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Intracranial Stenting or Angioplasty, including Endovascular Procedures

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Related Policies (if applicable)
None

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Coverage

Acute Ischemic Stroke
Endovascular intra-arterial mechanical embolectomy or thrombectomy **may be considered medically necessary** in the treatment of acute ischemic stroke when the following criteria have been met:

- Angiographic studies have confirmed proximal arterial occlusion of the anterior circulation of the brain, in any of the following anterior intracranial arteries:
  - Intracranial internal carotid; OR
  - Middle cerebral artery (M1 or M2); OR
  - Anterior cerebral artery (A1 or A2); **AND**
- Neuroimaging is consistent with early ischemic change, evidence of substantial and clinically significant neurologic deficits, without hemorrhage; **AND**
- Evidence of salvageable brain tissue in the affected vascular territory (see **NOTE 1**); **AND**

- Intra-arterial mechanical embolectomy is performed within 12 hours of onset of symptoms OR within 24 hours of symptom onset if there is evidence of a mismatch between specific clinical and imaging criteria (see **NOTE 2**); **AND**
- NIH (National Institutes of Health) Stroke Scale (NIHSS) score of 2 or greater; **AND**
- CT (computed tomography) or MRI (magnetic resonance imaging) scan has ruled out intracranial hemorrhage or arterial dissection.

NOTE 1: For patient selection information for endovascular mechanical embolectomy used for acute ischemic stroke, including evidence of salvageable brain tissue, refer to Table 1 in the Description.

NOTE 2: For trial selection criteria used for patients 12 to 25 hours post infarct, refer to Table 2 in the Description.

NOTE 3: Retrievable stents used for mechanical embolectomy include, Merci® Retriever, Penumbra System®, Solitaire™ Flow Restoration Device, or the Trevo® Retriever Devices. (Refer to Table 3 in the Regulatory Status within Description for a listing of all devices addressed in this policy.)

Endovascular interventions, such as intra-arterial mechanical embolectomy, thrombectomy, angioplasty or non-retrievable stenting, including treatment of acute ischemic stroke, **are considered experimental, investigational and/or unproven** when the above criteria are not met.

Atherosclerotic Cerebrovascular Disease

Intracranial percutaneous transluminal angioplasty (PTA), with or without stenting, **is considered experimental, investigational and/or unproven** in the treatment of atherosclerotic cerebrovascular disease (CVD).

Cerebral Aneurysms

Intracranial stent placement **may be considered medically necessary** as part of the endovascular treatment of intracranial/cerebral aneurysms when surgical treatment is not appropriate and standard endovascular techniques do not allow for complete isolation of the aneurysm, such as a wide-neck aneurysm (4 mm or more) or a sack-to-neck ratio less than 2:1.

Intracranial flow-diverting stents with the U.S. Food and Drug Administration (FDA) approval for the treatment of intracranial aneurysms **may be considered medically necessary** as part of the endovascular treatment of intracranial aneurysms that are not amenable to surgical treatment or standard endovascular therapy **AND** meet the following anatomic criteria:

- 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.

Intracranial stent placement **is considered experimental, investigational and/or unproven** in the treatment of intracranial aneurysms except as noted above.

Venous or sinus stenting for any indication, including but not limited to pseudotumor/intracranial hypertension (not atherosclerosis related) **is considered experimental, investigational and/or unproven**.

NOTE 4: This policy only addresses endovascular therapies used on intracranial vessels.

NOTE 5: 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.

Policy Guidelines

There are no specific procedure codes for intracranial angioplasty and stent placement.

If occlusion of a vascular malformation is performed as part of the treatment of an aneurysm, CPT code 61624 may be used.

For endovascular interventions for acute stroke, the components of the procedure are reported separately.

Description

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

Cerebrovascular Diseases
Cerebrovascular diseases (CVDs) 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 (i.e., stents), and angioplasty with or without stenting have been investigated for the treatment of CVDs.

<u>Acute Stroke</u>

Acute stroke is the fifth leading cause of death in the United States (U.S.); further, it is the leading cause of adult disability. (1) 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 (i.e., 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. (2)

Intracranial Arterial Stenosis

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

Intracranial Aneurysms

Compared with acute ischemic stroke, cerebral aneurysms have a much lower incidence in the U.S., with prevalence between 0.5% and 6% of the population. (3) However, they are associated with significant morbidity and mortality due to subarachnoid hemorrhage resulting from aneurysm rupture.

Idiopathic Intracranial Hypertension (IIH)

IIH is also referred to as pseudotumor cerebri or benign intracranial hypertension. It is characterized by an increase in intracranial pressure (ICP) in the absence of an identifiable cause. The extra pressure can lead to severe headaches and vision loss. About 19 out of 20 people with IIH are women. Being overweight or obese also makes IIH more likely. (98)

Patient Selection for Endovascular Mechanical Embolectomy for Acute Ischemic Stroke

The major 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 (ASPECTS), 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. (4) Table 1 lists the criteria used by other trials (descriptions of the trial names can be found in the Rationale of this policy):

Table 1: Trial Selection Criteria for Salvageable Brain Tissue

Trial	Inclusion or Exclusion	Criteria
REVASCAT: Jovin et al., 2015 (5)	Exclusion	Hypodensity on CT or restricted diffusion demonstrated by: • An ASPECTS score of less than 7 on CT, CT perfusion CBV, CTA source imaging; OR • An ASPECTS score of less than 6 on DWI MRI).

ESCAPE: Goyal et al., 2015 (6)	Exclusion	Baseline non-contrast CT with extensive early ischemic changes of ASPECTS 0 to 5 in the territory of symptomatic intracranial occlusion; OR other confirmation of a moderate-to-large core defined 1 of 3 ways: • On a single phase, multiphase, or dynamic CTA: no or minimal collaterals in a region greater than 50% of the 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 less than 6 **AND** in the symptomatic MCA territory; OR • On CT perfusion (<8 cm coverage): a region of low CBV and very low CBF greater than one-third of the CT perfusion-imaged symptomatic MCA territory.
EXTEND-IA: Campbell et al., 2015 (7)	Inclusion	Based on CT perfusion imaging using CT or MRI with a T-max more than 6-second delay perfusion volume and either CT regional CBF or DWI infarct core volume as follows: • Mismatch ratio greater than 1.2; AND • Absolute mismatch volume greater than 10 mL; AND • Infarct core lesion volume less than 70 mL.

SWIFT PRIME: Saver et al., 2015 (8)	Exclusion	Related to imaging-demonstrated core infarct and hypoperfusion:
		• MRI-assessed core infarct lesion greater than: 50 cm^3 for subjects age 18 to 79 years; 20 cm^3 for subjects age 80 to 85 years;
		• CT-assessed core infarct lesion greater than: 40 cm^3 for subjects age 18 to 79 years; 15 cm^3 for subjects age 80 to 85 years;
		  • For all subjects, severe hypoperfusion lesion (≥10-second T-max lesion >100 cm^3);
		  • For all subjects, ischemic penumbra of 15 cm^3 or more and mismatch ratio greater than 1.8.

ASPECTS: Alberta Stroke Program Early Computed Tomography Score; CBF: cerebral blood flow; CBV: cerebral blood volume; cm: centimeter; CT: computed tomography; CTA: computed tomography angiography; DWI: diffusion-weighted imaging; MCA: middle cerebral artery; ml: milliliter; MRI: magnetic resonance imaging; T-max: Time to maximum plasma concentration. ESCAPE: Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA: Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial; REVASCAT: Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT PRIME: Solitaire™ With the Intention For Thrombectomy as PRIMary Endovascular Treatment

The RCTs demonstrating a benefit to endovascular mechanical embolectomy in acute stroke generally had some inclusion criteria to reflect stroke severity 3 or 4 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 (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) studies enrolled patients from 6 up to 24 hours of the 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 [MRI]) or perfusion CT) (see Table 2).

Table 2: Trial Selection Criteria for Patients 6 to 25 Hours Post Infarct

Trial	Inclusion or Exclusion	Criteria
DAWN Trial Nogueira et al., (2018) (9)	Inclusion	Six 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) (10)	Inclusion	Six 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.

cm: centimeter; ml: milliliter; NIHSS: National Institutes of Health Stroke Scale; DAWN: Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE 3: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3.

Common Assessments of Stroke or Disability Impairments

National Institute of Health Stroke Scale (NIHSS)

The NIHSS is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. (11) The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0. The 11 items accessed are level of consciousness, horizontal eye movement, visual field test, facial palsy, motor arm,

motor leg, limb ataxia, sensory, language, speech, and inattention. The following is a description of each NIHSS level:

- Score of 0 = No Stroke Symptoms,
- Score of 0-4 = Minor Stroke,
- Score of 5-15 = Moderate Stroke,
- Score of 16-20 = Moderate to Severe Stroke,
- Score of 21-42 = Severe Stroke.

Modified Rankin Scale (mRS)

The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It has become the most widely used clinical outcome measure for stroke clinical trials. (12) The following is a description of each mRS score:

0: The patient has no residual symptoms.
1: No significant disability despite symptoms: able to carry out all usual duties and activities.
2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.
3: Moderate disability; requiring some help, but able to walk without assistance.
4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6: Dead.

Regulatory Status

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

Acute Stroke

Table 3 summarizes the first-generation devices with the FDA clearance for the endovascular treatment of acute stroke and subsequent approval of stent retrievers. Please note, this list is not all inclusive; refer to the FDA website for an up-to-date listing of approved devices.

