DRAFT

BlueCross BlueShield of Alabama

Name of Policy:

Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

Policy #: 263
Category: Surgery

Latest Review Date: April 2018
Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

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

Cerebrovascular diseases include a range of processes affecting the cerebral vascular system, including arterial thromboembolism, arterial stenosis, and arterial aneurysms, all of which can lead to restrictions in cerebral blood flow due to ischemia or hemorrhage. Endovascular techniques, including endovascular 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 U.S., Canada, Europe and Japan and is the leading cause of adult disability in the U.S. Eighty-seven percent of strokes are ischemic and 13% hemorrhagic. Differentiation between the two types of stroke is necessary to determine the appropriate treatment. Ischemic stroke occurs when an artery to the brain is blocked by a blood clot, which forms in the artery (thrombotic), or when another substance (i.e., plaque, fatty material) or a blood clot travels to an artery in the brain causing a blockage (embolism). Recanalization of the vessel, particularly in the first few hours after occlusion, has been shown to reduce rates of disability and death.

Treatment

The prompt use of intravenous (IV) thrombolytic therapy with recombinant tissue plasminogen activator (tPA) to recanalize occluded blood vessels has been associated with improved outcomes in multiple randomized controlled trials (RCTs) and meta-analyses. Therefore, use of IV tPA in ischemic stroke patients presenting within three hours (up to 4.5 hours in some cases) of stroke onset in expert centers is recommended.

Despite the potential benefits of IV tPA in eligible patients who present within the appropriate time window, limitations to reperfusion therapy with IV tPA have prompted investigations of alternative acute stroke therapies. These limitations include:

- **Requirement for treatment within 4.5 hours of stroke onset.** Relatively few patients present for care within the time window in which tPA has shown benefit. In addition, determining the time of onset of symptoms is challenging in patients awakening with symptoms of acute stroke; patients with symptoms on awakening are considered to have symptom onset when they went to sleep. In 2010 to 2011, fewer than 10% of all ischemic stroke patients arrived at the hospital and received IV tPA within the three hour window.
- **Risks associated with IV tPA therapy.** tPA is associated with increased risk of intracranial bleeding. It is contraindicated in hemorrhagic stroke and in some ischemic

stroke patients for whom the risk of bleeding outweighs the potential benefit, such as those with mild or resolving symptoms, hypocoagulable state, or advanced age.
- **Variable recanalization rates.** For patients receiving tPA, recanalization rates are around 21% and range from about 4% in the distal internal carotid artery and basilar artery to about 32% in the middle cerebral artery. The treatment of large-vessel strokes with IV tPA may be less successful.

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.

Several types of endovascular treatments for ischemic strokes have been considered:
- **Intra-arterial fibrinolytic therapy (i.e., intra-arterial tPA).** Although tPA only has approval from the U.S. Food and Drug Association (FDA) for its intravenous route of delivery, intra-arterial tPA has been 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.
- **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.
- **Endovascular mechanical embolectomy.** Endovascular embolectomy devices remove or disrupt clots by a number of mechanisms. Four devices have FDA approval for treatment of acute stroke (see "Approved Governing Bodies" section), 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 evidence review focuses on the devices listed above with an indication for endovascular embolectomy for acute stroke. Additional retrievable stent devices are under investigation, such as the Embolus Retriever with Interlinked Cages (ERIC, MicroVention, Tustin, CA).

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 (e.g., calcium channel blockers) and transluminal balloon angioplasty may be used. 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 review.

Intracranial Atherosclerotic Stenosis

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% to 12% per year with atherosclerosis of the intracranial anterior circulation and 2.5% to 15% per year with lesions of the posterior (vertebrobasilar) circulation.

Treatment

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 one month of the initial recurrence. Surgical approaches have met with limited success. The widely quoted extracranial-intracranial (EC/IC) bypass study randomized 1377 patients with symptomatic atherosclerosis of the internal carotid or middle cerebral arteries to medical care or EC/IC bypass. The outcomes in the 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 have focused on the vertebrobasilar circulation. Two endovascular devices have FDA approval for treatment of symptomatic intracranial stenosis and are considered here (see "Approved Governing Bodies").

Intracranial Aneurysms

Compared with acute ischemic stroke, cerebral aneurysms have a much lower incidence among the U.S. population, with prevalence between 0.5% and 6% of the population. However, they are associated with significant morbidity and mortality due to subarachnoid hemorrhage resulting from aneurysm rupture.

Treatment
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 has grown, stenting was also used in smaller berry aneurysms as an approach to decrease the rate of retreatment needed in patients who receive coiling. A randomized trial has demonstrated that treatment of ruptured intracranial aneurysms with coiling leads to improved short-term outcome compared with surgical clipping; however, patients who receive coiling need more repeat/follow-up procedures. In 2011, the Pipeline® Embolization Device, which falls into a new device category called "intracranial aneurysm flow diverters," or flow-diverting stent, received FDA premarket approval for endovascular treatment of large or giant wide-necked intracranial aneurysms in the internal carotid artery. The Pipeline device is a braided, wire mesh device that is placed within the parent artery of an aneurysm to redirect blood flow away from the aneurysm with the goal of preventing aneurysm rupture and possibly decreasing aneurysm size.

Policy:

Effective for dates of service on and after May 1, 2018:

Intracranial stent placement meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage as part of the **endovascular treatment of intracranial aneurysms** for patients **when surgical treatment is not appropriate and standard endovascular techniques do not allow for complete isolation of the aneurysm**(e.g., wide-neck aneurysm (4mm or more) or sack-to-neck ratio less than 2:1).

Intracranial flow diverting stents with FDA approval for the treatment of intracranial aneurysms meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage as part of the **endovascular treatment of intracranial aneurysms for patients with large or giant wide-necked intracranial aneurysms, with a size of 10mm or more and a neck diameter of 4mm or more, in the internal carotid artery from the petrous to the superior hypophyseal segments AND are not amenable to surgical treatment or standard endovascular therapy.**

Intracranial stent placement does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** in the **treatment of intracranial aneurysms except as noted above.**

Intracranial percutaneous transluminal angioplasty with or without stenting does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** in the **treatment of atherosclerotic cerebrovascular disease**.

The use of endovascular mechanical embolectomy with an FDA approved device for the treatment of **acute ischemic stroke meets** Blue Cross and Blue Shield of Alabama **as part of the treatment of acute ischemic stroke for patients who meet all of the following criteria**:

- Have a demonstrated occlusion within the proximal intracranial anterior circulation (intracranial internal carotid artery, or M1 or M2 segments of the middle cerebral artery, or A1 or A2 segments of the anterior cerebral artery); **AND**
- Can receive endovascular mechanical embolectomy:
    - within 12 hours of symptom onset **OR**
    - within 24 hours of symptom onset if there is evidence of a mismatch between specific clinical and imaging criteria which meets the following criteria:

        - 6 to 24 hours related to mismatch between severity of clinical deficit and infarct volume:
            - ≥80 years of age, score ≥10 on the NIHSS, and had an infarct volume <21 mL; **OR**
            - ≤80 years age, score of ≥10 on the NIHSS, and had an infarct volume <31 mL; **OR**
            - ≤80 years of age, had a score ≥20 on the NIHSS, and had an infarct volume of 31 to <51 mL

            OR

        - 6 to 16 hours related to mismatch between severity of clinical deficit and infarct volume:
            - Infarct size of <70 mL; **AND**
            - Ratio of ischemic tissue volume to infarct volume of ≥1.8; **AND**
            - Ischemic penumbra of ≥15 cm^3

- Have evidence of substantial and clinically significant neurological deficits (i.e. NIHSS score ≥2); **AND**
- Have evidence of salvageable brain tissue in the affected vascular territory; **AND**
- Have no evidence of intracranial hemorrhage or arterial dissection on computed tomography (CT) or magnetic resonance imaging.

Endovascular mechanical embolectomy does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational for the treatment of acute ischemic stroke when the above criteria are not met.**

Other endovascular interventions (angioplasty, stenting) do not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational for the treatment of acute ischemic stroke.**

Effective for dates of service on and after October 1, 2015 through April 30, 2018:
Intracranial stent placement meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage as part of the **endovascular treatment of intracranial aneurysms** for patients **when surgical treatment is not appropriate and standard endovascular techniques do not**

allow for complete isolation of the aneurysm(e.g., wide-neck aneurysm (4mm or more) or sack-to-neck ratio less than 2:1).

Intracranial flow diverting stents with FDA approval for the treatment of intracranial aneurysms meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage as part of the **endovascular treatment of intracranial aneurysms for patients with large or giant wide-necked intracranial aneurysms, with a size of 10mm or more and a neck diameter of 4mm or more, in the internal carotid artery from the petrous to the superior hypophyseal segments AND are not amenable to surgical treatment or standard endovascular therapy.**

Intracranial stent placement does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** in the **treatment of intracranial aneurysms except as noted above.**

Intracranial percutaneous transluminal angioplasty with or without stenting does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** in the **treatment of atherosclerotic cerebrovascular disease**.

The use of endovascular mechanical embolectomy with an FDA approved device for the treatment of **acute ischemic stroke meets** Blue Cross and Blue Shield of Alabama **as part of the treatment of acute ischemic stroke for patients who meet <u>all</u> of the following criteria**:

- Have a demonstrated occlusion within the proximal intracranial anterior circulation (intracranial internal carotid artery, or M1 or M2 segments of the middle cerebral artery, or A1 or A2 segments of the anterior cerebral artery); **AND**
- Can receive endovascular mechanical embolectomy within 12 hours of symptom onset; **AND**
- Have evidence of substantial and clinically significant neurological deficits (i.e. NIHSS score ≥2); **AND**
- Have evidence of salvageable brain tissue in the affected vascular territory; **AND**
- Have no evidence of intracranial hemorrhage or arterial dissection on computed tomography (CT) or magnetic resonance imaging.

Endovascular mechanical embolectomy does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational for the treatment of acute ischemic stroke when the above criteria are not met.**

Other endovascular interventions (angioplasty, stenting) do not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational for the treatment of acute ischemic stroke.**

<u>Effective for dates of service on or after July 1, 2014 through September 30, 2015:</u>
Intracranial stent placement meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage as part of the **endovascular treatment of intracranial aneurysms** for patients

when surgical treatment is not appropriate and standard endovascular techniques do not allow for complete isolation of the aneurysm(e.g., wide-neck aneurysm (4mm or more) or sack-to-neck ratio less than 2:1).

Intracranial flow diverting stents with FDA approval for the treatment of intracranial aneurysms meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage as part of the **endovascular treatment of intracranial aneurysms for patients with large or giant wide-necked intracranial aneurysms, with a size of 10mm or more and a neck diameter of 4mm or more, in the internal carotid artery from the petrous to the superior hypophyseal segments AND are not amenable to surgical treatment or standard endovascular therapy.**

Intracranial stent placement does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** in the **treatment of intracranial aneurysms except as noted above.**

Intracranial percutaneous transluminal angioplasty with or without stenting does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** in the **treatment of atherosclerotic cerebrovascular disease**.

Endovascular interventions (**mechanical embolectomy, angioplasty, stenting) do not meet** Blue Cross and Blue Shield Alabama's medical criteria for coverage and is considered **investigational** in the **treatment of acute stroke**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent update literature review through February 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Endovascular Interventions for Acute Ischemic Stroke

Endovascular Interventions for Anterior Circulation Acute Ischemic Strokes

The evidence review will focus on the available RCTs and other comparative studies.

Systematic Reviews

Multiple systematic reviews and meta-analyses of RCTs evaluating endovascular therapy for acute stroke have been published, with varying inclusion criteria. The most relevant of the systematic reviews include the results of a series of RCTs published after 2014 comparing endovascular therapies with standard care; these are the focus of this review. Some systematic reviews have focused only on mechanical embolectomy, while others have evaluated endovascular therapies more broadly.

