Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

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

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

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

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

Based on review of available data, the Company may consider intracranial flow diverting stents with U.S. Food and Drug Administration (FDA) approval for the treatment of intracranial aneurysms to be **eligible for coverage** as part of the endovascular treatment of intracranial aneurysms that meet patient selection criteria and are not amenable to surgical treatment or standard endovascular therapy.

Patient Selection Criteria
Coverage eligibility will be considered when the criterion below is met:

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

Based on review of available data, the Company may consider the use of endovascular mechanical embolectomy with a device with FDA approval for the treatment of acute ischemic stroke as part of the treatment of acute ischemic stroke for patients who meet all of the following criteria to be **eligible for coverage**:

- 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 (see Policy Guidelines section); AND
- Have evidence of substantial and clinically significant neurological deficits (see Policy Guidelines section); AND

- Have evidence of salvageable brain tissue in the affected vascular territory (see Policy Guidelines section); AND
- Have no evidence of intracranial hemorrhage or arterial dissection on computed tomography (CT) or magnetic resonance imaging.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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

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

Based on review of available data, the Company considers endovascular interventions for the treatment of acute ischemic stroke when the above patient selection criteria is not met to be **investigational.***

Policy Guidelines

Patient Selection for Endovascular Mechanical Embolectomy for Acute Ischemic Stroke
The major randomized controlled trials (RCTs) demonstrating a benefit with endovascular mechanical embolectomy vary in criteria for selecting patients based on the presence or absence of salvageable brain tissue. Several RCTs use the Alberta Stroke Program Early Computed Tomography Score, which is a 10-point quantitative computed tomography (CT) score to assess the presence of early ischemic changes. MR CLEAN (Berkhemer et al, 2015) did not specify imaging criteria to demonstrate salvageable brain tissue. Table PG1 lists the criteria used by other trials.

Table PG1. Trial Selection Criteria for Salvageable Brain Tissue

Trial	Inclusion or Exclusion	Criteria
REVASCAT (Jovin et al, 2015)	Exclusion	Hypodensity on CT or restricted diffusion demonstrated by: • An ASPECTS <7 on CT, CT perfusion CBV, CTA source imaging; OR • An ASPECTS <6 on DWI MRI
ESCAPE (Goyal et al, 2015)	Exclusion	• Baseline non–contrast CT with extensive early ischemic changes of ASPECTS of 0-5 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 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 CBF, ASPECTS <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
EXTEND-IA (Campbell et al, 2015)	Inclusion	Based on CT perfusion imaging using CT or MRI with a Tmax more than 6-s delay perfusion volume and either CT regional CBF or DWI infarct core volume as follows: • Mismatch ratio >1.2; AND • Absolute mismatch volume >10 mL; AND • Infarct core lesion volume <70 mL
SWIFT-PRIME (Saver et al, 2015)	Exclusion	Related to imaging-demonstrated core infarct and hypoperfusion: • MRI-assessed core infarct lesion greater than: ○ 50 cm^3 for subjects age 18-79 y; ○ 20 cm^3 for subjects age 80-85 y; • CT-assessed core infarct lesion greater than: ○ 40 cm^3 for subjects age 18-79 y; ○ 15 cm^3 for subjects age 80-85 y; • For all subjects, severe hypoperfusion lesion (≥10-s Tmax lesion >100 cm^3); • For all subjects, ischemic penumbra of ≥15 cm^3 and mismatch ratio >1.8

ASPECTS: Alberta Stroke Program Early Computed Tomography Score; CBF: cerebral blood flow; CBV: cerebral blood volume; CT: computed tomography; CTA: computed tomography angiography; DWI: diffusion-weighted imaging; MCA: middle cerebral artery; MRI: magnetic resonance imaging.

The RCTs demonstrating a benefit to endovascular mechanical embolectomy in acute stroke generally had some inclusion criteria to reflect stroke severity—with the exception of the EXTEND-IA trial. The REVASCAT and ESCAPE trials both required a baseline (poststroke) National Institutes of Health Stroke Scale (NIHSS) score of 6 or higher. MR CLEAN specified a clinical diagnosis of acute stroke with a deficit on the NIHSS score of 2 points or more; SWIFT-PRIME specified an NIHSS score of 8 or more and less than 30 at the time of randomization.

The DAWN and DEFUSE 3 studies enrolled patients from 6 up to 24 hours of the time last time known to be well if there was evidence of a mismatch between specific clinical and imaging criteria (infarct size and volume was assessed with the use of diffusion-weighted magnetic resonance imaging or perfusion CT) (see Table PG2).

Table PG2. Trial Selection Criteria for Patients 6 to 25 Hours Post Infarct

Trial	Inclusion or Exclusion	Criteria
DAWN Trial (Nogueira et al, 2018)	Inclusion	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
DEFUSE 3 Trial (Albers et al, 2018)	Inclusion	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

NIHSS: National Institutes of Health Stroke Scale.

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

This policy only addresses endovascular therapies used on intracranial vessels.

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

Background/Overview

CEREBROVASCULAR DISEASES
Cerebrovascular diseases include a range of processes affecting the cerebral vascular system, including arterial thromboembolism, arterial stenosis, and arterial aneurysms, all of which can restrict cerebral blood flow due to ischemia or hemorrhage. Endovascular techniques, including endovascular mechanical embolectomy with various devices types of devices (ie, stents), and angioplasty with or without stenting have been investigated for the treatment of cerebrovascular diseases.

Acute Stroke
Acute stroke is the third leading cause of death in the United States, Canada, Europe, and Japan; further, it is the leading cause of adult disability in the United States. Eighty-seven percent of strokes are ischemic and 13% hemorrhagic. Differentiation between the 2 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 (ie, plaque, fatty material) travels to an artery in the brain causing a blockage (embolism). Recanalization of the artery, particularly in the first few hours after occlusion, reduces 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 and meta-analyses. Therefore, use of IV tPA in ischemic stroke patients presenting within 3 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 and 2011, fewer than 10% of all ischemic stroke patients arrived at the hospital and received IV tPA within the 3-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 4% in the distal internal carotid artery and basilar artery to 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 alternatives or second lines to the established intravenous tPA therapy.

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

- **Intra-arterial fibrinolytic therapy (ie, intra-arterial tPA).** Although tPA-only has approval from the U.S. FDA for its IV route of delivery, intra-arterial tPA has been considered for patients who fail to present within the window of treatment for IV tPA or who have failed to show benefit from IV 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 the 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: 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 uses 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).

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 occurs about 3 to 14 days after the acute bleed in about 30% of patients

experiencing subarachnoid hemorrhage and is a significant contributor to morbidity and mortality in patients who survive the initial bleed. In cases refractory to medical measures, rescue invasive therapies including intra-arterial vasodilator infusion therapy (eg, calcium channel blockers) and transluminal balloon angioplasty may be used. The mechanism of disease, patient population, and time course of therapy differ for delayed cerebral ischemia occurring after subarachnoid hemorrhage compared with ischemic stroke due to atheroembolic disease. Therefore, this indication for endovascular intervention is not addressed in this evidence review.

Intracranial Arterial Stenosis
It is estimated that intracranial atherosclerosis causes about 8% of all ischemic strokes. Intracranial stenosis may contribute to stroke in 2 ways: either due to embolism or low-flow ischemia in the absence of collateral circulation. Recurrent annual stroke rates are estimated at 4% to 12% per year with atherosclerosis of the intracranial anterior circulation and 2.5% to 15% per year with lesions of the posterior (vertebrobasilar) circulation.

