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Acute Ischemic Stroke: Treatments

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Policy

Aetna considers mechanical embolectomy (mechanical thrombectomy) by means of micro-guidewires, micro-snare, and retrievers (e.g., the L5 Retriever, the MERCI device, the Penumbra System, and the TREVO Retriever; not an all-inclusive list) experimental and investigational for the treatment of acute ischemic stroke because its effectiveness has not been established.

Aetna considers hypothermia experimental and investigational for the treatment of acute ischemic stroke because its effectiveness has not been established.

Aetna considers transcranial ultrasound (e.g., the CLOTBUST-HF device), alone or in combination with tissue plasminogen activator, experimental and investigational for the treatment of acute ischemic stroke because its effectiveness has not been established.

Aetna considers intra-arterial infusion of spasmolytics (e.g., papaverine) experimental and investigational for the treatment of subarachnoid hemorrhage because its effectiveness has not been established.

Aetna considers intra-arterial infusion of calcium antagonists (e.g., nicardipine) experimental and investigational for the treatment of subarachnoid hemorrhage because its effectiveness has not been established.

Aetna considers tirilazad experimental and investigational for the treatment of subarachnoid hemorrhage because its effectiveness has not been established.

Background

Acute ischemic stroke (AIS) is among the leading causes of death and disability in developed countries. Traditional treatment entails the use of anti-coagulants

http://qawww.aetna.com/cpb/medical/data/700_799/0789_draft.html
and/or aspirin. Within the appropriate time-window, various endovascular approaches have been employed to manage patients with AIS. Endovascular therapy comprises a number of pharmacological and mechanical procedures. Intravenous (IV) thrombolysis including the use of tissue plasminogen activator (tPA) is an accepted treatment for AIS administered within 3 hours of onset. Mechanical procedures including the use of various micro-guidewires, micro-snare, and retrievers (e.g., the mechanical embolus removal in cerebral ischemia [MERCi] device, the L5 Retriever, and the Penumbra System) offer the promise of effective treatment for patients in whom pharmacological thrombolysis is contraindicated or might be ineffective. However, the clinical value of mechanical procedures (embolectomy/thrombectomy) in improving health outcomes of patients with AIS has not been established.

In a prospective, observational, cohort study, González et al (2007) evaluated the safety and effectiveness of thrombus extraction using a micro-snare in patients with AIS. Consecutive patients with AIS (less than 6 hours of ischemia for anterior circulation and less than 24 hours for posterior circulation) who had been previously excluded from IV tPA thrombolysis were included and followed-up for 3 months. Mechanical embolectomy with a micro-snare of 2 to 4 mm was undertaken as the first treatment. Low-dose intra-arterial (IA) thrombolysis or angioplasty was used if needed. Thrombolysis in Myocardial Infarction (TIMI) grade and modified Rankin Scale (mRS) score were used to evaluate vessel re-canalization and clinical effectiveness, respectively. A total of 9 patients (mean age of 55 years, range of 17 to 69 years) were included. Their basal mean National Institutes of Health Stroke Scale (NIHSS) score was 16 (range of 12 to 24). In 7 out of the 9 patients (77.8 %) the clot was removed, giving a TIMI grade of 3 (n = 4) and TIMI grade 2 (n = 3). Occlusion sites were: middle cerebral artery (MCA, n = 4), basilar artery (n = 2) and anterior cerebral artery plus MCA (n = 1). The mean time for re-canalization from the start of the procedure was 50 mins (range of 50 to 75 mins). At 3 months, the mRS score was 0 (n = 2) and 3 to 4 (n = 3; 2 patients died). The authors concluded that the micro-snare is a safe procedure for mechanical thrombectomy with a good re-canalization rate. Moreover, they stated that further studies are needed to determine the role of the micro-snare in the treatment of AIS.

Bose and associates (2008) noted that recent findings suggested that mechanical thrombectomy may have potential as a treatment for AIS. In a prospective, single-arm, trial, these investigators evaluated the safety and performance of the Penumbra System (PS), a novel mechanical device designed to reduce clot burden in acute stroke due to large-vessel occlusive disease. Patients with an acute neurological deficit consistent with acute stroke, presenting within 8 hours of symptom onset and an angiographically verified occlusion (TIMI grade 0 or 1) of a treatable intra-cranial vessel were enrolled in this study. The primary end point was re-vascularization of the target vessel to TIMI grade 2 or 3. Secondary end points were the proportion of subjects who achieved a mRS score of 2 or less, or a 4-point improvement on the NIHSS score at 30-day follow-up, as well as all-cause mortality. A total of 23 subjects were enrolled, and 21 target vessels were treated in 20 subjects by the PS. At baseline, mean age was 60 years, mean mRS score was 4.6, and mean NIHSS score was 21. Post-procedure, all 21 of the treated vessels (100 %) were successfully re-vascularized by the PS to TIMI 2 or 3. At 30-day follow-up, 9 subjects (45 %) had a 4-point or more NIHSS improvement or an
mRS of 2 or less. The all-cause mortality rate was 45 % (9 of 20), which is lower than expected in this severe stroke cohort, where 70 % of the subjects at baseline had either an NIHSS score of more than 20 or a basilar occlusion. The authors concluded that early clinical experience suggested that the Penumbra System allows re-vascularization in certain subjects experiencing AIS.

Smith (2007) noted that 2 major randomized trials of IV thrombolytic therapy have established clear clinical benefit, especially for strokes caused by small-vessel occlusion. Ischemic stroke caused by large-vessel intra-cranial occlusion carries higher morbidity, however, and IV thrombolytics are less capable of opening these large vessels. This observation makes a case for delivering thrombolytics directly into the clot, or simply removing the clot mechanically. Intra-arterial thrombolytic drugs have been shown to be effective for treating MCA occlusions in a major randomized trial. In the past two years, a family of mechanical thrombectomy catheters designed to remove rather than dissolve the offending clot has received Food and Drug Administration (FDA) clearance (e.g., the MERCI device). Such devices offer alternative therapy to patients who cannot receive thrombolytics, and can also be used in combination with thrombolytics to safely restore cerebral perfusion. Thomassen and Bakke (2007) stated that mechanical embolectomy works well on large-volume proximal occlusions for which there was previously no effective treatment. Early safety trials are promising, effectiveness in terms of re-

In a prospective, non-randomized, multi-center trial, Smith et al (2005) examined the safety and effectiveness of the Merci retriever to open occluded intra-cranial large vessels within 8 hours of the onset of stroke symptoms. All patients were ineligible for IV tPA. Primary outcomes were re-

re-canalization and safety; secondary outcomes were neurological outcome at 90 days in re-

Canalized versus non re-

Canalized patients. Re-

Canalization was achieved in 46 % (69/151) of patients on intention-to-treat analysis, and in 48 % (68/141) of patients in whom the device was deployed. This rate is significantly higher than that expected using an historical control (Prollyse in Acute Cerebral Thromboembolism II [PROACT II] trial) of 18 % (p < 0.0001). Clinically significant procedural complications occurred in 10 of 141 (7.1 %) patients. Symptomatic intra-