Table 3. FDA-Cleared Mechanical Embolectomy Devices for Acute Stroke

Device	510(k) Number for Original Device	FDA Approval Date for Original Device	Indications
Penumbra System® (Reperfusion CatheterRED™ 43)	K22808	Dec 2022	Patients with acute ischemic stroke within 8 h of symptom onset who are ineligible for or who fail IV t-PA

Esperance™ Aspiration Catheter System (Wallaby Medical)	K211697	Nov 2021	Patients with acute ischemic stroke within 8 h of symptom onset who are ineligible for or who fail IV t-PA
Embotrap® III Revascularization Device (Neuravi Ltd)	K211338	July 2021	Patients with acute ischemic stroke within 8 h of symptom onset who are ineligible for or who fail IV t-PA
ZOOM™ 71 Reperfusion Catheter (Imperative Care, Inc)	K211476	June 2021	Patients with acute ischemic stroke within 8 h of symptom onset who are ineligible for or who fail IV t-PA
ZOOM Reperfusion Catheter (Imperative Care, Inc)	K210996	April 2021	Patients with acute ischemic stroke within 8 h of symptom onset who are ineligible for or who fail IV t-PA
Tigertriever™ and Tigertriever 17 Resvascularization Devices (Rapid Medical, Ltd)	K203592	Mar 2021	Patients with acute ischemic stroke within 8 h of symptom onset who are ineligible for or who fail IV t-PA
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 hours 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® NXT ProVue Retriever (Stryker Neurovascular)	K210202	Aug 2021	Patients with acute ischemic stroke within 6 hours of symptom onset who fail IVt-PA; patients with acute ischemic stroke within 8 h of symptom onset who are ineligible for or who fail IV t-PA; patients with smaller core infarcts may start therapy as late as 24 h after last seen well

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.
EmboTrap® II Revascularization Device	K173452	May 2018	Patients with ischemic stroke within 8 hours of symptom onset who are ineligible for or who fail IV t-PA.

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

Intracranial 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; the 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 (percutaneous transluminal angioplasty) 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 the FDA through the premarket approval (PMA) 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. (13) 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. (14)

In 2018, Surpass Streamline™ Flow Diverter (Stryker Neurovascular) was approved by the FDA through the PMA process (P170024) for use in the endovascular treatment of patients (18 years of age and older) with unruptured large or giant saccular wide-neck (neck width ≥4 mm or dome-to-neck ratio <2) or fusiform intracranial aneurysms in the internal carotid artery from the petrous segment to the terminus arising from a parent vessel with a diameter ≥2.5 mm and ≤5.3 mm. The approval was based on 1-year results of the Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide Neck Aneurysms (SCENT) study. (15) The SCENT study is continuing follow-up to 5 years post-procedure as a post-approval study.

Other Stent Devices
The following stents have been approved by the 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 the 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.
- *Neuroform™ Atlas Stent System:* In 2019, the Neuroform Atlas Stent System (Stryker) was approved by the FDA through the PMA process (P190031) based on the pivotal ATLAS study including 201 patients with up to 12 months of follow-up. The approved indication is "for use with neurovascular embolization coils in the anterior circulation of the neurovasculature for the endovascular treatment of patients greater than or equal to 18 years of age with saccular wide-necked (neck width greater or equal to 4 mm or a dome-to-neck ratio of < 2) intracranial aneurysms arising from a parent vessel with a diameter of greater than or equal to 2.0 mm and less than or equal to 4.5 mm." Product Code: QCA.
- *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 the 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 the 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 and >4.5 mm. In 2018, the LVIS™ and LVIS™ Jr. were approved through the PMA process (P170013).
- *PulseRider Aneurysm Neck Reconstruction Device*: In 2017, the PulseRider Aneurysm Neck Reconstruction Device (Pulsar Vascular, Inc.) was approved by the FDA through the HDE process (H160002) for use with neurovascular embolic coils for treatment of unruptured wide-necked intracranial aneurysms with neck width at least 4 mm or dome to neck ratio >2.

Rationale

This medical policy was created in September 2012, updated periodically with literature review from the PubMed database. The most recent literature search was performed through February 20, 2023.

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Endovascular Interventions for Anterior Circulation Acute Ischemic Stroke

Clinical Context and Therapy Purpose

The purpose of endovascular interventions in individuals experiencing acute ischemic stroke is to remove thrombus and restore blood flow in a timely manner to salvage brain tissue that is not infarcted. The intervention must be performed as quickly as possible during the narrow window during which reperfusion is beneficial.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with acute ischemic stroke caused by an intracranial large artery occlusion in the proximal anterior circulation who can be treated within a certain window following symptom onset (see studies for time window), regardless of whether they receive intravenous (IV) alteplase.

Patients experiencing stroke symptoms may be seen in primary or emergency care. Most hospitals are able to treat acute ischemic stroke with IV alteplase; however, transfer to a tertiary stroke center may be necessary for patients who are eligible for endovascular mechanical embolectomy.

Interventions

Endovascular embolectomy devices remove or disrupt clots by a number of mechanisms. Several devices have the U.S. Food and Drug Administration (FDA) approval for treatment of acute stroke (see Regulatory Status section). The first-generation devices were the Merci® Retriever, and Penumbra System®. The second-generation devices included stent retrievers: 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 System® 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. The EmboTrap® Revascularization Device (Neuravi Ltd.) was cleared with the Solitaire™ and Trevo® as predicate devices.

This medical policy 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) (16-17)

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 (e.g., calcium channel blockers) and transluminal balloon angioplasty may be used. (18-19) 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 medical policy.

Comparators
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 RCTs and meta-analyses. (3) Therefore, use of IV tPA in ischemic stroke patients presenting within three hours (up to 4.5 hours in some cases) of stroke onset in expert centers is recommended.

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

- Requirement for treatment within 4.5 hours of stroke onset: Relatively few patients present for care within the time window in which tPA has shown benefit. In addition, determining the time of onset of symptoms is challenging in patients awakening with symptoms of acute stroke; patients with symptoms on awakening are considered to have symptom onset when they went to sleep. In 2010 and 2011, fewer than 10% of all ischemic stroke patients arrived at the hospital and received IV tPA within the 3-hour window. (20)
- 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. (21) 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 line treatment to the established intravenous tPA therapy.

Outcomes
Relevant outcomes in studies that evaluate acute ischemic stroke treatment include overall survival, functional status (e.g., disability or disability-free survival), and quality of life. Intermediate outcomes may include the success of revascularization. Rates of treatment-related adverse effects, including vessel perforation, hemorrhage, or thrombus formation in a new site, are important safety outcomes.

Standardized, validated neurologic scales, disability measures, or handicap scales used in the evaluation of neuro-thrombectomy devices include the modified Rankin Scale (mRS), the National Institutes of Health Stroke Scale (NIHSS), the Barthel Index, or the Glasgow Outcome Scale (GOS).

The most commonly used instrument in studies assessed is the mRS, a clinician-reported measure of global disability. The mRS can be administered using a structured interview, checklist or clinician-directed. Scores of 0 to 2 indicate subjects have no to slight disability. The highest score, a 6, indicates death. The mRS has been well studied, including its test-retest reliability, interrater reliability, and validity (construct and convergent). The instrument's limitations include being subject to the negative effect of comorbidities, which are common in stroke patients, as well as factors such as socioeconomic status and surgery.

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.

Another frequently used measure of neurologic impairment is the NIHSS, which is a clinician-administered 15-item scale that measures global impairment after a stroke, developed for use in acute stroke therapy trials. Higher scores refer to worse impairment. Functional status using the modified Rankin Scale and mortality is evaluated at 90 days. Longer term mortality is also of interest.

<u>Selection criteria</u>
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

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 medical policy. 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. (22) 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] [23], Kidwell et al. [2013] [24], Broderick et al. [2013] [25], Berkhemer et al. [2015] [4], Goyal et al. [2015] [6], Campbell et al. [2015] [7], Saver et al. [2015] [8] and Jovin et al. [2015] [5], with a total of 2423 patients. 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%] versus 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 et al. (2015) study (22), Chen et al. (2015) (26), reported a similar OR for 90-day functional independence as Badhiwala.

Roaldsen et al. (2021) conducted a Cochrane systematic review of 19 RCTs in patients with acute ischemic stroke (N=3793) to compare the efficacy of endovascular therapy plus medical treatment to medical treatment alone. (27) Most patients had an anterior large artery occlusion and underwent endovascular therapy within 6 hours of symptom onset. The primary outcome (modified Rankin Scale, 0 to 2), occurred more commonly among patients who received endovascular therapy (risk ratio [RR], 1.50; 95% CI, 1.37 to 1.63). Risk of death was lower in patients who received endovascular therapy than patients who received only medical treatment (RR, 0.85; 95% CI, 0.75 to 0.97). Symptomatic intracranial hemorrhage was similar between groups during the acute phase and at the end of follow-up.

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. (28) 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] [4], Goyal et al. [2015] [6], Campbell et al. [2015] [7], Saver et al. [2015] [8], and Jovin et al. [2015] [5],) 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 OR 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 et al. (2015) (22) 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. (29-33)

Randomized Controlled Trials (RCTs)

Endovascular Therapies versus 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. A high-level overview of the major RCTs follows, with summary results in Table 5. Subsequently, in this section, select trials are described in more detail.

Fifteen RCTs with a total of 3,282 patients (range, 70 to 656) 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 13 studies with the populations and interventions of interest are

the focus of this discussion. The most clinically relevant and consistently reported finding was a comparison between treatment and control groups in the proportion of patients with a mRS score between 0 and 2 at 90 days. Among the 13 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%. With the exception of MR Rescue (Kidwell et al. [2013] [24]), 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 or during an interim analysis. 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

Jovin et al. (2015) reported on results of the Randomized Trial of REVASCularization with Solitaire™ FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within 8 Hours of Symptom OnseT (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. (5) 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). IV 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 computed tomography (CT) imaging or a score of less than 6 on diffusion-weighted magnetic resonance imaging (MRI). The trial was halted early for loss of equipoise given the results of the Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial (EXTEND-IA), Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE), and Multicenter Randomized Clinical trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (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 versus 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% versus 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% versus 15.5%; p=0.60) or 90-day rates of symptomatic intracranial hemorrhage (1.9% in each group; p=1.00).

