Medical Policy Manual

**Topic:** Mechanical Embolectomy for Treatment of Acute Stroke  
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**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**DESCRIPTION**

Mechanical embolectomy devices are being studied as an alternative, or adjunct to intravenous tPA therapy, and, among patients contraindicated for tPA, as a primary therapy for the treatment of ischemic stroke.

**Background**

The majority of strokes are caused by thrombotic or embolic occlusion, and these frequently present as acute neurologic emergencies. Standard treatment options for acute stroke include thrombolysis with intravenous tissue plasminogen activator (tPA) if patients present early (within 4.5 hours of stroke symptom onset), and supportive medical care if patients present late or do not otherwise meet criteria for thrombolysis. Endovascular interventions, including mechanical embolectomy/thrombectomy, are another method of acute stroke treatment. Mechanical embolectomy/thrombectomy is an endovascular technique to physically remove or disrupt an intracranial occlusion with a device inserted via percutaneous catheter to the site of the occlusion.

Mechanical embolectomy devices, also known as thrombectomy or neurothrombectomy devices, are being studied as an alternative, or adjunct to intravenous tPA therapy and, among patients contraindicated for tPA, as a primary therapy for the treatment of ischemic stroke. Mechanical
embolectomy devices used to extract clots in ischemic stroke can be categorized into one of the following types: clot retriever, aspiration or suction device, snare, ultrasound technology, or laser.[1]

**Regulatory Status**

The following devices have received 510(k) clearance from the US Food and Drug Administration (FDA) for mechanical embolectomy in acute stroke. Marketing clearance via the 510(k) process does not require data regarding clinical efficacy.

In August 2004, the Merci Retriever® (Concentric Medical) was cleared by the FDA. 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.

A modified Merci Retriever, also manufactured by Concentric Medical, Inc., received 510(k) clearance from the FDA in May 2006. 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 radiological procedures in the neuro-, peripheral, and coronary vasculature.

In December 2007, the Penumbra System® (Penumbra Inc.) was cleared through the 510(k) process. With the Penumbra device, an opening at the tip of a percutaneous catheter utilizes suction to extract the clot. The Penumbra System is intended for use in the revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease (in the internal carotid, middle cerebral – first (M1) and second (M2) segments, basilar, and vertebral arteries) within 8 hours of symptom onset.

In March 2012, the Solitaire™ FR device was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to the Merci Retriever device, based on a randomized controlled trial (RCT) of 113 patients submitted to the FDA comparing the Merci and Solitaire devices. Indications for the device are patients with ischemic stroke due to large intracranial vessel occlusion who are ineligible for intravenous tPA, or who fail intravenous tPA.

The Trevo® Pro Retriever™ device (Stryker® Neurovascular) along with later versions, the Modified Trevo® Retriever and the Trevo® XP ProVue Retriever, have been cleared for marketing by the FDA through the 510(k) process. The 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 U.S. 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.

**MEDICAL POLICY CRITERIA**

I. Use of endovascular mechanical embolectomy with a device that is approved by the U.S. Food and Drug Administration for the treatment of acute ischemic stroke may be considered **medically necessary** for the treatment of acute ischemic stroke when clinical records document all of the following criteria (I. A-E) are met:

A. Arterial occlusion is demonstrated; AND
B. Endovascular mechanical embolectomy can be received within an estimated 12 hours of symptom onset; AND

C. Evidence of clinically significant neurological deficit (see Policy Guidelines); AND

D. Salvageable brain tissue is present in the affected vascular territory; AND

E. There is no evidence of intracranial hemorrhage on CT or MRI.

II. Mechanical Embolectomy is considered **not medically necessary** for the treatment of acute stroke when the above criteria are not met.

**POLICY GUIDELINES**

**Stroke Assessment Scales**

Stroke assessment scales\(^2\) may be used to measure neurological deficit, which may include, but are not limited to the following:

- National Institutes of Health Stroke Scale (NIHSS)
- Face Arm Speech Test (FAST)
- Cincinnati Prehospital Stroke Scale (CPSS)
- Los Angeles Prehospital Stroke Screen (LAPSS)
- Recognition of Stoke in the Emergency Room (ROSIER) scale

**SCIENTIFIC EVIDENCE\(^3,4\)**

The principal outcomes associated with treatment of acute ischemic stroke are clinically relevant improvements in short and long-term neurological outcomes, as measured by a validated instrument (such as the National Institutes of Health Stroke Scale [NIHSS]). Measures of disability, such as those provided by the Rankin Scale or modified Rankin Scale (mRS), may also be reported. Mechanical embolectomy devices are proposed as an alternative or adjunct to tPA or as a primary therapy for patients in whom tPA is contraindicated.