Canal hemorrhages was observed in 11 of 141 (7.8 %) patients. Good neurological outcomes (mRS score less than or equal to 2) were more frequent at 90 days in patients with successful re-

Canalization compared with patients with unsuccessful re-

Canalization (46 % versus 10 %; relative risk [RR]; 4.4; 95 % confidence interval [CI]; 2.1 to 9.3; p < 0.0001), and mortality was less (32 % versus 54 %; RR, 0.59; 95 % CI: 0.39 to 0.89; p = 0.01). The authors concluded that the MERCI retriever can significantly restore vascular patency during AIS within 8 hours of stroke symptom onset and provides an alternative intervention for patients who are otherwise ineligible for thrombolytics. However, there are various drawbacks with the findings of this study (Oliveira-Filho et al, 2009):
Neurological outcome was a secondary end point in the MERCI trial, and there was no evidence that treated patients had improved outcome at 90 days compared with PROACT II historical controls.

On an intention-to-treat basis, patients in the MERCI trial had a higher re-
canalization rate (TIMI 2 or 3 flow as reported by the local operator) than the spontaneous re-canalization rate for historical controls (46 % versus 18 %). However, while the device is intended to restore blood flow by removing thrombus, MERCI has been criticized because there was no confirmation that blood flow was actually restored by embolectomy as opposed to clot disruption and ensuing distal embolization. In addition, the study lacked a specific definition of TIMI re-canalization.

Overall mortality by intention-to-treat analysis was higher in MERCI than in PROACT II historical controls (44 % versus 27 %), which may be due, at least in part, to older patients with slightly more severe strokes at baseline in MERCI compared with PROACT II. Although MERCI patients had a higher rate of symptomatic intra-cranial hemorrhage than the historical controls (8 % versus 2 %, respectively), the 8 % rate in MERCI is similar to the 6.4 % rate seen with IV tPA treatment in the National Institute of Neurological Disorders and Stroke trial.

Procedural complications in MERCI, including embolization, dissection, subarachnoid hemorrhage (SAH), vessel perforation, and groin hemorrhages, occurred in 13 % and were considered clinically significant in 7 %.

The Canadian Coordinating Office for Health Technology Assessment (2005) stated that "[t]he Merci Retrieval System is another step in the development of new approaches for treating ischemic stroke. It provides an addition option when thrombolysis has failed or is inappropriate. Use of the device requires a high skill level. Data on the effectiveness of the device are limited; it is expected that the results of ongoing trials will provide further information".

An assessment prepared for the Agency for Healthcare Research and Quality concluded that future well-designed studies investigating mechanical thrombus disruption to reduce stroke-related mortality and disability are needed (Sharma et al, 2005). In addition, the California Technology Assessment Forum (2007) concluded that the use of the Merci retriever for the emergent treatment of AIS does not meet CTAF criteria.

Smith and co-workers (2008) stated that first-generation MERCI devices achieved re-
canalization rates of 48 % and, when coupled with IA thrombolytic drugs, re-
canalization rates of 60 % have been reported; and enhancements in embolectomy device design may improve re-
canalization rates. The Multi-MERCI was an international, multi-center, prospective, single-arm trial of thrombectomy in patients with large-vessel stroke treated within 8 hours of symptom onset.

Patients with persistent large-vessel occlusion after IV tPA treatment were included. Once the newer generation (L5 Retriever) device became available, investigators were instructed to use the L5 Retriever to open vessels and could subsequently use older generation devices and/or IA tPA. Primary outcome was re-
canalization of the target vessel. A total of 164 patients received thrombectomy and 131 were initially treated with the L5 Retriever. Mean age +/- SD was 68 +/-
16 years, and baseline median (inter-quartile range) NIHSS score was 19 (15 to 23). Treatment with the L5 Retriever resulted in successful re-canalization in 75 of 131 (57.3 %) treatable vessels and in 91 of 131 (69.5 %) after adjunctive therapy (IA tPA, mechanical). Overall, favorable clinical outcomes (mRS 0 to 2) occurred in 36 % and mortality was 34%; both outcomes were significantly related to vascular re-canalization. Symptomatic intra-cerebral hemorrhage occurred in 16 patients (9.8 %); 4 (2.4 %) of these were parenchymal hematoma type II.

Clinically significant procedural complications occurred in 9 (5.5 %) patients. The authors concluded that higher rates of re-canalization were associated with a newer generation thrombectomy device compared with first-generation devices, but these differences did not achieve statistical significance. Mortality trended lower and the proportion of good clinical outcomes trended higher, consistent with better re-canalization.

Kobayashi et al (2008) reported of the first 2 cases of AIS treated with the MERCI device at the authors’ department. One did not meet the inclusion criteria for systemic thrombolysis, and the second did not improve despite r-IPA treatment. In both cases, improvement of flow in the MCA was achieved and moderate neurological improvement was observed at 3-month follow-up. The authors stated that more controlled trials are needed to establish the utility of mechanical embolectomy in the treatment of stroke.

Josephson et al (2009) noted that IA thrombolysis and mechanical embolectomy have been studied for endovascular treatment of stroke. The MERCI and Multi-MERCI trials of mechanical embolectomy with or without adjuvant IA thrombolysis demonstrated effective re-canalization, but with a higher mortality compared with control patients in the PROACT II trial of IA thrombolysis. Differences in trial design may account for this mortality difference. These investigators identified patients in the MERCI and Multi-MERCI trials who would have been eligible for PROACT II. Rates of good outcome (mRS less than or equal to 2) and mortality at 90 days were compared, adjusting for differences in baseline NIHSS score and age. A total of 68 patients enrolled in MERCI and 81 enrolled in Multi-MERCI were eligible for PROACT II. In both unadjusted and adjusted analyses, PROACT II-eligible embolectomy patients showed a trend toward better clinical outcomes compared to the PROACT II control-arm (adjusted, MERCI 35.4 % [p = ns], Multi-MERCI 42.8 % [p = 0.048], PROACT II control, 25.4 %). In both unadjusted and adjusted analyses, mortality rates did not significantly differ between embolectomy patients and PROACT II control patients (adjusted analysis, MERCI 29.1 %, Multi-MERCI 18.0 %, PROACT II control, 27.1 %). Compared with the PROACT II treatment group, embolectomy groups showed similar rates of good outcome and mortality. The authors concluded that differences in mortality and proportion of good outcome between the MERCI/Multi-MERCI trials and the PROACT II trial are explained by differences in study design and baseline characteristics of patients. Mechanical embolectomy and IA thrombolysis may each be reasonable strategies for AIS; a randomized trial is necessary to confirm these results.