Table 4a. Summary of Randomized Controlled Trials of Endovascular Therapy versus Standard Care

Trial (Study)	**Intervention**		**N**	**90-Day Modified Rankin Scale Score 0-2**	
	Group	*Treatment Description*		*Per Group Rate, %*	*Between Group Difference (95% CI)*
RESILIENT (Martins et al. [2020]) (34)	Intervention	Intra-arterial thrombectomy and guideline-based care	111	35.1	OR=2.55 (1.34 to 4.88)
	Control	Guideline-based care alone	110	20	
DEFUSE 3 (Albers et al. [2018]) (10)	Intervention	Endovascular therapy + standard medical therapy[b]	92	45	OR=2.7 (1.6 to 4.5)
	Control	Standard medical therapy[b]	90	17	
DAWN (Nogueira et al. [2018]) (9)	Intervention	Endovascular therapy + standard care[b]	107	49	ARR=36% (24% to 47%)
	Control	Standard care[b]	99	13	
EASI (Khoury et al. [2017]) (35)	Intervention	Endovascular therapy + standard care (IV tPA if indicated)	40[a]	50	P=0.36
	Control	Standard care (IV tPA if indicated)	37[a]	38	

PISTE (Muir et al. [2017]) (36)	Intervention	Endovascular therapy + medical therapy with IV tPA	33[a]	51	OR=2.1 (0.7 to 6.9)
	Control	Medical therapy with IV tPA	32[a]	40	
THERAPY (Mocco et al. [2016]) (37)	Intervention	Aspiration thrombectomy (Penumbra) + IV tPA	55[a]	38	OR=1.4 (0.6 to 3.3)
	Control	IV tPA	53[a]	30	
THRACE (Bracard et al. [2016]) (38)	Intervention	Endovascular therapy + IV tPA	202	53	OR=1.6 (1.1 to 2.3)
	Control	IV tPA alone	200	42	
REVASCAT (Jovin et al. [2015]) (5)	Intervention	Solitaire stent retriever w/wo IV tPA	103	43.7	ARR=15.5% OR=2.1 (1.1 to 4.0)
	Control	Medical therapy (IV tPA if indicated)	103	28.2	
EXTEND-IA (Campbell et al. [2015] (7)	Intervention	Endovascular therapy + IV tPA	35	71	OR=3.8 (1.4 to 1.0)
	Control	IV tPA alone	35	40	
ESCAPE (Goyal et al. [2015] (6)	Intervention	Endovascular therapy w/wo IV tPA	165	53	RR=1.8 (1.4 to 2.4)
	Control	Medical therapy (IV tPA if indicated)	150	29.3	
SWIFT-PRIME (Saver et al. [2015]) (8)	Intervention	Solitaire stent retriever + IV tPA	98	60	ARR=25% OR=1.7 (1.23 to 2.33)
	Control	IV tPA alone	98	35	
MR CLEAN (Berkhemer et al. [2015]) (4)	Intervention	Intra-arterial therapy w/wo IV tPA	233	32.6	ARR=13.5% OR=2.05 (1.36 to 3.09)

	Control	Medical therapy (IV tPA if indicated)	267	19.1	
MR RESCUE (Kidwell et al. [2013]) (24)	Intervention	Mechanical embolectomy (MERCI or Penumbra) w/wo IV tPA	64	18.75	P=0.48
	Control	Medical therapy (IV tPA if indicated)	54	20.3	
SYNTHESIS EXP (Ciccone et al. [2013]) (23)	Intervention	Intra-arterial therapy w/wo IV tPA	181	30.4	OR=0.71 (0.44 to 1.14)
	Control	IV tPA alone	181	34.8	
IMS III (Broderick et al. [2013]) (25)	Intervention	Endovascular therapy + IV tPA	434	38.7	Adjusted difference: 1.5% (-6.1 to 9.1)
	Control	IV tPA alone	222	40.8	

ARR: absolute risk reduction; CI: confidence interval; IV: intravenous; OR: odds ratio; RR: relative risk; tPA: tissue plasminogen activator; w/wo: with/without; NS: not significant; NR: not reported; SITS-MOST: Safe Implementation of Thrombolysis in Stroke-Monitoring Study; DAWN: Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE 3: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; EASI: Endovascular Acute Stroke Intervention; ESCAPE: Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA: Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial; IMS III: Interventional Management of Stroke III; MR CLEAN: Multicenter Randomized Clinical trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE: Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; PISTE: Pragmatic Ischaemic Stroke Thrombectomy Evaluation; RESILIENT: Randomization of Endovascular Treatment with Stent-retriever and/or Thromboaspiration versus Best Medical Therapy in Acute Ischemic Stroke due to Large Vessel Occlusion Trial; REVASCAT: Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT-PRIME: Solitaire™ With the Intention For Thrombectomy as PRIMary Endovascular Treatment; SYNTHESIS-EXP: Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke; THERAPY: Assess the Penumbra System in the Treatment of Acute Stroke; THRACE: Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke.

[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.

Table 4b. Summary of Randomized Controlled Trials of Endovascular Therapy versus Standard Care

Trial (Study)	**Mortality**		**Symptomatic Intracranial Hemorrhage**	
	Per Group Rate, %	*Between Group Difference (95% CI)*	*Per Group Rate, %*	*Between Group Difference (95% CI)*
RESILIENT (Martins et al. [2020]) (34)/Intervention	24.3	OR=0.75 (0.41 to 1.36) At 90 days	4.5	OR=0.99 (0.26 to 3.78) According to the SITS-MOST criteria
Control	30		4.5	
DEFUSE 3 (Albers et al. [2018]) (10) /Intervention	14	OR=0.55 (0.3 to 1.0)	7	OR=1.5 (0.4 to 6.6)
Control	26		4	
DAWN (Nogueira et al. [2018]) (9)/Intervention	19	ARR=1% (-10% to 11%)	6	ARR=3% (-3% to 8%)
Control	18		3	
EASI (Khoury et al. [2017]) (35) /Intervention	28	NR	7.5	NR
Control	24		5.7	
PISTE (Muir et al. [2017]) (36) /Intervention	21	OR=1.6 (0.3 to 8.4)	0	
Control	13		0	
THERAPY (Mocco et al. [2016]) (37) /Intervention	12	OR=2.3(0.8 to 6.8)	9.3	OR=1.0 (0.3 to 3.9)
Control	24		9.7	
THRACE (Bracard et al. [2016]) (38) /Intervention	12	OR=0.8 (0.5 to 1.2)	2	OR=1.4 (0.3 to 6.3)
Control	13		2.0	

REVASCAT (Jovin et al. [2015]) (5) /Intervention	18.4	p=0.60	1.9	p=NS
Control	15.5		1.9	
EXTEND-IA (Campbell et al. [2015] (7) /Intervention	20	OR=0.38 (0.1 to 1.6)	6	Risk difference, -6 (-13 to 2)
Control	9		0	
ESCAPE (Goyal et al. [2015] (6) /Intervention	10.4	RR=0.5 (0.3 to 1.00)		
Control	19.05			
SWIFT-PRIME (Saver et al. [2015]) (8) /Intervention	9	RR=0.74 (0.33 to 1.68)	0	p=0.12
Control	12			
MR CLEAN (Berkhemer et al. [2015]) (4) /Intervention	18.9	p=NS	7.7	p=NS
Control	18.4		6.4	
MR RESCUE (Kidwell et al. [2013]) (24) /Intervention	21	p=NS	4	p=NS
Control	21		4	
SYNTHESIS EXP (Ciccone et al. [2013]) (23) /Intervention			6	p=NS
Control			6	
IMS III (Broderick et al. [2013]) (25) /Intervention	19.1	p=0.52	11.5	p=0.02
Control	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; NS: not significant; NR: not reported; SITS-MOST: Safe Implementation of Thrombolysis in Stroke-Monitoring Study; DAWN: Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE 3: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; EASI: Endovascular Acute Stroke Intervention; ESCAPE: Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA: Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-

Arterial; IMS III: Interventional Management of Stroke III; MR CLEAN: Multicenter Randomized Clinical trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE: Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; PISTE: Pragmatic Ischaemic Stroke Thrombectomy Evaluation; RESILIENT: Randomization of Endovascular Treatment with Stent-retriever and/or Thromboaspiration versus Best Medical Therapy in Acute Ischemic Stroke due to Large Vessel Occlusion Trial; REVASCAT: Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT-PRIME: Solitaire™ With the Intention For Thrombectomy as PRIMary Endovascular Treatment; SYNTHESIS-EXP: Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke; THERAPY: Assess the Penumbra System in the Treatment of Acute Stroke; THRACE: Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke.

[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.

Campbell et al. (2015) reported on results of the EXTEND-IA trial comparing endovascular therapy with tPA alone. (7), 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 computed tomography angiography (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 endpoints: 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% versus 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.

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. (6) 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 endpoint (90-day modified Rankin Scale score), the relative odds of improving 1 point on the modified Rankin Scale was 2.6 (95% CI, 1.7 to 3.8) in the endovascular treatment group as compared to control. Endovascular treatment group subjects also had lower 90-day modified Rankin Scale scores (median, 2 vs. 4, respectively; p<.001) and were more likely to have 90 day modified Rankin Scale scores of 0 to 2 (53% vs. 29.3%; rate ratio, 1.8; 95% CI, 1.4 to 2.4; p<.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=.04).

Saver et al. (2015) reported on results of the Solitaire™ With the Intention For Thrombectomy as PRIMary Endovascular Treatment (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. (39) Eligible patients had moderate-to-severe neurologic deficits, imaging-confirmed occlusion of the intracranial ICA and/or the first segment of the MCA, were receiving or had received IV tPA, and were able to undergo endovascular treatment within six hours of symptom onset. 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.

Enrolled patients were mainly White (88% to 90%) with few Black (9% to 11%) and Hispanic (8% to 9%) patients. 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% versus 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.

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 endpoint RCT with 500 subjects conducted at 16 centers in the Netherlands. (4) 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 [IQR], 2-5) among intervention subjects, compared with a median score of 4 (IQR, 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 (AEs) 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% versus 0.4%; p<0.001).