Treatment
Medical treatment typically includes either anticoagulant therapy (ie, warfarin) or antiplatelet therapy (eg, aspirin). The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial assessed the incidence of stroke brain hemorrhage or death among patients randomized to 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. Also, if symptoms could be attributed to low-flow ischemia, agents to increase mean arterial blood pressure and avoid orthostatic hypotension may be recommended. However, medical therapy has been considered less than optimal. For example, in patients with persistent symptoms despite antithrombotic therapy, the subsequent rate of stroke or death has been extremely high, estimated in 1 study at 45%, with recurrent events within 1 month of the initial event. Surgical approaches have met with limited success. The widely cited extracranial-intracranial bypass study randomized 1377 patients with symptomatic atherosclerosis of the internal carotid or middle cerebral arteries to medical care or extracranial-intracranial bypass. Outcomes in both groups were similar, suggesting that the extracranial-intracranial 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 intracranial circulation, due to technical difficulties in the 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 PTA as a minimally invasive treatment of this difficult-to-treat population. Most published studies of intracranial PTA have focused on vertebrobasilar circulation. Two endovascular devices have FDA approval for treatment of symptomatic intracranial stenosis and are considered here.

Intracranial Aneurysms
Compared with acute ischemic stroke, cerebral aneurysms have a much lower incidence in the United States, 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 to treat 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 has also been 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 or follow-up procedures. In 2011, the Pipeline Embolization Device, which falls into a new device category called “intracranial aneurysm flow diverters,” or flow-diverting stents, received FDA premarket approval for endovascular treatment of large or giant wide-necked intracranial aneurysms in the internal carotid artery. The Pipeline device is a braided, wire mesh device that is placed within the parent artery of an aneurysm to redirect blood flow away from the aneurysm, with the goal of preventing aneurysm rupture and possibly decreasing aneurysm size.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Several devices for endovascular treatment of intracranial arterial disease were cleared for marketing by FDA through the 510(k) process or the humanitarian device exemption (HDE) process. By indication, approved devices are as follows.

Acute Stroke
Merci®‡ Retriever
In 2004, the Merci Retriever (Concentric Medical) was cleared for marketing 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 or effectiveness exist when the Merci Retriever is used for thrombus removal vs foreign body removal from the neurovasculature. In 2006, a modified Merci Retriever, also manufactured by Concentric Medical, was cleared for marketing by FDA through the 510(k) process. The clearance notes that the Modified Merci Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing an ischemic stroke. Patients who are ineligible for tPA or who fail IV 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®‡
In 2007, the Penumbra System (Penumbra) was cleared for marketing by FDA 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 8 hours of symptom onset. FDA product code: NRY.

Solitaire™‡ FR
In 2012, the Solitaire FR device (Covidien/ev3 Neurovascular) 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, 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 IV tPA, or who fail IV tPA. FDA product code: NRY.

Trevo Pro Retriever™‡
In 2012, the Trevo Pro Retriever device (Stryker Neurovascular) 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 of 178 patients from 27 centers in the United States 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.

Table 1 summarizes the devices with FDA clearance for the endovascular treatment of acute stroke.

Table 1. 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; acquired by Stryker Neurovascular 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)	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)	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)	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 Arterial Stenosis
Two devices were approved by the FDA through the HDE process for atherosclerotic disease. This form of the FDA approval is available for devices used to treat conditions with an incident rate of 4000 or fewer cases per year; FDA only requires data showing "probable safety and effectiveness." Devices with their labeled indications are as follows.

Neurolink System®‡
"The Neurolink system [Guidant] 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
"The Wingspan Stent System [Boston Scientific] with Gateway PTA Balloon Catheter is indicated for use in improving cerebral artery lumen diameter in patients with intracranial atherosclerotic disease, refractory to medical therapy, in intracranial vessels with ≥50% stenosis that are accessible to the system."

Intracranial Aneurysms
In 2011, the Pipeline®‡ Embolization Device (Covidien/eV3 Neurovascular), an intracranial aneurysm flow-diverter, was approved by FDA through the premarket approval process (P100018) for the endovascular treatment of adults (≥22 years) with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments. Approval was based on the Pipeline for Uncoilable for Failed Aneurysms Study, a single-arm, open-label feasibility study, reported by Becske et al (2013) that included 108 patients, ages 30 to 75 years, with unruptured large and giant wide-necked aneurysms.

Three stents have been approved by FDA through the HDE process for treatment of intracranial aneurysms.

Neuroform™‡ Microdelivery Stent System
In 2002, based on a series of approximately 30 patients with 6-month follow-up, the Neuroform Microdelivery Stent System (Stryker) was approved by FDA through the HDE process (H020002) for use with embolic coils for the treatment of wide-neck intracranial aneurysms that cannot be treated by surgical clipping.

Enterprise™‡ Vascular Reconstruction Device and Delivery System
In 2007, based on a series of approximately 30 patients with 6-month follow-up, the Enterprise Vascular Reconstruction Device and Delivery (Cordis Neurovascular) was approved by FDA through the HDE process (H060001) for use with embolic coils for the treatment of wide-neck, intracranial, saccular or fusiform aneurysms.

The Low-Profile Visualized Intraluminal Support Device
In 2014, the Low-Profile Visualized Intraluminal Support Device (LVIS™ and LVIS™ Jr.; MicroVention)‡ was approved by FDA through the HDE process (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 of 2.5 mm or greater and 4.5 mm or smaller.

Centers for Medicare and Medicaid Services (CMS)
A Medicare national coverage determination on intracranial angioplasty and stenting was released by the CMS in 2008. This decision was based on a review of available studies at that time, which consisted of several uncontrolled case series. The CMS review indicated that this evidence was promising and that, while further well-designed randomized controlled trials were needed to confirm whether outcomes were improved, coverage should be allowed. The national coverage determination contained the following coverage determinations:

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

Rationale/Source

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 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
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 systematic reviews include the results of a series of RCTs published after 2014 comparing endovascular therapies with standard care; they are the focus of this evidence review. Some systematic reviews have focused only on mechanical embolectomy, while others have evaluated endovascular therapies more broadly.

Badhiwala et al (2015) reported on results of a 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 IV tPA, in adults with acute stroke. Eight trials were included (Ciccone et al [2013], Kidwell et al [2013], Broderick et al [2013], Berkhemer et al [2015], Goyal et al [2015], Campbell et al [2015], Saver et al [2015], Jovin et al [2015]), with a total of 2423 patients. (These specific RCTs are described individually below.) Studies were assessed as having a low risk of bias overall based on Cochrane criteria. In a meta-analysis, the use of endovascular intervention led 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%] vs 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%; OR=1.71; 95% CI, 1.18 to 2.49; p=0.005). However, there was significant heterogeneity (I^2=75.4%) in the analysis of functional improvement outcomes. Reviewers conducted a number of sensitivity analyses around predictors of functional outcomes, and found the following factors 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 IV 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 study, Chen et al (2015) reported a similar odds 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 2899 patients, 1575 randomized to endovascular recanalization arms and 1324 to control arms. In addition to the 8 trials that compared mechanical embolectomy with standard care (Ciccone et al [2013], Kidwell et al [2013], Broderick et al[2013], Berkhemer et al [2015], Goyal et al [2015], Campbell et al [2015], Saver et al [2015], Jovin et al

