Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

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I. Description

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

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

For individuals who have symptomatic intracranial arterial stenosis who receive intracranial percutaneous transluminal angioplasty with or without stenting, the evidence includes 2 RCTs and a number of nonrandomized comparative studies and case series. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, and treatment-related mortality and morbidity. Both available RCTs have demonstrated no significant benefit with endovascular therapy. In particular, the SAMMPRIS trial was stopped early due to harms, because the rate of stroke or death at 30 days posttreatment was higher in the endovascular arm, which received percutaneous angioplasty with stenting. Follow-up of SAMMPRIS subjects has demonstrated no long-term benefit from endovascular therapy. Although some nonrandomized studies have suggested a benefit from endovascular therapy, the available evidence from 2 RCTs does not suggest that intracranial percutaneous transluminal angioplasty with or without stenting improves outcomes for individuals with symptomatic intracranial stenosis. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who have intracranial aneurysm(s) who receive endovascular coiling with intracranial stent placement or intracranial placement of a flow-diverting stent, the evidence includes an RCT, several nonrandomized comparative studies, and multiple single-arm studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related mortality and morbidity. The available nonrandomized comparative studies have reported occlusion rates for stent-assisted coiling that are similar to or higher than coiling alone and recurrence rates that may be lower than those for coiling alone. For stent-assisted coiling with self-expanding stents, some evidence has also shown that adverse event rates are relatively high, and a nonrandomized comparative trial has reported that mortality is higher with stent-assisted coiling than with coiling alone. For placement of flow-diverting stents, a pragmatic RCT and registry study have compared flow diversion with standard management (observation, coil embolization, or parent vessel occlusion) in patients for whom flow diversion was considered a promising treatment. The pragmatic study was stopped early after crossing a predefined safety boundary when 16% of patients treated with flow diversion were dead or dependent at 3 months or later. Flow diversion was also not as effective as the investigators had hypothesized. A nonrandomized study comparing the flow-diverting stents with endovascular coiling for intracranial aneurysmsms has demonstrated higher rates of aneurysm obliteration in those treated with the Pipeline endovascular device than those treated with coiling, with similar rates of good clinical outcomes. The evidence does not provide high certainty whether stent-assisted coiling or placement of a flow-diverting stent improves outcomes for patients with intracranial aneurysms because the risk-benefit ratio cannot be adequately defined. The evidence is insufficient to determine the effects of the technology on health outcomes.
Clinical input obtained in 2011 indicated strong support for the use of stent-assisted coiling for the treatment of aneurysms that are not amenable to surgery or simple coiling. Clinical input obtained in 2014 indicated general support for the use of flow-diverting stents for certain types of aneurysms when surgical treatment is not appropriate.

**Background**

Cerebrovascular diseases include a range of processes affecting the cerebral vascular system, including arterial thromboembolism, arterial stenosis, and arterial aneurysms, all of which can lead to restrictions in cerebral blood flow due to ischemia or hemorrhage. Endovascular techniques, including endovascular pharmacologic thrombolysis, endovascular mechanical embolectomy; using one of several types of devices, endovascular deployment of several types of stents, and angioplasty with or without stenting have been investigated for treatment of cerebrovascular diseases.

**Acute Stroke**

Acute stroke is the third leading cause of death in the United States, Canada, Europe, and Japan and is the leading cause of adult disability in the United States. Eighty-seven percent of strokes are ischemic and 13% hemorrhagic. Differentiation between the 2 types of stroke is necessary to determine the appropriate treatment. Ischemic stroke occurs when an artery to the brain is blocked by a blood clot, which forms in the artery (thrombotic), or when another substance (i.e., plaque, fatty material) or a blood clot travels to an artery in the brain causing a blockage (embolism). Recanalization of the vessel, particularly in the first few hours after occlusion, reduces rates of disability and death.

The prompt use of intravenous (IV) thrombolytic therapy with recombinant tissue plasminogen activator (tPA) to recanalize occluded blood vessels has been associated with improved outcomes in multiple randomized controlled trials (RCTs) and meta-analyses. Therefore, use of IV tPA in ischemic stroke patients presenting within 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 to 2011, fewer than 10% of all ischemic stroke patients arrived at the hospital and received IV tPA within the 3-hour window.
- **Risks associated with IV tPA therapy.** tPA is associated with increased risk of intracranial bleeding. It is contraindicated in hemorrhagic stroke and in some ischemic stroke patients for whom the risk of bleeding outweighs the potential benefit, such as those with mild or resolving symptoms, hypocoagulable state, or advanced age.
- **Variable recanalization rates.** For patients receiving tPA, recanalization rates are around 21% and range from about 4% in the distal internal carotid artery and basilar artery to
about 32% in the middle cerebral artery. The treatment of large-vessel strokes with IV tPA may be less successful.

Researchers have studied intra-arterial tPA, transcranial ultrasound energy, and mechanical clot destruction or clot removal as alternatives or second lines, to the established intravenous tPA therapy.

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

- **Intra-arterial fibrinolytic therapy (ie, intra-arterial tPA).** Although tPA only has approval from the U.S. Food and Drug Administration (FDA) for its intravenous route of delivery, intra-arterial tPA has been considered for patients who fail to present within the window of treatment for intravenous tPA or who have failed to show benefit from intravenous tPA. It is also frequently used in conjunction with other endovascular devices.

- **Acute angioplasty and/or stent deployment.** Balloon angioplasty and balloon-expandable stents have been investigated for acute stroke. Given concern for higher risks of complications in the cerebral vasculature with the use of balloon-expandable stents, self-expanding stents have gained more attention. At present, no balloon- or self-expandable stent has FDA approval for treatment of acute stroke.

- **Endovascular mechanical embolectomy.** Endovascular embolectomy devices remove or disrupt clots by a number of mechanisms. Four devices are considered here (see Regulatory Status section): the Merci® Retriever, Penumbra System®, Solitaire™ Flow Restoration Device, and the Trevo® Retriever. With the Merci® device, a microcatheter is passed through the thrombus from a larger, percutaneous catheter positioned proximal to the occlusion. A helical snare is deployed, and the catheter and clot are withdrawn together. With the Penumbra® device, an opening at the tip of the percutaneous catheter uses suction to extract the clot. Both the Solitaire Flow Restoration Device and the Trevo Retriever are retrievable stents, which are positioned to integrate the clot with the stent for removal with the stent’s struts.

This evidence review focuses on the devices listed above with an indication for endovascular embolectomy for acute stroke.

An additional clinical situation in which endovascular therapies may be used in the treatment of acute ischemic stroke is in the setting of cerebral vasospasm following intracranial (subarachnoid) hemorrhage. Delayed cerebral ischemia (DCI) occurs about 3 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. The mechanism of disease, patient population, and time course of therapy differ for DCI occurring after subarachnoid hemorrhage compared with ischemic stroke due to atheroembolic disease. Therefore, this indication for endovascular intervention will not be addressed in this evidence review.

**Intracranial Atherosclerotic Disease**

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

**Treatment**

Medical treatment typically includes either anticoagulant therapy (i.e., warfarin) or antiplatelet therapy (e.g., aspirin). The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial compared the incidence of stroke brain hemorrhage or death among patients randomized to receive aspirin or warfarin. The trial found that over a mean 1.8 years of follow-up, warfarin provided no benefit over aspirin and was associated with a significantly higher rate of complications. In addition, if symptoms could be attributed to low-flow ischemia, agents to increase mean arterial blood pressure and avoidance of orthostatic hypotension may be recommended. However, medical therapy has been considered less than optimal. For example, in patients with persistent symptoms despite antithrombotic therapy, the subsequent rate of stroke or death has been extremely high, estimated in one study at 45%, with recurrent events occurring within 1 month of the initial event. Surgical approaches have met with limited success. The widely quoted extracranial-intracranial (EC/IC) bypass study randomized 1377 patients with symptomatic atherosclerosis of the internal carotid or middle cerebral arteries to medical care or EC/IC bypass. Outcomes in the 2 groups were similar, suggesting that the EC/IC bypass is ineffective in preventing cerebral ischemia. Due to inaccessibility, surgical options for the posterior circulation are even more limited.

Percutaneous transluminal angioplasty (PTA) has been approached cautiously for use in intracranial circulation, due to technical difficulties in catheter and stent design and the risk of embolism, which may result in devastating complications if occurring in the posterior fossa or brain stem. However, improvement in the ability to track catheterization, allowing catheterization of tortuous vessels, and the increased use of stents have created ongoing interest in exploring PTA as a minimally invasive treatment of this difficult-to-treat population. The majority of published studies of intracranial PTA have focused on the vertebrobasilar circulation. Two endovascular devices have FDA approval for treatment of symptomatic intracranial stenosis and are considered here (see Regulatory Status section).

**Intracranial Aneurysms**

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

**Treatment**

Surgical clipping of intracranial aneurysms has been used since the 1960s, but the feasibility of clipping for aneurysms depends on the aneurysm location. Intracranial stents are also being used to
treat cerebral aneurysms. Stent-assisted coiling began as an approach to treat fusiform or wide-neck aneurysms in which other surgical or endovascular treatment strategies may not be feasible. As experience has grown, stenting has also been used in smaller berry aneurysms as an approach to decrease the rate of retreatment needed in patients who receive coiling. A randomized trial has demonstrated that treatment of ruptured intracranial aneurysms with coiling leads to improved short-term outcome compared with surgical clipping; however, patients who receive coiling need more repeat or follow-up procedures. In 2011, the Pipeline Embolization Device, which falls into a new device category called “intracranial aneurysm flow diverters,” or flow-diverting stents, received FDA premarket approval for endovascular treatment of large or giant wide-necked intracranial aneurysms in the internal carotid artery. The Pipeline device is a braided, wire mesh device that is placed within the parent artery of an aneurysm to redirect blood flow away from the aneurysm, with the goal of preventing aneurysm rupture and possibly decreasing aneurysm size.

**Regulatory status**

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

**Acute Stroke**

**The Merci® Retriever.** In August 2004, the Merci® Retriever (Concentric Medical, Mountain View, CA) was cleared for marketing by FDA through the 510(k) process. This device was judged equivalent to a predicate device, the Concentric Retriever, which was indicated for endovascular foreign body removal. FDA clearance indicated that the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Clinical Study established that no new issues of safety or effectiveness exist when the Merci Retriever is used for thrombus removal versus foreign body removal from the neurovasculature. In May 2006, a modified Merci Retriever, also manufactured by Concentric Medical, was cleared for marketing by FDA through the 510(k) process. The clearance notes that the Modified Merci Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke. Patients who are ineligible for intravenous tPA or who fail intravenous tPA therapy are candidates for treatment. The device also has clearance for retrieval of foreign bodies misplaced during interventional radiologic procedures in the neuro-, peripheral, and coronary vasculature.

**The Penumbra System®.** In December 2007, the Penumbra System® (Penumbra, Alameda, CA) was cleared for marketing by FDA through the 510(k) process. FDA determined that this device was substantially equivalent to existing devices for use in the revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease (in the internal carotid, middle cerebral [M1 and M2] segments, basilar, and vertebral arteries) within 8 hours of symptom onset.