Kidwell et al. (2013) reported on the MR RESCUE trial. (24) 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.

Ciccone et al. (2013) reported on the Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke (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). (23) Endovascular therapy consisted of intra-arterial tPA, mechanical embolectomy (using the Solitaire™, Penumbra System®, 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 System® 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.

Broderick et al. (2013) reported on the results of the Interventional Management of Stroke III (IMS III) trial, an open-label RCT with a planned enrollment of 900 patients. (25) 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% versus 5.8%, respectively; p=0.02), as was asymptomatic intracerebral hemorrhage (27.4% versus 18.9%, p=0.01). There were no significant differences between groups in other AEs, 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. (40) 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 thrombolysis in cerebral infarction (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 System® 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 (MRA) findings and outcomes among 306 (47%) of 656 who had baseline CT or MRA available. (41) 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 versus 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 versus 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 Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3) and Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) trials evaluated whether it was possible to extend the time window for mechanical thrombectomy after acute ischemic stroke.

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. (10) DEFUSE 3 was conducted at 38 sites in the U.S. 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 National Institutes of Health Stroke Scale Score (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).

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. (9) 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 U.S., 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% versus 18%, respectively; p=1.00). In a post-hoc analysis of DAWN assessing the impact of periprocedural and technical factors and patient characteristics on revascularization and outcome, the authors found that patients requiring ≥3 thrombectomy passes with the Trevo stent retriever and those with a baseline National Institutes of Health Stroke Scale score >17 had a reduced chance of favorable outcome at 3 months. (42)

Jovin et al. (2022) conducted a systematic review and individual patient data meta-analysis of 6 RCTs that treated 585 patients known to be well 6 to 24 hours earlier (including DEFUSE 3, DAWN, ESCAPE, REVASCAT, and RESILIENT), known as the Analysis of Pooled Data from Randomized Studies of Thrombectomy More Than 6 Hours After Last Known Well collaboration (AURORA). (43) Thrombectomy improved 90-day disability as assessed by the Rankin Scale (adjusted OR, 2.45; 95% CI, 1.83 to 3.54; p<.0001). Thrombectomy also improved independence in activities of daily living (modified Rankin Scale score, 0 to 2) compared to medical therapy alone (45.9% vs. 19.3%; p<.0001). Mortality at 90 days and intracerebral hemorrhage were similar between therapies. Treatment effects were more pronounced among patients who underwent randomization within 12 to 24 hours of symptom onset compared to patients randomized within 6 to 12 hours of symptom onset.

Subsection Summary: RCTs Comparing Endovascular Therapies with Noninterventional Care

A number of RCTs have compared endovascular therapies with noninterventional care for acute stroke, with more recent 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] [23], Kidwell et al. [2013] [24], Broderick et al. [2013] [25]) 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. Not all studies published after 2015 have shown a benefit of endovascular therapy in major clinical outcomes, possibly due to small sample sizes and lack of power to detect differences.

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 Solitaire With the Intention for Thrombectomy (SWIFT) 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. (44) Treatment was initiated

within 8 hours of symptom onset in patients who had unsuccessful IV tPA or were ineligible for IV tPA. This trial was halted early after an interim analysis found revascularization without symptomatic intracranial hemorrhage occurred in 61% of Solitaire patients compared with 24% of Merci® patients. Mortality rates at 90 days were 17% with Solitaire™ versus 38% with Merci (p=0.001). A follow-up analysis of complications of endovascular procedures using the SWIFT study data was published in 2014. (45) 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% versus 1.1%, p=0.013).

In the Thrombectomy Revascularization of large Vessel Occlusions (TREVO 2) Study, 178 patients were randomized to mechanical embolectomy with either the Trevo® Retriever or the Merci® Retriever for large vessel occlusion strokes. (46) Revascularization rates were 86% in the Trevo® group and 60% in the Merci® group (p<0.001). Procedure-related AEs 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) (47) evaluated the benefit added by stent retrievers to IV tPA using pooled patient-level data from the SWIFT study (44), and the Thrombectomy Revascularization of large Vessel Occlusions (STAR) trial, a prospective, single-arm trial of the Solitaire™ device (48), along with data from the National Institute for Neurological Disorders (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. (49) Eligible patients had large vessel intracranial occlusion acute ischemic stroke with an NIHSS score of at least eight within 8 hours of onset. The primary effectiveness outcome was the rate of an 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.

Cao et al. (2020) completed a multicenter, prospective, open label RCT at 7 Chinese stroke centers that compared the efficacy and safety of the RECO self-expanding clot retriever to Solitaire FR in patients with acute intracranial large vessel occlusion. (50) In the RECO Flow Restoration Device Versus Solitaire FR With the Intention for Thrombectomy (REDIRECT) study, patients with an acute ischemic stroke within 8 hours after symptom onset and a baseline National Institutes of Health Stroke Scale score ≥8 and ≤24 were randomly assigned to RECO (n=67) or Solitaire FR (n=69). The primary efficacy endpoint was a modified thrombolysis in cerebral infarction reperfusion grade ≥2 within 3 passes. Results revealed that the treatment groups were similar with regard to the primary efficacy endpoint (91% RECO vs. 87% Solitaire FR; p=0.5861). No serious adverse device effects were observed, with symptomatic intracerebral hemorrhage rates (1.5% vs. 7.2%; p=0.1027), and the rates of serious adverse events (6% vs. 1.4%; p=0.205) within 24 hours after the procedure were similar between the groups. No differences between the groups were seen regarding rate of functional independence (63% vs. 46%; p=0.0609), 90-day all-cause mortality (13% vs. 23%; p=0.1848), or procedure duration (p=0.5986).

Subsection 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 were generally rated as having low risk of bias in systematic reviews. 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
Clinical Context and Therapy Purpose
The purpose of endovascular interventions in patients experiencing acute ischemic stroke is to remove thrombus and restore blood flow in a timely manner to salvage brain tissue that is not infarcted. The intervention must be performed as quickly as possible during the narrow window during which reperfusion is beneficial.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with acute ischemic stroke caused by an occlusion of the basilar artery. 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. (51)

Individuals experiencing stroke symptoms may be seen in primary or emergency care. Most hospitals are able to treat acute ischemic stroke with IV alteplase; however, transfer to a tertiary stroke center may be necessary for patients who are eligible for endovascular mechanical embolectomy.

Interventions
Endovascular embolectomy devices remove or disrupt clots by a number of mechanisms. Several devices have U.S. Food and Drug Administration (FDA) approval for treatment of acute stroke (see Regulatory Status section). The first-generation devices were the Merci Retriever and Penumbra System. The second-generation devices included stent retrievers: the 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 proxima 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. The EmboTrapRevascularization Device (Neuravi Ltd.) was cleared with the Solitaire and Trevo as predicate devices.

This medical policy 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 (MicroVention) (16-17).

Comparators
The prompt use of IV thrombolytic therapy with recombinant tPA to recanalize occluded blood vessels has been associated with improved outcomes in multiple RCTs and meta-analyses. (3) 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. (20)

- Risks associated with IV tPA therapy. Intravenous tPA is associated with an 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, a 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. (21) 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 IV tPA therapy.

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. (52)

Outcomes

Relevant outcomes in studies that evaluate acute ischemic stroke treatment include overall survival, functional status (e.g., disability or disability-free survival), and quality of life. Intermediate outcomes may include the success of revascularization. Rates of treatment-related adverse effects, including vessel perforation, hemorrhage, or thrombus formation in a new site, are important safety outcomes.

Standardized, validated neurologic scales, disability measures, or handicap scales used in the evaluation of neurothrombectomy devices include the modified Rankin Scale, the National Institutes of Health Stroke Scale, the Barthel Index, or the Glasgow Outcome Scale.

The most commonly used instrument in studies is the modified Rankin Scale, a clinician-reported measure of global disability. The modified Rankin Scale can be administered using a structured interview or checklist or clinician-directed. Scores of 0 to 2 indicate subjects have no to slight disability. The highest score, a 6, indicates death. The modified Rankin Scale has been well studied, including its test-retest reliability, interrater reliability, and validity (construct and convergent). The instrument's limitations include being subject to the negative effect of comorbidities, which are common in stroke patients, as well as factors such as socioeconomic status and surgery.

Results pertaining to 3 specific outcomes are the focus here: the proportion of patients with 90-day modified Rankin Scale 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; modified Rankin Scale scores ranging from 0 to 2 correspond to functional independence, and so represent a clinically useful measure of

disability. Prior studies of endovascular 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.

Another frequently used measure of neurologic impairment is the National Institutes of Health Stroke Scale, which is a clinician-administered 15-item scale that measures global impairment after a stroke, developed for use in acute stroke therapy trials. Higher scores refer to worse impairment. Functional status using the modified Rankin Scale and mortality is evaluated at 90 days. Longer term mortality is also of interest.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

Liu et al. (2020) reported results of the Basilar Artery Occlusion Endovascular Intervention versus Standard Medical Treatment (BEST) multicenter, open-label, RCT with blinded outcome assessment conducted at 28 stroke centers in China comparing endovascular plus standard medical therapy (n=66) to standard medical therapy (n=65) for treatment of acute strokes due to vertebrobasilar artery occlusion.(53) Patients had an acute ischemic stroke consistent with acute occlusion of the basilar artery presenting within 8 hours of vertebrobasilar occlusion and a prestroke score of 0 to 2 on the modified Rankin Scale. The primary outcome was a modified Rankin Scale score of 3 or lower (indicating ability to walk unassisted) at 90 days. Patients in both groups meeting criteria for IV thrombolysis received IV alteplase and received standard medical therapy following the American Heart Association/American Stroke Association guidelines. The trial was designed with a sample size of 344 patients but was terminated prematurely by the steering committee based on the recommendation of the data and safety monitoring board because of excessive crossovers and poor recruitment. Characteristics of the study are shown in Table 5 and results are shown in Table 6. In the intention-to-treat analysis, there was not a statistically significant difference in the proportion of participants with a modified Rankin Scale of 0 to 3 at 90 days (28/66 [42%] in the endovascular group versus 21/65 [32%] in the standard therapy group; adjusted OR = 1.7, 95% CI, 0.8 to 3.7). The 90-day mortality rates were 33% versus 38% in the endovascular and standard therapy groups, respectively (p=0.54).

