the Merci[®] Retriever, Penumbra System[®], Solitaire[™] Flow Restoration Device and the Trevo[®] Retriever. With the Merci device, a microcatheter is passed through the thrombus from a larger, percutaneous catheter positioned proximal to the occlusion. A helical snare is deployed, and the catheter and clot are withdrawn together. With the Penumbra device, an opening at the tip of the percutaneous catheter utilizes suction to extract the clot. Both the Solitaire Flow Restoration Device and the Trevo Retriever are retrievable stents, which are positioned to integrate the clot with the stent for removal with the stent's struts.

This policy focuses on the four devices with an indication for endovascular embolectomy for acute stroke.

Intracranial Atherosclerotic Disease

It is estimated that intracranial atherosclerosis causes about 8% of all ischemic strokes. Intracranial stenosis may contribute to stroke in 2 ways: either due to embolism or low flow ischemia in the absence of collateral circulation. Recurrent annual stroke rates are estimated at 4% to 12% per year with atherosclerosis of the intracranial anterior circulation and 2.5% to 15% per year with lesions of the posterior (vertebrobasilar) circulation. Medical treatment typically includes either anticoagulant therapy (ie, warfarin) or antiplatelet therapy (eg, aspirin). The "Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial was a randomized trial that compared the incidence of stroke brain hemorrhage or death among patients randomized to receive either aspirin or warfarin. The trial found that over a mean 1.8 years of follow-up, warfarin provided no benefit over aspirin and was associated with a significantly higher rate of complications. In addition, if symptoms could be attributed to low flow ischemia, agents to increase mean arterial blood pressure and avoidance of orthostatic hypotension may be recommended. However, medical therapy has been considered less than optimal. For example, in patients with persistent symptoms despite antithrombotic therapy, the subsequent rate of stroke or death has been extremely high, estimated in 1 study at 45%, with recurrent events occurring within 1 month of the initial recurrence. Surgical approaches have met with limited success. The widely quoted extracranial-intracranial (EC/IC) bypass study randomized 1377 patients with symptomatic atherosclerosis of the internal carotid or middle cerebral arteries to medical care or EC/IC bypass. The outcomes in the 2 groups were similar, suggesting that the EC/IC bypass is ineffective in preventing cerebral ischemia. Due to inaccessibility, surgical options for the posterior circulation are even more limited.

Percutaneous transluminal angioplasty (PTA) has been approached cautiously for use in the intracranial circulation, due to technical difficulties in catheter and stent design and the risk of embolism, which may



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result in devastating complications if occurring in the posterior fossa or brain stem. However, improvement in the ability to track catheterization, allowing catheterization of tortuous vessels, and the increased use of stents have created ongoing interest in exploring PTA as a minimally invasive treatment of this difficult-to-treat population. The majority of published studies of intracranial PTA has focused on the vertebrobasilar circulation. Two endovascular devices have FDA approval for treatment of symptomatic intracranial stenosis and are considered here (see "Regulatory Status").

Cerebral Aneurysms

Compared with acute ischemic stroke, cerebral aneurysms have a much lower incidence among the U.S. population, with prevalence between 0.5% and 6% of the population. However, they are associated with significant morbidity and mortality due to subarachnoid hemorrhage resulting from aneurysm rupture. Surgical clipping of intracranial aneurysms has been used since the 1960s, but the feasibility of clipping for aneurysms depends on the aneurysm location. Intracranial stents are also being used in the treatment of cerebral aneurysms. Stent-assisted coiling began as an approach to treat fusiform or wide-neck aneurysms in which other surgical or endovascular treatment strategies may not be feasible. As experience grew, stenting was also used in smaller berry aneurysms as an approach to decrease the rate of retreatment needed in patients who receive coiling. A randomized trial has demonstrated that treatment of ruptured intracranial aneurysms with coiling leads to improved short-term outcome compared with surgical clipping; however, patients who receive coiling need more repeat/follow-up procedures. In 2011, the Pipeline[®] Embolization Device, which falls into a new device category called "intracranial aneurysm flow diverters," or flow-diverting stent, received FDA premarket approval for endovascular treatment of large or giant wide-necked intracranial aneurysms in the internal carotid artery. The Pipeline device is a braided, wire mesh device that is placed within the parent artery of an aneurysm to redirect blood flow away from the aneurysm with the goal of preventing aneurysm rupture and possibly decreasing aneurysm size.

FDA or Other Governmental Regulatory Approval

U.S. FDA

Several devices for endovascular treatment of intracranial arterial disease have received clearance by FDA through either the 510(k) process or through the humanitarian device exemption (HDE) process. By indication, approved devices are as follows:

Acute Stroke

1. The Merci Retriever (Concentric Medical, Mountain View, CA). In August 2004, the Merci Retriever (Concentric Medical, Mountain View, CA) was cleared by FDA through the 510(k) process. This device was judged equivalent to a predicate device, the Concentric Retriever, which was indicated for endovascular foreign body removal. The FDA clearance indicated that the Mechanical Embolus Removal in Cerebral Ischemia (MERCi) Clinical Study established that no new issues of safety and effectiveness exist when the Merci Retriever is used for thrombus removal versus foreign body removal from the neurovasculature. A modified Merci Retriever, also manufactured by Concentric Medical Inc., received 510(k) clearance from FDA in May 2006. The clearance notes that the Modified Merci Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke. Patients who are ineligible for intravenous tPA or who fail intravenous tPA therapy are candidates for treatment. The device also has clearance for retrieval of



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- foreign bodies misplaced during interventional radiologic procedures in the neuro, peripheral, and coronary vasculature.
2. The Penumbra System (Penumbra Inc., Alameda, CA). In December 2007, the Penumbra System (Penumbra Inc., Alameda, CA) was cleared through the 510(k) process. FDA determined that this device was substantially equivalent to existing devices for use in the revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease (in the internal carotid, middle cerebral - M1 and M2 segments, basilar, and vertebral arteries) within 8 hours of symptom onset.
 3. The Solitaire FR device (Covidien/ ev3 Neurovascular, Irvine, CA). In March 2012, the Solitaire FR device was cleared for marketing by FDA through the 510(k) process. FDA determined that this device was substantially equivalent to the Merci Retriever device, based on a randomized controlled trial (RCT) of 113 patients submitted to FDA comparing the Merci and Solitaire devices. Indications for the device are patients with ischemic stroke due to large intracranial vessel occlusion who are ineligible for intravenous tPA, or who fail intravenous tPA.
 4. The Trevo Pro Retriever device (Stryker Neurovascular, Kalamazoo, MI). In August 2012, the Trevo Pro Retriever device (Stryker Neurovascular, Kalamazoo, MI) was cleared for marketing by FDA through the 510(k) process. FDA determined that this device was substantially equivalent to the Merci Retriever device, based on an RCT of 178 patients from 27 centers in the U.S. and Europe that compared the Trevo device with the Merci device. Indications for the device are patients with acute ischemic stroke due to large intracranial vessel occlusion who are ineligible for or fail intravenous tPA.

Intracranial Stenosis

Currently 2 devices have received approval for atherosclerotic disease from FDA through HDE process. This form of FDA approval is available for devices used to treat conditions with an incidence of 4,000 or less per year; FDA only requires data showing "probable safety and effectiveness." Devices with their labeled indications are as follows:

1. Neurolink System[®] (Guidant, Santa Clara, CA). "The Neurolink system is indicated for the treatment of patients with recurrent intracranial stroke attributable to atherosclerotic disease refractory to medical therapy in intracranial vessels ranging from 2.5 to 4.5 mm in diameter with $\geq 50\%$ stenosis and that are accessible to the stent system."
2. Wingspan[™] Stent System (Boston Scientific, Fremont, CA). "The Wingspan Stent System with Gateway PTA Balloon Catheter is indicated for use in improving cerebral artery lumen diameter in patients with intracranial atherosclerotic disease, refractory to medical therapy, in intracranial vessels with $\geq 50\%$ stenosis that are accessible to the system."

Intracranial Aneurysms

In 2011, FDA granted premarket approval to the Pipeline Embolization Device (Covidien/ eV3 Neurovascular, Irvine, CA), an intracranial aneurysm flow diverter, for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments (P100018). Approval was based on the Pipeline for Uncoilable or Failed Aneurysms Study, a single-arm, open-label feasibility study that included 108 patients aged 30 to 75 years with unruptured large and giant wide-necked aneurysms.



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Two stents have received FDA approval through the HDE program for treatment of intracranial aneurysms:

1. Neuroform™⁺ Microdelivery Stent System (Stryker, Kalamazoo, MI). In 2002, based on a series of approximately 30 patients with 6-month follow-up, the Neuroform Microdelivery Stent System was approved (HDE) for use with embolic coils for treatment of wide-neck intracranial aneurysms that cannot be treated by surgical clipping (H020002).
2. Enterprise™⁺ Vascular Reconstruction Device and Delivery System (Cordis Neurovascular Inc., Miami Lakes, FL) In 2007, based on a series of approximately 30 patients with 6-month follow-up, the Enterprise Vascular Reconstruction Device and Delivery was approved (HDE) for use with embolic coils for treatment of wide-neck, intracranial, saccular or fusiform aneurysms (H060001).

Centers for Medicare and Medicaid Services (CMS)

A Medicare national coverage determination (NCD) on intracranial angioplasty and stenting was released by the CMS in January 2007. This decision was based on a review of available studies at that time, which consisted of several uncontrolled case series. CMS review indicated that this evidence was promising and that, while further well-designed RCTs were needed to confirm whether outcomes were improved, coverage should be allowed. The NCD contained the following coverage determinations:

1. "Medicare coverage for angioplasty and or stenting for symptomatic patients with greater than 70 percent intracranial arterial stenosis; and
2. Medicare coverage for intracranial angioplasty and stenting for other patients within the context of Category B investigational device exemption (IDE) trials under coverage with evidence development (CED) within a registry.