**The Solitaire™ FR device.** In March 2012, the Solitaire™ FR device (Covidien/ev3 Neurovascular, Irvine, CA) was cleared for marketing by FDA through the 510(k) process. FDA determined that this device was substantially equivalent to the Merci Retriever device, based on an RCT, of 113 patients, submitted to FDA comparing the Merci and Solitaire devices. Indications for the device are patients with ischemic stroke due to large intracranial vessel occlusion who are ineligible for intravenous tPA, or who fail intravenous tPA.
The Trevo Pro Retriever™ device. In August 2012, the Trevo Pro Retriever™ device (Stryker Neurovascular, Kalamazoo, MI) was cleared for marketing by FDA through the 510(k) process. FDA determined that this device was substantially equivalent to the Merci Retriever device, based on an RCT of 178 patients from 27 centers in the United States and Europe that compared the Trevo device with the Merci device. Indications for the device are patients with acute ischemic stroke due to large intracranial vessel occlusion who are ineligible for or fail intravenous tPA. Later versions of the Trevo® Retriever are called the Modified Trevo® Retriever, the Trevo® ProVue Retriever, and the Modified Trevo® ProVue Retriever; the name Trevo Retriever is used throughout this review. In February 2018, the FDA expanded the indication for the Trevo Retriever to include patients experiencing acute ischemic stroke up to 24 hours from symptom onset. FDA product code: NRY.

A summary of the devices with FDA clearance for the endovascular treatment of acute stroke is provided in Table 1.

### Table 1. FDA-Cleared Mechanical Embolectomy Devices for Acute Stroke

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

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

### Intracranial 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 an incidence of 4000 or less per year; FDA only requires data showing “probable safety and effectiveness.” Devices with their labeled indications are as follows:

**Neurolink System® (Guidant, Santa Clara, CA).** “The Neurolink system is indicated for the treatment of patients with recurrent intracranial stroke attributable to atherosclerotic disease refractory to medical therapy in intracranial vessels ranging from 2.5 to 4.5 mm in diameter with ≥50% stenosis and that are accessible to the stent system.”

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

### Intracranial Aneurysms

In 2011, the Pipeline® Embolization Device (Covidien/ev3 Neurovascular, Irvine, CA), an intracranial aneurysm flow diverter, was approved by FDA though 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 (P100018). 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 to 75 years with unruptured large and giant wide-necked aneurysms.

Three 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, Kalamazoo, MI) was approved by FDA through the HDE process for use with embolic coils for treatment of wide-neck intracranial aneurysms that cannot be treated by surgical clipping (H020002).

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

**The Low-Profile Visualized Intraluminal Support Device.** In July 2014, the Low-Profile Visualized Intraluminal Support Device (LVIS™ and LVIS™ Jr.) (MicroVention, Tustin, CA) was approved by FDA through the HDE process (H130005) for use with embolic coils for the treatment of unruptured, wide neck (neck, ≥4 mm or dome to neck ratio, <2), intracranial, saccular aneurysms arising from a parent vessel with a diameter of 2.5 mm or greater and 4.5 mm or smaller.

**Patient Selection for Endovascular Mechanical Embolectomy for Acute Ischemic Stroke**

The major randomized controlled trials (RCTs) demonstrating a benefit to with endovascular mechanical embolectomy varied in criteria for selecting patients based on the presence/absence of salvageable brain tissue. Several RCTs use the Alberta Stroke Program Early Computed Tomography Score (ASPECTS), which is a 10-point quantitative topographic computed tomography (CT) score to assess the presence of early ischemic changes. MR CLEAN (Berkhemer et al, 2015) did not specify imaging criteria to demonstrate salvageable brain tissue. The following criteria were used by other trials:

- **REVASCAT** (Jovin et al, 2015). *Exclusion* criteria were as follows: Hypodensity on CT or restricted diffusion demonstrated by:
  - An ASPECTS of less than 7 on CT, CT perfusion cerebral blood volume (CBV), computed tomography angiography (CTA) source imaging; OR
  - An ASPECTS score of less than 6 on diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI).
- **ESCAPE** (Goyal et al, 2015). *Exclusion* criteria were as follows:
  - Baseline non-contrast CT with extensive early ischemic changes of ASPECTS 0 to 5 in the territory of symptomatic intracranial occlusion; OR
  - Other confirmation of a moderate-to-large core defined 1 of 3 ways:
    - On a single phase, multiphase or dynamic CTA: no or minimal collaterals in a region greater than 50% of the middle cerebral artery (MCA) territory when
compared with pial filling on the contralateral side (multiphase/dynamic CTA preferred); OR

- On CT perfusion (≥8 cm coverage): a low CBV and very low cerebral blood flow (CBF) ASPECTS less than 6 AND in the symptomatic MCA territory; OR
- On CT perfusion (<8 cm coverage): a region of low CBV and very low CBF greater than 1/3 of the CT perfusion-imaged symptomatic MCA territory.

- **EXTEND-IA** (Campbell et al, 2015). Inclusion criteria were based on CT perfusion imaging using CT or MRI with a Tmax more than 6-second delay perfusion volume and either CT regional cerebral blood flow or DWI infarct core volume as follows:
  - Mismatch ratio greater than 1.2; AND
  - Absolute mismatch volume greater than 10 mL; AND
  - Infarct core lesion volume less than 70 mL.

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

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

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

- **DAWN Trial** (Nogueira et al, 2018). Inclusion criteria (6 to 24 hours) related to mismatch between severity of clinical deficit and infarct volume:
  - 80 years of age or older, score of 10 or higher on the NIHSS, and had an infarct volume of less than 21 mL; OR
  - Younger than 80 years age, score of 10 or higher on the NIHSS, and had an infarct volume of less than 31 mL; OR
  - Younger than 80 years of age, had a score of 20 or higher on the NIHSS, and had an infarct volume of 31 to less than 51 mL
• DEFUSE 3 Trial (Albers et al, 2018). Inclusion criteria (6 to 16 hours) related to mismatch between severity of clinical deficit and infarct volume:
  - Infarct size of <70 mL; AND
  - Ratio of ischemic tissue volume to infarct volume of ≥1.8; AND
  - Ischemic penumbra of 15 cm3 or more.

II. Criteria/Guidelines

A. Intracranial stent placement is covered (subject to Limitations and Administrative Guidelines) as part of the endovascular treatment of intracranial aneurysms for patients meeting all of the following criteria:
   1. Surgical treatment is not appropriate; and
   2. 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.

B. Intracranial flow diverting stents with FDA approval for the treatment of intracranial aneurysms are covered (subject to Limitations and Administrative Guidelines) as part of the endovascular treatment of intracranial aneurysms for patients meeting all of the following criteria:
   1. The intracranial aneurysm meets anatomic criteria, meaning that they are used for the treatment of large or giant wide-necked intracranial aneurysms with a size of 10 mm or more and a neck diameter of 4 mm or more in the internal carotid artery from the petrous to the superior hypophyseal segments; and
   2. The intracranial aneurysm is not amenable to surgical treatment or standard endovascular therapy.

C. The use of endovascular mechanical embolectomy with a device with FDA approval for the treatment of acute ischemic stroke is covered (subject to Limitations and Administrative Guidelines) as part of the treatment of acute ischemic stroke for patients who meet all of the following criteria:
   1. 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);
   2. 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
   3. Have evidence of substantial and clinically significant neurological deficits;
   4. Have evidence of salvageable brain tissue in the affected vascular territory; and
   5. Have no evidence of intracranial hemorrhage or arterial dissection on computed tomography (CT) or magnetic resonance imaging.

III. Limitations

A. Intracranial stent placement is not covered in the treatment of intracranial aneurysms except as noted in Criteria/Guidelines A and B above.

B. Intracranial percutaneous transluminal angioplasty with or without stenting is not covered in the treatment of atherosclerotic cerebrovascular disease.
C. Endovascular interventions are not covered for the treatment of acute ischemic stroke when Criteria/Guidelines C.1-4 above is not met.

IV. Administrative Guidelines

A. Precertification is required for all non-emergent conditions. To precertify, complete HMSA’s Precertification Request and fax or mail the for, or use iExchange with the following documentation:
   1. Clinical notes including neurosurgical and neuroradiological consultation reports (if available); and
   2. MRA, CTA or standard angiography brain report.

B. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

C. Applicable codes:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>61624</td>
<td>Transcatheter permanent occlusion or embolization (eg, for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method; central nervous system (intracranial, spinal cord)</td>
</tr>
<tr>
<td>61630</td>
<td>Balloon angioplasty, intracranial (e.g., atherosclerotic stenosis), percutaneous</td>
</tr>
<tr>
<td>61635</td>
<td>Transcatheter placement of intravascular stent(s), intracranial (e.g., atherosclerotic stenosis), including balloon angioplasty, if performed</td>
</tr>
<tr>
<td>61645</td>
<td>Percutaneous arterial transluminal mechanical thrombectomy and/or infusion for thrombolysis, intracranial, any method, including diagnostic angiography, fluoroscopic guidance, catheter placement, and intraprocedural pharmacological thrombolytic injection(s)</td>
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<table>
<thead>
<tr>
<th>ICD-10-CM Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I63.00-I63.9</td>
<td>Cerebral infarction code range</td>
</tr>
<tr>
<td>I66.01-I66.9</td>
<td>Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction, code range</td>
</tr>
<tr>
<td>I67.0-I67.9</td>
<td>Other cerebrovascular diseases code range (includes I67.1 Cerebral aneurysm, nonruptured)</td>
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</table>

D. The following codes are only used for inpatient services:

<table>
<thead>
<tr>
<th>ICD-10-PCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>037G34Z, 037G3DZ, 037G3ZZ, 037G44Z, 037G4DZ, 037G4ZZ</td>
<td>Surgical, upper arteries, dilation, intracranial artery, code by approach (percutaneous or percutaneous endoscopic) and device (drug-eluting intraluminal device, intraluminal device, or no device)</td>
</tr>
<tr>
<td>03CG3ZZ, 03CG4ZZ, 03CH3ZZ, 03CH4ZZ, 03CJ3ZZ, 03CJ4ZZ</td>
<td>Surgical, upper arteries, extirpation, codes for the various arteries of the head, and percutaneous or percutaneous endoscopic approaches</td>
</tr>
</tbody>
</table>
V. Scientific Background

This evidence review was originally created in December 2002 and updated periodically with literature reviews. The most recent update with literature review covered the period through February 5, 2018.

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

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

Endovascular Interventions for Acute Ischemic Stroke

Endovascular Interventions for Anterior Circulation Acute Ischemic Strokes

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

Systematic Reviews

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

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

- Use of angiographic imaging confirming proximal arterial occlusion (OR=2.24; 95% CI, 1.72 to 2.9; p<0.001 for interaction).
- Use of IV tPA and endovascular therapy (OR=2.07; 95% CI, 1.46 to 2.92; p=0.018 for interaction).
- Use of stent retriever for mechanical thrombectomy (OR=2.39; 95% CI, 1.88 to 3.04; p<0.001 for interaction).

