Medical Policy

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Title: Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

Description/Background

CEREBROVASCULAR DISEASES

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

Acute Stroke

Acute stroke is a leading cause of death in the United States; further, it is a leading cause of adult disability.[8] The risk of stroke among Black patients is nearly double the risk among White patients, and Black patients have a higher risk of death due to stroke than other racial groups. Eighty-seven percent of strokes are ischemic and 13% hemorrhagic. Differentiation between the two types of stroke is necessary to determine the appropriate treatment. Ischemic stroke occurs when an artery to the brain is blocked by a blood clot, which forms in the artery (thrombotic), or when another substance (i.e., plaque, fatty material) 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.[9]

Racial differences in the utilization of endovascular therapy for acute stroke have been reported. Sheriff et al (2022) analyzed the Get With The Guidelines-Stroke database; between 2015 and 2019, Black patients had lower odds of receiving endovascular therapy compared to non-Hispanic Whites (adjusted odds ratio [aOR], 0.83; 95% confidence interval [CI], 0.76 to

0.90).[10] At 3 months, functional independence as assessed by the modified Rankin Scale was less common among Black (aOR, 0.84; 95% CI, 0.75 to 0.95) and Asian (aOR, 0.79; 95% CI, 0.65 to 0.98) individuals compared to non-Hispanic Whites. de Havenon et al (2021) found that Black patients were less likely to receive endovascular therapy compared to White patients(odds ratio [OR], 0.75; 95% CI, 0.70 to 0.81) according to National Inpatient Sample data from 2016 to 2018.[11] Kim et al (2022) conducted a retrospective study of 40,814 acute ischemic strokes that occurred in Texas during 2019 which found that Black patients received endovascular therapy less frequently than White patients (4.1% vs. .3%, respectively; adjusted relative risk [aRR], 0.76; 95% CI, 0.66 to 0.88; p<.001) despite similar rates of hospital admission.[12] The rate of receipt of endovascular therapy was similar between White and Hispanic patients.

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 among the US population, with prevalence between 0.5% and 6% of the population.[13] However, they are associated with significant morbidity and mortality due to subarachnoid hemorrhage resulting from aneurysm rupture.

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 1 summarizes the first-generation devices with FDA clearance for the endovascular treatment of acute stroke and subsequent approval of stent retrievers.

Table 1. Food and Drug Administration-Cleared Mechanical Embolectomy Devices for Acute Stroke

Device	510(k) No. for Original Device	Approval Date for Original Device	Indications
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 Revascularization Devices (Rapid Medical, Ltd)	K203592	March 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 h of symptom onset
Stent retrievers			
Solitaire™ FR revascularization Device (Covidien/ev3 Neurovascular)	K113455	Mar 2012	Patients with acute ischemic stroke due to large intracranial vessel occlusion who are ineligible for or who fail IV tPA
Trevo® NXT ProVue Retriever (Stryker Neurovascular)	K210502	August 2021	Patients with acute ischemic stroke within 6 h 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

IV: intravenous; tPA: tissue plasminogen activator.

Intracranial Arterial Stenosis

Two devices were approved by FDA through the HDE process for atherosclerotic disease. This form of FDA approval is available for devices used to treat conditions with 4,000 or fewer incidents per year; FDA only requires data showing “probable safety and effectiveness.” Devices with their labeled indications are as follows.

Neurolink System®

“The Neurolink system [Guidant] is indicated for the treatment of patients with recurrent intracranial stroke attributable to atherosclerotic disease refractory to medical therapy in intracranial vessels ranging from 2.5 to 4.5 mm in diameter with ≥ 50% stenosis and that are accessible to the stent system.”

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

Intracranial Aneurysms
In 2011, the Pipeline® Embolization Device (Covidien/ eV3 Neurovascular, Irvine, CA), an intracranial aneurysm flow diverter, was approved by the FDA through the premarket approval process for the endovascular treatment of adults (≥22 years of age) with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments.[14] Approval was based on the Pipeline for Uncoilable for Failed Aneurysms Study, a single-arm, open-label feasibility study that included 108 patients, ages 30-75 years, with unruptured large and giant wide-necked aneurysms.[15]

In 2018, Surpass Streamline Flow Diverter (Stryker Neurovascular) was approved by the FDA through the premarket approval 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 one-year results of the Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide Neck Aneurysms (SCENT) study. The SCENT study is continuing follow-up up to five years post-procedure as a post-approval study.

The following stents have been approved by FDA through the HDE program 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 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 if "for use with neurovascular embolization coils in the anterior circulation of the neuro-vasculature for the endovascular treatment of patients greater or equal to 18 years of age with saccular wide-necked (neck 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 treatment of wide-neck, intracranial, saccular or fusiform aneurysms.

The Low-Profile Visualized Intraluminal Support Device
In July 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 or greater and 4.5 mm or smaller. In 2018, the LVIS™ and LVIS™ Jr. were approved through the PMA process (P17013).

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 greater than 2.

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Intracranial stent placement is considered established as part of the endovascular treatment of intracranial aneurysms for individuals when surgical treatment is not appropriate and standard endovascular techniques do not allow for complete isolation of the aneurysm, e.g., wide-neck aneurysm (≥4 mm) or sack-to-neck ratio less than 2:1.

Intracranial flow-diverting stents with U.S. Food and Drug Administration (FDA) approval for the treatment of intracranial aneurysms may be considered established as part of the endovascular treatment of intracranial aneurysms that meet anatomic criteria (see Inclusionary and Exclusionary Guidelines) and are not amenable to surgical treatment or standard endovascular therapy.

The use of endovascular mechanical embolectomy with a device with FDA approval for the treatment of acute ischemic stroke may be considered established as part of the treatment of acute ischemic stroke for patients who meet selection criteria (see Inclusionary and Exclusionary Guidelines).

Intracranial stent placement is considered **experimental/investigational** in the treatment of intracranial aneurysms when selection criteria are not met.

Intracranial percutaneous transluminal angioplasty with or without stenting is considered **experimental/investigational** in the treatment of atherosclerotic cerebrovascular disease.

Endovascular interventions are considered **experimental/investigational** for the treatment of acute ischemic stroke when selection criteria are not met.

Inclusionary and Exclusionary Guidelines

Inclusions

- Intracranial stent placement is considered established as part of the endovascular treatment of intracranial aneurysms for individuals when surgical treatment is not appropriate and standard endovascular techniques do not allow for complete isolation of the aneurysm, e.g., wide-neck aneurysm (≥4 mm) or a sack-to-neck ratio less than 2:1.

- Intracranial flow-diverting stents with U.S. Food and Drug Administration (FDA) approval for the treatment of intracranial aneurysms may be considered established as part of the endovascular treatment of large or giant wide-necked intracranial aneurysms, with a size of 10 mm or more and a neck diameter of 4 mm or more, in the internal carotid artery from the petrous to the superior hypophyseal segments and are not amenable to surgical treatment or standard endovascular therapy.

- The use of endovascular mechanical embolectomy with a device with FDA approval for the treatment of acute ischemic stroke may be considered established as part of the treatment of acute ischemic stroke for patients who meet all of the following criteria:
  - Have a demonstrated occlusion within the proximal intracranial anterior circulation (intracranial internal carotid artery, or M1 or M2 segments of the middle cerebral artery, or A1 or A2 segments of the anterior cerebral artery); AND
  - Can receive endovascular mechanical embolectomy within 12 hours of symptom onset OR within 24 hours of symptom onset if there is evidence of a mismatch between specific clinical and imaging criteria AND
  - Have evidence of substantial and clinically significant neurological deficits; AND
  - Have evidence of salvageable brain tissue in the affected vascular territory; AND
  - Have no evidence of intracranial hemorrhage or arterial dissection on computed tomography or magnetic resonance imaging.

Exclusions

- Intracranial stent placement in the treatment of intracranial aneurysms when the above inclusionary criteria are not met.
- Intracranial percutaneous transluminal angioplasty with or without stenting in the treatment of atherosclerotic cerebrovascular disease.
- Endovascular interventions for the treatment of acute ischemic stroke when the above inclusionary criteria are not met.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

61624 61635 61645

Other codes (investigational, not medically necessary, etc.):

61630

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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

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

ENDOVASCULAR INTERVENTIONS FOR ANTERIOR CIRCULATION ACUTE ISCHEMIC STROKES

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 review.

Populations
The relevant populations of interest are patients 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 alteplase.

Patients experiencing stroke symptoms may be seen in primary or emergency care. Most hospitals are able to treat acute ischemic stroke with intravenous alteplase; however, transfer to an 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 proximal to the occlusion. A helical snare is deployed, and the catheter and clot are withdrawn together. With the Penumbra device, an opening at the tip of the percutaneous catheter uses suction to extract the clot. Both the Solitaire Flow Restoration Device and the Trevo Retriever are retrievable stents, which are positioned to integrate the clot with the stent for removal with the stent's struts. The EmboTrap Revascularization Device (Neuravi Ltd.) was cleared with the Solitaire and Trevo as predicate devices.

This evidence review focuses on the devices listed above with an indication for endovascular embolectomy for acute stroke. Additional retrievable stent devices are under investigation, such as the Embolus Retriever with Interlinked Cages (ERIC; MicroVention).[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 evidence review.

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 randomized controlled trials and meta-analyses.[13] 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 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 line to the established intravenous tPA therapy.

Outcomes

The relevant outcomes in studies that evaluate acute ischemic stroke treatment include 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 (mRS), the National Institutes of Health Stroke Scale (NIHSS), the Barthel Index, or the Glasgow Outcome Scale.

The most commonly used instrument in studies is the mRS, a clinician-reported measure of global disability. The mRS 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 six, 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 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 mRS and mortality is evaluated at 90 days. Longer term mortality is also of interest.

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.

Review of Evidence

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

Badhiwala et al (2015) reported on results of a meta-analysis of RCTs evaluating mechanical embolectomy after acute ischemic stroke.[22] Eligible studies were RCTs comparing endovascular therapy with standard care, including the use of intravenous (IV) tissue plasminogen activator (tPA), in adult participants 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],[1] Goyal et al [2015],[3] Campbell et al [2015],[4] Saver et al [2015],[5] and Jovin et al [2015][2]), with a total of 2423 patients. Studies were assessed as having low risk of bias overall with the

Cochrane Collaboration's tool. In a meta-analysis, the use of endovascular intervention lead to proportional treatment benefit across mRS scores (odds ratio [OR], 1.56; 95% confidence interval [CI], 1.14 to 2.13; p=.005). Patients treated with endovascular intervention were more likely than standard care patients to have functional independence at 90 days (44.6% for endovascular treatment [95% CI, 36.6% to 52.8%]; 31.8% for standard treatment [95% CI, 24.6% to 40.0%]), with an associated absolute risk difference of 12.0% (95% CI, 3.8% to 20.3%; OR=1.71; 95% CI, 1.18 to 2.49; p=.005). However, there was significant heterogeneity ($I2$=75.4%) in the analysis of functional improvement outcomes. Reviewers conducted a number of sensitivity analyses around predictors of functional outcomes, and found that the following factors were associated with functional outcomes:

- Use of angiographic imaging confirming proximal arterial occlusion (OR=2.24; 95% CI, 1.72 to 2.9; p<.001 for interaction).
- Use of IV tPA and endovascular therapy (OR=2.07; 95% CI, 1.46 to 2.92; p=.018 for interaction).
- Use of stent retriever for mechanical thrombectomy (OR=2.39; 95% CI, 1.88 to 3.04; p<.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 review, Chen et al (2015) reported similar odds for 90-day functional independence as Badhiwala.[26]

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 use in subanalyses of RCTs, there has been some focus on the specific efficacy of stent retrievers for acute stroke

Bush et al (2016) conducted a meta-analysis of RCTs using predominantly stent retriever devices for acute stroke treatment.[28] Trials that compared endovascular therapy with stent retrievers with medical management (defined as IV tPA unless it was contraindicated) were included. However, it is not specified how the authors defined a threshold to determine whether stent retrievers were "predominantly" used. The analysis included 5 trials (Berkhemer et al [2015],[1] Goyal et al [2015],[3] Campbell et al [2015],[4] Saver et al [2015],[5] and Jovin et al [2015][2]) 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 an odds for more favorable mRS score of 2.2 (95% CI, 1.66 to 2.98; p<.001; I^2=46.38%). Similar to the findings

from the Badhiwala meta-analysis, there were no significant between-group differences in 90-day mortality rates or symptomatic intracranial hemorrhage rates.

Other related systematic reviews have reported similar results. [29,30,31,32,33]

Bai et al (2023) published a Cochrane review of RCTs that compared different types of endovascular therapy in the setting of acute ischemic stroke.[101] Four RCTs were considered, and the analysis was based on 2 trials that compared thromboaspiration with stent retrieval thrombectomy. The analysis found that modified Rankin scale scores at 3 months, all-cause mortality at 3 months, and rates of intracranial hemorrhage at 24 hours were similar with both types of endovascular therapy.

Zaidat et al (2023) conducted a systematic review and meta-analysis (MASTRO I) of 51 articles (5 RCTs, 7 registry studies, 39 cohort studies) that described outcomes with 3 stent retriever devices: EmboTrap, Solitaire, and Trevo.[102] Modified Rankin Scale scores of 0 to 2 at 90 days were significantly more common with EmboTrap (57.4%) than Trevo (50.0%; p=.013) and Solitaire (14.5%; p<.001). Mortality was higher with Solitaire (20.4%) compared to the other 2 devices (EmboTrap, 11.2% and Trevo, 14.5%; both p<.05). There was no statistical difference in mortality between EmboTrap and Trevo. Intracranial hemorrhage was also lower with EmboTrap (3.9%) and Trevo (4.6%) compared to Solitaire (7.7%; both p<.05). Rates of recanalization were similar between groups.