Assessment of the safety and efficacy for mechanical embolectomy involves a determination of whether the intervention improves health outcomes compared to standard treatment. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Randomization controls for baseline differences between groups which may impact findings. In addition, a controlled study design reduces the influence of confounding factors on observed results.

**Literature Appraisal**

The review of evidence below focuses on systematic reviews and RCTs.

**Systematic Reviews**
In 2015, Badhiwala et al reported results of a meta-analysis of RCTs evaluating mechanical embolectomy after acute ischemic stroke. Eligible studies were RCTs comparing endovascular therapy with standard care, including the use of intravenous (IV) plasminogen activator (tPA), in adult participants with acute stroke. Eight trials were included (Ciccone et al, Kidwell et al, Broderick et al, Berkhemer et al, Goyal et al, Campbell et al, Saver et al, Jovin et al), with a total of 2423 patients. Studies were assessed as having low risk of bias overall with the Cochrane Collaboration’s tool. In a meta-analysis, the use of endovascular intervention lead to proportional treatment benefit across modified Rankin Scale (mRS) scores (odds ratio [OR], 1.56; 95% confidence interval [CI], 1.14 to 2.13; p=0.005). Patients treated with endovascular intervention were more likely than standard care patients to have functional independence at 90 days (44.6% for endovascular treatment [95% CI, 36.6% to 52.8%]; 31.8% for standard treatment [95% CI, 24.6% to 40.0%]), with an associated absolute risk difference of 12.0% (95% CI, 3.8% to 20.3%; OR=1.71; 95% CI, 1.18 to 2.49; p=0.005). However, there was significant heterogeneity ($I^2=75.4\%$) in the analysis of functional improvement outcomes. The authors conducted a number of sensitivity analyses around predictors of functional outcomes, and found that the following factors were associated with functional outcomes:

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

There were no significant differences between endovascular intervention group and standard care group patients in rates of symptomatic intracranial hemorrhage or death at 90 days. In a meta-analysis including the same 8 trials included in the Badhiwala study, Chen et al reported a similar OR for 90 day functional independence as Badhiwala.

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 with a total of 108,082 patients, including RCTs, observational studies, guideline statements, and review articles. Six RCTs comparing endovascular therapy with standard management were included. Although pooled results of the trial results are not presented, the authors do 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 (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.

A number of systematic reviews have been published which have incorporated some of the RCTs comparing endovascular therapies and standard therapy.

In 2014, Fargen et al published a meta-analysis of prospective RCTs evaluating endovascular therapies for acute stroke, which included 4 previously identified RCTs (Broderick et al, Ciccone et al, Kidwell et al, and 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 a pooled analysis of the subgroup of patients with large vessel occlusion, patients randomized to endovascular therapy were more likely to have a mRS score of 0-2 at 90 days than patients randomized to standard of care (38.3% vs 25.8%; OR 1.67, 95% CI 1.29 to 2.16; P=0.0001).
In 2015 Kappelhof et al. published results of a systematic review and meta-analysis of studies comparing outcomes for mechanical therapy and intra-arterial thrombolysis for acute ischemic stroke due to intracranial internal carotid artery (ICA) occlusion, with separate results reported for intracranial and extracranial occlusions.\cite{23} The overall review included 32 studies, 6 of which (N=95) reported outcomes for intracranial occlusion treated by intraarterial 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 reported 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).

In 2014, a Blue Cross and Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) Assessment evaluated endovascular therapy for acute ischemic stroke in adults.\cite{24} The Assessment identified 5 multicenter randomized controlled trials (RCTs) meeting selection criteria, 3 of which compared endovascular treatment with standard stroke care (Broderick et al.\cite{17}, Ciccone et al.\cite{18}, and Kidwell et al.\cite{7} [summarized in more detail below]) and 2 of which compared newer and older endovascular treatments (Saver et al.\cite{25} and Nogueira et al.\cite{26}). The TEC 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 newest 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, BCBSA issued a special report to update the literature of the previous 2014 TEC Assessment. The updated Assessment focused on 4 RCTs published from 2014-2015 comparing endovascular mechanical embolectomy with medical 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.