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

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

Hong et al conducted a meta-analysis of RCTs comparing endovascular recanalization therapy with standard care in acute ischemic stroke. This analysis included 15 RCTs with a total of 2899 patients, 1575 randomized to endovascular recanalization arms and 1324 to control arms. In addition to the 8 trials which compared mechanical embolectomy with standard care (Ciccone et al, Kidwell et al, Broderick et al, Berkhemer et al, Goyal et al, Campbell et al, Saver et al, Jovin et al), this meta-analysis also included 2 trials evaluating intra-arterial pro-urokinase, 3 trials evaluating intra-arterial urokinase, 1 evaluating intra-arterial with IV tPA, and 1 evaluating intra-arterial tPA with mechanical thrombectomy. In a random-effects model including all trials, endovascular recanalization was associated with greater proportions of patients with mRS scores of 0 to 2 (43.3% vs 31.9%; OR=1.79; 95% CI, 1.34 to 2.4; p<0.001). For safety outcomes, when all trials were included, rates of symptomatic intracranial hemorrhage were higher in endovascular recanalization arms, although the between-group difference was not statistically significant (5.8% vs 4.6%; OR=1.19; 95% CI, 0.83 to 1.69; p=0.345).
In another meta-analysis, Kennedy et al compared local mechanical and/or pharmacologic endovascular therapy, with or without IV thrombolysis, with standard care control that included IV thrombolysis when appropriate. Eleven RCTs were included, the 8 trials comparing mechanical embolectomy with standard care (Ciccone et al, Kidwell et al, Broderick et al, Berkhemer et al, Goyal et al, Campbell et al, Saver et al, Jovin et al), along with 2 trials comparing intra-arterial tPA with IV tPA alone, one of which was very small (n=7), and one evaluating intra-arterial tPA with mechanical thrombectomy. In a meta-analysis of all trials, patients in the local endovascular therapy groups had higher rates of functional independence than those treated with standard care (OR=1.78; 95% CI, 1.262 to 2.51; p<0.001). In subanalyses limited to trials that used imaging selection, that used stent retriever devices in at least half of cases, or in which IV tPA was used in conjunction with endovascular therapy as appropriate, the use of local endovascular therapy remained significantly associated with higher rates of functional independence, with stronger effect sizes than in the overall analysis. However, in a subanalysis limited to trials in which endovascular arm patients did not receive IV tPA, there was no significant between-group difference in 90-day functional independence (OR=1.45; 95% CI, 0.597 to 3.54, p>0.05).

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

Bush et al (2016) conducted a meta-analysis of RCTs using predominantly stent retriever devices for acute stroke treatment. Trials that compared endovascular therapy with stent retrievers with medical management (defined as 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, Goyal et al, Campbell et al, Saver et al, Jovin et al) 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 OR for more favorable mRS score of 2.2 (95% CI, 1.66 to 2.98; p<0.001; I²=46.38%). Similar to the findings from the Badhiwala meta-analysis, there were no significant between-group differences in 90-day mortality rates or symptomatic intracranial hemorrhage rates.

Other related systematic reviews have reported similar results.

In 2015, an updated draft Blue Cross and Blue Shield Association (BCBSA) TEC Assessment assessed endovascular therapy for acute ischemic stroke in adults to reflect several RCTs published after an earlier TEC Assessment. The Assessment focused on 4 RCTs published from 2014 to 2015 comparing endovascular mechanical embolectomy with medical therapy (Berkhemer et al, Campbell et al, Goyal et al, Saver et al). The Assessment made the following observations and conclusions:

“Four recent well-designed and well-conducted RCTs have demonstrated reduced disability among adults with acute ischemic stroke treated with mechanical embolectomy compared with standard medical care, usually IV tPA. These 4 RCTs address some of the limitations in 3 RCTs published in 2013, which showed no significant benefit to endovascular therapy. In particular, trials demonstrating a benefit to endovascular therapy either exclusively used stent retriever devices or allowed the treating physician to select a device, mostly a stent retriever device, and had high rates of mechanical embolectomy device use in patients randomized to endovascular therapy.”
The draft Assessment also concluded that the use of endovascular treatment with mechanical embolectomy in adults with radiologically confirmed large vessel, anterior circulation acute ischemic stroke met TEC criteria. The specific RCTs are described in more detail below.

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

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

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

Randomized Controlled Trials

RCTs Comparing Endovascular Therapies With 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. Five prospective, open-label, blinded end point (PROBE design) RCTs comparing endovascular therapy with standard care in the treatment of acute stroke were published from 2014 to 2015 and are the focus of this discussion. A high-level overview of the major RCTs follows, with a summary of results in Table 2. Subsequently in this section, select trials are described in more detail.

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

Fourteen RCTs with a total of 3061 patients (range, 70-656 patients) compared endovascular mechanical embolectomy with standard care for acute ischemic stroke. In 2 studies, the population and intervention delivered were not consistent with the target population and intervention; the remaining 12 studies with the populations and interventions of interest are the focus of this discussion. The most clinically relevant and consistently reported finding was a comparison between treatment and control groups in the proportion of patients with 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 0-2. Across the studies, the absolute difference between treatment and control groups in proportion of patients with 90-day functional independence ranged from 1.55% to 36%. With the exception of MR Rescue [Kidwell et al], all studies published before 2016 reported a statistically significant improvement in the proportion of patients with functional independence at 90 days, with 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. Therefore, most studies published later do not have the power to detect clinically meaningful differences at the achieved sample size but are consistent in direction with the earlier studies.

**Treatment Within 6 to 8 Hours of Symptom Onset**

**REVASCAT Trial.** In 2015, Jovin et al reported results of the REVASCAT trial, which compared endovascular therapy using the Solitaire stent-retriever device with medical therapy, including IV tPA when indicated, within 8 hours of stroke onset among 206 patients. Eligible patients had an occlusion within the proximal anterior circulation that could be treated within 8 hours of stroke onset, a prestroke mRS score of 0 to 1, and a baseline National Institutes of Health Stroke Scale (NIHSS) score of at least 6 points (NIHSS score range, 0-42; higher scores associated with greater deficit). Intravenous tPA was administered before randomization. Patients were excluded if they had imaging-based evidence of a large ischemic core, indicated by an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of less than 7 on non-contrast CT imaging or a score of less than 6 on diffusion-weighted MRI. The trial was halted early for loss of equipoise given the results of the EXTEND-IA, ESCAPE, and MR CLEAN trials (described below) after the first planned interim analysis (when the first 25% of patients [n=174] reached 90 days of follow-up).

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

See Table on next page.
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>N</th>
<th>90-Day Modified Rankin Scale Score 0-2</th>
<th>Mortality</th>
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<td>Between-Group Difference Per Group Rate Between-Group Difference Per Group Rate Between-Group Difference</td>
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<td>Group</td>
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<td>Treatment Description</td>
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<td></td>
<td>Intervention</td>
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<td>DEFUSE 3</td>
<td>Intervention Endovascular therapy + standard medical therapy(^b)</td>
<td>92</td>
<td>45</td>
<td>OR=2.7 (1.6 to 4.5)</td>
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<td>(Albers [2018])</td>
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<td>Control</td>
<td>90</td>
<td>17</td>
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<td>DAWN</td>
<td>Intervention Endovascular therapy + standard care(^b)</td>
<td>107</td>
<td>49</td>
<td>ARR=36% (24% to 47%)</td>
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<td>(Nogueira</td>
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<td>[2018])</td>
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<tr>
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<td>Control</td>
<td>99</td>
<td>13</td>
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<td>EASI</td>
<td>Intervention Endovascular therapy + standard care (IV tPA if indicated)</td>
<td>40</td>
<td>50</td>
<td>p=0.36</td>
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<td>(Khoury</td>
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<td>[2017])</td>
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<td>Control</td>
<td>37</td>
<td>38</td>
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<td>PISTE</td>
<td>Intervention Endovascular therapy + medical therapy with IV tPA</td>
<td>33</td>
<td>51</td>
<td>OR=2.1 (0.7 to 6.9)</td>
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<td>(Muir [2017])</td>
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<td>Control</td>
<td>32</td>
<td>40</td>
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<td>THERAPY</td>
<td>Intervention Aspiration thrombectomy (Penumbra) + IV tPA</td>
<td>55</td>
<td>38</td>
<td>OR=1.4 (0.6 to 3.3)</td>
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<td>(Mocco [2016])</td>
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<tr>
<td>Control</td>
<td>Intervention</td>
<td>Description</td>
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<td>Percentage</td>
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</tr>
<tr>
<td>IV tPA alone</td>
<td>IV tPA alone</td>
<td>IV tPA alone</td>
<td>53</td>
<td>30</td>
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<td>THRACE (Bracard [2016])</td>
<td>Intervention</td>
<td>Endovascular therapy + IV tPA</td>
<td>202</td>
<td>53</td>
</tr>
<tr>
<td>Control</td>
<td>Intervention</td>
<td>Medical therapy (IV tPA if indicated)</td>
<td>103</td>
<td>28.2%</td>
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<tr>
<td>REVASCAT (Jovin, 2015)</td>
<td>Intervention</td>
<td>Solitaire stent retriever w/wo IV tPA</td>
<td>103</td>
<td>43.7%</td>
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<tr>
<td>Control</td>
<td>Intervention</td>
<td>Medical therapy (IV tPA if indicated)</td>
<td>103</td>
<td>28.2%</td>
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<tr>
<td>EXTEND-IA (Campbell, 2015)</td>
<td>Intervention</td>
<td>Endovascular therapy + IV tPA</td>
<td>35</td>
<td>71%</td>
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<td>Intervention</td>
<td>Medical therapy (IV tPA if indicated)</td>
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<tr>
<td>ESCAPE (Goyal, 2015)</td>
<td>Intervention</td>
<td>Endovascular therapy w/wo IV tPA</td>
<td>165</td>
<td>53%</td>
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<td>Medical therapy (IV tPA if indicated)</td>
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<td>SWIFT-PRIME (Saver, 2015)</td>
<td>Intervention</td>
<td>Solitaire stent retriever + IV tPA</td>
<td>98</td>
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<tr>
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<td>Intervention</td>
<td>Medical therapy (IV tPA if indicated)</td>
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<td>35%</td>
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<td>MR CLEAN (Berkhemer, 2015)</td>
<td>Intervention</td>
<td>Intra-arterial therapy w/wo IV tPA</td>
<td>233</td>
<td>32.6%</td>
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<tr>
<td>Control</td>
<td>Medical therapy (IV tPA if indicated)</td>
<td>267</td>
<td>19.1%</td>
<td>18.4%</td>
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</table>
## Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Intervention</th>
<th>n</th>
<th>3 Month Mortality</th>
<th>p-value</th>
<th>6 Month Mortality</th>
<th>p-value</th>
<th>1 Year Mortality</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>MR RESCUE</strong></td>
<td><strong>Mechanical embolectomy (MERCI or Penumbra) w/wo IV tPA</strong></td>
<td>64</td>
<td>18.75%</td>
<td>0.48</td>
<td>21%</td>
<td>NS</td>
<td>4%</td>
<td>NS</td>
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<tr>
<td>Control</td>
<td>Medical therapy (IV tPA if indicated)</td>
<td>54</td>
<td>20.3%</td>
<td></td>
<td>21%</td>
<td></td>
<td>4%</td>
<td></td>
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<tr>
<td><strong>SYNTHESIS</strong></td>
<td><strong>Intra-arterial therapy w/wo IV tPA</strong></td>
<td>181</td>
<td>30.4%</td>
<td></td>
<td>6%</td>
<td>NS</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>IV tPA alone</td>
<td>181</td>
<td>34.8%</td>
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<td><strong>IMS III</strong></td>
<td><strong>Endovascular therapy + IV tPA</strong></td>
<td>434</td>
<td>38.7%</td>
<td>0.52</td>
<td>19.1%</td>
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<tr>
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<td>IV tPA alone</td>
<td>222</td>
<td>40.8%</td>
<td></td>
<td>21.6%</td>
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<td>18.9%</td>
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</table>

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

a Trial stopped early due to publication of results of other trials.
b Patients were enrolled in DEFUSE 3 and DAWN after the accepted window of time for which IV thrombolytic therapy is typically administered.
**EXTEND-IA Trial.** In 2015, Campbell et al reported results of the EXTEND-IA trial comparing endovascular therapy with tPA alone. This trial enrolled patients with ischemic stroke who were receiving IV tPA within 4.5 hours after stroke onset. Eligible patients had an occlusion of the internal carotid artery (ICA) or M1 or M2 segments of the middle cerebral artery (MCA) on computed tomography angiography (CTA), were able to receive endovascular therapy within 6 hours of stroke onset, and were functionally independent prior to the stroke. Patients were evaluated prior to enrollment with computed tomography (CT) perfusion imaging, and were required to have evidence of salvageable brain tissue and an ischemic core with a volume of less than 70 mL. Computed tomography (CT) perfusion imaging was analyzed with an operator-independent postprocessing software. Enrollment was planned for 100 patients. The trial’s data safety and monitoring board reviewed data for the first 70 enrolled patients after the results of the MR CLEAN trial were published and stopped EXTEND-IA for efficacy based on prespecified criteria. The first 70 patients were randomized to either IV tPA plus endovascular therapy with the Solitaire FR retrievable stent (n=35) or no further therapy (IV tPA only; n=35). The study used 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.