In 2015, Badhiwala et al reported results of a systematic review and meta-analysis of RCTs evaluating mechanical embolectomy after acute ischemic stroke. Eligible studies were RCTs comparing endovascular therapy with standard care, including the use of intravenous tPA, in adult participants with acute stroke. Eight trials were included (Ciccone et al, Kidwell et al, Broderick et al, Berkhemer et al, Goyal et al, Campbell et al, Saver et al, and Jovin et al), with a total of 2423 patients. (These specific RCTs are described individually below). Studies were assessed as having low risk of bias overall with the Cochrane Collaboration's tool. In a meta-analysis, the use of endovascular intervention lead to proportional treatment benefit across modified Rankin scale (mRS) scores (odds ratio [OR], 1.56; 95% confidence interval [CI], 1.14 to 2.13; p=0.005). Patients treated with endovascular intervention were more likely than standard care patients to have functional independence at 90 days (44.6% for endovascular treatment [95% CI, 36.6% to 52.8%]; 31.8% for standard treatment [95% CI, 24.6% to 40.0%]), with an associated absolute risk difference of 12.0% (95% CI, 3.8% to 20.3%; odds ratio [OR], 1.71; 95% CI, 1.18 to 2.49; p=0.005). However, there was significant heterogeneity (I2=75.4%) in the analysis of functional improvement outcomes. The authors conducted a number of sensitivity analyses around predictors of functional outcomes, and found that the following factors were associated with functional outcomes:

- Use of angiographic imaging confirming proximal arterial occlusion (OR=2.24; 95% CI, 1.72 to 2.9; p<0.001 for interaction).
- Use of intravenous tPA and endovascular therapy (OR=2.07; 95% CI, 1.46 to 2.92; p=0.018 for interaction).

- Use of stent retriever for mechanical thrombectomy (OR=2.39; 95% CI, 1.88 to 3.04; p<0.001 for interaction).

There were no significant differences between endovascular intervention group and standard care group patients in rates of symptomatic intracranial hemorrhage or death at 90 days.

In a meta-analysis including the same 8 trials included in the Badhiwala et al study, Chen et al reported a similar odds ratio for 90 day functional independence as Badhiwala.

Hong et al (2015) conducted a meta-analysis of RCTs comparing endovascular recanalization therapy with standard care in acute ischemic stroke. This analysis included 15 RCTs with a total of 2,899 patients, 1575 randomized to endovascular recanalization arms and 1324 to control arms. In addition to the 8 trials which compared mechanical embolectomy with standard care (Ciccone et al, Kidwell et al, Broderick et al, Berkhemer et al, Goyal et al, Campbell et al, Saver et al, and Jovin et al), this review also included 2 trials evaluating intra-arterial pro-urokinase, 3 trials evaluating intra-arterial urokinase, 1 evaluating intra-arterial with intravenous tPA, and 1 evaluating intra-arterial tPA with mechanical thrombectomy. In a random-effects model including all trials, endovascular recanalization was associated with greater proportions of patients with mRS of 0-2 (43.3% vs 31.9%, OR 1.79, 95% CI 1.34 to 2.4, P<0.001). For safety outcomes, when all trials were included, rates of symptomatic intracranial hemorrhage (SICH) were higher in endovascular recanalization arms, although the between-group difference was not statistically significant (5.8% vs 4.6%, OR 1.19, 95% CI 0.83 to 1.69, P=0.345).

In another meta-analysis, Kennedy et al (2013) compared local mechanical and/or pharmacologic endovascular therapy, with or without intravenous thrombolysis, with standard-care control that included intravenous thrombolysis when appropriate. Eleven RCTs were included, the 8 trials comparing mechanical embolectomy with standard care (Ciccone et al, Kidwell et al, Broderick et al, Berkhemer et al, Goyal et al, Campbell et al, Saver et al, and Jovin et al), along with 2 trials comparing intra-arterial tPA with intravenous tPA alone, one of which was very small (n=7), and one evaluating intra-arterial tPA with mechanical thrombectomy. In a meta-analysis of all trials, patients in the local endovascular therapy groups had higher rates of functional independence than those treated with standard care (OR 1.78, 95% CI 1.262 to 2.51, P<0.001). In subanalyses limited to trials that used imaging selection, that used stent-retriever devices in at least half of cases, or in which intravenous tPA was used in conjunction with endovascular therapy as appropriate, the use of local endovascular therapy remained significantly associated with higher rates of functional independence, with stronger effect sizes than in the overall analysis. However, in a subanalysis limited to trials in which endovascular arm patients did not receive intravenous tPA, there was no significant between-group difference in 90-day functional independence (OR 1.45, 95% CI 0.597 to 3.54, P>0.05).

Given the disproportionate benefit associated with stent retriever use in subanalyses of RCTs, there has been some focus on the specific efficacy of stent retrievers for acute stroke.

Bush et al (2016) conducted a meta-analysis of RCTs using predominantly stent retriever devices for acute stroke treatment. Trials that compared endovascular therapy with stent

retrievers with medical management (defined as intravenous tPA unless it was contraindicated) were included. However, it is not specified how the authors defined a threshold to determine whether stent retrievers were "predominantly" used. The analysis included 5 trials (Berkhemer et al, Goyal et al, Campbell et al, Saver et al, and Jovin et al) with a total of 1287 patients. In pooled analysis for the review's primary outcome, mRS at 90 days, patients randomized to endovascular therapy had an OR for more favorable mRS of 2.2 (95% CI, 1.66 to 2.98; $p<0.001$; $I2=46.38\%$). Similar to the findings from the Badhiwala meta-analysis, there were no significant between-group differences in 90-day mortality rates or rates of symptomatic intracranial hemorrhage.

Other related systematic reviews have reported similar results.

In 2015, an updated draft Blue Cross and Blue Shield Association (BCBSA) TEC Assessment assessed endovascular therapy for acute ischemic stroke in adults to reflect several RCTs published after an earlier TEC Assessment. The Assessment focused on four RCTs published from 2014 to 2015 comparing endovascular mechanical embolectomy with medical therapy (Berkhemer et al, Campbell et al, Goyal et al, Saver et al). The Assessment made the following observations and conclusions:

> "Four recent well-designed and well-conducted RCTs have demonstrated reduced disability among adults with acute ischemic stroke treated with mechanical embolectomy compared with standard medical care, usually IV tPA. These four RCTs address some of the limitations in three RCTs published in 2013, which showed no significant benefit to endovascular therapy. In particular, trials demonstrating a benefit to endovascular therapy either exclusively used stent retriever devices or allowed the treating physician to select a device, mostly a stent retriever device, and had high rates of mechanical embolectomy device use in patients randomized to endovascular therapy."

The Assessment concluded that the use of endovascular treatment with mechanical embolectomy in adults with radiologically confirmed large vessel, anterior circulation acute ischemic stroke meets the BCBSA Technology Evaluation Center (TEC) criteria. The specific RCTs are described in more detail below.

In 2015, Prabhakaran et al published results from a systematic review of studies evaluating thrombolysis and mechanical thrombectomy in acute stroke. The authors included 68 articles (total N= 108,082 patients), including RCTs, observational studies, guideline statements, and review articles. Six RCTs comparing endovascular therapy with standard management were included. Although pooled trial results were not presented, the authors did report that, across the available RCTs, rates of substantial reperfusion (Thrombolysis in Cerebral Infarction [TICI] score 2b or 3) were positively associated with the proportion of patients with a good clinical outcome (modified Rankin Scale [mRS], 0-2) at 90 days, while time to reperfusion was negatively associated with the proportion of patients with a good clinical outcome at 90 days.

Zheng and Xie (2015) conducted a meta-analysis of RCTs comparing endovascular therapy with intravenous tPA, with analysis stratified by whether computed tomography angiography

(CTA) was used to select patients for endovascular therapy. The review included 7 RCTs with 2217 patients (Berkhemer et al, Broderick et al, Ciccone et al, Kidwell et al, Campbell et al, and Goyal et al), of which 4 used CTA to select patients. Endovascular therapy was associated with functional independence at 90 days in patients who underwent CTA-based selection (RR=1.75; 95% CI, 1.48 to 2.06; I2=0.05%), but not in patients who did not undergo CTA-based selection (RR=0.99; 05% CI, 0.85 to 1.14; I2=0.0%). All-cause mortality was not significantly associated with 90-day mortality, regardless of whether patients were selected with CTA.

Earlier published systematic reviews have incorporated some of the RCTs comparing endovascular therapies and standard therapy or were published before RCTs were available. The results are less relevant given the availability of more recent RCT data.

Randomized Controlled Trials

RCTs Comparing Endovascular Therapies with Non-Interventional Care

From 2012-2015, results from eight large randomized trials comparing endovascular therapies with standard of care for acute ischemic stroke were published. Several additional trials that began enrollment around 2013 and 2014 were stopped early after the publication of trials during 2014 and 2015. Therefore, the sample sizes in the trials published after 2015 are much smaller that originally designed and the power to detect clinically important differences is low. Five prospective, open-label, blinded end point (PROBE design) RCTs comparing endovascular therapy with standard care in the treatment of acute stroke were published from 2014 to 2015 and are the focus of this discussion. A high level overview of the major RCTs follows, with a summary of results in Table 1. Subsequently, in this section, select trials are described in more detail.

Although the RCTs report on a number of outcomes, results pertaining to 3 specific outcomes are the focus here: the proportion of patients with 90-day modified Rankin scale (mRS) score of 0-2, short-term mortality rate, and rates of symptomatic intracranial hemorrhage (sICH). The primary goal of rapid revascularization in acute stroke is to reduce rates of significant disability; mRS scores of 0-2 correspond to functional independence, so represent a clinically useful measure of disability. Prior studies of endovascular therapy and thrombolytic therapy for acute stroke have been associated with increased risks of sICH, so this is another important safety-related outcome to evaluate.

There were 14 randomized controlled trials (RCTs) with a total of 3061 patients (range, 70-656) which compared endovascular mechanical embolectomy with standard care for acute ischemic stroke. In two studies, the population and intervention delivered were not consistent with the target population and intervention; the remaining 12 studies with the populations and interventions of interest are the focus of this discussion. The most clinically-relevant and consistently reported finding was a comparison between treatment and control groups in the proportion of patients with a mRS score at 90 days of 0-2. Among the 12 studies reporting on the population and intervention of interest, all provide some information on the proportion of patients with 90-day mRS of 0-2. Across the studies, the absolute difference between treatment and control groups in proportion of patients with 90-day functional independence ranged from 1.55% to 36%. With the exception of MR Rescue [Kidwell et al], all studies published before 2016 reported a statistically significant improvement in the proportion of patients with

functional independence at 90 days, with odds ratios ranging from 1.7 to 3.8. Among the 6 studies published before 2016 reporting on the populations and interventions of interest, mortality rates and sICH rates did not differ significantly between study groups. It is not possible to draw conclusions about the safety or harm of the procedure from this finding; the lack of significant difference may be due to inadequate sample sizes. Among the studies published after 2015, most were stopped well before the original planned sample size because of benefit shown in earlier studies. Therefore, most studies published later do not have the power to detect clinically meaningful differences at the achieved sample size but are consistent in direction with the earlier studies.

Treatment within 6-8 Hours of Symptom Onset

REVASCAT Trial

The following criteria were used for the REVASCAT Trial:

Exclusion criteria were as follows: Hypodensity on CT or restricted diffusion demonstrated by:

- An ASPECTS of less than 7 on CT, CT perfusion cerebral blood volume (CBV), computed tomography angiography (CTA) source imaging; OR
- An ASPECTS score of less than 6 on diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI).

In 2015, Jovin et al reported results of the REVASCAT trial, which compared endovascular therapy using the Solitaire stent-retriever device with medical therapy, including IV tPA when indicated, within eight hours of stroke onset among 206 patients. Eligible patients had an occlusion within the proximal anterior circulation that could be treated within eight hours of stroke onset, a prestrike mRS score of zero to one, and a baseline National Institutes of Health Stroke Scale (NIHSS) score of at least six points (NIHSS score range, 0-42; higher scores associated with greater deficit). Intravenous tPA was administered before randomization. Patients were excluded if that had imaging-based evidence of a large ischemic core, indicated by an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of less than seven on non–contrast CT imaging or a score of less than six on diffusion-weighted MRI. The trial was halted early for loss of equipoise given the results of the EXTEND-IA, ESCAPE, and MR CLEAN trials (described below) after the first planned interim analysis (when the first 25% of patients [n=174] reached 90 days of follow-up).

One hundred three patients were randomized to mechanical embolectomy, of which 98 successfully underwent thrombectomy. Rates of tPA use between the groups did not differ significantly (68.0% in the mechanical embolectomy group, 77.7% in the control group). For the study's primary outcome, the OR for improvement in the distribution of the mRS score was 1.7 (95% CI, 1.05 to 2.8), favoring mechanical embolectomy. A greater proportion of patients in the mechanical embolectomy group was functionally independent (mRS score, 0-2; 43.7% vs 28.2% in the control group; absolute risk difference, 15.5%; adjusted OR=2.1; 95% CI, 1.1 to 4.0). There were no significant differences between the mechanical embolectomy and the control groups in 90-day mortality (18.4% vs 15.5%; p=0.60) or 90-day rates of symptomatic intracranial hemorrhage (1.9% in each group; p=1.00).