[2015]), this meta-analysis also included 2 trials evaluating intra-arterial pro-urokinase, 3 trials evaluating intra-arterial urokinase, one evaluating intra-arterial with IV tPA, and one 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 scores of 0 to 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 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 (2016) compared local mechanical and/or pharmacologic endovascular therapy, with or without IV thrombolysis, with a standard care control that included IV thrombolysis when appropriate. Eleven RCTs were included, the 8 trials comparing mechanical embolectomy with standard care (Ciccone et al [2013], Kidwell et al [2013], Broderick et al [2013], Berkhemer et al [2015], Goyal et al [2015], Campbell et al [2015], Saver et al [2015], Jovin et al [2015]), along with 2 trials comparing intra-arterial tPA with IV 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, 1.26 to 2.51; p<0.001). In subgroup analyses limited to trials that used imaging selection, that used stent retriever devices in at least half of cases, or in which IV 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 subgroup analysis limited to trials in which endovascular arm patients did not receive IV 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 used in subgroup analyses 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 using stent retrievers with medical management (defined as IV tPA unless it was contraindicated) were included. However, it was not specified how reviewers defined a threshold to determine whether stent retrievers were “predominantly” used. The analysis included 5 trials (Berkhemer et al [2015], Goyal et al [2015], Campbell et al [2015], Saver et al [2015], Jovin et al [2015]) with a total of 1287 patients. In pooled analysis for the review’s primary outcome (mRS scores at 90 days), patients randomized to endovascular therapy had odds for more favorable mRS score of 2.2 (95% CI, 1.66 to 2.98; p<0.001; I^2=46.38%). Similar to the findings from the Badhiwala meta-analysis, there were no significant between-group differences in 90-day mortality rates or symptomatic intracranial hemorrhage rates.

Other related systematic reviews have reported similar results.

In 2015, an updated draft Blue Cross and Blue Shield Association TEC Assessment assessed endovascular therapy for acute ischemic stroke in adults to reflect several RCTs published after an earlier TEC Assessment (2014). The draft Assessment focused on 4 RCTs published from 2014 to 2015 comparing endovascular mechanical embolectomy with medical therapy (Berkhemer et al [2015], Goyal et al [2015], Campbell et al [2015], Saver et al [2015]). 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 4 RCTs address some of the limitations in 3 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 draft Assessment also concluded that the use of endovascular treatment with mechanical embolectomy in adults with radiologically confirmed large vessel, anterior circulation acute ischemic stroke met TEC criteria. The specific RCTs are described in more detail below.

Prabhakaran et al (2015) published results from a systematic review of studies evaluating thrombolysis and mechanical thrombectomy in acute stroke. Reviewers 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, reviewers reported 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 (mRS score, 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 IV tPA, with analysis stratified by whether computed tomography angiography (CTA) was used to select patients for endovascular therapy. Reviewers included 6 RCTs with 2217 patients (Ciccone et al [2013], Kidwell et al [2013], Broderick et al [2013], Berkhemer et al [2015], Goyal et al [2015], Campbell et al [2015]), of which four used CTA to select patients. Endovascular therapy was associated with functional independence at 90 days in patients who underwent CTA-based selection (relative risk [RR], 1.75; 95% CI, 1.48 to 2.06; I^2=0.05%), but not in patients who did not undergo CTA-based selection (RR=0.99; 05% CI, 0.85 to 1.14; I^2=0.0%). All-cause mortality was not significantly associated with 90-day mortality, regardless of whether patients were selected with CTA.

Earlier systematic reviews and meta-analyses incorporated some RCTs comparing endovascular therapies with 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

Endovascular Therapies vs Noninterventional Care

From 2012 to 2015, results from 8 large RCTs comparing endovascular therapies with the standard of care for acute ischemic stroke were published. Several additional trials that began enrolling patients 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 than 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 for the treatment of acute stroke were published after 2015 and are the focus of this discussion. A high-level overview of the major RCTs follows, with summary results in Table 2. Subsequently, in this section, select trials are described in more detail.

Although the RCTs reported on a number of outcomes, results pertaining to 3 specific outcomes are the focus here: the proportion of patients with 90-day mRS scores between 0 and 2, short-term mortality rates, and rates of symptomatic intracranial hemorrhage. The primary goal of rapid revascularization in acute stroke is to reduce rates of significant disability; mRS scores ranging from 0 to 2 correspond to functional independence, and 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 symptomatic intracranial hemorrhage, so this is another important safety-related outcome to evaluate.

Fourteen RCTs with a total of 3061 patients (range, 70-656 patients) compared endovascular mechanical embolectomy with standard care for acute ischemic stroke. In 2 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 an mRS score between 0 and 2 at 90 days. Among the 12 studies reporting on the populations and interventions of interest, all provide some information on the proportion of patients with 90-day mRS scores of 0, 1, or 2. Across the studies, the absolute difference between treatment and control groups in the proportion of patients with 90-day functional independence ranged from 1.55% to 36%. Except 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 ORs 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 symptomatic intracranial hemorrhage 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 differences may be due to inadequate sample sizes. Among the studies published after 2015, most were stopped well before the originally planned sample size was enrolled 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 to 8 Hours of Symptom Onset

REVASCAT Trial. Jovin et al (2015) reported on results of the REVASCAT trial, which compared endovascular therapy using the Solitaire stent retriever device with medical therapy, including IV tPA when

indicated, within 8 hours of stroke onset among 206 patients. Eligible patients had an occlusion of the proximal anterior circulation that could be treated within 8 hours of stroke onset, a prestroke mRS score of 0 to 1, and a baseline National Institutes of Health Stroke Scale (NIHSS) score of at least 6 points (NIHSS score range, 0-42; higher scores associated with greater deficit). Intravenous tPA was administered before randomization. Patients were excluded if they had imaging-based evidence of a large ischemic core, indicated by an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of less than 7 on non–contrast CT imaging or a score of less than 6 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 whom 98 successfully underwent thrombectomy. Rates of tPA use between groups did not differ significantly (68.0% in the mechanical embolectomy group vs 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 2. 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])[39]	Intervention	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])[40]	Intervention	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])[41]	Intervention	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])[42]	Intervention	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])[43]	Intervention	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])[44]	Intervention	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])[22]	Intervention	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])[20]	Intervention	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])[19]	Intervention	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])[21]	**Intervention**	**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])[18]	Intervention	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])[16]	Intervention	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])[15]	Intervention	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])[17]	Intervention	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.

EXTEND-IA Trial. Campbell et al (2015) reported on results of the EXTEND-IA trial comparing endovascular therapy with tPA alone. This trial enrolled patients with ischemic stroke who received 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 CTA and were able to receive endovascular therapy within 6 hours of stroke onset; further, the patients were functionally independent before the stroke. Patients were evaluated before enrollment with 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. CT perfusion imaging was analyzed with 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 IV tPA plus endovascular therapy using the Solitaire FR retrievable stent (n=35) or no further therapy (IV tPA-only; n=35). The trial used 2 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 0 or 1 at day 3).