Randomized Controlled Trials

Endovascular Therapies vs Noninterventional Care

From 2012 to 2015, results from 8 large RCTs comparing endovascular therapies with standard of care for acute ischemic stroke were published. Several additional trials that began enrollment around 2013 and 2014 were stopped early after the publication of trials during 2014 and 2015. Therefore, the sample sizes in the trials published after 2015 are much smaller than originally designed and the power to detect clinically important differences is low. A high-level overview of the major RCTs follows, with a summary of results in Table 2. Subsequently in this section, select trials are described in more detail.

Fifteen RCTs with a total of 3,282 patients (range, 70-656 patients) compared endovascular mechanical embolectomy with standard care for acute ischemic stroke. In 2 studies, the population and intervention delivered were not consistent with the target population and intervention; the remaining 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 12 studies reporting on the populations and interventions of interest, all provide some information on the proportion of patients with 90-day mRS scores of 0, 1, or 2. Across the studies, the absolute difference between treatment and control groups in proportion of patients with 90-day functional independence ranged from 1.55% to 36%. Except 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 difference may be due to inadequate sample sizes. Among the studies published after 2015, most were stopped well before the original planned sample size because of benefit shown in earlier studies 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 Six to Eight Hours of Symptom Onset

Jovin et al (2015) reported on results of the Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (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.[2] 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 NIHSS score of at least 6 points NIHSS score range, 0-42; higher scores associated with greater deficit). Intravenous tPA was administered before randomization. Patients were excluded if that 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. 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 the groups did not differ significantly (68.0% in the mechanical embolectomy group, 77.7% in the control group). For the study's primary outcome, the OR for improvement in the distribution of the mRS score was 1.7 (95% CI, 1.05 to 2.8), favoring mechanical embolectomy. A greater proportion of patients in the mechanical embolectomy group was functionally independent (mRS score, 0-2; 43.7% vs 28.2% in the control group; absolute risk difference, 15.5%; adjusted OR=2.1; 95% CI, 1.1 to 4.0). There were no significant differences between the mechanical embolectomy and the control groups in 90-day mortality (18.4% vs 15.5%; p=.60) or 90-day rates of symptomatic intracranial hemorrhage (1.9% in each group; p=1.00).

Table 2. Summary of Randomized Controlled Trials of Endovascular Therapy vs Standard Care

Trial (Study)	Intervention		N	90-Day Modified Rankin Scale Score 0-2		Mortality		Symptomatic Intracranial Hemorrhage	
	Group	Treatment Description		Per Group Rate, %	Between-Group Difference (95% CI)	Per Group Rate, %	Between-Group Difference (95% CI)	Per Group Rate, %	Between-Group Difference (95% CI)
RESILIENT (Martins [2020])[34]	Intervention	Intrarterial thrombectomy and guideline-based care	111	35.1	OR=2.55 (1.34 to 4.88)	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	Guideline-based care alone	110	20		30		4.5	
DEFUSE 3 (Albers [2018])[7]	Intervention	Endovascular therapy + standard medical therapy[b]	92	45	OR=2.7 (1.6 to 4.5)	14	OR=0.55 (0.3 to 1.0)	7	OR=1.5 (0.4 to 6.6)
	Control	Standard medical therapy[b]	90	17		26		4	
DAWN (Nogueira [2018])[6]	Intervention	Endovascular therapy + standard care[b]	107	49	ARR=36% (24% to 47%)	19	ARR=1% (-10% to 11%)	6	ARR=3% (-3% to 8%)
	Control	Standard care[b]	99	13		18		3	

EASI (Khoury [2017])[35]	Intervention	Endovascular therapy + standard care (IV tPA if indicated)	40[a]	50	p=0.36	28	NR	7.5	NR
	Control	Standard care (IV tPA if indicated)	37[a]	38		24		5.7	
PISTE (Muir [2017])[36]	Intervention	Endovascular therapy + medical therapy with IV tPA	33[a]	51	OR=2.1 (0.7 to 6.9)	21	OR=1.6 (0.3 to 8.4)	0	
	Control	Medical therapy with IV tPA	32[a]	40		13		0	
THERAPY (Mocco [2016])[37]	Intervention	Aspiration thrombectomy (Penumbra) + IV tPA	55[a]	38	OR=1.4 (0.6 to 3.3)	12	OR=2.3 (0.8 to 6.8)	9.3	OR=1.0 (0.3 to 3.9)
	Control	IV tPA alone	53[a]	30		24		9.7	
THRACE (Bracard [2016])[38]	Intervention	Endovascular therapy + IV tPA	202	53	OR=1.6 (1.1 to 2.3)	12	OR=0.8 (0.5 to 1.2)	2	OR=1.4 (0.3 to 6.3)
	Control	IV tPA alone	200	42		13		2	
REVASCAT (Jovin [2015])[2]	Intervention	Solitaire stent retriever w/wo IV tPA	103	43.7	• ARR=15.5% • OR=2.1 (1.1 to 4.0)	18.4	p=0.60	1.9	p=*NS*

	Control	Medical therapy (IV tPA if indicated)	103	28.2		15.5		1.9	
EXTEND-IA (Campbell [2015])[4]	Intervention	Endovascular therapy + IV tPA	35	71	OR=3.8 (1.4 to 1.0)	20	OR=0.38 (0.1 to 1.6)	6	Risk difference, -6 (-13 to 2)
	Control	IV tPA alone	35	40		9		0	
ESCAPE (Goyal [2015])[3]	Intervention	Endovascular therapy w/wo IV tPA	165	53	RR=1.8 (1.4 to 2.4)	10.4	RR=0.5 (0.3 to 1.00)		
	Control	Medical therapy(IV tPA if indicated	150	29.3		19.05			
SWIFT-PRIME (Saver [2015])[5]	Intervention	Solitaire stent retriever + IV tPA	98	60	• ARR=25% • OR=1.70 (1.23 to 2.33)	9	RR=0.74 (0.33 to 1.68)	0	p=0.12
	Control	IV tPA alone	98	35		12		3	
MR CLEAN (Berkhemer [2015])[1]	Intervention	Intra-arterial therapy w/wo IV tPA	233	32.6	• ARR=13.5% • OR=2.05 (1.36 to 3.09)	18.9	p=*NS*	7.7	p=*NS*
	Control	Medical therapy (IV tPA if indicated)	267	19.1		18.4		6.4	

MR RESCUE (Kidwell [2013])[24]	Intervention	Mechanical embolectomy (MERCI or Penumbra) w/wo IV tPA	64	18.75	p=0.48	21	p=*NS*	4	p=*NS*
	Control	Medical therapy (IV tPA if indicated)	54	20.3		21		4	
SYNTHESIS Expansion (Ciccone [2013])[23]	Intervention	Intra-arterial therapy w/wo IV tPA	181	30.4	OR=0.71 (0.44 to 1.14)			6	p=*NS*
	Control	IV tPA alone	181	34.8				6	
IMS III (Broderick [2013])[25]	Intervention	Endovascular therapy + IV tPA	434	38.7	Adjusted difference: 1.5% (-6.1 to 9.1)	19.1	p=0.52	11.5	p=0.02
	Control	IV tPA alone	222	40.8		21.6		18.9	

ARR: absolute risk reduction; CI: confidence interval; IV: intravenous; OR: odds ratio; RR: relative risk; tPA: tissue plasminogen activator; w/wo: with/without; 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 Neuro-intervention 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.[4] This trial enrolled patients with ischemic stroke who were receiving IV tPA within 4.5 hours after stroke onset. Eligible patients had an occlusion of the internal carotid artery (ICA) or M1 or M2 segments of the middle cerebral artery (MCA) on computed tomography angiography (CTA) and were able to receive endovascular therapy within six hours of stroke onset, further patients were functionally independent prior to the stroke. Patients were evaluated prior to 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 an operator-independent postprocessing software. Enrollment was planned for 100 patients. The trial's data safety and monitoring board reviewed data for the first 70 enrolled patients after the results of the MR CLEAN trial were published and stopped EXTEND-IA for efficacy based on prespecified criteria. The first 70 patients were randomized to either IV tPA plus endovascular therapy with the Solitaire FR retrievable stent (n=35) or no further therapy (IV tPA only; n=35). The study used 2 coprimary end points: reperfusion (measured as the percentage reduction in perfusion-lesion volume between the initial imaging and imaging at 24 hours) and early neurologic improvement (defined as a reduction of ≥8 points on the NIHSS or a score of 0 or 1 at day 3).

The demographics of the randomized groups were similar at baseline. About 25% of clinically eligible patients were excluded on the basis of perfusion imaging criteria. In the endovascular group, 8 (22.9%) of 35 patients did not undergo mechanical embolectomy, most commonly because most of the thrombus was lysed before angiography (n=4). Endovascular therapy subjects had increased reperfusion at 24 hours, with a median reperfusion of 100% (percentage reduction in perfusion-lesion volume), compared with 37% for the tPA-only group (adjusted OR=4.7; 95% CI, 2.5 to 9.0; p<0.001). Of the endovascular therapy subjects, 28 (80%) of 35 had early neurologic improvement compared with 13 (37%) of 35 of the tPA-only subjects (adjusted OR=6.0; 95% CI, 2.0 to 18.0; p=0.002). Rates of reperfusion of at least 90% at 24 hours without symptomatic intracerebral hemorrhage were higher in endovascular therapy patients (89% vs 34%; adjusted OR=27.0; 95% CI, 5.5 to 135.0; p<0.001). Safety outcomes, including death, symptomatic intracerebral hemorrhage, and parenchymal hematoma, did not differ significantly between groups.

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.[3] 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 IA tPA, or guideline-based stroke care (n=150). Use of retrievable stents was recommended. Enrollment was planned for 316 subjects. The trial was stopped early on the

advice of its data safety monitoring board, after an unplanned interim analysis following publication of MR CLEAN trial results, because ESCAPE's prespecified efficacy boundary had been crossed.

Of the 165 patients randomized to the intervention group, 151 (91.5%) underwent endovascular therapy, most commonly with a retrievable stent (130/151 [86.1%] of those who underwent an endovascular procedure) and most often with the Solitaire stent (100/130 [77.0%] of those who received a retrievable stent). In the intervention group, 120 (72.7%) also received IV tPA. Of the 150 control group subjects, 118 (78.6%) received IV tPA. For the study's primary end point (90-day mRS score), the relative odds of improving 1 point on the mRS 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 mRS scores (median, 2 vs 4, respectively; p<0.001) and were more likely to have 90-day mRS scores of 0 to 2 (53% vs 29.3%; rate ratio, 1.8; 95% CI, 1.4 to 2.4; p<0.001). Ninety-day mortality was 10.4% among endovascular treatment group subjects and 19.0% in control group subjects (rate ratio, 0.5; 95% CI, 0.3 to 1.0; p=0.04).

Saver et al (2015) reported 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.[5] Eligible patients had moderate-to-severe neurologic deficits, imaging-confirmed occlusion of the intracranial ICA and/or the first segment of the MCA, were receiving or had received IV tPA, and were able to undergo endovascular treatment within six hours of symptom onset. In addition, eligible patients were required to have ischemic penumbral imaging analysis showing a small-to-moderate core infarct. For the first 71 patients enrolled, the infarct core size was defined based on CT perfusion imaging analyzed with an operator-independent postprocessing software. For the remainder of the study, infarct core size could be determined by CT perfusion imaging or non–contrast CT with a small-to-moderate core infarct based on ASPECTS. Patients were randomized to mechanical embolectomy with the Solitaire 2 or the Solitaire FR device (n=98) or to ongoing IV tPA (n=98). Enrollment was planned for a maximum of 833 subjects, but stopped at 196 subjects after an interim analysis, following publication of the results of the MR CLEAN and ESCAPE trials, showed that results met SWIFT PRIME's prespecified efficacy criteria.

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

Berkhermer et al (2015) reported initial results of the MR CLEAN trial, an open-label, blinded end point RCT with 500 subjects conducted at 16 centers in the Netherlands.[1] Eligible patients had 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 randomly assigned to standard stroke treatment (n=267 [53.4%]) or intra-arterial treatment (n=233 [46.6%]). Most patients in both groups (87.1% in the intervention group, 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 patients (7.3%) in the intervention group did not receive intra-arterial therapy, most commonly (n=8) due to clinical improvement before the start of the intervention. Among the 233 patients randomized to intra-arterial therapy, 195 (83.7%) received mechanical therapies, with retrievable stents used in 190 patients (81.5%) and other devices in 5 patients (2.1%) patients. Twenty-four patients (10.3%) received additional intra-arterial thrombolytic agents. Intra-arterial intervention was not performed after catheterization in 20 subjects for the following reasons: intracranial artery stenosis, occlusion, tortuosity, or dissection (n=10), no clot or targetable clot visible for intra-arterial therapy (n=8), or other technical problems (n=2).

For the study's primary outcome (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; favors 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 computed tomography (CT) angiography was available for 187 control subjects, of whom 141 (75.4%) had no intracranial occlusion compared with 68 (32.9%) of 207 control subjects with follow-up CTA available (unadjusted OR=6.27; 95% CI, 4.03 to 9.74). The 30-day mortality rate was 18.9% in the intervention group and 18.4% in the control group (p=*NS*). Rates of serious adverse events during the 90-day follow-up did not differ significantly between groups (p=0.31). Symptomatic intracerebral hemorrhage occurred in 7.7% of intervention subjects and 6.4% of control subjects, which was not a significant difference. However, intervention subjects were more likely to demonstrate a new ischemic stroke in different vascular territory (5.6% vs 0.4%; p<0.001).