Table 1. Summary of Randomized Controlled Trials of Endovascular Therapy vs Standard Care

Trial (Study)	Intervention		N	90-Day Modified Rankin Scale Score 0-2		Mortality		Symptomatic Intracranial Hemorrhage	
	Group	**Treatment Description**		**Per Group Rate, %**	**Between-Group Difference (95% CI)**	**Per Group Rate, %**	**Between-Group Difference (95% CI)**	**Per Group Rate, %**	**Between-Group Difference (95% CI)**
DEFUSE 3 (Albers [2018])	IN[c]	Endovascular therapy + standard medical therapy[b]	92	45	OR=2.7 (1.6 to 4.5)	14	OR=0.55 (0.3 to 1.0)	7	OR=1.5 (0.4 to 6.6)
	Control	Standard medical therapy[b]	90	17		26		4	
DAWN (Nogueira [2018])	IN[c]	Endovascular therapy + standard care[b]	107	49	ARR=36% (24% to 47%)	19	ARR=1% (-10% to 11%)	6	ARR=3% (-3% to 8%)
	Control	Standard care[b]	99	13		18		3	
EASI (Khoury [2017])	IN[c]	Endovascular therapy + standard care (IV tPA if indicated)	40[a]	50	p=0.36	28	NR	7.5	NR
	Control	Standard care (IV tPA if indicated)	37[a]	38		24		5.7	
PISTE (Muir [2017])	IN[c]	Endovascular therapy + medical therapy with IV tPA	33[a]	51	OR=2.1 (0.7 to 6.9)	21	OR=1.6 (0.3 to 8.4)	0	
	Control	Medical therapy with IV tPA	32[a]	40		13		0	
THERAPY (Mocco [2016])	IN[c]	Aspiration thrombectomy (Penumbra) + IV tPA	55[a]	38	OR=1.4 (0.6 to 3.3)	12	OR=2.3 (0.8 to 6.8)	9.3	OR=1.0 (0.3 to 3.9)
	Control	IV tPA alone	53[a]	30		24		9.7	
THRACE (Bracard [2016])	IN[c]	Endovascular therapy + IV tPA	202	53	OR=1.6 (1.1 to 2.3)	12	OR=0.8 (0.5 to 1.2)	2	OR=1.4 (0.3 to 6.3)
	Control	IV tPA alone	200	42		13		2	
REVASCAT (Jovin [2015])	IN[c]	Solitaire stent retriever w/wo IV tPA	103	43.7	• ARR=15.5% • OR=2.1 (1.1 to 4.0)	18.4	p=0.60	1.9	p=*NS*
	Control	Medical therapy (IV tPA if indicated)	103	28.2		15.5		1.9	
EXTEND-IA (Campbell [2015])	IN[c]	Endovascular therapy + IV tPA	35	71	OR=3.8 (1.4 to 1.0)	20	OR=0.38 (0.1 to 1.6)	6	Risk difference, -6 (-13 to 2)
	Control	IV tPA alone	35	40		9		0	

ESCAPE (Goyal [2015])	IN[c]	Endovascular therapy w/wo IV tPA	165	53	RR=1.8 (1.4 to 2.4)	10.4	RR=0.5 (0.3 to 1.00)		
	Control	Medical therapy (IV tPA if indicated)	150	29.3		19.05			
SWIFT-PRIME (Saver [2015])	IN[c]	Solitaire stent retriever + IV tPA	98	60	• ARR=25% • OR=1.70 (1.23 to 2.33)	9	RR=0.74 (0.33 to 1.68)	0	p=0.12
	Control	IV tPA alone	98	35		12		3	
MR CLEAN (Berkhemer [2015])	IN[c]	Intra-arterial therapy w/wo IV tPA	233	32.6	• ARR=13.5% • OR=2.05 (1.36 to 3.09)	18.9	p=*NS*	7.7	p=*NS*
	Control	Medical therapy (IV tPA if indicated)	267	19.1		18.4		6.4	
MR RESCUE (Kidwell [2013])	IN[c]	Mechanical embolectomy (MERCI or Penumbra) w/wo IV tPA	64	18.75	p=0.48	21	p=*NS*	4	p=*NS*
	Control	Medical therapy (IV tPA if indicated)	54	20.3		21		4	
SYNTHESIS Expansion (Ciccone [2013])	IN[c]	Intra-arterial therapy w/wo IV tPA	181	30.4	OR=0.71 (0.44 to 1.14)			6	p=*NS*
	Control	IV tPA alone	181	34.8				6	
IMS III (Broderick [2013])	IN[c]	Endovascular therapy + IV tPA	434	38.7	Adjusted difference: 1.5% (-6.1 to 9.1)	19.1	p=0.52	11.5	p=0.02
	Control	IV tPA alone	222	40.8		21.6		18.9	

ARR: absolute risk reduction; CI: confidence interval; IV: intravenous; OR: odds ratio; RR: relative risk; tPA: tissue plasminogen activator; w/wo: with/without.

[a] Trial stopped early due to publication of results of other trials.

[b] Patients were enrolled in DEFUSE 3 and DAWN after the accepted window of time for which IV thrombolytic therapy is typically administered.

[c] intervention

EXTEND-IA Trial

Inclusion criteria for the Extend-IA Trial were based on CT perfusion imaging using CT or MRI with a Tmax more than 6-second delay perfusion volume and either CT regional CBF or DWI infarct core volume as follows:

- Mismatch ratio greater than 1.2; AND
- Absolute mismatch volume greater than 10 mL; AND
- Infarct core lesion volume less than 70 mL.

In 2015, Campbell et al reported results of the EXTEND-IA trial comparing endovascular therapy with tPA alone. This trial enrolled patients with ischemic stroke who were receiving IV tPA within 4.5 hours after stroke onset. Eligible patients had an occlusion of the internal carotid artery (ICA) or M1 or M2 segments of the middle cerebral artery (MCA) on computed tomography angiography (CTA), were able to receive endovascular therapy within six hours of stroke onset; further, the patients were functionally independent prior to the stroke. Patients were evaluated prior to enrollment with computed tomography (CT) perfusion imaging, and were required to have evidence of salvageable brain tissue and an ischemic core with a volume of less than 70 mL. Computed tomography (CT) perfusion imaging was analyzed with an operator-independent postprocessing software. Enrollment was planned for 100 patients. The trial's data safety and monitoring board reviewed data for the first 70 enrolled patients after the results of the MR CLEAN trial were published and stopped EXTEND-IA for efficacy based on prespecified criteria. The first 70 patients were randomized to either IV tPA plus endovascular therapy with the Solitaire FR retrievable stent (n=35) or no further therapy (IV tPA only; n=35). The study used two coprimary end points: reperfusion (measured as the percentage reduction in perfusion-lesion volume between the initial imaging and imaging at 24 hours) and early neurologic improvement (defined as a reduction of ≥8 points on the NIHSS or a score of zero or one at day three).

The demographics of the randomized groups were similar at baseline. About 25% of clinically eligible patients were excluded on the basis of perfusion imaging criteria. In the endovascular group, eight (22.9%) of 35 patients did not undergo mechanical embolectomy, most commonly because most of the thrombus was lysed before angiography (n=4). Endovascular therapy subjects had increased reperfusion at 24 hours, with a median reperfusion of 100% (percentage reduction in perfusion-lesion volume), compared with 37% for the tPA-only group (adjusted OR=4.7; 95% CI, 2.5 to 9.0; p<0.001). Of the endovascular therapy subjects, 28 (80%) of 35 had early neurologic improvement compared with 13 (37%) of 35 of the tPA-only subjects (adjusted OR=6.0; 95% CI, 2.0 to 18.0; p=0.002). Rates of reperfusion of at least 90% at 24 hours without symptomatic intracerebral hemorrhage were higher in endovascular therapy patients (89% vs 34%; adjusted OR=27.0; 95% CI, 5.5 to 135.0; p<0.001). Safety outcomes, including death, symptomatic intracerebral hemorrhage, and parenchymal hematoma, did not differ significantly between groups.

ESCAPE Trial

Exclusion criteria for the ESCAPE Trial were as follows:

- Baseline non–contrast CT with extensive early ischemic changes of ASPECTS 0 to 5 in the territory of symptomatic intracranial occlusion; OR
- Other confirmation of a moderate-to-large core defined 1 of 3 ways:
    - On a single phase, multiphase, or dynamic CTA: no or minimal collaterals in a region greater than 50% of the middle cerebral artery (MCA) territory

when compared with pial filling on the contralateral side (multiphase/dynamic CTA preferred); OR
    - On CT perfusion (>8 cm coverage): a low CBV and very low cerebral blood flow (CBF), ASPECTS less than 6 AND in the symptomatic MCA territory; OR
    - On CT perfusion (<8 cm coverage): a region of low CBV and very low CBF greater than one-third of the CT perfusion-imaged symptomatic MCA territory.

Also in 2015, Goyal et al reported results of the ESCAPE trial that compared endovascular therapy with guideline-based stroke care, including IV tPA if indicated. Patients with acute stroke were eligible if they presented within 12 hours of stroke onset, had a proximal intracranial occlusion in the anterior circulation, and had non–contrast CT or CTA with the following findings: (1) small infarct core; (2) proximal artery occlusion, defined by occlusion of the MCA trunk and its immediate branches, with or without intracranial occlusion of the ICA; and (3) moderate-to-good collateral circulation, defined as filling of 50% or more of the MCA pial artery circulation on CTA. A small infarct core was defined as a score of six to ten on the ASPECTS, which is a ten point scoring system designed to quantify the extent of ischemic changes in the MCA territory. Patients received IV tPA if they met local guidelines. Patients were randomized to endovascular treatment (n=165), which could include any Food and Drug Administration (FDA)–approved stent retriever or aspiration device, balloon angioplasty, guidewire manipulation, and/or IA tPA, or guideline-based stroke care (n=150). Use of retrievable stents was recommended. Enrollment was planned for 316 subjects. The trial was stopped early on the advice of its data safety monitoring board, after an unplanned interim analysis following publication of MR CLEAN trial results, because ESCAPE's prespecified efficacy boundary had been crossed.

Of the 165 patients randomized to the intervention group, 151 (91.5%) underwent endovascular therapy, most commonly with a retrievable stent (130/151 [86.1%] of those who underwent an endovascular procedure), most often with the Solitaire stent (100/130 [77.0%] of those who received a retrievable stent). In the intervention group, 120 (72.7%) also received IV tPA. Of the 150 control group subjects, 118 (78.6%) received IV tPA. For the study's primary end point (90-day mRS score), compared with the control group, in the endovascular treatment group the relative odds of improving one point on the mRS was 2.6 (95% CI, 1.7 to 3.8). Endovascular treatment group subjects compared with control group subjects also had lower 90-day mRS scores (median, two vs four, respectively; $p<0.001$) and were more likely to have 90-day mRS scores of zero to two (53% vs 29.3%; rate ratio, 1.8; 95% CI, 1.4 to 2.4; $p<0.001$). Ninety-day mortality was 10.4% among endovascular treatment group subjects and 19.0% in control group subjects (rate ratio, 0.5; 95% CI, 0.3 to 1.0; $p=0.04$).

SWIFT-PRIME Trial

Exclusion criteria for the SWIFT-PRIME Trial was related to imaging-demonstrated core infarct and hypoperfusion:

- MRI-assessed core infarct lesion greater than:
    - 50 cm^3 for subjects age 18 to 79 years;
    - 20 cm^3 for subjects age 80 to 85 years;

- CT-assessed core infarct lesion greater than:
    - 40 cm^3 for subjects age 18 to 79 years;
    - 15 cm^3 for subjects age 80 to 85 years;
- For all subjects, severe hypoperfusion lesion (≥10-second Tmax lesion >100 cm^3);
- For all subjects, ischemic penumbra of 15 cm^3 or more and mismatch ratio greater than 1.8.

In 2015, Saver et al reported results of the SWIFT-PRIME trial comparing IV tPA followed by mechanical embolectomy using a stent retriever device with IV tPA alone in patients presenting with acute ischemic stroke. Eligible patients had moderate-to-severe neurologic deficits, imaging-confirmed occlusion of the intracranial ICA and/or the first segment of the MCA, were receiving or had received IV tPA, and were able to undergo endovascular treatment within six hours of symptom onset. In addition, eligible patients were required to have ischemic penumbral imaging analysis showing a small-to-moderate core infarct. For the first 71 patients enrolled, the infarct core size was defined based on CT perfusion imaging analyzed with an operator-independent postprocessing software; for the remainder of the study, infarct core size could be determined by CT perfusion imaging or non–contrast CT with a small-to-moderate core infarct based on ASPECTS. Patients were randomized to mechanical embolectomy with the Solitaire 2 or the Solitaire FR device (n=98) or to ongoing IV tPA (n=98). Enrollment was planned for a maximum of 833 subjects, but stopped at 196 subjects after an interim analysis, following publication of the results of the MR CLEAN and ESCAPE trials, showed that results met SWIFT-PRIME's prespecified efficacy criteria.