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, 8 (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 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. Goyal et al (2015) reported on 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 6 to 10 on the ASPECTS, which is a 10-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 FDA–approved stent retriever or aspiration device, balloon angioplasty, guidewire manipulation, and/or intra-arterial 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 the 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 trial's primary end point (90-day mRS score), compared with the control group, in the endovascular treatment group, the relative odds of improving 1 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, 2 vs 4, respectively; p<0.001) and were more likely to have 90-day mRS scores of 0 to 2 (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. Saver et al (2015) reported on 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 6 hours of symptom onset. Also, 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 the 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 (89%) patients. 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. Berkhemer et al (2015) reported on 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 an acute ischemic stroke caused by an intracranial occlusion of the distal intracranial carotid artery, MCA (M1 or M2), or anterior cerebral artery (A1 or A2), and a score of 2 or higher on the NIHSS. Initiation of intra-arterial treatment had to be possible within 6 hours of stroke onset. Patients were randomized 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, 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. The analysis was intention-to-treat. One control group patient received intra-arterial treatment, and 17 (7.3%) patients 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 (81.5%) patients and other devices in 5 (2.1%) patients. Twenty-four (10.3%) patients received additional intra-arterial thrombolytic agents. The intra-arterial intervention was not performed after catheterization in 20 subjects for the following reasons: intracranial artery stenosis, occlusion, tortuosity, or dissection (n=10); lack of clot or targetable clot visible for intra-arterial therapy (n=8); or other technical problems (n=2).

For the study's primary outcome (mRS score at 90 days), the median score was 3 (interquartile range, 2-5) among intervention subjects, compared with a median score of 4 (interquartile range, 3-5) among control subjects, with an unadjusted common OR of 1.66 (95% CI, 1.21 to 2.28; favoring intervention). Twenty-seven (11.6%) intervention subjects had an mRS score of 0 or 1 at 90 days, compared with 16 (6.0%) control subjects (unadjusted OR=2.06; 95% CI, 1.08 to 3.92). Follow-up CTA was available for 187 control subjects, of whom 141 (75.4%) had no intracranial occlusion, compared with 68 (32.9%) of 207 control subjects with follow-up CTA available (unadjusted OR=6.27; 95% CI, 4.03 to 9.74). The 30-day mortality

rate was 18.9% in the intervention group and 18.4% in the control group (p=*NS*). Rates of serious adverse events during the 90-day follow-up did not differ significantly between groups (p=0.31). Symptomatic intracerebral hemorrhage occurred in 7.7% of intervention subjects and 6.4% of control subjects, which did not differ significantly. 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 (2013) reported on the MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy) trial. MR RESCUE was an open-label, blinded-outcome RCT of 118 patients from 22 North American sites. All patients had large vessel, anterior circulation ischemic strokes and were stratified by penumbral pattern, as determined by pretreatment CT or MRI of the brain. Patients were randomized to standard stroke treatment (n=54) or mechanical embolectomy (n=64) using the Merci Retriever or Penumbra System within 8 hours after presentation of symptoms. Eight patients in the embolectomy group also had tPA. The primary hypothesis of the trial was that patients with favorable penumbral patterns (at-risk area of viable ischemic cerebral tissue of ≤70% and a small, ≤90 mL, 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 mRS score. In the embolectomy group, 67% achieved revascularization, but this was not superior to standard care. Mean mRS scores were the same (3.9) in both groups, and pretreatment imaging patterns did not show any relation 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. Ciccone et al (2013) reported on the SYNTHESIS Expansion trial, which evaluated 362 patients randomized within 4.5 hours of the onset of various types of acute ischemic strokes to endovascular therapy (n=181) or IV tPA (n=181). Endovascular therapy consisted of intra-arterial tPA, mechanical embolectomy (using the Solitaire, Penumbra, Trevo Merci devices), or a combination of these treatments. Among patients randomized to endovascular therapy, endovascular treatment was completed in 163 patients. In 109 patients, regional intra-arterial infusion of tPA and fragmentation of the thrombus with a micro guidewire were used. In 56 patients, a device was added; the most widely used devices were Solitaire FR in 18 patients, Penumbra in 9 patients, Trevo in 5 patients, and Merci in 5 patients. No significant differences in 90-day survival without disability (mRS score range, 0-1) occurred between the endovascular therapy (30.4%) group and tPA group (34.8%; adjusted OR=0.71; 95% CI, 0.44 to 1.14; p=0.16). Within 7 days, fatal or nonfatal symptomatic intracranial hemorrhage occurred in each group at a rate of 6%. Rates of other serious adverse events also did not differ significantly between groups. While there were different treatment approaches in the endovascular group, these results would suggest endovascular therapy is not superior to tPA.

IMS III Trial. Broderick et al (2013) reported on the results of the IMS III trial, an open-label RCT with a planned enrollment of 900 patients. This trial enrolled patients with acute ischemic stroke who presented within 3 hours of symptom onset and had a moderate-to-severe neurologic deficit on presentation. Patients were randomized to IV tPA alone or IV tPA plus endovascular intervention. Patients randomized to the endovascular group underwent immediate angiography followed by endovascular intervention if a treatable

vascular occlusion was present. The 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 an mRS score of 2 or less at 90 days. The trial was stopped prematurely due to futility after enrollment of 656 patients. At that point, the primary outcome had been reached by 40.8% of patients in the endovascular group and 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 than in 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 trialists 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 RR for an mRS score of 2 or less at 90 days was not statistically significant (RR=1.18; 95% CI, 0.66 to 2.1).

Tomsick et al (2015) published a subgroup analysis of the IMS III trial focusing on subjects with intracranial 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 score of 2 to 3 and 76% had a modified TICI (mTICI) scores of 2 or 3 (partial or full perfusion) after IV tPA, which may have limited the potential benefit for device-related revascularization. Ninety-day mRS scores were higher with higher mTICI scores: of 32 subjects with an mTICI score of 0, 3.1% had an mRS score of 0 to 2 at 90 days, compared with 12.5%, 19.4%, 46.3%, and 80% for subjects with mTICI scores of 1 (n=16), 2a (n=67), 2b (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, trialists 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, Demchuk et al (2014) evaluated the association between baseline CT or magnetic resonance angiography findings and outcomes among 306 (47%) of 656 who had baseline CT or magnetic resonance angiography 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 mRS score, 0-2) was seen with proximal occlusions between groups (41.3% of endovascular therapy subjects vs 38% of controls; 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. 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. 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 5 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 3 of the 2013 trials (Ciccone et al [2013], Kidwell et al [2013], Broderick et al [2013]) had relatively low utilization of the newer generation retrievable stents (Solitaire FR, Trevo). Also, IMS III and SYNTHESIS Expansion 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, 2 noninferiority RCTs comparing newer devices with the Merci Retriever were completed as part of the FDA application for approval of the Solitaire and the Trevo devices. Both studies reported device superiority over the Merci device. In the SWIFT (Solitaire FR With the Intention for Thrombectomy) study, recanalization rates with Solitaire were compared with the Merci Retrieval System in a randomized, prospective noninferiority trial of 113 patients with moderate or severe large vessel occlusion strokes. Treatment was initiated within 8 hours of symptom onset in patients who had unsuccessful IV tPA or were ineligible for IV tPA. This trial was halted early after an interim analysis found revascularization without symptomatic intracranial hemorrhage occurred in 61% of Solitaire patients compared with 24% of Merci patients. Mortality rates at 90 days were 17% with Solitaire vs 38% with Merci (p=0.001). A follow-up analysis of complications of endovascular procedures using the SWIFT study data was published in 2014. This analysis included 144 patients with acute ischemic stroke (31 patients treated with the Solitaire FR device during the SWIFT trial roll-in period, 113 patients randomized to the Solitaire FR or Merci device). Major periprocedural complications, including symptomatic intracranial hemorrhage, air emboli, vessel dissection, major groin complications, and emboli to new vascular territories, were seen in 18 (12.5%) of 144 of patients. Complication rates were similar for patients receiving the Solitaire FR and Merci devices, except 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 mechanical embolectomy with either the Trevo Retriever or the Merci Retriever for large vessel occlusion strokes. Revascularization rates were 86% in the Trevo group and 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% and 24% (p=0.18), respectively.

