Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

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 TPA and supportive care for acute stenosis, and as an alternative to risk factor modification for chronic stenosis. For cerebral aneurysms, stent-assisted coiling has been evaluated as an alternative to endovascular coiling in patients whose anatomy is not amenable to simple coiling.

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.\textsuperscript{1} Eighty-seven percent of strokes are ischemic and 13% hemorrhagic. Differentiation between the 2 types of stroke is necessary to determine the appropriate treatment. Ischemic stroke occurs when an artery to the brain is blocked by a blood clot, which forms in the artery (thrombotic), or when another substance (ie, plaque, fatty material) or a blood clot travels to an artery in the brain causing a blockage (embolism).\textsuperscript{2} Recanalization of the vessel, particularly in the first few hours after occlusion, reduces rates of disability and death.\textsuperscript{3}

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.\textsuperscript{4} 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 (eg, calcium channel blockers) and transluminal balloon angioplasty may be used.\(^7,8\) 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 2 ways: either due to embolism or low-flow ischemia in the absence of collateral circulation. Recurrent annual stroke rates are estimated at 4% to 12% per year with atherosclerosis of the intracranial anterior circulation and 2.5% to 15% per year with lesions of the posterior (vertebrobasilar) circulation. Medical treatment typically includes either anticoagulant therapy (ie, warfarin) or antiplatelet therapy (eg, aspirin). The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial was 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 1 study at 45%, with recurrent events within 1 month of the initial event. Surgical approaches have met with limited success. The widely cited extracranial-intracranial (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 PTA as a minimally invasive treatment of this difficult-to-treat population. Most published studies of intracranial PTA have focused on vertebrobasilar circulation. Two endovascular devices have FDA approval for treatment of symptomatic intracranial stenosis and are considered here (see Regulatory Status section).

**Cerebral Aneurysms**

Compared with acute ischemic stroke, cerebral aneurysms have a much lower incidence among the U.S. population, with prevalence between 0.5% and 6% of the population.\(^9\) However, they are
Associated with significant morbidity and mortality due to subarachnoid hemorrhage resulting from aneurysm rupture. 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/follow-up procedures. In 2011, the Pipeline® Embolization Device, which falls into a new device category called “intracranial aneurysm flow diverters,” or flow-diverting stent, received FDA premarket approval for endovascular treatment of large or giant wide-necked intracranial aneurysms in the internal carotid artery. The Pipeline device is a braided, wire mesh device that is placed within the parent artery of an aneurysm to redirect blood flow away from the aneurysm with the goal of preventing aneurysm rupture and possibly decreasing aneurysm size.

Regulatory Status

Several devices for endovascular treatment of intracranial arterial disease were cleared for marketing by FDA through either 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. FDA product code: NRY.

- **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. FDA product code: NRY.

- **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. FDA product code: NRY.

- **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. 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>Approval Date</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merci® Retriever (Concentric Medical, CA; acquired by Stryker Neurovascular, MI, in 2011)</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, Alameda, CA)</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>
</tbody>
</table>

**Stent retrievers**

<table>
<thead>
<tr>
<th>Device</th>
<th>Approval Date</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitaire™ FR Revascularization Device (Covidien/ev3 Neurovascular, Irvine, CA)</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, Kalamazoo, MI)</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 4000 or fewer incidents 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 through the premarket approval process for the endovascular treatment of adults (≥22 years) with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments (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, Miami Lakes, FL) was approved by FDA through the HDE process for use with embolic coils for treatment of wide-neck, intracranial, saccular or 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.

### Related Policies

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

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

Intracranial stent placement is considered **not medically necessary** in the treatment of intracranial aneurysms except as noted above.

Intracranial percutaneous transluminal angioplasty with or without stenting is considered **not medically necessary** in the treatment of atherosclerotic cerebrovascular disease.

The use of endovascular mechanical embolectomy with a device with FDA approval for the treatment of acute ischemic stroke may be considered **medically necessary** as part of the treatment of acute ischemic stroke for patients who meet all of the following criteria:

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

Endovascular interventions are considered **not medically necessary** for the treatment of acute ischemic stroke when the above criteria are not met.

**Benefit Application**

The BCBS FEP contract stipulates that FDA-approved biologics, drugs and certain devices may not be considered investigational when used for their intended purpose and thus these products may only be assessed based on medical necessity.
Policy Guidelines

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 cm³ for subjects age 18 to 79 years;
    - 20 cm³ for subjects age 80 to 85 years;
  - CT-assessed core infarct lesion greater than:
    - 40 cm³ for subjects age 18 to 79 years;
    - 15 cm³ for subjects age 80 to 85 years;
For all subjects, severe hypoperfusion lesion ($\geq$10-second Tmax lesion larger than 100 cm$^3$); outer
For all subjects, ischemic penumbra of 15 cm$^3$ re more and mismatch ratio great 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.

**Other Policy Guidelines**

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

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

**Rationale**

Assessment of efficacy for therapeutic intervention involves determining whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

**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**

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

An earlier (2014) BCBSA TEC Assessment evaluated endovascular therapy for acute ischemic stroke in adults. The Assessment identified 5 multicenter RCTs meeting selection criteria, 3 of which compared endovascular treatment with standard stroke care (Broderick et al, Ciccone et al, Kidwell et al), and 2 of which included newer and older endovascular treatments (Saver et al, Nogueira et al). The Assessment made the following overall observations and conclusions:

“The 3 RCTs published in early 2013 concluded that endovascular treatment is no more effective than IV tPA in reducing disability among patients with acute ischemic stroke treated 3 to 8 hours after symptom onset. Although specific aspects of these trials have been criticized, we identified no RCTs that demonstrate endovascular treatments produce better health outcomes. Use of newer FDA-cleared endovascular devices was allowed. A major limitation in generalizing from these studies is that the number of patients treated with each of these newer devices was small. Therefore, as noted by critics of the trials, evidence on the new devices may not substantively impact the overall outcomes. If the newer devices are more effective than the older ones, the results might be dominated by the performance of the less effective, older device(s).”