In the intervention group, a stent retriever was successfully deployed in 87 patients (89%). At 90 days, 60% of endovascular therapy group patients were functionally independent (mRS score, 0-2) compared with 35% of control subjects (absolute risk reduction, 25%; OR=1.70; 95% CI, 1.23 to 2.33; p<0.001). Endovascular therapy group patients compared with controls were more likely to have successful (≥90%) reperfusion at 27 hours (83% vs 40%, respectively; OR=2.05; 95% CI, 1.45 to 2.91; p<0.001). Rates of death and serious adverse events did not differ significantly between groups.

MR CLEAN Trial

The MR CLEAN Trial did not specify imaging criteria to demonstrate salvageable brain tissue.

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. 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 two or higher on the National Institutes of Health Stroke Scale (NIHSS). Initiation of intra-arterial treatment had to be possible within six 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 five 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 three (IQR 2-5) among intervention subjects, compared with a median score of four (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 zero or one 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).

MR RESCUE Trial

Kidwell et al reported on the MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy) trial in 2013. MR RESCUE was an open-label, blinded-outcome randomized controlled trial (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 eight hours after presentation of symptoms. Eight patients in the embolectomy group also tPA. The primary hypothesis of the study was that patients with favorable penumbral patterns (at-risk area of viable ischemic cerebral tissue of 70% or less and a small, 90 mL or less, area of predicted core infarct) would benefit more from mechanical embolectomy than patients with non-penumbral patterns (large infarct area and small or absent penumbra [viable ischemic cerebral tissue]), as determined by the 90-day Modified Rankin Scale. 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.

SYNTHESIS Expansion Trial

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 nine patients, Trevo in five patients, and Merci in five 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 seven 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.

IMS-III Trial

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 three 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 two 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, Tomsick 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. 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]).

Treatment Beyond 6 Hours of Symptom Onset

While the other trials assessing endovascular treatment focused on patients who were treated within the first several hours (generally within 6 to 8 hours) after the onset of stroke symptoms, the DEFUSE 3 and DAWN trials evaluated whether it was possible to extend the time window for mechanical thrombectomy after acute ischemic stroke.

DEFUSE 3 Trial

The DEFUSE3 Trial used the following inclusion criteria:

- 6-16 hours related to mismatch between severity of clinical deficit and infarct volume:
  - Infarct size of <70mL; AND
  - Ratio of ischemic tissue volume to infarct volume of ≥ 1.8; AND
  - Ischemic penumbra of ≥15cm^3

Albers et al (2018) reported on results of DEFUSE 3, a multicenter, open-label RCT with blinded outcome assessment including patients 6 to 16 hours after they were last known to be well and who had remaining ischemic brain tissue that was not yet infarcted. DEFUSE 3 was conducted at 38 sites in the United States from May 2016 to May 2017. Patients were assigned to thrombectomy plus standard medical therapy (n=92) or standard medical therapy alone

(n=90). The median age was 70 years, half of the participants were women, the median NIHSS score was 16, and 10% of the participants received IV tPA. Approximately 50% of the patients had a "wake-up" stroke. The trial was originally designed to enroll a maximum of 476 participants but was stopped early for efficacy. The proportion of patients who were functionally independent (mRS score ≤2) at 90 days was 45% in the thrombectomy group and 17% in the standard care group (OR=2.67; 95% CI, 1.60 to 4.48; p<0.001). The proportion of patients with symptomatic intracranial hemorrhage was 7% in the thrombectomy group and 4% in the standard care group (OR=1.47; 95% CI, 0.40 to 6.55; p=0.75). The 90-day mortality rate was 14% in the thrombectomy group and 26% in the standard care group (OR=0.55; 95% CI, 0.30 to 1.02; p=0.05). The rate of serious adverse events was 43% and 53%, respectively (p=0.18).

DAWN Trial

The DAWN Trial used the following inclusion criteria:

- 6-24 hours related to mismatch between severity of clinical deficit and infarct volume:
  - ≥80 years of age, score ≥10 on the NIHSS, and had an infarct volume <21 mL; OR
  - ≤80 years age, score of ≥10 on the NIHSS, and had an infarct volume <31 mL; OR
  - ≤80 years of age, had a score ≥20 on the NIHSS, and had an infarct volume of 31 to <51 mL

Nogueira et al (2018) reported on results of the DAWN trial, a multicenter, Bayesian, adaptive, open-label RCT with blinded outcome assessment sponsored by Stryker Neurovascular. DAWN included patients who had last been known to be well 6 to 24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume. DAWN was conducted at 26 sites in the United States, Canada, Europe, and Australia from September 2014 through February 2017. Patients were assigned to thrombectomy plus standard care (n=107) or standard care alone (n=99). Very few patients were treated with IV tPA because patients were generally enrolled after the accepted window of time in which IV tPA is administered. The adaptive trial was originally designed for a sample size ranging from 150 to 500 patients but was stopped early due to efficacy. The mean age was 70 years, and the median NIHSS score was 17. Approximately 55% of the patients had a "wake-up" stroke. The proportion of patients with functional independence (mRS score ≤2) at 90 days was 49% in the thrombectomy group and 13% in the standard care group (adjusted difference, 33%; 95% credible interval, 24% to 44%; posterior probability of superiority, >0.999). The proportion of patients with symptomatic intracranial hemorrhage at 24 hours was 6% in the thrombectomy group and 3% in the standard care group (p=0.50). The 90-day mortality rate was similar between groups (19% vs 18%, respectively; p=1.00).

Section Summary: RCTs Comparing Endovascular Therapies with Noninterventional Care

A number of RCTs have compared endovascular therapies with noninterventional care for acute stroke, with the five more recent (2014-2015) studies demonstrating a significant benefit associated with endovascular care. The more recently published trials addressed some of the limitations of previous studies. In the IMS III and SYNTHESIS Expansion trials, sizable proportions of the endovascular therapy groups did not receive an endovascular device. All

three of the 2013 trials (Broderick et al, Kidwell et al, Ciccone et al) all had relatively low utilization of the newer generation retrievable stents (Solitaire FR, Trevo). In addition, IMS III and the Ciccone et al study did not require a radiologically proven intracranial occlusion for study eligibility. In contrast, the 2014-2015 trials, which demonstrated a benefit to endovascular therapy, either exclusively used stent retriever devices or allowed the treating physician to select a device, mostly a stent retriever device, and had high rates of mechanical embolectomy device use in patients randomized to endovascular therapy.

RCTs Comparing Different Endovascular Therapies
In 2012, two non-inferiority RCTs comparing newer devices with 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 non-inferiority trial of 113 patients with moderate or severe large vessel occlusion strokes. Treatment was initiated within eight hours of symptom onset in patients who had unsuccessful IV tPA or were ineligible for IV tPA. This trial was halted early after an interim analysis found revascularization without symptomatic intracranial hemorrhage occurred in 61% of Solitaire patients compared with 24% of Merci patients. Mortality rates at 90 days were 17% with Solitaire versus 38% with Merci (p=0.001). A follow up analysis of complications of endovascular procedures using the SWIFT study data was published in 2013. This analysis included 144 patients with acute ischemic stroke (31 patients treated with the Solitaire FR device during the SWIFT trial roll-in period and 113 patients randomly assigned to the Solitaire FR or Merci device). Major peri-procedural complications, including symptomatic intracranial hemorrhage, air emboli, vessel dissection, major groin complications, and emboli to new vascular territories, were seen in 18/144 (12.5%) of all patients. Complication rates were similar for patients receiving the Solitaire FR and Merci devices, with the exception of symptomatic cerebral hemorrhage, which was significantly less common in the Solitaire FR group (10.9% vs 1.1%, p=0.013).

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

In 2015, Saposnik et al evaluated the added benefit added by stent retrievers to intravenous tPA using pooled patient-level data from the SWIFT study and the STAR trial, a prospective, single-arm trial of the solitaire device, along with data from the NINDS tPA Stroke Study, a RCT evaluating intravenous tPA. Of 915 patients included in the pooled analysis, 312 were treated with placebo, 312 with intravenous tPA, 106 with stent retrievers alone, and 160 with intravenous tPA and stent retrievers. The authors used a shift analysis which used a proportional odds model to evaluate the association between treatment and each of the 7 mRS categories. The use of stent retrievers (alone or with tPA) was associated with a higher probability of functional independence (mRS 0-2) at 90 days: 41% of those treated with tPA alone, 69.8% of

those treated with stent retrievers, and 72.8% of those treated with stent retrievers and tPA had functional independence at 90 days.

Nogueria et al (2018) compared use of the Penumbra 3-D stent retriever and an aspiration-based mechanical thrombectomy device with the Penumbra aspiration system alone in 198 patients from 25 North American sites enrolled from May 2012 through November 2015. Eligible patients had large vessel intracranial occlusion acute ischemic stroke with an NIHSS score of at least 8 within 8 hours of onset. The primary effectiveness outcome was the rate of a mTICI score of 2 to 3, with a 15% noninferiority margin. One hundred ninety patients were included in the primary analysis. Eighty-two (87%) of 94 patients in the 3-D stent retriever group had a mTICI score of 2 to 3 compared with 79 (82%) of 96 in the aspiration alone group (difference, 4.9%; 90% CI, -3.6% to 13.5%). The incidence of the device- and procedure-related serious adverse events within 24 hours of the procedure was 4 (4%) of 98 patients in the 3-D stent retriever group and 5 (5%) of 100 in the aspiration alone group.

Nonrandomized Comparative Studies
A number of nonrandomized comparative studies have compared endovascular interventions with historic controls or control patients from their same institution who received standard stroke care (e.g., Rai et al, Urra et al, Song et al, Alexandrov et al, Taschner et al).

For the treatment of acute stroke involving the anterior circulation, more direct evidence on the effectiveness of endovascular therapies, compared with standard treatment, is available from the RCTs described above. Therefore, nonrandomized comparative studies that compare specific types of endovascular interventions are the focus in the following section. 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.

Kappelhof et al (2015) 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. The overall review included 32 studies, six of which (N=95) reported outcomes for intracranial occlusion treated by intra-arterial thrombolysis and eight 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 non-significantly different rates of death (29% vs 40%; P=0.085) and symptomatic intracranial hemorrhage (12.2% vs 11.7%; P=0.085).

Turk et al (2015) conducted a retrospective, single-center review to compare clinical and cost-related outcomes for three 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. 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.

Kass-Hout et al (2015) compared retrievable stenting with the Merci and Penumbra devices in a retrospective analysis of 287 patients who underwent mechanical embolectomy at a single center. In binary logistic regression, receiving a retrievable stent was an independent predictor of a good functional outcome (adjusted OR=2.27; 95% CI, 1.018 to 5.05; p=0.045). Broussalis et al (2013) compared the Merci device with newer retrievable stents (Trevo and Solitaire devices) in 122 patients treated with endovascular interventions and reported that recanalization rates were higher with the newer devices (82% vs 62%, p=0.016). Mendonca et al (2014) compared the Trevo versus Solitaire devices in a prospective, nonrandomized comparison of 33 patients with anterior cerebral circulation occlusions. No significant differences between devices were found in rates of revascularization, symptomatic intracranial hemorrhage, improvements in Modified Rankin Scale, and mortality. In a similar but smaller study, Fesl et al compared 14 patients treated with a newer retrievable stent compared with 16 patients treated with an older device. Recanalization rates were higher in the retrievable stent group (93% vs 56%, p<0.05).

Section Summary: Endovascular Interventions for Anterior Circulation Acute Ischemic Strokes
From 2013 to 2015, 8 published RCTs compared endovascular therapies with noninterventional care for patients with acute stroke due to anterior circulation occlusions. Several additional trials were stopped early after the trials published in 2013 through 2015. Five trials published from 2014 to 2015 all demonstrated a significant benefit regarding reduced disability at 90 days posttreatment. The trials that demonstrated a benefit for endovascular therapy either exclusively used stent retriever devices or permitted treating physicians to select a device, mostly a stent retriever device, and had high rates of mechanical embolectomy device use in patients randomized to endovascular therapy. All studies that demonstrated a benefit for endovascular therapy required demonstration of a large vessel and anterior circulation occlusion for enrollment. Also, they were characterized by fast time-to-treatment. Two trials published in 2018 demonstrated that it was possible to extend the time window for mechanical thrombectomy up to about 24 hours for select patients. To achieve results in real-world settings similar to those in the clinical trials, treatment times, clinical protocols, and patient selection criteria should be similar to those in the RCTs.