Kidwell et al (2013) reported on the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (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 magnetic resonance imaging of the brain. Patients were randomly assigned to standard stroke treatment (n=54) or mechanical embolectomy (n=64) using the Merci Retriever or Penumbra System within 8 hours after presentation of symptoms. Eight patients in the embolectomy group also had tPA. The primary hypothesis of the study was that

patients with favorable penumbral patterns (at-risk area of viable ischemic cerebral tissue of ≤ 70% 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 receive endovascular therapy (n=181) or IV tPA (n=181).[23] Endovascular therapy consisted of intra-arterial tPA, mechanical embolectomy (using the Solitaire, Penumbra, Trevo Merci devices) or a combination of these treatments. Among the patients randomized to endovascular therapy, endovascular treatment was actually completed in 163 patients. In 109 patients, regional intra-arterial infusion of tPA and fragmentation of the thrombus with a micro guidewire were used. In 56 patients, a device was added; the most widely used devices were Solitaire FR in 18 patients, Penumbra in 9 patients, Trevo in 5 patients and Merci in 5 patients. No significant differences in 90-day survival without disability (mRS score range, 0-1) occurred between the endovascular therapy (30.4%) group and tPA group (34.8%; adjusted OR=0.71; 95% CI, 0.44 to 1.14; p=0.16). Within seven days, fatal or nonfatal symptomatic intracranial hemorrhage occurred in each group at a rate of 6%. Rates of other serious AEs also did not differ significantly between groups. While there were different treatment approaches in the endovascular group, these results suggest that endovascular therapy is not superior to tPA.

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

intracerebral hemorrhage. In a predefined subgroup analysis, the authors reported that for the subgroup of patients with ICA, M1, or basilar artery occlusion who received tPA within 120 minutes of stroke onset (n=124), the relative risk (RR) for 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.[39] This analysis included 200 subjects, 65 with intracranial ICA and 135 with M1 segments as the target vessel for revascularization. Of these, at angiography, 82% had an arterial occlusive lesion score of 2 to 3 and 76% had a modified TICI score of 2 to 3 and 76% had a modified TICI 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 a 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, the authors found no clear differences in clinical or revascularization outcomes across revascularization methods, which included standard microcatheter thrombolysis (n=51), the EKOS catheter (n=14), the Merci retriever (n=77), the Penumbra device (n=39), the Solitaire device (n=4), and other methods (n=15).

In another IMS III subgroup analysis, Demchuk et al (2014) evaluated the association between baseline CT or magnetic resonance angiography (MRA) findings and outcomes among 306 (47%) of 656 patients who had baseline CT or MRA imaging available.[40] Ninety-two percent of those with angiography available had arterial occlusions demonstrated, 220 of which were proximal occlusions. Endovascular therapy group subjects with proximal occlusions had higher 24-hour recanalization rates than those with IV tPA only (84.3% of endovascular therapy subjects vs 56% of controls; p<.001). However, no difference in the primary outcome (90-day mRS score, 0-2), was seen with proximal occlusions between groups (41.3% of endovascular therapy subjects vs 38% of controls; RR=1.07; 99% CI, 0.67 to 1.70).

Treatment Beyond Six 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 Neuro-intervention 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 the DEFUSE 3 trial, a multicenter, open-label trial 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.[7] DEFUSE 3 was conducted at 38 sites in the United States from May 2016 to May 2017. Patients were assigned to thrombectomy plus standard medical therapy (n=92) or to standard medical therapy alone (n=90). The median age was 70 years, half of the participants were

women, the median NIHSS score was 16, and 10% of the participants received IV tPA. Approximately 50% of the patients had a “wake-up” stroke. The trial was originally designed to enroll a maximum of 476 participants but was stopped early for efficacy. The proportion of patients who were functionally independent (score ≤2 on the modified Rankin scale) 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<.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=.75). The 90-day mortality rate was 14% in the thrombectomy group vs 26% in standard care (OR=0.55; 95% CI, 0.30 to 1.02; p=.05). The rate of serious adverse events was 43% and 53%, respectively (p=.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.[6] DAWN included patients who had last been known to be well 6 to 24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume. DAWN was conducted at 26 sites in the United States, Canada, Europe, and Australia from September 2014 through February 2017. Patients were assigned to thrombectomy plus standard care (n=107) or to standard care alone (n=99). Very few patients were treated with IV tPA since 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 (score ≤2 on the modified Rankin scale) 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=.50). The 90-day mortality rate was similar in the 2 groups (19% vs 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.[41]

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 DEFUSE3, 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).[42] 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.

Section Summary: RCTs Comparing Endovascular Therapies with Noninterventional Care

A number of RCTs have compared endovascular therapies with noninterventional care for acute stroke, with the 5 more recent (2014-2015) studies demonstrating a significant benefit associated with endovascular care. The more recently published trials addressed some of the limitations of previous studies. In the IMS III and SYNTHESIS Expansion trials, sizable proportions of the endovascular therapy groups did not receive an endovascular device. All 3 of the 2013 trials (Ciccone et al [2013],[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 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.[43] 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=.001). A follow-up analysis of complications of endovascular procedures using the SWIFT study data was published in 2014.[44] 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 the 144 of patients. Complication rates were similar for patients receiving the Solitaire FR and Merci devices, with the exception of symptomatic cerebral hemorrhage, which was significantly less common in the Solitaire FR group (10.9% vs 1.1%, p=.013).

In the Thrombectomy Revascularization of large Vessel Occlusions (TREVO 2) Study, 178 patients were randomized to receive mechanical embolectomy with either the Trevo Retriever or the Merci Retriever for large vessel occlusion strokes.[45] Revascularization rates were 86% in the Trevo group and 60% in the MERCI group (p<0.001). Procedure-related adverse events occurred in 15% of the Trevo group and 23% in the Merci group (p=0.183). Mortality rates at 90 days were 33% and 24% (p=0.18), respectively.

Saposnik et al (2015)[46] evaluated the benefit added by stent retrievers to IV tPA using pooled patient-level data from the SWIFT study [43] and the Solitaire FR Thrombectomy for Acute Revascularization (STAR) trial, a prospective, single-arm trial of the Solitaire device,[47] along with data from the National Institute for Neurological Disorders 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 used 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.[48] Eligible patients had large-vessel intracranial occlusion acute ischemic stroke with an NIHSS score of at least eight within eight hours of onset. The primary effectiveness outcome was the rate of a modified Thrombolysis in Cerebral Infarction (mTICI) grade 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 an mTICI grade 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 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.[49] 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=.5861). No serious adverse device effects were observed, with symptomatic intracerebral hemorrhage rates (1.5% vs. 7.2%; p=.1027), and the rates of serious adverse events (6% vs. 1.4%; p=.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=.0609), 90-day all-cause mortality (13% vs. 23%; p=.1848), or procedure duration (p=.5986).

Nogueira et al (2024) conducted a noninferiority RCT that compared the pRESET stent retriever to the Solitaire stent retriever in patients with large vessel occlusion strokes who were undergoing thrombectomy.[103] Patients were included within 8 hours of symptom onset. Of the 340 randomized patients, 90-day functional independence was achieved by 54.9% of the

pRESET group and 57.5% of the Solitaire group (absolute difference, -2.57%; 95% CI, -11.42 to 6.28). The pRESET group met the criteria for noninferiority. Rates of symptomatic intracranial hemorrhage and 90-day mortality were similar between groups.

Section Summary: Endovascular Interventions for Anterior Circulation Acute Ischemic Strokes
From 2013 to 2015, 8 published RCTs compared endovascular therapies with non-interventional 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 in terms of 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. In addition, 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 Basilar Artery Acute Ischemic Strokes

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 review.

Patients
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.[50]

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 EmboTrap Revascularization Device (Neuravi Ltd.) was cleared with the Solitaire and Trevo as predicate devices.

This evidence review focuses on the devices listed above with an indication for endovascular embolectomy for acute stroke. Additional retrievable stent devices are under investigation, such as the Embolus Retriever with Interlinked Cages (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.[13] 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 (modified Rankin Scale scores of 4 or 5, or death) in 68% of patients with basilar artery occlusion.[51]

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.

Review of Evidence

Systematic Reviews

Several systematic reviews have assessed the efficacy of endovascular therapy in patients with stroke due to basilar artery occlusion. Two similar meta-analyses included the 4 available RCTs (N=988, BEST, BASICS, ATTENTION, BAOCHE).55,56, In the analysis by Adusumilli et al (2023), the primary outcome of 90-day modified Rankin Scale scores of 0 to 3 was significantly higher with endovascular therapy (rate ratio, 1.54; 95% CI, 1.16 to 2.04; p=.002) compared to medical therapy.55, Mortality at 90 days was lower with endovascular therapy (rate ratio, 0.76; 95% CI, 0.65 to 0.90; p=.002) but rates of symptomatic intracranial hemorrhage were higher (rate ratio, 7.48; 95% CI, 2.27 to 24.61; p<.001) compared to medical therapy. The analysis by Yu et al (2023) reported 90-day modified Rankin Scale scores and 90-day mortality rates that favored endovascular treatment. The rate of symptomatic intracranial hemorrhage was also higher in the endovascular therapy group.[104]

Randomized Controlled Trials

Jovin et al (2022) conducted an RCT (Basilar Artery Occlusion Chinese Endovascular [BAOCHE]) that compared thrombectomy with the Solitaire device plus medical therapy to medical therapy alone in patients with basilar artery stroke who presented within 6 and 24 hours of symptom onset.[105] The trial was conducted at multiple certified stroke centers in China and had blinded outcome assessment. Thrombolysis was allowed if given within 4.5 hours. Characteristics of the study are shown in Table 3 and results are shown in Table 4. The primary outcome, modified Rankin Scale score of 0 to 3 at 90 days, occurred in 46% of the thrombectomy group and 24% of the medical therapy group (adjusted rate ratio, 1.81; 95% CI, 1.26 to 2.6; p<.001). Symptomatic intracranial hemorrhage was similar between groups. There was no significant difference in mortality rates of within 90 days.

Tao et al (2022) conducted an RCT (Endovascular Treatment for Acute Basilar-Artery Occlusion, ATTENTION) that compared endovascular therapy within 12 hours and best medical care in patients with basilar artery occlusion.[106] The primary outcome of good functional status at 90 days (defined as a modified Rankin Scale score of 0 to 3) occurred in 46% of the thrombectomy group and 23% of the best medical care group (rate ratio, 2.06; 95% CI, 1.46 to 2.91). Death within 90 days was lower in the thrombectomy group (37%) than the best medical care group (55%).

Langezaal et al (2021) conducted an RCT (Basilar Artery International Cooperation Study, BASICS) of endovascular therapy or standard medical care in 300 patients with stroke due to basilar artery occlusion.[107] Patients were included if they presented within 6 hours of symptom onset. Intravenous thrombolysis was used in most patients (almost 80% of both groups) and had to be started within 4.5 hours of symptom onset. The primary outcome (favorable function, defined as a modified Rankin Scale score of 0 to 3) occurred in 44.2% of the endovascular therapy group and 37.7% of the medical care group. Mortality at 90 days was similar between groups. Symptomatic intracranial hemorrhage was more common with endovascular therapy (4.5%) than with standard medical care (0.7%), but not significantly (p=.06).

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.[44] Patients had an acute ischaemic stroke consistent with acute occlusion of the basilar artery presenting within 8 hours of vertebrobasilar occlusion and a prestroke score of 0–2 on the mRS. The primary outcome was a mRS score of 3 or lower (indicating ability to walk unassisted) at 90 days. Patients in both groups meeting criteria for intravenous thrombolysis received intravenous 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 3 and results are shown in Table 4. In the ITT analysis, there was not a statistically significant difference in the proportion of participants with a mRS of 0–3 at 90 days (28 / 66 [42%] in the endovascular group vs 21 / 65 [32%] in the standard therapy group; adjusted odds ratio = 1.7, 95% CI, 0.8 to 3.7). The 90-day mortality rates were 33% vs 38% in the endovascular and standard therapy groups respectively (p=.54).

Table 3. Summary of RCT Characteristics of Endovascular Treatment of Basilar Artery Occlusion

Trial	Countries	Sites	Dates	Participants	Interventions	
Jovin et al 2022	China	NR	2016 to 2021	Patients aged 18 years or older; occlusion of the basilar artery or intracranial segments of both arteries that could be treated within 6 to 24 hours of symptom onset	n=110 thrombectomy plus medical therapy	n=107 medical therapy
Tao et al 2022	China	36	2021 to 2022	Patients aged 18 years or older; moderate to severe acute ischemic stroke consistent with basilar artery occlusion that could be treated within 6 to 24 hours of symptom onset	n=226 thrombectomy plus best medical care	n=114 best medical care
Langezaal et al 2021	Netherlands Brazil Germany France	23	2011 to 2019	Patients aged 18 years or older with basilar artery occlusion	n=154 endovascular therapy	n=146 standard medical care

	Italy Switzerland Czech Republic					
Liu 2020[52], BEST; NCT02441556	China	28	2015 to 2017	Patients ages 18 years or older; had an acute ischaemic 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; NR: not reported.