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

Of the 165 patients randomized to the intervention group, 151 (91.5%) underwent endovascular therapy, most commonly with a retrievable stent (130/151 [86.1%] of those who underwent an endovascular procedure), most often with the Solitaire stent (100/130 [77.0%] of those who received a retrievable stent). In the intervention group, 120 (72.7%) also received IV tPA. Of the 150 control group subjects, 118 (78.6%) received IV tPA. For the study’s primary end point (90-day mRS score), compared with the control group, in the endovascular treatment group the relative odds of improving 1 point on the mRS was 2.6 (95% CI, 1.7 to 3.8). Endovascular treatment group subjects compared with control group subjects also had lower 90-day mRS scores (median, 2 vs 4, respectively; p<0.001) and were more likely to have 90-day mRS scores of 0 to 2 (53% vs 29.3%; rate ratio, 1.8; 95% CI, 1.4 to 2.4; p<0.001). Ninety-day mortality was 10.4% among endovascular treatment group subjects and 19.0% in control group subjects (rate ratio, 0.5; 95% CI, 0.3 to 1.0; p=0.04).

SWIFT-PRIME Trial. In 2015, Saver et al reported results of the SWIFT-PRIME trial comparing IV tPA followed by mechanical embolectomy using a stent retriever device with IV tPA alone in patients presenting with acute ischemic stroke. Eligible patients had moderate-to-severe neurologic deficits, imaging-confirmed occlusion of the intracranial ICA and/or the first segment of the MCA, were receiving or had received IV tPA, and were able to undergo endovascular treatment within 6 hours of symptom onset. In addition, eligible patients were required to have ischemic penumbral imaging analysis showing a small-to-moderate core infarct. For the first 71 patients enrolled, the infarct core size was defined based on CT perfusion imaging analyzed with an operator-independent postprocessing software; for the remainder of the study, infarct core size could be determined by CT perfusion imaging or non–contrast CT with a small-to-moderate core infarct based on ASPECTS. Patients were randomized to mechanical embolectomy with the Solitaire 2 or the Solitaire FR device (n=98) or to ongoing IV tPA (n=98). Enrollment was planned for a maximum of 833 subjects, but stopped at 196 subjects after an interim analysis, following publication of the results of the MR CLEAN and ESCAPE trials, showed that results met SWIFT-PRIME’s prespecified efficacy criteria.

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

MR CLEAN Trial. In 2015, Berkhermer et al reported initial results of the MR CLEAN trial (Multicenter Randomized Clinical trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), an open-label, blinded end point RCT with 500 subjects conducted at 16 centers in the Netherlands. Eligible patients had acute ischemic stroke caused by an intracranial occlusion of the distal intracranial carotid artery, middle cerebral artery (M1 or M2), or anterior cerebral artery
(A1 or A2), and a score of 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. Analysis was intention-to-treat. One control group patient received intra-arterial treatment, and 17 patients (7.3%) in the intervention group did not receive intra-arterial therapy, most commonly (n=8) due to clinical improvement before the start of the intervention. Among the 233 patients randomized to intra-arterial therapy, 195 (83.7%) received mechanical therapies, with retrievable stents used in 190 patients (81.5%) and other devices in 5 patients (2.1%). Twenty-four patients (10.3%) received additional intra-arterial thrombolytic agents. No intra-arterial intervention was performed following catheterization in 20 subjects because of intracranial artery stenosis, occlusion, tortuosity, or dissection (n=10), no clot or targetable clot visible for intra-arterial therapy (n=8), or other technical problems (n=2).

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

**MR RESCUE Trial.** Kidwell et al reported on the MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy) trial in 2013. MR RESCUE was an open-label, blinded-outcome 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 (MRI) 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 tissue plasminogen activator (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, ranging from a score of 0 (no symptoms) to 6 (dead). In the embolectomy group, 67% achieved revascularization, but this was not superior to standard care. Mean mRS scores were the same (3.9) in both groups, and pretreatment imaging patterns did not show any relation to treatment outcomes in any group. Overall mortality (21% at 90 days) and symptomatic intracranial hemorrhage (4%) did not differ across groups.

SYNTHESIS Expansion Trial. In 2013, Ciccone et al reported on the SYNTHESIS Expansion trial of 362 patients randomized within 4.5 hours of the onset of various types of acute ischemic strokes to receive endovascular therapy (n=181) or IV tPA (n=181). Endovascular therapy consisted of intra-arterial tPA, mechanical embolectomy (using the Solitaire, Penumbra, Trevo Merci devices) or a combination of these treatments. Among the patients randomized to endovascular therapy, endovascular treatment was actually completed in 163 patients. In 109 patients, regional intra-arterial infusion of tPA and fragmentation of the thrombus with a microguidewire were used. In 56 patients, a device was added; the most widely used devices were Solitaire FR in 18 patients, Penumbra in 9 patients, Trevo in 5 patients, and Merci in 5 patients. No significant differences in 90-day survival without disability (mRS score range, 0-1) occurred between the endovascular therapy group and tPA group (30.4% vs 34.8%, respectively, 0.71; 95% CI, 0.44 to 1.14; p=0.16). Within 7 days, fatal or nonfatal symptomatic intracranial hemorrhage occurred in each group at a rate of 6%. Rates of other serious AEs also did not differ significantly between groups. While there were different treatment approaches in the endovascular group, these results suggest endovascular therapy is not superior to tPA.

IMS III Trial. Also in 2013, Broderick et al reported the results of the IMS III trial, an open-label RCT with a planned enrollment of 900 patients. This trial enrolled patients with acute ischemic stroke who presented within 3 hours of symptom onset and had a moderate-to-severe neurologic deficit on presentation. Patients were randomized to IV tPA alone or IV tPA plus endovascular intervention. Patients randomized to the endovascular group underwent immediate angiography followed by endovascular intervention if a treatable vascular occlusion was present. Endovascular intervention consisted of either endovascular delivery of tPA at the site of occlusion or mechanical thrombectomy, at the discretion of the treating physician. Potential endovascular interventions included thrombectomy (using the Merci Retriever, Penumbra System, or Solitaire FR revascularization device) or endovascular delivery of tPA (using the Micro-Sonic SV infusion system [EKOS] or a standard microcatheter). The primary outcome was 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 AEs, 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).
In 2015, Tomsick et al published a subgroup analysis of the IMS III trial focusing on subjects with intracranial ICA or M1 occlusion. This analysis included 200 subjects, 65 with intracranial ICA and 135 with M1 segments as the target vessel for revascularization. Of these, at angiography, 82% had an arterial occlusive lesion score of 2 to 3 and 76% had a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2 to 3 (partial or full perfusion) after IV-tPA, which may have limited the potential benefit for device-related revascularization. Ninety-day mRS scores were higher with higher mTICI scores: of 32 subjects with an mTICI score of 0, 3.1% had an mRS score of 0 to 2 at 90 days, compared with 12.5%, 19.4%, 46.3%, and 80% for subjects with mTICI scores of 1 (n=16), 2a (n=67), 2b (n=80), and 3 (n=5), respectively. To account for potential bias in the choice of endovascular therapy, propensity score analysis was used to compare subjects with different endovascular therapy modalities for the primary study outcomes. After propensity score adjustment, 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 evaluated the association between baseline CT or magnetic resonance angiography (MRA) findings and outcomes among 306 of 656 (47%) who had baseline CT or MRA imaging available. Ninety-two percent of those with angiography available had arterial occlusions demonstrated, 220 of which were proximal occlusions. Endovascular therapy group subjects with proximal occlusions had higher 24-hour recanalization rates than those with IV tPA only (84.3% of endovascular therapy subjects vs 56% of controls; p<0.001). However, no difference in the primary outcome (90-day mRS score, 0-2), was seen with proximal occlusions between groups (41.3% of endovascular therapy subjects vs 38% of controls; RR=1.07; 99% CI, 0.67 to 1.70).

**Treatment Beyond 6 Hours of Symptom Onset**

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

**DEFUSE 3 Trial.** Albers et al (2018) reported on results of DEFUSE 3, a multicenter, open-label RCT with blinded outcome assessment including patients 6 to 16 hours after they were last known to be well and who had remaining ischemic brain tissue that was not yet infarcted. DEFUSE 3 was conducted at 38 sites in the United States from May 2016 to May 2017. Patients were assigned to thrombectomy plus standard medical therapy (n=92) or standard medical therapy alone (n=90). The median age was 70 years, half of the participants were women, the median NIHSS score was 16, and 10% of the participants received IV tPA. Approximately 50% of the patients had a “wake-up” stroke. The trial was originally designed to enroll a maximum of 476 participants but was stopped early for efficacy. The proportion of patients who were functionally independent (mRS score ≤2) at 90 days was 45% in the thrombectomy group and 17% in the standard care group (OR=2.67; 95% CI, 1.60 to 4.48; p<0.001). The proportion of patients with symptomatic intracranial hemorrhage was 7% in the thrombectomy group and 4% in the standard care group (OR=1.47; 95% CI, 0.40 to 6.55; p=0.75). The 90-day mortality rate was 14% in the thrombectomy group and 26%
in the standard care group (OR=0.55; 95% CI, 0.30 to 1.02; p=0.05). The rate of serious adverse events was 43% and 53%, respectively (p=0.18).

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

Section Summary: RCTs Comparing Endovascular Therapies With Noninterventional Care
A number of RCTs have compared endovascular therapies with noninterventional care for acute stroke, with the 5 more recent (2014-2015) studies demonstrating a significant benefit associated with endovascular care. The more recently published trials addressed some of the limitations of previous studies. In the IMS III and SYNTHESIS Expansion trials, sizable proportions of the endovascular therapy groups did not receive an endovascular device. All 3 of the 2013 trials (Broderick et al, Kidwell et al, Ciccone et al) all had relatively low utilization of the newer generation retrievable stents (Solitaire FR, Trevo). In addition, IMS III and the Ciccone et al study did not require a radiologically proven intracranial occlusion for study eligibility. In contrast, the 2014-2015 trials, which demonstrated a benefit to endovascular therapy, either exclusively used stent retriever devices or allowed the treating physician to select a device, mostly a stent retriever device, and had high rates of mechanical embolectomy device use in patients randomized to endovascular therapy.