Endovascular Interventions for Stroke due to 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. Reperfusion therapies have received particular attention as a therapy for basilar artery occlusion because, though relatively rare, basilar artery occlusions have high likelihood of severe disability or death. In one registry study, for example, investigators found severe outcomes (Modified Rankin Scale score of four or five, or death) in 68% of patients with basilar artery occlusion.

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 2005-2012. Patients who received endovascular therapies (including endovascular mechanical recanalization and/or intra-arterial with optional IV thrombolytic therapy) were compared with those who received standard medical therapy (IV thrombolytic therapy and/or medical antithrombotic treatment.) Seventy-eight percent of the patients received endovascular intervention, with thrombectomy alone in 67 patients. Devices used included the Merci system in 43%, the Solitaire FR device in 13%, and the Trevo retriever in 18%, with devices not available in the U.S. in the remaining 25%. Endovascular patients were more likely to achieve a 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 three, compared with 8% in the standard medical therapy group.

Non-comparative studies have reported on endovascular therapies for acute basilar artery occlusion. Son et al (2016) 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, three-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).

Huo et al (2016) reported outcomes for 36 consecutive patients with acute basilar artery occlusion treated with the Solitaire stent. Recanalization (TICI grade ≥2b) was successful in 94.4% of patients. However, mortality at 90 days was high (30.56%). Of note, 30 (83.3%) patients had stenosis in the occluded artery and 25 patients (69.4% of all patients in the series) also underwent angioplasty.

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 led 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 three 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 three 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: Endovascular Interventions for Stroke Due to Basilar Artery Occlusion
The evidence for the use of endovascular interventions for stroke due to basilar artery occlusions is limited, consisting on multiple noncomparative studies and one prospective

registry study comparing endovascular therapy with standard medical therapy. These studies indicate that high rates of recanalization can be achieved with mechanical thrombectomy. However, additional comparative studies are needed to demonstrate that mechanical thrombectomy is superior to standard therapy.

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."

Evidence about the role of endovascular stenting for treatment of symptomatic intracranial atherosclerotic disease consists of at least two 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, predictors of outcomes based on symptomatology, predictors of outcomes based on lesion morphology and arterial access, and clinical outcomes with the Wingspan system.

<u>Randomized Controlled Trials</u>
In 2015, Zaidat et al published results of the VISSIT trial, an RCT comparing a balloon-expandable stent plus medical management with medical management alone among patients with symptomatic intracranial stenosis of 70% or greater. Eligible patients had stenosis of 70% to 99% of the internal carotid, middle cerebral, intracranial vertebral, or basilar arteries with a transient ischemic attack (TIA) or stroke attributable to the territory of the target lesion within the prior 30 days. Enrollment was planned for up to 250 participants. However, an early unplanned analysis was conducted by the trial sponsor after the results of the SAMMPRIS trial were published (see below). A total of 112 patients were enrolled from 2009 to 2012 and randomized to balloon-expandable stent (Vitesse stent) plus medical management (stent group; n=59) or medical management alone (medical group; n=53). Medical management included clopidogrel (75 mg daily) for the first three months postenrollment and aspirin (81-325 mg/d) for the duration of the study, along with management of hypercholesterolemia and/or hypertension,

if necessary. The study used a primary composite end point that included any stroke in the same territory as the presenting event within one year of randomization and "hard TIA" in the same territory as the presenting event from two days to one year after randomization. Among 29 patients who met one of the primary end points within one year of randomization, eight patients (15.1%) were in the medical group and 21 (36.2%) were in the stent group (risk difference, 21.1%; 95% CI, 5.4% to 36.8%; p=0.02). The rates of stroke within 30 days of randomization or TIA within two to 30 days of randomization were 9.4% in the medical group and 24.1% in the stent group (risk difference, 14.7%; 95% CI, 1.2% to 28.2%; p=0.05). The 30-day all-cause mortality rate was 5.2% and 0% in the stent and medical groups, respectively (risk difference, 5.2%; 95% CI, -0.5% to 10.9%; p=0.25). The authors concluded that results did not support the use of a balloon-expandable stent for patients with symptomatic intracranial stenosis.

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

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

In 2015, Lutsep et al published a subgroup analysis of the SAMMPRIS trial results to evaluate whether outcomes differed for patients whose qualifying events occurred on or off

antithrombotic therapy. Similar to the overall trial results, outcomes were worse in the stent group than in the best medical management group: of the 284 patients on antithrombotic therapy at the time of the qualifying event, 140 patients were randomized to medical management and 144 to stenting; in Kaplan-Meier analysis, two year rates of the primary end point were 15.6% in the medical management group and 21.6% in the stent group (p=0.043). In other subgroup analyses of the SAMMPRIS trial results, 2-year event rates were higher in the stent group for most variables evaluated. The interaction between treatment and the subgroup variables was not significant for any variable.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) randomized 16 patients with symptomatic vertebral artery stenosis to endovascular therapy (balloon angioplasty or stenting) or best medical treatment alone. Endovascular intervention was technically successful in all eight patients, but two patients experienced TIAs 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 three patients in each arm died of myocardial infarction (MI) or carotid territory stroke, and one 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. Technical success (<30% residual stenosis on immediate post-procedure angiography) occurred in 5/10 patients treated with angiography (nine randomized to angiography and one 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 angiography 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, which generally concluded that additional evidence from RCTs would be needed to conclude that stenting should be used in practice.

In 2016, Abuzinadah conducted a systematic review and meta-analysis of studies reporting the rates of stroke recurrence or death (the primary outcome) in symptomatic intracranial vertebrobasilar stenosis with medical or endovascular treatment. 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 with medical therapy for intracranial atherosclerosis (e.g., Tang et al, Qureshi et al, Samaniego et al).

Section Summary: Endovascular Interventions for Symptomatic Intracranial Atherosclerotic Disease

The strongest evidence on the efficacy of endovascular treatment for symptomatic intracranial stenosis is from the SAMMPRIS RCT and the subsequent VISSIT RCT. The SAMMPRIS 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. The VISSIT RCT similarly found no benefit with endovascular treatment. These studies support the conclusion that outcomes of endovascular treatment are worse than medical therapy in patients with symptomatic intracranial stenosis.

Stent-assisted Endovascular Treatment of Intracranial Aneurysms

Self-expanding Stent Assisted Coiling for Intracranial Aneurysms

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, i.e., 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. The authors included ten retrospective cohort studies, ranging in size from nine 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.

In 2015, Ryu et al conducted a systematic review of studies reporting complications after stent-assisted coiling of ruptured intracranial aneurysms, with a focus on the association of complications with antiplatelet therapy. The review included 33 studies, three of which were

prospective and the remaining 30 retrospective (total N=1090 patients). In pooled analysis, thromboembolic complications occurred in 108 patients (event rate, 11.2%; 95% CI, 9.2% to 13.6%). Intraprocedural hemorrhage occurred in 46 (event rate, 5.4%; 95% CI, 4.1% to 7.1%).

Nonrandomized Comparative Studies
The largest comparative series describing use of stents compared with coiling alone for treating intracranial aneurysms was described by Piotin et al (2010). They reported on a series of 1137 patients (1325 aneurysms) treated between 2002 and 2009. In this series, 1109 aneurysms (83.5%) were treated without stents (coiling), and 216 (16.5%) were treated with stents (15 balloon-expandable and 201 self-expandable stents). Permanent neurologic procedure-related complications occurred in 7.4% (16 of 216) of the procedures with stents versus 3.8% (42 of 1109) in the procedures without stents (logistic regression p=0.644; odds ratio [OR], 1.289; 95% CI, 0.439 to 3.779). Procedure-induced mortality occurred in 4.6% (10 of 216) of the procedures with stents versus 1.2% (13 of 1109) in the procedures without stents (logistic regression p=0.006; OR=0.116; 95% CI, 0.025 to 0.531). At the time of publication, the authors had followed 53% (114 of 216) of aneurysms treated with stents and 70% (774 of 1109) of aneurysms treated without stents, with angiographic recurrence in 14.9% (17 of 114) versus 33.5% (259 of 774), respectively (p<0.001; OR=0.349; 95% CI, 0.2038 to 0.5960).

Additional smaller nonrandomized comparative studies, both prospective and retrospective, have evaluated stent-assisted coiling, compared with coiling alone, balloon-assisted coiling, or surgical clipping.

Hetts et al (2014) 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, non-randomized, multicenter Matrix and Platinum Science (MAPS) Trial, which was designed to compare bare-metal aneurysm coils and polymer-coated aneurysm coils. 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 one 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 two years (adjusted OR 1.1; P=0.94).

Consoli et al (2016) compared stent-assisted coiling with balloon-assisted coiling in patients with unruptured wide-necked intracranial aneurysms treated at a single center. The study included 268 patients with 286 aneurysms, 117 (122 aneurysms) of whom were treated with stent-assisted coiling and 151 (164 aneurysms) of whom were treated with balloon-assisted coiling. At discharge, 97.9% and 97.3% of those in the balloon-assisted and stent-assisted groups, respectively, had mRS of 0-1 (statistical comparison not reported). After 6 months, 97.9% and 98% of those in the balloon-assisted and stent-assisted groups, respectively, had mRS of 0-1, while mortality rates were 2.6% and 1.7% in the balloon-assisted and stent-assisted groups, respectively (statistical comparisons not reported). At 6 months, aneurysm recurrence

rates were 11.1% and 5.8% in the balloon-assisted and stent-assisted groups, respectively. In multivariable analysis, the use of stent-assisted coiling was significantly associated with complete occlusion at the end of the procedure (regression coefficient not reported; p=0.024) and complete occlusion after 6 months (regression coefficient not reported; p=0.05).

A 2011 nonrandomized comparative study by Hwang et al, reported on 126 aneurysms treated with stent-assisted coiling and 86 treated with coil alone. At 2-year follow-up, the authors reported rates of occlusion and recurrence. Progressive occlusion was noted in 42.5% (17/40) of the stent group and 39.5% (34/86) of the nonstented group, a difference that was not statistically significant. The rates of aneurysm recurrence also did not differ statistically between groups. There was aneurysm recurrence in 17.5% of patients in the stent group versus 21.0% in the nonstent group.

Liu et al (2014) 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. 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 non-significantly different).

Colby et al (2012) reported on 90 consecutive patients undergoing treatment for para-ophthalmic aneurysms, 30 of whom were treated with coil alone versus 60 who were treated with stent-assisted coils. On initial angiography following the procedure, complete occlusion of the aneurysm was achieved in 43.3% of stented patients compared with 31.7% of nonstented patients. At a mean of 14.5 months follow-up the recurrence rate was lower for the stented group at 15.4% (4/26) versus 41.5% (17/41) in the nonstented group ($p<0.05$).

Comparison between Endovascular Devices for Intracranial Aneurysms

Nonrandomized studies, which have been summarized in a systematic review by King et al (2015), report comparisons between devices used for stent-assisted coiling of intracranial aneurysms.

King et al (2015) reviewed published studies reporting on stent-assisted coiling with the Neuroform and Enterprise systems to compare outcomes between the devices. The analysis included 47 studies with a total of 4039 patients (4238 aneurysms; 2111 and 2127 treated with the Neuroform and Enterprise systems, respectively). Most studies were retrospective (81%). Compared with those treated with the Enterprise system, patients treated with the Neuroform system were more likely to have deployment failure (2.3% vs 0.2%, $p<0.001$), had a higher mortality rate (2.8% vs 1.8%, p=0.04), were less likely to have 100% aneurysm occlusion at last follow up (61.1% vs 74.7%,$p<0.001$), and were more likely to have recanalization (13.9% vs 10.6%, p=0.02). However, conclusions that can be drawn from these findings are limited by the potential for bias in the underlying studies and between-study heterogeneity.

Single-arm Series
There are a large number of single-arm series reporting on outcomes of stent-assisted coiling.

