Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

Description

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 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.

Background

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, 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 United States (US), Canada, Europe and Japan, and is the leading cause of adult disability in the US.(1) 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.(2) While spontaneous thrombolysis does occur, treatment of ischemic stroke has focused on the use of intravenous tissue plasminogen activator (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 three
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, (e.g., 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 (i.e., intra-arterial tPA). Although tPA only has approval from the US Food and Drug Association (FDA) for its intravenous route of delivery, IA tPA has been 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.

An additional clinical situation in which endovascular therapies may be used in the treatment of acute ischemic stroke is in the setting of cerebral vasospasm following intracranial (subarachnoid) hemorrhage. Delayed cerebral ischemia (DCI) occurs about 3-14 days following the acute bleed in about 30% of patients experiencing subarachnoid hemorrhage, and is a significant contributor to morbidity and mortality in patients who survive the initial bleed. In cases refractory to medical measures, rescue invasive therapies including intra-arterial vasodilator infusion therapy (eg, calcium channel blockers) and transluminal balloon angioplasty may be used. (3,4) The mechanism of disease, patient population, and time course of therapy differ for DCI occurring post-subarachnoid hemorrhage compared with ischemic stroke due to atheroembolic disease. Therefore, this indication for endovascular intervention will not be addressed in this policy.

Intracranial Atherosclerotic Disease

It is estimated that intracranial atherosclerosis causes about 8% of all ischemic strokes. Intracranial stenosis may contribute to stroke in two ways: either due to embolism or low flow ischemia in the absence of collateral circulation. Recurrent annual stroke rates are estimated at 4–12% per year with atherosclerosis of the intracranial anterior circulation and 2.5–15% per year with lesions of the posterior (vertebrobasilar) circulation. Medical treatment typically includes either anticoagulant therapy (i.e., warfarin) or antiplatelet therapy (e.g., 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 one 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 1,377 patients with symptomatic atherosclerosis of the internal carotid or middle cerebral arteries to medical care or EC/IC bypass. The outcomes in the two 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 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 US population, with prevalence between 0.5%-6% of the population.(5) 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 to 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.

Regulatory Status

Several devices for endovascular treatment of intracranial arterial disease have received clearance by the US 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, Mountainview, CA). In August 2004, “The Merci® Retriever" (Concentric Medical, Mountainview, CA) was cleared by the U.S. Food and Drug Administration (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 the 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 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. The 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 the FDA through the 510(k) process. The 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 the 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 tissue plasminogen activator tPA, or who fail intravenous tissue plasminogen activator 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 the FDA through the 510(k) process. The 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 tissue plasminogen activator tPA. Later versions of the Trevo® Retriever are called the Modified Trevo® Retriever, the Trevo® ProVue Retriever, and the Modified Trevo® ProVue Retriever; the name Trevo Retriever is used throughout this Assessment.

Intracranial Stenosis:

Currently two devices have received approval for atherosclerotic disease from the U.S. Food and Drug Administration (FDA) through the humanitarian device exemption (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; the 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 ≥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 ≥50% stenosis that are accessible to the system.”

Intracranial Aneurysms:

In 2011, the 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).(6) Approval was based on the Pipeline for Uncooilable for Failed Aneurysms Study, a single-arm, open-label feasibility
study that included 108 patients aged 30-75 with unruptured large and giant wide-necked aneurysms.(7)

Three stents have received FDA approval through the Humanitarian Device Exemption (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).

3. **The Low-Profile Visualized Intraluminal Support Device (LVIS™ and LVIS™ Jr.) (MicroVention, Inc., Tustin, CA)** in July 2014, received HDE approval in July 2014 (H130005) for use with embolic coils for the treatment of unruptured, wide neck (neck ≥ 4 mm or dome to neck ratio < 2), intracranial, saccular aneurysms arising from a parent vessel with a diameter ≥ 2.5 mm and ≤ 4.5 mm.

Related Policies

7.01.68 Extracranial Carotid Angioplasty/Stenting

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Intracranial stent placement may be considered medically necessary 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.

Intracranial flow diverting stents with FDA approval for the treatment of intracranial aneurysms may be considered medically necessary as part of the endovascular treatment of intracranial aneurysms that meet anatomic criteria (see “Policy Guidelines”) and are not amenable to surgical treatment or standard endovascular therapy.

Intracranial stent placement is considered not medically necessary in the treatment of intracranial aneurysms except as noted above.

Intracranial percutaneous transluminal angioplasty with or without stenting is considered not medically necessary in the treatment of atherosclerotic cerebrovascular disease.

Endovascular interventions (mechanical embolectomy, angioplasty, stenting) are considered not medically necessary in the treatment of acute stroke.
Policy Guidelines

Flow – diverting stents are indicated for the treatment of large or giant wide-necked intracranial
aneurysms, with a size of 10 mm or more and a neck diameter of 4 mm or more, in the internal carotid
artery from the petrous to the superior hypophyseal segments.

These policy statements are not intended to address the use of rescue endovascular therapies,
including intra-arterial vasodilator infusion and intracranial percutaneous transluminal angiography, in
the setting of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage.

Rationale

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention
improves health outcomes. The optimal study design for this purpose is a randomized controlled trial
(RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures,
also known as surrogate outcome measures, may also be adequate if there is an established link
between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and
uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to
biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the
condition.

Endovascular Interventions for Acute Ischemic Stroke
The evidence review will focus on the available RCTs and other comparative studies. Following is a
summary of the key literature to date.

Randomized Controlled Trials

RCTs Comparing Endovascular Therapies with Non- Interventional Care
From 2012-2014, results from three large, randomized trials of endovascular therapies for acute
ischemic stroke were published.

In 2014, Berkhermer et al reported initial results of the MR CLEAN trial (Multicenter Randomized
Clinical trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), an open-label,
blinded end-point RCT with 500 subjects conducted at 16 centers in the Netherlands. (8) Eligible
patients had acute ischemic stroke caused by an intracranial occlusion of the distal intracranial carotid
artery, middle cerebral artery (M1 or M2), or anterior cerebral artery (A1 or A2), and a score of 2 or
higher on the National Institutes of Health Stroke Scale (NIHSS). Initiation of intra-arterial treatment had
to be possible within 6 hours of stroke onset. Patients were randomly assigned to standard stroke
treatment (N=267; 53.4%) or intra-arterial treatment (N=233; 46.6%). Most patients in both groups
(87.1% in the intervention group and 90.6% in the control group) received IV alteplase, at a median of
85 and 87 minutes after stroke onset, respectively. Patients in the intra-arterial group underwent arterial
catheterization with a microcatheter to the level of the occlusion. Specific treatment options included
delivery of a thrombolytic agent, mechanical thrombectomy, or both, at the discretion of the local
interventionist. Intra-arterial thrombolytic agents were either alteplase or urokinase; mechanical
treatment could involve thrombus retraction, aspiration, wire disruption, or use of a retrievable stent.
Analysis was intention-to-treat. One control group patient received intra-arterial treatment, and 17 patients (7.3%) in the intervention group did not receive intra-arterial therapy, most commonly (N=8) due to clinical improvement before the start of the intervention. Among the 233 patients randomized to intra-arterial therapy, 195 (83.7%) received mechanical therapies, with retrievable stents used in 190 patients (81.5%) and other devices in 5 patients (2.1%). Twenty-four patients (10.3%) received additional intra-arterial thrombolytic agents. No intra-arterial intervention was performed following catheterization in 20 subjects because of intracranial artery stenosis, occlusion, tortuosity, or dissection (N=10), no clot or targetable clot visible for intra-arterial therapy (N=8), or other technical problems (N=2).