Saposnik et al (2015) evaluated the benefit added by stent retrievers to IV 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, an RCT evaluating IV tPA. Of 915 patients included in the pooled analysis, 312 were treated with placebo, 312 with IV tPA, 106 with stent retrievers alone, and 160 with IV tPA and stent retrievers. The authors employed a shift analysis, which uses 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

score, 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.

Noguiera 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 historical controls or control patients (standard stroke care) from their same institution (eg, Rai et al [2012], Urra et al [2014], Song et al [2014], Alexandrov et al [2011], Taschner et al [2011]).

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 have assessed specific types of endovascular interventions are the focus of this section. These studies offer 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) conducted a literature review 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. Reviewers included 32 studies, 6 of which (n=95 patients) reported on outcomes for intracranial occlusion treated by intra-arterial thrombolysis and 8 of which (n=115 patients) reported on outcomes for intracranial occlusion treated by mechanical thrombectomy. None of the recently published RCTs of endovascular therapy were included in the review (studies published through July 2013), which specifically reported on 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 no significant difference in rates of death (29% vs 40%; p=0.085) or symptomatic intracranial hemorrhage (12.2% vs 11.7%; p=0.085).

Turk et al (2015) conducted a retrospective, single-center review comparing clinical and cost-related outcomes for 3 endovascular interventions for acute stroke: the Penumbra System, stent retriever with local

aspiration, and a "Direct Aspiration First Pass Technique" (ADAPT), which involves direct aspiration with a large bore catheter. Two hundred twenty-two patients underwent endovascular therapies for acute stroke during the study, 128 (58%) with the Penumbra System, 30 (13%) with a stent retriever, and 64 (29%) with ADAPT. Recanalization rates (TICI scores, 2b/3) were higher in the ADAPT group than in the Penumbra group (95% vs 73%; p=0.003), but no significant differences were seen across groups in 90-day mRS 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, 1.02 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 using endovascular interventions and reported that recanalization rates were higher with the newer devices (82% vs 62%, p=0.016). Mendonca et al (2014) evaluated the Trevo and 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 mRS scores, or mortality. In a similar but smaller study, Fesl et al (2011) compared 14 patients treated with a newer retrievable stent 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, those occlusions have a high likelihood of severe disability or death. For example, in a registry study, Schonewille et al (2009) found severe outcomes (mRS scores of 4 or 5, or death) in 68% of patients with basilar artery occlusion.

A limited number of studies have evaluated endovascular interventions for basilar artery occlusion. Broussalis et al (2013) reported on results from a prospective registry study of 99 patients with posterior circulation stroke caused by basilar artery occlusion from 2005 to 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-seven patients received endovascular intervention, with thrombectomy alone in 67 patients. Devices used included the Merci system in 43%, the Solitaire FR device in 13%, and the Trevo retriever in 18%, with devices not available in the United States in the remaining 25%. Endovascular patients were more likely to achieve a TICI score of 3 (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 an mRS score of 3 compared with 8% in the standard medical therapy group.

Noncomparative studies have reported on endovascular therapies for acute basilar artery occlusion. Son et al (2016) reported on outcomes for 31 subjects with acute basilar artery occlusion treated using 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 scores, ≥2b) did not differ between devices (84.6% with Solitaire vs 100% with Penumbra; p=0.168); similarly, 3-month mRS scores did not differ between the groups (3.6 with Solitaire vs 3.2 with Penumbra; p=0.726).

Huo et al (2016) reported on outcomes for 36 consecutive patients with acute basilar artery occlusion treated with the Solitaire stent. Recanalization (TICI score ≥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) also underwent angioplasty.

In a single-center case series of 24 patients with acute basilar artery occlusion 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 (2014) reported that mechanical thrombectomy led to successful recanalization (TICI scores, ≥2b) in 18 (75%) of patients. Eight (33%) patients had a favorable clinical outcome (mRS scores, 0-2) at 3 months. Park et al (2013) reported on results from a single-center case series of 16 patients with acute basilar artery occlusion treated with endovascular interventions, primarily the Penumbra or Solitaire FR devices. The authors reported that successful revascularization (TICI scores, ≥2a) was achieved in 81.3% of patients, with favorable clinical outcome (mRS scores, 0-2) at 3 months in 56.3% of patients. While these studies would suggest that endovascular intervention is feasible for acute basilar artery occlusion (and may be associated with favorable outcomes), the studies lacked concurrent comparison groups and had 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 of multiple noncomparative studies and a prospective registry study comparing endovascular therapy with standard medical therapy. These studies indicated that high rates of recanalization could 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 have received FDA approval through the humanitarian device exemption process. The Neurolink System was approved based on the Stenting of Symptomatic Atherosclerosis Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) trial, 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% 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 for the Wingspan device offered the following conclusions and FDA appears to have based its approval of Wingspan in part on the favorable comparison with 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 on the role of endovascular stenting for treatment of symptomatic intracranial atherosclerotic disease includes 2 RCTs, a number of nonrandomized comparative studies, and numerous single-arm series. The most clinically relevant RCTs, nonrandomized comparative studies, and systematic reviews are reviewed next. Since publication of the RCT evidence, there continues to be single-arm publications (ie, 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.

Randomized Controlled Trials

Zaidat et al (2015) published the results of the VISSIT trial, an RCT comparing a balloon-expandable stent plus medical management with medical management alone among patients who had 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 Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial were published (see below). A total of 112 patients were enrolled from 2009 to 2012 and randomized to the 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 3 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 trial used a primary composite end point that included any stroke in the same territory as the presenting event within 1 year of randomization and "hard TIA" in the same territory as the presenting event from 2 days to 1 year after randomization. Among 29 patients who met one of the primary end points within 1 year of randomization, 8 (15.1%) patients 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 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 the 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 SAMMPRIS trial was an RCT comparing aggressive medical management alone with aggressive medical management plus stenting in patients who had symptomatic cerebrovascular disease and intracranial stenosis between 70% and 99%. This trial used the Wingspan stent system implanted by experienced neurointerventionalists credentialed to participate in the trial. The authors planned to enroll 750 patients based on power calculations. However, the trial was stopped early for futility after 451 patients had been randomized, 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 5.8% (95% CI, 3.4% to 9.7%; p=0.002) in the medical management group. At the time of trial termination, mean follow-up was 11.9 months. Kaplan-Meier estimates of the primary outcome (stroke or death at 1 year) was 20.5% (95% CI, 15.2% to 26.0%) in the stenting group and 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, as reported by Derdeyn et al (2014), also 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 qualifying artery beyond 30 days after enrollment or stroke or death within 30 days after a revascularization procedure of the qualifying lesion. During a median follow-up of 32.4 months, 34 (15%) of 227 of patients in the best medical management group and 52 (23%) of 224 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 concluded that the benefits of aggressive medical management over percutaneous angioplasty and stenting among patients with intracranial stenosis persist over long-term follow-up.

Lutsep et al (2015) 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, 2-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 8 patients, but 2 patients experienced TIAs during endovascular treatment. During a mean follow-up of 4.7 years, no patient in either treatment group experienced a vertebrobasilar territory stroke, but 3 patients in each arm died of myocardial infarction or carotid territory stroke, and 1 patient in the endovascular arm had a nonfatal carotid territory stroke. The investigators concluded that patients with vertebral artery stenosis were more likely to have carotid territory stroke and myocardial infarction during follow-up than 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.