Rationale/Source

Endovascular interventions for acute ischemic stroke

Until recent publications of RCTs, the available literature related to the use of endovascular interventions for acute ischemic stroke primarily consisted of a large number of small, single-arm studies reporting outcomes following endovascular interventions. Some of these studies have included comparison groups, consisting either of historic controls or nonconcurrent controls of patients treated with an alternative strategy. Systematic reviews of single-arm studies have also been published. The evidence review will focus on the RCTs and comparative studies, with less emphasis on single-arm studies without a comparison group. Following is a summary of the key literature to date.

Randomized controlled trials. From 2012-2013, results from 3 large randomized trials of endovascular therapies for acute ischemic stroke were published.

Kidwell et al reported on the MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy) trial in 2013. MR RESCUE was an open-label, blinded-outcome RCT of 118 patients from 22 North American sites. All patients had large vessel, anterior circulation ischemic strokes and were stratified by penumbral pattern, as determined by pretreatment computed tomography or magnetic resonance imaging of the brain. Patients were randomly assigned to standard stroke treatment (n=54) or mechanical embolectomy (n=64) using the Merci Retriever or Penumbra System within 8 hours after presentation of symptoms. Eight patients in the embolectomy group also tPA. The primary hypothesis of the study was that patients with favorable penumbral patterns (at-risk area of viable ischemic cerebral tissue of 70% or less



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and a small, 90 mL or less, area of predicted core infarct) would benefit more from mechanical embolectomy than patients with nonpenumbra patterns (large infarct area and small or absent penumbra [viable ischemic cerebral tissue]), as determined by the 90-day Modified Rankin Scale, ranging from a score of 0 (no symptoms) to 6 (dead). In the embolectomy group, 67% achieved revascularization, but this was not superior to standard care. Mean Modified Rankin Scale scores were the same (3.9) in both groups and pretreatment imaging patterns did not show any relationship to treatment outcomes in any group. Overall mortality (21% at 90 days) and symptomatic intracranial hemorrhage (4%) did not differ across groups.

In 2013, Ciccone et al reported on the SYNTHESIS Expansion trial of 362 patients randomized within 4.5 hours of the onset of various types of acute ischemic strokes to receive endovascular therapy (n=181) or intravenous (IV) tPA (n=181). Endovascular therapy consisted of intra-arterial tPA, mechanical embolectomy (using the Solitaire, Penumbra, Trevo or Merci device) or a combination of these treatments. Among the patients randomized to endovascular therapy, endovascular treatment was actually completed in 163 patients. In 109 patients, regional intra-arterial infusion of tPA and fragmentation of the thrombus with a microguidewire were used. In 56 patients, a device was added; the most widely used devices were Solitaire FR in 18 patients, Penumbra in 9 patients, Trevo in 5 patients, and Merci in 5 patients. No significant differences in 90-day survival without disability (Modified Rankin Scale score, 0-1) occurred between the endovascular therapy group and tPA group (30.4% vs 34.8%, respectively, 0.71; 95% confidence interval [CI], 0.44 to 1.14; p=0.16). Within 7 days, fatal or nonfatal symptomatic intracranial hemorrhage occurred in each group at a rate of 6%. Rates of other serious adverse events were also not significantly different between groups. While there were different treatment approaches in the endovascular group, these results suggest endovascular therapy is not superior to tPA.

Also in 2013, Broderick et al reported the results of the IMS III trial, an open-label RCT with a planned enrollment of 900 patients. This trial enrolled patients with acute ischemic stroke who presented within 3 hours of symptom onset and had a moderate to severe neurologic deficit on presentation. Patients were randomized to IV tPA alone or IV tPA plus endovascular intervention. Patients randomized to the endovascular group underwent immediate angiography followed by endovascular intervention if a treatable vascular occlusion was present. Endovascular intervention consisted of either endovascular delivery of tPA at the site of occlusion or mechanical thrombectomy, at the discretion of the treating physician. Potential endovascular interventions included thrombectomy (using the Merci retriever, Penumbra System, or Solitaire FR revascularization device) or endovascular delivery of tPA (using the Micro-Sonic SV infusion system (EKOS) or a standard microcatheter). The primary outcome was a modified Rankin score of 2 or less at 90 days. The trial was stopped prematurely due to futility after enrollment of 656 patients. At this point, the primary outcome had been reached by 40.8% of patients in the endovascular group compared with 38.7% of patients in the IV tPA group. The adjusted difference in the primary outcome was 1.5%, with a 95% CI for the difference of -6.1 to 9.1. Subarachnoid hemorrhage was more frequent in the endovascular group compared with the tPA group (11.5% vs 5.8%, respectively; p=0.02), as was asymptomatic intracerebral hemorrhage (27.4% vs 18.9%, p=0.01). There were no significant differences between groups in other adverse events, including death and symptomatic intracerebral hemorrhage.

Strengths of these 3 trials evaluating endovascular treatments for acute stroke include their randomized design and multisite recruitment. A potential strength was that, in general, the endovascular intervention



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was left to the discretion of the treating physician, which could allow for greater generalizability; on the other hand, the variability in specific endovascular treatments used may make it difficult to draw conclusions about the efficacy of mechanical embolectomy. In the IMS III and SYNTHESIS Expansion trials, sizable proportions of the endovascular therapy groups did not receive an endovascular device: in IMS III, 138/334 of those who received endovascular therapy received intra-arterial tPA only; in SYNTEHSIS Expansion 109/165 of those who received endovascular therapy received intra-arterial tPA with clot fragmentation with a guidewire but without device deployment. In addition, the 3 trials all had relatively low utilization of the newer generation retrievable stents (Solitaire FR and Trevo devices), which may be relevant as several studies have demonstrated superiority of the newer generation retrievable stents compared with older neuroendovascular devices. For the IMS III trial, there was a longer time to endovascular procedure than in early trials of endovascular interventions; given evidence that longer time to reperfusion is associated with poorer outcomes, the delay in revascularization in the endovascular group may have contributed to worse clinical outcomes in that group.

In 2012, 2 noninferiority RCTs comparing newer devices with the Merci Retriever were completed as part of the U.S. FDA application for approval of the Solitaire device and the Trevo device. Both studies reported device superiority over the Merci device. In the SWIFT (Solitaire FR with the Intention for Thrombectomy) study, recanalization rates with Solitaire were compared with the Merci Retrieval System in a randomized, prospective noninferiority trial of 113 patients with moderate or severe large vessel occlusion strokes. Treatment was initiated within 8 hours of symptom onset in patients who had unsuccessful IV tPA or were ineligible for IV tPA. This trial was halted early after an interim analysis found revascularization without symptomatic intracranial hemorrhage occurred in 61% of Solitaire patients compared with 24% of Merci patients. Mortality rates at 90 days were 17% with Solitaire versus 38% with Merci ($p=0.001$). A follow up analysis of complications of endovascular procedures using the SWIFT study data was published in 2013. This analysis included 144 patients with acute ischemic stroke (31 patients treated with the Solitaire FR device during the SWIFT trial roll-in period and 113 patients randomly assigned to the Solitaire FR or Merci device). Major periprocedural complications, including symptomatic intracranial hemorrhage, air emboli, vessel dissection, major groin complications, and emboli to new vascular territories, were seen in 18/144 (12.5%) of all patients. Complication rates were similar for patients receiving the Solitaire FR and Merci devices, with the exception of symptomatic cerebral hemorrhage, which was significantly less common in the Solitaire FR group (10.9% vs 1.1%, $p=0.013$).

In the TREVO 2 (Thrombectomy Revascularization of large Vessel Occlusions) Study, 178 patients were randomized to receive mechanical embolectomy with either the Trevo Retriever or the Merci Retriever for large vessel occlusion strokes. Revascularization rates were 86% in the Trevo group versus 60% in the MERCI group ($p<0.001$). Procedure-related adverse events occurred in 15% of the Trevo group and 23% in the Merci group; $p=0.183$). Mortality rates at 90 days were 33% versus 24% ($p=0.18$), respectively.

To follow up on the SWIFT and TREVO 2 trials, Molina et al published the protocol for an industry-sponsored, prospective, multicenter, randomized trial of the Solitaire FR device compared with standard medical therapy for patients with acute ischemic stroke presenting within 8 hours of symptom onset (REVASCAT). Planned enrollment is 690 patients.



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Systematic reviews. In 2013, Singh et al published results from a systematic review and meta-analysis of RCTs evaluating the use of endovascular therapy for patients with acute ischemic stroke. The authors included 5 randomized trials that enrolled 1197 patients with acute ischemic stroke. The 5 trials included the IMS III, SYNTHESIS Expansion, and MR RESCUE trials that are described above. Additional trials included a pilot trial including 54 patients for the SYNTHESIS Expansion trial, reported by Ciccone et al in 2010, and a small feasibility study including 7 patients to compare intra-arterial tPA to standard IV tPA, reported by Sen et al in 2009. The systematic review found that there were no significant improvements in any of the outcomes evaluated in patients who received endovascular therapies compared with those receiving IV thrombolysis. Endovascular therapies appeared to have benefit in patients with severe stroke, although the authors note that this effect needs to be evaluated in randomized trials.