Fields et al (2010) stated that AIS is the leading cause of severe disability and the third leading cause of death in the United States. Intravenous tissue plasminogen activator (IV tPA) remains the most widely advocated treatment, but this therapy is limited by a narrow time window (less than 4.5 hrs after stroke onset), exclusion of patients with coagulopathy and re-canalization rates of less than 50 %. As a
result, only 5% of acute stroke patients are treated with IV tPA. Endovascular mechanical thrombectomy may be employed, either as a stand-alone therapy or as an adjunct to IV tPA, and has several potential advantages, including a wider time window (up to 8 hrs), the capacity for use in coagulopathic patients and higher re-canalization rates (up to 82%). Nonetheless, mechanical thrombectomy has engendered controversy because no randomized trials have yet been performed to support its use. The authors concluded that the results of ongoing trials are needed to ascertain the patient populations most likely to benefit from this therapy.

Sugiura and colleagues (2008) examined the safety and effectiveness of combined IV recombinant- tPA (r-tPA) and simultaneous endovascular therapy (ET) as primary rather than rescue therapy for hyper-acute MCA occlusion. A total of 29 patients eligible for IV r-tPA, who were diagnosed as having MCA (M1 or M2) occlusion within 3 hours of onset, underwent thrombolysis. In the combined group, patients were treated by IV r-tPA (0.6 mg/kg for 60 mins) and simultaneous ET (intra-arterial r-tPA, mechanical thrombus disruption with micro-guidewire, and balloon angioplasty) initiated as soon as possible. In the IV group, patients were treated by IV r-tPA only. The improvement of the NIHSS score at 24 hrs was 11.0 +/- 4.8 in the combined group versus 5.0 +/- 4.3 in the IV group (p < 0.001). In the combined group, successful re-canalization was observed in 14 (88%) of 16 patients with no symptomatic intra-cranial hemorrhage, and 10 (63%) of 16 patients had favorable outcomes (mRS 0, 1) at 3 months. The authors concluded that aggressive combined therapy with IV r-tPA and simultaneous ET markedly improved the clinical outcome of hyper-acute MCA occlusion without significant adverse effect. Moreover, they stated that additional randomized study is needed to confirm these findings.

Stead et al (2008) performed a systematic review and meta-analysis of mechanical thrombectomy in the treatment of ischemic stroke and assessed factors for technical and clinical success and survival. These researchers searched the literature using Medline and Embase for January 1, 2000 through March 1, 2006. Studies were limited to those in human beings; there were no language or study design restrictions. Validity assessment was performed using the Newcastle-Ottawa Scale. The pooled cohort was compared with a historical cohort matched for sex, age, and NIHSS. The search yielded 114 publications. Two authors determined inclusibility (inter-rater agreement, kappa = 0.94). Mean pre-procedure NIHSS score was 20.4. The MCA (36%) and the posterior circulation (38%) were the most frequently occluded areas. The clot was accessible in 85% of the patients. Hemorrhage occurred in 22% of the patients. Of 81 patients with concurrent thrombolysis, 18.5% had hemorrhage compared with 27.3% of 66 patients without thrombolysis (p = 0.21). Of the 126 patients with accessible clots, 36% had a good mRS (less than or equal to 2) and 29% died; in patients with inaccessible clots, 24% had a good mRS and 38% died. Factors associated with clinical success were younger age (p = 0.001) and lower NIHSS score at admission to the hospital (p = 0.001). Compared with a matched cohort, patients who received mechanical intervention were 14.8 times more likely to have a good mRS (95% CI: 4.4 to 50.0; p < 0.001). The authors concluded that percutaneous mechanical embolectomy in the treatment of AIS is feasible and seems to provide an option for some patients seen after the interval for administration of IV tPA therapy has elapsed.
Broderick (2009) reviewed advances in ET for AIS. Data from primate studies, randomized studies of IV r-tPA, as well as non-randomized and randomized studies of ET were reviewed. Clinical trial data demonstrate the superiority of endovascular treatment with thrombolytic medication or mechanical methods to re-open arteries compared with control patients from the PROACT II Trial treated with heparin alone. However, these same clinical trials, as well as pre-clinical primate models, indicate that re-canalization, whether by endovascular approaches or standard-dose r-tPA, is unlikely to improve clinical outcome after a certain time point. Although the threshold beyond which re-perfusion has no or little benefit has yet to be conclusively defined, accumulated data to this point indicate an overall threshold of approximately 6 to 7 hours. In addition, although the risk of symptomatic intra-cerebral hemorrhage is similar in trials of IV lytics and endovascular approaches, endovascular approaches have distinctive risk profiles that can impact outcome. The author concluded that the treatment of AIS is evolving with new tools to re-open arteries and salvage the ischemic brain. Ongoing randomized trials of these new approaches are prerequisite next steps to demonstrate whether re-perfusion translates into clinical effectiveness.

The American Heart Association/American Stroke Association Stroke Council/Clinical Cardiology Council’s guidelines for the early management of adults with ischemic stroke (Adams et al, 2007) stated that:

Although the Merci device is a reasonable intervention for extraction of IA thrombi in carefully selected patients, the panel also recognizes that the utility of the device in improving outcomes after stroke is unclear. The panel also recommends that the device be studied in additional clinical trials that will define its role in the emergency management of stroke. The usefulness of other mechanical endovascular treatments is not established. These devices should be used in the setting of clinical trials.

Guidelines from the Institute for Clinical Systems Improvement (ICSI, 2010) state that the utility of mechanical embolectomy devices, including the MERCI and Penumbra, in improving clinical outcomes "remains unclear." Furthermore, the Australian National Stroke Foundation’s clinical guidelines for acute stroke management (2010) found insufficient evidence for the use of mechanical embolectomy. The Stroke Foundation of New Zealand (2010) reached similar conclusions about the lack of evidence for mechanical embolectomy. Guidelines on stroke from the Scottish Intercollegiate Guidelines Network (SIGN, 2008) concluded: "Mechanical clot retrieval devices should be further evaluated in randomised controlled trials." The National Institute for Health and Clinical Excellence’s clinical guideline on the diagnosis and initial management of acute stroke and transient ischemic attack (NICE, 2008) did not mention the use of mechanical embolectomy.

In addition, the American Heart Association’s scientific statement on indications for the performance of intra-cranial endovascular neuro-interventional procedures (Meyers et al, 2009) stated that; (i) although the Concentric Merci device can be useful for extraction of intra-arterial thrombi in appropriately selected patients, the utility of the device in improving outcomes after stroke remains unclear, and (ii) the usefulness of other endovascular devices is not yet established, but they may be beneficial.
The Trevo Retriever (Concentric Medical, Mountain View, CA) is designed to remove thrombus in patients with acute stroke. There is currently a clinical trial that evaluates the performance of the Trevo Retriever versus the Merci Retriever in restoring blood flow to the brain of patients experiencing an acute ischemic stroke in a large vessel (the TREVO2 Trial).