Table 5. Summary of RCT Characteristics of Endovascular Treatment of Basilar Artery Occlusion

Trial	Countries	Sites	Dates	Participants	Interventions	
Liu 2020 (53) BEST; NCT02441556	China	28	2015-2017	Patients aged 18 years or older; had an acute ischemic stroke consistent with acute occlusion of the basilar artery; could be randomized within 8 hours of symptom onset; had a prestroke score of 0–2 on the mRS	N=66 Endovascular therapy plus standard medical therapy	N=65 Standard medical therapy

mRS: modified Rankin Scale; RCT: randomized controlled trial.

Table 6. Results of RCTs of Endovascular Therapy of Basilar Artery Occlusion

Trial (Study)	N	90 Day Modified Rankin Scale Score 0-3		Mortality		Symptomatic Intracranial Hemorrhage	
		Per Group Rate, %	Between Group Difference (95% CI)	Per Group Rate, %	Between Group Difference (95% CI)	Per Group Rate, %	Between Group Difference (95% CI)
Liu 2020 (53)							
Endovascular therapy plus standard medical therapy		42%	OR=1.7 (0.8 to 3.7)	33%	0.8 (0.4 to 1.6)	8%	NA; p=0.06
Standard medical therapy		32%		38%		0	

CI: confidence interval; NA: not available; OR: odds ratio; RCT: randomized controlled trial.

The purpose of the limitations tables (Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]

Liu 2020 (53)			4:14 (22%) of 65 patients received endovascular treatment because patients' families did not accept only standard medical therapy after randomization		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Liu et al. 2020 (53)				1, 3: Study terminated early due to high crossovers and poor recruitment		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

<u>Section Summary: Endovascular Interventions for Stroke due to Basilar Artery Occlusion</u>

The evidence for the use of endovascular interventions for stroke due to basilar artery occlusions is limited. One RCT has been conducted but it was terminated early due to high crossovers and poor recruitment. There was not a statistically significant difference in the proportion of participants with a modified Rankin Scale of 0 to 3 at 90 days or in 90-day mortality rates in the endovascular and standard therapy groups. At least 2 additional RCTs are ongoing.

Endovascular Interventions for Symptomatic Intracranial Atherosclerotic Disease

Clinical Context and Therapy Purpose

The purpose of endovascular interventions in individuals with intracranial atherosclerotic disease is to prevent stroke or recurrent stroke.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with severe stenosis (70 to 99% of the diameter of a major intracranial artery).

Interventions

Devices for treatment of intracranial stenosis have received the FDA approval through the HDE process. The Neurolink System® was approved based on the Stenting of Symptomatic Atherosclerosis Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) trial, a prospective, nonrandomized, multicenter, international study of 61 patients. (13) The Wingspan™ Stent System was evaluated in a prospective study of 45 patients enrolled at 12 international centers. (54) 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 the 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." (13)

Comparators

Medical treatment typically includes either anticoagulant therapy (i.e., warfarin) or antiplatelet therapy (e.g., aspirin). The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) assessed the incidence of stroke brain hemorrhage or death among patients randomized to aspirin or warfarin. (55) 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. (56) 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 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 percutaneous transluminal angioplasty as a minimally invasive treatment of this difficult-to-treat population. Most published studies of intracranial percutaneous transluminal angioplasty have focused on vertebrobasilar circulation.

Outcomes

The outcomes of interest are stroke, death, function and quality of life. Treatment-related adverse effects, including vessel perforation, hemorrhage, or thrombus formation in a new site, are important safety outcomes. Evidence for both short-term (30-day) and long-term (out to 2-years) outcomes are needed.

Study Selection Criteria

Methodologically credible studies were included that met the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Luo et al. (2023) completed a Cochrane review that evaluated endovascular therapy plus conventional medical treatment versus medical treatment alone for symptomatic intracranial artery stenosis. (57) The review included 4 RCTs (N=989) and identified 2 ongoing RCTs. All trials had a high risk of performance bias, and the certainty of included evidence ranged from low to moderate. Characteristics and moderate certainty results of the review are found in Tables 9 and 10. The review also included various subgroup analyses. Overall, endovascular therapy plus conventional medical treatment was found to increase the risk of the primary outcome (short-term stroke and death [i.e., within 3 months of randomization]) in patients with recent symptomatic intracranial artery stenosis. It was also found to increase the risk of short-term

ipsilateral stroke (RR, 3.26; 95% CI, 1.94 to 5.48; moderate certainty), short-term ischemic stroke (RR, 2.24; 95% CI, 1.30 to 3.87; moderate certainty), and long-term death or stroke (RR, 1.49; 95% CI, 1.12 to 1.99; moderate certainty). Long-term results that were reported appeared to be due to the early risks of endovascular therapy.

Table 9. Systematic Review & Meta-analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Luo et al. (2023) (57)	NR-2022	4	Adults with symptomatic intracranial artery stenosis related to atherosclerotic factors	989 (NR)	RCT	Short-term follow-up: mean 30 days Long-term follow-up: mean 12 months

NR: not reported; RCT: randomized controlled trial

Table 10. Systematic Review & Meta-analysis Results

Study	Short-term death or stroke	Short-term ipsilateral stroke	Short-term ischemic stroke	Long-term death or stroke
Luo et al. (57)				
Total N	989	989	989	970
Risk ratio (95% CI)	2.93 (1.81 to 4.75)	3.26 (1.94 to 5.48)	2.24 (1.30 to 3.87)	1.49 (1.12 to 1.99)
I^2	0%	0%	0%	45%
Test for overall effect: Z(p)	4.36 (p<.0001)	4.47 (p<.00001)	2.89 (p=.004)	2.71 (p=.007)

CI: confidence interval.

Randomized Controlled Trials

Zaidat et al. (2015) published the results of the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (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. (58) 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 post enrollment 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 endpoint 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 1 of the primary endpoints 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 (CVD) and intracranial stenosis between 70% and 99%. (59) This trial used the Wingspan™ stent system implanted by experienced neuro-interventionalists 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 AEs 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. (60) Primary endpoints (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 endpoint event, with a significantly higher cumulative probability of a primary endpoint in the stenting group than in the best medical management group (p=0.025). Compared with the best medical management group, subjects in the stenting group had higher rates of any stroke (59/224 [26%] versus 42/227 [19%], p=0.047) and major hemorrhage (29/224 [13%] versus 10/227 [4%], p<0.001). The authors concluded 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. (61) 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, two-year event rates were higher in the stent group for most variables evaluated. (62) 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. (63) 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 (MI) 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. (64) 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 versus 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.

Postmarket Surveillance

Alexander et al. (2019) reported results from the Wingspan Stent System Post Market Surveillance (WEAVE) postmarketing surveillance study. (65) WEAVE was an FDA-mandated, prospective, single-arm study evaluating the rate of stroke and death within 72 hours poststenting in patients who met the FDA on-label usage criteria. One hundred fifty-two consecutive patients were enrolled at 24 hospitals. The study was designed to enroll 389 patients but was stopped early when the second, predetermined interim data analysis indicated that the safety benchmarks were met. The primary outcome included 2 nonfatal strokes and 2 deaths from strokes for a total of 4 patients (2.6%) with an event of stroke, bleed, or death.

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

Clinical Context and Therapy Purpose

The purpose of endovascular interventions in patients with intracranial aneurysm is to remove the aneurysm from the circulation and prevent possible rupture (or if the aneurysm had already ruptured, to stop bleeding and prevent re-rupture) or to divert blood flow away from an aneurysm.

The following PICO was used to select literature to inform this policy.

Populations

The population of interest are individuals with intracranial aneurysms. Treatment decisions depend on patient and aneurysm-characteristics. Small (<7 mm) asymptomatic aneurysms can generally be observed. Larger and asymptomatic aneurysms may be considered for treatment according to anatomical location and morphological characteristics of the aneurysm and relative risks for specific treatments. The FDA approved endovascular treatments have specific specifications regarding aneurysm characteristics (see Regulatory section) although they have been used off-label for challenging lesions in other locations.

Interventions

Self-expanding stents have FDA approval through the humanitarian device exemption (HDE) program for the endovascular treatment intracranial aneurysms.

Intracranial stents are 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.

In 2011, the Pipeline Embolization Device, which falls into a new device category called “intracranial aneurysm flow diverters,” or flow-diverting stents, received the 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. According to the FDA documentation, the Surpass Streamline Flow Diverter has the same mechanism of action as the approved Pipeline Embolization Device.

Comparators
Small asymptomatic aneurysms can generally be observed without surgery. Surgical clipping of intracranial aneurysms has been used since the 1960s, but the feasibility of clipping for aneurysms depends on the aneurysm location.

Outcomes
The Executive Summary of an FDA meeting of the Neurological Devices Advisory Panel in 2018 to discuss evaluation of benefits and risks of new endovascular medical devices intended to treat intracranial aneurysms stated the primary safety outcomes for regulatory review have traditionally have been focused on neurological deaths and major ipsilateral strokes (defined as an increase ≥4 points in the National Institutes of Health Stroke Scale (NIHSS) score during the stroke event) and the percentage of patients who had a disabling stroke (defined as mRS score ≥3 assessed at a minimum of 90 days post-stroke event) within 6 months to 1 year of treatment. (66) The FDA is considering an additional outcome of to assess functional independence defined as the change in the mRS score at 1-year post-treatment compared to pre-procedure. The FDA has traditionally used a composite efficacy outcome defined as the percent of patients demonstrating a Raymond I classification for complete occlusion (i.e., 100% aneurysmal occlusion) without retreatment of the target aneurysm or significant parent artery stenosis (≥ 50%) evaluated within 1-year post-procedure.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Self-Expanding Stent-Assisted Coiling for Intracranial Aneurysms
The literature search did not identify any randomized trials of self-expanding stent-assisted treatment of intracranial aneurysms compared with standard neurosurgical treatment (i.e., surgical clipping or endovascular coils). The available evidence 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. (67) 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% versus 19.4%; OR=2.75; 95% CI, 1.95 to 3.86; p<0.000) and lower rates of recurrence (16.2% versus 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 two 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. (68) 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). (69) 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 versus 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 versus 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) versus 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 Trial (MAPS) Trial. (70) 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% versus 33%; p<0.000) and had aneurysms with the lower dome-to-neck ratio (1.3 versus 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% versus 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. (71) 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).