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.

Several published systematic reviews have incorporated some of the RCTs comparing endovascular therapies and standard therapy. In 2015, Fargen et al published a meta-analysis of prospective RCTs evaluating endovascular therapies for acute stroke, which included 4 RCTs (Broderick et al, Ciccone et al, Kidwell et al, Berkhemer et al) but not the more recently published RCTs by Campbell et al, Goyal et al, Saver et al, and Jovin et al. In pooled analysis of the subgroup of patients with large vessel occlusion, patients randomized to endovascular therapy were more likely to have an mRS score of 0 to 2 at 90 days than patients randomized to standard care (38.3% vs 25.8%; odds ratio [OR],
1.67; 95% confidence interval [CI], 1.29 to 2.16; p<0.001). In 2013, Singh et al published results from a systematic review and meta-analysis of RCTs evaluating the use of endovascular therapy for patients with acute ischemic stroke. The systematic review found no significant improvements in any of the outcomes evaluated in patients who received endovascular therapies compared with those receiving IV thrombolysis. The results of these systematic reviews are less relevant given the availability of more recent RCT data.

Several systematic reviews were published before RCT results were available, including those by Mokin et al (2012), Almekhlafi et al (2013), Baker et al (2011), and Stead et al (2008).

**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. 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.

**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 that had imaging-based evidence of a large ischemic core, indicated by an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of less than 7 on non–contrast 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).

**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.\(^\text{15}\) 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.\(^{20}\) 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.\(^{13}\) 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 2013.19 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).18 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 2014, 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).

**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.

**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 studies are briefly described here. One of the larger nonrandomized, comparative studies was by Rai et al, which included 223 patients with acute strokes involving the internal carotid artery, the middle cerebral artery, or the bifurcation of the middle cerebral artery. A total of 100 patients were treated with IV thrombolysis and 123 patients were treated with an endovascular intervention. The primary outcome measure was a good clinical outcome at 3 months, defined as an mRS score of 2 or less. A good clinical outcome was achieved by 44.7% in the endovascular group and 26% in the IV thrombolysis group (OR for good outcome, 2.3; 95% CI, 1.3 to 4.1; p=0.003).

Other prospective comparative studies include those by Urra et al, which assessed 78 patients with acute ischemic stroke due to large vessel occlusion and mild symptoms; Song et al evaluated stent retrievers and intra-arterial thrombolysis among 105 patients; Alexandrov et al, which evaluated the Penumbra system in 125 acute stroke patients; and Taschner et al, in which 22 patients were treated with the Penumbra system and compared with matched controls treated with tPA.

**Nonrandomized, Comparative Studies Evaluating Specific Endovascular Interventions**

Some nonrandomized comparative studies have compared the outcomes of different types of endovascular interventions.

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).

For example, 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.

**Noncomparative Studies**

Many single-arm studies have reported results from various endovascular interventions for acute stroke. Many of the studies predated the IMS III, SYNTHESIS Expansion, MR RESCUE, and MR CLEAN RCTs outlined earlier. Representative studies include Flint et al, which reported outcomes from 80 patients treated with the Merci device for occlusion of the intracranial internal carotid artery; Lin et al, which reported outcomes from 75 patients with internal carotid artery terminus occlusions who received endovascular interventions with either intra-arterial thrombolitics or mechanical embolectomy with the Merci device. Multiple small, single-center case series and other smaller case series, which often included only intermediate outcomes such as vessel recanalization evaluating endovascular treatments for acute stroke, also exist in the literature. Multiple noncomparative retrospective and prospective studies reporting outcomes from endovascular therapies with the newer generation stent-retriever devices, which are currently FDA-approved (eg, Solitaire FR, Trevo) and with non-FDA approved devices (eg, Penumbra Separator 3D) have been published. While these studies do not directly provide evidence about the benefit of endovascular interventions compared with standard care for acute stroke, they do suggest significant variability in clinical outcomes at 3 months in patients treated with stent-retriever devices, with rates of good clinical outcomes ranging from 39% to 77%.

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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 intra-arterial with optional IV thrombolytic therapy) were compared with those who received standard medical therapy (IV thrombolytic therapy and/or medical antithrombotic treatment.) Seventy-eight percent of the patients received endovascular intervention, with thrombectomy alone in 67 patients. Devices used included the Merci system in 43%, the Solitaire FR device in 13%, and the Trevo retriever in 18%, with devices not available in the 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.

A number of studies have reported noncomparative evaluations of 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 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).

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%.\(^8\) 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.\(^8\) 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.\(^8\) 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 (\( p = 0.043 \)).

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**Table:**

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<thead>
<tr>
<th>Section: Medicine</th>
<th>Effective Date: January 15, 2016</th>
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</thead>
<tbody>
<tr>
<td>Subsection: Medicine</td>
<td>Original Policy Date: December 7, 2011</td>
</tr>
<tr>
<td>Subject: Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)</td>
<td>Page: 21 of 47</td>
</tr>
</tbody>
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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. A 2005 Cochrane review of angioplasty and stenting for vertebral artery stenosis identified only the CAVATAS trial for inclusion and concluded: “... there is currently insufficient evidence to support the routine use of percutaneous transluminal angioplasty (PTA) and stenting for vertebral artery stenosis. Endovascular treatment of vertebral artery stenosis should only be performed within the context of randomized controlled trials.” In addition, the authors noted: “[l]ittle is known about the natural history of vertebral artery stenosis and what constitutes best medical treatment. Future trials should concentrate on comparing different medical treatment such as antiplatelet and anticoagulant drugs, as well as comparing endovascular intervention with medical treatment.”