For the study’s primary outcome (modified Rankin scale score at 90 days), the median score was 3 (IQR 2-5) among intervention subjects, compared with a median score of 4 (IQR 3-5) among control subjects, with an unadjusted common odds ratio (OR) of 1.66 (95% confidence interval [CI] 1.21 to 2.28; favors intervention). Twenty-seven (11.6%) intervention subjects had a modified Rankin score of 0 or 1 at 90 days, compared with 16 (6.0%) control subjects (unadjusted OR 2.06; 95% CI 1.08 to 3.92). Follow-up computed tomography (CT) angiography was available for 187 control subjects, of whom 141 had no intracranial occlusion (75.4%), compared with 68/207 (32.9%) of control subjects with follow-up CT angiography available (unadjusted OR 6.27; 95% CI 4.03 to 9.74). The thirty-day mortality rate was 18.9% in the intervention group, compared with 18.4% in the control group (p=NS). Rates of serious adverse events during the 90-day follow up period did not differ significantly between groups (P=0.31). Symptomatic intracerebral hemorrhage occurred in 7.7% of intervention subjects compared with 6.4% of control subjects, which was not a significant difference. However, intervention subjects were more likely to demonstrate a new ischemic stroke in different vascular territory (5.6% vs 0.4%; P<0.001).

Kidwell et al reported on the MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy) trial in 2013.(9) 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 had 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 and a small, 90 mL or less, area of predicted core infarct) would benefit more from mechanical embolectomy than patients with nonpenumbral 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. In a predefined subgroup analysis, the authors reported that for the subgroup of patients with ICA, M1, or basilar artery occlusion who received tPA within 120 minutes of stroke onset (N=124), the relative risk (RR) for a modified Rankin score of 2 or less at 90 days was not statistically significant: RR 1.18 (95% CI 0.66 to 2.1).

In 2014, Tomisk et al published a subgroup analysis of the IMS-III trial focusing on subjects with intracranial internal carotid artery (ICA) or M1 occlusion. This analysis included 200 subjects, 65 with intracranial ICA and 135 with M1 segments as the target vessel for revascularization. Of these, at angiography, 82% had an arterial occlusive lesion (AOL) score of 2-3 and 76% had a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2-3 (partial or full perfusion) after IV-tPA, which may have limited the potential benefit for device-related revascularization. Ninety-day Rankin scale scores were higher with higher mTICI scores: of 32 subjects with an mTICI score of 0, 3.1% had a modified Rankin scale score of 0-2 at 90 days, compared with 12.5%, 19.4%, 46.3%, and 80% for subjects with mTICI scores of 1 (total N=16), 2a (total N=67), 2b (total N=80) and 3 (N=5), respectively. To account for potential bias in the choice of endovascular therapy, propensity score analysis was used to compare subjects with different endovascular therapy modalities for the primary study outcomes. After propensity score adjustment, the authors found no clear differences in clinical or revascularization
outcomes across revascularization methods, which included standard microcatheter thrombolysis (N=51), the Ekos catheter (N=14), the Merci retriever (N=77), the Penumbra device (N=39), the Solitaire device (N=4), and other methods (N=15).

In another IMS-III subgroup analysis, Demchuck et al evaluated the association between baseline CT or magnetic resonance (MR) angiography findings and outcomes among 306 (47% of 656) who had baseline CT or MR angiographic imaging available. (13) Ninety-two percent of those with angiography available had arterial occlusions demonstrated, 220 of which were proximal occlusions. Endovascular therapy group subjects with proximal occlusions had higher 24-hour recanalization rates than those with IV tPA only (84.3% of endovascular therapy subjects vs 56% of controls; P<0.001). However, no difference in the primary outcome, 90-day modified Rankin scale score of 0-2, was seen with proximal occlusions between groups (41.3% of endovascular therapy subjects vs 38% of controls; relative risk [RR] 1.07 [99% CI 0.67 to 1.70]).

Strengths of these 4 trials evaluating endovascular treatments for acute stroke include their randomized design and multisite recruitment. A potential strength was that, in general, the endovascular intervention 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 of 334 of those who received endovascular therapy received intra-arterial tPA only; in SYNTHEHSIS Expansion 109 of 165 of those who received endovascular therapy received intra-arterial tPA with clot fragmentation with a guidewire but without device deployment. (10) In contrast, in the most recently-published trial, MR CLEAN, most intervention-group subjects (83.7%) received an endovascular mechanical therapy. In addition, the 3 trials published in 2013 (Broderick et al, Kidwell et al, Ciccone et al) 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. Again, the Berkhemer et al (MR CLEAN) study differed in that a high proportion of intervention subjects received a retrievable stent (81.5%). 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 contrast with IMS III and the Ciccone et al study, MR CLEAN required a radiologically proven intracranial occlusion for study eligibility.

RCTs Comparing Different Endovascular Therapies

In 2012, 2 noninferiority RCTs comparing newer devices to the Merci Retriever were completed as part of the U.S. Food and Drug Administration (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. (14) 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 to 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.(15) 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. (16) Revascularization rates were 86% in the Trevo group versus 60% in the MERCI group (p<0.0001). Procedure-related adverse events occurred in 15% of the Trevo group and 23% in the Merci group; p=0.1826). 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. have 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.(17)

**Systematic reviews**

In 2014, a Blue Cross and Blue Shield Association (BCBSA) TEC Assessment evaluated endovascular therapy for acute ischemic stroke in adults.(18) The Assessment identified 5 multicenter RCTs meeting selection criteria, 3 of which compared endovascular treatment with standard stroke care (Broderick et al(11), Ciccone et al(10), and Kidwell et al(9), and 2 of which newer and older endovascular treatments (Saver et al(14) and Nogueira et al(16)). The Assessment made the overall observations and conclusions:

“The 3 RCTs published in early 2013 concluded that endovascular treatment is no more effective than IV tPA in reducing disability among patients with acute ischemic stroke treated 3 to 8 hours after symptom onset. Although specific aspects of these trials have been criticized, we identified no RCTs that demonstrate endovascular treatments produce better health outcomes. Use of newer FDA-cleared endovascular devices was allowed. A major limitation in generalizing from these studies is that the number of patients treated with each of these newer devices was small. Therefore, as noted by critics of the trials, evidence on the newest devices may not substantively impact the overall outcomes. If the newer devices are more effective than the older ones, the results might be dominated by the performance of the less effective, older device(s).”