In a 2013 systematic review and meta-analysis, Singh and others consolidated the evidence from 5 RCTs for the use of endovascular therapy (ET) in patients with acute ischemic stroke (N=1197).\cite{27} One of the reviewed studies did not include mechanical embolectomy devices in the trial.\cite{28} In addition, a trial included in the review defined endovascular therapy as intraarterial thrombolysis with recombinant tissue plasminogen activator [tPA], mechanical clot disruption or retrieval, or a combination of these approaches.\cite{18} Seven hundred eleven patients received ET, and 486 received intravenous (IV) tPA. There was no significant improvement in any of the outcomes in patients receiving ET compared with those receiving IV tPA. On subgroup analysis, ET was found to have better outcomes in patients with severe stroke (National Institutes of Health Stroke Scale score ≥20),
showing a dose-response gradient and improving excellent, good, and fair outcomes by an additional 4%, 7%, and 13%, respectively, compared with IV thrombolysis. Authors concluded that ET was not superior to IV thrombolysis for acute ischemic strokes (level B recommendation).

Several systematic reviews were published prior to the publication of several recent RCTs and as a result will not be summarized. These systematic reviews include Mokin et al.[29] (2012), Almekhlafi et al.[30] (2012), Baker et al.[31] (2011), and Stead et al.[32] (2008).

Randomized Controlled Trials

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 section. These most recent studies are of particular importance as they are well-designed, primarily assessed newer devices and addressed the methodological limitations noted in previous RCTs.

REVASCAT Trial

In 2015, Jovin et al., reported results of the REVASCAT trial, which compared endovascular therapy with the Solitaire stent-retriever device with medical therapy, including IV tPA when indicated, within 8 hours of stroke onset among 206 patients.[22] Eligible patients had an occlusion within the proximal anterior circulation which could be treated within 8 hours of stroke onset and a prestrike mRS score of 0-1, and a baseline National Institutes of Health Stroke Scale (NIHSS) score of at least 6 points (NIHSS score range 0-42; higher scores associated with greater deficit). Intravenous tPA was administered before randomization. Patients were excluded if they had imaging-based evidence of a large ischemic core, indicated by an Alberta Stroke Program Early Computed Tomography Score 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 after the first 25% of patients (n=174) reached 90-day of follow up.

One hundred and 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 and 77.7% in the control group). For the study’s primary outcome, the odds ratio (OR) for improvement in the distribution of the mRS score was 1.7 (95% confidence interval [CI] 1.05 to 2.8), favoring mechanical embolectomy. A greater proportion of patients in the mechanical embolectomy group were 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 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.[11] 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 intracranial anterior (ICA) or M1 or M2 segments of the middle cerebral artery (MCA) on 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. CT perfusion imaging was analyzed with an operator-independent post-processing 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 co-primary 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.[20] 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 noncontrast 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, as 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 Alberta Stroke Program Early Computed Tomography Score (ASPECTS), which is a 10-point scoring system designed to quantify the extent of ischemic changes in the MCA territory. Patients received IV tPA if they met local guidelines. Patients were randomized to endovascular treatment (n=165), which could include any FDA-approved stent retriever or aspiration device, balloon angioplasty, guidewire manipulation, and/or IA tPA, or guideline-based stroke care (n=150). Use of retrievable stents was recommended. Enrollment was planned for 316 subjects. The trial was stopped early on the advice of its data safety monitoring board, after an unplanned interim analysis following publication of MR CLEAN trial results, because ESCAPE’s prespecified efficacy boundary had been crossed.

Of the 165 patients randomized to the intervention group, 151 (91.5%) underwent endovascular therapy, most commonly with a retrievable stent (130/151 [86.1%] of those who underwent an endovascular procedure), 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. The study’s primary end point was the 90-day mRS score. Compared to the control group, the relative odds of improving 1 point on the mRS was 2.6 (95% CI, 1.7 to 3.8) in the endovascular treatment group. Endovascular treatment group subjects compared with control group subject 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 [RR], 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 (RR=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.31 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 noncontrast CT with a small-to-moderate core infarct based on ASPECTS score. 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 2014, 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.19 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 National Institutes of Health Stroke Scale (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 and 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.