Qureshi et al (2013) published results from another small RCT comparing angioplasty alone with angioplasty plus a balloon-expanding stent for 18 subjects who had moderate intracranial 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 postprocedure angiography) occurred in 5 of 10 patients treated with angiography (9 randomized to angiography, 1 crossover from group randomized to stent placement) and 5 of 8 patients treated with stent placement. Rates of stroke or death were low in both groups (1 of 10 in the angiography group vs none in the stent placement group). This trial suggests that angioplasty with stenting is feasible in patients with severe intracranial stenosis, but the small sample size and lack of statistical comparisons limit conclusions that can be drawn.

Systematic Reviews
Before publication of the SAMMPRIS trial results, several systematic reviews evaluated 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.

Abuzinadah et al (2016) conducted a systematic review and meta-analysis of studies reporting on the rates of stroke recurrence or death (the primary outcome) in symptomatic intracranial vertebrobasilar stenosis with medical or endovascular treatment. Reviewers identified 23 studies involving 592 medical treatment patients and 480 endovascular treatment patients. In pooled analysis, the stroke or death rates were 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, 1.3; 95% CI, 1.0 to 1.7). The stroke recurrence rates were 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 (incidence rate ratio, 1.1; 95% CI, 0.8 to 1.5).

Nonrandomized Comparative Studies
A number of nonrandomized retrospective or registry-based studies have provided relatively weak evidence on the comparative efficacy of endovascular procedures vs medical therapy for intracranial atherosclerosis (eg, Tang et al [2011], Qureshi et al [2008], Samaniego et al [2009]).

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 and VISSIT RCTs. The SAMMPRIS trial was stopped early due to harms because 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 humanitarian device exemption program for the endovascular treatment intracranial aneurysms. The literature search did not identify any randomized trials of self-expanding stent-assisted treatment of intracranial aneurysms compared with standard neurosurgical treatment (ie, surgical clipping or endovascular coils). The available evidence includes single-arm case series, registry studies, nonrandomized comparative studies, and a systematic review of nonrandomized comparative studies.

Systematic Reviews
Hong et al (2014) reported on the results of a systematic review and meta-analysis of studies that compared stent-assisted coiling with coiling alone for the treatment of intracranial aneurysms. Reviewers included 10 retrospective cohort studies, ranging in size from 9 to 1109 patients. In pooled analysis, compared with coiling alone, stent-assisted coiling was associated with higher rates of progressive thrombosis (37.5% vs 19.4%; OR=2.75; 95% CI, 1.95 to 3.86; p<0.000) and lower rates of recurrence (16.2% vs 34.4%; OR=0.35; 95% CI, 0.25 to 0.49; p<0.000). The mortality rate 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 did not differ significantly between the 2 groups.

Ryu et al (2015) conducted a systematic review of studies reporting complications after stent-assisted coiling of ruptured intracranial aneurysms, with a focus on complications related to antiplatelet therapy. They included 33 studies, 3 of which were prospective and the other 30 were 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 the use of stents and 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 (83.5%) aneurysms 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% (16/216) of those with stents vs 3.8% (42/1109) of those without stents (logistic regression p=0.644; OR=1.289; 95% CI, 0.439 to 3.779). Procedure-induced mortality occurred in 4.6% (10/216) of the procedures with stents vs 1.2% (13/1109) in those without (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% (114/216) of aneurysms treated with stents and 70% (774/1109) of aneurysms treated without, with angiographic recurrence in 14.9% (17/114) vs 33.5% (259/774), respectively (p<0.001; OR=0.349; 95% CI, 0.204 to 0.596).

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 using stent-assisted coiling with those treated using coiling alone for patients who had unruptured intracranial aneurysms who were enrolled in the prospective, nonrandomized, multicenter Matrix and Platinum Science (MAPS) Trial. The trial compared bare-metal aneurysm coils with polymer-coated aneurysm coils. One hundred thirty-seven patients received a stent-assisted coil, and 224 patients received coiling alone. Patients treated with stent-assisted coiling more often had wide-neck aneurysms (62% vs 33%; p<0.000) and had aneurysms with the lower dome-to-neck ratio (1.3 vs 1.8; p<0.000). Periprocedural serious adverse events occurred in 6.6% of those treated with stent-assisted-coiling, compared with 4.5% of those treated with coiling alone (p=0.039). At 1 year, ischemic strokes were more common in patients who received a stent-assisted coil than in patients who received a coil alone (8.8% vs 2.2%; p=0.005). However, in multivariable analysis, stent use did not independently predict ischemic stroke at 2 years (adjusted OR=1.1; p=0.94).

Consoli et al (2016) compared stent-assisted coiling with balloon-assisted coiling in patients who had unruptured wide-necked intracranial aneurysms treated at a single center. The study included 268 patients (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 scores of 0 or 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 score of 0 or 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 nonrandomized comparative study by Hwang et al (2011) from Korea 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 (p=*NS*). The rates of aneurysm recurrence also did not differ statistically between groups. The aneurysm recurrence rate was 17.5% of patients in the stent group and 21.0% in the nonstent group.

Liu et al (2014) retrospectively compared outcomes for patients who had posterior communicating artery aneurysms treated using stent-assisted coiling with those treated using coiling alone. 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 nonstented patients (statistical comparison not reported). At last follow-up (mean, 14.3 months for stent-assisted coiling and 13.2 months for nonstent patients), the aneurysm recurrence rates were 10.6% in stent-assisted coiling patients and 28.1% of nonstent patients (p=0.014). Procedural complications occurred in 10.7% of stent-assisted coiling patients compared with 11.5% of nonstent patients (p=*NS*).

Colby et al (2012) reported on 90 consecutive patients undergoing treatment for para-ophthalmic aneurysms, 30 of whom were treated with coil alone and 60 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 14.5-month follow-up, the recurrence rate was lower in the stented group (15.4% [4/26]) than in the nonstented group (41.5% [17/41]; p<0.05).

Comparison Between Endovascular Devices for Intracranial Aneurysms
Nonrandomized studies, summarized in a systematic review by King et al (2015), have compared devices used for stent-assisted coiling of intracranial aneurysms. Reviewers evaluated published studies reporting on stent-assisted coiling with the Neuroform and Enterprise systems to assess outcomes between the devices. The analysis included 47 studies with a total of 4039 patients (4238 aneurysms; 2111 treated with Neuroform and 2127 with Enterprise). Most (81%) studies were retrospective. Compared with those treated using the Enterprise system, patients treated using the Neuroform system were more likely to have deployment failure (2.3% vs 0.2%, p<0.001) and a higher mortality rate (2.8% vs 1.8%, p=0.04), less likely to have 100% aneurysm occlusion at last follow-up (61.1% vs 74.7%, p<0.001), and more likely to have recanalization (13.9% vs 10.6%, p=0.02). However, conclusions drawn from these findings are influenced by the potential for bias in the underlying studies and between-study heterogeneity.

Single-Arm Series
A large number of single-arm series have reported outcomes for stent-assisted coiling.

Systematic Reviews
A literature review by Shapiro et al (2012) identified 39 articles (total N=1517 patients), most of which were single-arm, retrospective series. Most patients treated had unruptured aneurysms, but 22% had ruptured

aneurysms. Reviewers noted a large amount of heterogeneity in reporting outcomes data, particularly for adverse events. The periprocedural mortality rate was 2.1%, and the overall complication rate was 19%. Immediately after 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 focusing only on ruptured aneurysms was published by Bodily et al (2011). This review selected 17 articles that described treatment in 212 patients. Technical success was high (93%), and 2% of patients required open surgery due to stent failure or intraoperative aneurysm rupture. Sixty-three percent (130/207) of aneurysms were successfully occluded. The overall mortality rate was 19%, and 14% of patients had poor clinical outcomes. A relatively high rate of adverse events was reported, with 8% of patients having acute procedure-related intracranial bleeding and 6% (16/288) having a clinically significant thromboembolic event.