RCTs Comparing Different Endovascular Therapies
In 2012, 2 noninferiority RCTs comparing newer devices with the Merci Retriever were completed as part of the FDA application for approval of the Solitaire™ and the Trevo™ devices. Both studies reported device superiority over the Merci device. In the SWIFT (Solitaire FR With the Intention for Thrombectomy) study, recanalization rates with Solitaire were compared with the Merci Retrieval System in a randomized, prospective noninferiority trial of 113 patients with moderate or severe large vessel occlusion strokes. Treatment was initiated within 8 hours of symptom onset in patients who had unsuccessful IV tPA or were ineligible for IV tPA. This trial was halted early after an interim analysis found revascularization without symptomatic intracranial hemorrhage occurred in 61% of Solitaire patients compared with 24% of Merci patients. Mortality rates at 90 days were 17% with Solitaire versus 38% with Merci (p=0.001). A follow-up analysis of complications of endovascular procedures using the SWIFT study data was published in 2014. This analysis included 144 patients
with acute ischemic stroke (31 patients treated with the Solitaire FR device during the SWIFT trial roll-in period and 113 patients randomly assigned to the Solitaire FR or Merci device). Major periprocedural complications, including symptomatic intracranial hemorrhage, air emboli, vessel dissection, major groin complications, and emboli to new vascular territories, were seen in 18 of 144 (12.5%) of all patients. Complication rates were similar for patients receiving the Solitaire FR and Merci devices, with the exception of symptomatic cerebral hemorrhage, which was significantly less common in the Solitaire FR group (10.9% vs 1.1%, p=0.013).

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

Saposnik et al (2015) evaluated the benefit added by stent retrievers to IV tPA using pooled patient-level data from the SWIFT study48 and the STAR trial, a prospective, single-arm trial of the Solitaire device,52 along with data from the NINDS tPA Stroke Study, an RCT evaluating IV tPA. Of 915 patients included in the pooled analysis, 312 were treated with placebo, 312 with IV tPA, 106 with stent retrievers alone, and 160 with IV tPA and stent retrievers. The authors employed a shift analysis, which uses a proportional odds model, to evaluate the association between treatment and each of the 7 mRS categories. The use of stent retrievers (alone or with tPA) was associated with a higher probability of functional independence (mRS score, 0-2) at 90 days: 41% of those treated with tPA alone, 69.8% of those treated with stent retrievers, and 72.8% of those treated with stent retrievers and tPA had functional independence at 90 days.

Noguiera et al (2018) compared use of the Penumbra 3-D stent retriever and an aspiration-based mechanical thrombectomy device with the Penumbra aspiration system alone in 198 patients from 25 North American sites enrolled from May 2012 through November 2015.53 Eligible patients had large vessel intracranial occlusion acute ischemic stroke with an NIHSS score of at least 8 within 8 hours of onset. The primary effectiveness outcome was the rate of a mTICI score of 2 to 3, with a 15% noninferiority margin. One hundred ninety patients were included in the primary analysis. Eighty-two (87%) of 94 patients in the 3-D stent retriever group had a mTICI score of 2 to 3 compared with 79 (82%) of 96 in the aspiration alone group (difference, 4.9%; 90% CI, -3.6% to 13.5%). The incidence of the device- and procedure-related serious adverse events within 24 hours of the procedure was 4 (4%) of 98 patients in the 3-D stent retriever group and 5 (5%) of 100 in the aspiration alone group.

Nonrandomized Comparative Studies
A number of nonrandomized comparative studies have compared endovascular interventions with historical controls or control patients from their same institution who received standard stroke care.

For the treatment of acute stroke involving the anterior circulation, more direct evidence on the effectiveness of endovascular therapies is available from the RCTs described above. Therefore, nonrandomized comparative studies that have assessed specific types of endovascular interventions are the focus of this section. These studies offer information on the comparative
efficacy of different devices, which is important in the interpretation and comparison of studies that may use different or multiple devices in endovascular treatments of acute stroke.

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

Turk et al conducted a retrospective, single-center review comparing clinical and cost-related outcomes for 3 endovascular interventions for acute stroke: the Penumbra system, stent retriever with local aspiration, and a “Direct Aspiration First Pass Technique” (ADAPT), which involves direct aspiration with a large bore catheter. Two hundred twenty-two patients underwent endovascular therapies for acute stroke during the study, 128 (58%) with the Penumbra system, 30 (13%) with a stent retriever, and 64 (29%) with ADAPT. Recanalization rates (TICI scores, 2b/3) were higher in the ADAPT group than the Penumbra group (95% vs 73%; p=0.003), but no significant differences were seen across groups in 90-day mRS scores.

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

These studies offer some information on the comparative efficacy of different devices, which is important in the interpretation and comparison of studies that may use different or multiple devices in endovascular treatments of acute stroke.

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

**Endovascular Interventions for Stroke Due to Basilar Artery Occlusion**

Posterior circulation strokes account for about 20% of all acute ischemic strokes; occlusion of the basilar artery is implicated in about 8% of posterior strokes. Reperfusion therapies have received particular attention as a therapy for basilar artery occlusion because, though relatively rare, basilar artery occlusions have high likelihood of severe disability or death. For example, in 1 registry study, investigators found severe outcomes (mRS scores of 4 or 5, or death) in 68% of patients with basilar artery occlusion.

A limited number of studies have evaluated endovascular interventions for basilar artery occlusion. In 2013, Broussalis et al reported results from a prospective registry study of 99 patients with posterior circulation stroke caused by basilar artery occlusion from 2005 to 2012. Patients who received endovascular therapies (including endovascular mechanical recanalization and/or intraarterial with optional IV thrombolytic therapy) were compared with those who received standard medical therapy (IV thrombolytic therapy and/or medical antithrombotic treatment.) Seventy-eight percent of the patients received endovascular intervention, with thrombectomy alone in 67 patients. Devices used included the Merci system in 43%, the Solitaire FR device in 13%, and the Trevo retriever in 18%, with devices not available in the United States in the remaining 25%. Endovascular patients were more likely to achieve a TICI score of 3 (full perfusion with filling of all distal branches) (36% vs 9%, p=0.017); after 90 days, more than 61% of patients who received endovascular therapy achieved an mRS score of 3 compared with 8% in the standard medical therapy group.

Noncomparative studies have reported on endovascular therapies for acute basilar artery occlusion. Son et al reported outcomes for 31 subjects with acute basilar artery occlusion treated with mechanical thrombectomy with the Solitaire stent (n=13) or manual aspiration thrombectomy using the Penumbra reperfusion catheter (n=18) at a single center. Successful recanalization (TICI scores, ≥2b) did not differ between devices (84.6% with the Solitaire stent vs 100% with the Penumbra catheter; p=0.168); similarly, 3-month mRS scores did not differ between the groups (3.6 with the Solitaire stent vs 3.2 with the Penumbra catheter; p=0.726).

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

In a single-center case series of 24 patients with acute basilar artery occlusion treated with a stent-retriever device with or without IV or intra-arterial tPA and/or percutaneous transluminal angioplasty or permanent stent placement, Mohlenbruch et al reported that mechanical thrombectomy lead to successful recanalization (TICI scores, ≥2b) in 75% of patients. Eight patients (33%) had a favorable clinical outcome (mRS scores, 0-2) at 3 months. Park et al reported results from a single-center case series of 16 patients with acute basilar artery occlusion who were treated with endovascular interventions, primarily the Penumbra or Solitaire FR devices. The authors reported that successful revascularization (TICI scores, ≥2a) was achieved in 81.3% of patients, with favorable clinical outcome (mRS scores, 0-2) at 3 months in 56.3% of patients. While these studies suggest that endovascular intervention is feasible for acute basilar artery occlusion and may be associated with favorable outcomes, they are limited by lack of concurrent comparison groups and by potential selection bias.

**Section Summary: Endovascular Interventions for Stroke Due to Basilar Artery Occlusion**
The evidence for the use of endovascular interventions for stroke due to basilar artery occlusions is limited, consisting on multiple noncomparative studies and 1 prospective registry study comparing endovascular therapy with standard medical therapy. These studies indicate that high rates of recanalization can be achieved with mechanical thrombectomy. However, additional comparative studies are needed to demonstrate that mechanical thrombectomy is superior to standard therapy.

**Endovascular Interventions for Symptomatic Intracranial Atherosclerotic Disease**
Two devices for treatment of intracranial stenosis received FDA approval through the humanitarian device exemption (HDE) process. The Neurolink System® was approved based on the Stenting of Symptomatic Atherosclerosis Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) trial, a prospective, nonrandomized, multicenter, international study of 61 patients. The Wingspan™ Stent System was evaluated in a prospective study of 45 patients enrolled at 12 international centers. The SSYLVIA study reported an all-stroke rate of 13.1% over a mean follow-up of 216 days; the Wingspan study reported an all-stroke rate of 9.5% over a mean follow-up of 174 days.

The FDA summary of safety and effectiveness offered the following conclusions and appears to have based its approval in part on the favorable comparison to the Neurolink device:

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

Evidence on the role of endovascular stenting for treatment of symptomatic intracranial atherosclerotic disease includes 2 RCTs, a number of nonrandomized comparative studies, and numerous single-arm series. The most clinically relevant RCTs, nonrandomized comparative studies, and systematic reviews are reviewed next. Since publication of the RCT evidence, there continue to be single-arm publications (ie, with all subjects receiving endovascular stents) describing various aspects of stenting for intracranial stenosis, including utilization trends,
predictors of outcomes based on symptomatology, predictors of outcomes based on lesion morphology and arterial access, and clinical outcomes with the Wingspan system.

**Randomized Controlled Trials**

In 2015, Zaidat et al published results of the VISSIT trial, an RCT comparing a balloon-expandable stent plus medical management with medical management alone among patients with symptomatic intracranial stenosis of 70% or greater. Eligible patients had stenosis of 70% to 99% of the internal carotid, middle cerebral, intracranial vertebral, or basilar arteries with a transient ischemic attack (TIA) or stroke attributable to the territory of the target lesion within the prior 30 days. Enrollment was planned for up to 250 participants. However, an early unplanned analysis was conducted by the trial sponsor after the results of the SAMMPRIS trial were published (see below). A total of 112 patients were enrolled from 2009 to 2012 and randomized to balloon-expandable stent (Vitesse stent) plus medical management (stent group; n=59) or medical management alone (medical group; n=53). Medical management included clopidogrel (75 mg daily) for the first 3 months postenrollment and aspirin (81-325 mg/d) for the duration of the study, along with management of hypercholesterolemia and/or hypertension, if necessary. The study used a primary composite end point that included any stroke in the same territory as the presenting event within 1 year of randomization and hard TIA in the same territory as the presenting event from 2 days to 1 year after randomization. Among 29 patients who met one of the primary end points within 1 year of randomization, 8 patients (15.1%) were in the medical group and 21 (36.2%) were in the stent group (risk difference, 21.1%; 95% CI, 5.4% to 36.8%; p=0.02). The rates of stroke within 30 days of randomization or TIA within 2 to 30 days of randomization were 9.4% in the medical group and 24.1% in the stent group (risk difference, 14.7%; 95% CI, 1.2% to 28.2%; p=0.05). The 30-day all-cause mortality rate was 5.2% and 0% in the stent and medical groups, respectively (risk difference, 5.2%; 95% CI, -0.5% to 10.9%; p=0.25). The authors concluded that results did not support the use of a balloon-expandable stent for patients with symptomatic intracranial stenosis.