A 2006 Cochrane review addressed angioplasty for intracranial artery stenosis. The authors identified no RCTs but 79 publications consisting of case series with 3 or more cases. The safety profile showed an overall perioperative rate of stroke of 7.9% (95% CI, 5.5% to 10.4%) and perioperative stroke or death of 9.5% (95% CI, 7.0% to 12.0%). The authors concluded the evidence insufficient to recommend angioplasty with or without stent placement in routine practice for the prevention of stroke in patients with intracranial artery stenosis.

Groschel et al conducted a systematic review on outcomes after stenting for intracranial atherosclerosis. The authors identified 31 studies including 1177 procedures, which had mainly been performed in patients with a symptomatic (98%) intracranial high-grade stenosis (mean, 78.7%) with high technical success rates (median, 96%; IQR, 90%-100%). The periprocedural minor or major stroke
and death rates ranged from 0% to 50% (median, 7.7%). Periprocedural complications were significantly higher in the posterior than the anterior circulation (12.1% vs 6.6%, p<0.01), but did not differ between patients treated with a balloon-mounted stent (n=906) versus those treated with a self-expandable stent (n=271; 9.5% vs 7.7%, respectively; p=0.47). Restenosis greater than 50% occurred more frequently after the use of a self-expandable stent (16/92 [17.4%]; mean follow-up time, 5.4 months) than a balloon-mounted stent (61/443 [13.8%]; mean follow-up time, 8.7 months; p<0.001). The authors concluded that although intracranial stenting appears to be feasible, AEs vary widely, and thus given a high rate of restenoses and no clear impact of new stent devices on outcome, the widespread application of intracranial stenting outside the setting of randomized trials and in inexperienced centers currently does not seem to be justified.

In 2014, 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 studies that were retrospective or based on registry data provide relatively weak evidence on the comparative efficacy of endovascular procedures versus medical therapy for intracranial atherosclerosis. A representative sample of such studies is given next. All are limited by their nonrandomized treatment assignments and systematic differences between groups.

Tang et al retrospectively compared 53 patients with at least 70% intracranial stenosis treated with stenting and 61 patients treated with medical therapy matched for age, sex, vascular risk factors, degree of baseline stenosis, and baseline functional status. After a mean follow-up of 17.3 months, a composite outcome of stroke, TIA, or vascular death did not differ between the stent group and the medical therapy group (22.6% vs 24.6%, respectively; p=0.99). A good functional outcome, defined as an mRS scores of 0 to 3, was more frequent in the stent group than in the medical therapy group (94.3% vs 78.7%, respectively; p=0.045).

Qureshi et al compared outcomes of angioplasty with (n=22) or without stenting (n=22) in patients with symptomatic intracranial stenosis 50% or greater who were identified retrospectively from a registry (angioplasty was used preferentially in patients with more technically challenging lesions). At 12 months, no differences in stroke-related outcomes or mortality were noted (stroke-free survival of 95% and 93% after stenting and angioplasty alone, respectively). The small sample, nonrandom treatment assignment, and event rates prevented valid comparisons. Further, comparison with medical therapy is required.

Samaniego et al retrospectively reviewed outcomes at a single institution comparing study of best medical therapy with angioplasty and stenting in 111 patients with symptomatic intracranial atherosclerotic disease treated from July 2004 to September 2007. Treatment decisions were made
by a multidisciplinary committee. Important baseline differences between the best medical therapy and angioplasty groups, respectively, included presenting with acute stroke (74% vs 57%) or TIA (26% vs 43%), to the emergency department (53% vs 28%), to outpatient (19% vs 47%), or prior TIA (19% vs 55%). The best medical therapy group also had more diffuse disease (vs single lesions) than the angioplasty group (67% vs 28%, respectively). In this series, 31 lesions were treated with the Wingspan system, 12 with the Neuroform stent, and 14 with various balloon-expandable stent systems. Mean follow-up was 14 months in both groups. Combined ischemic end points of TIA, stroke, and vascular death were similar (24% [n=14] in the best medical therapy group, 28% [n=15] in the angioplasty and stenting group). However, inability to account for nonrandom treatment assignment and systematic differences between groups prevents conclusions.

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 neurologic procedure-related complications occurred in 7.4% (16/216) of those with stents versus 3.8% (42/1109) of those without stents (logistic regression p=0.644; OR=1.289; 95% CI, 0.439 to 3.779). Procedure-induced mortality occurred in 4.6% (10/216) of the procedures with stents versus 1.2% (13/1109) in the procedures without stents (logistic regression p=0.006; OR=0.116; 95% CI, 0.025 to 0.531). At the time of publication, the authors had followed 53% (114/216) 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<0.001; OR=0.349; 95% CI, 0.2038 to 0.5960).

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 of 14.5-month follow-up, the recurrence rate was lower for the stented group at 15.4% (4/26) than 41.5% (17/41) in the nonstented group (p<0.05).

A nonrandomized 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) and 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.