Several systematic reviews were published before RCT results were available. Mokin et al published a systematic review in 2012 that evaluated clinical outcomes from endovascular therapy compared with thrombolysis. The authors selected studies that used either thrombolysis or endovascular therapy for patients with acute ischemic stroke due to internal carotid artery occlusion. Included studies reported on functional outcomes past 30 days, mortality rates beyond 30 days, and rates of symptomatic intracerebral hemorrhage. A total of 28 studies were reviewed, including 385 patients treated with thrombolysis and 584 patients treated with endovascular therapy. There were no differences in mortality between the thrombolysis and endovascular groups (27.3% vs 32.0% respectively, $p=0.12$). A favorable clinical outcome, defined as a Rankin Scale of greater than 2 or a Barthel Index of 90 to 100, was attained by a greater percentage of patients in the endovascular group compared with the thrombolysis group (33.6% vs 24.9%, $p=0.004$). Symptomatic intracranial hemorrhage was also more common in the endovascular group compared with thrombolysis (11.1% vs 4.9%, $p=0.001$).

Almekhlafi et al published a systematic review of observational studies of endovascular treatment in 2012. The authors identified 16 eligible studies and classified them according the type of device used. There were 4 studies ($n=357$) that used the Merci device, 8 studies ($n=455$) that used the Penumbra System, and 4 studies ($n=113$) that used a retrievable stent. Mean procedural time was 120 minutes for the Merci device, compared with 65 and 55 minutes for the Penumbra and retrievable stents. The successful recanalization rate was 59.1% for the Merci group, 86.6% for the Penumbra system, and 92.9% for the retrievable stent group.

Baker et al published a systematic review of neurothrombectomy devices for the treatment of acute ischemic stroke in 2011. This review included any human studies that reported on outcomes following thrombectomy. A total of 87 articles met the inclusion criteria: 62 case series or case reports, 18 prospective single-arm studies, and 7 retrospective single-arm studies. The rate of successful recanalization, defined as Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 or 3, ranged from 43% to 100% across all studies. Higher rates of recanalization were reported with the Penumbra System (83%-100%) compared with either the Merci Retriever (43%-78%) or other devices (50%-90%). Clinical effectiveness was determined by a posttreatment Rankin score of 0 to 2, a measure that was available in 17 of 25 studies. There was a wide range of clinical effectiveness, from 15% to 60% of treated patients. The rate of symptomatic intracranial hemorrhage ranged from 0% to 25%, and the rate of asymptomatic intracranial hemorrhage ranged from 1% to 43%.



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In 2008, Stead et al conducted a systematic review and meta-analysis of percutaneous clot removal devices. The authors identified 14 case series and 8 case reports with a total of 147 patients. The Merci Retriever was utilized for 17 patients; a variety of mechanical embolectomy devices (with coronary or peripheral vascular indications) were used in other studies. Patients were similar in that they were diagnosed with large vessel disease but were otherwise heterogeneous. Emboli were accessible in 85% of patients. In all studies, postprocedural blood flow was measured using the TIMI grade. A flow rate representing full recanalization was achieved in 67 of 146 patients (45.6%). Partial or full recanalization was achieved in 101 of 146 patients (68.7%). When embolectomy methods were compared, superiority of 1 device over others was not demonstrated in accessing the lesion, retrieving the clot, or in clinical outcome. Pooled data were compared with the placebo arm and intra-arterial thrombolysis arm of the PROACT II (Prolyse in Acute Cerebral Thromboembolism II) study, comparing IV and intra-arterial (tPA use. Partial or full recanalization rate in the placebo group was 18%; the rate was 66% in the intra-arterial group. However, the authors acknowledge that 81 patients (55.1%) in the meta-analysis also received thrombolytics, and the comparative role of thrombolytics against mechanical thrombectomy is unknown. The authors concluded that there was a modest survival benefit in the mechanical thrombectomy patients compared with historical controls, while recognizing the limitation of small study sizes and nonrandomized comparator groups.

Nonrandomized comparative studies. A number of nonrandomized comparative studies have been published that compare endovascular interventions with historic controls or control patients from their same institution who received standard stroke care and are briefly described here. One of the larger nonrandomized, comparative studies was by Rai et al, which included 223 patients with acute strokes involving the internal carotid artery, the middle cerebral artery, or the bifurcation of the middle cerebral artery. A total of 100 patients were treated with IV thrombolysis, and 123 patients were treated with an endovascular intervention. The primary outcome measure was a good clinical outcome at 3 months, defined as a Modified Rankin Scale score of 2 or less. A good clinical outcome was achieved by 44.7% in the endovascular group and 26% in the IV thrombolysis group (odds ratio for good outcome, 2.3; 95% CI, 1.3 to 4.1; $p=0.003$).

Alexandrov et al treated 125 patients presenting with acute stroke with the Penumbra System. Outcomes of embolectomy were compared with historic controls who were treated with IV tPA in a previous clinical trial. Embolectomy patients had a similar stroke severity score but were younger and had a longer time from onset of treatment to symptoms. The rate of recanalization was 82% for the embolectomy patients, higher than the 40% recanalization rate reported with tPA. However, mortality at 3 months was higher in the embolectomy group compared with tPA (32.8% vs 14.1%, respectively; $p=0.008$), and the rate of favorable functional outcome was lower (25% vs 39%, respectively; $p=0.046$).

Taschner et al treated 22 consecutive patients with acute ischemic stroke and a National Institutes of Health Stroke Scale (NIHSS) score of at least 7 with the Penumbra System. Outcomes from this group of patients were compared with patients treated with tPA who were matched for stroke score and location. Recanalization with embolectomy was successful in 25 of 32 target vessels (78%) compared with 17/32 (53%) with tPA. A favorable outcome, defined as a stroke score of 0 to 1 or an improvement of at least 10 points, was present in 2 of 20 (10%) of patients treated with embolectomy, compared with 7/20 (35%) treated with tPA.



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In 2005, Smith et al reported the results of the MERCI trial. This was a multicenter (25 centers), prospective nonrandomized trial of this device for patients with symptoms of acute stroke for less than 8 hours who were not candidates for thrombolytic therapy, either because of contraindications (approximately 25%) or because symptoms were present for more than 3 hours. A total of 1809 patients were screened to identify the 151 patients enrolled in the trial. Chief reasons for exclusion were NIHSS too low or improving, intracranial hemorrhage, or inability to obtain consent. Of the 151 patients, 141 had the device deployed. Recanalization was achieved in 46% (69/151) of patients on an intention-to-treat analysis and in 48% (68/141) of patients in whom the device was employed. (One patient had “spontaneous” recanalization.) Clinically significant procedural complications occurred in 10 patients (7.1%), and symptomatic intracranial hemorrhages were observed in 11 (7.8%). Good neurologic outcomes were more frequent at 90 days in those with successful recanalization compared with those with unsuccessful recanalization (46% vs 10%, respectively; $p < 0.001$), and mortality was less (32% vs 54%, respectively; $p = 0.01$). The MERCI investigators compared their patients with the placebo arm of the PROACT II study to determine safety and efficacy of mechanical embolectomy.

In 2008, Smith et al reported the results of the Multi MERCI trial, a prospective, international, multicenter, single-arm study. As with the MERCI trial, patients were eligible if they presented with 8 hours of onset of symptoms from large-vessel stroke. In addition to the MERCI indications, patients were eligible if they received IV tPA but failed to completely recanalize their occluded vessel. A total of 1088 patients were screened to enroll 177 patients. Of these, 164 patients had the device deployed. A newer generation device was available for 131 of the 164 patients, and patients could be treated with adjuvant intra-arterial tPA, depending on the operator. Recanalization was achieved in 55% (90/164) on intention-to-treat analysis and in 58% (88/151) in the per-protocol analysis. Two patients recanalized spontaneously. Procedural complications occurred in 9 patients (5.5%), and symptomatic intracranial hemorrhage was observed in 16 (9.8%). In comparison with patients who did not recanalize, 90-day neurologic outcomes favored patients in whom flow was restored (49% vs 10%, respectively; $p = 0.001$). An average of 3 attempts was made on each patient. This report also compares their results with the placebo arm of the PROACT II trial. The validity of the MERCI and multi MERCI trials have been questioned, particularly related to their use of patients from the PROACT II study as historical controls, because the inclusion criteria for the MERCI trial for location of occlusion differed from those used in PROACT II. In addition, questions have been raised about MERCI's use of recanalization as an outcome measure, rather than a clinical outcome, and about the reliability of the TIMI perfusion score reported in MERCI.

Nonrandomized, comparative studies evaluating specific endovascular intervention. Some nonrandomized comparative studies have compared the outcomes of different types of endovascular interventions. For example, Broussalis et al compared the Merci device with newer retrievable stents (Trevo and Solitaire devices) in 122 patients treated with endovascular interventions and reported that recanalization rates were higher with the newer devices (82% vs 62%, $p = 0.016$). Mendonca et al compared the Trevo versus Solitaire devices in a prospective, nonrandomized comparison of 33 patients with anterior cerebral circulation occlusions. No significant differences between devices were found in rates of revascularization, symptomatic intracranial hemorrhage, improvements in Modified Rankin Scale, and mortality. In a similar but smaller study, Fesl et al compared 14 patients treated with a newer retrievable stent compared with 16 patients treated with an older device. Recanalization rates were higher in the retrievable stent group (93%

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vs 56%, $p < 0.05$). These studies offer some information on the comparative efficacy of different devices, which is important in the interpretation and comparison of studies that may use different or multiple devices in endovascular treatments of acute stroke.