Table 4. Results of RCTs of Endovascular Therapy of Basilar Artery Occlusion

Trial (Study)	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)
Jovin et al 2022						
Thrombectomy plus medical therapy	46%	ARR=1.81 (1.26 to 2.60)	31%	Risk ratio=0.75 (0.54 to 1.04)	6%[a]	Risk ratio=5.18 (0.64 to 42.18)
Medical therapy	24%		42%		1%	
Tao et al 2022						
Thrombectomy plus best medical care	46%	Rate ratio=2.06 (1.46 to 2.91)	37%	Risk ratio=0.66 (0.52 to 0.82)	5%	Not assessed
Best medical care	23%		55%		0%	
Langezaal et al 2021						
Endovascular therapy	44.2%	Risk ratio=1.18 (0.92 to 1.50)	38.3%	Risk ratio=0.87 (0.68 to 1.12)	4.5%	Risk ratio=6.9 (0.9 to 53.0)
Standard medical care	37.7%		43.2%		0.7%	
Liu 2020[52]						
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	

ARR=adjusted rate ratio; CI: confidence interval; NA: not available; OR: odds ratio; RCT: randomized controlled trial.
[a] Per Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria

The purpose of the limitations tables (Tables 5 and 6) 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 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Jovin et al 2022	4: Chinese population		2: few patients received thrombolytic therapy, possibly due to financial constraints for patients		
Tao et al 2022	4: Chinese population		2: few patients received thrombolytic therapy, possibly due to financial constraints for patients		
Langezaal et al 2021	1: inclusion criteria	1: almost 30% of			

	changed due to low enrollment 4: no study centers in the U.S.	patients received treatment outside the trial			
Liu 2020[52]	4: Chinese population		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 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Jovin et al 2022		1: not blinded to treatment assignment				
Tao et al 2022		1: not blinded to treatment assignment				
Langezaal et al 2021		1: not blinded to treatment assignment				
Liu 2020[52]				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.

Section Summary: Endovascular Interventions for Stroke Due to Basilar Artery Occlusion

The evidence for the use of endovascular interventions for stroke due to basilar artery occlusions includes 4 RCTs and meta-analyses of these RCTs. Three of the RCTs were conducted in China and the other was multinational with no study sites in the United States, which limits applicability to the U.S. population. Results among these studies are inconsistent for functional outcomes and 90-day mortality as well as the use of concomitant medical therapies. Systematic reviews of both RCTs and observational studies support the efficacy of endovascular therapy for improving functional outcomes and reducing mortality, but rates of symptomatic intracranial hemorrhage are higher with endovascular therapy than with medical therapy.

ENDOVASCULAR INTERVENTIONS FOR SYMPTOMATIC INTRACRANIAL ATHEROSCLEROTIC DISEASE

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

Devices for treatment of intracranial stenosis received the FDA approval through the humanitarian device exemption (HDE) process. The Neurolink System was approved based on the Stenting of Symptomatic Atherosclerosis Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) trial, a prospective, nonrandomized, multicenter, international study of 61 patients.[14] The Wingspan Stent System was evaluated in a prospective study of 45 patients enrolled at 12 international centers.[53] 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 of the Wingspan device offered the following conclusions, and the FDA appears to have based its approval in part on the favorable comparison to the Neurolink device:

"…the probable benefit to health from using the Wingspan Stent System with Gateway PTA Balloon Catheter for treating transcranial stenosis outweighs the risk of illness or injury when used in accordance with the Instructions for Use and when taking into account the probable risks and benefits of currently available alternative forms of treatment."[14]

Comparators

Medical treatment typically includes either anticoagulant therapy (i.e., warfarin) or antiplatelet therapy (e.g., aspirin). The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial assessed the incidence of stroke brain hemorrhage or death among patients randomized to aspirin or warfarin.[54] 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.[55] Outcomes in both groups were similar, suggesting that the extracranial-intracranial bypass is ineffective in preventing cerebral ischemia. Due to inaccessibility, surgical options for the posterior circulation are even more limited.

Percutaneous transluminal angioplasty (PTA) has been approached cautiously for use in intracranial circulation, due to technical difficulties in the catheter and stent design and the risk of embolism, which may result in devastating complications if occurring in the posterior fossa or brain stem. However, improvement in the ability to track catheterization, allowing catheterization of tortuous vessels, and the increased use of stents have created ongoing interest in 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.

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.

Review of Evidence

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.[56] 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 7 and 8. 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[ie, 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 7. Systematic Review & Meta-analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Luo et al (2023) [56,]	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 8. 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 (2023)[56,]				
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.

Other meta-analyses support the Luo et al (2023) Cochrane review. Yeo et al (2024) conducted a patient-level meta-analysis of RCTs that compared stenting and best medical therapy for intracranial arterial stenosis.[108] Among the 7 included RCTs (N=1425), the risk of stroke or death within the first 30 days was higher with stenting than with best medical therapy (RR, 2.22; interquartile range, 1.28 to 3.86; I2=0%). Intracranial hemorrhage and death were significantly higher among patients who received a stent. Similarly, an analysis of 11 studies (N=1915) by Shi et al (2023) did not identify a benefit of endovascular therapy combined with medical therapy over medical therapy alone among patients with symptomatic intracranial

artery stenosis, but there was a suggestion of harm due to increased incidence of death or stroke, cerebral hemorrhage, and disabling stroke or death.[109]

Randomized Controlled Trials

Gao et al (2022) published the results of the CASSISS trial, which randomized 380 patients with stroke or transient ischemic attack due to severe intracranial stenosis (70% to 99%) to either stenting plus medical therapy or medical therapy alone.[110] The trial was conducted to determine whether more selective patient inclusion criteria or more experience among surgeons might overcome the lack of benefit or harm identified in prior RCTs. The study was conducted at 8 centers in China and patients were followed for 3 years. The primary outcome (a composite of stroke within 30 days, death within 30 days, or stroke in the qualifying artery territory between 30 days and 1 year) was similar in both groups (hazard ratio, 1.10; 95% CI, 0.52 to 2.35; p=.82). Mortality at 3 years was similar between groups (p=.08).

Zaidat et al (2015) published results of the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) trial, an RCT comparing a balloon-expandable stent plus medical management to medical management alone among patients with symptomatic intracranial stenosis of 70% or greater.[57] Eligible patients had stenosis of 70% to 99% of the internal carotid, middle cerebral, intracranial vertebral, or basilar arteries with a transient ischemic attack (TIA) or stroke attributable to the territory of the target lesion within the prior 30 days. Enrollment was planned for up to 250 participants. However, an early unplanned analysis was conducted by the trial sponsor after the results of the SAMMPRIS trial were published (see below). A total of 112 patients were enrolled from 2009 to 2012 and randomized to balloon-expandable stent (Vitesse stent) plus medical management (stent group; n=59) or medical management alone (medical group; n=53). Medical management included clopidogrel (75 mg daily) for the first 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 end point that included any stroke in the same territory as the presenting event within one year of randomization and “hard TIA” in the same territory as the presenting event from two days to one year after randomization. Among 29 patients who met one of the primary end points within 1 year of randomization, 8 patients (15.1%) were in the medical group and 21 (36.2%) were in the stent group (risk difference, 21.1%; 95% CI, 5.4% to 36.8%; p=.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=.05). The 30-day all-cause mortality rate was 5.2% and 0% in the stent and medical groups, respectively (risk difference, 5.2%; 95% CI, -0.5% to 10.9%; p=.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 a RCT comparing aggressive medical management alone with aggressive medical management plus stenting in patients who had symptomatic cerebrovascular disease and an intracranial stenosis of between 70% and 99%.[58] This trial used the Wingspan stent system implanted by experienced neuro-interventionalists who had been credentialed to participate in the trial. The authors planned to enroll approximately 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=.002) in the medical management group. At the time of trial termination, the mean follow-up was 11.9 months. Kaplan-Meier estimates of the primary outcome of stroke or death at 1 year was 20.5% (95% CI, 15.2 to 26.0) in the stenting group and 12.2% (95% CI, 8.4 to 17.6; p=.009) in the medical management group. These results represented an excess rate of early adverse events with stenting over what was expected together with a decreased rate of stroke and death in the medical management group compared with expected values.

The SAMMPRIS investigators, as reported by Derdeyn et al (2014), also published results from long-term subject follow-up.[59] Primary end points (in addition to stroke or death within 30 days of enrollment) included ischemic stroke in the qualifying artery beyond 30 days after enrollment or stroke or death within 30 days after a revascularization procedure of the qualifying lesion. During a median follow-up of 32.4 months, 34 (15%) of 227 patients in the best medical management group and 52 (23%) of 224 of patients in the stenting group had a primary end point event, with a significantly higher cumulative probability of a primary end point in the stenting group than in the best medical management group (p=.025). Compared with the best medical management group, subjects in the stenting group had higher rates of any stroke (59/224 [26%] vs 42/227 [19%], p=.047) and major hemorrhage (29/224 [13%] vs 10/227 [4%], p<.001). The authors concluded that the benefits of aggressive medical management over percutaneous angioplasty and stenting among patients with intracranial stenosis persist over long-term follow-up.

Lutsep et al (2015) published a subgroup analysis of the SAMMPRIS trial results to evaluate whether outcomes differed for patients whose qualifying events occurred on or off antithrombotic therapy.[60] 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=.043). In other subgroup analyses of the SAMMPRIS trial results, 2-year event rates were higher in the stent group for most variables evaluated.[61] The interaction between treatment and the subgroup variables was not significant for any variable.

The Carotid And Vertebral Artery Transluminal Angioplasty Study randomized 16 patients with symptomatic vertebral artery stenosis to endovascular therapy (balloon angioplasty or stenting) or best medical treatment alone.[62] Endovascular intervention was technically successful in all 8 patients, but 2 patients experienced transient ischemic attacks. During a mean follow-up of 4.7 years, no patient in either treatment group experienced a vertebrobasilar territory stroke, but three patients in each arm died of myocardial infarction or carotid territory stroke, and one patient in the endovascular arm had a nonfatal carotid territory stroke. The investigators concluded that patients with vertebral artery stenosis were more likely to have carotid territory stroke and MI during follow-up than have recurrent vertebrobasilar stroke. While they noted the trial failed to show a benefit of endovascular treatment of vertebral artery stenosis, the small number of patients enrolled severely limits conclusions.

Qureshi et al (2013) published results from another small RCT comparing angioplasty alone with angioplasty plus a balloon-expanding stent among 18 subjects with moderate intracranial stenosis (≥50%) with documented failure of medical treatment or severe stenosis (≥70%) with or without failure of medical treatment.[63] Technical success (<30% residual stenosis on immediate post procedure angiography) occurred in 5 of 10 patients treated with angiography (9 randomized to angiography, 1 crossover from the group randomized to stent placement) and 5 of 8 patients treated with stent placement. Rates of stroke or death were low in both groups: one of ten in the angiography group and none in the stent placement group. This study suggests that angioplasty with stenting is feasible in patients with severe intracranial stenosis, but the small size and lack of statistical comparisons limit conclusions that can be drawn.

Post market Surveillance
Alexander et al 2019 reported results from the Wingspan Stent System Post Market Surveillance (WEAVE) post marketing surveillance study.[64] WEAVE was an FDA mandated, prospective, single-arm study evaluating the rate of stroke and death within 72 hours post stenting in patients who met the FDA on-label usage criteria. 152 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, VISSIT, and CASSISS 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 and CASSISS RCTs 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 review.

Populations
The population of interest are patients 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 program for the endovascular treatment of 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 FDA premarket approval for the 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 states the primary safety outcomes for regulatory review have traditionally 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.[65] The FDA is considering an additional outcome 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 percentage 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.

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.

Review of Evidence

Randomized Controlled Trial
Darsaut et al (2023) conducted a pragmatic, unblinded RCT of surgical clipping compared to endovascular treatment in 291 patients with unruptured intracranial aneurysms.[111] Adults with modified Rankin Scale score <3 with at least 10 years of life expectancy were included. Patients with multiple aneurysms were evaluated based on one aneurysm. The composite primary outcome was failure of aneurysm occlusion, intracranial hemorrhage during follow-up, or residual aneurysms at 1 year. The primary outcome occurred in 9% of patients who received surgical clipping and 19% of patients who received endovascular therapy (relative risk, 2.07; 95% CI, 1.12 to 3.83; p=.021). However, surgery was associated with a higher rate of complications including neurologic deficits (p=.04) and hospitalization beyond 5 days (p<.001).

Self-Expanding Stent-Assisted Coiling for Intracranial Aneurysms
A literature search did not identify any randomized trials of self-expanding stent-assisted treatment of intracranial aneurysms compared with standard neurosurgical treatment (i.e., surgical clipping or endovascular coils). The available evidence consists of single-arm case series, registry studies, nonrandomized comparative studies, and a systematic review of nonrandomized comparative studies.

Systematic Reviews
Hong et al (2014) reported results of a systematic review and meta-analysis of studies that compared stent-assisted coiling with coiling alone for the treatment of intracranial aneurysms.[66] Reviewers included 10 retrospective cohort studies, ranging in size from 9 to 1109 patients. In a pooled analysis, compared with coiling alone, stent-assisted coiling was associated with higher rates of progressive thrombosis (37.5% vs 19.4%; OR=2.75; 95% CI, 1.95 to 3.86; p<.000) and lower rates of recurrence (16.2% vs 34.4%; OR=0.35; 95% CI, 0.25 to 0.49; p<.000). Mortality was 9.1% for stent-assisted coiling compared with 2.6% for coiling alone, although the difference was not statistically significant (OR=2.31; 95% CI, 0.68 to 7.82; p=.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.[67] They included 33 studies, 3 of which were prospective and the remaining 30 retrospective (N=1090 patients). In a pooled analysis, thromboembolic complications occurred in 108 patients (event rate, 11.2%; 95% CI, 9.2% to 13.6%). Intraprocedural hemorrhage occurred in 46 patients (event rate, 5.4%; 95% CI, 4.1% to 7.1%).