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

A large 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 (self-expanding) Leo (Balt Extrusion) stents. The overall mortality rate was 1.9%; procedure-related complications occurred in 28 (6.9%) patients. Angiographic follow-up data, obtained from 6 months to 7 years postprocedure (mean, 19.2 months), were available for 440 (94%) patients. For the total of 467 aneurysms with follow-up, complete occlusion occurred in 194 (41.6%) aneurysms, near-complete occlusion (>95% occlusion but minimal residual filling with coils at the neck) occurred in 242 (51.8%) aneurysms, and incomplete occlusion (<95%) occurred in 31 (6.6%) aneurysms. At 6-month follow-up, recanalization occurred in 38 aneurysms (8% of all aneurysms with follow-up available). The authors concluded that stents were 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 noncomparative studies in which at least some patients were treated with devices commercially available in the United States are summarized in Table 3. Interpretation of these studies is limited by potential selection bias and lack of comparison groups. 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 3. Noncomparative Studies of Stent-Assisted Endovascular Treatment of Aneurysms

Study	Study Type	Population	Intervention	Primary Outcome
Feng et al	Retrospective	97 patients with	Endovascular treatment	• 100% of patients had technically

Study	Study Type	Population	Intervention	Primary Outcome
(2016)	case series	intracranial saccular aneurysms (13 with rupture)	with LVIS	successful treatment • 98.9% met the primary end point of safety (absence of new transient or permanent neurologic deficit or death) • Over mean 7.8-mo FU, no patient had new neurologic deterioration or died • Among 76 patients with DSA at FU, 59.21% had complete occlusion
Aydin et al (2015)	Retrospective case series	80 patients with wide-necked intracranial aneurysm (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%) had permanent neurologic deficits
Chalouhi et al (2013)	Retrospective case series	76 patients with PCA aneurysms (1 institution)	Of 71 successful interventions: endovascular coiling (n=60) with or without Neuroform stent assistance (n=4) or balloon assistance (n=4), 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, 85% favorable outcomes (mild, moderate, no disability)
Chen et al (2013)	Retrospective case series	10 patients with large and giant fusiform aneurysms of the vertebrobasilar arteries (1 institution)	Endovascular treatment with stent placement (Neuroform or Leo self-expanding, 5 patients), stent-assisted coiling (3 patients), or occlusion of proximal artery (2 patients)	• 9 patients had good outcomes; 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 (1 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 12- to 18-mo FU, 5 (5%) had delayed complications, with 3% having 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 (1 institution)	Endovascular treatment with coiling with stent assistance using Neuroform (62 aneurysms), Enterprise (32 aneurysms), Wingspan (1 aneurysm), or a combination (5 aneurysms) or stenting alone (2 aneurysms)	• 100% of patients had technically successful treatment • 9 patients had new neurologic symptoms after procedure, 1 with long-term disability. One procedure-related death. • Of 85 aneurysms with initial FU imaging available (usually at 6 mo postprocedure), 77 (90.6%) were

Study	Study Type	Population	Intervention	Primary Outcome
				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 successfully deployed in 113 patients with 117 aneurysms • 99 patients had grade 1 or 2 occlusion (complete or aneurysm neck) on immediate postprocedure imaging • Intraprocedure major thrombotic events occurred in 7 (5.9%) and major infarcts on postprocedure imaging in 9 (7.7%) • Of 92 aneurysms with FU imaging available, 71 (77%) had grade 1 or 2 occlusion

DSA: digital subtraction angiography; FU: follow-up; 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 have reported higher complete occlusion rates with stenting and lower recurrence rates. However, some evidence has shown that adverse event rates are relatively high with stenting, and 1 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 not amenable to surgical therapy, making comparisons with 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 the FDA premarket approval. The device's approval was based on the industry-sponsored Pipeline for Uncoilable or Failed Aneurysms (PUFA) study, a multicenter, prospective, single-arm trial (2013) of the device for treatment of ICA aneurysms that were uncoilable or had failed coiling. Investigators enrolled 108 patients at 10 centers with unruptured large- or giant-necked aneurysms measuring at least 10 mm in diameter, with aneurysm necks of at least 4 mm, who underwent placement of 1 or more Pipeline devices. One patient was excluded from evaluations of the device effectiveness and safety due to unsuccessful catheterization. Four patients were excluded from the evaluation of the device effectiveness. Two patients had 2 qualifying aneurysms treated, so the "effectiveness cohort" was 106 aneurysms in 104 patients. Seventy-eight (73.6%) of 106 aneurysms met the study's combined primary effectiveness end point of complete occlusion

at day 180 without major stenosis or use of adjunctive coils. For 6 (5.6%) of the 107 patients who underwent any catheterization, a primary safety end point (occurrence of major ipsilateral stroke or neurologic death at 180 days) occurred.

Randomized Controlled Trials

No randomized trials evaluating intracranial aneurysms were identified comparing flow-diverting stent treatment with standard neurosurgical treatment (ie, 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 4 include all patients and the subset of patients with proximal carotid aneurysms.

Table 4. 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) (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 on results of a systematic review of studies comparing flow-diverting devices with endovascular coiling for intracranial aneurysms, which included 9 retrospective comparative studies (total N=863 subjects). Reviewers included studies of patients 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 the pooled analysis, the use of flow-diverting devices was associated with a significantly higher complete occlusion rate than coil embolization therapy (OR=3.13; 95% CI, 2.11 to 4.65; I^2=18%) or stent-assisted coiling (OR=2.08; 95% CI, 1.34 to 3.24; I^2=0%). Rates of overall morbidity did not differ significantly between patients treated with flow-diverting devices and coil embolization therapy or between flow-diverting devices and stent-assisted coiling.

In a study not included in the Zhou review and which included more patients than any single study in that review, van Rooij et al (2014) reported on 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%) patients, 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, 2 patients had ruptured dissecting aneurysms, 2 died, 1 patient had permanent morbidity, and 2 aneurysms were not occluded at 30-month follow-up. Direct comparisons with outcomes from alternative treatments were not reported.

Single-Arm Series

Systematic Reviews

Multiple noncomparative studies have reported on outcomes from flow-diverting stent-assisted treatment of intracranial aneurysms 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 [2015]) reviewed 18 studies published from 2009 to 2014 (total N=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, the mean incidence rate was 8.3% (range, 0%-23.1%). The man permanent morbidity occurred in 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 Brinjikji et al (2013) and Arrese et al (2013) similarly reported high estimates for aneurysm occlusion rates (≈75%), but relatively high rates of morbidity and mortality.

Noncomparative Studies
Since those reviews, a number of noncomparative studies evaluating flow-diverting stents for the treatment of aneurysms have been published. The largest cohort study identified was by Kallmes et al (2015), who retrospectively analyzed 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 10 mm, 59 of which were in the posterior circulation, 179 of which were in a non-ICA anterior circulation location and less than 10 mm, and 10 of which had no aneurysm size specified. The overall neurologic morbidity and mortality rate was 8.4%, highest in the posterior circulation group (16.4%) and lowest in the less than 10-mm ICA group (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 (7.3%) and lowest in the less than 10-mm ICA group (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 3 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 by Chiu et al (2015), is from a series of 98 patients with 119 aneurysms treated with the Pipeline Embolization Device and followed for at least 2 years. Of the 119 aneurysms, all had clinical follow-up, and 88.8% had imaging follow-up for 2 or more years postprocedure. Aneurysm occlusion rates were 81.6%, 84.1%, and 93.2% at 6-month, 1-year, and 2-year follow-ups, respectively. Three (2.8%) cases of in-stent stenosis occurred. From 0 to 6 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, mean angiographic follow-up was available to 15.7 months (range, 8-21 months) and mean clinical follow-up was available for 16.9 months (range 10-22 months). Five (5.8%) patients developed ischemic complications.