Baker and colleagues (2011) described the state of the evidence supporting use of neurothrombectomy devices in the treatment of AIS. Medline, SCOPUS, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Web of Science were searched, without language restrictions, from their inception through May 2010. The Medline and Cochrane Central Register of Controlled Trials searches were updated through November 2010. Two independent investigators screened citations for human studies of any design or case series or case reports of patients with an AIS that evaluated a neurothrombectomy device and reported at least 1 clinical effectiveness outcome or harm. Using standardized protocols, 2 independent investigators extracted information about study characteristics and outcomes, and a third reviewer resolved disagreement. A total of 87 articles met eligibility criteria, including 18 prospective single-group studies, 7 non-comparative retrospective studies, and 62 case series or case reports. Two FDA-cleared devices, the MERCI Retriever (Concentric Medical, Mountain View, CA) (40 %) and the Penumbra System (Penumbra, Alameda, CA) (9 %), represented a large portion of the available data. All prospective and retrospective studies provided data on successful recanalization with widely varying rates (43 % to 78 % with the MERCI Retriever and 83 % to 100 % with the Penumbra System). Rates of harms, including symptomatic (16 studies; 0 % to 10 % with the MERCI Retriever and 0 % to 11 % with the Penumbra System) or asymptomatic (13 studies; 28 % to 43 % and 1 % to 30 %, respectively) intra-cranial hemorrhage and vessel perforation or dissection (11 studies; 0 % to 7 % and 0 % to 5 %, respectively), also varied by device. Predictors of harm included older age, history of stroke, and higher baseline stroke severity scores, whereas successful recanalization was the sole predictor of good outcomes. Most available data are from single-group, non-comparative studies. In addition, the patient population most likely to benefit from these devices is undetermined. The authors concluded that currently available neurothrombectomy devices offer intriguing treatment options in patients with AIS. They stated that future trials should use a randomized design, with adequate power to show equivalency or non-inferiority between competing strategies or devices, and strive to identify populations that are most likely to benefit from use of neurothrombectomy devices. Furthermore, future studies should also examine if neurothrombectomy devices affect final health outcomes associated with stroke rather than improving re-canlization alone when compared with contemporary controls.

In an editorial that accompanied the afore-mentioned study, Khatri (2011) stated that "[t]he uncertainty about the effectiveness of neurothrombectomy is unsettling ... [i]f neurothrombectomy devices do not provide net benefit beyond that of intravenous rt-PA, then our current use of these devices is wasteful and perhaps even harmful ... It is premature to compare different devices until we first establish the clinical benefit of neurothrombectomy over thrombolysis. Until then, expansion of the use of neurothrombectomy is unjustified". Furthermore, in a
review on endovascular stroke treatment, Grunwald et al (2011) noted that mechanical re-canalization devices can potentially have a clinically relevant impact in the interventional treatment of stroke, but at the present time, a randomized study would be beneficial.

In summary, although mechanical embolectomy has been used for removing clot in selected patients, its clinical value for improving outcomes following stroke is unproven. Further investigation is needed to ascertain its role in the management of patients with AIS.

Cerebral vasospasm remains a major source of morbidity and death in patients with aneurysmal SAH. When vasospasm becomes refractory to maximal medical management consisting of induced hypertension and hypervolemia and administration of calcium channel antagonists, endovascular therapies should be considered. The primary goal of endovascular treatment is to increase cerebral blood flow (CBF) to prevent cerebral infarction. Two of the more frequently studied endovascular treatments are transluminal balloon angioplasty (TBA) and IA papaverine infusion. Other pharmacological vasodilating agents for the treatment of cerebral vasospasm include IA nimodipine, nicardipine, verapamil, and milrinone.

Elliott and colleagues (1998) tested the hypothesis that TBA is superior to papaverine infusion for the treatment of proximal anterior circulation arterial vasospasm following SAH. Between 1989 and 1995, 125 vasospastic distal internal carotid artery or proximal MCA vessel segments were treated in 52 patients. Blood flow velocities of the involved vessels were assessed by using transcranial Doppler (TCD) monitoring in relation to the day of treatment with TBA or papaverine infusion. Balloon angioplasty and papaverine infusion cohorts were compared based on mean pre- and post-treatment velocity at 24 and 48 hrs using the 1-tailed, paired-samples t-test. Balloon angioplasty alone was performed in 101 vessel segments (81 %) in 39 patients (75 %), whereas papaverine infusion alone was used in 24 vessel segments (19 %) in 13 patients (25 %). Although repeated treatment after TBA was needed in only 1 vessel segment, repeated treatment following papaverine infusion was required in 10 vessel segments (42 %) in 6 patients because of recurrent vasospasm (p < 0.001). Seven vessel segments (29 %) with recurrent spasm after papaverine infusion were treated with TBA. Although vessel segments treated with papaverine demonstrated a 20 % mean decrease in blood flow velocity (p < 0.009) on post-treatment Day 1, velocities were not significantly lower than pre-treatment levels by post-treatment Day 2 (p = 0.133). Balloon angioplasty resulted in a 45 % mean decrease in velocity to a normal level following treatment (p < 0.001), a decrease that was sustained. The authors concluded that TBA is superior to papaverine infusion for the permanent treatment of proximal anterior circulation vasospasm following aneurysmal SAH.

Hoh and Ogilvy (2005) reviewed clinical series of endovascular treatment of cerebral vasospasm reported in the English language literature. Transluminal balloon angioplasty produced clinical improvement in 62 % of patients, significantly improved mean TCD velocities (p < 0.05), significantly improved CBF in 85 % of patients as studied by (133)Xenon techniques and serial single photon emission computerized tomography, and was associated with 5.0 % complications and 1.1
% vessel rupture. Intra-arterial papaverine therapy produced clinical improvement in 43% of patients but only transiently, requiring multiple treatment sessions (1.7 treatments per patient); significantly improved mean TCD velocities (p < 0.01) but only for less than 48 hrs; improved CBF in 60% of patients but only for less than 12 hrs; and was associated with increases in intra-cranial pressure and 9.9% complications. Intra-arterial nicardipine therapy produced clinical improvement in 42% of patients, significantly improved mean TCD velocities (p < 0.001) for 4 days, and was associated with no complications in the authors’ small series. These investigators have adopted a treatment protocol at their institution of TBA and IA nicardipine therapy as the endovascular treatments for medically refractory cerebral vasospasm.

In a review on neuro-interventional for the treatment of vasospasm, Brisman and colleagues (2006) stated that they favor the use of TBA over IA anti-spasmolytics due to the increased durability and long-lasting effects of the former and lower risk profile. Also, in a review on endovascular treatment of vasospasm following SAH, Abdenour and associates (2007) noted that in Europe, nimodipine is widely used whereas nicardipine and verapamil are the major molecules administered in North America where intravenous nimodipine is not FDA-approved. Papaverine is less used nowadays because of its short duration of action and of the risk of aggravation of raised intra-cranial pressure.