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. (72) 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*).

<u>Comparison Between Endovascular Devices for Intracranial Aneurysms</u>

Systematic Reviews

Nonrandomized studies, summarized in a systematic review by King et al. (2015), have compared devices used for stent-assisted coiling of intracranial aneurysms. (73) 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% versus 0.2%, p<0.001) and a higher mortality rate (2.8% versus 1.8%, p=0.04), less likely to have 100% aneurysm occlusion at last follow-up (61.1% versus 74.7%, p<0.001), and more likely to have recanalization (13.9% versus 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.

Nonrandomized Comparative Studies

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. (74) 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 post-procedure (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. (75) 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 U.S. are summarized in Table 11. 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 11. Noncomparative Studies of Stent-Assisted Endovascular Treatment of Aneurysms

Study	Study Type	Patient Population	Intervention	Primary Outcome
ATLAS IDE study: Jankowitz et al. (2019) (76), (30 patients enrolled through September 2015) FDA SSED (77), (201 patients enrolled	Prospective, multicenter (25 sites)	201 patients with wide-necked intracranial aneurysm (neck ≥4 mm or dome-to-neck ratio <2), parent vessel diameter of 2.0–4.5 mm, the aneurysm	Neuroform Atlas stent and approved coils	• 100% occlusion, without retreatment or significant stenosis: 84.7% (95% CI, 78.6, 90.9) • Any serious adverse event: 51 (28%) • Cerebrovascular event: 18 (11%) unruptured

through October 2016)		is intracranial (encompassing the entire posterior circulation and aneurysms at or distal to the superior hypophyseal artery in the anterior circulation)		• Any major ipsilateral stroke or neurologic death: 4.4% (95% CI, 1.9, 8.5)
US LVIS pivotal trial: Fiorella et al. (2018) (78) FDA SSED (79)	Prospective, multicenter (21 sites)	153 patients with unruptured or ruptured (>30 days since occurrence) wide-necked (neck ≥4 mm or dome to neck ratio <2) intracranial, saccular aneurysms (≥4 mm and <20 mm maximum diameter in any plane) from a parent vessel with a diameter ≥2.0 mm and ≤4.5 mm which were amenable to endovascular coil embolization	LVIS devices	• 100% occlusion, without retreatment or significant stenosis: 71% (95% CI, 63 to 77) • Disabling stroke with mRS score ≥ 3 or neurological death: 6% (95% CI, 3 to 11)
Feng et al. (2016) (80)	Retrospective case series	97 patients with intracranial saccular	Endovascular treatment with low profile visualized	• 100% of patients had technically successful treatment

		aneurysms (13 with rupture)	intraluminal support	• 98.9% met the primary endpoint of safety (absence of new transient or permanent neurologic deficit or death) • Over mean 7.8-month follow-up, no patient had new neurologic deterioration or died • Among 76 patients with digital angiography imaging at follow up, 59.21% had complete occlusion
Aydin et al. (2015) (81)	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%) patients had permanent neurologic deficits
Chalouhi et al. (2013) (82)	Retrospective case series	76 patients with posterior cerebellar artery aneurysms (1 institution)	Of 71 successful endovascular coiling (n=60), with or without Neuroform™ stent assistance (n=4) or balloon assistance (n=4), or	• 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

			parent vessel trapping (n=11)	hospital, 85% favorable outcomes (mild, moderate, no disability)
Chen et al. (2013) (83)	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) (84)	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 follow up at 12 to 18 months, 5 patients (5%) had delayed complications, with 3% of patients with thromboembolic events • Of 93 patients with anatomic evaluation available, aneurysms recurred in 9.7%
Johnson et al. (2013) (85)	Retrospective case series	91 patients with complex middle cerebral artery	Endovascular treatment with coiling with stent	• 100% of patients had technically successful treatment

		aneurysms not amenable to coiling enrolled (1 institution)	assistance using Neuroform™ (62 aneurysms), Enterprise™ (32 aneurysms), Wingspan™ (1 aneurysm), or a combination (5 aneurysms) or stenting along (2 aneurysms)	• 9 patients had new neurologic symptoms following the procedure, one with long-term disability. One procedure-related death. • Of 85 aneurysms with initial follow-up imaging available (usually at 6 months postprocedure), 77 (90.6%) were completely occluded, and 4 (4.7%) required retreatment
Kulcsar et al. (2013) (86)	Retrospective case series	117 patients with wide-necked cerebral aneurysms	Endovascular treatment with Neuroform™ stent-assisted coiling	• Stents were successfully deployed in 113 patients with 117 aneurysms • 99 patients had grade 1 or 2 occlusion (complete or aneurysm neck) on immediate postprocedure imaging • Intra-procedure major thrombotic events occurred in 7 cases (5.9%) and major infarcts on postprocedure imaging in 9 cases (7.7%) • Of 92 aneurysms with follow-up imaging available, 71 (77%) had grade 1 or 2 occlusion

DSA: digital subtraction angiography; FU: follow-up; IDE: Investigational Device Exemption; LVIS: low-profile visualized intraluminal support; MCA: middle cerebral artery; PCA: posterior cerebellar artery. US: United States

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 AE 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 Studies 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 PUFA study, a multicenter, prospective, single-arm trial (2013) of the device for treatment of ICA aneurysms that were uncoilable or had failed coiling. (14) 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 endpoint 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 endpoint (occurrence of major ipsilateral stroke or neurologic death at 180 days) occurred.

The Surpass Streamline Flow Diverter received the FDA premarket approval in 2018. According to FDA documentation, the Surpass diverter has the same mechanism of action as the Pipeline diverter. The device was approved based on the pivotal Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide Neck Aneurysms (SCENT) prospective, single-arm study. (3, 87) Patients were enrolled and treated between 2012 and 2015 at 25 sites in the U.S. and 1 site in the Netherlands. Two-hundred and thirty-six patients had been enrolled and 180 had 1-year data included in the FDA report. Eligible patients had a single targeted intracranial aneurysm located in the internal carotid artery distribution up to the terminus with a neck ≥4 mm or no discernible neck and an aneurysm size ≥10 mm (including saccular, fusiform and dissecting configuration) and had a vessel diameter between

2.5 mm and 5.3 mm at both the proximal and distal segments. The incidence of major ipsilateral stroke defined as an increase in the NIHSS score from baseline by ≥4 points during stroke event or neurological death 10.6% (19/180, 95% CI, 6.5 to 16.0). Five of the patients experiencing major ipsilateral stroke also suffered neurological death. The percent of patients experiencing disabling stroke defined as mRS of 3 or higher measured at least 90 days after stroke event was 6.1% (11/180, 95% CI, 3.1 to 10.7). Forty-one (22.8%) of patients had improved mRS scores at 12-months compared to baseline. The percent of patients with 100% occlusion (Raymond-Roy Class I) without clinically significant stenosis (clinically significant stenosis defined as >50% stenosis) of the parent artery was 62.8% (113/180).

Systematic Reviews

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). (90) 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. Xin et al. (2019) reported results of a similar systematic review of 11 observational studies, several of which overlapped with Zhou. (91) Results with respect to occlusion rate compared to coil embolization and mortality were similar.

Randomized Controlled Trials

No randomized trials evaluating intracranial aneurysms were identified comparing flow-diverting stent treatment with standard neurosurgical treatment (i.e., surgical clipping or endovascular coils) from the time of the FDA approval of the first flow-diverter until 2017. (88)

Raymond et al. (2017) reported on results of the Flow Diversion in the Treatment of Intracranial Aneurysm Trial (FIAT). (88) 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%). Characteristics of the trial are shown in Table 22. Results shown in Table 22 include all patients and the subset of patients with proximal carotid aneurysms.

Kiselev et al. (2018) reported results of the Study of Complex intracranial Aneurysms Treatment (SCAT) trial of flow diversion versus parent vessel occlusion and bypass in patients with complex anterior circulation aneurysms conducted in 2 neurosurgical centers in Russia. (89) One hundred and eleven patients were randomized; 55 into the flow diversion group and 56 into the parent vessel occlusion with bypass group. There was a baseline imbalance with respect to age and aneurysm neck size, so the authors included only 40 patients in each group, selected after propensity score matching. The mean age of subjects was 54 years old and approximately three-quarters of the patients were women. Patients were followed for 12 months. The aneurysms were in the following segments: A2 segment of anterior cerebral artery (n=1), anterior communicating artery (n=3), cavernous carotid artery (n=29), ophthalmic segment of internal carotid artery (n=9), communicating segment of internal carotid artery (n=11), M1 segment (n=20) and M2 segment of middle cerebral artery (n=7). The median aneurysm size by MRI was 12 mm (interquartile range, 9 to 16.75) in the bypass group and 15 mm (interquartile range, 9 to 20.5) in the flow diversion group. Study characteristics are shown in Table 12 and results are shown in Table 13. Outcome definitions were unclear. Of the 40 patients included in analysis, 97.5% in the flow diversion group and 80% in the bypass group had a 'good clinical outcome' (difference between groups, p=0.029). The overall morbidity and mortality rates were 15% and 5%, respectively, but rates by group were not reported. The rate of complete occlusion at 12 months was 65% in the flow diversion group and 97.5% in the bypass group (p=0.001).