Systematic Reviews
A systematic review by Shapiro et al (2012) identified 39 articles reporting on 1517 patients, most of which were single-arm, retrospective series. The majority of patients treated had unruptured aneurysms, but 22% of patients had ruptured aneurysms. The authors noted a large amount of heterogeneity in reporting outcome data, particularly for adverse events. The periprocedural mortality rate was 2.1%, and the overall complication rate was 19%. Immediately following treatment, approximately 45% of patients had occlusion of the aneurysm. At an average of 13 months posttreatment, the stroke rate in the stented area was 3.2%.

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

Nonrandomized Comparative Studies
Since the publication of the Shapiro and Bodily systematic reviews, a number of non-comparative studies evaluating the use of stent-assisted endovascular treatments in intracranial aneurysms have been published.

The largest study, reported by Geyik et al (2013), included 468 patients with wide-necked cerebral aneurysms who underwent stent-assisted coiling with the Enterprise, Neuroform, Wingspan, or Leo (self-expanding, Balt, Montmorency, France) stents. Overall mortality was 1.9%; procedure-related complications occurred in 28 patients (6.9%). Angiographic follow up data, obtained at six months to seven years postprocedure (mean 19.2 months), were available for 440 patients (94%). For the total of 467 aneurysms with follow up, complete occlusion occurred in 194 aneurysms (41.6%), near-complete occlusion (>95% occlusion but minimal residual filling with coils at the neck) occurred in 242 aneurysms (51.8%), and incomplete occlusion (<95% occlusion) occurred in 31 aneurysms (6.6%). At six month follow-up, recanalization occurred in 38 aneurysms (8% of all aneurysms with follow up available). The authors conclude that stents are associated with high rates of occlusion and low rates of recurrence over long-term follow up.

In a larger study, Lee et al (2016) reported on 1038 patients treated with endovascular coiling, 296 of whom underwent stent-assisted coiling, with a focus on predictors of procedural rupture. Three cases of procedural rupture occurred among patients treated with stent-assisted coiling.

Other representative non-comparative studies in which at least some patients are treated with devices commercially available in the United States are summarized in Table 2. Interpretation of these studies is limited by potential selection bias and no comparison group. In general, these series demonstrate high rates of technical success of stent deployment with high rates of aneurysm occlusion; however, variable complication rates, particularly related to thromboembolic events were observed.

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

Study	Study Type	Patient Population	Intervention	Primary Outcome
Feng et al (2016)	Retrospective case series	97 patients with intracranial saccular aneurysms (13 with rupture)	Endovascular treatment with LVIS	• 100% of patients had technically successful treatment • 98.9% met the primary end point of safety (absence of new transient or permanent neurologic deficit or death) • Over mean follow-up of 7.8 mo, no patient had new neurologic deterioration or died • Among 76 patients with DSA imaging at follow-up, 59.21% had complete occlusion
Aydin et al (2015)	Retrospective case series	80 patients with wide-necked intracranial aneurysm at 3 institutions	Endovascular treatment with stent placement (LEO Baby stent)	• 97.5% of patients had technically successful treatment • 7.5% had periprocedural or delayed thromboembolic events; 3 (3.8%) patients had permanent neurologic deficits
Chalouhi et al (2013)	Retrospective case series	76 patients with posterior cerebellar artery (PICA) aneurysms at a single institution	Of 71 successful interventions: Endovascular coiling (n=60) with or without Neuroform stent assistance (4 patients) or balloon assistance (4 patients) or parent vessel trapping (n=11)	• 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, no disability) were achieved in 85%
Chen et al 2013	Retrospective case series	10 patients with large and giant fusiform aneurysms of the vertebrobasilar arteries at a single institution	Endovascular treatment with stent placement (Neuroform or Leo [self-expanding, Balt, Montmorency, France], 5 patients), stent-assisted coiling (3 patients), or occlusion of proximal artery (2 patients)	• 9 patients had a good outcome; 1 patient died after stenting procedure. • Stent deployment was generally feasible in the vertebrobasilar system.
Gentric et al 2013	Prospective cohort; industry-sponsored	107 patients with unruptured cerebral aneurysms enrolled at one of 10 European institutions	Endovascular treatment with Neuroform stent-assisted coiling	• 94.4% of patients had technically successful treatment. 66.4% of patients had complete occlusion immediately postprocedure. • At follow up at 12-18 mo, 5 patients (5%) had delayed complications, with 3% of patients with thromboembolic events. • Of 93 patients with anatomic evaluation available, aneurysms recurred in 9.7%.
Johnson et al 2013	Retrospective case series	91 patients with complex MCA aneurysms not amenable to 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 stenting along (2 aneurysms), endovascular treatment with stenting alone	• 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 (usually at 6 mo postprocedure), 77 (90.6%) were completely occluded, and 4 (4.7%) required retreatment.
Kulcsar et al 2013	Retrospective case series	117 patients with wide-necked cerebral aneurysms	Endovascular treatment with Neuroform stent-assisted coiling	• Stents were successfully deployed in 113 patients with 117 aneurysms • 99 patients had grade 1 or 2 occlusion (complete or aneurysm neck) on

				immediate postprocedure imaging • Intraprocedural major thrombotic events occurred in 7 cases (5.9%) and major infarcts on postprocedure imaging in 9 cases (7.7%) • Of 92 aneurysms with follow-up imaging available, 71 (77%) had grade 1 or 2 occlusion

DSA: digital subtraction angiography; LVIS: low profile visualized intraluminal support; MCA: middle cerebral artery; PCA: posterior cerebellar artery

Subsection Summary: Self-Expanding Stent-Assisted Coiling for Intracranial Aneurysms

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 AE rates are relatively high with stenting, and one nonrandomized comparative trial reported higher mortality with stent-assisted coiling than 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. However, it is recognized that patients who are candidates for endovascular therapy for aneurysms frequently have aneurysms in locations that are not amenable to surgical therapy, making comparisons to surgical therapy unlikely. Given the relative rarity of intracranial aneurysms, there may be legitimate barriers to clinical trials.

Flow-diverting Stents for Intracranial Aneurysms

Pivotal Study for FDA Approval

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 Un-coilable or Failed Aneurysms (PUFA) study, a multicenter, prospective, single-arm trial of the device for treatment of internal carotid artery aneurysms that were un-coilable or had failed coiling, for which results were published in 2013. Investigators enrolled 108 patients at ten centers with unruptured large- or giant-necked aneurysms measuring at least ten mm in diameter, with aneurysm 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 (two patients), insufficient aneurysm size on treatment angiography (one patient), and unsuccessful catheterization of the distal parent vessel (one patient). Two patients had two 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 end point of complete occlusion at day 180 without major stenosis or use of adjunctive coils. Six of

the 107 patients (5.6%) who underwent any catheterization, a primary safety end point (occurrence of major ipsilateral stroke or neurologic death at 180 days) occurred.

Randomized Controlled Trials

There were no randomized trials of flow-diverting stent treatment of intracranial aneurysms compared with standard neurosurgical treatment, i.e., surgical clipping or endovascular coils from the time of FDA approval until 2017.

Raymond et al (2017) reported on results of the Flow Diversion in the Treatment of Intracranial Aneurysm Trial (FIAT). FIAT was an investigator-initiated, pragmatic, multicenter RCT and registry study integrated into clinical practice at 3 Canadian hospitals enrolling 112 patients between May 2011, and February 2015. Seventy-eight patients were randomized (39 in each group) to flow diversion or standard management (physician's choice of observation, coil embolization, parent vessel occlusion, or clip placement), and 34 additional patients received flow diversion within the registry. Inclusion criteria were pragmatic; patients with an aneurysm for which flow diversion was considered a promising treatment were eligible unless they had a contraindication. The trial was originally powered to include 200 patients in the pilot phase and 250 patients in the pivotal phase but was stopped early due to safety concerns. Patient mean age was about 58 years, mean aneurysm size was approximately 16 mm in the RCT arm and 19 mm in the registry arm, and mean aneurysm neck was 5 mm. Approximately two-thirds of the aneurysms were in the proximal carotid, 13% were in another anterior location, and 18% were in posterior circulation. The physician's choice in the standard care group (selected at the time of randomization) was coil embolization (with or without stent placement) in 25 (64%) patients, parent vessel occlusion in 10 (26%) patients, observation in 4 (10%) patients, and surgical clipping in no patients. Twelve (16%) of 75 patients (95% CI, 9% to 27%) who were allocated to or received flow diversion were dead (n=8) or dependent (n=4) at 3 months or more, which crossed a predefined safety boundary. In the RCT portion of the study, morbidity or mortality occurred in 5 patients in the flow diversion group (13%; 95% CI, 5% to 29%) and in 5 patients in the standard treatment group (13%; 95% CI, 5% to 28%). The primary efficacy outcome was a composite including complete or near-complete occlusion of the aneurysm between 3 and 12 months and an independent functional outcome (mRS score ≤2). Sixteen (42%) patients (95% CI, 27% to 59%) in the flow diversion group failed to reach the primary outcome compared with 14 (36%) patients in the standard treatment group (95% CI, 22% to 53%). Results shown in Table 3 include all patients and the subset of patients with proximal carotid aneurysms.

Table 3. Summary of RCT Results of Flow-Diverting Stents for Intracranial Aneurysms

Study (Trial)	Primary Efficacy Outcome	Death	Any Stroke	Any SAE or Complication	Residual Aneurysm
Raymond et al (2017)[113] (FIAT)					
All patients					
N	77	77	77	77	77
Flow diversion (95% CI), %	58 (41 to 73)[a]	5 (1 to 19)	13 (5 to 29)	29 (16 to 46)	18 (8 to 35)
Standard treatment (95% CI), %	64 (47 to 78)[a]	5 (1 to 19)	10 (3 to 25)	10 (3 to 25)	21 (10 to 37)
Treatment effect (95% CI)	NR	NR	NR	NR	NR
Patients with proximal carotid aneurysms					

N	54	54	54	54	54
Flow diversion (95% CI), %	42 (NR)[a]	4 (NR)	8 (NR)	39 (NR)	12 (NR)
Standard treatment (95% CI), %	36 (NR)[a]	4 (NR)	11 (NR)	14 (NR)	21 (NR)

CI: confidence interval; NR: not reported; SAE: serious adverse event.
a The primary efficacy outcome was a composite of complete or near-complete occlusion of the aneurysm between 3 and 12 months and an independent functional outcome (mRS score ≤2).

Nonrandomized Comparative Studies

Zhou et al (2015) reported results of a systematic review of studies comparing flow-diverting devices with endovascular coiling for intracranial aneurysms which included 9 retrospective comparative studies with a total of 863 subjects. This review included studies with ruptured or unruptured aneurysms. Across the 9 studies, 305 patients were treated with flow-diverting devices, 558 with coil embolization therapy, and 324 with stent-assisted coiling alone. In pooled analysis, the use of flow diverting devices was associated with a significantly higher complete occlusion rate when compared with coil embolization therapy (OR 3.13, 95% CI 2.11 to 4.65, I2=18%) or with stent-assisted coiling (OR 2.08, 95% CI 1.34 to 3.24, I2=0%). Rates of overall morbidity were not significantly different between flow diverting device- and coil embolization therapy-treated patients, or between flow diverting device- and stent-assisted coiling.

In a 2014 study which was not included in the Zhou et al review and which included more patients than any single study in that review, 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 diverters, two patients had ruptured dissecting aneurysms, two deaths occurred, one patient had permanent morbidity, and two aneurysms were not occluded at 30 months follow-up. Direct comparisons with outcomes from alternative treatments are not reported.

Single-arm Series

Systematic Reviews

Multiple non-comparative 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 systematic review identified (reported by Briganti et al in 2015) reviewed 18 studies published from 2009 to 2014 with 1483 patients (1704 aneurysms). Most (87.5%) treated aneurysms were in the anterior circulation and most (87.5%) were saccular in morphology. In the 17 studies reporting procedural complications, mean incidence was 8.3% (range, 0%-23.1%). Permanent morbidity occurred in a mean 3.5% of patients (range: 0%-15%), while the mean mortality rate was 3.4% (range, 0.5%-8%). Across the 18 studies, aneurysms were completely occluded in a mean 81.5% of cases (range, 69%-100%).

Earlier systematic reviews by Brinjiki et al (2013) et al and Arrese et al (2013) similarly reported high estimates for aneurysm occlusion rates (approximately 75%), but relatively high rates of morbidity and mortality.

Noncomparative Studies
Since the publication of these two meta-analyses, a number of non-comparative studies evaluating flow-diverting stents in the treatment of aneurysms have been published.