Furthermore, Platz and associates (2008) reported a possible new side effect of IA administration of papaverine. After the treatment of cerebral vasospasm in a SAH patient by IA papaverine into the left posterior cerebral artery, severe mesencephalic extravasation of blood and contrast media was detected. After reviewing the literature, the authors concluded that interruption of the blood-brain barrier by papaverine most likely combined with a secondary hyperperfusion phenomena, and perhaps a direct toxic effect on brain tissue was the mechanism of this major complication. They stated that in treating vasospasm in areas with a high density of perforating arteries, especially in the posterior circulation, papaverine should be used cautiously because a safe regimen has yet to be established. In this situation, alternative agents such as calcium channel blockers could be considered, but evidence-based data are still missing.

In the Canadian best practice recommendations for management of SAH and intracerebral hemorrhage (Canadian Stroke Network/Heart & Stroke Foundation of Canada, 2006), IA papaverine was not mentioned as a option.

In a Cochrane review, Rinkel et al (2005) examined if calcium antagonists improve outcome in patients with aneurysmal SAH. These investigators searched the Cochrane Stroke Group Trials Register (September 2003). In addition, they searched MEDLINE (1966 to October 2003) and EMBASE (1980 to October 2003), hand-searched 2 Russian journals (1990 to 2003) and contacted trialists and pharmaceutical companies (in 1995 and 1996) to identify further studies. All unconfounded, truly randomized controlled trials comparing any calcium antagonist with control were included in this analysis. Two reviewers independently extracted the data and assessed trial quality. Trialists were contacted to obtain missing information. These researchers analyzed 12 trials totaling 2,844 patients with SAH (1,396 in the treatment group and 1,448 in the control group). The drugs analyzed were: nimodipine (8 trials, 1,574 patients),
nicardipine (2 trials, 954 patients), AT877 (1 trial, 276 patients) and magnesium (1 trial, 40 patients). Overall, calcium antagonists reduced the risk of poor outcome: RR 0.82 (95% CI: 0.72 to 0.93); the absolute risk reduction was 5.1%, the corresponding number of patients needed to treat to prevent a single poor outcome event was 20. For oral nimodipine alone the RR was 0.70 (0.58 to 0.84). The RR of death on treatment with calcium antagonists was 0.90 (95% CI: 0.76 to 1.07), that of clinical signs of secondary ischemia 0.67 (95% CI: 0.60 to 0.76), and that of CT- or MR-confirmed infarction 0.80 (95% CI: 0.71 to 0.89). The authors concluded that calcium antagonists reduce the risk of poor outcome and secondary ischemia after aneurysmal SAH. The results for "poor outcome" depend largely on a single large trial with oral nimodipine; the evidence for nicardipine, AT877 and magnesium is inconclusive. The evidence for nimodipine is not beyond every doubt, but given the potential benefits and modest risks of this treatment, against the background of a devastating natural history, oral nimodipine (60 mg every 4 hours) is currently indicated in patients with aneurysmal SAH. Intravenous administration of calcium antagonists cannot be recommended for routine practice on the basis of the present evidence.

Weyer et al (2006) noted that cerebral vasospasm and delayed cerebral ischemia remain common complications of aneurysmal SAH, and yet therapies for cerebral vasospasm are limited. Despite a large number of clinical trials, only calcium antagonists have strong evidence supporting their effectiveness. These investigators performed a systematic review of the literature on the treatment of cerebral vasospasm. A literature search for randomized controlled trials of therapies used for prevention or treatment of cerebral vasospasm and/or delayed cerebral ischemia was conducted, and 41 articles meeting the review criteria were found. Study characteristics and primary results of these articles are reviewed. Key indicators of quality were poor when averaged across all studies, but have improved greatly over time. The only proven therapy for vasospasm is nimodipine. Trilazad is not effective, and studies of hemodynamic maneuvers, magnesium, statin medications, endothelin antagonists, steroid drugs, anti-coagulant/anti-platelet agents, and intra-thecal fibrinolytic drugs have yielded inconclusive results. The following conclusions were made: nimodipine is indicated after SAH and trilazad is not effective. More study of hemodynamic maneuvers, the effectiveness of other calcium channel antagonists such as nicardipine delivered by other routes (e.g., intra-thecally), magnesium, statin drugs, endothelin antagonists, and intra-thecal fibrinolytic therapy is warranted.

Shah et al (2009) examined the safety and tolerability of super-selective intra-arterial magnesium sulfate in combination with intra-arterial nicardipine in patients with cerebral vasospasm after SAH. Patients were treated in a prospective protocol at 2 teaching medical centers. Emergent cerebral angiography was performed if there was either clinical, ultrasound, and/or CT perfusion deficits suggestive of cerebral vasospasm. Intra-arterial magnesium sulfate (0.25 to 1 g) was administered via a microcatheter in the affected vessels in combination with nicardipine (2.5 to 20.0 mg). Mean arterial pressures (MAP) and intra-cranial pressures (ICP) were monitored during the infusion. Immediate and sustained angiographic and clinical improvement was determined from post-treatment angiograms and clinical follow-up. Angiographical and clinical outcomes were compared to 2 published case series that has used nicardipine alone. A total of 58 vessels were treated in 14 patients (mean age of 42 years; 11 women) with acute
SAH. The treatment was either intra-arterial nicardipine and magnesium sulfate alone or in conjunction with primary angioplasty. Forty vessels (69%) had immediate angiographical improvement with intra-arterial nicardipine and magnesium sulfate alone and 18 vessels (31%) required concomitant balloon angioplasty with complete reversal of the vasospasm. Re-treatment was required in 13 vessels (22%) and the median time for retreatment was 2 days (range of 1 to 13 days). Nicardipine treatment resulted in the reduction of MAP (12.3 mmHg, standard error [SE] 1.34, p < 0.0001) without any significant change in ICP. Magnesium sulfate infusion was not associated with change in MAP or ICP. Among 31 procedures, immediate neurological improvement was observed in 22 (71%) procedures. In 12 (86%) patients, there were no infarctions in the follow-up CT scan acquired between 24 and 48 hrs. No statistical significant difference was observed in angiographical and clinical outcome of patients treated with the combination therapy in comparison with historical controls treated with nicardipine alone. The authors concluded that administration of intra-arterial magnesium sulfate in combination with nicardipine was well-tolerated in patients with SAH and cerebral vasospasm without a significant change in MAP and ICP. They stated that the efficacy of this combination therapy should be evaluated in a larger, controlled setting.