Additional representative studies, with a focus on series including more than 50 patients, are summarized in Table 5.

Table 5. Noncomparative Studies of Flow-Diverting Stent-Assisted Endovascular Treatment of Aneurysms

Study	Study Type	Patient Population	Intervention	Primary Outcomes
Strauss et al (2016)	Retrospective case series	60 patients with 67 anterior or posterior circulation aneurysms	Silk flow-diverting stent (Balt Extrusion)	• 10 patients had periprocedural complications, 4 of whom died • Among 60 aneurysms with available FU imaging (median, 15-mo posttreatment), 88% had good angiographic results (complete or near-complete occlusion)
Fischer et al (2015)	Retrospective case series	121 patients with 130 intracranial saccular sidewall aneurysms	P64 Flow-Modulated Device (phenox)	• 1 patient had pulmonary artery embolism, and 2 patients had ischemic lesions with transient neurologic deficits in the periprocedural period • Of 93 aneurysms with available DWI (median, 279 d), 79.6% had complete aneurysm occlusion
Brasiliense et al (2016)	Prospective case series	59 patients (70 aneurysms) who had 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 ≤7 mm (1 institution)	Pipeline Embolization Device	• Complications in 3% (1 distal parenchymal hemorrhage, 2 ischemic events) • At last FU (mean, 6.3 mo), 72% of aneurysms completely occluded • Retreatment required in 8%
Lubicz et al (2015)	Retrospective review of prospectively collected data	58 patients with 70 intracranial aneurysms (2 institutions)	SILK artery reconstruction device (Balt Extrusion)	• No periprocedural deaths occurred • Overall permanent neurologic morbidity was 5.5% • At long-term FU, 73% had complete occlusion, 16% had neck remnants, 11% had incomplete occlusion
Wakhloo et al (2015)	Prospective multicenter trial at 24 centers	165 patients with 190 intracranial aneurysms	Surpass flow-diverting device (Stryker Neurovascular)	• At 6-mo FU, permanent neurologic morbidity was 6% and mortality was 2.7% • Neurologic death during FU occurred in 1.6% of patients with anterior circulation aneurysms and 7.4% with posterior circulation aneurysms • Ischemic stroke at ≤30 d, SAH at ≤7 d, and intraparenchymal hemorrhage at ≤7 d occurred in 3.7%, 2.5%, and 2.5% of subjects, respectively
Kan et al (2012)	Prospective case series (registry)	56 patients with intracranial aneurysm (7 institutions)	Pipeline Embolization Device	• 6/123 devices incompletely deployed • Among 19 patients with 6-mo FU, 13 had complete aneurysm occlusion • 4 fatal postprocedural hemorrhages occurred
Piano et al	Retrospective	101 patients with	Flow-diverting stent	• 86% of aneurysms evaluated at 6-mo

Study	Study Type	Patient Population	Intervention	Primary Outcomes
(2013)	case series	intracranial aneurysm (1 institution)	placement (Pipeline Embolization Device or SILK device), with or without endovascular coiling	FU showed complete occlusion
Toma et al (2013)	Retrospective case series	84 patients with intracranial aneurysm (1 institution)	Flow-diverting stent	• 61% of aneurysms resolved at 12 mo • 9.5% of patients had a new, permanent neurologic deficit and 5.9% had procedure-related mortality

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

Subsection Summary: Flow-Diverting Stents for Intracranial Aneurysms

One 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. Sixteen percent of patients who were randomized to flow diversion or received flow diversion at any time were dead or dependent at 3 months or later, which crossed a predefined safety boundary. The efficacy of flow diversion was also below expectations. While 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 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, 8 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 regarding reduced disability at 90 days posttreatment. The trials that demonstrated a benefit for 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. Studies that demonstrated a benefit for endovascular therapy required demonstration of a large vessel, 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 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 that the technology results in a meaningful 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 several case series. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related mortality and morbidity. These studies have indicated 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 2 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 have 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 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 2 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 that the technology is unlikely to improve the net health outcome.

For individuals who have intracranial aneurysm(s) who receive endovascular coiling with intracranial stent placement or intracranial placement of a flow-diverting stent, the evidence includes an RCT, 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 have reported occlusion rates for stent-assisted coiling that are similar to or higher than coiling alone and recurrence rates that may be lower than those for coiling alone. For stent-assisted coiling with self-expanding stents, some evidence has also shown that adverse event rates are relatively high, and a nonrandomized comparative trial has 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 has 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. The evidence does not provide high certainty whether stent-assisted coiling or placement of a flow-diverting stent improves outcomes for patients with intracranial aneurysms because the risk-benefit ratio cannot be adequately defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 02/23/2006

Policy # 00198
Original Effective Date: 02/23/2006
Current Effective Date: 06/20/2018

Current Effective Date: 06/20/2018

02/01/2006	Medical Director review
02/15/2006	Medical Policy Committee review
02/23/2006	Quality Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
04/02/2008	Medical Director review
04/16/2008	Medical Policy Committee approval. No change in policy statement. Rationale totally rewritten with focus on FDA approved devices.
04/02/2009	Medical Director review
04/15/2009	Medical Policy Committee approval. No change to coverage eligibility.
04/08/2010	Medical Policy Committee approval
04/21/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/07/2011	Medical Policy Committee review
04/13/2011	Medical Policy Implementation Committee approval. Changed title from "Percutaneous Transluminal Angioplasty of Intracranial Atherosclerotic Stenoses With or Without Stenting" to "Endovascular Procedures (Angioplasty and/or Stenting) for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)". Added that intracranial stent placement is eligible for coverage as part of the endovascular treatment of intracranial aneurysms for patients when surgical treatment is not appropriate and standard endovascular techniques do not allow for complete isolation of the aneurysm, e.g., wide-neck aneurysm (4mm or more) or sack-to-neck ratio less than 2:1. Added that intracranial stent placement in the treatment of intracranial aneurysms, except as noted above, is investigational.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2014	Medical Policy Committee review
04/23/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Policy 00366 (Mechanical Embolectomy for Treatment of Acute Stroke) retired and combined with this policy.
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. Added new coverage statement for Intracranial flow diverting stents with FDA approval and patient selection criterion. Updated rationale and references.
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. Policy statement revised to indicate that mechanical embolectomy for acute stroke may be considered medically necessary with criteria.
10/01/2016	Coding update
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. No change to coverage.
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Policy statements changed to reflect extension of the time window for mechanical thrombectomy up to 24 hours after symptom onset for select patients. Added Policy Guidelines section.

Next Scheduled Review Date: 06/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code			
CPT	36227, 36228, 61624, 61630, 61635, 61645, 61650, 61651			
HCPCS	No codes			
ICD-10 Diagnosis	I60.00-I60.02	I60.11-I60.12	I60.2	I60.30-I60.31
	I60.4	I60.50-I60.52	I60.6-I60.8	I63.00-I63.9
	I66.01-I66.9	I67.0-I67.9		

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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