Nonrandomized, comparative studies of endovascular intervention in basilar artery occlusion. Posterior circulation strokes account for about 20% of all acute ischemic strokes; occlusion of the basilar artery is implicated in about 8% of posterior strokes. Despite its relative rarity, basilar artery occlusion has received particular attention for reperfusion therapies because its natural history has a dismal course, with a high likelihood of severe disability or death. In 1 registry study, for example, investigators found severe outcomes (Modified Rankin Scale score of 4 or 5, or death) in 68% of patients with basilar artery occlusion. We identified 1 nonrandomized, comparative study that evaluated endovascular interventions for basilar artery occlusion. In 2013, Broussalis et al reported results from a prospective registry study of 99 patients with posterior circulation stroke caused by basilar artery occlusion from 2005-2012. Patients who received endovascular therapies (including endovascular mechanical recanalization and/or intra-arterial with optional IV thrombolytic therapy) were compared with those who received standard medical therapy (IV thrombolytic therapy and/or medical antithrombotic treatment.) Seventy-eight percent of the patients received endovascular intervention, with thrombectomy alone in 67 patients. Devices used included the Merci system in 43%, the Solitaire FR device in 13%, and the Trevo retriever in 18%, with devices not available in the U.S. in the remaining 25%. Endovascular patients were more likely to achieve a TIC1 3 score (full perfusion with filling of all distal branches) (36% vs 9%, $p = 0.017$); after 90 days, more than 61% of patients who received endovascular therapy achieved a Modified Rankin Scale score of 3, compared with 8% in the standard medical therapy group.

Single-arm studies evaluating specific endovascular interventions. A number of studies have reported results from various endovascular interventions for acute stroke. Many of the studies predated the IMS III, SYNTHESIS Expansion, and MR RESCUE RCTs outlined earlier. Representative studies include Flint et al (2007), which reported outcomes from 80 patients treated with the Merci device for occlusion of the intracranial internal carotid artery; Lin et al (2009), which reported outcomes from 75 patients with internal carotid artery terminus occlusions who received endovascular interventions with either intra-arterial thrombolytics or mechanical embolectomy with the Merci device. Multiple small, single-center case series and other smaller case series that often include only intermediate outcomes such as vessel recanalization evaluating endovascular treatments for acute stroke exist in the literature.

In 2013, multiple noncomparative studies reporting outcomes from endovascular therapies with the newer generation stent-retriever devices (Solitaire FR and Trevo) were published. The studies are summarized in Table 1. While these studies do not directly provide evidence about the benefit of endovascular interventions compared with standard care for acute stroke, they do suggest significant variability in clinical outcomes at 3 months in patients treated with stent-retriever devices, with rates of good clinical outcomes ranging from 39% to 77%.

Table 1. Noncomparative Studies of Stent-Retrievers

Study	Study Type	Patient	Intervention	Primary Outcome
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		Population		
Broussalis et al (2013)	Retrospective case series	50 patients with large cerebral artery stroke at a single institution	Trevo device, with or without intra-arterial tPA for applicable patients and/or stent; IV tPA given for patients presenting <4.5 h from onset (66% of patients)	52% of patients achieved TICI score 3; 30% TICI score 2b; and 12% TICI score 2ab 3-mo Modified Rankin Scale score 0-2 in 61% of patients
Cheang et al (2013)	Retrospective case series	60 patients with acute ischemic stroke (anterior and posterior circulation) at a single institution	Solitaire FR, with or without angioplasty, stenting, and/or Penumbra in addition to the Solitaire; not specified if IV tPA given	73.3% of patients achieved successful recanalization (TICI score \geq 2b) Good clinical outcomes at 3 mo were more common in patients who successfully recanalized: 57% of patients who achieved successful recanalization had good clinical outcome vs 6.25% with unsuccessful recanalization (Spearman $r=0.45$; 95% CI, 0.22 to 0.63; Fisher's exact $p<0.001$)
Cohen et al (2013)	Case series	31 patients with acute proximal middle cerebral artery ischemic stroke at a single institution	Solitaire AB stent (Covidien/eV3; retrievable stent available in Europe), with or without implanted stent; IV tPA given if neurointerventionalist team not available within 30 min of presentation and patient <3 h from stroke onset	Stent-based thrombectomy lead to TIMI grade 3 recanalization in 87% of patients 3-mo Modified Rankin Scale score 0-2 in 77% of patients
Gratz et al (2014)	Retrospective case series	227 patients with acute	Solitaire FR stent, with or without thromboaspiration	70.9% of patients achieved successful

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		anterior circulation ischemic stroke at a single institution	intra-arterial thrombolysis, percutaneous transluminal angioplasty, or intracranial or extracranial stent placement; not specified if IV tPA given	recanalization (TICI score 2b–3) 3-month Modified Rankin Scale score 0-2 in 39% of patients. Predictors of a favorable clinical outcome included successful reperfusion, higher ASPECT score, younger age, lower admission NIHSS score, and absence of diabetes
Mokin et al (2013)	Retrospective case series	101 patients with acute ischemic stroke presenting to 10 centers	Solitaire FR stent, with or without other endovascular therapies; IV tPA given in 29% of patients	88% of patients achieved successful recanalization (TIMI score ≥ 2) 1-mo Modified Rankin Scale score 0-2 in 38% of patients. Predictors of a favorable clinical outcome included lower admission NIHSS score, successful recanalization, and presence/ absence of intracranial hemorrhage
Pereira et al (2013)	Prospective cohort; industry-sponsored	202 patients with acute large vessel anterior circulation stroke within 8 h of symptom onset; enrolled at 14 centers	Solitaire FR stent, with rescue therapy with intra-arterial tPA and/or mechanical thrombectomy for failed recanalization; IV tPA given for patients meeting institutional clinical criteria	79.2% of patients achieved successful recanalization (TICI score $\geq 2b$) with the Solitaire FR stent alone 3-mo Modified Rankin Scale score 0-2 in 57.9% of patients
Sanak et al (2013)	Prospective case series	50 patients with acute middle cerebral, distal	Solitaire AB stent, with or without intra-arterial tPA ; IV tPA given for patients	94% of patients achieved successful recanalization (TICI



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		internal carotid artery, or basilar artery stroke at a single institution	presenting within 4.5 h of symptoms onset	score $\geq 2a$) 3-mo Modified Rankin Scale score 0-2 in 60% of patients. Recanalization time predicted good clinical outcome
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Single-arm studies evaluating endovascular intervention in basilar artery occlusion. In 2013, several studies reported noncomparative evaluations of endovascular therapies for acute basilar artery occlusion. In a single-center case series of 24 patients with acute basilar artery occlusion who were treated with a stent-retriever device with or without IV or intra-arterial tPA and/or percutaneous transluminal angioplasty or permanent stent placement, Mohlenbruch et al reported that mechanical thrombectomy lead to successful recanalization (TICI score, $\geq 2b$) in 75% of patients. Eight patients (33%) had a favorable clinical outcome (Modified Rankin Scale score, 0-2) at 3 months. Park et al reported results from a single-center case series of 16 patients with acute basilar artery occlusion who were treated with endovascular interventions, primarily the Penumbra or Solitaire FR devices. The authors reported that successful revascularization (TICI score, $\geq 2a$) was achieved in 81.3% of patients, with favorable clinical outcome (Modified Rankin Scale score, 0-2) at 3 months in 56.3% of patients. While these studies suggest that endovascular intervention is feasible for acute basilar artery occlusion and may be associated with favorable outcomes, they are limited by lack of concurrent comparison groups and by potential selection bias.

Section Summary

The strongest evidence on the efficacy of endovascular mechanical embolectomy for acute ischemic stroke comes from 3 large RCTs that failed to demonstrate significant benefits from the use of endovascular mechanical embolectomy compared with usual therapy. These RCTs have some limitations, particularly related to relatively low use of embolectomy devices in general and of newer stent-retriever devices in particular, in their mechanical embolectomy groups. However, in the absence of additional studies to contradict the RCT results, the evidence is currently insufficient to conclude that endovascular mechanical thrombectomy is as beneficial as alternative treatment for acute ischemic stroke; therefore, it is considered investigational. There is ongoing interest in the efficacy of stent-retriever devices in acute stroke and of endovascular interventions for basilar artery occlusion, which has a poor prognosis without treatment.

Endovascular interventions for symptomatic intracranial atherosclerotic disease

Two devices for treatment of intracranial stenosis received FDA approval through the HDE process. The NeuroLink System was approved based on the Stenting of Symptomatic Atherosclerosis Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) study, a prospective, nonrandomized, multicenter, international study of 61 patients. The Wingspan Stent System was evaluated in a prospective study of 45 patients enrolled at 12 international centers. The SSYLVIA study reported an all-stroke rate of 13.1% of subjects over a mean follow up of 216 days; the Wingspan study reported an all-stroke rate of 9.5% over a mean follow up of 174 days.



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The FDA summary of safety and effectiveness concluded offered the following conclusions and appears to have based its approval in part on the favorable comparison to the NeuroLink device:

“...the probable benefit to health from using the Wingspan Stent System with Gateway PTA Balloon Catheter for treating transcranial stenosis outweighs the risk of illness or injury when used in accordance with the Instructions for Use and when taking into account the probable risks and benefits of currently available alternative forms of treatment.”

Evidence about the role of endovascular stenting for treatment of symptomatic intracranial atherosclerotic disease consists of at least 2 RCTs, a number of nonrandomized comparative studies, and numerous single-arm series. The most clinically relevant studies are reviewed next.