In 2013, Kadkhodayan et al reported results from a nonrandomized comparison of the Neuroform and Enterprise systems in the treatment of intracranial aneurysms not amenable to surgical clipping based on evaluation of prospectively collected registry data. Patients who received the Neuroform device (n=160) were enrolled starting in February 2003, and patients who received the Enterprise device (n=98) were enrolled starting in March 2007. Indications for the devices differed slightly based on FDA HDE criteria: both have an indication for wide-necked aneurysms (neck, ≥4 mm or a dome-to-neck ratio, <2 mm) not amenable to surgical clipping. For the Enterprise, stents were used for saccular or fusiform aneurysms arising from a parent vessel with a diameter of 2.5 mm or more and 4 mm or less; for the Neuroform, stents were used for saccular aneurysms arising from a parent vessel with a
diameter of 2 mm or more and 4.5 mm or less. The authors reported that Enterprise deployment success was high (108/115 attempts [93.9%]) compared with Neuroform (173/214 attempts [80.8%], p=0.001). Rates of stent movement, misplacement, and symptomatic hemorrhage were similar for the 2 stent types, but symptomatic thromboembolic events were more frequent with the Enterprise stent (8.7% vs 1.4%, p=0.002).

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<0.001) and had aneurysms with lower dome-to-neck ratio (1.3 vs 1.8; p<0.001). 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).

Liu et al compared outcomes for patients with posterior communicating artery aneurysms treated with stent-assisted coiling with those treated with coiling alone in a retrospective comparative study. A total of 291 coiling procedures were performed, including 56 aneurysms treated with a self-expandable stent. Complete aneurysm occlusion on initial angiography occurred in 41.1% of stent-assisted coiling patients compared with 35.3% of 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 (stated to be nonsignificantly different).

**Single-Arm Series**

A large number of single-arm series have reported outcomes for stent-assisted coiling. 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.
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. Other representative noncomparative studies are summarized in Table 2.

Interpretation of these studies is limited by potential selection bias and no comparison group. In general, these series demonstrate high rates of technical success of stent deployment with high rates of aneurysm occlusion; however, variable complication rates, particularly related to thromboembolic events were observed. Long-term follow-up, particularly beyond 1 year, is limited.

Table 2. 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>
<tbody>
<tr>
<td>Chalouhi et al (2013)</td>
<td>Retrospective case series</td>
<td>76 patients with PCA aneurysms at a single institution</td>
<td>Endovascular coiling, with or without Neuroform stent assistance (4 patients) or balloon assistance (4 patients)</td>
<td>• 93.4% of patients had technically successful treatment; remaining patients required surgical clipping&lt;br&gt;• 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%</td>
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<tr>
<td>Chen et al (2013)</td>
<td>Retrospective case series</td>
<td>10 patients with large and giant fusiform aneurysms of the vertebrobasilar arteries at a single institution</td>
<td>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)</td>
<td>• 9 patients had a good outcome; 1 patient died after stenting procedure&lt;br&gt;• Stent deployment was generally feasible in the vertebrobasilar system</td>
</tr>
<tr>
<td>Gentric et al (2013)</td>
<td>Prospective cohort; industry-sponsored</td>
<td>107 patients with unruptured cerebral aneurysms enrolled at one of 10 European institutions</td>
<td>Endovascular treatment with Neuroform stent-assisted coiling</td>
<td>• 94.4% of patients had technically successful treatment. 66.4% of patients had complete occlusion immediately postprocedure&lt;br&gt;• At follow-up at 12-18 mo, 5 patients (5%) had delayed complications, with 3% of patients with thromboembolic events</td>
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</tbody>
</table>
### Study Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Population</th>
<th>Intervention</th>
<th>Primary Outcome</th>
</tr>
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<tbody>
<tr>
<td>Johnson et al (2013)¹⁰⁹</td>
<td>Retrospective case series</td>
<td>91 patients with complex MCA aneurysms not amenable to coiling enrolled at a single institution</td>
<td>Endovascular treatment with coiling with stent assistance using Neuroform (62 aneurysms), Enterprise (32 aneurysms), Wingspan (1 aneurysm), or a combination (5 aneurysms) or with stenting alone (2 aneurysms), endovascular treatment with stenting alone</td>
<td>Of 93 patients with anatomic evaluation available, aneurysms recurred in 9.7%</td>
</tr>
<tr>
<td>Kulcsar et al (2013)¹¹⁰</td>
<td>Retrospective case series</td>
<td>117 patients with wide-necked cerebral aneurysms</td>
<td>Endovascular treatment with Neuroform stent-assisted coiling</td>
<td>All patients had technically successful treatment</td>
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<td></td>
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<td>9 patients had new neurologic symptoms following the procedure, 1 with long-term disability. There was 1 procedure-related death.</td>
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<td>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</td>
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</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

In 2011, the Pipeline Embolization Device, which is categorized as a flow-diverting stent, received FDA premarket approval. The device's approval was based on the industry-sponsored Pipeline for Uncoilable or Failed Aneurysms (PUFA) study, a multicenter, prospective, single-arm trial 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.

The literature search did not identify any randomized trials of flow-diverting stent treatment of intracranial aneurysms compared with standard neurosurgical treatment (ie, surgical clipping or endovascular coils). The available evidence related to the use of flow-diverting stents consists of 1 nonrandomized comparative study and multiple single-arm case series.