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial was an RCT comparing aggressive medical management alone with aggressive medical management plus stenting in patients with symptomatic cerebrovascular disease and an intracranial stenosis of between 70% and 99%. This trial used the Wingspan stent system implanted by experienced neurointerventionalists 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=0.002) 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=0.009) in the medical management group. These results represented an excess rate of early AEs with stenting over what was expected together with a decreased rate of stroke and death in the medical management group compared with expected values.

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

In 2015, Lutsep et al published a subgroup analysis of the SAMMPRIS trial results to evaluate whether outcomes differed for patients whose qualifying events occurred on or off antithrombotic therapy. Similar to the overall trial results, outcomes were worse in the stent group than in the best medical management group: of the 284 patients on antithrombotic therapy at the time of the qualifying event, 140 patients were randomized to medical management and 144 to stenting; in Kaplan-Meier analysis, 2-year rates of the primary end point were 15.6% in the medical management group and 21.6% in the stent group (p=0.043). In other subgroup analyses of the SAMMPRIS trial results, 2-year event rates were higher in the stent group for most variables evaluated. The interaction between treatment and the subgroup variables was not significant for any variable.

The Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS) randomized 16 patients with symptomatic vertebral artery stenosis to endovascular therapy (balloon angioplasty or stenting) or best medical treatment alone. Endovascular intervention was technically successful in all 8 patients, but 2 patients experienced TIAs at the time of endovascular treatment. During a mean follow-up of 4.7 years, no patient in either treatment group experienced a vertebrobasilar territory stroke, but 3 patients in each arm died of myocardial infarction (MI) or carotid territory stroke, and 1 patient in the endovascular arm had a nonfatal carotid territory stroke. The investigators concluded that patients with vertebral artery stenosis were more likely to have carotid territory stroke and MI during follow-up than have recurrent vertebrobasilar stroke. While they noted the trial failed to show a benefit of endovascular treatment of vertebral artery stenosis, the small number of patients enrolled severely limits conclusions.

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

**Systematic Reviews**
Before publication of the SAMMPRIS trial results, several systematic reviews addressed the role of stenting for intracranial atherosclerosis, which generally concluded that additional evidence from RCTs would be needed to conclude that stenting should be used in practice.

In 2016, Abuzinadah conducted a systematic review and meta-analysis of studies reporting the rates of stroke recurrence or death (the primary outcome) in symptomatic intracranial vertebrobasilar stenosis with medical or endovascular treatment. The authors identified 23 studies involving 592 medical treatment patients and 480 endovascular treatment patients. In pooled analysis, the stroke or death rates were 14.8 per 100 person-years (95% CI, 9.5 to 20.1) in the medical therapy group and 8.9 per 100 person-years (95% CI, 6.9 to 11.0) in the endovascular group (incidence rate ratio [IRR], 1.3; 95% CI, 1.0 to 1.7). The stroke recurrence rates were 9.6 per 100 person-years (95% CI, 5.1 to 14.1) in the medical group and 7.2 per 100 person-years (95% CI, 5.5 to 9) in the endovascular group (IRR=1.1; 95% CI, 0.8 to 1.5).

**Nonrandomized Comparative Studies**

A number of nonrandomized retrospective or registry-based studies provided relatively weak evidence on the comparative efficacy of endovascular procedures versus medical therapy for intracranial atherosclerosis (eg, Tang et al, Qureshi et al, Samaniego et al).

**Section Summary: Endovascular Interventions for Symptomatic Intracranial Atherosclerotic Disease**

The strongest evidence on the efficacy of endovascular treatment for symptomatic intracranial stenosis is from the SAMMPRIS RCT and the subsequent VISSIT RCT. The SAMMPRIS trial was stopped early due to harms, because the rate of stroke or death at 30 days following treatment was higher in the endovascular arm, which received percutaneous angioplasty with stenting. Follow-up of the SAMMPRIS subjects has demonstrated no long-term benefit from endovascular therapy. The VISSIT RCT similarly found no benefit with endovascular treatment. These studies support the conclusion that outcomes of endovascular treatment are worse than medical therapy in patients with symptomatic intracranial stenosis.

**Stent-Assisted Endovascular Treatment of Intracranial Aneurysms**

**Self-Expanding Stent-Assisted Coiling for Intracranial Aneurysms**

Three self-expanding stents, the Neuroform Microdelivery Stent System, the Enterprise Vascular Reconstruction Device and Delivery System, and the Low-Profile Visualized Intraluminal Support Device, have FDA approval through the HDE program for the endovascular treatment intracranial aneurysms. The literature search did not identify any randomized trials of self-expanding stent-assisted treatment of intracranial aneurysms compared with standard neurosurgical treatment (ie, surgical clipping or endovascular coils). The available evidence consists of single-arm case series, registry studies, nonrandomized comparative studies, and 1 systematic review of nonrandomized comparative studies.

**Systematic Reviews**

In 2014, Hong et al reported results of a systematic review and meta-analysis of studies that compared stent-assisted coiling with coiling alone for the treatment of intracranial aneurysms. The
authors included 10 retrospective cohort studies, ranging in size from 9 to 1109 patients. In pooled analysis, compared with coiling alone, stent-assisted coiling was associated with higher rates of progressive thrombosis (37.5% vs 19.4%; OR=2.75; 95% CI, 1.95 to 3.86; p<0.000) and lower rates of recurrence (16.2% vs 34.4%; OR=0.35; 95% CI, 0.25 to 0.49; p<0.000). Mortality was 9.1% for stent-assisted coiling compared with 2.6% for coiling alone, although the difference was not statistically significant (OR=2.31; 95% CI, 0.68 to 7.82; p=0.18). Similarly, permanent complication rates and thromboembolic complication rates did not differ significantly between the 2 groups.

In 2015, Ryu et al conducted a systematic review of studies reporting complications after stent-assisted coiling of ruptured intracranial aneurysms, with a focus on the association of complications with antiplatelet therapy. The review included 33 studies, 3 of which were prospective and the remaining 30 retrospective (total N=1090 patients). In pooled analysis, thromboembolic complications occurred in 108 patients (event rate, 11.2%; 95% CI, 9.2% to 13.6%). Intraprocedural hemorrhage occurred in 46 (event rate, 5.4%; 95% CI, 4.1% to 7.1%).

**Nonrandomized Comparative Studies**

The largest comparative series describing use of stents and coiling alone for treating intracranial aneurysms was described by Piotin et al. They report 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 neurological procedure-related complications occurred in 7.4% (16/216) of those with stents versus 3.8% (42/1109) of those without stents (logistic regression p=0.644; OR=1.289; 95% CI, 0.439–3.779). Procedure-induced mortality occurred in 4.6% (10/216) of the procedures with stents versus 1.2% (13/1109) in the procedures without stents (logistic regression p=0.006; odds ratio: 0.116; 95% CI, 0.025–0.531). 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 stents, with angiographic recurrence in 14.9% (17/114) versus 33.5% (259/774), respectively (p<0.0001; OR=0.3485; 95% CI, 0.2038 to 0.5960).

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 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 (MAPS) Trial. 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<0.000) and had aneurysms with lower dome-to-neck ratio (1.3 vs 1.8; p<0.000). Periprocedural serious AEs occurred in 6.6% of those treated with stent-assisted-coiling, compared with 4.5% of those treated with coiling alone (p=0.039). At 1 year, ischemic strokes were more common in patients who received a stent-assisted coil than in patients who received a coil alone (8.8% vs 2.2%; p=0.005). However, in multivariable analysis, stent use did not independently predict ischemic stroke at 2 years (adjusted OR=1.1; p=0.94).
Consoli et al compared stent-assisted coiling with balloon-assisted coiling in patients with unruptured wide-necked intracranial aneurysms treated at a single center. The study included 268 patients (286 aneurysms), 117 (122 aneurysms) of whom were treated with stent-assisted coiling and 151 (164 aneurysms) of whom were treated with balloon-assisted coiling. At discharge, 97.9% and 97.3% of those in the balloon-assisted and stent-assisted groups, respectively, had mRS scores of 0 or 1 (statistical comparison not reported). After 6 months, 97.9% and 98% of those in the balloon-assisted and stent-assisted groups, respectively, had mRS score of 0 or 1, while mortality rates were 2.6% and 1.7% in the balloon-assisted and stent-assisted groups, respectively (statistical comparisons not reported). At 6 months, aneurysm recurrence rates were 11.1% and 5.8% in the balloon-assisted and stent-assisted groups, respectively. In multivariable analysis, the use of stent-assisted coiling was significantly associated with complete occlusion at the end of the procedure (regression coefficient not reported; \( p=0.024 \)) and complete occlusion after 6 months (regression coefficient not reported; \( p=0.05 \)).

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

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

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

**Comparison Between Endovascular Devices for Intracranial Aneurysms**

Nonrandomized studies, summarized in a 2015 systematic review by King et al, have compared devices used for stent-assisted coiling of intracranial aneurysms. King et al reviewed 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%, \( p<0.001 \)) and
have a higher mortality rate (2.8% vs 1.8%, p=0.04), less likely to have 100% aneurysm occlusion at last follow-up (61.1% vs 74.7%, p<0.001), and more likely to have recanalization (13.9% vs 10.6%, p=0.02). However, conclusions drawn from these findings are influenced by the potential for bias in the underlying studies and between-study heterogeneity.

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

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

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

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

The largest study, reported by Geyik et al, included 468 patients with wide-necked cerebral aneurysms who underwent stent-assisted coiling with the Enterprise, Neuroform, Wingspan, or Leo (self-expanding, Balt, Montmorency, France) stents. Overall mortality was 1.9%; procedure-related complications occurred in 28 patients (6.9%). Angiographic follow-up data, obtained at 6 months to 7 years postprocedure (mean, 19.2 months), were available for 440 patients (94%). For the total of 467 aneurysms with follow-up, complete occlusion occurred in 194 aneurysms (41.6%), near-complete occlusion (>95% occlusion but minimal residual filling with coils at the neck) occurred in 242 aneurysms (51.8%), and incomplete occlusion (<95% occlusion) occurred in 31 aneurysms (6.6%). At 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 another relatively large study, Lee et al reported on 1038 patients treated with endovascular coiling, 296 of whom underwent stent-assisted coiling, with a focus on predictors of procedural
rupture. Three cases of procedural rupture occurred among patients treated with stent-assisted coiling.

Other representative noncomparative studies are summarized in Table 3. Interpretation of these studies is limited by potential selection bias and no comparison group. In general, these series demonstrate high rates of technical success of stent deployment with high rates of aneurysm occlusion; however, variable complication rates, particularly related to thromboembolic events were observed.