The largest cohort study identified was by Kallmes et al (2015), who conducted a retrospective analysis of patients treated with the Pipeline device at 17 centers worldwide. The authors identified 793 patients with 906 aneurysms who were enrolled in the International Retrospective Study of Pipeline Embolization Device (IntrePED) registry. Of the total number of aneurysms, 311 were in the anterior ICA circulation and at least 10 mm, 349 of which were in the anterior circulation and less than 10mm, 59 of which were in the posterior circulation, 179 of which were in a non-ICA anterior circulation location and less than 10mm, and ten 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 10mm 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). In a subsequent study using data from the same registry, Brinjikji et al (2015) reported on risk factors for hemorrhagic complications after Pipeline device placement. Twenty patients had an intraparenchymal hemorrhage, most often (75%) within 30 days of treatment. The only procedure- or device-related variable associated with intraparenchymal hemorrhage was receiving three or more Pipeline devices (OR=4.10; 95% CI, 1.34 to 12.58; p=0.04). Additional analyses from this registry have evaluated the effect of age on outcomes after Pipeline placement and differences in complication rates between aneurysms treated with the Pipeline with or without coil embolization.

The longest follow-up reported is from a 2015 series of 98 patients with 119 aneurysms treated with the Pipeline Embolization Device and followed for at least two years. Of the 119 aneurysms, 100% had clinical follow-up and 88.8% had imaging follow-up up to two or more years postprocedure. Aneurysm occlusion rates were 81.6%, 84.1%, and 93.2% at six months, one year, and two year follow-ups, respectively. Three cases (2.8%) of in-stent stenosis occurred. From zero to six months, rates of TIA, minor stroke, and major stroke were 4.2%, 3.4%, and 0.8%, respectively.

Guedon et al (2016) reported on late ischemic complications after flow diverting stent placement. Among 86 patients treated at a single institution, angiographic follow up was available to a mean 15.7 months ([SD=11.8 months; median, 13 months; range, 8-21 months) and clinical follow-up was available to a mean 16.9 months (SD=12.9 months; median, 14 months; range 10-22 months). Five (5.8%) patients developed ischemic complications.

Additional representative studies, with a focus on series with more than 50 patients, are summarized in Table 4.

Table 4. Noncomparative Studies of Flow-Diverting Stent-Assisted Endovascular Treatment of Aneurysms

Study	Study Type	Patient Population	Intervention	Primary Outcome
Strauss et al (2016)	Retrospective case series	60 patients with anterior- or posterior circulation aneurysms (67 aneurysms)	Silk flow diverting stent (Balt Extrusion, Montmorency, France)	• 10 patients had periprocedural complications, 4 resulting in mortality • Among 60 aneurysms with available follow up imaging (median 15 mo post-treatment), 88% had good angiographic results (complete or near-complete occlusion)
Fischer et al (2015)	Retrospective case series	121 patients with intracranial saccular sidewall aneurysms (130 aneurysms)	P64 Flow-Modulated Device (phenox, Bochum, Germany)	• 1 patient had pulmonary artery embolism and 2 patients had ischemic lesions with transient neurologic deficits in the periprocedural period. • Among 93 aneurysms with available DWI at a median 279 d, 79.6% had complete aneurysm occlusion
Brasiliense et al (2016)	Prospective case series	59 patients with 70 aneurysms who underwent routine postprocedural MRI after placement of flow diversion	Pipeline Embolization Device	• 5.1% had clinically apparent neurologic symptoms postprocedure • 62.7% had ischemic lesions on DWI postprocedure
Chalouhi et al (2015)	Retrospective case series	100 patients with aneurysms 7mm or less treated at one institution	Pipeline Embolization Device placement	• Complications occurred in 3% (1 distal parenchymal hemorrhage; 2 ischemic events). • At last followup (mean 6.3 mo), 72% of aneurysms were completely occluded. • Retreatment was required in 8%.
Lubicz et al (2014)	Retrospective review of prospectively-collected data	58 patients with 70 intracranial aneurysms treated at 2 institutions	SILK artery reconstruction device (Balt Extrusion, Montmorency, France)	• No periprocedural deaths occurred. • Overall permanent neurological morbidity was 5.5% • At long-term follow up, 73% had complete occlusion, 16% had

				neck remnants, and 11% had incomplete occlusion
Wakhloo et al (2014)	Prospective multicenter trial at 24 centers	165 patients with 190 intracranial aneurysms	Surpass flow diverting device (Stryker Neurovascular, Fremont, CA)	• At 6 month follow up, permanent neurological morbidity was 6% and permanent neurological mortality was 2.7%. • Neurologic death during follow-up occurred in 1.6% of patients with anterior circulation aneurysms and 7.4% with posterior circulation aneurysms. • Ischemic stroke at ≤30 days, SAH at ≤7 days, and intraparenchymal hemorrhage at ≤7 days occurred in 3.7%, 2.5%, and 2.5% of subjects, respectively.
Kan et al (2013)	Prospective case series (registry)	56 patients with intracranial aneurysm treated at 7 institutions	Pipeline Embolization Device placement	• 6/123 devices incompletely deployed • Among 19 patients with 6-mo follow-up, 68% (13 patients) had complete aneurysm occlusion • 4 fatal postprocedural hemorrhages occurred
Piano et al (2013)	Retrospective case series	101 patients with intracranial aneurysm at a single institution	Flow-diverting stent placement (Pipeline Embolization Device or SILK device), with or without endovascular coiling	• 86% of aneurysms evaluated at 6-mo follow-up showed complete occlusion
Toma et al (2013)	Retrospective case series	84 patients with intracranial aneurysm at a single institution	Flow-diverting stent placement	• 61% of aneurysms had resolved at 12 mo • 9.5% of patients had a new, permanent neurologic deficit and 5.9% of patients had procedure-related mortality

DWI: diffusion-weighted imaging; FU: follow-up; MRI: magnetic resonance imaging; SAH: subarachnoid hemorrhage

Section Summary: Flow-Diverting Stents for Intracranial Aneurysms
A recent RCT has evaluated flow-diverting stents. The FIAT pragmatic RCT and registry study compared flow diversion with standard management (observation, coil embolization, or parent vessel occlusion) in patients for whom flow diversion was considered a promising treatment. FIAT was stopped early due to safety concerns after 112 participants (78 in the randomized part of the study and 34 in the registry) were enrolled. Morbidity and mortality were lower for proximal carotid aneurysms than for posterior circulation aneurysms and results of flow diversion were more encouraging for aneurysms amenable to coil embolization, patients allocated to standard treatment appeared to do at least as well as those assigned to flow diversion.

One nonrandomized study, which 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 in those treated with coiling, with similar rates of good clinical outcomes. Single-arm series have suggested that there are high rates (≥70%) of aneurysmal occlusion after flow-diverting stent placement. As for self-expanding stents for aneurysms, patients who are candidates for endovascular therapy for aneurysms frequently have aneurysms in locations amenable to surgical therapy, making comparisons with surgical therapy unlikely.

Summary of Evidence
For individuals who have acute ischemic stroke due to occlusion of an anterior circulation vessel who receive endovascular mechanical embolectomy, the evidence includes randomized clinical trials (RCTs) comparing endovascular therapy with standard care and systematic reviews of these RCTs. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related mortality and morbidity. From 2013 to 2015, eight RCTs were published comparing endovascular therapies with noninterventional care for acute stroke in patients with anterior circulation occlusions. Several trials that were ongoing at the time of publication of these 8 RCTs were stopped early and results with the limited enrollment have been published. Trials published from 2014 to 2015 demonstrated a significant benefit in terms of reduced disability at 90 days posttreatment. The trials that demonstrated a benefit to endovascular therapy either exclusively used stent retriever devices or allowed the treating physician to select a device, mostly a stent retriever device, and had high rates of mechanical embolectomy device use in patients randomized to endovascular therapy. All studies that demonstrated a benefit to endovascular therapy required demonstration of a large-vessel, anterior circulation occlusion for enrollment. In addition, they were characterized by fast time-to-treatment. Two trials published in 2018 demonstrated that it was possible to extend the window for mechanical thrombectomy up to about 24 hours for select patients. To achieve results in real-world settings similar to those in the clinical trials, treatment times, clinical protocols, and patient selection criteria should be similar to those in the RCTs. The evidence is sufficient to determine quantitatively that the technology results in a large improvement in the net health outcome.

For individuals who have acute ischemic stroke due to basilar artery occlusion who receive endovascular mechanical embolectomy, the evidence includes a nonrandomized comparative study and a several case series. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related mortality and morbidity. These studies indicate that high rates of recanalization can be achieved with mechanical thrombectomy. However, additional comparative studies are needed to demonstrate that mechanical thrombectomy is superior to standard therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have symptomatic intracranial arterial stenosis who receive intracranial percutaneous transluminal angioplasty with or without stenting, the evidence includes two RCTs and a number of nonrandomized comparative studies and case series. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, and treatment-related mortality and morbidity. Both available RCTs demonstrated no significant benefit with endovascular therapy. In particular, the SAMMPRIS trial was stopped early due to harms, because the rate of stroke or death at 30 days posttreatment 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. Although some nonrandomized studies have suggested a benefit from endovascular therapy, the available evidence from two RCTs does not suggest that intracranial percutaneous transluminal angioplasty with or without stenting improves outcomes for individuals with symptomatic intracranial stenosis. The evidence is sufficient to determine qualitatively that the technology is unlikely to improve the net health outcome.

For individuals who have intracranial aneurysms who receive endovascular coiling with intracranial stent placement or intracranial placement of a flow diverting stent, the evidence includes several nonrandomized comparative studies and multiple single-arm studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related mortality and morbidity. The available nonrandomized comparative studies report occlusion rates for stent-assisted coiling that are similar to or higher than coiling alone and recurrence rates that may be lower than for coiling alone. For stent-assisted coiling with self-expanding stents, there is also some evidence that adverse event rates are relatively high, and one nonrandomized comparative trial reported that mortality is higher with stent-assisted coiling than with coiling alone. For placement of flow-diverting stents, a pragmatic RCT and registry study have compared flow diversion with standard management (observation, coil embolization, or parent vessel occlusion) in patients for whom flow diversion was considered a promising treatment. The pragmatic study was stopped early after crossing a predefined safety boundary when 16% of patients treated with flow diversion were dead or dependent at 3 months or later. Flow diversion was also not as effective as the investigators had hypothesized. A nonrandomized study comparing 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.

Practice Guidelines and Position Statements

Society of Vascular and Interventional Neurology

In 2016, the Society of Vascular and Interventional Neurology (SVIN) published recommendations on comprehensive stroke center requirements and endovascular stroke systems of care. The recommendations were based on 5 multicenter, prospective, randomized, open-label, blinded end point clinical trials that demonstrated the benefits of endovascular therapy with mechanical thrombectomy in acute ischemic strokes with large vessel occlusions. Their recommendation pertinent to this evidence review is:

"Endovascular mechanical thrombectomy, in addition to treatment with IV tPA [intravenous tissue plasminogen activator] in eligible patients, is recommended for anterior circulation large vessel occlusion ischemic strokes in patients presenting within 6 h of symptom onset."

American Heart Association and American Stroke Association

In 2018, the AHA and the American Stroke Association published joint guidelines for the early management of patients with acute ischemic stroke. These guidelines include several recommendations relevant to the use of endovascular therapies for acute stroke:

Table 5. Recommendations on Use of Endovascular Therapies to Manage Acute Stroke

Recommendation	COR	LOE
"Mechanical thrombectomy requires the patient to be at an experienced stroke center with rapid access to cerebral angiography, qualified neurointerventionalists, and a comprehensive periprocedural care team. Systems should be designed, executed, and monitored to emphasize expeditious assessment and treatment. Outcomes for all patients should be tracked. Facilities are encouraged to define criteria that can be used to credential individuals who can perform safe and timely intra-arterial revascularization procedures."	I	C
"Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: • "Prestroke mRS score 0 to 1, • "Causative occlusion of the internal carotid artery or MCA (M1), • "Age ≥18 years, • NIHSS score of ≥6, • "ASPECTS of ≥6, and • "Treatment can be initiated (groin puncture) within 6 hours of symptom onset."	I	A
In selected patients with acute ischemic stroke within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.	I	A
"The technical goal of the thrombectomy procedure should be a reperfusion to a modified TICI 2b/3 angiographic result to maximize the probability of a good functional clinical outcome."	I	A
"As with intravenous alteplase, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible and within the therapeutic window."	I	B-R
• "Use of stent retrievers is indicated in preference to the MERCI device." • "The use of mechanical thrombectomy devices other than stent retrievers may be reasonable in some circumstances."	I IIb	A B-NR
"The use of proximal balloon guide catheter or a large bore distal access catheter rather than a cervical guide catheter alone in conjunction with stent retrievers may be beneficial. Future studies should examine which systems provide the highest recanalization rates with the lowest risk for nontarget embolization."	IIa	C-LD
In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the	IIa	B-R

Recommendation	COR	LOE
anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable.		
"In carefully selected patients with anterior circulation occlusion who have contraindications to intravenous r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable. There are inadequate data available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time-based or nontime based (eg, prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications)."	IIa	C
"Although the benefits are uncertain, use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs."	IIb	B-R
"Although the benefits are uncertain, use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries."	IIb	C
"Although the benefits are uncertain, use of mechanical thrombectomy with stent retrievers may be reasonable for patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score of >1, ASPECTS <6, or NIHSS score <6 and causative occlusion of the internal carotid artery or proximal MCA (M1). Additional randomized trial data are needed."	IIb	B-R
In patients under consideration for mechanical thrombectomy, observation after IV alteplase to assess for clinical response should not be performed.	III	B-R
"Use of salvage technical adjuncts including intra-arterial fibrinolysis may be reasonable to achieve these angiographic results"	IIb	C-LD
"Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of intravenous alteplase might be considered, but the consequences are unknown."	IIb	C-EO

AIS: acute ischemic stroke; ASPECTS: Alberta Stroke Program Early Computed Tomography Score; COR: class of recommendation; LOE: level of recommendation; LVO: large vessel occlusion; MCA: middle cerebral artery; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; r-tPA: recombinant tissue plasminogen activator; TICI: Thrombolysis in Cerebral Infarction.