Randomized Controlled Trial

Boisseau et al (2023) published results of the Stenting in the Treatment of Aneurysm Trial (STAT), which was a multicenter RCT that compared stent-assisted coiling of unruptured intracranial aneurysms compared to coiling alone.[112] Study subjects (n=205) had a risk of aneurysm recurrence (e.g., large aneurysms [≥10 mm], postcoiling recurrent aneurysm, or small aneurysms with a wide neck [≥4 mm]). The primary outcome was treatment failure, which was a composite of initial failure to treat the aneurysm, aneurysm rupture, need for retreatment, dependency, death, or residual aneurysm seen on angiography at 12 months). The primary outcome occurred in 30.1% of patients who underwent stent-assisted coiling versus 27.3% of patients who underwent coiling alone (relative risk, 1.10; 95% CI, 0.7 to 1.7; p=.66). These results may be limited by Type 2 error, since the difference between groups was smaller than expected possibly due to the study being underpowered.

Nonrandomized Comparative Studies

The largest comparative series describing use of stents and coiling alone for treating intracranial aneurysms was described by Piotin et al (2010).[68] They reported on a series of 1137 patients (1325 aneurysms) treated between 2002 and 2009. In this series, 1109 aneurysms (83.5%) were treated without stents (coiling) and 216 (16.5%) were treated with stents (15 balloon-expandable and 201 self-expandable stents). Permanent neurologic procedure-related complications occurred in 7.4% (16/216) of those with stents vs 3.8% (42/1109) of those without stents (logistic regression p=0.644; OR=1.289; 95% CI, 0.439 to 3.779). Procedure-induced mortality occurred in 4.6% (10/216) of the procedures with stents versus 1.2% (13/1109) in those without (logistic regression p=.006; OR=0.116; 95% CI, 0.025 to 0.531). At the time of publication, the authors had followed 53% (114/216) of aneurysms treated with stents and 70% (774/1109) of aneurysms treated without, with angiographic recurrence in 14.9% (17/114) vs 33.5% (259/774), respectively (p<.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 to coiling alone, balloon-assisted coiling, or surgical clipping.

Hetts et al (2014) compared outcomes for patients treated with stent-assisted coiling and those treated with coiling alone for patients with unruptured intracranial aneurysms enrolled in the prospective, nonrandomized, multicenter Matrix and Platinum Science Trial.[69] The trial compared bare-metal aneurysm coils and polymer-coated aneurysm coils. One-hundred thirty-seven patients received a stent-assisted coil and 224 patients received coiling alone. Patients treated with stent-assisted coiling more often had wide-neck aneurysms (62% vs 33%; p<.000) and had aneurysms with lower dome-to-neck ratio (1.3 vs 1.8; p<.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=.039). At 1-year, ischemic strokes were more common in patients who received a stent-assisted coil than in patients who received a coil alone (8.8% vs 2.2%; p=.005). However, in multivariable analysis, stent use did not independently predict ischemic stroke at 2 years (adjusted OR=1.1; p=.94).

Consoli et al (2016) compared stent-assisted coiling with balloon-assisted coiling in patients with unruptured wide-necked intracranial aneurysms treated at a single center.[70] 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=.024) and complete occlusion after 6 months (regression coefficient not reported; p=.05).

Liu et al (2014) retrospectively compared outcomes for patients with posterior communicating artery aneurysms treated with stent-assisted coiling with those treated with coiling alone.[71] A total of 291 coiling procedures were performed, including 56 aneurysms treated with a self-expandable stent. Complete aneurysm occlusion on initial angiography occurred in 41.1% of stent-assisted coiling patients compared with 35.3% of non-stented patients (statistical comparison not reported). At last follow-up (mean, 14.3 months for stent-assisted coiling and 13.2 months for non-stent patients), aneurysms recurred in 10.6% of stent-assisted coiling patients compared with 28.1% of non-stent patients (p=.014). Procedural complications occurred in 10.7% of stent-assisted coiling patients compared with 11.5% of non-stent patients (p=*NS*).

Comparison Between Endovascular Devices for Intracranial Aneurysms

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.[72] 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 with the Enterprise system, patients treated with the Neuroform system were more likely to have deployment failure (2.3% vs 0.2%, p<.001) and have a higher mortality rate (2.8% vs 1.8%, p=.04), less likely to have 100% aneurysm occlusion at last follow-up (61.1% vs 74.7%, p<.001), and more likely to have recanalization (13.9% vs 10.6%, p=.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, Montmorency, France) stents.[73] Overall mortality was 1.9%; procedure-related complications occurred in 28 (6.9%) patients. Angiographic follow-up data, obtained at 6 months to 7 years post procedure (mean, 19.2 months), were available for 440 patients (94%). For the total of 467 aneurysms with follow-up, complete occlusion occurred in 194 aneurysms (41.6%), near-complete occlusion (>95% occlusion but minimal residual filling with coils at the neck) occurred in 242 (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 are associated with high rates of occlusion and low rates of recurrence over long-term follow-up.

In a larger study, Lee et al (2016) reported on 1038 patients treated with endovascular coiling, 296 of whom underwent stent-assisted coiling, with a focus on predictors of procedural rupture.[74] Three cases of procedural rupture occurred among patients treated with stent-assisted coiling.

Other representative noncomparative studies in which at least some patients were treated with devices commercially available in the United States are summarized in Table 7. Interpretation of these studies is limited by potential selection bias and lack of comparison group. In general, these series demonstrate high rates of technical success of stent deployment with high rates of aneurysm occlusion; however, variable complication rates, particularly related to thromboembolic events were observed.

Table 9. Noncomparative Studies of Stent-Assisted Endovascular Treatment of Aneurysms

Study	Study Type	Population	Intervention	Primary Outcome
ATLAS IDE study: Jankowitz et al (2019)[75] (30 patients enrolled through September 2015) FDA SSED[76] (201 patients enrolled through October 2016)	Prospective, multicenter (25 sites)	201 patients with widenecked intracranial aneurysm (neck ≥4 mm or dome-to-neck ratio <2), parent vessel diameter of 2.0–4.5 mm, the aneurysm is intracranial (encompassing the entire posterior circulation and aneurysms at or distal to the superior hypophyseal artery in the anterior circulation)	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 Any Major Ipsilateral Stroke or Neurologic Death: 4.4% (95% CI, 1.9, 8.5)
US LVIS pivotal trial	Prospective, multicenter (21 sites)	153 patients with unruptured or ruptured (>30 days since	LVIS devices	100% occlusion, without retreatment or significant

Fiorella et al (2018)[77] FDA SSED [78]		occurrence) widenecked (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		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)[79]	Retrospective case series	97 patients with intracranial saccular aneurysms (13 with rupture)	Endovascular treatment with LVIS	100% of patients had technically successful treatment 98.9% met the primary end point of safety (absence of new transient or permanent neurologic deficit or death) Over mean 7.8-mo FU, no patient had new neurologic deterioration or died Among 76 patients with DSA at FU, 59.21% had complete occlusion
Aydin et al (2015)[80]	Retrospective case series	80 patients with widenecked Intracranial aneurysm (3 institutions)	Endovascular treatment with stent placement (Leo Baby stent)	97.5% of patients had technically successful treatment 7.5% had periprocedural or delayed thromboembolic events; 3 (3.8%) had permanent neurologic deficits
Chalouhi et al (2013)[81]	Retrospective case series	76 patients with PCA aneurysms (1 institution)	Of 71 successful interventions: endovascular coiling (n=60) with or without Neuroform stent assistance (n=4) or balloon assistance (n=4), or parent vessel trapping (n=11)	93.4% of patients had technically successful treatment; remaining patients required surgical clipping Among 67 patients who had successful endovascular treatments and who did not die in the hospital, 85% favorable outcomes (mild, moderate, no disability)
Chen et al (2013)[82]	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), stentassisted	9 patients had good outcomes; 1 patient died after stenting procedure Stent deployment was generally feasible in the vertebrobasilar system

			coiling (3 patients), or occlusion of proximal artery (2 patients)	
Gentric et al (2013)[83]	Prospective cohort; industry-sponsored	107 patients with unruptured cerebral aneurysms (1 of 10 European institutions)	Endovascular treatment with Neuroform stentassisted coiling	94.4% of patients had technically successful treatment; 66.4% of patients had complete occlusion immediately postprocedure At 12- to 18-mo FU, 5 (5%) had delayed complications, with 3% having thromboembolic events Of 93 patients with anatomic evaluation available, aneurysms recurred in 9.7
Johnson et al (2013)[84]	Retrospective case series	91 patients with complex MCA aneurysms not amenable to coiling enrolled (1 institution)	Endovascular treatment with coiling with stent assistance using Neuroform (62 aneurysms), Enterprise (32 aneurysms), Wingspan (1 aneurysm), or a combination (5 aneurysms) or stenting alone (2 aneurysms)	100% of patients had technically successful treatment 9 patients had new neurologic symptoms after procedure, 1 with long-term disability. One procedure-related death. Of 85 aneurysms with initial FU imaging available (usually at 6 mo postprocedure), 77 (90.6%) were completely occludedand 4 (4.7%) required retreatment
Kulcsar et al (2013)[85]	Retrospective case series	117 patients with widenecked cerebral aneurysms	Endovascular treatment with Neuroform stentassisted coiling	Stents successfully deployed in 113 patients with 117 aneurysms 99 patients had grade 1 or 2 occlusion (complete or aneurysm neck) on immediate postprocedure imaging Intraprocedure major thrombotic events occurred in 7 (5.9%) and major infarcts on postprocedure imaging in 9 (7.7%) Of 92 aneurysms with FU imaging available, 71 (77%) had grade 1 or 2 occlusion

CI: confidence interval; DSA: digital subtraction angiography; FDA: Food and Drug Administration; FU: follow-up; LVIS: low-profile visualized intraluminal support; MCA: middle cerebral artery; mRS: modified Rankin Scale; PCA: posterior cerebellar artery; SSED: Summary of Safety and Effectiveness Data; 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 reported higher complete occlusion rates with stenting, and lower recurrence rates. However, some evidence shows that adverse event rates are relatively high with stenting, and 1 nonrandomized comparative trial reported higher mortality with stent-assisted coiling than with coiling alone. This evidence is insufficient to determine whether stent-assisted coiling improves outcomes for patients with intracranial aneurysms because the risk-benefit ratio cannot be adequately defined. However, it is recognized that patients who are candidates for endovascular therapy for aneurysms frequently have aneurysms in locations that are not amenable to surgical therapy, making comparisons to surgical therapy unlikely. Given the relative rarity of intracranial aneurysms, there may be legitimate barriers to clinical trials.

Flow-Diverting Stents for Intracranial Aneurysms

Pivotal Studies for FDA Approval

In 2011, the Pipeline Embolization Device, which is categorized as a flow-diverting stent, received FDA premarket approval. The device's approval was based on the industry-sponsored Pipeline for Uncoilable or Failed Aneurysms (PUFA) study, a multicenter, prospective, single-arm trial (2013) of the device for treatment of ICA aneurysms that were uncoilable or had failed coiling.[15] Investigators enrolled 108 patients at 10 centers with unruptured large- or giant-necked aneurysms measuring at least 10 mm in diameter, with aneurysm necks of at least 4 mm, who underwent placement of 1 or more Pipeline devices. One patient was excluded from evaluations of the device effectiveness and safety due to unsuccessful catheterization. Four patients were excluded from evaluation of the device effectiveness. Two patients had 2 qualifying aneurysms treated, so the "effectiveness cohort" was 106 aneurysms in 104 patients. Seventy-eight (73.6%) of 106 aneurysms met the study's combined primary effectiveness end point of complete occlusion at day 180 without major stenosis or use of adjunctive coils. For 6 (5.6%) of the 107 patients who underwent any catheterization, a primary safety end point (occurrence of major ipsilateral stroke or neurologic death at 180 days) occurred.

The Surpass Streamline Flow Diverter received 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.[13,86] 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 were 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 and neurological death

was 10.6% (19/180) and 2.8% (5/180), respectively. 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%) 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 (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 (N=863 subjects).[89] 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 pooled analysis, the use of flow- diverting devices was associated with a significantly higher complete occlusion rate compared with coil embolization therapy (OR=3.13; 95% CI, 2.11 to 4.65; I^2=18%) or with 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[90]. Results with respect to occlusion rate compared to coil embolization and mortality were similar.

Randomized Controlled Trials

No randomized trials evaluating intracranial aneurysms comparing flow-diverting stent treatment with standard neurosurgical treatment (i.e., surgical clipping or endovascular coils) from the time of FDA approval of the first flow-diverter until 2017.[87]

Raymond et al (2017) reported on results of the Flow Diversion in the Treatment of Intracranial Aneurysm Trial (FIAT).[87] FIAT was an investigator-initiated, pragmatic, multicenter RCT and registry study integrated in clinical practice in 3 Canadian hospitals enrolling 112 patients between May 2011, and February 2015. Seventy-eight patients were randomized (39 in each group) to either 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. The 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 study 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. The mean age was about 58 years, mean aneurysm size was approximately 16 mm in the RCT and 19 mm in the registry, 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. This 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 10. Results are shown in Table 11 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 (PVO) and bypass in patients with complex anterior circulation aneurysms conducted in 2 neurosurgical centers in Russia.[88] One hundred eleven patients were randomized; 55 into the flow diversion group and 56 into the PVO 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 who were 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 twelve months. The aneurysms were in the following segments: A2 segment of anterior cerebral artery (n=1), anterior communicating artery (n=3), cavernous carotid (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 bypass group and 15 mm (interquartile range, 9 to 20.5) in group of flow diversion. Study characteristics are shown in Table 8 and results are shown in Table 9. 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=.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=.001).