Randomized controlled trials. The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) was an RCT comparing aggressive medical management alone to aggressive medical management plus stenting in patients with symptomatic cerebrovascular disease and an intracranial stenosis of between 70% and 99%. This trial used the Wingspan stent system implanted by experienced neurointerventionalists who had been credentialed to participate in the trial. The authors had planned for an enrollment of approximately 750 patients based on power calculations. However, the trial was stopped early for futility after 451 patients had been randomized. The trial was terminated due to an excess of the primary outcome, stroke or death, at 30 days in the stenting group. In the stenting group, the rate of stroke or death at 30 days was 14.7% (95% CI, 10.7 to 20.1) compared with a rate of 5.8% (95% CI, 3.4 to 9.7; $p=0.002$) in the medical management group. At the time of termination, the mean follow-up was 11.9 months. Kaplan-Meier estimates of the primary outcome of stroke or death at 1 year was 20.5% (95% CI, 15.2 to 26.0) in the stenting group compared with 12.2% (95% CI, 8.4 to 17.6; $p=0.009$) in the medical management group. These results represented an excess rate of early adverse events with stenting over what was expected together with a decreased rate of stroke and death in the medical management group compared with expected values.

The SAMMPRIS investigators have published results from long-term subject follow up. Primary end points (in addition to stroke or death within 30 days of enrollment) included ischemic stroke in the territory of the qualifying artery beyond 30 days after enrollment or stroke or death within 30 days after a revascularization procedure of the qualifying lesion. During a median follow up of 32.4 months, 34 of 227 (15%) of patients in the best medical management group and 52 of 224 (23%) of patients in the stenting group had a primary end point event, with a significantly higher cumulative probability of a primary end point in the stenting group than in the best medical management group ($p=0.025$). Compared with the best medical management group, subjects in the stenting group had higher rates of any stroke (59/224 [26%] vs 42/227 [19%], $p=0.047$) and major hemorrhage (29/224 [13%] vs 10/227 [4%], $p<0.001$). The authors conclude that the benefits of aggressive medical management over percutaneous angioplasty and stenting among patients with intracranial stenosis persist over long-term follow up.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) randomized 16 patients with symptomatic vertebral artery stenosis to endovascular therapy (balloon angioplasty or stenting) or best medical treatment alone. Endovascular intervention was technically successful in all 8 patients, but 2 patients experienced TIAs at the time of endovascular treatment. During a mean follow-up of 4.7 years, no



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patient in either treatment group experienced a vertebrobasilar territory stroke, but 3 patients in each arm died of myocardial infarction (MI) or carotid territory stroke, and 1 patient in the endovascular arm had a nonfatal carotid territory stroke. The investigators concluded that patients with vertebral artery stenosis were more likely to have carotid territory stroke and MI during follow-up than have recurrent vertebrobasilar stroke. While they noted the trial failed to show a benefit of endovascular treatment of vertebral artery stenosis, the small number of patients enrolled severely limits conclusions.

Systematic reviews. Before the publication of the SAMMPRIS trial results, several systematic reviews addressed the role of stenting for intracranial atherosclerosis. A 2005 Cochrane review of angioplasty and stenting for vertebral artery stenosis identified only the CAVATAS trial for inclusion and concluded, "... there is currently insufficient evidence to support the routine use of PTA and stenting for vertebral artery stenosis. Endovascular treatment of vertebral artery stenosis should only be performed within the context of randomized controlled trials." In addition, the authors noted, "[l]ittle is known about the natural history of vertebral artery stenosis and what constitutes best medical treatment. Future trials should concentrate on comparing different medical treatment such as antiplatelet and anticoagulant drugs as well as comparing endovascular intervention with medical treatment."

A 2006 Cochrane Review addressed angioplasty for intracranial artery stenosis. The authors identified no RCTs but 79 publications of interest consisting of case series with 3 or more cases. The safety profile showed an overall perioperative rate of stroke of 7.9% (95% CI, 5.5% to 10.4%) and perioperative stroke or death of 9.5% (95% CI, 7.0% to 12.0%). The authors concluded the evidence insufficient to recommend angioplasty with or without stent placement in routine practice for the prevention of stroke in patients with intracranial artery stenosis.

Groschel et al conducted a systematic review on outcomes after stenting for intracranial atherosclerosis. The authors identified 31 studies including 1177 procedures, which had mainly been performed in patients with a symptomatic (98%) intracranial high-grade stenosis (mean: 78.7%) with high technical success rates (median, 96%; interquartile range, 90%-100%). The periprocedural minor or major stroke and death rates ranged from 0% to 50%, with a median of 7.7%. Periprocedural complications were significantly higher in the posterior versus the anterior circulation (12.1% vs 6.6%, $p < 0.01$), but did not differ between patients treated with a balloon-mounted stent ($n=906$) versus those who had been treated with a self-expandable stent ($n=271$; 9.5% vs 7.7%, respectively; $p=0.47$). Restenosis greater than 50% occurred more frequently after the use of a self-expandable stent (16/92; 17.4%; mean follow-up time, 5.4 months) than a balloon-mounted stent (61/443; 13.8%; mean follow-up time, 8.7 months; $p < 0.001$). The authors concluded that although intracranial stenting appears to be feasible, adverse events vary widely, and thus given a high rate of restenoses and no clear impact of new stent devices on outcome, the widespread application of intracranial stenting outside the setting of randomized trials and in inexperienced centers currently does not seem to be justified.

Nonrandomized, comparative studies. A number of nonrandomized studies that were retrospective, or based on registry data, provide relatively weak evidence on the comparative efficacy of endovascular procedures compared with medical therapy for intracranial atherosclerosis. A representative sample of such



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studies is given below. All are limited by their nonrandomized treatment assignments and systematic differences between groups.

Tang et al performed a retrospective comparison of 53 patients with at least 70% intracranial stenosis treated with stenting, compared with 61 patients treated with medical therapy matched for age, gender, vascular risk factors, degree of baseline stenosis, and baseline functional status. After a mean follow-up of 17.3 months, a composite outcome of stroke, transient ischemic attack (TIA), or vascular death was not different for the stent group compared with medical therapy (22.6% vs 24.6%, respectively; $p=0.99$). A good functional outcome, defined as a Modified Rankin Scale score of 0-3, was more frequent in the stent group compared with medical therapy (94.3% vs 78.7%, respectively; $p=0.045$).

Qureshi et al compared outcomes of angioplasty with ($n=22$) or without stenting ($n=22$) in patients with symptomatic intracranial stenosis 50% or greater identified retrospectively from a registry (angioplasty was used preferentially in patients with more technically challenging lesions). At 12 months, no differences in stroke-related outcomes or mortality were noted (stroke-free survival of 95% and 93% after stenting and angioplasty alone, respectively), the small sample, nonrandom treatment assignment, and event rates prevent valid comparisons. Further, comparison with medical therapy is required.

Samaniego et al retrospectively reviewed outcomes at a single institution comparing study of best medical therapy with angioplasty and stenting in 111 patients with symptomatic intracranial atherosclerotic disease treated from July 2004 to September 2007. Treatment decisions were made by a multidisciplinary committee. Important baseline differences between the best medical therapy and angioplasty groups, respectively, included presenting with acute stroke (74% vs 57%) or TIA (26% vs 43%), emergency department (53% vs 28%), or outpatient (19% vs 47%) presentation, or prior TIA (19% vs 55%). The best medical therapy group also had more diffuse disease, respectively (67% vs 28%) rather than single lesions. In this series, 31 lesions were treated with the Wingspan system, 12 with the Neuroform stent, and 14 with various balloon-expandable stent systems. Mean follow-up was 14 months in both groups. Combined ischemic end points of TIA, stroke, and vascular death were similar, 24% ($n=14$) in the best medical therapy group and 28% ($n=15$) in the angioplasty and stenting group. However, inability to account for nonrandom treatment assignment and systematic differences between groups prevents conclusions.

Section summary

The strongest evidence on the efficacy of endovascular treatment for symptomatic intracranial stenosis is from the SAMMPRIS RCT. This trial was stopped early due to harms, as the rate of stroke or death at 30 days following treatment was higher in the endovascular arm, which received percutaneous angioplasty with stenting. Follow up of the SAMMPRIS subjects has demonstrated no long-term benefit from endovascular therapy. This supports the conclusion that outcomes of endovascular treatment are worse than medical therapy in patients with symptomatic intracranial stenosis.

Stent-assisted treatment of intracranial aneurysms

Self-expanding stents. Two self-expanding stents, the Neuroform Microdelivery Stent System and the Enterprise Vascular Reconstruction Device and Delivery System, have FDA approval through the HDE program for the endovascular treatment intracranial aneurysms. The literature search did not identify any



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randomized trials of self-expanding stent-assisted treatment of intracranial aneurysms compared with standard neurosurgical treatment, ie, surgical clipping or endovascular coils. The available evidence consists of single-arm case series, registry studies, and nonrandomized comparative studies.

Nonrandomized comparative studies. The largest comparative series describing use of stents compared with coiling alone for treating intracranial aneurysms was described by Piotin et al. They report on a series of 1137 patients (1325 aneurysms) treated between 2002 and 2009. In this series, 1109 aneurysms (83.5%) were treated without stents (coiling), and 216 (16.5%) were treated with stents (15 balloon-expandable and 201 self-expandable stents). Permanent neurologic procedure-related complications occurred in 7.4% (16 of 216) of the procedures with stents versus 3.8% (42 of 1109) in the procedures without stents (logistic regression $p=0.644$; odds ratio [OR], 1.289; 95% CI, 0.439 to 3.779). Procedure-induced mortality occurred in 4.6% (10 of 216) of the procedures with stents versus 1.2% (13 of 1109) in the procedures without stents (logistic regression $p=0.006$; OR=0.116; 95% CI, 0.025 to 0.531). Thus far, the authors have followed 53% (114 of 216) of aneurysms treated with stents and 70% (774 of 1109) of aneurysms treated without stents, with angiographic recurrence in 14.9% (17 of 114) versus 33.5% (259 of 774), respectively ($p<0.001$; OR=0.349; 95% CI, 0.2038 to 0.5960).