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 odds ratio (OR) of 1.66 (95% confidence interval [CI], 1.21 to 2.28; favors intervention). Twenty-seven (11.6%) intervention subjects had a 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 68/207 (32.9%) of control subjects with follow-up CT angiography available (unadjusted OR=6.27; 95% CI, 4.03 to 9.74). The thirty-day mortality rate was 18.9% in the intervention group, compared with 18.4% in the control group (p=NS). Rates of serious adverse events (AEs) during the 90-day follow-up period did not differ significantly between groups (p=0.31). Symptomatic intracerebral hemorrhage occurred in 7.7% of intervention subjects compared with 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 and colleagues reported on the MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy) trial in 2013.[7] MR RESCUE was a randomized, controlled, open-label, blinded outcome trial 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 computed tomography (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 received 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% or less and a small, 90 ml or less, area of predicted core infarct) would benefit more from mechanical embolectomy than patients with nonpenumbral 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 relationship to treatment outcomes in any group. Overall mortality (21% at 90 days) and symptomatic intracranial hemorrhage (4%) did not differ across groups.

**SYNTHESIS Expansion Trial**

In 2013, Ciccone et al., reported on the SYNTHESIS Expansion trial of 362 patients randomized within 4.5 hours of the onset of various types of acute ischemic strokes to receive endovascular
therapy (n=181) or IV tPA (n=181). Endovascular therapy consisted of intraarterial tPA, mechanical embolectomy (using the Solitaire, Penumbra, Trevo, or Merci devices) or a combination of these treatments. Endovascular treatment was completed in 163 of the 181 patients randomized to endovascular therapy. No significant differences in 90-day survival without disability (modified Rankin score 0-1) occurred between the endovascular therapy group and TPA group (30.4% vs. 34.8%, respectively, 0.71; 95% confidence interval (CI), 0.44 to 1.14; p=0.16). Within 7 days, fatal or nonfatal symptomatic intracranial hemorrhage occurred in each group at a rate of 6%. Rates of other serious adverse events were also not significantly different 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

In 2013, Broderick et al., reported the results of the IMS III trial, an open-label RCT that compared IV thrombolysis with either mechanical thrombectomy or endovascular tPA at the site of the occlusion. In the latter group, the treatment choice was made at the discretion of the treating physician. The study had a planned enrollment of 900 patients, but was halted prematurely in April 2012 for futility when an interim analysis of the 656 enrolled patients showed no significant between-group differences in outcomes. In a predefined subgroup analysis of the IMS III RCT (summarized below), the authors reported that for the subgroup of patients with ICA, middle cerebral artery, first branch (M1), or basilar artery occlusion who received tPA within 120 minutes of stroke onset (N=124), the relative risk (RR) for a modified Rankin 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 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 (AOL) score of 2-3 and 76% had a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2-3 (partial or full perfusion) after IV-tPA, which may have limited the potential benefit for device-related revascularization. Ninety-day Rankin scale scores were higher with higher mTICI scores: of 32 subjects with an mTICI score of 0, 3.1% had a modified Rankin scale score of 0-2 at 90 days, compared with 12.5%, 19.4%, 46.3%, and 80% for subjects with mTICI scores of 1 (total N=16), 2a (total N=67), 2b (total 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).

Demchuck et al., evaluated the association between baseline CT or magnetic resonance (MR) angiographic findings and outcomes among 306 (47% of 656) who had baseline CT or MR angiographic 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 modified Rankin scale score of 0-2, was seen with proximal occlusions between groups (41.3% of endovascular therapy subjects vs 38% of controls; relative risk [RR] 1.07 [99% CI 0.67 to 1.70]).
A number of RCTs have compared endovascular therapies with noninterventional care for acute stroke, with the 5 recent (2014-2015) studies consistently reporting a significant benefit associated with endovascular care. The later-published RCTs 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.) had relatively low utilization of the newer generation retrievable stents (Solitaire FR and Trevo devices). 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.

A number of studies compared different mechanical embolization devices including the following RCTs. These RCTs documented the improvements in the most recent generation of these devices.

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.[25] 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 2013.[35] 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 18/144 (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.[26] Revascularization rates were 86% in the Trevo group versus 60% in the MERCI group (p<0.001). Procedure-related adverse events occurred in 15% of the Trevo group and 23% in the Merci group; p=0.183). Mortality rates at 90 days were 33% versus 24% (p=0.18), respectively.