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.(19) 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,(20) and a small feasibility study including 7 patients to compare intra-arterial tPA to standard IV
tPA, reported by Sen et al. in 2009.(21) 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.(19) 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. (22) published a systematic review in 2012 that evaluated clinical outcomes from endovascular therapy compared to 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 <2 or a Barthel index of 90-100, was attained by a greater percentage of patients in the endovascular group compared to the thrombolysis group (33.6% vs. 24.9%, p=0.004). Symptomatic intracranial hemorrhage was also more common in the endovascular group compared to thrombolysis (11.1% vs. 4.9%, p=0.001).

Almekhlafi et al. (23) 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 to 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. (24) 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 of these were case series or case reports, 18 were prospective single-arm studies, and 7 were retrospective single-arm studies. The rate of successful recanalization, defined as Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 or 3, ranged from 43-100% across all studies. Higher rates of recanalization were reported with the Penumbra System (83-100%) compared to either the Merci Retriever (43-78%) or other devices (50-90%). Clinical effectiveness was determined by a post-treatment Rankin score of 0-2, a measure that was available in 17/25 studies. There was a wide range of clinical effectiveness, from 15% to 60% of treated patients. The rate of symptomatic intracranial hemorrhage ranged from 0-25%, and the rate of asymptomatic intracranial hemorrhage ranged from 1-43%.

In 2008, Stead and colleagues conducted a systematic review and meta-analysis of percutaneous clot removal devices. (25) 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, post-procedural 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 one device over others was not demonstrated in accessing the lesion, retrieving the clot, or in clinical outcome. Pooled data were compared to the placebo arm and intra-arterial thrombolysis arm of the PROACT II (Prolyse in Acute Cerebral Thromboembolism II) study, (26) comparing intravenous and intra-arterial tissue plasminogen activator (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 to historical controls, while recognizing the limitation of small study sizes and non-randomized comparator groups.

Non-Randomized Comparative Studies
A number of non-randomized, comparative studies have been published that compare endovascular interventions with historical 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. (27) 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 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% confidence interval [CI]: 1.3 to 4.1, p=0.003).

Urra et al conducted a prospective comparative study comparing endovascular therapy with IV thrombolysis alone in patients presenting with acute ischemic stroke due to large vessel occlusion and mild symptoms (NIHSS score ≤ 5).(28) The study included 78 patients, 34 treated with endovascular therapy and 44 treated medically. Compared with medical therapy alone, endovascular therapy was associated with higher rates of successful revascularization (91.2% vs 63.4%; P=0.006), but also higher rates of symptomatic intracranial hemorrhage (11.8% vs 0%; P=0.033). After adjusting for covariates, endovascular therapy was not significantly associated with modified Rankin scale score at 3 months.

Song et al compared treatment with stent-retriever devices and intra-arterial thrombolysis among 105 patients with acute ischemic stroke treated at a single institution.(29) Fifty-five patients were treated with the Solitaire stent-retriever device, while 50 patients were treated with intra-arterial thrombolysis with urokinase. After adjusting for occlusion site and rescue treatment, treatment with the stent-retriever was associated with successful reperfusion (82.0% vs 47.3%; adjusted OR 5.21; 95% CI 1.92 to 13.14) and likelihood of a favorable clinical outcome at 3 months (54.05 vs 43.6%; OR 3.40; 95% CI 1.31 to 8.84). Rates of mortality and symptomatic intracranial hemorrhage did not differ significantly between groups.

Alexandrov et al. (30) treated 125 patients presenting with acute stroke with the Penumbra system. Outcomes of embolectomy were compared with historical 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, this was higher than the 40% recanalization rate reported with TPA. However, mortality at 3 months was higher in the embolectomy group compared to tPA (32.8% vs. 14.1%, p=0.008), and the rate of favorable functional outcome was lower (25% vs. 39%, p=0.046).

Taschner et al. (31) 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 to patients treated with tPA who were matched for stroke score and location. Recanalization with embolectomy was successful in 25/32 target vessels (78%) compared to 17/32 (53%) with tPA. A favorable outcome, defined as a stroke score of 0-1 or an improvement of at least 10 points, was present in 2/20 (10%) of patients treated with embolectomy, compared with 7/20 (35%) treated with tPA.

In 2005, Smith and colleagues reported the results of the MERCI trial. (32) 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 1,809 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 intent-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 to those with unsuccessful recanalization (46% vs. 10%, respectively; p<0.0001), and mortality was less (32% vs. 54%, respectively; p=0.01). The MERCI investigators compared their patients to the placebo arm of the PROACT II study to determine safety and efficacy of mechanical embolectomy.

In 2008, Smith and colleagues reported the results of the Multi MERCI trial, a prospective, international, multicenter, single-arm study. (33) 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 intravenous tPA but failed to completely recanalize their occluded vessel. A total of 1,088 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 to 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, since the inclusion criteria for the MERCI trial for location of occlusion differed from those used in PROACT II.(34) 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.(35)
Liebeskind et al conducted a pooled analysis of MERCI and Multi MERCI subjects to assess whether lesion configuration (I, L, or T clots and functional lesions based on collateral flow patterns) was associated with clinical outcomes in ICA strokes treated with mechanical thrombectomy. (36) Seventy-two patients were included in the analysis, 32.6%, 31.9%, and 8.3% of whom received IV tPA, intra-arterial tPA, and other endovascular devices in addition to the MERCI, respectively. The presence of a functional T lesion, with insufficient collateral flow to ipsilateral anterior cerebral arteries, was associated with successful revascularization (TIMI grade 2-3; adjusted OR 0.25; 95% CI 0.09 to 0.69; P=0.007) and 90-day good clinical outcomes (adjusted OR 0.08; 95% CI 0.01 to 0.69; P=0.021).

Nonrandomized, Comparative Studies Evaluating Specific Endovascular Intervention
Some non-randomized comparative studies have compared the outcomes of different types of endovascular interventions.

Kappelhof et al published results of a systematic review and meta-analysis of studies comparing outcomes for mechanical therapy and intra-arterial thrombolysis for acute ischemic stroke due to ICA occlusion, with separate results reported for intracranial and extracranial occlusions. (37) The overall review included 32 studies, 6 of which (N=95) reported outcomes for intracranial occlusion treated by intra-arterial thrombolysis and 8 of which (N=115) reported outcomes for intracranial occlusion treated by mechanical thrombectomy. None of the recently-published RCTs of endovascular therapy were included in the review, which included studies published through July 2013 and specifically reporting outcomes for ICA occlusions. In the subset of studies reporting on intracranial occlusions, overall outcome rates were 55% recanalization, 12% symptomatic intracranial hemorrhage, 34% mortality, and 25% favorable outcome. Compared with intra-arterial fibrinolysis, mechanical thrombectomy was associated with a higher recanalization rate (69% vs 38%; P<0.001), a higher rate of favorable outcomes (34% vs 14%; P<0.001), with nonsignificantly different rates of death (29% vs 40%; P=0.085) and symptomatic intracranial hemorrhage (12.2% vs 11.7%; P=0.085).