Table 10. Summary of RCT Characteristics of Flow-Diverting Stents for Intracranial Aneurysms

Trial	Countries	Sites	Dates	Participants	Interventions	
Raymond et al (2017)[87] (FIAT; NCT01349582)	Canada	3	2011 to 2015	Patients with an aneurysm for which flow diversion was considered a promising treatment (clinical judgment)	N=39 Arterial (not intraaneurysmal) flow-diverting device with or without coil embolization	N=39 Best standard treatment selected according to clinical judgment
Kiseleva et al (2018)[88] (SCAT; NCT03269942)	Russia	2	2015 to 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=55 Parent vessel occlusion and bypass

Table 11. Summary of Randomized Controlled Trial 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)[87] (FIAT)				Any SAE or Complication	Residual aneurysm
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)
Kiseleva et al (2018)[88]				Total major complications	Complete occlusion at 12 mon
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 (modified Rankin Scale score ≤2).
b The primary outcome was 'good' or 'acceptable' clinical outcome. It was variably defined as neurological deterioration and neurological morbidity defined as modified Rankin Scale score increase by more than 1 modified Rankin Scale or ≥ 4

Study limitations related to relevance and design and conduct of trials of flow-diverting stents are shown below in Tables 12 and 13 respectively. FIAT was a pragmatic trial and as such, the population included both on- and off-label aneurysms, allowed multiple flow divertors and best standard therapy comparator as per clinical judgment.

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Raymond et al (2017)[87] FIAT)	1. Population included both on label and off-label use and several anatomic locations	1. Multiple flow divertors were allowed	1. Best standard therapy not clearly defined		2. Death and dependency reported at 3 months
Kiseleva et al (2018)[88]		1. Multiple flow divertors Were allowed		1: Key morbidity and mortality outcomes not reported by group	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other. b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other. c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other. d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other. e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 13. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Raymond et al (2017)[87] (FIAT)		1,2: Patients, staff, outcome assessors not blinded				
Kiseleva et al (2018)[88]	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 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.

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).[98] 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).[99] 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-yearfollow-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 14 and the results in Table 15.

Table 14. Summary of Nonrandomized Trial Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment 1	Treatment 2	Follow-Up
Hanel et al (2022) (SCENT)	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	N/A	3 years

N/A: not applicable.

Table 15. 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) [92,] (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, the patients who were 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 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 that there are high rates (≥ 70%+) of aneurysmal occlusion after flow-diverting stent placement. One randomized study demonstrated adequate aneurysm occlusion with the Surpass 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.

SUMMARY OF EVIDENCE
For individuals who have acute ischemic stroke due to occlusion of an anterior circulation vessel who receive endovascular mechanical embolectomy, the evidence includes randomized clinical trials (RCTs) comparing endovascular therapy with standard care and systematic reviews of these RCTs. The 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 in terms of reduced disability at 90 days posttreatment. The trials that demonstrated a benefit to endovascular therapy either exclusively used stent retriever devices or allowed the treating physician to select a device, mostly a stent retriever device, and had high rates of mechanical embolectomy device use in patients randomized to endovascular therapy. Studies that demonstrated a benefit to endovascular therapy required demonstration

of a large-vessel, anterior circulation occlusion for enrollment. In addition, they were characterized by fast time-to-treatment. Two trials published in 2018 demonstrated that it was possible to extend the window for mechanical thrombectomy up to about 24 hours for select patients. To achieve results in real-world settings similar to those in the clinical trials, treatment times, clinical protocols, and patient selection criteria should be similar to those in the RCTs. The evidence is sufficient to determine that the technology results in an 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 4 RCTs and observational studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related mortality and morbidity. Results among these studies are inconsistent for functional outcomes and 90-day mortality. Systematic reviews of both RCTs and observational studies support the efficacy of endovascular therapy for improving functional outcomes and reducing mortality, but rates of symptomatic intracranial hemorrhage are higher with endovascular intervention than with medical therapy. The generalizability of the RCT results may be limited due to lack of inclusion of any U.S. populations. The evidence is insufficient to determine the effects of that the technology results in an improvement in the net health outcome.

For individuals who have symptomatic intracranial stenosis due to atherosclerosis who receive of intracranial percutaneous transluminal angioplasty with or without stenting, the evidence includes systematic reviews and 3 major RCTs. Relevant outcomes are overall survival (OS), symptoms, morbid events, functional outcomes, and treatment-related mortality and morbidity. All available RCTs demonstrated no significant benefit with endovascular therapy. In particular, the SAMMPRIS trial was stopped early due to harms, because the rate of stroke or death at 30 days posttreatment was higher in the endovascular arm, which received percutaneous angioplasty with stenting. Follow-up of the SAMMPRIS subjects has demonstrated no long-term benefit from endovascular therapy. Although some nonrandomized studies have suggested a benefit from endovascular therapy, the available evidence from two RCTs does not suggest that intracranial percutaneous transluminal angioplasty with or without stenting improves outcomes for individuals with symptomatic intracranial stenosis. The evidence is sufficient to determine qualitatively that the technology is unlikely to improve the net health outcome.

For individuals who have intracranial 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. The relevant outcomes are overall survival (OS), morbid events, functional outcomes, and treatment-related mortality and morbidity. The available nonrandomized comparative studies report occlusion rates for stent-assisted coiling that are similar to or higher than coiling alone and recurrence rates that may be lower than for coiling alone. For stent-assisted coiling with self-expanding stents, some evidence also shows that adverse event rates are relatively high, and 1 nonrandomized comparative trial reported that mortality is higher with stent-assisted coiling than with coiling alone. For placement of flow-diverting stents, a pragmatic RCT and registry study compared flow diversion with standard management (observation, coil

embolization, or parent vessel occlusion) in patients for whom flow diversion was considered a promising treatment. The pragmatic study was stopped early after crossing a predefined safety boundary when 16% of patients treated with flow diversion were dead or dependent at 3 months or later. Flow diversion was also not as effective as the investigators had hypothesized. A systematic review comparing the flow-diverting stents to endovascular coiling for intracranial aneurysms demonstrated higher rates of aneurysm obliteration in those treated with the Pipeline endovascular device than those treated with coiling, with similar rates of good clinical outcomes. 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 Surpass flow diverter device. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2014 Input

In response to requests, the Blue Cross Blue Shield Association received input from 4 physician specialty societies and 2 academic medical centers in 2014. Input focused on the use of flow-diverting stents such as the Pipeline Embolization Device for the treatment of intracranial aneurysms. There was general support for the use of intracranial stent placement for intracranial aneurysms meeting the criteria outlined in the policy statements. There was also general support for the use of flow-diverting stents for the treatment of intracranial aneurysms and general support for the statement that flow-diverting stents are preferable to other stents for certain aneurysm characteristics.

There was general support for the use of endovascular interventions for the treatment of acute stroke, particularly for patients who have failed to respond to intravenous tissue plasminogen activator (tPA) and patients who present outside the range of time for which tPA would be considered ($\leq$8 hours of last known normal state or symptom onset).

2011 Input

In response to requests, the Blue Cross Blue Shield Association received input from 3 physician specialty societies and 3 academic medical centers in 2011. For treatment of intracranial stenosis, most providing input would consider use of this technology in selected patients who remained symptomatic from intracranial atherosclerotic disease, despite maximum medical therapy. There was unanimous support for use of this technology in

selected patients with intracranial aneurysms; i.e., in those patients for whom surgical treatment is not possible and for whom endovascular treatment (coils) does not completely isolate the aneurysm.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Society of Vascular and Interventional Neurology

In 2016, the Society of Vascular and Interventional Neurology (2016) published recommendations on comprehensive stroke center requirements and endovascular stroke systems of care.[91] The recommendations were based on five multicenter, prospective, randomized, open-label, blinded end point clinical trials that demonstrated the benefits of endovascular therapy with mechanical thrombectomy in acute ischemic strokes with large vessel occlusions. Their recommendation pertinent to this evidence review is:

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

American Heart Association and American Stroke Association

In 2018, the American Heart Association and the American Stroke Association (update 2019) published joint guidelines for the early management of patients with acute ischemic stroke.[92,93] These guidelines include several recommendations relevant to the use of endovascular therapies for acute stroke.

Table 16. 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."	I IIb	A B-NR
"The use of proximal balloon guide catheter or a large bore distal access catheter rather than a cervical guide catheter alone in conjunction with stent retrievers may be beneficial. Future studies should examine which systems provide the highest recanalization rates with the lowest risk for nontarget embolization."	IIa	C-LD
In selected patients with acute ischemic stroke 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 intravenous r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable. There are inadequate data available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time-based or nontime based (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	~~C~~ 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

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

The AHA and ASA also published joint guidelines on the management of patients with unruptured intracranial aneurysms in 2015.[94] These guidelines included the following recommendations relevant to the use of endovascular therapies for aneurysms (see Table 13).

Table 17. 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; LOE: level of recommendation.

In 2022, the AHA and ASA released a scientific statement on endovascular treatment and thrombolysis for acute ischemic stroke in patients with premorbid disability ordementia.[100] The statement reports that several observational studies have evaluated the safety of endovascular therapy (including mechanical thrombectomy) in this patient population which suggests the potential of these patients to retain their pre-stroke level of disability; however, results also show a generally worse prognosis overall and more higher-quality registries and clinical trials are needed to validate results.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

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

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 18.

Table 18. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Endovascular interventions for acute ischemic stroke			
Ongoing			
NCT05983757	A Phase III, Randomized, Multicenter, Investigational, Open Label Clinical Trial That Will Examine Whether Treatment With Endovascular Thrombectomy is Superior to Standard Medical Therapy Alone in Patients Who Suffer a Distal Medium Vessel Occlusion Ischemic Strokes	564	Dec 2026
NCT06143488	Endovascular Therapy Versus Best Medical Treatment for Acute Large Vessel Occlusion Stroke With Low NIHSS	264	Sept 2025
NCT06101667	Efficacy and Safety of Endovascular Recanalization for Acute Basilar Artery Occlusion With Extended Time Window -- A Multicenter, Prospective, Open-label, Blind Endpoint, Randomized Controlled Trial (ANGEL-BAO）	224	Dec 2025
NCT06155032	Study of Rescue Endovascular Therapy for Progressive Acute Mild Ischemic Stroke With Large Vascular Occlusion--- A Multi-centered, Prospective, Open-label, Blind Endpoint, Randomized Controlled Trial (RESCUE END-LOW)	272	Mar 2026
NCT06146790	Evaluation of Endovascular Treatment in Acute Intracranial Distal Medium Vessel Occlusion Stroke - a Multicenter, Randomized Controlled, Clinical Trial	564	Mar 2026

NCT05827042	Endovascular Thrombectomy Alone Versus Intravenous Thrombolysis Plus Endovascular Thrombectomy on Acute Basilar Artery Occlusion - a Multicenter, Randomized Controlled, Clinical Trial	338	Mar 2026
NCT05911568	Treatment With Endovascular Intervention for Stroke Patients With Existing Disability	1060	Apr 2028
NCT06289985	STEP: StrokeNet Thrombectomy Endovascular Platform	2000	Sept 2028
NCT03876457	SELECT 2: A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke	352	Dec 2023 (active not recruiting)
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 Patients With a Large Infarct Core (ANGEL-ASPECT)	456	May 2023
NCT04167527	Endovascular Therapy for Low NIHSS Ischemic Strokes	200	Dec 2023
Endovascular interventions for symptomatic intracranial atherosclerotic disease			
Published			
NCT05757505	The Efficacy and Safety of the Intracranial Stent (Tonbridge) in Endovascular Treatment of Symptomatic Intracranial Atherosclerotic Stenosis: A Prospective, Multicenter, Randomized Controlled, Non-inferiority Trial	200	Dec 2025
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 de Novo Stenosis	180	Apr 2023
Stent-assisted endovascular treatment of intracranial aneurysms			

Ongoing			
NCT05755516	Efficacy and Safety of the Self-expanding Intracranial Stent (Tonbridge) for Endovascular Treatment of Intracranial Aneurysms: A Prospective, Multi-center, Randomized, Open, Parallel Positive Controlled, Non-inferiority Trial	204	Apr 2025
NCT06158087	Prospective, Multicenter, Single-arm Clinical Trial to Evaluate the Safety and Efficacy of pEGASUS Stent System for Assisted Endovascular Treatment of Intracranial Aneurysms	130	Jun 2026
NCT02998229[a]	ARTISSE Aneurysm Treatment Using Intrasaccular Flow Diversion With the ARTISSE™ Device	150	Nov 2024
NCT04548856	Microsurgical Clipping and Endovascular Embolization Comparative Prospective Randomized Trial	4	May 2025
Unpublished			
NCT01340612	Stenting in the Treatment of Large, Wide-necked or Recurring Intracranial Aneurysms	205	Apr 2023
NCT03494920	DIRECT-SAFE: A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval	295	Sep 2021
NCT03993340	Rescue Stenting for Failed Endovascular Thrombectomy in Acute Ischemic Stroke (ReSET)	78	July 2021

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Government Regulations
National:

CMS National Coverage Determination (NCD) for Percutaneous Transluminal Angioplasty (PTA) (20.7)
Implementation date 3/11/13

Indications and Limitations of Coverage
B. Nationally Covered Indications

*[Please refer to the NCD for all conditions and criteria. Indications related only to **intracranial arterial disease** (the focus of this policy) have been extracted from the NCD and are listed below.]*

The PTA is covered when used under the following conditions:

- Concurrent with Intracranial Stent Placement in FDA-Approved Category B IDE Clinical Trials
  Effective November 6, 2006, Medicare covers PTA and stenting of intracranial arteries for the treatment of cerebral artery stenosis ≥ 50% in patients with intracranial atherosclerotic disease when furnished in accordance with the FDA-approved protocols governing Category B IDE clinical trials. CMS determines that coverage of intracranial PTA and stenting is reasonable and necessary under these circumstances.