Reddy and Yeh (2009) stated that injectable nicardipine is increasingly being used to manage neurovascular conditions. To better understand its place in therapy, these investigators conducted an evidenced-based literature review. A total of 223 article abstracts were identified; after independent review by 2 individuals and a supplemental manual search, 29 were deemed relevant and were included in this review. Nicardipine has been studied or recommended for management of hypertension in many neurovascular settings (e.g., ischemic stroke, intra-cerebral hemorrhage, craniotomy, and spinal surgery), for vasospasm in aneurysmal SAH, and in acute traumatic brain injury. In the management of hypertension in acute stroke, nicardipine is one of several recommended options available; expert opinion forms the basis of these recommendations in clinical guidelines, with limited randomized controlled trial evidence to support its use. Among the various anti-hypertensive agents, nicardipine has the highest drug acquisition cost. In 2 meta-analyses, intravenous nicardipine had no impact on patient outcomes (death, disability) in patients with acute traumatic brain injury (RR 0.25, 95% CI: 0.05 to 1.27) or in patients with aneurysmal SAH (RR 0.97, 95% CI: 0.78 to 1.20). Intrar-arterial nicardipine reduced angiographical diameter (p value not reported) and peak systolic velocities on transcranial Doppler images (p < 0.001) in published case series. Given nicardipine's high cost relative to that of other agents and the limited evidence to support its use in patients with neurovascular conditions, this drug should be considered only in patients who have failed or have contraindications to alternative agents in the management of hypertension. The authors stated that although intra-arterial nicardipine appears to be promising in aneurysmal SAH, well-designed studies are needed in this setting before its use can be routinely recommended.

In a Cochrane review, Zhang et al (2010) evaluated the safety and effectiveness of trilazad (a non-glucocorticoid, 21-aminosteroid that inhibits lipid peroxidation) in patients with aneurysmal SAH. These investigators searched the Cochrane Stroke Group Trials Register (last searched October 2009); the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2009);
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MEDLINE (1966 to October 2009); EMBASE (1980 to October 2009); and the Stroke Trials Directory, the National Center for Complementary and Alternative Medicine, and the National Institute of Health Clinical Trials Database (searched October 2009). They hand-searched 10 Chinese journals, searched the reference lists of relevant publications, and contacted the manufacturers of tirilazad. Randomised trials of tirilazad started within 4 days of SAH onset, compared with placebo or open control in patients with aneurysmal SAH documented by angiography and computerised tomography scan or cerebrospinal fluid examination, or both. These researchers extracted data relating to case fatality, poor outcome (death, vegetative state, or severe disability), delayed cerebral ischaemia (or symptomatic vasospasm), cerebral infarction and adverse events of treatments. They pooled the data using the Peto fixed-effect method for dichotomous data. The authors included 5 double-blind, placebo-controlled trials involving 3,821 patients; there was no significant heterogeneity. Oral or intravenous nimodipine was used routinely as a background treatment in both groups in all trials. There was no significant difference between the 2 groups at the end of follow-up for the primary outcome, death (odds ratio (OR) 0.89, 95 % CI: 0.74 to 1.06), or in poor outcome (death, vegetative state or severe disability) (OR 1.04, 95 % CI: 0.90 to 1.21). During the treatment period, fewer patients developed delayed cerebral ischemia in the tirilazad group than in the control group (OR 0.80, 95 % CI: 0.69 to 0.93). Subgroup analyses did not demonstrate any significant difference in effects of tirilazad on clinical outcomes. Leukocytosis and prolongation of Q-T interval occurred significantly more frequently in the treatment group in only 1 trial evaluating tirilazad at high dose. There was no significant difference in infusion site disorders or other laboratory parameters between the 2 groups. The authors concluded that there is no evidence that tirilazad, in addition to nimodipine, reduces mortality or improves poor outcome in patients with aneurysmal SAH.

Tenser and colleagues (2011) reviewed the initial studies of the Merci Retriever and Penumbra System for mechanical clot extraction. Baseline patient characteristics, as well as revascularization rates and clinical outcome, were examined. Baseline National Institutes of Health Stroke Scale scores were greater than those observed in previous IV tPA studies, consistent with large-vessel occlusion. Successful re-occlusion occurred more frequently than with IV tPA and was associated with improved clinical outcome and mortality. Symptomatic intra-cranial hemorrhage and mortality rates were greater than those seen with IV tPA. Mechanical clot extraction can be performed safely in patients with large-vessel occlusions, and successful re-occlusion resulted in better clinical outcomes than those without. The authors concluded that mechanical thrombectomy provides a therapeutic option for ischemic stroke patients who are ineligible for, or who do not respond to, IV thrombolitics. Moreover, they stated that further studies, including randomized clinical trials, are needed to validate these findings.

In a review on "Mechanical thrombectomy devices for treatment of stroke" Radoslav and Saver (2012) stated that "Mechanical thrombectomy devices work well in large, proximal arteries, rapidly debulking large clot burdens that are resistant to chemical fibrinolysis. Conversely, mechanical thrombectomy devices are currently not well suited for distal arterial branches (hard to navigate to and device diameters too large) and are not options for penetrator occlusions, while
chemical fibrinolysis works well on those targets ... Definitive data regarding the
efficacy of mechanical thrombectomy devices in improving final clinical outcome
over medical therapy alone awaits the conclusion of ongoing trials. One trial, the
Interventional Management of Stroke 3 (IMS 3) Trial, has been stopped for futility.
However, the implications for IMS 3 for mechanical thrombectomy may be limited,
as many patients enrolled in the endovascular arm of IMS 3 were treated with intra
-arterial fibrinolytics drugs rather than mechanical thrombectomy, essentially none
of the patients were treated with the most technically efficacious device class, the
stent retrievers, and the trial included large number of patients with no occlusions
or small, distal occlusions, which are less likely to benefit from mechanical
retrieval“.

Furthermore, an UpToDate review on “Reperfusion therapy for acute ischemic
stroke” (Oliveira-Filho and Samuels, 2012) states that “The 2012 ACCP guidelines
concluded that the available data regarding mechanical thrombectomy in acute
ischemic stroke are of low quality and leave considerable uncertainty regarding the
impact of this intervention on survival and functional outcome. A 2011 systematic
review identified 87 studies published through November 2010 that evaluated
mechanical clot disruption devices for acute ischemic stroke. All 87 studies were
uncontrolled, only 18 were prospective, and only 3 of those used blinded outcome
assessment. Nearly half of the data came from studies evaluating the Merci
Retriever and the Penumbra System (40 % and 9 %, respectively). For these and
other thrombectomy devices, the included studies reported widely varying
outcome rates of successful recanalization, good clinical outcome, symptomatic
intracranial hemorrhage, vessel injury, and mortality. The one clear finding was
that successful recanalization predicted a good outcome. However, given the
methodologic limitations of the available studies, the investigators concluded that
randomized trials are necessary to establish whether mechanical clot disruption
devices improve patient outcome ..... Thus, although the Merci and Penumbra
devices are approved for clot removal in carefully selected patients, their clinical
utility for improving outcomes after stroke is unproven. Further study in
randomized controlled trials is needed before the role of mechanical clot disruption
devices is defined for the emergency management of acute ischemic stroke”.