For example, Turk et al conducted a retrospective, single-center review to compare clinical and cost-related outcomes for 3 endovascular interventions for acute stroke: the Penumbra system, stent retriever with local aspiration, and a “Direct Aspiration First Pass Technique” (ADAPT), which involves direct aspiration with a large bore catheter. (38) Two hundred twenty-two patients underwent endovascular therapies for acute stroke during the study time period, 128 (58%) with the Penumbra system, 30 (13%) underwent with a stent retriever, and 64 (29%) underwent ADAPT. Recanalization rates (TICI 2b/3) were higher in the ADAPT group compared with the Penumbra group (95% vs 73%; P=0.0027), but no significant differences were seen across groups in 90-day modified Rankin scale scores.

Broussalis et al. (39) 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 and colleagues compared the Trevo versus Solitaire devices in a prospective, non-randomized comparison of 33 patients with anterior cerebral circulation occlusions. (40) 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. (41) 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% 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. (42) 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 one registry study, for example, investigators found severe outcomes (modified Rankin score of 4 or 5, or death) in 68% of patients with basilar artery occlusion. (43)

A limited number of studies have 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 to 2012. (44) 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 United States in the remaining 25%. Endovascular patients were more likely to achieve a TICI 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, MR RESCUE, and MR CLEAN 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 thrombolitics or mechanical embolectomy with the Merci device. (46) Multiple small, single-center case series (47-48) and other smaller case series that often include only intermediate outcomes such as vessel recanalization (49-52) evaluating endovascular treatments for acute stroke, exist in the literature.

In 2013 and 2014, multiple noncomparative studies reporting outcomes from endovascular therapies with the newer generation stent-retriever devices which are currently FDA-approved (Solitaire FR and Trevo) and with non-FDA approved devices, such as the Penumbra Separator 3D, 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Primary Outcome</th>
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<tr>
<td>Zaidat et al (2014)(53)</td>
<td>Retrospective cohort (post-approval registry)</td>
<td>354 patients with acute ischemic stroke at 24 centers</td>
<td>Solitaire FR used as a first treatment choice</td>
<td>■ 40.2% of patients achieved TICI score 3; 72.5% TICI score ≥2b; 87.5% TICI score ≥2a. ■ 90-day modified Rankin scale score ≤2 in 42% of patients (N=315 with available 90-day outcomes)</td>
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<td>Behme et al (2014) (54)</td>
<td>Retrospective cohort study</td>
<td>129 patients with acute ischemic stroke due to large vessel occlusion at 2 centers; 16% with vertebrobasilar occlusion</td>
<td>Penumbra Separator 3D (investigational device), with intra-arterial eptifibatide; IV tPA given for eligible patients (78%)</td>
<td>■ 74% of patients achieved successful recanalization (TICI score ≥2b) ■ 90-day modified Rankin scale score 0-2 in 43% of patients ■ 90-day all-cause mortality 30%</td>
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<td>Mendonca et al (2014)(55)</td>
<td>Prospective case series</td>
<td>33 patients with acute ischemic stroke and angiographically-confirmed anterior circulation occlusion</td>
<td>A single Trevo (N=13) or Solitaire (N=20) device, with or without intra-arterial tPA; IV tPA given for eligible patients (38% of Trevo group and 50% of Solitaire group)</td>
<td>■ TICI score ≥2a recanalization achieved in 10 patients (77%) with the Trevo and in 12 patients 60% with the Solitaire. • At 3 months, 38% of Trevo patients and 40% of Solitaire patients had a good clinical outcome (P=0.435)</td>
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<td>Eugene et al (2014)(56)</td>
<td>Prospective case series</td>
<td>39 patients with acute ischemic stroke with at least 1 year of follow up available</td>
<td>Solitaire device, with or without IV tPA as indicated.</td>
<td>■ TICI score ≥2b achieved in 39/40 patients. ■ 62.5% of patients had a good clinical outcome. ■ Among 39 patients with available MRI at 1 year, intracranial artery abnormalities occurred in 10 patients.</td>
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<td>Gascou et al (2014)(57)</td>
<td>Prospective cohort study</td>
<td>144 patients with acute ischemic stroke with large vessel occlusion</td>
<td>Stent-retriever device used as first-line therapy (Solitaire FR in 138 subjects; Revive stent-retriever system in 6 subjects; Trevo device in 2 subjects)</td>
<td>■ 12.3% and 7.6% of subjects had embolic complications and symptomatic intracranial hemorrhages, respectively.</td>
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<td>Parilla et al (2014)(58)</td>
<td>Retrospective cohort study</td>
<td>150 patients with acute stroke treated at a single institution, N=116 aged &lt;80 years and N=34 aged ≥80 years</td>
<td>Stent-retriever device, with IV tPA for patients presenting &lt;4.5 h from stroke onset</td>
<td>Subjects), with IV tPA for patients presenting &lt;4.5 h from onset</td>
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<td>Nikoubashman et al (2014)(59)</td>
<td>Retrospective cohort study</td>
<td>113 patients who had mechanical stent-retriever thrombectomy for acute ischemic stroke and had available CT scan within 4.5 hours after thrombectomy</td>
<td>Solitaire FR or Trevo device, with or without IV and intra-arterial tPA</td>
<td>Proportion of patients achieving TICI &gt;2b score (88.2% for octogenarians vs 93.9%; P=0.1) and rates of symptomatic hemorrhage (5.95 for octogenarians vs 2.65; P=0.3) were similar for age groups</td>
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<td>Binning et al (2014)(60)</td>
<td>Retrospective analysis of prospectively collected cohort</td>
<td>52 patients with ischemic stroke treated at a single U.S. institution, 27 treated within 8 h of symptom onset and 25 treated beyond 8 h of symptom onset</td>
<td>Trevo device, with or without other intra-arterial devices and IV tPA</td>
<td>Postintervention subarachnoid hyperdensities occurred in 27/113 subjects (24%)</td>
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<td>Study</td>
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| Broussalis et al (2013)(61) | 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 2a  
□ 3-mo modified Rankin scale score 0-2 in 61% of patients |
| Cheang et al (2013)(62) | 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 ≥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 =0.45; 95% CI, 0.22 to 0.63; Fisher exact, p<0.001) |
| Cohen et al (2013)(63) | 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)(64) | Retrospective case series | 227 patients with acute anterior circulation ischemic stroke at a single institution | Solitaire FR stent, with or without thromboaspiration intra-arterial thrombolysis, percutaneous transluminal angioplasty, or intracranial or extracranial stent placement; not specified if IV tPA given | □ 70.9% of patients achieved successful recanalization (TICI score 2b-3)  
□ 3-mo Modified Rankin Scale score 0-2 in 39% of patients. Predictors of a favorable clinical outcome included successful reperfusion, higher ASPECT score, younger |
<table>
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<tr>
<th>Study/Source</th>
<th>Study Design</th>
<th>Study Details</th>
<th>Procedure and Treatment Details</th>
<th>Outcomes</th>
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</table>
| Mokin et al (2013)(65)             | 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)  
3-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)67             | 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 ≥2b) with the Solitaire FR stent alone  
3-mo Modified Rankin Scale score 0-2 in 57.9% of patients |
| Sanak et al (2013)68               | Prospective case series | 50 patients with acute middle cerebral, distal internal carotid artery, or basilar artery stroke at a single institution | Solitaire AB stent, with or without intra-arterial tPA; IV tPA given for patients presenting within 4.5 h of symptoms onset | 94% of patients achieved successful recanalization (TICI score ≥2a)  
3-mo Modified Rankin Scale score 0-2 in 60% of patients. Recanalization time predicted good clinical outcome |