C. Nationally Non-Covered Indications
All other indications for PTA with or without stenting to treat obstructive lesions of the vertebral and cerebral arteries remain noncovered.
All other indications for PTA without stenting for which CMS has not specifically indicated coverage remain noncovered.

D. Other
Coverage of PTA with stenting not specifically addressed or discussed in this NCD is at local Medicare Administrative Contractor discretion.

Local:
N/A

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Extracranial Carotid Angioplasty Stenting
Endovascular Therapies for Extracranial Vertebral Artery Disease
Percutaneous Transluminal Angioplasty (PTA) for the Treatment of Cerebral Vasospasm

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References

1. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. Jan 01 2015; 372(1): 11-20. PMID 25517348
2. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. Jun 11 2015; 372(24): 2296-306. PMID 25882510
3. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. Mar 12 2015; 372(11): 1019-30. PMID25671798

4. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. Mar 12 2015; 372(11): 1009-18. PMID25671797
5. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. Jun 11 2015; 372(24): 2285-95. PMID 25882376
6. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med. Jan 04 2018; 378(1): 11-21.PMID 29129157
7. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med. Feb 22 2018; 378(8): 708-718. PMID29364767
8. U.S. Centers for Disease Control and Prevention. Stroke facts. May 25, 2021. https://www.cdc.gov/stroke/facts.htm. Accessed March 8, 2022.
9. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke. Mar 2007; 38(3): 967-73. PMID 17272772
10. Sheriff F, Xu H, Maud A, et al. Temporal Trends in Racial and Ethnic Disparities in Endovascular Therapy in Acute Ischemic Stroke. J Am Heart Assoc. Mar 15 2022; 11(6):e023212. PMID 35229659. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9075329/pdf/JAH3-11-e023212.pdf
11. de Havenon A, Sheth K, Johnston KC, et al. Acute Ischemic Stroke Interventions in the United States and Racial, Socioeconomic, and Geographic Disparities. Neurology. Dec07 2021; 97(23): e2292-e2303. PMID 34649872
12. Kim Y, Sharrief A, Kwak MJ, et al. Underutilization of Endovascular Therapy in Black Patients With Ischemic Stroke: An Analysis of State and Nationwide Cohorts. Stroke. Mar2022; 53(3): 855-863. PMID 35067099
13. Meyers PM, Schumacher HC, Higashida RT et al. Indications for the performance of intracranial endovascular neurointerventional procedures: a scientific statement from the American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Interdisciplinary Council on Peripheral Vascular Disease and Interdisciplinary Council on Quality of Care and Outcomes Research. Circulation 2009;119(16):2235-49.
14. FDA Summary of Safety and Effectiveness. 2011. Available online at http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100018b.pdf.
15. Becske T, Kallmes DF, Saatci I et al. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. Radiology 2013; 267(3):858-68.
16. Kahles T, Garcia-Esperon C, Zeller S, et al. Mechanical thrombectomy using the new ERIC Retrieval device is feasible, efficient, and safe in acute ischemic stroke: A Swiss stroke center experience. AJNR Am J Neuroradiol. Jan 2016;37(1):114-119. PMID 26294644
17. Vizient. Vascular technologies. Coronary, peripheral, and neurovascular devices. Technology watch. 2019. https://www.vizientinc.com/our-solutions/supply-chain-solutions/tech-watch. Accessed April 26, 2023.
18. Abruzzo T, Moran C, Blackham KA, et al. Invasive interventional management of post-hemorrhagic cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. J Neurointerv Surg. May 2012;4(3):169-177. PMID 22374130

19. Diringer MN, Bleck TP, Claude Hemphill J, 3rd, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. Sep 2011;15(2):211-240. PMID 21773873
20. Schwamm LH, Ali SF, Reeves MJ, et al. Temporal trends in patient characteristics and treatment with intravenous thrombolysis among acute ischemic stroke patients at Get With The Guidelines-Stroke hospitals. Circ Cardiovasc Qual Outcomes. Sep 1 2013;6(5):543-549. PMID 24046398
21. Bhatia R, Hill MD, Shobha N, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke. Oct 2010;41(10):2254-2258. PMID 20829513
22. Badhiwala JH, Nassiri F, Alhazzani W, et al. Endovascular thrombectomy for acute ischemic stroke: a meta-analysis. JAMA. Nov 3 2015;314(17):1832-1843. PMID 26529161
23. Ciccone A, Valvassori L, Nichelatti M, et al. Endovascular treatment for acute ischemic stroke. N Engl J Med. Mar 7 2013;368(10):904-913. PMID 23387822
24. Kidwell CS, Jahan R, Gornbein J, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med. Mar 7 2013;368(10):914-923. PMID 23394476
25. Broderick JP, Palesch YY, Demchuk AM et al. Endovascular therapy after intravenous t-PA versus t- PA alone for stroke. N Engl J Med 2013; 368(10):893-903.
26. Chen CJ, Ding D, Starke RM, et al. Endovascular vs medical management of acute ischemic stroke. Neurology. Dec 1 2015;85(22):1980-1990. PMID 26537058
27. Roaldsen MB, Jusufovic M, Berge E, et al. Endovascular thrombectomy and intra-arterial interventions for acute ischaemic stroke. Cochrane Database Syst Rev. Jun 14 2021; 6:CD007574. PMID 34125952
28. Bush CK, Kurimella D, Cross LJ, et al. Endovascular treatment with stent-retriever devices for acute ischemic stroke: a meta-analysis of randomized controlled trials. PLoS One. 2016;11(1):e0147287. PMID 26807742
29. Hong KS, Ko SB, Lee JS, et al. Endovascular recanalization therapy in acute ischemic stroke: updated meta-analysis of randomized controlled trials. J Stroke. Sep 2015;17(3):268-281. PMID 26437993
30. Kennedy SA, Baerlocher MO, Baerlocher F, et al. Meta-analysis of local endovascular therapy for acute ischemic stroke. J Vasc Interv Radiol. Mar 2016;27(3):307-321 e302. PMID 26803573
31. Grech R, Schembri M, Thornton J. Stent-based thrombectomy versus intravenous tissue plasminogen activator in acute ischaemic stroke: A systematic review and meta-analysis. Interv Neuroradiol. Dec 2015;21(6):684-690. PMID 26490828
32. Marmagkiolis K, Hakeem A, Cilingiroglu M, et al. Safety and efficacy of stent retrievers for the management of acute ischemic stroke: comprehensive review and meta-analysis. JACC Cardiovasc Interv. Nov 2015;8(13):1758-1765. PMID 26476611
33. Touma L, Filion KB, Sterling LH, et al. Stent retrievers for the treatment of acute ischemic stroke: a systematic review and meta-analysis of randomized clinical trials. JAMA Neurol. Mar 1 2016;73(3):275-281. PMID 26810499

34. Martins SO, Mont'Alverne F, Rebello LC, et al. Thrombectomy for Stroke in the Public Health Care System of Brazil. N Engl J Med. Jun 11 2020; 382(24): 2316-2326. PMID32521133
35. Khoury NN, Darsaut TE, Ghostine J, et al. Endovascular thrombectomy and medical therapy versus medical therapy alone in acute stroke: A randomized care trial. J Neuroradiol. Jun 2017;44(3):198-202. PMID 28238522
36. Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry. Jan 2017;88(1):38-44. PMID 27756804
37. Mocco J, Zaidat OO, von Kummer R, et al. Aspiration thrombectomy after intravenous alteplase versus intravenous alteplase alone. Stroke. Sep 2016;47(9):2331-2338. PMID 27486173
38. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol. Oct 2016;15(11):1138-1147. PMID 27567239
39. Tomsick TA, Yeatts SD, Liebeskind DS, et al. Endovascular revascularization results in IMS III: intracranial ICA and M1 occlusions. J Neurointerv Surg. Nov 2015;7(11):795-802. PMID 25342652
40. Demchuk AM, Goyal M, Yeatts SD, et al. Recanalization and clinical outcome of occlusion sites at baseline CT angiography in the Interventional Management of Stroke III trial. Radiology. Oct 2014;273(1):202-210. PMID 24895878
41. Tekle WG, Hassan AE, Jadhav AP, et al. Impact of Periprocedural and Technical Factors and Patient Characteristics on Revascularization and Outcome in the DAWN Trial. Stroke. Jan 2020; 51(1): 247-253. PMID 31744425
42. Jovin TG, Nogueira RG, Lansberg MG, et al. Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): a systematic review and individual patient data meta-analysis. Lancet. Jan 15 2022; 399(10321): 249-258. PMID 34774198
43. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet. Oct 6 2012;380(9849):1241-1249. PMID 22932715
44. Akins PT, Amar AP, Pakbaz RS, et al. Complications of endovascular treatment for acute stroke in the SWIFT Trial with Solitaire and Merci Devices. AJNR Am J Neuroradiol. Sep 12 2014;35(3):524-528. PMID 24029392
45. Nogueira RG, Lutsep HL, Gupta R, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet. Oct 6 2012;380(9849):1231-1240. PMID 22932714
46. Saposnik G, Lebovic G, Demchuk A, et al. Added benefit of stent retriever technology for acute ischemic stroke: a pooled analysis of the NINDS tPA, SWIFT, and STAR Trials. Neurosurgery. Sep 2015;77(3):454-461. PMID 26280825
47. Pereira VM, Gralla J, Davalos A, et al. Prospective, multicenter, single-arm study of mechanical thrombectomy using Solitaire Flow Restoration in acute ischemic stroke. Stroke. Oct 2013;44(10):2802-2807. PMID 23908066
48. Nogueira RG, Frei D, Kirmani JF, et al. Safety and efficacy of a 3-dimensional stent retriever with aspiration-based thrombectomy vs aspiration-based thrombectomy alone in

acute ischemic stroke intervention: a randomized clinical trial. JAMA Neurol. Mar 1 2018;75(3):304-311. PMID 29296999
49. Cao J, Lin H, Lin M, et al. RECO Flow Restoration Device Versus Solitaire FR With the Intention for Thrombectomy Study (REDIRECT): a prospective randomized controlled trial. J Neurosurg. Jun 05 2020; 134(5): 1569-1577. PMID 32502991
50. Mattle HP, Arnold M, Lindsberg PJ, et al. Basilar artery occlusion. Lancet Neurol. Nov 2011;10(11):1002-1014. PMID 22014435
51. Schonewille WJ, Wijman CAC, Michel P, et al. Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study. The Lancet Neurology. 2009;8(8):724-730.
52. Liu X, Dai Q, Ye R et al. Endovascular treatment versus standard medical treatment for vertebrobasilar artery occlusion (BEST): an open label, randomised controlled trial. Lancet Neurol. 2020 Feb;19(2). PMID 31831388
53. Bose A, Hartmann M, Henkes H et al. A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses: the Wingspan study. Stroke 2007; 38(5):1531-7.
54. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* Mar 31 2005;352(13):1305-1316. PMID 15800226
55. EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. *N Engl J Med.* Nov 7 1985;313(19):1191-1200. PMID 2865674
56. Luo J, Wang T, Yang K, et al. Endovascular therapy versus medical treatment for symptomatic intracranial artery stenosis. Cochrane Database Syst Rev. Feb 03 2023; 2(2): CD013267. PMID 36738471
57. Zaidat OO, Fitzsimmons BF, Woodward BK, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. JAMA. Mar 24-31 2015;313(12):1240-1248. PMID 25803346
58. Chimowitz MI, Lynn MJ, Derdeyn CP et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011; 365(11):993-1003.
59. Derdeyn CP, Chimowitz MI, Lynn MJ et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. Lancet 2013.
60. Lutsep HL, Barnwell SL, Larsen DT, et al. Outcome in patients previously on antithrombotic therapy in the SAMMPRIS trial: subgroup analysis. Stroke. Mar 2015;46(3):775-779. PMID 25593135
61. Lutsep HL, Lynn MJ, Cotsonis GA, et al. Does the stenting versus aggressive medical therapy trial support stenting for subgroups with intracranial stenosis? Stroke. Nov 2015;46(11):3282-3284. PMID 26382173
62. Coward LJ, McCabe DJ, Ederle J et al. Long-term outcome after angioplasty and stenting for symptomatic vertebral artery stenosis compared with medical treatment in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. Stroke 2007; 38(5):1526-30.