Colby et al reported on 90 consecutive patients undergoing treatment for para-ophthalmic aneurysms, 30 of whom were treated with coil alone versus 60 who were treated with stent-assisted coils. On initial angiography following the procedure, complete occlusion of the aneurysm was achieved in 43.3% of stented patients compared with 31.7% of nonstented patients. At a mean of 14.5 months follow-up the recurrence rate was lower for the stented group at 15.4% (4/26) versus 41.5% (17/41) in the nonstented group ($p<0.05$).

A nonrandomized comparative study from Korea reported on 126 aneurysms that were treated with stent-assisted coiling compared with 86 patients treated with coil alone. At 2-year follow-up, the authors reported rates of occlusion and recurrence. Progressive occlusion was noted in 42.5% of the stent group (17/40) compared with 39.5% of the nonstented group (34/86), a difference that was not statistically significant. The rates of aneurysm recurrence were also not statistically different between groups. Recurrence occurred in 17.5% of patients in the stent group versus 21.0% in the nonstent group.

In 2013, Kadkhodayan et al reported results from a nonrandomized comparison of the Neuroform and Enterprise systems in the treatment of intracranial aneurysms not amenable to surgical clipping based on evaluation of prospectively collected registry data. Patients who received the Neuroform device ($n=160$) were enrolled starting in February 2003, and patients who received the Enterprise device ($n=98$) were enrolled starting in March 2007. Indications for the devices differed slightly based on FDA HDE criteria: both have an indication for wide-necked aneurysms (neck ≥ 4 mm or a dome-to-neck ratio < 2 mm) not amenable to surgical clipping. For the Enterprise, stents were used for saccular or fusiform aneurysms arising from a parent vessel with a diameter of ≥ 2.5 mm and ≤ 4 mm; for the Neuroform, stents were used for saccular aneurysms arising from a parent vessel with a diameter of ≥ 2 mm and ≤ 4.5 mm. The authors reported that Enterprise deployment success was high (108 of 115 attempts, 93.9%) compared with Neuroform (173 of 214 attempts, 80.8%, $p=0.001$). Rates of stent movement, misplacement, and symptomatic hemorrhage



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were similar for the 2 stent types, but symptomatic thromboembolic events were more frequent with the Enterprise stent (8.7% vs 1.4%, $p=0.002$).

Single-arm series. There are a large number of single-arm series reporting on outcomes of stent-assisted coiling. A systematic review by Shapiro et al identified 39 articles reporting on 1517 patients, most of which were single-arm, retrospective series. The majority of patients treated had unruptured aneurysms, but 22% of patients had ruptured aneurysms. The authors noted a large amount of heterogeneity in reporting outcome data, particularly for adverse events. The periprocedural mortality rate was 2.1%, and the overall complication rate was 19%. Immediately following treatment, approximately 45% of patients had occlusion of the aneurysm. At an average of 13 months posttreatment, the stroke rate in the stented area was 3.2%.

A systematic review that was restricted to ruptured aneurysms was published by Bodily et al in 2011. This review included 17 articles that described treatment in 212 patients. Technical success was high at 93%, and 2% of patients required open surgery due to stent failure or intraoperative aneurysm rupture. A total of 63% (130/207) of aneurysms were successfully occluded. The overall mortality rate was 19%, and 14% of patients had poor clinical outcomes. There was a relatively high rate of adverse events reported, with 8% of patients having an acute intracranial bleed related to the procedure, and 6% (16/288) having a clinically significant thromboembolic event.

Since the publication of the Shapiro and Bodily systematic reviews, a number of noncomparative studies evaluating the use of stent-assisted endovascular treatments in intracranial aneurysms have been published. The largest study, reported by Geyik et al, included 468 patients with wide-necked cerebral aneurysms who underwent stent-assisted coiling with the Enterprise, Neuroform, Wingspan, or Leo (self-expanding, Balt, Montmorency, France) stents. Overall mortality was 1.9%; procedure-related complications occurred in 28 patients (6.9%). Angiographic follow up data, obtained at 6 months to 7 years postprocedure (mean 19.2 months), were available for 440 patients (94%). For the total of 467 aneurysms with follow up, complete occlusion occurred in 194 aneurysms (41.6%), near-complete occlusion (>95% occlusion but minimal residual filling with coils at the neck) occurred in 242 aneurysms (51.8%), and incomplete occlusion (<95% occlusion) occurred in 31 aneurysms (6.6%). At 6-month follow-up, recanalization occurred in 38 aneurysms (8% of all aneurysms with follow up available). The authors conclude that stents are associated with high rates of occlusion and low rates of recurrence over long-term follow up. Other representative noncomparative studies are summarized in Table 2. Interpretation of these studies is limited by potential selection bias and no comparison group. In general, these series demonstrate high rates of technical success of stent deployment with high rates of aneurysm occlusion; however, variable complication rates, particularly related to thromboembolic events were observed. Long-term follow up, particularly beyond 1 year, is limited.

Table 2. Noncomparative Studies of Stent-Assisted Endovascular Treatment of Aneurysms

Study	Study Type	Patient Population	Intervention	Primary Outcome
Chalouhi	Retrospective	76 patients with	Endovascular coiling,	93.4% of patients had



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et al (2013)	case series	posterior cerebellar artery (PICA) aneurysms at a single institution	with or without Neuroform stent assistance (4 patients) or balloon assistance (4 patients)	technically successful treatment; remaining patients required surgical clipping Among 67 patients who had successful endovascular treatments and who did not die in the hospital, favorable outcomes (mild, moderate, no disability) were achieved in 85%
Chen et al 2013	Retrospective case series	10 patients with large and giant fusiform aneurysms of the vertebrobasilar arteries at a single institution	Endovascular treatment with stent placement (Neuroform or Leo [self-expanding, Balt, Montmorency, France], 5 patients), stent-assisted coiling (3 patients), or occlusion of proximal artery (2 patients)	9 patients had a good outcome; 1 patient died after stenting procedure. Stent deployment was generally feasible in the vertebrobasilar system.
Gentric et al 2013	Prospective cohort; industry-sponsored	107 patients with unruptured cerebral aneurysms enrolled at one of 10 European institutions	Endovascular treatment with Neuroform stent-assisted coiling	94.4% of patients had technically successful treatment. 66.4% of patients had complete occlusion immediately postprocedure. At follow up at 12-18 mo, 5 patients (5%) had delayed complications, with 3% of patients with thromboembolic events. Of 93 patients with anatomic evaluation available, aneurysms recurred in 9.7%.
Johnson et al 2013	Retrospective case series	91 patients with complex MCA aneurysms not amenable to	Endovascular treatment with coiling with stent assistance using Neuroform (62	All patients had technically successful treatment. 9 patients had new neurologic symptoms



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		coiling enrolled at a single institution	aneurysms), Enterprise (32 aneurysms), Wingspan (1 aneurysm), or a combination (5 aneurysms) or with stenting along (2 aneurysms), endovascular treatment with stenting alone	following the procedure, one with long-term disability. There was 1 procedure-related death. Of 85 aneurysms with initial follow-up imaging available (usually at 6 mo postprocedure), 77 (90.6%) were completely occluded, and 4 (4.7%) required retreatment.
Kulcsar et al 2013	Retrospective case series	117 patients with wide-necked cerebral aneurysms	Endovascular treatment with Neuroform stent-assisted coiling	Stents were successfully deployed in 113 patients with 117 aneurysms 99 patients had grade 1 or 2 occlusion (complete or aneurysm neck) on immediate postprocedure imaging Intraprocedure major thrombotic events occurred in 7 cases (5.9%) and major infarcts on postprocedure imaging in 9 cases (7.7%) Of 92 aneurysms with follow-up imaging available, 71 (77%) had grade 1 or 2 occlusion

Flow-diverting stents. In 2011, the Pipeline Embolization Device, which is categorized as a flow-diverting stent, received FDA premarket approval. The device's approval was based on the industry-sponsored Pipeline for Uncoilable or Failed Aneurysms (PUFA) study, a multicenter, prospective, single-arm trial of the device for treatment of internal carotid artery aneurysms that were uncoilable or had failed coiling, for which results were published in 2013. Investigators enrolled 108 patients at 10 centers with unruptured large- or giant-necked aneurysms measuring at least 10 mm in diameter, with aneurysm necks of at least 4 mm who underwent placement of 1 or more Pipeline devices. One patient was excluded from evaluations of the device effectiveness and safety due to unsuccessful catheterization. Four patients were excluded from evaluation of the device effectiveness due to aneurysm location in a nonqualifying segment of the internal carotid artery (2 patients), insufficient aneurysm size on treatment angiography (1 patient), and unsuccessful catheterization of the distal parent vessel (1 patient). Two patients had 2 qualifying aneurysms

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treated, so the “effectiveness cohort” was 106 aneurysms in 104 patients. Seventy-eight of 106 aneurysms (73.6%) met the study’s combined primary effectiveness end point of complete occlusion at day 180 without major stenosis or use of adjunctive coils. Six of the 107 patients (5.6%) who underwent any catheterization, a primary safety end point (occurrence of major ipsilateral stroke or neurologic death at 180 days) occurred. The literature search did not identify any randomized trials of flow-diverting stent treatment of intracranial aneurysms compared with standard neurosurgical treatment, ie, surgical clipping or endovascular coils. The available evidence related to the use of flow-diverting stents consists of 1 nonrandomized comparative study and multiple single-arm case series.