Table 12. Summary of RCT Characteristics of Flow-Diverting Stents for Intracranial Aneurysms

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Raymond et al. (2017) (88) (FIAT; NCT01349582)	Canada	3	2011-2015	Patients harboring an aneurysm for which flow diversion was considered a	N=39 Arterial (not intraaneurysmal) flow-diverting device with or	N=39 Best standard treatment selected

				promising treatment (clinical judgment)	without coil embolization	according to clinical judgment
Kiselev et al. (2018) (89), (SCAT; NCT03269942)	Russia	2	2015-2017	Patients with anterior circulation complex aneurysms with neck wider than 4 mm, where dome/neck ratio ≤2:1; suitable for flow diversion and occlusion with bypass; not eligible for coiling or direct clipping	N=55 Flow diversion: multiple flow-diverting devices used	N=56 Parent vessel occlusion and bypass

FIAT: Flow Diversion in the Treatment of Intracranial Aneurysm Trial; N: number; NCT: National Clinical Trial; RCT: randomized controlled trial.

Table 13. Summary of RCT Results of Flow-Diverting Stents for Intracranial Aneurysms

Study; Trial	Primary Efficacy Outcome	Death	Any Stroke	Complications	Residual Aneurysm or Complete Occlusion
Raymond et al. (2017) (88) (FIAT; NCT01349582)					
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)
Kiselev et al. (2018) (89)				**Total major complications**	**Complete occlusion at 12 months**
N	80			80	80
Flow diversion (95% CI), %	97.5[b]	NR by group	NR by group	5	65
Bypass treatment (95% CI), %	80[b]			22.5	97.5
Treatment effect (95% CI)	NR. p=0.029			NR; p=0.048	NR; p<0.01

CI: confidence interval; NR: not reported; SAE: serious adverse event; RCT: randomized controlled trial.
[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).
[b] The primary outcome was 'good' or 'acceptable' clinical outcome. It was variably defined as neurological deterioration and neurological morbidity defined as mRS score increase by more than 1 or mRS ≥ 4

Study limitations related to relevance and to design and conduct of trials of flow-diverting stents are shown below in Tables 14 and 15 respectively. FIAT was a pragmatic trial and as such, the population included both on- and off-label aneurysms, allowed multiple flow diverters and best standard therapy comparator as per clinical judgment.

Table 14. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Raymond et al. (2017) (88) (FIAT; NCT01349582)	1. Population included both on-label and off-label use and several anatomic locations	1. Multiple flow-diverters were allowed	1. Best standard therapy not clearly defined		2. Death and dependency reported at 3 months

Kiselev et al. (2018) (89)		1. Multiple flow-diverters were allowed		1: Key morbidity and mortality outcomes not reported by group	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment:
[a]: Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use;
[b]: Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest;
[c]: Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively;
[d]: Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported;
[e]: Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 15. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Raymond et al. (2017) (88) (FIAT; NCT01349582)		1, 2 Patients, staff, outcome assessors not blinded				
Kiselev et al. (2018) (89)	1: Only a subset of randomized patients included and matched using propensity scores	1, 2, 3: Blinding unclear	2: Outcome definitions unclear	1, 2: Only a subset of randomized patients included in analysis		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment:

[a]: Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias;
[b]: Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician;
[c]: Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication;
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e]: Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference;
[f]: Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p-values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Comparative Studies

Kan et al. (2022) evaluated the treatment of large and giant posterior communicating artery aneurysms with the Surpass streamfline flow diverter (SCENT trial). (92) The Surpass flow diverter was implanted in 180 patients with uncoilable or treatment failure internal carotid artery aneurysms. The 3-year safety and effectiveness outcomes were published by Hanel et al. (2022). (93) The primary effectiveness outcome in the 3-year follow-up data was the proportion of patients who had complete aneurysm occlusion without clinically significant stent stenosis or retreatment. The primary safety outcome was defined as either neurological death or disabling stroke (defined as an increase in the National Institutes of Health Stroke Scale [NIHSS] score ≥4). The primary effectiveness endpoint was met by 71.8% (79 out of 110) of patients; no patients in the 3-year follow-up cohort who achieved complete occlusion underwent retreatment. The primary safety composite outcome was reported in 12.2% (22 out of 180) of patients, and there were 4 cases of aneurysm rupture. The study characteristics are summarized in Table 16 and the results in Table 17.

Table 16. Summary of Nonrandomized Trial Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment 1	Treatment 2	Follow-up
Hanel et al. (2022) (93)	Cohort	USA and various European sites	2012 to 2015	Patients with large (10–24mm) or giant (≥25mm) wide-neck (≥4mm) unruptured or not acutely ruptured internal carotid artery aneurysms	Flow diversion utilizing the Surpass Streamline flow diverter	NA	3 years

N/A: not applicable; USA: United States of America.

Table 17. Summary of Nonrandomized Trials Study Results

Study	Complete aneurysm occlusion without stenosis[a] or retreatment	Composite of: disabling stroke[b] or neurological death
Hanel et al. (2022) (93) (SCENT)		
Total N	110	180
% of patients who met the endpoint (95% CI)	71.8% (62.4% to 80.0%)	12.2% (7.8% to 17.9%)

CI: confidence interval.

[a] Clinically significant in-stent stenosis defined as >50%.

[b]Disabling stroke defined as National Institutes of Health Stroke Scale score of ≥ 4.

Subsection Summary: Flow-Diverting Stents for Intracranial Aneurysms

Two RCTs 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 three 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.

SCAT compared flow diversion to parent vessel occlusion and bypass in patients with complex anterior circulation aneurysms. The publication included analysis of only 80 of the 111 randomized patients. Outcome definitions were unclear in the publication. Of the patients included in the analysis, 'good clinical outcome' was higher in the flow diversion group. Rates of overall morbidity and mortality were not reported by group. The rate of complete occlusion at 12 months was higher in the bypass group.

One systematic review, 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 there are high rates (≥70%) of aneurysmal occlusion after flow-diverting stent placement. One randomized study demonstrated adequate aneurysm occlusion with the Suprass flow diverter device. 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.

Idiopathic Intracranial Hypertension (IIH)

Raynald et al. (2022) published a prospective, single center, case-controlled study of 181 subjects comparing medical treatment (n=121 [69%]) to stenting (n=60 [33.1%]) with 1, 3, and 6-month follow-ups. (99) The two groups underwent 1:1 matching using propensity score analysis, and the clinical outcomes were compared. The patients received either stenting or medical treatment. Compared with the medical treatment group, the stenting group had a higher prevalence of visual disturbances (86.8% vs. 70%, p=0.007) and papilledema (89.3% vs. 63.3%, p<0.001). CSF pressure was higher in the stenting group than in the medical treatment group (311.7 mmH_2O vs. 282.3 mmH_2O, p=0.001). Additionally, the stenting group stenosis rate (75.5% vs. 70.9%, p=0.010) and pressure gradient (15.0 mmH_2O vs. 11.0 mmH_2O, p=0.001) was higher than in those receiving medical treatment. Subjects undergoing stenting had rapid signs of improvement in both their symptoms and papilledema compared to the control group. This matched-control study shows that stenting has a greater efficacy rate and rapid resolution of papilledema and its respective symptoms compared with medical treatment. Study limitations include prospective single center study and short term follow up of results.

Cappuzzo et al. (2018) conducted a retrospective chart review to report one group's experience with transverse sinus stenting in the treatment of IIH and assess its effectiveness. (100) Each patient's presenting signs and symptoms and whether those symptoms improved with treatment were reviewed. The average opening lumbar puncture (LP) pressure preprocedure, average pressure gradient across the obstructed segment prior to stenting, treatment failure rate (need for shunt placement), and mean follow-up period were calculated. The mean opening LP pressure preprocedure was 35.6 cm H2O (median 32 cm H2O). The mean pressure gradient measured proximally and distally to the area of focal obstruction within the transverse sinus was 16.5 cm H2O (median 15 cm H2O). Postprocedurally, 14 patients (77.8%) continued to have headaches; 6 (33.3%) continued to have visual disturbances. No patients continued to have auditory bruit (0%) or papilledema (0%). One patient (5.6%) had new-onset tinnitus postprocedure. Overall improvement of symptoms was noted in 16 patients (88.9%) postprocedure, with 1 patient (5.6%) requiring shunt placement and 2 other patients (11.1%) requiring postprocedural LP to monitor intracranial pressure to determine candidacy for further surgical interventions to treat residual symptoms. The mean duration of follow-up was 194.2 days. Transverse sinus stenting is a rapidly developing technique that has shown good effectiveness and safety in the literature. Authors of the present study found that stenting a flow-obstructed transverse sinus in patients with IIH was a safe and effective way to treat the condition. Further investigation, including a prospective trial of this condition with long-term follow-up, is necessary to further elucidate the effectiveness of this technique. This study is subject to the inherent limitations and biases of a retrospective analysis including recall bias and selection bias. Additionally, only those patients with focal and transverse sinus stenosis noted on diagnostic angiography and a clinical diagnosis of IIH were selected to undergo transverse sinus stenting.