63. Qureshi AI, Chaudhry SA, Siddiq F, et al. A randomized trial comparing primary angioplasty versus stent placement for symptomatic intracranial stenosis. J Vasc Interv Neurol. Dec 2013;6(2):34-41. PMID 24358415
64. Alexander MJ, Zauner A, Chaloupka JC et al. WEAVE Trial: Final Results in 152 On-Label Patients. Stroke. 2019 Apr;50(4). PMID 31125298
65. Food and Drug Administration. FDA Executive Summary General Issues: Meeting to Discuss the Evaluation of Safety and Effectiveness of Endovascular Medical Devices Intended to Treat Intracranial Aneurysms. https://www.fda.gov/media/111329/download
66. Hong Y, Wang YJ, Deng Z, et al. Stent-assisted coiling versus coiling in treatment of intracranial aneurysm: a systematic review and meta-analysis. PLoS One. 2014;9(1):e82311. PMID 24454690
67. Ryu CW, Park S, Shin HS, et al. Complications in stent-assisted endovascular therapy of ruptured intracranial aneurysms and relevance to antiplatelet administration: a systematic review. AJNR Am J Neuroradiol. Jul 2 2015;36(9):1682-1688. PMID 26138136
68. Piotin M, Blanc R, Spelle L et al. Stent-assisted coiling of intracranial aneurysms: clinical and angiographic results in 216 consecutive aneurysms. Stroke 2010; 41(1):110-5.
69. Hetts SW, Turk A, English JD, et al. Stent-assisted coiling versus coiling alone in unruptured intracranial aneurysms in the matrix and platinum science trial: safety, efficacy, and mid-term outcomes. AJNR Am J Neuroradiol. Apr 2014;35(4):698-705. PMID 24184523
70. Consoli A, Vignoli C, Renieri L, et al. Assisted coiling of saccular wide-necked unruptured intracranial aneurysms: stent versus balloon. J Neurointerv Surg. Jan 2016;8(1):52-57. PMID 25428449
71. Liu YQ, Wang QJ, Zheng T, et al. Single-centre comparison of procedural complications, clinical outcome, and angiographic follow-up between coiling and stent-assisted coiling for posterior communicating artery aneurysms. J Clin Neurosci. Dec 2014;21(12):2140-2144. PMID 25037315
72. King B, Vaziri S, Singla A, et al. Clinical and angiographic outcomes after stent-assisted coiling of cerebral aneurysms with Enterprise and Neuroform stents: a comparative analysis of the literature. J Neurointerv Surg. Dec 2015;7(12):905-909. PMID 25352581
73. Geyik S, Yavuz K, Yurttutan N et al. Stent-assisted coiling in endovascular treatment of 500 consecutive cerebral aneurysms with long-term follow-up. AJNR Am J Neuroradiol 2013; 34(11):2157-62.
74. Lee KM, Jo KI, Jeon P, et al. Predictor and prognosis of procedural rupture during coil embolization for unruptured intracranial aneurysm. J Korean Neurosurg Soc. Jan 2016;59(1):6-10. PMID 26885280
75. Jankowitz BT, Hanel R, Jadhav AP et al. Neuroform Atlas Stent System for the treatment of intracranial aneurysm: primary results of the Atlas Humanitarian Device Exemption cohort. J Neurointerv Surg. 2019 Aug;11(8). PMID 30670625
76. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): Neuroform Atlas Stent System (P180031). 2019. https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180031B.pdf Accessed April 26, 2023

77. Fiorella D, Boulos A, Turk AS et al. The safety and effectiveness of the LVIS stent system for the treatment of wide-necked cerebral aneurysms: final results of the pivotal US LVIS trial. J Neurointerv Surg. 2019 Apr;11(4). PMID 30297543
78. Food and Drug Administration (FDA). SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED): Low-Profile Visualized Intraluminal Support (LVIS) and LVIS Jr (P170013). 2018. https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170013B.pdf Accessed April 26, 2023.
79. Feng Z, Fang Y, Xu Y, et al. The safety and efficacy of low profile visualized intraluminal support (LVIS) stents in assisting coil embolization of intracranial saccular aneurysms: a single center experience. J Neurointerv Surg. Nov 2016;8(11):1192-1196. PMID 26747876
80. Aydin K, Arat A, Sencer S, et al. Stent-assisted coiling of wide-neck intracranial aneurysms using low-profile LEO Baby Stents: initial and midterm results. AJNR Am J Neuroradiol. Oct 2015;36(10):1934-1941. PMID 26021624
81. Chalouhi N, Jabbour P, Starke RM et al. Endovascular treatment of proximal and distal posterior inferior cerebellar artery aneurysms. J Neurosurg 2013; 118(5):991-9.
82. Chen Z, Yang Y, Miao H et al. Endovascular treatment for large and giant fusiform aneurysms of the vertebrobasilar arteries. Clin Imaging 2013; 37(2):227-31.
83. Gentric JC, Biondi A, Piotin M et al. Safety and efficacy of neuroform for treatment of intracranial aneurysms: a prospective, consecutive, French multicentric study. AJNR Am J Neuroradiol 2013; 34(6):1203-8.
84. Johnson AK, Heiferman DM, Lopes DK. Stent-assisted embolization of 100 middle cerebral artery aneurysms. J Neurosurg 2013; 118(5):950-5
85. Kulcsar Z, Goricke SL, Gizewski ER et al. Neuroform stent-assisted treatment of intracranial aneurysms: long-term follow-up study of aneurysm recurrence and in-stent stenosis rates. Neuroradiology 2013; 55(4):459-65.
86. Food and Drug Administration. PMA P170024: Summary of Safety and Effectiveness (SSED). https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170024B.pdf Accessed April 26, 2023.
87. Raymond J, Gentric JC, Darsaut TE, et al. Flow diversion in the treatment of aneurysms: a randomized care trial and registry. J Neurosurg. Sep 2017;127(3):454-462. PMID 27813466
88. Kiselev R, Orlov K, Dubovoy A et al. Flow diversion versus parent artery occlusion with bypass in the treatment of complex intracranial aneurysms: Immediate and short-term outcomes of the randomized trial. Clin Neurol Neurosurg. 2018 Sep;172:183-189. PMID 3005
89. Zhou G, Zhu YQ, Su M, et al. Flow-diverting devices versus coil embolization for intracranial aneurysms: a systematic literature review and meta-analysis. World Neurosurg. Nov 14 2015. PMID 26585732
90. Xin WQ, Xin QQ, Yuan Y et al. Comparison of Flow Diversion and Coiling for the Treatment of Unruptured Intracranial Aneurysms. World Neurosurg. 2019 Aug;128:464-472. PMID 31132489
91. English JD, Yavagal DR, Gupta R, et al. Mechanical thrombectomy-ready comprehensive stroke center requirements and endovascular stroke systems of care: recommendations from the Endovascular Stroke Standards Committee of the Society

of Vascular and Interventional Neurology (SVIN). Interv Neurol. Mar 2016;4(3-4):138-150. PMID 27051410
92. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. Mar 2018;49(3):e46-e110. PMID 29367334
93. Powers WJ, Rabinstein AA, Ackerson T et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019 Dec;50(12). PMID 31662037
94. Thompson BG, Brown RD, Jr., Amin-Hanjani S, et al. Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. Aug 2015;46(8):2368-2400. PMID 26089327
95. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Percutaneous Transluminal Angioplasty (PTA) (20.7). Implementation Date 3/11/2013.
96. Vizient. Vascular technologies. Coronary, peripheral, and neurovascular devices. Technology watch. 2019. https://www.vizientinc.com/-media/documents/sitecorepublishingdocuments/public/vasculartechnologiestechwatch.pdf. Accessed April 26, 2023.
97. Wang T, Luo J, Wang X, et al. Endovascular therapy versus medical treatment for symptomatic intracranial artery stenosis. Cochrane Database Syst Rev. Aug 11 2020; 8: CD013267. PMID 32789891
98. Kan P, Mohanty A, Meyers PM, et al. Treatment of large and giant posterior communicating artery aneurysms with the Surpass streamline flow diverter: results from the SCENT trial. J Neurointerv Surg. May 12 2022. PMID 35551072
99. Hanel RA, Cortez GM, Coon AL, et al. Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide-Neck Aneurysms - SCENT: 3- year outcomes. J Neurointerv Surg. Nov 14 2022. PMID 36375835
100. Ganesh A, Fraser JF, Gordon Perue GL, et al. Endovascular Treatment and Thrombolysis for Acute Ischemic Stroke in Patients With Premorbid Disability or Dementia: A Scientific Statement From the American Heart Association/American Stroke Association. Stroke. May 2022; 53(5): e204-e217. PMID 35343235
101. Bai X, Zhang X, Gong H, et al. Different types of percutaneous endovascular interventions for acute ischemic stroke. Cochrane Database Syst Rev. May 30 2023; 5(5): CD014676. PMID 37249304
102. Zaidat OO, Ikeme S, Sheth SA, et al. MASTRO I: Meta-Analysis and Systematic Review of thrombectomy stent retriever outcomes: comparing functional, safety and recanalization outcomes between EmboTrap, Solitaire and Trevo in acute ischemic stroke. J Comp Eff Res. May 2023; 12(5): e230001. PMID 37039285
103. Nogueira RG, Lobsien D, Klisch J, et al. Thrombectomy With the pRESET vs Solitaire Stent Retrievers as First-Line Large Vessel Occlusion Stroke Treatment: A Randomized Clinical Trial. JAMA Neurol. Feb 01 2024; 81(2): 170-178. PMID 38165690

104. Yu Y, Lou Y, Cui R, et al. Endovascular treatment versus standard medical treatment for basilar artery occlusion: a meta-analysis of randomized controlled trials. J Neurosurg. Sep 01 2023; 139(3): 732-740. PMID 36738467
105. Jovin TG, Li C, Wu L, et al. Trial of Thrombectomy 6 to 24 Hours after Stroke Due to Basilar-Artery Occlusion. N Engl J Med. Oct 13 2022; 387(15): 1373-1384. PMID 36239645
106. Tao C, Nogueira RG, Zhu Y, et al. Trial of Endovascular Treatment of Acute Basilar-Artery Occlusion. N Engl J Med. Oct 13 2022; 387(15): 1361-1372. PMID 36239644
107. Langezaal LCM, van der Hoeven EJRJ, Mont'Alverne FJA, et al. Endovascular Therapy for Stroke Due to Basilar-Artery Occlusion. N Engl J Med. May 20 2021; 384(20): 1910-1920. PMID 34010530
108. Yeo JYP, Yau CE, Ong NY, et al. Comparing the Impact of Stenting vs. Medical Therapy for Intracranial Arterial Stenosis : A Systematic Review and One-stage and Two-stage Meta-Analysis of Randomized Clinical Trials. Clin Neuroradiol. Jan 03 2024. PMID 38172262
109. Shi T, Chen S, Long Y, et al. Safety and efficacy of stenting for symptomatic intracranial artery stenosis: a systematic review and meta-analysis. Front Pharmacol. 2023; 14: 1122842. PMID 37361212
110. Gao P, Wang T, Wang D, et al. Effect of Stenting Plus Medical Therapy vs Medical Therapy Alone on Risk of Stroke and Death in Patients With Symptomatic Intracranial Stenosis: The CASSISS Randomized Clinical Trial. JAMA. Aug 09 2022; 328(6): 534-542. PMID 35943472
111. Darsaut TE, Findlay JM, Bojanowski MW, et al. A Pragmatic Randomized Trial Comparing Surgical Clipping and Endovascular Treatment of Unruptured Intracranial Aneurysms. AJNR Am J Neuroradiol. Jun 2023; 44(6): 634-640. PMID 37169541
112. Boisseau W, Darsaut TE, Fahed R, et al. Stent-Assisted Coiling in the Treatment of Unruptured Intracranial Aneurysms: A Randomized Clinical Trial. AJNR Am J Neuroradiol. Apr 2023; 44(4): 381-389. PMID 36927759

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through April 8, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
4/16/03	4/16/03	4/1/03	Joint policy established
3/19/04	3/19/04	3/26/04	Maintenance review
6/15/05	6/15/05	5/19/05	Routine maintenance
1/1/07	11/1/06	11/19/06	Routine maintenance
5/1/07	3/1/07	5/1/07	New codes and indications added
1/1/08	10/16/07	11/11/07	Routine maintenance
3/1/09	12/21/08	12/21/08	Routine maintenance
5/1/12	2/21/12	2/21/12	Status on policy updated to established, title changed from "Percutaneous Transluminal Angioplasty for Cerebral Vascular Disease" to "Endovascular Procedures for Intracranial Arterial Disease"
5/1/14	2/28/14	3/3/14	Routine maintenance. Added the following to the medical policy statement: "Endovascular interventions (mechanical embolectomy, angioplasty, stenting) are considered experimental/ investigational in the treatment of acute stroke." Description, rationale and references updated. Added procedure codes 37184-37185 and 61624.
3/1/16	12/10/15	12/10/15	Routine maintenance Added (Atherosclerosis and Aneurysms) to title Mechanical embolectomy for acute stroke and intracranial flow diverting stents for aneurysms updated to established for patients meeting policy criteria.

11/1/16	8/16/16	8/16/16	Routine maintenance Removed codes 37184, 37185 Added codes 61645, 61650, 61651 – effective 1/1/16 Moved code 61630 from established to E/I – effective 1/1/17 Updated Description/Background, Rationale & References
11/1/17	8/15/17	8/15/17	Routine maintenance
9/1/18	6/19/18	6/19/18	Routine maintenance
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance CPT 61650, 61651 removed from policy, not appropriate
9/1/21	6/15/21		Routine maintenance, references added. Policy statements unchanged.
9/1/22	6/21/22		Routine maintenance
9/1/23	6/13/23		Routine maintenance Vendor: N/A (ky)
9/1/24	6/11/24		Routine maintenance Vendor: N/A (ky)

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ENDOVASCULAR PROCEDURES FOR INTRACRANIAL ARTERIAL DISEASE (ATHEROSCLEROSIS AND ANEURYSMS)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; refer to medical policy criteria.
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.