Table 6. Recommendations on Management of Unruptured Intracranial Aneurysms

Recommendation	COR	LOE
"...coil embolization may be superior to surgical clipping with respect to procedural morbidity and mortality, length of stay, and hospital costs, so it may be reasonable to choose endovascular therapy over surgical clipping in the treatment of select unruptured intracranial aneurysms, particularly in cases for which surgical morbidity is high, such as at the basilar apex and in the elderly"	IIb	B
"...coil embolization may be superior to surgical clipping with respect to procedural morbidity and mortality, length of stay, and hospital costs, so it may be reasonable to choose endovascular therapy over surgical clipping in the treatment of select unruptured intracranial aneurysms, particularly in cases for which surgical morbidity is high, such as at the basilar apex and in the elderly"	IIb	B
"Endovascular treatment of unruptured intracranial aneurysms is recommended to be performed at high-volume centers."	I	B

COR: class of recommendation; LOE: level of recommendation.

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.

Key Words:

intracranial stenting, flow diverting stent, intracranial angioplasty, Percutaneous Transluminal Angioplasty, mechanical embolectomy, stroke, cerebral aneurysm, revascularization, Intracranial Circulation, Vertebrobasilar Stenosis, Angioplasty, Merci® Retriever, Penumbra System®, Solitaire™, Trevo Pro Retriever™, Neurolink®, Neurolink System, Wingspan Stent System, Pipeline® Embolization Device, Neuroform ™ Microdelivery Stent System, Enterprise™, Low Profile Visualized Intraluminal Support Device

Approved by Governing Bodies:

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

Acute Stroke

The Merci® Retriever (Concentric Medical, Mountain View, CA)

In August 2004, the Merci® Retriever was cleared by FDA through the 510(k) process. This device was judged equivalent to a predicate device, the Concentric Retriever, which was indicated for endovascular foreign body removal. 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 neuro-vasculature. A modified Merci Retriever, also manufactured by Concentric Medical Inc., received 510(k) clearance from FDA in May 2006. The clearance notes that the Modified Merci Retriever is intended to restore blood flow in the neuro-vasculature 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. FDA product code: NRY

The Penumbra System® (Penumbra Inc., Alameda, CA)

In December 2007, the Penumbra System® was cleared through the 510(k) process. FDA determined that this device was substantially equivalent to existing devices for use in the revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease (in the internal carotid, middle cerebral - Ml and M2 segments, basilar, and vertebral arteries) within eight hours of symptom onset. FDA product code: NRY

The Solitaire™ FR device (Covidien/ev3 Neurovascular, Irvine, CA)

In March 2012, the Solitaire™ FR device was cleared for marketing by FDA through the 510(k) process. FDA determined that this device was substantially equivalent to the Merci Retriever device, based on a randomized controlled trial (RCT) of 113 patients submitted to FDA comparing the Merci and Solitaire devices. Indications for the device are patients with ischemic stroke due to large intracranial vessel occlusion who are ineligible for intravenous tPA, or who fail intravenous tPA. FDA product code: NRY

The Trevo Pro Retriever™ device (Stryker Neurovascular, Kalamazoo, MI)
In August 2012, the Trevo Pro Retriever™ device was cleared for marketing by FDA through the 510(k) process. FDA determined that this device was substantially equivalent to the Merci Retriever device, based on an RCT of 178 patients from 27 centers in the U.S. and Europe that compared the Trevo device with the Merci device. Indications for the device are patients with acute ischemic stroke due to large intracranial vessel occlusion who are ineligible for or fail intravenous tPA. 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 review. In February 2018, FDA expanded the indication for the Trevo® Retriever to include patients experiencing acute ischemic stroke up to 24 hours from symptom onset. FDA product code: NRY.

A summary of the devices with FDA clearance for the endovascular treatment of acute stroke is provided in Table 7.

Table 7: FDA-Cleared Mechanical Embolectomy Devices for Acute Stroke

Device	510(k) No. for Original Device	Approval Date for Original Device	Indications
Merci® Retriever (Concentric Medical, Mountain View, CA; acquired by Stryker Neurovascular, Kalamazoo, MI, in 2011)	K033736	Aug 2004 (modified device approved May 2006)	Patients with acute ischemic stroke and who are ineligible for or who fail IV tPA therapy
Penumbra System® (Penumbra, Alameda, CA)	K072718	Dec 2007	Patients with acute ischemic stroke secondary to intracranial large-vessel occlusive disease within 8 h of symptom onset
Stent retrievers			
Solitaire™ FR Revascularization Device (Covidien/ev3 Neurovascular, Irvine, CA)	K113455	Mar 2012	Patients with acute ischemic stroke due to large intracranial vessel occlusion who are ineligible for or who fail IV tPA
Trevo® Retriever device (Stryker Neurovascular, Kalamazoo, MI)	K122478	Aug 2012	Patients with acute ischemic stroke due to large intracranial vessel occlusion who are ineligible for or who fail IV tPA

FDA: Food and Drug Administration; IV: intravenous; tPA: tissue plasminogen activator.

Intracranial Stenosis

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:

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."

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, 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) with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments (P100018). Approval was based on the Pipeline for Uncoilable for Failed Aneurysms Study, a single-arm, open-label feasibility study that included 108 patients aged 30 to 75 years with unruptured large and giant wide-necked aneurysms.

Three stents have received FDA approval through the Humanitarian Device Exemption (HDE) program for treatment of intracranial aneurysms.

Neuroform™ Microdelivery Stent System (Stryker, Kalamazoo, MI)
In 2002, based on a series of approximately 30 patients with six-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).

Enterprise™ Vascular Reconstruction Device and Delivery System (Cordis Neurovascular Inc., Miami Lakes, FL))
In 2007, based on a series of approximately 30 patients with six-month follow-up, the Enterprise Vascular Reconstruction Device and Delivery System (Cordis Neurovascular, Inc.) was approved (HDE) for use with embolic coils for treatment of wide-neck, intracranial, saccular or fusiform aneurysms (H060001).

The Low-Profile Visualized Intraluminal Support Device (LVIS™ and LVIS™ Jr.) (MicroVention, Inc., Tustin, CA)
In July 2014, the Low Profile Visualized Intraluminal Support Device received HDE approval (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.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

CPT codes specific for intracranial angioplasty and stent placement:

61630 Balloon angioplasty, intracranial (e.g., atherosclerotic stenosis) percutaneous

61635 Transcatheter placement of intravascular stent(s), intracranial (e.g., atherosclerotic stenosis), including balloon angioplasty, if performed

CPT code for occlusion of a vascular malformation performed as part of the treatment of an aneurysm:

61624 Transcatheter permanent occlusion or embolization (e.g., for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method; central nervous system (intracranial, spinal cord)

Diagnostic studies of cervicocerebral arteries codes (e.g., **36221-36228**) describe non-selective and selective arterial catheter placement and diagnostic imaging.

CPT code for mechanical embolectomy:

61645 percutaneous arterial transluminal mechanical thrombectomy and/or infusion for thrombolysis, intracranial, any method, including diagnostic angiography, fluoroscopic guidance, catheter placement, and intraprocedural pharmacological thrombolytic injection(s) **(Effective 01/01/2016)**

Previous Coding:

CPT Codes:

Prior to 01/01/2016, there was not a specific CPT code for **mechanical embolectomy**. It is recommended that physicians code the components of the procedure separately so they would submit codes for the catheterization (e.g., **36221-36228**) and the intervention (e.g., **37184-37186**).

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Policy History:

Medical Policy Group, February 2006 **(4)**
Medical Review Committee, February 2006
Medical Policy Administration Committee, June 2006
Available for comment July 5-August 18, 2006
Medical Policy Group, June 2009 **(1)**
Medical Policy Group, December 2010 **(1):** Coding update-Added change of verbiage to code 75960
Medical Policy Panel, May 2012
Medical Policy Panel Group, August 2012 **(2):** Policy extensively updated with literature review. Policy statements changed to medically necessary for selected patients with intracranial aneurysms. Added statement that transluminal angioplasty with and without stenting is

investigational. Title change, Description, Key Points, References updated to support policy changes.
Medical Policy Administration Committee, September 2012
Available for comments September 18 through November 1, 2012
Medical Policy Group, September 2013 **(4):** 2013 Update to Key Points and References
Medical Policy Group, December 2013 **(3):** 2014 Coding Update – added existing code 61624; moved code 75960 to previous coding (deleted effective 01/01/2014)
Medical Policy Panel January 2014
Medical Policy Group January 2014 **(4):** All policy documentation in policy #298, "Mechanical Embolectomy for Treatment of Acute Stroke", was added to this policy 263 and then policy 298 was archived. Title of this policy was changed to reflect the integration of policy 298. Update to Description, Key Points, Key Words, Approved Governing bodies, Coding and References related to intracranial and endovascular interventions; no change to policy statements or intention of coverage related to either procedure.
Medical Policy Panel June 2014
Medical Policy Group 2014 **(4):** Added indication for flow-diverting stents to the policy section. updated Key Points & References.
Medical Policy Administration Committee August 2014
Available for comment August 8 through September 22, 2014
Medical Policy Panel, January 2015
Medical Policy Group, January 2015**(4):** Updates to Description, Key Points, Approved Governing Bodies, Key Words, Current Coding and References. Added "with FDA approval for the treatment of intracranial aneurysms" and "AND are not amenable to surgical treatment or standard endovascular therapy" to the Intracranial flow diverting stents policy statement.
Medical Policy Panel, September 2015
Medical Policy Group, September 2015 **(4)**: Updates to Description, Key Points, Approved Governing Bodies, and References. Policy statement added " The use of endovascular mechanical embolectomy with an FDA approved device for the treatment of acute ischemic stroke meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage" when certain criteria are met. Coding section updated. Removed CPT 35475 (error), removed code description for 37184-37186 (codes remain on policy).
Medical Policy Administration Committee October 2015
Available for comment October 2 through November 15, 2015
Medical Policy Group **(4):** Clarified policy statement that mechanical embolectomy does not meet for acute ischemic stroke when the above criteria are not met. Further clarified by adding statement for "other endovascular interventions" are investigational.
Medical Policy Group, November 2015: 2016 Annual Coding Update; added new CPT code 61645 to current coding; moved CPT coding section 36221-36228 to previous coding section.
Medical Policy Panel, April 2016
Medical Policy Group, May 2016 **(4):** Updates to Description, Key Points, Coding, and References. No change to policy statement.
Medical Policy Panel, September 2017
Medical Policy Group, September 2017 **(4):** Updates to Key Points, References, and Coding; Removed policy statements for dates of service November 1, 2012 through June 30th, 2014; Removed CPT code 75960 from Previous Coding section. It was deleted 01/01/2014.
Medical Policy Panel, April 2018

Medical Policy Group, May 2018 **(4):** Updates to Key Points, Policy, Current Coding, and References. Updated policy statement to include coverage for mechanical embolectomy within 24 hours with evidence of mismatch between specific clinical and imaging criteria.
Medical Policy Administration Committee: May 2018
Available for comment May 2 through June 15, 2018