IV: intravenous; NIHSS: National Institutes of Health Stroke Scale; TICI: Thrombolysis in Cerebral Infarction; tPA: tissue plasminogen activator.
Single-Arm Studies Evaluating Of Endovascular Intervention In Basilar Artery Occlusion
A number of studies have reported noncomparative evaluations of endovascular therapies for acute basilar artery occlusion. Son et al reported outcomes for 31 subjects with acute basilar artery occlusion treated with mechanical thrombectomy with the Solitaire stent (N=13) or manual aspiration thrombectomy using the Penumbra reperfusion catheter (N=18) at a single center. Successful recanalization (TICI score ≥2b) did not differ between devices: 84.6% with the Solitaire stent compared with 100% with the Penumbra catheter (P=0.168); similarly, 3-month modified Rankin scale scores did not differ between the groups (3.6 with the Solitaire stent vs 3.2 with the Penumbra catheter; P=0.726). 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 ≥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, ≥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 4 large RCTs published from 2013 to 2014. Three of these trials 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. The most recently-published trial, MR CLEAN, addresses some of the limitations of the earlier trials, with a high proportion of intervention subjects receiving newer-generation stent-retriever devices and with inclusion criteria that required the presence of a proximal arterial occlusion. With the MR CLEAN results, there is now some RCT evidence that endovascular mechanical thrombectomy may improve outcomes of acute ischemic stroke. Results of additional ongoing randomized controlled trials of mechanical embolectomy will be needed to support or refute the MR CLEAN results. Based on the currently-available body of evidence, mechanical embolectomy for acute ischemic stroke 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 humanitarian device exemption (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.
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.” (74)

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 RCTs, nonrandomized comparative studies, and systematic reviews are reviewed next. Since the publication of the RCT evidence, there continue to be single arm publications (i.e., with all subjects receiving endovascular stents) describing various aspects of stenting for intracranial stenosis, including utilization trends,(75), predictors of outcomes based on symptomatology,(76), predictors of outcomes based on lesion morphology and arterial access,(77) and clinical outcomes with the Wingspan system.(78)

**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 70-99%. (79) 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% confidence interval [CI]: 10.7-20.1) compared to a rate of 5.8% (95% CI: 3.4-9.7, 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: 15.2-26.0) in the stenting group compared to 12.2% (95% CI: 8.4-17.6, 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 to expected values.

The SAMMPRIS investigators have published results from long-term subject follow up.(80) Primary endpoints (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 an median follow up of 32.4 months, 34/227 (15%) of patients in the best medical management group and 52/224 (23%) of patients in the stenting group had a primary endpoint event, with a significantly higher cumulative probability of a primary endpoint in the stenting group than in the best medical management group (p=0.0252). 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%], [=0.047]) and major hemorrhage (29/224[13%] vs.10/227 [4%], p=0.0009). 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. (81) Endovascular intervention was technically successful in all 8 patients, but 2 patients experienced TIA at the time of endovascular treatment. During a mean follow-up of 4.7 years, no 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.

In 2013, Qureshi et al published results from another small RCT comparing angioplasty alone with angioplasty with a balloon-expanding stent among 18 subjects with moderate intracranial stenosis (stenosis ≥ 50%) with documented failure of medical treatment or severe stenosis (≥70%) with or without failure of medical treatment. (82) Technical success (<30% residual stenosis on immediate post-procedure angiography) occurred in 5/10 patients treated with angioplasty (9 randomized to angioplasty and 1 crossover from group randomized to stent placement) and 5/8 patients treated with stent placement. Rates of stroke or death were low in both groups: 1/10 in the angioplasty group and 0/8 in the stent placement group. This study suggests that angioplasty with stenting is feasible in patients with severe intracranial stenosis, but the small size and lack of statistical comparisons limit conclusions that can be drawn.

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 percutaneous transluminal angioplasty (PTA) and stenting for vertebral artery stenosis. Endovascular treatment of vertebral artery stenosis should only be performed within the context of randomized controlled trials.” (83) In addition, the authors noted, “little 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. (84) 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. (85) The authors identified 31 studies including 1,177 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% to 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.

In 2014, Abuzinadah conducted a systematic review and meta-analysis of studies reporting the rates of stroke recurrence or death (the primary outcome) in symptomatic intracranial verteobasilar stenosis with medical or endovascular treatment. (86) The authors identified 23 studies involving 592 medical treatment patients and 480 endovascular treatment patients. In pooled analysis, the stroke or death rate was 14.8 per 100 person-years (95% CI 9.5 to 20.1) in the medical therapy group and 8.9 per 100 person-years (95% CI 6.9 to 11.0) in the endovascular group (incidence rate ratio [IRR] 1.3; 95% CI 1.0 to 1.7). The stroke recurrence rate was 9.6 per 100 person-years (95% CI 5.1 to 14.1) in the medical group and 7.2 per 100 person-years (95% CI 5.5 to 9) in the endovascular group (IRR 1.1; 95% CI 0.8 to 1.5).

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 to medical therapy for intracranial atherosclerosis. A representative sample of such studies is given below. All are limited by their nonrandomized treatment assignments and systematic differences between groups.

Tang et al. (87) 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, TIA, or vascular death was not different for the stent group compared to medical therapy (22.6% vs. 24.6%, respectively; p=0.99). A good functional outcome, defined as a modified Rankin Score of 0-3, was more frequent in the stent group compared to 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). (88) 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 to angioplasty and stenting in 111 patients with symptomatic intracranial atherosclerotic disease treated from July 2004 to September 2007. (89) 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 endpoints 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
Three self-expanding stents, the Neuroform Microdelivery Stent System, the Enterprise Vascular Reconstruction Device and Delivery System, and the Low-Profile Visualized Intraluminal Support Device, have FDA approval through the HDE program for the endovascular treatment intracranial aneurysms. The literature search did not identify any 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, nonrandomized comparative studies, and one systematic review of nonrandomized comparative studies.

Systematic Reviews
In 2014, Hong et al reported results of a systematic review and meta-analysis of studies that compared stent-assisted coiling with coiling alone for the treatment of intracranial aneurysms. (90) The authors included 10 retrospective cohort studies, ranging in size from 9 to 1109 patients. In pooled analysis, compared with coiling alone, stent-assisted coiling was associated with higher rates of progressive thrombosis (37.5% vs 19.4%; OR 2.75; 95% CI 1.95 to 3.86; P<0.00001) and lower rates of recurrence (16.2% vs 34.4%; OR 0.35; 95% CI 0.25 to 0.49; P<0.00001). Mortality was 9.1% for stent-assisted coiling, compared with 2.6% for coiling alone, although the difference was not statistically significant (OR 2.31; 95% CI 0.68 to 7.82; P=0.18). Similarly, permanent complication rates and thromboembolic complication rates were not significantly different between the two groups.