Alshekhlee et al (2012) stated that mechanical thrombectomy is a promising
adjuvant or stand-alone therapy for AIS caused by occlusion of a large vessel in
patients beyond the systemic thrombolysis therapeutic window. These
investigators reviewed the clinical and angiographical outcomes of mechanical
thrombectomy with use of the Merci retriever device. Available literature published
to date on the major trials and observational studies involving the Merci retriever
was reviewed. In addition to the review, results from studies involving the Merci
retriever were compared to results from Prolyse in Acute Cerebral
Thromboembolism II (PROACT II) and the Penumbra device studies. The
predictors for favorable outcome following re-vascularization with the Merci device
were reviewed on the basis of published stratified analyses. Favorable clinical
outcome was defined in the Merci experience by a mRS score of less than or
equal to 2 at 90 days following AIS. Presented in this review were a total of 1,226
patients treated with the Merci device; 305 patients were from 2 pivotal trials
involving the device, and the remaining 921 patients were from observational
studies in the Merci registry. The 90-day mRS score of less than or equal to 2 was
achieved in 32 % of the patient group, with an overall mortality rate of 35.2 %.
Symptomatic intra-cerebral hemorrhage was identified in 7.3% of patients treated with Merci retriever, a result comparable to that in the PROACT II and Penumbra thrombectomy trials. Successful re-canalization, lower NIHSS score, and younger age were identified as the strongest predictors of favorable outcomes. The authors concluded that mechanical thrombectomy with the Merci retriever device is a safe treatment modality for AIS patients presenting with a large-vessel occlusion within 8 hours of symptom onset. Moreover, they stated that although the Merci retriever showed a good re-canalization rate, there are currently no randomized clinical trials to assess its clinical effectiveness in comparison with systemic thrombolysis within a window of 3 to 4.5 hours or with standard of care beyond a 4.5-hour window.

Hussain et al (2012) noted that the effectiveness of IV systemic thrombolysis is limited in patients with severe AIS and large-vessel occlusion. Mechanical thrombectomy has been the mainstay therapy in large-vessel occlusion. These investigators reviewed the evidence regarding the Penumbra aspiration device. The pivotal single-arm prospective trial that led to its approval by the FDA enrolled 125 patients within 8 hours of symptom onset and demonstrated an 82% re-canalization rate, to TIMI scores of 2 and 3. The risk of symptomatic intra-cranial hemorrhage was 10%, and a mRS score of less than or equal to 2 was 25%. In the post-marketing registry, 157 vessels were treated, with 87% achieving TIMI 2 and 3 re-canalization and 41% having a mRS score of less than or equal to 2. The authors concluded that the Penumbra aspiration system is an effective tool to safely re-vascularize large-vessel occlusions in patients within 8 hours of onset of AIS who are either refractory to or excluded from IV thrombolytic therapy. Moreover, they stated that further prospective, randomized controlled trials will be needed to address whether this ability translates into neurologic improvement and better functional outcomes.

San Roman et al (2012) examined the safety and effectiveness of the new TREVO stent-like retriever in consecutive patients with acute stroke. These researchers conducted a prospective, single-center study of 60 patients (mean age of 71.3 years; male 47%) with stroke lasting less than 8 hours in the anterior circulation (n = 54) or less than 12 hours in the vertebra-basilar circulation (n = 6) treated if CT perfusion/CT angiography confirmed a large artery occlusion, ruled out a malignant profile, or showed target mismatch if symptoms were greater than 4.5 hours. Successful re-canalization (Thrombolysis In Cerebral Infarction 2b-3), good outcome (a mRS score of 0 to 2) and mortality at Day 90, device-related complications, and symptomatic hemorrhage (parenchymal hematoma Type 1 or parenchymal hematoma Type 2 and NIHSS score increment greater than or equal to 4 points) were prospectively assessed. Median (interquartile range) NIHSS score on admission was 18 (12 to 22). The median (interquartile range) time from stroke onset to groin puncture was 210 (173 to 296) minutes. Successful re-vascularization was obtained in 44 (73.3%) of the cases when only the TREVO device was used and in 52 (86.7%) when other devices or additional intra-arterial t-PA were also required. The median time (interquartile range) of the procedure was 80 (45 to 114) minutes. Good outcome was achieved in 27 (45%) of the patients and the mortality rate was 28.3%. Seven patients (11.7%) presented a symptomatic intra-cranial hemorrhage. No other major complications were detected. The authors concluded that the TREVO device was reasonably safe and effective in patients with severe stroke. They stated that these results support
further investigation of the TREVO device in multi-centric registries and randomized clinical trials.

Broderick et al (2013) stated that endovascular therapy is increasingly used after the administration of intravenous tissue plasminogen activator (t-PA) for patients with moderate-to-severe AIS. These investigators examined if a combined approach is more effective than intravenous t-PA alone. They randomly assigned eligible patients who had received intravenous t-PA within 3 hours after symptom onset to receive additional endovascular therapy or intravenous t-PA alone, in a 2:1 ratio. The primary outcome measure was a mRS score of 2 or less (indicating functional independence) at 90 days (scores range from 0 to 6, with higher scores indicating greater disability). The study was stopped early because of futility after 656 participants had undergone randomization (434 patients to endovascular therapy and 222 to intravenous t-PA alone). The proportion of participants with a mRS score of 2 or less at 90 days did not differ significantly according to treatment (40.8 % with endovascular therapy and 38.7 % with intravenous t-PA; absolute adjusted difference, 1.5 percentage points; 95 % CI: -6.1 to 9.1, with adjustment for the NIHSS score [8 to 19, indicating moderately severe stroke, or greater than or equal to 20, indicating severe stroke]), nor were there significant differences for the predefined subgroups of patients with an NIHSS score of 20 or higher (6.8 percentage points; 95 % CI: -4.4 to 18.1) and those with a score of 19 or lower (1.0 percentage point; 95 % CI: -10.8 to 8.8). Findings in the endovascular-therapy and intravenous t-PA groups were similar for mortality at 90 days (19.1 % and 21.6 %, respectively; p = 0.52) and the proportion of patients with symptomatic intracerebral hemorrhage within 30 hours after initiation of t-PA (6.2 % and 5.9 %, respectively; p = 0.83). The authors concluded that the trial showed similar safety outcomes and no significant difference in functional independence with endovascular therapy after intravenous t-PA, as compared with intravenous t-PA alone.

Ciccone et al (2013) noted that in patients with ischemic stroke, endovascular treatment results in a higher rate of re-canalization of the affected cerebral artery than systemic intravenous thrombolytic therapy. These researchers compared the clinical effectiveness of the 2 approaches. They randomly assigned 362 patients with AIS, within 4.5 hours after onset, to endovascular therapy (intra-arterial thrombolysis with recombinant t-PA; mechanical clot disruption or retrieval, or a combination of these approaches) or intravenous t-PA. Treatments were to be given as soon as possible after randomization. The primary outcome was survival free of disability (defined as a mRS score of 0 or 1 on a scale of 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability despite symptoms, and 6 death) at 3 months. A total of 181 patients were assigned to receive endovascular therapy, and 181 intravenous t-PA. The median time from stroke onset to the start of treatment was 3.75 hours for endovascular therapy and 2.75 hours for intravenous t-PA (p < 0.001). At 3 months, 55 patients in the endovascular-therapy group (30.4 %) and 63 in the intravenous t-PA group (34.8 %) were alive without disability (OR adjusted for age, sex, stroke severity, and atrial fibrillation status at baseline, 0.71; 95 % CI: 0.44 to 1.14; p = 0.16). Fatal or non-fatal symptomatic intra-cranial hemorrhage within 7 days occurred in 6 % of the patients in each group, and there were no significant differences between groups in the rates of other serious adverse events or the case fatality rate. The
authors concluded that the results of this trial in patients with AIS indicated that endovascular therapy is not superior to standard treatment with intravenous t-PA.