Nonrandomized Studies

A number of nonrandomized[36-44], comparative and noncomparative studies, were published. Results from these studies are limited by a lack of comparison group,[45] small sample size,[39,46-61] lack of short
and long-term follow-up, and the retrospective nature of the study design which limit conclusions concerning the use of this treatment for a broad patient population.

Other case series have compared outcomes of different devices or studied only intermediate outcomes such as vessel recanalization.[62-75]

Clinical Practice Guidelines

The American Heart Association and American Stroke Association[76]

The updated 2015 American Heart Association and American Stroke Association (AHA/ASA) guidelines for the Early Management of Patients with Acute Ischemic Stroke included the following conclusions related to mechanical thrombectomy:

“Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria (Class I; Level of Evidence A, indicating a strong recommendation based on high-quality evidence.):

- Prestroke mRS score 0 to 1,
- Acute ischemic stroke receiving intravenous r-tPA [recombinant tissue plasminogen activator] within 4.5 hours of onset according to guidelines from professional medical societies,
- Causative occlusion of the internal carotid artery or proximal MCA (M1),
- Age ≥18 years,
- NIHSS score of ≥6,
- ASPECTS of ≥6, and
- Treatment can be initiated (groin puncture) within 6 hours of symptom onset.

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 grade 2b/3 should be achieved as early as possible and within 6 hours of stroke onset (Class I; Level of Evidence B-R, indicating a strong recommendation based on moderate evidence.).

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, indicating a weak recommendation based on evidence with methodological limitations.). 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, indicating a moderate recommendation based on evidence with methodological limitations.). There are inadequate data available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time-based or non-time based (e.g., prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications).
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, indicating a weak recommendation based on evidence with methodological limitations.).

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, indicating a weak recommendation based on evidence with methodological limitations.).

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 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, indicating a weak recommendation based on moderate evidence.). 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, indicating observation has no benefit based on moderate evidence).

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, indicating a weak recommendation based on moderate evidence).”

Society of Interventional Radiology[77]

In a 2013 position statement the Society of Interventional Radiology (SIR) indicated that rapid treatment with mechanical thrombectomy devices improves outcomes for occlusions in large vessels. However, this statement was not based on a systematic review of the published evidence. Three references were provided to support the SIR position.[7,17,18] The SIR statement included the following conclusions:

1) Intraarterial stroke revascularization is beneficial to patients in whom IV tPA fails or who are not eligible for IV tPA;
2) Patients with a large vessel occlusion who are treated rapidly (even with first-generation techniques) have improved outcomes compared those treated with IV tPA alone;
3) Second-generation mechanical thrombectomy devices are the most effective therapy for large vessel occlusion;
4) Randomized trials of second-generation mechanical thrombectomy devices compared with IV tPA alone need to be performed and/or a national registry needs to be established;
5) Participation in research is critically important, but reimbursement for IA stroke revascularization should not be restricted to clinical trials; and
6) All IA cases should be contributed to a trial or national registry, including 90-day clinical outcomes.
Summary

The research for the use of endovascular mechanical embolectomy in individuals with acute ischemic stroke due to occlusion report a significant benefit in terms of reduced disability at 90-days post-treatment. The recent trials which demonstrated a benefit of endovascular therapy primarily used stent retriever devices. In addition, the benefit of mechanical embolectomy was limited by the time-to-treatment, with an increased benefit observed in patients with reduced time frame from symptom onset to embolectomy. Lastly, the American Heart Association and American Stroke Association recently updated their clinical practice guidelines regarding management of acute stroke to recommend endovascular therapy when specific criteria are met. Therefore, the use of endovascular mechanical embolectomy may be considered medically necessary in carefully selected patients with ischemic stroke when criteria are met.

The current research has not demonstrated mechanical embolectomy offers any additional benefit compared with standard treatments for acute stroke when the above criteria are not met. In addition, no clinical practice guidelines were identified which recommend endovascular mechanical embolectomy in patients who fall outside of the defined appropriateness criteria. Therefore, the use of mechanical embolectomy devices for acute stroke is considered not medically necessary when criteria are not met.

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of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI trials. Stroke. 2010 May;41(5):953-60. PMID: 20378867


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


**CROSS REFERENCES**

*Endovascular Angioplasty and/or Stenting for Intracranial Arterial Disease (Atherosclerotic and Aneurysms)*, Surgery, Policy No. 141

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