Nonrandomized comparative studies
The largest comparative series describing use of stents compared to coiling alone for treating intracranial aneurysms was described by Piotin and colleagues. (91) They report on a series of 1,137 patients (1,325 aneurysms) treated between 2002 and 2009. In this series, 1,109 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 neurological procedure-related complications occurred in
7.4% (16 of 216) of the procedures with stents versus 3.8% (42 of 1,109) in the procedures without stents (logistic regression p=0.644; odds ratio: 1.289; 95% CI: 0.439–3.779). Procedure-induced mortality occurred in 4.6% (10 of 216) of the procedures with stents versus 1.2% (13 of 1,109) in the procedures without stents (logistic regression p=0.006; odds ratio: 0.116; 95% CI: 0.025–0.531). Thus far, the authors have followed 53% (114 of 216) of aneurysms treated with stents and 70% (774 of 1,109) of aneurysms treated without stents, with angiographic recurrence in 14.9% (17 of 114) versus 33.5% (259 of 774), respectively (p<0.0001; odds ratio: 0.3485; 95% CI: 0.2038–0.5960).

Colby et al. (92) 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 to 31.7% of non-stented 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 non-stented group (p<0.05).

A nonrandomized comparative study from Korea (93) reported on 126 aneurysms that were treated with stent-assisted coiling compared to 86 patients treated with coil alone. At 2 years of follow-up, the authors reported rates of occlusion and recurrence. Progressive occlusion was noted in 42.5% of the stent group (17/40) compared to 39.5% of the non-stented 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 non-stent 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(94). 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 were similar for the two stent types, but symptomatic thromboembolic events were more frequent with the Enterprise stent (8.7% vs 1.4%, p = 0.0021).

Hetts et al compared outcomes for patients treated with stent-assisted coiling with those treated with coiling alone for patients with unruptured intracranial aneurysms enrolled in the prospective, nonrandomized, multicenter Matrix and Platinum Science (MAPS) Trial, which was designed to compare bare-metal aneurysm coils and polymer-coated aneurysm coils. (95) One-hundred thirty-seven patients were included who received a stent-assisted coil, along with 224 patients treated with coiling alone. Patients treated with stent-assisted coiling more often had wide-neck aneurysms (62% vs 33%; P<0.0001) and had aneurysms with lower dome-to-neck ratio (1.3 vs 1.8; P<0.0001). Periprocedural serious adverse events occurred in 6.6% of those treated with stent-assisted-coiling, compared with 4.5% of those treated with coiling alone (P=0.039). At 1 year, ischemic strokes were
more common in patients who received a stent-assisted coil than in patients who received a coil alone (8.8% vs 2.2%; P=0.005). However, in multivariable analysis, stent use did not independently predict ischemic stroke at 2 years (adjusted OR 1.1; P=0.94).

Liu et al compared outcomes for patients with posterior communicating artery aneurysms treated with stent-assisted coiling with those treated with coiling alone in a retrospective comparative study. (96) A total of 291 coiling procedures were performed, including 56 aneurysms treated with a self-expandable stent. Complete aneurysm occlusion on initial angiography occurred in 41.1% of stent-assisted coiling patients compared with 35.3% of non-stented patients (statistical comparison not reported). At last follow up (mean 14.3 months for stent-assisted coiling and 13.2 months for non-stent patients), aneurysms recurred in 10.6% of stent-assisted coiling patients compared with 28.1% of non-stent patients (P=0.014). Procedural complications occurred in 10.7% of stent-assisted coiling patients compared with 11.5% of non-stent patients (stated to be nonsignificantly different).

### 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. (97) identified 39 articles reporting on 1,517 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 post-treatment, 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. (98) 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.(99) 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 post-procedure (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 reoccurrence over long-term follow up. Other representative noncomparative studies are summarized in the table below. Interpretation of these studies is limited by potential selection bias and no comparison group In
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.

### Noncomparative Studies of Stent-Assisted Endovascular Treatment of Aneurysms

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Primary Outcome</th>
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| Chalouhi et al., 2013 (100) | Retrospective case series | 76 patients with posterior cerebellar artery (PICA) aneurysms at a single institution | Endovascular coiling, with or without Neuroform stent assistance (4 patients) or balloon assistance (4 patients). | - 93.4% of patients had 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, or no disability) were achieved in 85%. |
| Chen et al., 2013 (101) | 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 (102) | 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 post-procedure.  
- At follow up at 12-18 months, 5 patients (5%) had delayed complications, with 3% of patients with thromboembolic events.  
- Of 93 patients with anatomic evaluation available, aneurysms reoccurred in 9.7%. |
| Johnson et al., 2013 (103) | Retrospective case series | 91 patients with complex MCA aneurysms not amenable to coiling enrolled at a single institution | Endovascular treatment with coiling with stent assistance using Neuroform (62 aneurysms), Enterprise (32 aneurysms), Wingspan (1 aneurysm), or a combination (5 aneurysms) or with | - All patients had technically successful treatment.  
- 9 patients had new neurologic symptoms following the procedure, one with long-term disability. There was 1 procedure-related death.  
- Of 85 aneurysms with initial follow up imaging available |
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.(8) Investigators enrolled 108 patients at 10 centers with unruptured large- or giant-necked aneurysms measuring at least 10 mm in diameter with aneurysms necks of at least 4 mm who underwent placement of one 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 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 endpoint 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 endpoint (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 to standard neurosurgical treatment, i.e., surgical clipping or endovascular coils. The available evidence related to the use of flow-diverting stents consists of one 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 alone, 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 Ranking 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 did had a modified Rankin Scale score 0-2 (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.

In 2014, van Rooij et al reported outcomes for 550 consecutive patients treated with endovascular methods for intracranial aneurysms at a single European center from 2009 to 2013. Endovascular treatments consisted of selective coiling in 445 (80.8%), stent-assisted coiling in 68 (12.4%), balloon-assisted coiling in 13 (2.4%), parent vessel occlusion in 12 (2.2%) and flow diverter treatment in 12 (2.2%). Among the 11 patients treated with flow divertors, 2 patients had ruptured dissecting aneurysms, 2 deaths occurred, 1 patient had permanent morbidity, and 2 aneurysms were not occluded at 30 months follow-up. Direct comparisons with outcomes from alternative treatments are not reported.

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

Also in 2013, Arrese et al. reported results of a meta-analysis that used somewhat more restrictive inclusion criteria included 897 patients with 1018 aneurysms reported in a total of 15 studies. All studies that they included 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 neurological morbidity. Similar to the Brinjikji meta-analysis, this study found a high overall rate of complete aneurysmal occlusion (76.2% [95% CI 72.1-80.2]), 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%–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 find that p<0.001 for the Egger’s test for both early and late morbidity and aneurysm occlusion, suggestive of publication bias.

Since the publication of these two meta-analyses, several additional noncomparative studies evaluating flow-diverting stents in the treatment of aneurysms have been published. The largest cohort study identified was by Kallmes et al, who conducted a retrospective analysis of patients treated with the Pipeline device at 17 centers worldwide. The authors identified 793 patients with 906 aneurysms, 311 were in the anterior ICA circulation and at least 10 mm, 349 of which were in the anterior circulation and less than 10 mm, 59 of which were in the posterior circulation, 179 of which were in a non-ICA anterior circulation location and less than 10 mm, and 10 of which had no aneurysm size specified. Overall neurologic morbidity and mortality was 8.4%, highest in the posterior circulation group and lowest in the ICA, less than 10 mm group (16.4% vs 4.8%; P=0.01. The overall spontaneous rupture rate was 0.6%, and the intracranial hemorrhage rate was 2.4%. Ischemic stroke rates were 4.7%, again highest in the posterior circulation group and lowest in the ICA, less than 10 mm group (7.3% vs 2.7%; P=0.16).