Nonrandomized Comparative Studies

In 2013, Chalouhi et al reported outcomes from patients with unruptured, large or giant aneurysms treated with the Pipeline device enrolled in a registry compared with those treated with endovascular coiling. They identified a total of 229 patients during their data collection period from 2004 to 2013, 54 treated with the Pipeline device and 175 with coiling. Patients treated with the Pipeline device were significantly older and had significantly larger aneurysms that were more likely to be fusiform. Because of this, the authors excluded patients with fusiform or anterior communicating artery aneurysms and conducted their analysis in 160 patients (40 Pipeline patients, 120 coil patients) who were matched in a 1:3 ratio on the basis of patient age and aneurysm size. Aneurysm neck size, overall size, and anterior versus posterior circulation location were similar between groups. Of patients treated with the Pipeline device, 4 patients (10%) also required adjunctive coil placement. Of patients treated with endovascular coiling, 67 (56%) were treated with coiling, while 52 (43%) were treated with stent-assisted coiling and 1 (1%) with balloon-assisted coiling. Primary outcomes included obliteration of the aneurysm on follow-up imaging and clinical outcomes, measured by mRS scores of 0 to 2 (vs 3-6). At the time of latest follow-up, a higher proportion of aneurysms treated with the Pipeline device compared with those treated with coiling achieved complete obliteration (30/35 [86%] vs 37/90 [41%], p<0.001). However, angiographic follow-up was available for a greater proportion of patients treated with the Pipeline (35/40 [87.5%]) than those treated with coiling (90/120 [75%]), and the median angiographic follow-up time differed significantly between the groups (7 months in the Pipeline group, 12 months in the coil group; p<0.001). In terms of clinical outcomes, similar proportions of the Pipeline and the coil groups had mRS scores of 0 to 2 (35/38 [92%] in the Pipeline group vs 97/103 [94%] in the coiling group, p=0.8). Similar to the angiographic follow-up results, the median clinical follow-up time differed significantly between the groups. Treatment type was not significantly associated with rates of procedure-related
complications. While this study directly compared patients treated with the Pipeline endovascular device and those treated with coiling, it is limited by its nonrandomized, retrospective design. In particular, patients treated with coiling were treated in an earlier period (2004-2011) than those treated with the Pipeline device (2011-2012); this may have systematically biased the study in favor of the Pipeline device because aspects of neurointerventional care other than the device used may have differed over time.

In 2014, van Rooij et al reported outcomes for 550 consecutive patients treated with endovascular methods for intracranial aneurysms at a single European center from 2009 to 2013. Endovascular treatments consisted of selective coiling in 445 (80.8%), stent-assisted coiling in 68 (12.4%), balloon-assisted coiling in 13 (2.4%), parent vessel occlusion in 12 (2.2%), and flow-diverter treatment in 12 (2.2%). Among the 11 patients treated with flow diverters, 2 patients had ruptured dissecting aneurysms, 2 deaths occurred, 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**

Multiple noncomparative studies have reported 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 meta-analysis (by Brinjikji et al, published in 2013) included 1451 patients with 1654 aneurysms reported in a total of 29 studies published through 2012. The authors evaluated aneurysmal occlusion rates at 6 months, and procedure-related morbidity, mortality, and complications across studies. They found a high rate of complete aneurysmal occlusion (76%; 95% CI, 70% to 81%), but also a high rate of procedure-related morbidity and mortality (5% [95% CI, 4% to 7%] and 4% [95% CI, 3% to 6%], respectively).

Also in 2013, Arrese et al reported a meta-analysis that used somewhat more restrictive inclusion criteria and included 897 patients with 1018 aneurysms reported in 15 studies. All but 2 of the studies were included in the Brinjikji meta-analysis. Arrese et al determined rates of complete or nearly complete occlusion of the treated aneurysm with a patent parent artery and early procedure-related mortality and neurologic morbidity. Similar to the Brinjikji meta-analysis, the Arrese study found a high overall rate of complete aneurysmal occlusion (76.2%; 95% CI, 72.1 to 80.2), but also a high rate of procedure-related morbidity and mortality (2.8% [95% CI, 1.7% to 3.8%] and 7.3% [95% CI, 5.7% to 9%], respectively). The authors assessed for publication bias using funnel plots and the Egger test to assess whether the study estimate size was related to the sample size and found p less than 0.001 for the Egger test for both early and late morbidity and aneurysmal occlusion, suggestive of publication bias.

Since the publication of these 2 meta-analyses, a number of noncomparative studies evaluating flow-diverting stents in the treatment of aneurysms have been published. The largest cohort study identified was by Kallmes et al, who conducted a retrospective analysis of patients treated with the Pipeline device at 17 centers worldwide. The authors identified 793 patients with 906 aneurysms who were enrolled in the International Retrospective Study of Pipeline Embolization Device. Of the total number of aneurysms, 311 were in the anterior ICA circulation and at least 10 mm, 349 of which were in the anterior circulation and less than 10 mm, 59 of which were in the posterior circulation, 179 of which
were in a non-ICA anterior circulation location and less than 10 mm, and 10 of which had no aneurysm size specified. Overall neurologic morbidity and mortality was 8.4%, highest in the posterior circulation group and lowest in the ICA, less than 10-mm group (16.4% vs 4.8%; p=0.01). The overall spontaneous rupture rate was 0.6%, and the intracranial hemorrhage rate was 2.4%. Ischemic stroke rates were 4.7%, again highest in the posterior circulation group and lowest in the ICA, less than 10-mm group (7.3% vs 2.7%; p=0.16). In a subsequent study using data from the same registry, Brinjikji et al reported on risk factors for hemorrhagic complications after Pipeline device placement.\textsuperscript{116} 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).

The longest follow-up reported is from a series of 98 patients with 119 aneurysms treated with the Pipeline Embolization Device and followed for at least 2 years.\textsuperscript{117} Of the 119 aneurysms, 100% had clinical follow-up and 88.8% had imaging follow-up up to 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 cases (2.8%) 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.

Additional representative studies, with a focus on series with more than 50 patients, are summarized in Table 3.