Nonrandomized comparative studies. In 2013, Chalouhi et al reported outcomes from patients with unruptured, large or giant aneurysms treated with the Pipeline device enrolled in a registry compared with those treated with endovascular coiling. They identified a total of 229 patients enrolled during their data collection period from 2004-2013, 54 treated with the Pipeline device and 175 with coiling. Patients treated with the Pipeline device were significantly older and had significantly larger aneurysms that were more likely to be fusiform. Because of this, the authors excluded patients with fusiform or anterior communicating artery aneurysms and conducted their analysis in 160 patients (40 Pipeline and 120 coil patients) who were matched in a 1:3 ratio on the basis of patient age and aneurysm size. Aneurysm neck size, overall size, and anterior versus posterior circulation location were similar between the groups. Of the patients treated with the Pipeline device, 4 patients (10%) also required adjunctive coil placement. Of the patients treated with endovascular coiling, 67 (56%) were treated with coiling, while 52 (43%) were treated with stent-assisted coiling and 1 (1%) with balloon-assisted coiling. Primary outcomes included obliteration of the aneurysm on follow-up imaging and clinical outcomes, measured by Modified Rankin Scale score of 0-2 (vs 3-6). At the time of latest follow up, a higher proportion of aneurysms treated with the Pipeline device compared with those treated with coiling achieved complete obliteration (30/35 [86%] vs 37/90 [41%], $p<0.001$). However, angiographic follow-up was available for a greater proportion of patients treated with the Pipeline (35 /40 [87.5%]) than those treated with coiling (90/120 [75%]), and the median angiographic follow-up time differed significantly between the groups (7 months in the Pipeline group and 12 months in the coil group, $p<0.001$). In terms of clinical outcomes, similar proportions of the Pipeline and coil groups had a Modified Rankin Scale score 0 to 2 (35/38 [92%] in the Pipeline group vs 97/103 [94%], $p=0.8$). Similar to the angiographic follow up results, the median clinical follow-up time differed significantly between the groups. Treatment type was not significantly associated with rates of procedure-related complications. While this study directly compares patients treated with the Pipeline endovascular device and those treated with coiling, it is limited by its nonrandomized, retrospective design. In particular, patients treated with coiling were treated in an earlier period (2004-2011) than those treated with the Pipeline device (2011-2012); this may have systematically biased the study in favor of the Pipeline device because aspects of neurointerventional care other than the device used may have differed over time.

Single-arm series. Multiple noncomparative studies that report the outcomes from flow-diverting stent-assisted treatment of intracranial aneurysms have been published since the introduction of the Pipeline endovascular device. These studies have been summarized in several systematic reviews and meta-analyses. The largest meta-analysis by Brinjikji et al, published in 2013, included 1451 patients with 1654 aneurysms reported in a total of 29 studies published through 2012. The authors evaluated aneurysmal occlusion rates at 6 months, and procedure-related morbidity, mortality, and complications across studies.

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They found a high rate of complete aneurysmal occlusion (76% [95% CI, 70% to 81%]), but also a high rate of procedure-related morbidity and mortality (5% [95% CI, 4% to 7%] and 4% [95% CI, 3% to 6%], respectively).

Also in 2013, Arrese et al reported results of a meta-analysis that used somewhat more restrictive inclusion criteria that included 897 patients with 1018 aneurysms reported in a total of 15 studies. All but 2 of the studies were included in the Brinjikji meta-analysis. They authors determined rates of complete or nearly complete occlusion of the treated aneurysm with a patent parent artery and early procedure-related mortality and neurologic morbidity. Similar to the Brinjikji meta-analysis, this study found a high overall rate of complete aneurysmal occlusion (76.2% [95% CI, 72.1 to 80.2]), but also a high rate of procedure-related morbidity and mortality (2.8% [95% CI, 1.7%–3.8%] and 7.3% [95% CI, 5.7% to 9%], respectively). The authors assessed for publication bias using funnel plots and the Egger's test to assess whether the study estimate size is related to the size of the study, and found $p < 0.001$ for the Egger's test for both early and late morbidity and aneurysmal occlusion, suggestive of publication bias.

Since the publication of these 2 meta-analyses, several additional noncomparative studies evaluating flow-diverting stents in the treatment of aneurysms have been published. Representative studies are summarized in Table 3.

Table 3. Noncomparative Studies of Flow-Diverting Stent-Assisted Endovascular Treatment of Aneurysms

Study	Study Type	Patient Population	Intervention	Primary Outcome
Kan et al (2013)	Prospective case series (registry)	56 patients with intracranial aneurysm treated at 7 institutions	Pipeline Embolization Device placement	6/123 devices incompletely deployed Among 19 patients with 6-mo follow-up, 68% (13 patients) had complete aneurysm occlusion 4 fatal postprocedural hemorrhages occurred
Lin et al (2013)	Retrospective case series	41 patients with small (<10 mm) internal carotid artery aneurysm at a single institution	Pipeline Embolization Device placement	80% of patients had complete or near-complete aneurysm occlusion 1 patient (2.3%) had a major periprocedural complication (death)



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Malatesta et al (2013)	Retrospective case series	28 patients with intracranial aneurysm at a single institution	Flow-diverting stent placement (Pipeline Embolization Device or SILK artery reconstruction device [Balt Extrusion, Montmorency, France])	89% of aneurysms had complete occlusion at 12 mo 1 death occurred
Piano et al (2013)	Retrospective case series	101 patients with intracranial aneurysm at a single institution	Flow-diverting stent placement (Pipeline Embolization Device or SILK device), with or without endovascular coiling	86% of aneurysms evaluated at 6-mo follow-up showed complete occlusion
Toma et al (2013)	Retrospective case series	84 patients with intracranial aneurysm at a single institution	Flow-diverting stent placement	61% of aneurysms had resolved at 12 mo 9.5% of patients had a new, permanent neurologic deficit and 5.9% of patients had procedure-related mortality
Yavuz et al (2013)	Retrospective case series	25 patients with middle carotid artery aneurysm at the carotid bifurcation at a single institution	Pipeline Embolization Device placement	84% of patients had complete aneurysm occlusion

Section summary

There is a lack of RCT evidence on the efficacy of self-expanding stent-assisted coiling compared with coiling alone or surgical clipping for the treatment of intracranial aneurysms. Nonrandomized studies reported higher complete occlusion rates with stenting, and lower recurrence rates. However, there is also some evidence that adverse event rates are relatively high with stenting, and 1 nonrandomized comparative trial reported that mortality is higher with stent-assisted coiling compared with coiling alone. This evidence is insufficient to determine whether stent-assisted coiling improves outcomes for patients with intracranial aneurysms because the risk/benefit ratio cannot be adequately defined.

Similarly, no RCTs have evaluated flow-diverting stents. One nonrandomized study that compared the flow-diverting stents with endovascular coiling for intracranial aneurysms demonstrated higher rates of aneurysm obliteration in those treated with the Pipeline endovascular device than those treated with coiling, with



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similar rates of good clinical outcomes. However, given the lack of randomized trials, the evidence is insufficient to determine whether flow-diverting stents improves outcomes for patients with intracranial aneurysms.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from 3 physician specialty societies and 3 academic medical centers while this policy was under review in 2011. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

For treatment of intracranial stenosis, the majority of those providing input would consider use of this technology in selected patients who remained symptomatic from intracranial atherosclerotic disease despite maximum medical therapy. There was unanimous support for use of this technology in selected patients with intracranial aneurysms; ie, in those patients for whom surgical treatment is not possible and for whom endovascular treatment (coils) does not completely isolate the aneurysm.

Ongoing Studies

Endovascular interventions for acute ischemic stroke

A query of online site ClinicalTrials.gov on December 22, 2013, using the key words “endovascular” and “stroke” returned 62 studies. The following are RCTs that are evaluations of endovascular interventions compared with alternative treatment for acute stroke:

- Endovascular Arterial Reperfusion vs Intravenous Thrombolysis for Acute Ischemic Stroke (EARLY) study (NCT01869478). This is a randomized, single-blind safety/efficacy study to compare endovascular arterial reperfusion with mechanical thrombectomy/clot disruption (Penumbra aspiration system, Solitaire device, and/or Reflex catheter) and/or intracranial stent deployment with standard medical therapy including IV tPA for the treatment of acute stroke. The primary outcome is recanalization of the primary intracranial occlusion; secondary outcomes are modified Rankin Stroke Scale at 90 days. Enrollment is planned for 20 patients, with an estimated completion date of February 2015.
- Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) Trial (NCT01778335). This study randomly assigns patients with a confirmed symptomatic intracranial occlusion evaluated within 12 hours of last seen normal with a baseline NIHSS score greater than 5 at the time of randomization to an experimental group (endovascular mechanical thrombectomy or endovascular delivery of thrombolytic agent) or a control group (best medical therapy, including IV tPA if eligible). The primary outcome is proportion of patients who achieve a NIHSS score of 0 to 2 OR a Modified Rankin Scale score of 0 to 2 at 90 days. Enrollment is planned for 250 patients, and estimated completion date is listed as December 2014.
- RECO Flow Restoration Device Versus Intravenous t-PA for Stroke Within 4.5h of Symptom Onset: a Prospective Randomised Control Trial (RESTORE) trial (NCT01983644). This study randomly assigns patients with acute anterior circulation ischemic stroke presenting within 4.5 hours of symptom onset to an experimental group (endovascular mechanical thrombectomy with the RECO

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device, a self-expanding stent-retriever) or a control group (IV tPA). The primary outcome is Modified Rankin Scale score of 2 or less at 90 days postintervention. Enrollment is planned for 130 patients, with an estimated completion date of November 2015.