Summary of Evidence

For individuals who have acute ischemic stroke due to occlusion of an anterior circulation vessel who receive endovascular mechanical embolectomy, the evidence includes randomized controlled trials (RCTs) comparing endovascular therapy with standard care and systematic

reviews of these RCTs. Relevant outcomes are overall survival (OS), 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 eight 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 post-treatment. 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 RCT. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related mortality and morbidity. The RCT was terminated early due to high crossovers and poor recruitment. There was not a statistically significant difference in the proportion of participants with a modified Rankin Scale of 0 to 3 at 90 days or in 90-day mortality rates in the endovascular and standard therapy groups. Additional RCTs are ongoing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have symptomatic intracranial arterial stenosis who receive intracranial percutaneous transluminal angioplasty with or without stenting, the evidence includes a systematic review and 2 major RCTs. Relevant outcomes are OS, 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 Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial was stopped early due to harms, because the rate of stroke or death at 30 days post-treatment 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 two RCTs does not suggest that intracranial percutaneous transluminal angioplasty with or without stenting improves outcomes for individuals with symptomatic intracranial stenosis. The evidence is sufficient to determine 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 RCTs, several nonrandomized comparative studies, and multiple single-arm studies. Relevant outcomes are OS, 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) I n 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 systematic review 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. One randomized study demonstrated adequate aneurysm occlusion with the Suprass flow diverter device. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have pseudotumor/idiopathic intracranial hypertension (IIH) who receive venous or sinus stenting the evidence includes a prospective singe center case-controlled study and a retrospective chart review. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related mortality and morbidity. The studies showed some improvement of subjects after stenting but stated further investigation, including larger, prospective trials with long-term follow-up, is necessary to further evaluate the effectiveness of this technique. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

Society of Vascular and Interventional Neurology (SVIN)

In 2016, the SVIN published recommendations on comprehensive stroke center requirements and endovascular stroke systems of care. (94) The recommendations were based on five multicenter, prospective, randomized, open-label, blinded endpoint clinical trials that demonstrated the benefits of endovascular therapy with mechanical thrombectomy in acute ischemic strokes with large vessel occlusions. Their recommendation is:

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

American Heart Association (AHA) and American Stroke Association (ASA)

In 2018, the AHA and the ASA (updated 2019) published joint guidelines on the early management of patients with acute ischemic stroke. (95, 96) These guidelines included several recommendations relevant to the use of endovascular therapies for acute stroke.

Table 18. Recommendations on Use of Endovascular Therapies to Manage Acute Stroke

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

"The use of proximal balloon guide catheter or a large bore distal access catheter rather than a cervical guide catheter alone in conjunction with stent retrievers may be beneficial. Future studies should examine which systems provide the highest recanalization rates with the lowest risk for nontarget embolization."	IIa	C-LD
In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable.	IIa	B-R
"In carefully selected patients with anterior circulation occlusion who have contraindications to IV r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable. There are inadequate data available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time-based or non-time based (e.g., prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications)."	IIa	C
"Although the benefits are uncertain, use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs."	IIb	B-R
"Although the benefits are uncertain, use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries."	IIb	C
"Although the benefits are uncertain, use of mechanical thrombectomy with stent retrievers may be reasonable for patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score of >1, ASPECTS <6, or NIHSS score <6 and causative occlusion of the internal carotid artery or proximal MCA (M1). Additional randomized trial data are needed."	IIb	B-R
In patients under consideration for mechanical thrombectomy, observation after IV alteplase to assess for clinical response should not be performed.	III	B-R
"Use of salvage technical adjuncts including intra-arterial fibrinolysis may be reasonable to achieve these angiographic results."	IIb	C-LD
"Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of intravenous alteplase might be considered, but the consequences are unknown."	IIb	C-EO

AIS: acute ischemic stroke; ASPECTS: Alberta Stroke Program Early Computed Tomography Score; COR: class of recommendation; DAWN: Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neuro-Intervention with Trevo Study; DEFUSE 3: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 Study; IV: intravenous; LOE: level of evidence; LVO: large vessel

occlusion; MCA: middle cerebral artery; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; r-tPA: recombinant tissue plasminogen activator; TICI: Thrombolysis in Cerebral Infarction.

The 2 associations (AHA and ASA) also published joint guidelines on the management of patients with unruptured intracranial aneurysms in 2015. (97) These guidelines included the following recommendations relevant to the use of endovascular therapies for aneurysms (Table 19).

Table 19. Recommendations on Management of Unruptured Intracranial Aneurysms

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

COR: class of recommendation:

- Strength of recommendation – I (strong), II (moderate), IIb (weak), III (no benefit or harm);

LOE: level of evidence.

- Quality of evidence – A (high-quality/meta-analysis RCTs), B-R (randomized); B-NR (non-randomized), C-LD (limited data), C-EO (expert opinion).

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 20.

Table 20. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Endovascular Interventions for Acute Ischemic Stroke			
Ongoing			
NCT03876457	SELECT 2: A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke	352	Dec 2023
NCT02737189	Randomized Trial of Revascularization with Solitaire "Stentriever" Versus Best Medical Therapy in the Treatment of Acute Ischemic Stroke Due to Basilar Artery Occlusion Presenting Within 6-24 Hours of Symptom Onset	217	Jun 2022 (active, not recruiting)
NCT04551664	Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive	456	May 2023

	Patients With a Large Infarct Core (ANGEL-ASPECT)		
NCT04167527	Endovascular Therapy for Low NIHSS Ischemic Strokes	200	Dec 2023
Endovascular Interventions for Symptomatic Intracranial Atherosclerotic Disease			
Ongoing			
NCT04631055	A Prospective, Multicenter, Randomized Controlled Clinical Trial to Evaluate the Efficacy and Safety of Intracranial Drug-coated Balloon Catheters in the Treatment of Symptomatic Intracranial Atherosclerotic do Novo Stenosis	180	Dec 2022 (recruiting)
Stent-Assisted Endovascular Treatment of Intracranial Aneurysms			
Ongoing			
NCT01340612	Stenting in the Treatment of Large, Wide-necked or Recurring Intracranial Aneurysms	600	Jan 2026
NCT02998229[a]	ARTISSE Aneurysm Treatment Using Intrasaccular Flow Diversion With the ARTISSE™ Device	150	Nov 2026
NCT04548856	Microsurgical Clipping and Endovascular Embolization Comparative Prospective Randomized Trial	4	May 2025
Unpublished			
NCT03494920	DIRECT-SAFE: A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval	295	Sep 2021
NCT0399340	Rescue Stenting for Failed Endovascular Thrombectomy in Acute Ischemic Stroke (ReSET)	78	Jul 2021
NCT01763320	China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A Prospective Multicenter, Randomized Controlled Trial	380	Nov 2019
NCT01811134	Flow Diverter Stent for Endovascular Treatment of Unruptured Saccular Wide-necked Intracranial Aneurysms (EVIDENCE)	91	Mar 2020
Idiopathic Intracranial Hypertension treatments			
NCT05050864	Stenting Versus Neurosurgical Treatment of Idiopathic Intracranial Hypertension	276	Mar 2027 (recruiting)

NCT: National Clinical Trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	61624, 61630, 61635, 61645, 61650, 61651, 75894
HCPCS Codes	C2623

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
01/15/2024	Document updated with literature review. The following change was made to coverage: Venous or sinus stenting for any indication, including but not limited to pseudotumor/intracranial hypertension (not atherosclerosis related) is considered experimental, investigational and/or unproven. References 27, 43, 57, 92-93 and 98-100 added; others updated, and some removed.
08/15/2022	Reviewed. No changes.
07/15/2021	Document updated with literature review. Coverage unchanged. References 1, 12, 13, 17, 33, 41, 48, 51, 55, 63, 74, 76, 77, 85, 87, 89, and 92 added; others removed.

09/15/2020	Reviewed. No changes.
01/15/2020	Document updated with literature review. Criteria changed for "Acute Ischemic Stroke": 1) added "evidence of substantial and clinically significant neurologic deficits" for neuroimaging; 2) changed to 12 hours or within 24 hours of symptom onset to perform intra-arterial mechanical embolectomy; and 3) added "evidence of salvageable brain tissue in the affected vascular territory (refer to NOTE 1)". The following changed for endovascular interventions to include an added example of "treatment of acute ischemic stroke" which is considered experimental, investigational and/or unproven. NOTEs renumbered with the addition of NOTEs 1 and 2. References 9, 16, 17, 21, 36-40, 46, 57, 86, 87, 105-108; numerous references were removed.
04/18/2018	Document reviewed. Coverage unchanged.
07/15/2017	Reviewed. No changes.
12/15/2016	Document updated with literature review. Coverage unchanged. The following was added to the Coverage section for informational purposes: NOTE 3: 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. The following was added to Description: The FDA approval of Trevo® ProVue and XP ProVue Retrievers as Class II devices, for patients experiencing ischemic stroke within 6 hours of symptom onset and following the administration of IV-tPA within 3 hours of symptom onset.
09/15/2016	Reviewed. No changes.
01/15/2016	Document updated with literature review. The following was changed in coverage for Acute Ischemic Stroke: 1) Endovascular mechanical embolectomy using a retrievable stent (e.g., Merci® Retriever, Penumbra System®, Solitaire™ Flow Restoration Device) or the Trevo® Retriever may be considered medically necessary in the treatment of acute ischemic stroke in patients with occlusion of the anterior circulation (e.g., middle cerebral artery or internal carotid artery) confirmed by a radiological image and a National Institute of Health Stroke Score (NIHSS) greater than or equal to 2; and 2) Endovascular interventions, such as intra-arterial mechanical embolectomy, thrombectomy, angioplasty or non-retrievable stenting, are considered experimental, investigational and/or unproven when the above criteria are not met. The following was added to coverage for Cerebral Aneurysms: Intracranial flow diverting stents with U.S. Food and Drug Administration (FDA) approval for the treatment of intracranial aneurysms may be considered medically necessary as part of the endovascular treatment of intracranial aneurysms that are not amenable to surgical treatment or standard endovascular therapy AND meet the following anatomic criteria: 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.
10/15/2014	Document updated with literature review. The following was added: Endovascular interventions (mechanical embolectomy, angioplasty, stenting) are considered experimental, investigational and/or unproven in the treatment of acute stroke. For all other indications, coverage remains unchanged. Title was changed from: Intracranial Stenting or Angioplasty. Rationale and Description substantially revised. CPT/HCPCS code(s) updated.
09/15/2012	New medical document. Intracranial stent placement may be considered medically necessary when specific criteria are met; otherwise intracranial stent placement is considered experimental, investigational and unproven. Intracranial percutaneous transluminal angioplasty, with or without stenting, is considered experimental, investigational and unproven. (Coverage changed for stenting, but unchanged for angioplasty. This topic was previously addressed on MED202.032 Stenting for Vascular Occlusive Disease.)