**Table 3. 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>
<tbody>
<tr>
<td>Chalouhi et al (2015)\textsuperscript{118}</td>
<td>Retrospective case series</td>
<td>100 patients with aneurysms ≤7 mm treated at 1 institution</td>
<td>Pipeline Embolization Device placement</td>
<td>Complications in 3% (1 distal parenchymal hemorrhage, 2 ischemic events)</td>
</tr>
<tr>
<td>Lubicz et al (2015)\textsuperscript{119}</td>
<td>Retrospective review of prospectively collected data</td>
<td>58 patients with 70 intracranial aneurysms treated at 2 institutions</td>
<td>SILK artery reconstruction device (Balt Extrusion, Montmorency, France)</td>
<td>No periprocedural deaths occurred</td>
</tr>
<tr>
<td>Wakhloo et al (2015)\textsuperscript{120}</td>
<td>Prospective multicenter trial at 24 centers</td>
<td>165 patients with 190 intracranial aneurysms</td>
<td>Surpass flow-diverting device (Stryker Neurovascular, Fremont, CA)</td>
<td>At 6-mo FU, permanent neurologic morbidity was 6% and permanent neurologic mortality was 2.7%</td>
</tr>
</tbody>
</table>
Study | Study Type | Patient Population | Intervention | Primary Outcomes
---|---|---|---|---
Kan et al (2012) | Prospective case series (registry) | 56 patients with intracranial aneurysm treated at 7 institutions | Pipeline Embolization Device placement | SAH at ≤7 d, and intraparenchymal hemorrhage at ≤7 d occurred in 3.7%, 2.5%, and 2.5% of subjects, respectively • 6/123 devices incompletely deployed • Among 19 patients with 6-mo FU, 68% (13 patients) had complete aneurysm occlusion • 4 fatal postprocedural hemorrhages occurred
Piano et al (2013) | Retrospective case series | 101 patients with intracranial aneurysm at a single institution | Flow-diverting stent placement (Pipeline Embolization Device or SILK device), with or without endovascular coiling | 86% of aneurysms evaluated at 6-mo FU showed complete occlusion
Toma et al (2013) | Retrospective case series | 84 patients with intracranial aneurysm at a single institution | Flow-diverting stent placement | 61% of aneurysms resolved at 12 mo • 9.5% of patients had a new, permanent neurologic deficit and 5.9% of patients had procedure-related mortality

FU: follow-up; SAH: subarachnoid hemorrhage.

**Section Summary: Flow-Diverting Stents for Intracranial Aneurysms**

No RCTs have evaluated flow-diverting stents. One nonrandomized study that 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 those treated with coiling, with similar rates of good clinical outcomes. However, given the lack of randomized trials, the evidence is insufficient to determine whether flow-diverting stents improves outcomes for patients with intracranial aneurysms.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this policy are listed in Table 4.

**Table 4. 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>Endovascular interventions for acute ischemic stroke</td>
<td>Ongoing</td>
<td></td>
<td></td>
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</table>
| NCT01869478 | Endovascular Arterial Reperfusion vs. Intravenous Thrombolysis for Acute Ischemic Stroke (EARLY): A Randomized Pilot Study of Ultra-early (2 Hours) and Early (2-...
### Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

<table>
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<th>Status</th>
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<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>Ongoing</td>
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<td>Nov 2015</td>
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<tr>
<td>NCT01852201</td>
<td>POSITIVE: Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy</td>
<td>Ongoing</td>
<td>750</td>
<td>May 2016</td>
</tr>
<tr>
<td>NCT01429350</td>
<td>The THERAPY Trial: The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke</td>
<td>Ongoing</td>
<td>692</td>
<td>Dec 2016</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</td>
<td>Ongoing</td>
<td>690</td>
<td>Mar 2018</td>
</tr>
<tr>
<td>NCT02157532</td>
<td>Intra-arterial Thrombectomy as an Acute Treatment Intervention for Stroke: the Endovascular Acute Stroke Intervention (EASI) Trial</td>
<td>Ongoing</td>
<td>480</td>
<td>Jan 2020</td>
</tr>
<tr>
<td>NCT01455935</td>
<td>Wake up Symptomatic Stroke in Acute Brain Ischemia (WASSABI) Trial</td>
<td>Unpublished</td>
<td>90</td>
<td>Feb 2014 (last verified 2012)</td>
</tr>
</tbody>
</table>

#### Endovascular interventions for symptomatic intracranial atherosclerotic disease

##### Ongoing

- NCT01763320 China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS): A Prospective Multicenter, Randomized Controlled Trial | Ongoing      | 380        | Dec 2017   |

##### Unpublished

- NCT00816166 Phase III Study of Pharos Vitesse Neurovascular Stent System Compared to Best Medical Therapy for the Treatment of Ischemic Disease | Terminated      | 250        | Terminated |

#### Stent-assisted treatment of intracranial aneurysms

##### Ongoing

- NCT01340612 Stenting in the Treatment of Aneurysm Trial (STAT) | Ongoing      | 600        | Apr 2016   |
- NCT01349582 Flow Diversion in Intracranial Aneurysm Treatment (FIAT) | Ongoing      | 344        | Apr 2017   |
- NCT01811134 Flow Diverter Stent for Endovascular Treatment of Unruptured Saccular Wide-necked Intracranial Aneurysms (EVIDENCE) | Ongoing      | 130        | Nov 2017   |
- NCT01762137 LARGE Aneurysm Randomized Trial: Flow Division Versus Traditional Endovascular Coiling Therapy | Ongoing      | 316        | Apr 2018   |
- NCT01976026 DIVERT: Divergence of Flow in Intracranial VErtbral and Blood Blister-like Ruptured Aneurysms Trial: A Randomized Trial Comparing Pipeline Flow Diversion and Best-Standard-Treatment | Ongoing      | 420        | Jan 2021   |