Table 3. Noncomparative Studies of Stent-Assisted Endovascular Treatment of Aneurysms

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Population</th>
<th>Intervention</th>
<th>Primary Outcome</th>
</tr>
</thead>
</table>
| Chalouhi et al (2013) | Retrospective case series | 76 patients with PCA aneurysms at a single institution | Endovascular coiling, with or without Neuroform stent assistance (4 patients) or balloon assistance (4 patients) | • 93.4% of patients had technically successful treatment; remaining patients required surgical clipping  
  • Among 67 patients who had successful endovascular treatments and who did not die in the hospital, favorable outcomes (mild, moderate, no disability) were achieved in 85% |
| Chen et al (2013) | Retrospective case series | 10 patients with large and giant fusiform aneurysms of the vertebrobasilar arteries at a single institution | Endovascular treatment with stent placement (Neuroform or Leo [self-expanding, Balt, Montmorency, France], 5 patients), stent-assisted coiling (3 patients), or occlusion of proximal artery (2 patients) | • 9 patients had a good outcome; 1 patient died after stenting procedure  
  • Stent deployment was generally feasible in the vertebrobasilar system |
| Gentric et al (2013) | Prospective cohort; industry-sponsored | 107 patients with unruptured cerebral aneurysms (one of 10 European institutions) | Endovascular treatment with Neuroform stent-assisted coiling | • 94.4% of patients had technically successful treatment. 66.4% of patients had complete occlusion immediately postprocedure  
  • At follow-up at 12-18 mo, 5 patients (5%) had delayed complications, with 3% of patients with thromboembolic events  
  • Of 93 patients with anatomic evaluation available, aneurysms recurred in 9.7% |
| Johnson et al (2013) | Retrospective case series | 91 patients with complex MCA aneurysms not amenable to coiling enrolled at a single | Endovascular treatment with coiling with stent assistance using Neuroform (62 aneurysms), Enterprise (32 aneurysms), Wingspan (1 aneurysm), or a | • All patients had technically successful treatment  
  • 9 patients had new neurologic symptoms following the procedure, 1 |
institution combination (5 aneurysms) or with stenting alone (2 aneurysms), endovascular treatment with stenting alone with long-term disability. There was 1 procedure-related death.
• Of 85 aneurysms with initial follow-up imaging available (usually at 6 mo postprocedure), 77 (90.6%) were completely occluded, and 4 (4.7%) required retreatment

<table>
<thead>
<tr>
<th>Kulcsar et al (2013)</th>
<th>Retrospective case series</th>
<th>117 patients with wide-necked cerebral aneurysms</th>
<th>Endovascular treatment with Neuroform stent-assisted coiling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Stents were successfully deployed in 113 patients with 117 aneurysms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 99 patients had grade 1 or 2 occlusion (complete or aneurysm neck) on immediate postprocedure imaging</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Intraprocedure major thrombotic events occurred in 7 cases (5.9%) and major infarcts on postprocedure imaging in 9 cases (7.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Of 92 aneurysms with follow-up imaging available, 71 (77%) had grade 1 or 2 occlusion</td>
</tr>
</tbody>
</table>

MCA: middle cerebral artery; PCA: posterior cerebellar artery.

**Section Summary: Self-Expanding Stent-Assisted Coiling for Intracranial Aneurysms**

There is a lack of RCT evidence on the efficacy of self-expanding stent-assisted coiling compared with coiling alone or surgical clipping for the treatment of intracranial aneurysms. Nonrandomized studies reported higher complete occlusion rates with stenting, and lower recurrence rates. However, there is also some evidence that AE rates are relatively high with stenting, and 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.

**Flow-Diverting Stents for Intracranial Aneurysms**

**Pivotal Study for FDA Approval**

In 2011, the Pipeline Embolization Device, which is categorized as a flow-diverting stent, received FDA premarket approval. The device’s approval was based on the industry-sponsored Pipeline for Uncollapsible or Failed Aneurysms (PUFA) study, a multicenter, prospective, single-arm trial of the device for treatment of internal carotid artery aneurysms that were uncoilable or had failed coiling, for which results were published in 2013. 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 of 106 aneurysms (73.6%) met the study’s combined primary effectiveness end point of complete occlusion at day 180 without major stenosis or use of adjunctive coils. For 6 of the 107 patients (5.6%) who underwent any catheterization, a primary safety end point (occurrence of major ipsilateral stroke or neurologic death at 180 days) occurred.

**Randomized Controlled Trials**

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

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

**Table 4. Summary of RCT Results of Flow-Diversting Stents for Intracranial Aneurysms**

<table>
<thead>
<tr>
<th>Study (Trial)</th>
<th>Primary Efficacy Outcome</th>
<th>Death</th>
<th>Any Stroke</th>
<th>Any SAE or Complication</th>
<th>Residual Aneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raymond et al (2017)</td>
<td>All patients</td>
<td>N</td>
<td>77</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>Flow diversion (95% CI), %</td>
<td>58 (41 to 73)</td>
<td>5 (1 to 19)</td>
<td>13 (5 to 29)</td>
<td>29 (16 to 46)</td>
<td>18 (8 to 35)</td>
</tr>
</tbody>
</table>
Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

<table>
<thead>
<tr>
<th>Standard treatment (95% CI), %</th>
<th>Treatment effect (95% CI)</th>
<th>Patients with proximal carotid aneurysms</th>
<th>Flow diversion (95% CI), %</th>
<th>Standard treatment (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>64 (47 to 78)¹</td>
<td>NR</td>
<td>54</td>
<td>42 (NR)²</td>
<td>36 (NR)²</td>
</tr>
<tr>
<td>5 (1 to 19)</td>
<td>NR</td>
<td>54</td>
<td>4 (NR)</td>
<td>4 (NR)</td>
</tr>
<tr>
<td>10 (3 to 25)</td>
<td>NR</td>
<td>54</td>
<td>8 (NR)</td>
<td>11 (NR)</td>
</tr>
<tr>
<td>10 (3 to 25)</td>
<td>NR</td>
<td>54</td>
<td>39 (NR)</td>
<td>14 (NR)</td>
</tr>
<tr>
<td>21 (10 to 37)</td>
<td>NR</td>
<td>54</td>
<td>12 (NR)</td>
<td>21 (NR)</td>
</tr>
</tbody>
</table>

CI: confidence interval; NR: not reported; SAE: serious adverse event.

¹ The primary efficacy outcome was a composite of complete or near-complete occlusion of the aneurysm between 3 and 12 months and an independent functional outcome (mRS score ≤2).

Nonrandomized Comparative Studies

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

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

Single-Arm Series

Systematic Reviews

Multiple noncomparative studies have reported on outcomes from flow-diverting stent-assisted treatment of intracranial aneurysms since the introduction of the Pipeline endovascular device. These studies have been summarized in several systematic reviews and meta-analyses. The largest systematic review identified (reported by Briganti et al [2015]) reviewed 18 studies published from 2009 to 2014 (total N=1483 patients; 1704 aneurysms). Most (87.5%) treated aneurysms were in the anterior circulation, and most (87.5%) were saccular in morphology. In the 17 studies reporting procedural complications, the mean incidence rate was 8.3% (range, 0%-23.1%). The mean permanent morbidity occurred in 3.5% of patients (range, 0%-15%), while the mean mortality rate was 3.4% (range, 0.5%-8%). Across the 18 studies, aneurysms were completely occluded in a mean 81.5% of cases (range, 69%-100%).
Earlier systematic reviews by Brinjikji et al (2013) and Arrese et al (2013) similarly reported high estimates for aneurysm occlusion rates (≥75%), but relatively high rates of morbidity and mortality.

**Noncomparative Studies**

Since those reviews, a number of noncomparative studies evaluating flow-diverting stents for the treatment of aneurysms have been published. The largest cohort study identified was by Kallmes et al (2015), who retrospectively analyzed patients treated with the Pipeline device at 17 centers worldwide. The authors identified 793 patients with 906 aneurysms who were enrolled in the International Retrospective Study of Pipeline Embolization Device (IntrePED) registry. Of the total number of aneurysms, were in the anterior ICA circulation and at least 10 mm, 349 of which were in the anterior circulation and less than 10 mm, 59 of which were in the posterior circulation, 179 of which were in a non-ICA anterior circulation location and less than 10 mm, and 10 of which had no aneurysm size specified. The overall neurologic morbidity and mortality rate was 8.4%, highest in the posterior circulation group (16.4%) and lowest in the less than 10-mm ICA group (4.8%; p=0.01). The overall spontaneous rupture rate was 0.6%, and the intracranial hemorrhage rate was 2.4%. Ischemic stroke rates were 4.7%, again highest in the posterior circulation group (7.3%) and lowest in the less than 10-mm ICA group (2.7%; p=0.16). In a subsequent study using data from the same registry, Brinjikji et al (2015) reported on risk factors for hemorrhagic complications after Pipeline device placement. Twenty patients had an intraparenchymal hemorrhage, most often (75%) within 30 days of treatment. The only procedure- or device-related variable associated with intraparenchymal hemorrhage was receiving 3 or more Pipeline devices (OR=4.10; 95% CI, 1.34 to 12.58; p=0.04). Additional analyses from this registry have evaluated the effect of age on outcomes after Pipeline placement and differences in complication rates between aneurysms treated with the Pipeline with or without coil embolization.

The longest follow-up, reported by Chiu et al (2015), is from a series of 98 patients with 119 aneurysms treated with the Pipeline Embolization Device and followed for at least 2 years. Of the 119 aneurysms, all had clinical follow-up, and 88.8% had imaging follow-up for 2 or more years postprocedure. Aneurysm occlusion rates were 81.6%, 84.1%, and 93.2% at 6-month, 1-year, and 2-year follow-ups, respectively. Three (2.8%) cases of in-stent stenosis occurred. From 0 to 6 months, rates of TIA, minor stroke, and major stroke were 4.2%, 3.4%, and 0.8%, respectively.

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

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Primary Outcomes</th>
</tr>
</thead>
</table>
| Strauss et al (2016) | Retrospective case series | 60 patients with 67 anterior or posterior circulation aneurysms | Silk flow-diverting stent (Balt Extrusion)       | • 10 patients had periprocedural complications, 4 of whom died  
• Among 60 aneurysms with available FU imaging (median, 15-mo posttreatment), 88% had good outcomes |
### Section Summary: Self-Expanding Stent-Assisted Coiling for Intracranial Aneurysms