In an editorial that accompanied the afore-mention studies, Chimowitz (2013) stated that “A decision by Medicare to place a moratorium on reimbursement for endovascular treatment of acute ischemic stroke outside of randomized trials would facilitate recruitment in these urgently needed trials. Once the new trials are completed, endovascular treatment will have been given ample opportunity to prove itself”.

This CLOTBUST device encircles the head and directs ultrasonic sound to obstructed arteries to speed up the dissolving effect of clotbusting tPA drugs (Alberta Heritage Foundation, 2014). This device is currently under study. The CLOTBUST headframe, developed by Cerevast Therapeutics, automatically targets the clot-affected region without the need for a trained sonographer or vascular technician to perform the procedure. Clinical studies are examining whether the addition of the acoustic energy of ultrasound to conventional intravenous tPA therapy dissolves blood clots more completely and provides stroke patients with better long-term outcomes compared to IV tPA therapy alone.

In a multi-center, open-label, pilot study, Barreto and associates (2013) examined the effects of iPA plus the CLOTBUST-HF, a novel operator-independent ultrasound device, in patients with ischemic stroke caused by proximal intra-cranial occlusion. All patients received standard-dose IV tPA, and shortly after iPA bolus, the CLOTBUST-HF device delivered 2-hour therapeutic exposure to 2-MHz pulsed-wave ultrasound. Primary outcome was occurrence of symptomatic intra-cerebral hemorrhage. All patients underwent pre-treatment and post-treatment transcranial Doppler ultrasound or CT angiography; NIHSS scores were collected at 2 hours and modified Rankin scale at 90 days. Summary characteristics of all 20 enrolled patients were 60 % men, mean age of 63 (SD = 14) years, and median NIHSS of 15. Sites of pre-treatment occlusion were as follows: 14 of 20 (70 %) middle cerebral artery, 3 of 20 (15 %) terminal internal carotid artery, and 3 of 20 (15 %) vertebral artery. The median (interquartile range) time to tPA at the beginning of sonothrombolysis was 22 (13.5 to 29.0) minutes. All patients tolerated the entire 2 hours of insonation, and none developed symptomatic intra-cerebral hemorrhage. No serious adverse events were related to the study device. Rates of 2-hour re-canalization were as follows: 8 of 20 (40 %; 95 % CI: 19 % to 64 %) complete and 2 of 20 (10 %; 95 % CI: 1 % to 32 %) partial. Middle cerebral artery occlusions demonstrated the greatest complete re-canalization rate: 8 of 14 (57 %; 95 % CI: 29 % to 82 %). At 90 days, 5 of 20 (25 %, 95 % CI: 7 % to 49 %) patients had a modified Rankin scale of 0 to 1. The authors concluded that sonothrombolysis using a novel, operator-independent device, in combination with systemic tPA, seems safe, and re-canalization rates warrant evaluation in a phase III efficacy trial.

An UpToDate review on “Initial assessment and management of acute stroke” (Oliveira-Filho and Koroshetz, 2014) does not mention transcranial ultrasound as a therapeutic option.

Hong and colleagues (2014) noted that therapeutic hypothermia improves outcomes in experimental stroke models, especially after ischemia-reperfusion injury. In a prospective cohort study at 2 stroke centers, these researchers
investigated the clinical and radiological effects of therapeutic hypothermia in AIS patients after re-canalization. They enrolled patients with AIS in the anterior circulation with an initial NIHSS greater than or equal to 10 who had successful re-canalization (greater than or equal to thrombolysis in cerebral ischemia, 2b). Patients at center A underwent a mild hypothermia (34.5° C) protocol, which included mechanical ventilation, and 48-hour hypothermia and 48-hour re-warming. Patients at center B were treated according to the guidelines without hypothermia. Cerebral edema, hemorrhagic transformation, good outcome (3-month modified Rankin Scale, less than or equal to 2), mortality, and safety profiles were compared. Potential variables at baseline and during the therapy were analyzed to evaluate for independent predictors of good outcome. The hypothermia group (n = 39) had less cerebral edema (p = 0.001), hemorrhagic transformation (p = 0.016), and better outcome (p = 0.017) compared with the normothermia group (n = 36). Mortality, hemi-cranietomy rate, and medical complications were not statistically different. After adjustment for potential confounders, therapeutic hypothermia (odds ratio, 3.0; 95 % confidence interval, 1.0-8.9; P=0.047) and distal occlusion (OR, 7.3; 95 % CI: 1.3 to 40.3; p = 0.022) were the independent predictors for good outcome. Absence of cerebral edema (OR, 5.4; 95 % CI: 1.6 to 18.2; p = 0.006) and no medical complications (OR, 9.3; 95 % CI: 2.2 to 39.9; p = 0.003) were also independent predictors for good outcome during the therapy. The authors concluded that in patients with ischemic stroke, after successful re-canalization, therapeutic hypothermia may reduce risk of cerebral edema and hemorrhagic transformation, and lead to improved clinical outcomes.

An UpToDate review on “Initial assessment and management of acute stroke” (Oliveira-Filho and Koroshetz, 2014) states that “Induced hypothermia is not currently recommended for patients with ischemic stroke, outside of clinical trials. An NINDS-funded randomized trial (ICTU2/S3) evaluating the combination of hypothermia and thrombolysis versus thrombolysis alone is currently underway”.

CPT Codes / HCPCS Codes / ICD-9 Codes

**There is no specific code for mechanical embolectomy:**

CPT codes not covered for indications listed in the CPB:

- 37184
- 37185

HCPCS codes not covered for indications listed in the CPB:

- C1757 Catheter, thrombectomy/embolectomy
- C1876 Stent, non-coated/non-covered, with delivery system
- C1884 Embolization protective system
- C1887 Catheter, guiding (may include infusion/perfusion capability)
ICD-9 codes not covered for indications listed in the CPB:

433.00 - Occlusion of cerebral arteries
434.91

Intra-arterial infusion of spasmolytics or calcium antagonists:

CPT codes not covered for indications listed in the CPB:

37202

ICD-9 codes not covered for indications listed in the CPB:

430 Subarachnoid hemorrhage

The above policy is based on the following references:

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Oliveira-Filho J, Samuels OB. Reperfusion therapy for acute ischemic stroke. Last reviewed July 2012. UpToDate Inc., Waltham, MA.