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.
American Society of Interventional and Therapeutic Neuroradiology et al

In 2005, the American Society of Interventional and Therapeutic Neuroradiology (ASITN), the Society of Interventional Radiology (SIR), and the American Society of Neuroradiology (ASNR) jointly published a position paper on angioplasty and stenting for cerebral atherosclerosis. This position statement reviewed a number of case series and the SSYLVIA and the Wingspan multi-institutional studies. The following position statement was offered, although the underlying rationale and process for development for the position statement were not provided:

“The ASITN, SIR, and ASNR concur that sufficient evidence now exists to recommend that intracranial angioplasty with or without stenting should be offered to symptomatic patients with intracranial stenoses who have failed medical therapy. Endovascular interventions are intensive services provided to patients who are at very high risk for strokes and typically have multiple comorbidities. Similar to revascularization for extracranial carotid artery stenosis, patient benefit from revascularization for symptomatic intracranial arterial stenosis is critically dependent on a low per procedural stroke and death rate and should thus be performed by experienced neurointerventionists. We recommend reimbursement by third party insurers so that these patients may have access to such interventions. Continued attempts to improve the benefits of endovascular therapy are warranted.”

Society of Interventional Radiology

In 2013, SIR issued a position statement on endovascular acute ischemic stroke interventions. The SIR position statement indicates intra-arterial revascularization for stroke is beneficial when tPA is inappropriate or unsuccessful. SIR indicates, despite clinical trials finding mechanical thrombectomy is not a proven therapy, rapid treatment with mechanical thrombectomy devices improves outcomes for occlusions in large vessels. The need for clinical trials and/or a national registry is specified.

American Heart Association

In 2009, the American Heart Association (AHA) published a scientific statement on indications for intracranial endovascular neurointerventional procedures. The recommendation related to endovascular treatment of symptomatic intracranial stenoses was noted as class IIb, level of evidence C (usefulness/effectiveness is unknown/unclear). The level of evidence was the same for use of angioplasty and stenting in the treatment of acute ischemic stroke.

American Heart Association and American Stroke Association

In early 2013, AHA 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:

- “Intra-arterial treatment requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified interventionalists. An emphasis on expeditious
assessment and treatment should be made. Facilities are encouraged to define criteria that can be used to credential individuals who can perform intra-arterial revascularization procedures. Outcomes on all patients should be tracked (Class I; Level of Evidence C).

- “When mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and Trevo are generally preferred to coil retrievers such as Merci (Class I; Level of Evidence A).” The relative effectiveness of the Penumbra System versus stent retrievers is not yet characterized.
- “The Merci, Penumbra System, Solitaire FR, and Trevo thrombectomy devices can be useful in achieving recanalization alone or in combination with pharmacological fibrinolysis in carefully selected patients (Class IIa; Level of Evidence B).” Their ability to improve patient outcomes has not yet been established. These devices should continue to be studied in RCTs to determine the efficacy of such treatments in improving patient outcomes.
- “Intra-arterial fibrinolysis or mechanical thrombectomy is reasonable in patients who have contraindications to the use of intravenous fibrinolysis (Class IIa; Level of Evidence C).”
- “Rescue intra-arterial fibrinolysis or mechanical thrombectomy may be reasonable approaches to recanalization in patients with large-artery occlusion who have not responded to intravenous fibrinolysis. Additional randomized trial data are needed (Class IIb; Level of Evidence B).”
- “The usefulness of mechanical thrombectomy devices other than the Merci retriever, the Penumbra System, Solitaire FR, and Trevo is not well established (Class IIb; Level of Evidence C).” These devices should be used in the setting of clinical trials.
- “The usefulness of emergent intracranial angioplasty and/or stenting is not well established. These procedures should be used in the setting of clinical trials (Class IIb; Level of Evidence C).”

The 2013 guidelines were updated in 2015 to include the results of 8 clinical trials published after the 2013 guidelines. The updated guidelines include the following new or revised recommendations relevant to the use of endovascular therapies for acute stroke:

- “Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria (Class I; Level of Evidence A):
  o Prestroke mRS score 0 to 1,
  o Acute ischemic stroke receiving intravenous r-tPA [recombinant tissue plasminogen activator] within 4.5 hours of onset according to guidelines from professional medical societies,
  o Causative occlusion of the internal carotid artery or proximal MCA [middle cerebral artery] (M1),
  o Age ≥18 years,
  o NIHSS [National Institutes of Health Stroke Scale] score of ≥6,
  o ASPECTS [Alberta Stroke Program Early Computed Tomography Score] of ≥6, and
  o Treatment can be initiated (groin puncture) within 6 hours of symptom onset.”
- “As with intravenous r-tPA, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI [Thrombolysis in Cerebral Infarction] grade 2b/3 should be achieved as early as possible and within 6 hours of stroke onset (Class I; Level of Evidence B-R).”
- “When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischemic stroke who have causative
occlusion of the internal carotid artery or proximal MCA (M1) (Class IIb; Level of Evidence C). Additional randomized trial data are needed.”

- “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 (Class IIA; Level of Evidence C). There are inadequate data available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time-based or nontime based (eg, prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications).”

- “Although the benefits are uncertain, use of endovascular therapy 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, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries (Class IIb; Level of Evidence C).”