Representative studies, with a focus on series with more than 50 patients, are summarized in Table 3.

### Noncomparative Studies of Flow-Diverting Stent-Assisted Endovascular Treatment of Aneurysms

<table>
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<tr>
<th>Study</th>
<th>Study Type</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Primary Outcome</th>
</tr>
</thead>
</table>
| Lubicz et al (2014) (110) | Retrospective review of prospectively collected data | 58 patients with no intracranial aneurysms treated at 2 institutions | SILK artery recollection device (Balt Extrusion, Montmorency, France) | • No periprocedural deaths occurred.  
• Overall permanent neurological morbidity was 5.5%  
• At long term followup, 73% had complete occlusion, 16% had neck remnants, and 11% had incomplete occlusion |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Patients/Device Details</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wakhloo et al. (2014)(111)</td>
<td>Prospective trial</td>
<td>165 patients with 190 intracranial neurysms</td>
<td>• At 6 month follow up, permanent neurological morbidity was 6% and permanent neurological mortality was 2.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surpass flow diverting device (Styker Neurovascular, Fremont, Ca)</td>
<td>• Neurologic death during follow up occurred in 1.6% of patients with anterior circulation aneurysms and 7.4% with posterior circulation aneurysms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Ischemic stroke at ≤ SAH at ≤ days, and intraparenchymal hemorrhage at ≤7days occurred in 3.7%, 2.5%, and 2.5% of subjects respectively.</td>
</tr>
<tr>
<td>Kan et al., 2013 (112)</td>
<td>Prospective case series (registry)</td>
<td>56 patients with intracranial aneurysm treated at 7 institutions</td>
<td>• 6/123 devices incompletely deployed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pipeline Embolization Device placement.</td>
<td>• Among 19 patients with 6 month follow up, 68% (13 patients) had complete aneurysm occlusion.</td>
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<td></td>
<td></td>
<td>• 4 fatal post-procedural hemorrhages occurred.</td>
</tr>
<tr>
<td>Lin et al., 41 (113)</td>
<td>Retrospective case series</td>
<td>41 patients with small (&lt;10 mm) aneurysm at a single institution</td>
<td>• 80% of patients had complete or near-complete aneurysm occlusion.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pipeline Embolization Device placement</td>
<td>• One patient (2.3%) had a major periprocedural complication (death).</td>
</tr>
<tr>
<td>Malatesta et al., 2013 (114)</td>
<td>Retrospective case series</td>
<td>28 patients with intracranial aneurysm at a single institution</td>
<td>• 89% of aneurysms had complete occlusion at 12 months.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flow-diverting stent placement (Pipeline Embolization Device or SILK device) [Balt Extrusion, Montmorency, France])</td>
<td>• One death occurred.</td>
</tr>
<tr>
<td>Piano et al., 2013 (115)</td>
<td>Retrospective case series</td>
<td>101 patients with intracranial aneurysm at a single institution</td>
<td>• 86% of aneurysms evaluated at 6 month follow up showed complete occlusion.</td>
</tr>
</tbody>
</table>
Toma et al., 2013 (116)  Retrospective case series  84 patients with intracranial aneurysm at a single institution  Flow-diverting stent placement  • 61% of aneurysms had resolved at 12 months.  • 9.5% of patients had a new, permanent neurologic deficit and 5.9% of patients had procedure-related mortality.

Yavuz et al., 2013 (117)  Retrospective case series  25 patients with middle carotid aneurysm at the carotid bifurcation at a single institution  Pipeling Embolization Device placement  • 84% of patients had complete aneurysm occlusion.

SAH: subarachnoid hemorrhage

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 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.

Ongoing Studies

Endovascular Interventions for Acute Ischemic Stroke

A query of the online database ClinicalTrials.gov in December 2014 identified a large number of studies are evaluating endovascular intracranial interventions for acute stroke. The following are RCTs that are evaluations of endovascular interventions compared with alternative treatment for acute stroke:

- EndoVascular Treatment With Solitaire FR® vs. Best Medical Therapy in Acute Ischemic Stroke (RESILIENT) (NCT02216643) – This is a randomized, single-blinded trial to compare the Solitaire device with best medical therapy for patients with acute ischemic stroke in patients presenting up to 6 hours from stroke onset who are either ineligible for IV alteplase or have received IV alteplase therapy without recanalization. The primary outcome measure is modified Rankin scale score
distribution. Enrollment is planned for 690 subjects, with an estimated study completion date of October 2017.

- **Endovascular Acute Stroke Intervention Trial - the EASI Trial (NCT02157532)** – This is a randomized, single-blinded trial to compare mechanical thrombectomy with best standard treatment for patients with acute ischemic stroke with onset of symptoms less than 5 hours prior to randomization or symptom/imaging mismatch. Enrollment is planned for 480 subjects; the planned study completion date is January 2018 with follow up through January 2020.

- **Endovascular Arterial Reperfusion vs. Intravenous Thrombolytic Therapy 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 > 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. The study has been halted for efficacy at an enrollment of 316.

- **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 device, a self-expanding stent-retriever) or a control group (IV tPA). The primary outcome is modified Rankin scale score of ≤2 at 90 days post-intervention. 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 (rTPA). 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, but the study was terminated after interim analysis of 174 patients by its data safety and monitoring board.

- **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 stroke 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 wakening, 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, but the study status has not been recently verified.

- **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 2014 identified a large number of studies evaluating endovascular intracranial interventions for atherosclerotic disease or aneurysms. The following are randomized, controlled studies that are evaluations of endovascular interventions compared to alternative treatment for symptomatic intracranial atherosclerotic disease:

- **China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A Prospective Multi-center, Randomized Controlled Trial** (NCT01763320). This study randomly assigns patients with symptomatic intracranial stenosis (transient ischemic attack or non-severe 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 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 2017.

- **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 transient ischemic attack 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 endpoint is stroke or transient ischemic attack 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. This study has been terminated.
Stent-Assisted Treatment of Intracranial Aneurysms

The following are randomized, controlled studies that are evaluations of endovascular interventions (angioplasty or stenting) compared to 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 4-10 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 one intracranial aneurysm that is large (≥10mm), wide-necked (>4mm), 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 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 non-inferiority of the experimental procedure in terms of a combined safety and efficacy outcome at 180 days post-enrollment. Enrollment is planned for 316 patients, and the estimated study completion date is listed as April 2018.
Practice Guidelines and Position Statements

In 2005, The American Society of Interventional and Therapeutic Neuroradiology (ASITN), the Society of Interventional Radiology (SIR), and the American Society of Neuroradiology (ASNR) jointly published a position paper regarding angioplasty and stenting for cerebral atherosclerosis. (118) This position statement reviewed a number of case series and also the SSYLVIA and Wingspan multi-institutional studies. The following position statement was offered, although the underlying rationale and process for development for the position statement was not provided:

“The ASITN, SIR, and ASNR concur that sufficient evidence now exists to recommend that intracranial angioplasty with or without stenting should be offered to symptomatic patients with intracranial stenoses who have failed medical therapy. Endovascular interventions are intensive services provided to patients who are at very high risk for strokes and typically have multiple co-morbidities. Similar to revascularization for extracranial carotid artery stenosis, patient benefit from revascularization for symptomatic intracranial arterial stenosis is critically dependent on a low per procedural stroke and death rate and should thus be performed by experienced neurinterventionists. We recommend reimbursement by third party insurers so that these patients may have access to such interventions. Continued attempts to improve the benefits of endovascular therapy are warranted.”