- Endovascular Revascularization with Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke within 8 Hours (REVASCAT) study (NCT01692379). This study randomly assigns patients with stroke from a large vessel occlusion seen within 8 hours to either embolectomy or standard medical therapy including IV recombinant tPA. The primary outcome measure is the modified Rankin Stroke scale at 90 days. Enrollment is planned for 690 patients, and estimated completion date is listed as December 2015.
- Positive Stroke Clinical Trial (NCT01852201). This study randomly assigns patients with stroke who are ineligible for IV TPA to either embolectomy or standard medical therapy. The primary outcome measure is the Modified Rankin Scale at 90 days. Enrollment is planned for 750 patients, and estimated completion date is listed as May 2016.
- Wake up Symptomatic Stroke – Benefit of Intravenous Clot Busters or Endovascular Interventions (WASSABI) study (NCT01455935). This study randomizes patients who present with stroke symptoms upon waking, with an unknown duration of symptoms. Patients are randomized to 1 of 3 arms: medical therapy, IV thrombolysis, or endovascular intervention. The primary end point is the Modified Rankin Scale score at 90 days. Enrollment is planned for 90 patients, with an estimated completion date of February 2014.
- Solitaire FR as Primary Treatment for Acute Ischemic Stroke (SWIFT-PRIME) study (NCT01657461). This study, which has not yet started enrollment, plans to randomize patients with acute ischemic stroke presenting within 4.5 hours of onset to either IV thrombolysis alone or IV thrombolysis combined with endovascular intervention. The primary outcome is 90-day disability using the Modified Rankin Scale. Enrollment is planned for 833 patients, with estimated study completion listed as September 2018.
- Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY) study (NCT01429350). This study randomizes patients with acute ischemic stroke who meet criteria for IV thrombolysis to either IV thrombolysis alone or IV thrombolysis combined with endovascular intervention. The primary outcome is good functional status, as defined by a 90-day modified Rankin score of 0-2. Enrollment is planned for 692 patients, with estimated study completion listed as December 2016.

Endovascular Interventions for Symptomatic Intracranial Atherosclerotic Disease

A query of online site ClinicalTrials.gov on December 22, 2013 using the key words “endovascular” or “stent” and “intracranial” returned 82 studies, with some relevant to symptomatic intracranial atherosclerotic disease and some relevant to intracranial aneurysms. The following are RCTs that are evaluations of endovascular interventions compared with alternative treatment for symptomatic intracranial atherosclerotic disease:

- China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A Prospective Multicenter, Randomized Controlled Trial (NCT01763320). This study randomly assigns patients with symptomatic intracranial stenosis (TIA or nonsevere stroke within the past 12 months attributed to 70% to 99% stenosis of a major intracranial artery) to an intervention group (intracranial stenting) or a control group (medical therapy with aspirin and clopidogrel). The primary

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outcomes are the number of participants who suffer from Ischemic stroke, death, or cardiovascular events after enrollment or after any revascularization procedure of the qualifying lesion in the territory of the symptomatic intracranial artery within 30 days and between 30 days to 1 year after enrollment or any revascularization procedure of the qualifying lesion. Enrollment is planned for 380 patients, and estimated completion date is listed as December 2015.

- Phase III Study of Pharos Vitesse Neurovascular Stent System Compared to Best Medical Therapy for the Treatment of Ischemic Disease (NCT00816166). This study randomly assigns patients with TIA or stroke attributable to a neurovascular stenosis (70%-99%) within the prior 30 days to an experimental group (PHAROS neurovascular stent placement with medical therapy) or a control group (medical therapy). The primary effectiveness end point is stroke or TIA in the same territory as the presenting event within 12 months of enrollment. Enrollment is planned for 250 patients, and estimated completion date is listed as June 2014.

Stent-Assisted Treatment of Intracranial Aneurysms

The following are RCTs that are evaluations of endovascular interventions (angioplasty or stenting) compared with alternative treatment for intracranial aneurysms:

- Flow Diverter Stent for Endovascular Treatment of Unruptured Saccular Wide-necked Intracranial Aneurysms (EVIDENCE) (NCT01811134). This study randomly assigns patients with an unruptured saccular intracranial aneurysm with a neck diameter from 4 to 10 mm and with a sac diameter from 7-20 mm to an experimental group (Pipeline flow-diverter stent placement) or a control group (endovascular coiling with or without self-expandable stent placement). The primary outcome is percentage of patients with complete occlusion of the treated aneurysm at 1 year after enrollment. Enrollment is planned for 130 patients, with an estimated completion date of November 2017.
- Stenting in the Treatment of Aneurysm Trial (STAT) (NCT01340612). This study randomly assigns patients with at least 1 intracranial aneurysm that is large (≥ 10 mm), wide-necked (> 4 mm), or recurrent lesions after coiling for which endovascular treatment is judged possible to an experimental group (endovascular stenting with or without coiling) or a control group (endovascular coiling). The primary outcome is recurrence of the target aneurysm at 1 year after enrollment. Enrollment is planned for 600 patients, with an estimated completion date of April 2016.
- DIVERT: Diversion of Flow in Intracranial VERtebral and Blood Blister-like Ruptured Aneurysms Trial: A Randomized Trial Comparing Pipeline Flow Diversion and Best-Standard-Treatment (NCT01976026). This study randomly assigns patients with blood blister-like aneurysm or a dissecting aneurysm, responsible for a recent subarachnoid hemorrhage, to an experimental group (endovascular therapy with a flow-diverting stent) or a control group (best standard therapy, including conservative management, endovascular coiling with or without stenting, parent vessel occlusion, and surgical clipping). The primary outcomes are modified the modified Rankin scale score at 3 months and at least 1 year following enrollment. Enrollment is planned for 420 patients, and the estimated study completion date is listed as January 2021.
- Flow Diversion in Intracranial Aneurysm Treatment (FIAT) (NCT01349582). This study is a randomized, open-label trial including patients with an intracranial aneurysm judged to be "difficult" in whom "flow diversion is considered an appropriate if not the best but yet unproved therapeutic option by the participating clinician." Patients are randomly assigned to an experimental group (endovascular therapy with a flow-diverting stent) or a control group (best standard therapy). The

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primary outcome is the rate of success at 12 months following enrollment, defined as complete or near complete occlusion of the aneurysm combined with a modified Rankin score of 0-2. Enrollment is planned for 344 patients, and the estimated study completion date is listed as April 2017.

- LARGE Aneurysm Randomized Trial: Flow Diversion Versus Traditional Endovascular Coiling Therapy (NCT01762137). This study randomly assigns patients with a single wide-necked (≥ 4 mm) aneurysm of the internal carotid artery with a maximum diameter ≥ 10 mm to an experimental group (endovascular therapy with a flow-diverting stent) or a control group (endovascular coiling). The primary outcome is noninferiority of the experimental procedure in terms of a combined safety and efficacy outcome at 180 days postenrollment. Enrollment is planned for 316 patients, and the estimated study completion date is listed as April 2018.

Summary

For acute stroke, the strongest evidence on the efficacy of endovascular mechanical embolectomy for acute ischemic stroke comes from 3 large RCTs that failed to demonstrate significant benefits from the use of endovascular mechanical embolectomy compared with usual therapy. The evidence is currently insufficient to conclude that endovascular mechanical thrombectomy is as beneficial as alternative treatment for acute ischemic stroke; therefore, it is considered investigational.

For elective treatment of symptomatic intracranial stenosis, endovascular procedures with or without stenting have not been shown to be superior to best medical care. The strongest evidence on the efficacy of endovascular treatment for symptomatic intracranial stenosis is from the SAMMPRIS RCT, which was stopped early due to harms. This evidence suggests that the adverse event rate with endovascular procedures is relatively high and may outweigh the benefit in preventing recurrent ischemic events. As a result, endovascular procedures with or without stenting are considered investigational for the elective treatment of symptomatic intracranial stenosis.

For the treatment of intracranial aneurysms, there are no RCTs of stent-assisted coiling compared with coiling alone. Nonrandomized comparative studies report occlusion rates that are similar or higher than coiling alone, and recurrence rates that may be lower than for coiling alone. Results of clinical vetting indicated strong support for treatment of aneurysms that are not amenable to surgery or simple coiling. As a result, use of stent-assisted coiling for the treatment of intracranial aneurysms may be considered medically necessary when surgical treatment is not appropriate and standard endovascular techniques do not allow for complete isolation of the aneurysm.

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HCPCS	No codes
ICD-9 Diagnosis	430, 437.3
ICD-9 Procedure	00.45 thru 00.48, 00.62, 00.65, 39.74

Policy History

Original Effective Date: 02/23/2006
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 02/01/2006 Medical Director review
 02/15/2006 Medical Policy Committee review
 02/23/2006 Quality Care Advisory Council approval

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07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
04/02/2008	Medical Director review
04/16/2008	Medical Policy Committee approval. No change in policy statement. Rationale totally rewritten with focus on FDA approved devices.
04/02/2009	Medical Director review
04/15/2009	Medical Policy Committee approval. No change to coverage eligibility.
04/08/2010	Medical Policy Committee approval
04/21/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/07/2011	Medical Policy Committee review
04/13/2011	Medical Policy Implementation Committee approval. Changed title from "Percutaneous Transluminal Angioplasty of Intracranial Atherosclerotic Stenoses With or Without Stenting" to "Endovascular Procedures (Angioplasty and/or Stenting) for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)". Added that intracranial stent placement is eligible for coverage as part of the endovascular treatment of intracranial aneurysms for patients when surgical treatment is not appropriate and standard endovascular techniques do not allow for complete isolation of the aneurysm, e.g., wide-neck aneurysm (4mm or more) or sack-to-neck ratio less than 2:1. Added that intracranial stent placement in the treatment of intracranial aneurysms, except as noted above, is investigational.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2014	Medical Policy Committee review
04/23/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Policy 00366 (Mechanical Embolectomy for Treatment of Acute Stroke) retired and combined with this policy.

Next Scheduled Review Date: 04/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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