- “Endovascular therapy with stent retrievers may be reasonable for some patients <18 years of age with acute ischemic stroke who have demonstrated large vessel occlusion in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset, but the benefits are not established in this age group (Class IIb; Level of Evidence C).”

- “Although the benefits are uncertain, use of endovascular therapy with stent retrievers may be reasonable for patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS [modified Rankin Scale] score of >1, ASPECTS <6, or NIHSS score <6 and causative occlusion of the internal carotid artery or proximal MCA (M1) (Class IIb; Level of Evidence B-R). Additional randomized trial data are needed.”

- “Observing patients after intravenous r-tPA to assess for clinical response before pursuing endovascular therapy is not required to achieve beneficial outcomes and is not recommended. (Class III; Level of Evidence B-R).”

- “Use of stent retrievers is indicated in preference to the MERCI device. (Class I; Level of Evidence A). The use of mechanical thrombectomy devices other than stent retrievers may be reasonable in some circumstances (Class IIb, Level 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 (Class IIA; Level of Evidence C). Future studies should examine which systems provide the highest recanalization rates with the lowest risk for nontarget embolization.”

- “The technical goal of the thrombectomy procedure should be a TICI 2b/3 angiographic result to maximize the probability of a good functional clinical outcome (Class I; Level of Evidence A).”

- “Use of salvage technical adjuncts including intra-arterial fibrinolysis may be reasonable to achieve these angiographic results, if completed within 6 hours of symptom onset (Class IIb; Level of Evidence B-R).” However, these data derive from clinical trials that no longer reflect current practice, including use of fibrinolytic drugs that are not available. A clinically beneficial dose of intra-arterial r-tPA is not established, and r-tPA does not have FDA approval for intra-arterial use. As a consequence, endovascular therapy with stent retrievers is recommended over intra-arterial fibrinolysis as first-line therapy (Class I; Level of Evidence E).”

- “Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of intravenous r-tPA might be considered, but the consequences are unknown (Class IIb; Level of Evidence C).”
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.

Summary of Evidence

The evidence for the use of endovascular mechanical embolectomy in individuals with acute ischemic stroke due to occlusion of an anterior circulation vessel includes a number of randomized clinical trials (RCTs) comparing endovascular therapy with standard care. 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. The 5 more recent trials, published from 2014 to 2015, all demonstrated a significant benefit in terms of reduced disability at 90 days posttreatment. The trials that demonstrated a benefit to endovascular therapy either exclusively used stent retriever devices or allowed the treating physician to select a device, mostly a stent retriever device, and had high rates of mechanical embolectomy device use in patients randomized to endovascular therapy. All studies that demonstrated a benefit to endovascular therapy required demonstration of a large-vessel, anterior circulation occlusion for enrollment. In addition, they were characterized by fast time-to-treatment. To achieve results in real-world settings similar to those in the clinical trials, treatment times, clinical protocols, and patient selection criteria should be similar to those in the RCTs. The evidence is sufficient to determine quantitatively that the technology results in a large improvement in the net health outcome.

The evidence for the use of endovascular mechanical embolectomy in individuals with acute ischemic stroke due to basilar artery occlusion includes 1 nonrandomized comparative study and a number of case series. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related mortality and morbidity. These studies indicate that high rates of recanalization can be achieved with mechanical thrombectomy. However, additional comparative studies are needed to demonstrate that mechanical thrombectomy is superior to standard therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of intracranial percutaneous transluminal angioplasty with or without stenting in individuals with symptomatic intracranial stenosis 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 demonstrated no significant benefit with endovascular therapy. In particular, the SAMMPRIS trial was stopped early due to harms, because the rate of stroke or death at 30 days posttreatment was higher in the endovascular arm, which received percutaneous angioplasty with stenting. Follow-up of the SAMMPRIS subjects has demonstrated no long-term benefit from endovascular therapy. Although some nonrandomized studies have suggested a benefit from endovascular therapy, the available evidence from 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 qualitatively that the technology is unlikely to improve the net health outcome.
The evidence for the use of endovascular coiling with intracranial stent placement or intracranial placement of a flow-diverting stent for the treatment of intracranial aneurysms includes several nonrandomized comparative studies and multiple single-arm studies. Relevant outcomes are overall survival, morbidity events, functional outcomes, and treatment-related mortality and morbidity. The available nonrandomized comparative studies report occlusion rates for stent-assisted coiling that are similar to or higher than coiling alone and recurrence rates that may be lower than for coiling alone. For stent-assisted coiling with self-expanding stents, there is also some evidence that adverse event rates are relatively high, and 1 nonrandomized comparative trial reported that mortality is higher with stent-assisted coiling than with coiling alone. For placement of flow-diverting stents, 1 nonrandomized study comparing the flow-diverting stents with endovascular coiling for intracranial aneurysms demonstrated higher rates of aneurysm obliteration in those treated with the Pipeline endovascular device than those treated with coiling, with similar rates of good clinical outcomes. Overall, the available evidence is insufficient to determine 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.

**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."

**References**


50. Abou-Chebl A. Endovascular treatment of acute ischemic stroke may be safely performed with no time window limit in appropriately selected patients. Stroke. Sep 2010;41(9):1996-2000. PMID 20651271


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<td>Subsection: Medicine</td>
<td>Original Policy Date: December 7, 2011</td>
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<td>Subject: Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)</td>
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### Keywords

Neurolink System  
Percutaneous Transluminal Angioplasty, Intracranial Circulation  
Vertebrobasilar Stenosis, Angioplasty  
Wingspan Stent System

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**This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 4, 2015 and is effective January 15, 2016.**

**Signature on File**  
Deborah M. Smith, MD, MPH