In 2013, the Society of Interventional Radiology (SIR) issued a position statement on endovascular acute ischemic stroke interventions.(119) The SIR position statement indicates intra-arterial revascularization for stroke is beneficial when tPA is inappropriate or unsuccessful. The SIR indicates, despite clinical trials finding mechanical thrombectomy is not a proven therapy, rapid treatment with mechanical thrombectomy devices improves outcomes for occlusions in large vessels. The need for clinical trials and/or a national registry is specified.

In April 2009, the American Heart Association (AHA), along with several other organizations, published an AHA scientific statement on indications for intracranial endovascular neuro-interventional procedures. (6) The recommendation related to endovascular treatment of symptomatic intracranial stenoses was noted as Class IIb, Level of Evidence C (usefulness/effectiveness is unknown/unclear). The level of evidence was the same for use of angioplasty and stenting in the treatment of acute ischemic stroke.

In early 2013, the AHA and the American Stroke Association (ASA) published guidelines for the early management of patients with acute ischemic stroke.(120) These guidelines include several recommendations relevant to the use of endovascular therapies for acute stroke:

- “Intra-arterial treatment requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified interventionalists. An emphasis on expeditious assessment and treatment should be made. Facilities are encouraged to define criteria that can be used to credential individuals who can perform intra-arterial revascularization procedures. Outcomes on all patients should be tracked (Class I; Level of Evidence C).
- “When mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and Trevo are generally preferred to coil retrievers such as Merci (Class I; Level of Evidence A). The relative effectiveness of the Penumbra System versus stent retrievers is not yet characterized.
• “The Merci, Penumbra System, Solitaire FR, and Trevo thrombectomy devices can be useful in achieving recanalization alone or in combination with pharmacological fibrinolysis in carefully selected patients (Class IIa; Level of Evidence B). Their ability to improve patient outcomes has not yet been established. These devices should continue to be studied in randomized controlled trials to determine the efficacy of such treatments in improving patient outcomes.

• “Intra-arterial fibrinolysis or mechanical thrombectomy is reasonable in patients who have contraindications to the use of intravenous fibrinolysis (Class IIa; Level of Evidence C).

• “Rescue intra-arterial fibrinolysis or mechanical thrombectomy may be reasonable approaches to recanalization in patients with large-artery occlusion who have not responded to intravenous fibrinolysis. Additional randomized trial data are needed (Class IIb; Level of Evidence B).

• “The usefulness of mechanical thrombectomy devices other than the Merci retriever, the Penumbra System, Solitaire FR, and Trevo is not well established (Class IIb; Level of Evidence C). These devices should be used in the setting of clinical trials.

• “The usefulness of emergent intracranial angioplasty and/or stenting is not well established. These procedures should be used in the setting of clinical trials (Class IIb; Level of Evidence C).”

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force (USPSTF) recommendations for treatment of intracranial arterial disease were identified. USPSTF recommends against screening for asymptomatic carotid artery stenosis in the general population.

Summary

For acute stroke, the strongest evidence on the efficacy of endovascular mechanical embolectomy for acute ischemic stroke comes from 4 large randomized controlled trials (RCTs), 3 of which failed to demonstrate significant benefits from the use of endovascular mechanical embolectomy compared with usual therapy. The most recently-published trial, MR CLEAN, addresses some of the limitations of the earlier trials, with a high proportion of intervention subjects receiving newer-generation stent-retriever devices and with inclusion criteria that required the presence of a proximal arterial occlusion. With the MR CLEAN results, there is now some RCT evidence that mechanical thrombectomy may improve outcomes of acute ischemic stroke. Results of additional ongoing randomized controlled trials of mechanical embolectomy will be needed to support or refute the MR CLEAN 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 not medically necessary. 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 not medically necessary 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. Comparative trials with
and without stenting for this clinical situation are unlikely. As a result, use of stent-assisted coiling with traditional stents 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. Similarly, no RCTs address the use of flow-diverting stents for the treatment of intracranial aneurysms. Thus, flow-diverting stents may be considered medically necessary for the treatment of intracranial aneurysms when surgical treatment is not appropriate and the aneurysms meet anatomic criteria.

**Medicare National Coverage Determination**

A Medicare National Coverage Determination (NCD) on intracranial angioplasty and stenting was released by the Centers for Medicare and Medicaid Services (CMS) in January 2007. (121) This decision was based on a review of available studies at that time, which consisted of several uncontrolled case series. The 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."

**References**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)</th>
</tr>
</thead>
</table>


51. Abou-Chebl A. Endovascular treatment of acute ischemic stroke may be safely performed with no time window limit in appropriately selected patients. Stroke. Sep 2010;41(9):1996-2000. PMID 20651271


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<thead>
<tr>
<th>Source</th>
<th>Title</th>
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<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>December 2011</td>
<td>New Policy</td>
<td>Rationale and references updated with literature review. No change to policy.</td>
</tr>
<tr>
<td>December 2012</td>
<td>Update Policy</td>
<td>Policy updated with literature review, References 4-7 added. Editorial revisions made to rationale. No change to policy statement.</td>
</tr>
<tr>
<td>September 2013</td>
<td>Update Policy</td>
<td>Policy Background and Rationale sections extensively revised and reorganized to incorporate indications and devices previously included in policy 2.01.76 Mechanical Embolectomy for Treatment of Acute Stroke ( Archived ). Policy updated with literature review through adding reference numbers 1, 3-5, 11, 13-16, 43-51, 56, 60, 67, 70-84 and 86-88. Policy statement from 2.01.76 added; no other change to policy statements.</td>
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<tr>
<td>September 2014</td>
<td>Update Policy</td>
<td>Policy statement added to provide clarity for medically necessary intent for FDA approved devices and their intended uses. No new references.</td>
</tr>
<tr>
<td>March 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review through December 12, 2014. References 3-5, 9, 13-14, 19-20, 30-31, 38-39, 54-61, 69, 75-78, 82, 86, 90, 95-96, 106, and 109-111 added. Language added to policy guidelines to specify that policy statements do not apply to endovascular interventions to treat cerebral ischemia resulting from vasospasm after aneurysmal subarachnoid hemorrhage. Policy statements otherwise unchanged.</td>
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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 20, 2015 and is effective April 15, 2015.

Signature on file
Deborah M. Smith, MD, MPH