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Study Design</th>
<th>Participants</th>
<th>Procedure Details</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fischer et al (2015)</td>
<td>Retrospective case series</td>
<td>121 patients with 130 intracranial saccular sidewall aneurysms</td>
<td>P64 Flow-Modulated Device (phenox)</td>
<td>1 patient had pulmonary artery embolism, and 2 patients had ischemic lesions with transient neurologic deficits in the periprocedural period. Of 93 aneurysms with available DWI (median, 279 d), 79.6% had complete aneurysm occlusion.</td>
</tr>
<tr>
<td>Brasiliense et al (2016)</td>
<td>Prospective case series</td>
<td>59 patients (70 aneurysms) who had routine postprocedural MRI after placement of flow diversion</td>
<td>Pipeline Embolization Device</td>
<td>5.1% had clinically apparent neurologic symptoms postprocedure. 62.7% had ischemic lesions on DWI postprocedure.</td>
</tr>
<tr>
<td>Chalouhi et al (2015)</td>
<td>Retrospective case series</td>
<td>100 patients with aneurysms ≤7 mm (1 institution)</td>
<td>Pipeline Embolization Device</td>
<td>Complications in 3% (1 distal parenchymal hemorrhage, 2 ischemic events). At last FU (mean, 6.3 mo), 72% of aneurysms completely occluded. Retreatment required in 8%.</td>
</tr>
<tr>
<td>Lubicz et al (2015)</td>
<td>Retrospective review of prospectively collected data</td>
<td>58 patients with 70 intracranial aneurysms (2 institutions)</td>
<td>SILK artery reconstruction device (Balt Extrusion)</td>
<td>No periprocedural deaths occurred. Overall permanent neurologic morbidity was 5.5%. At long-term FU, 73% had complete occlusion, 16% had neck remnants, 11% had incomplete occlusion.</td>
</tr>
<tr>
<td>Wakhloo et al (2015)</td>
<td>Prospective multicenter trial at 24 centers</td>
<td>165 patients with 190 intracranial aneurysms</td>
<td>Surpass flow-diverting device (Stryker Neurovascular)</td>
<td>At 6-mo FU, permanent neurologic morbidity was 6% and mortality was 2.7%. Neurologic death during FU occurred in 1.6% of patients with anterior circulation aneurysms and 7.4% with posterior circulation aneurysms. Ischemic stroke at ≤30 d, SAH at ≤7 d, and intraparenchymal hemorrhage at ≤7 d occurred in 3.7%, 2.5%, and 2.5% of subjects, respectively.</td>
</tr>
<tr>
<td>Kan et al (2012)</td>
<td>Prospective case series (registry)</td>
<td>56 patients with intracranial aneurysm (7 institutions)</td>
<td>Pipeline Embolization Device</td>
<td>6/123 devices incompletely deployed. Among 19 patients with 6-mo FU, 13 had complete aneurysm occlusion. 4 fatal postprocedural hemorrhages occurred.</td>
</tr>
<tr>
<td>Piano et al (2013)</td>
<td>Retrospective case series</td>
<td>101 patients with intracranial aneurysm (1 institution)</td>
<td>Flow-diverting stent placement (Pipeline Embolization Device or SILK device), with or without endovascular coiling</td>
<td>86% of aneurysms evaluated at 6-mo FU showed complete occlusion.</td>
</tr>
<tr>
<td>Toma et al (2013)</td>
<td>Retrospective case series</td>
<td>84 patients with intracranial aneurysm (1 institution)</td>
<td>Flow-diverting stent</td>
<td>61% of aneurysms resolved at 12 mo. 9.5% of patients had a new, permanent neurologic deficit and 5.9% had procedure-related mortality.</td>
</tr>
</tbody>
</table>

**Note:** DWI: diffusion-weighted imaging; FU: follow-up; MRI: magnetic resonance imaging; SAH: subarachnoid hemorrhage.
One RCT has evaluated flow-diverting stents. The FIAT pragmatic RCT and registry study compared flow diversion with standard management (observation, coil embolization, or parent vessel occlusion) in patients for whom flow diversion was considered a promising treatment. FIAT was stopped early due to safety concerns after 112 participants (78 in the randomized part of the study and 34 in the registry) were enrolled. Sixteen percent of patients who were randomized to flow diversion or received flow diversion at any time were dead or dependent at 3 months or later, which crossed a predefined safety boundary. The efficacy of flow diversion was also below expectations. While morbidity and mortality were lower for proximal carotid aneurysms than for posterior circulation aneurysms and results of flow diversion were more encouraging for aneurysms amenable to coil embolization, patients allocated to standard treatment appeared to do at least as well as those assigned to flow diversion.

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

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

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

For individuals who have symptomatic intracranial arterial stenosis who receive intracranial percutaneous transluminal angioplasty with or without stenting, the evidence includes 2 RCTs and a number of nonrandomized comparative studies and case series. Relevant outcomes are overall survival, symptoms, morbid events, functional outcomes, and treatment-related mortality and morbidity. Both available RCTs have demonstrated no significant benefit with endovascular therapy. In particular, the SAMMPRIS trial was stopped early due to harms, because the rate of stroke or death at 30 days posttreatment was higher in the endovascular arm, which received percutaneous angioplasty with stenting. Follow-up of SAMMPRIS subjects has demonstrated no long-term benefit from endovascular therapy. Although some nonrandomized studies have suggested a benefit from endovascular therapy, the available evidence from 2 RCTs does not suggest that intracranial percutaneous transluminal angioplasty with or without stenting improves outcomes for individuals with symptomatic intracranial stenosis. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who have intracranial aneurysm(s) who receive endovascular coiling with intracranial stent placement or intracranial placement of a flow-diverting stent, the evidence includes an RCT, several nonrandomized comparative studies, and multiple single-arm studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related mortality and morbidity. The available nonrandomized comparative studies have reported occlusion rates for stent-assisted coiling that are similar to or higher than coiling alone and recurrence rates that may be lower than those for coiling alone. For stent-assisted coiling with self-expanding stents, some evidence has also shown that adverse event rates are relatively high, and a nonrandomized comparative trial has reported that mortality is higher with stent-assisted coiling than with coiling alone. For placement of flow-diverting stents, a pragmatic RCT and registry study have compared flow diversion with standard management (observation, coil embolization, or parent vessel occlusion) in patients for whom flow diversion was considered a promising treatment. The pragmatic study was stopped early after crossing a predefined safety boundary when 16% of patients treated with flow diversion were dead or dependent at 3 months or later. Flow diversion was also not as effective as the investigators had hypothesized. A nonrandomized study comparing the flow-diverting stents with endovascular coiling for intracranial aneurysms has demonstrated higher rates of aneurysm obliteration in those treated with the Pipeline endovascular device than those treated with coiling, with similar rates of good clinical outcomes. The evidence does not provide high certainty whether stent-assisted coiling or placement of a flow-diverting stent improves outcomes for patients with intracranial aneurysms because the risk-benefit ratio cannot be adequately defined. The evidence is insufficient to determine the effects of the technology on health outcomes.
SUPPLEMENTAL INFORMATION

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, input was received from 4 physician specialty societies and 2 academic medical centers while this policy was under review in 2014. Request for clinical input in 2014 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) or who present outside the range of time for which tPA would be considered (within 8 hours of last known normal state or symptom onset).

2011 Input
In response to requests, input was received from 4 physician specialty societies and 2 academic medical centers while this policy was under review in 2014. 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 select patients with intracranial aneurysms; ie, 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

Society of Vascular and Interventional Neurology
In 2016, the Society of Vascular and Interventional Neurology published recommendations on comprehensive stroke center requirements and endovascular stroke systems of care. The recommendations were based on 5 multicenter, prospective, randomized, open-label, blinded endpoint 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 published guidelines for the early management of patients with acute ischemic stroke. These guidelines include several recommendations relevant to the use of endovascular therapies for acute stroke (see Table 6).

**Table 6. Recommendations on Use of Endovascular Therapies to Manage Acute Stroke**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Mechanical thrombectomy requires the patient to be at an experienced stroke center with rapid access to cerebral angiography, qualified neurointerventionalists, and a comprehensive periprocedural care team. Systems should be designed, executed, and monitored to emphasize expeditious assessment and treatment. Outcomes for all patients should be tracked. Facilities are encouraged to define criteria that can be used to credential individuals who can perform safe and timely intra-arterial revascularization procedures.”</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
| “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  |
| IIb B-NR |
| “The use of proximal balloon guide catheter or a large bore distal access catheter rather than a cervical guide catheter alone in conjunction with stent retrievers may be beneficial. Future studies should examine which systems provide the highest recanalization rates with the lowest risk for nontarget embolization.” | IIa | C-LD |
| In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the 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” | IIa | C   |
Recommendation | COR | LOE
---|---|---
Contraindications are time-based or nontime based (e.g., prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications).” | 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 M2 or M3 portion of the MCAs.” | IIb | 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 anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.” | IIb | B-R

“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 pre-stroke 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 | C-LD

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

“Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of intravenous alteplase might be considered, but the consequences are unknown.” | IIb | C-EO

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

The 2 associations also published joint guidelines on the management of patients with unruptured intracranial aneurysms in 2015.136 These guidelines included the following recommendations relevant to the use of endovascular therapies for aneurysms (see Table 7).

Table 7. Recommendations on Management of Unruptured Intracranial Aneurysms

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“...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”</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>“...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”</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>“Endovascular treatment of unruptured intracranial aneurysms is recommended to be performed at high-volume centers.”</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

COR: class of recommendation; LOE: level of recommendation.
**U.S. Preventive Services Task Force Recommendations**

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

**Medicare National Coverage**

A Medicare National Coverage Determination (NCD) on intracranial angioplasty and stenting was released by the Centers for Medicare and Medicaid Services (CMS) in January 2007. This decision was based on a review of available studies at that time, which consisted of several uncontrolled case series. CMS review indicated that this evidence was promising and that, while further well-designed RCTs were needed to confirm whether outcomes were improved, coverage should be allowed. The NCD contained the following coverage determinations:

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

**Ongoing and Unpublished Clinical Trials**

**Table 8. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endovascular interventions for acute ischemic stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01852201</td>
<td>POSITIVE: Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy</td>
<td>33</td>
<td>Mar 2018 (suspended)</td>
</tr>
<tr>
<td>NCT01983644</td>
<td>RECO Flow Restoration Device Versus Intravenous t-PA for Stroke Within 4.5h of Symptom Onset: a Prospective Randomized Control Trial (RESTORE)</td>
<td>130</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02216643*</td>
<td>Randomization of Endovascular Treatment With Solitaire FR® vs. Best Medical Therapy in Acute Ischemic Stroke Due to Large Vessel Occlusion Trial (RESILIENT)</td>
<td>690</td>
<td>Sep 2019</td>
</tr>
<tr>
<td>NCT02737189</td>
<td>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</td>
<td>318</td>
<td>Dec 2020</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01455935</td>
<td>Wake up Symptomatic Stroke in Acute Brain Ischemia (WASSABI) Trial</td>
<td>90</td>
<td>Feb 2014 (unknown)</td>
</tr>
<tr>
<td><strong>Endovascular interventions for symptomatic intracranial atherosclerotic disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
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</tr>
<tr>
<td>NCT01763320</td>
<td>China Angioplasty &amp; Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A Prospective Multicenter, Randomized Controlled Trial</td>
<td>380</td>
<td>Dec 2017</td>
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<tr>
<td><strong>Stent-assisted endovascular treatment of intracranial aneurysms</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01340612</td>
<td>Stenting in the Treatment of Aneurysm Trial (STAT)</td>
<td>600</td>
<td>Jan 2020</td>
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<tr>
<td>NCT03269942</td>
<td>Results of Revascularization Versus Endovascular Flow Diversion</td>
<td>110</td>
<td>Jun 2018</td>
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<tr>
<td></td>
<td>in Treatment of Complex Intracranial Aneurysms of Anterior Circulation</td>
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<td></td>
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<tr>
<td>NCT01340612</td>
<td>Stenting in the Treatment of Large, Wide-necked or Recurring</td>
<td>600</td>
<td>Jan 2020</td>
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</tbody>
</table>
Intracranial Aneurysms

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Study Title</th>
<th>Enrollment</th>
<th>Start Date</th>
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<tbody>
<tr>
<td>NCT02998229*</td>
<td>ARTISSE Aneurysm Treatment Using Intrasaccular Flow Diversion With the ARTISSE™ Device</td>
<td>150</td>
<td>Nov 2020</td>
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<tr>
<td>NCT01716117a</td>
<td>The Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide Neck Aneurysms (SCENT Trial)</td>
<td>180</td>
<td>Dec 2020</td>
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Unpublished

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<th>NCT Number</th>
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<tbody>
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<td>NCT01762137</td>
<td>LARGE Aneurysm Randomized Trial: Flow Diversion Versus Traditional Endovascular Coiling Therapy</td>
<td>23</td>
<td>Feb 2017 (terminated)</td>
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<td>NCT01811134</td>
<td>Flow Diverter Stent for Endovascular Treatment of Unruptured Saccular Wide-necked Intracranial Aneurysms (EVIDENCE)</td>
<td>130</td>
<td>Nov 2017</td>
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VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References


