Annals of Internal Medicine | Review

Neurothrombectomy Devices for the Treatment of Acute Ischemic Stroke: State of the Evidence

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Background: Acute ischemic strokes are associated with poor outcomes and high health care burden. Evidence exists evaluating the use of neurothrombectomy devices in patients receiving currently recommended treatments that may have limited efficacy.

Purpose: To describe the state of the evidence supporting use of neurothrombectomy devices in the treatment of acute ischemic stroke.

Data Sources: 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.

Study Selection: Two independent investigators screened citations for human studies of any design or case series or case reports of patients with an acute ischemic stroke that evaluated a neurothrombectomy device and reported at least 1 clinical effectiveness outcome or harm.

Data Extraction: Using standardized protocols, 2 independent investigators extracted information about study characteristics and outcomes, and a third reviewer resolved disagreement.

Data Synthesis: 87 articles met eligibility criteria, including 18 prospective single-group studies, 7 noncomparative retrospective studies, and 62 case series or case reports. Two U.S. Food and Drug Administration (FDA)–cleared devices, the MERCI Retriever (Concentric Medical, Mountain View, California) (40%) and the Penumbra System (Penumbra, Alameda, California) (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) intracranial 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.

Limitations: Most available data are from single-group, noncomparative studies. In addition, the patient population most likely to benefit from these devices is undetermined.

Conclusion: Currently available neurothrombectomy devices offer intriguing treatment options in patients with acute ischemic stroke. Future trials should use a randomized design, with adequate power to show equivalency or noninferiority between competing strategies or devices, and strive to identify populations that are most likely to benefit from use of neurothrombectomy devices.

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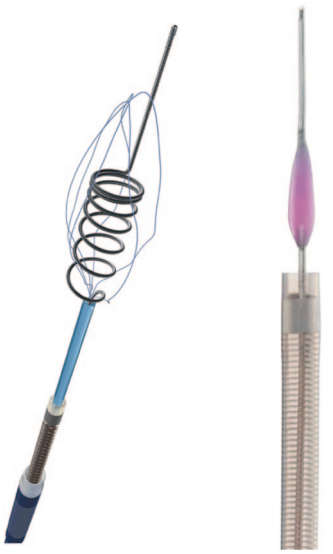
Stroke is the third leading cause of death in the United States—an estimated 795 000 new or recurrent events occur annually, and most are classified as ischemic in nature (1, 2). Patient variables associated with worse outcomes and increased health care burden include occlusions of large intracranial vessels, high disease severity scores at baseline, and older age (3–7). Although successful recanalization of the occluded cerebral vessel during the acute ischemic event is associated with lower 3-month mortality and improved functional outcomes (7, 8), currently approved pharmacologic treatments, including intravenous thrombolysis, have limited efficacy in these populations (9, 10).

Neurothrombectomy devices offer many potential advantages over pharmacologic thrombolysis, including more rapid achievement of recanalization, enhanced efficacy in treating large-vessel occlusions, and a potentially lower risk for hemorrhagic events (11). Currently, 2 neurothrombectomy devices are cleared by the U.S. Food and Drug Administration (FDA) through its 510(k) process: the MERCI Retriever (Concentric Medical, Mountain View, California) and the Penumbra System (Penumbra, Alameda, California) (12–15) (**Figure 1**). Evidence supports the benefits and safety of these devices, although studies are limited to prospective, single-group studies or retrospective designs. Various ongoing clinical trials are evaluating the effect of these devices, as well as other off-label devices, for treating acute ischemic stroke. The goal of this report is to describe the state of the evidence for use of neurothrombectomy devices for treating acute ischemic stroke.

See also:

Web-Only
Appendix Table
CME quiz
Conversion of graphics into slides

Figure 1. **U.S. Food and Drug Administration–cleared devices for treating acute ischemic stroke.**



Left. MERCI Retriever (Concentric Medical, Mountain View, California). Image used with permission from Concentric Medical. **Right.** Penumbra System (Penumbra, Alameda, California). Image used with permission from Penumbra.

METHODS

This review is based on a technical brief produced by the University of Connecticut/Hartford Hospital Evidence-based Practice Center for the Agency for Healthcare Research and Quality (16). The full report, including literature search strategies and detailed evidence tables, is available at www.effectivehealthcare.ahrq.gov (16). We developed and followed a standard protocol for all steps of this review.

Key Questions

We formulated the following key questions with input from a technical expert panel that included experts in clinical neurology and interventional radiology, as well as a neurology association representative.

1. What neurothrombectomy devices are in clinical use or development for treating acute ischemic stroke?

2. From a systematic literature scan, provide a synthesis of trial variables, including study design, patient characteristics, comparators used, outcomes measured, and harms reported.

3. What variables may influence outcomes?

Data Sources and Searches

We searched MEDLINE, SCOPUS, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Web of Science from the earliest possible date until May 2010. We updated the MEDLINE and Cochrane Central Register of Controlled Trials searches through November 2010. We used such terms as *mechanical thrombectomy* and *endovascular device* and text and Medical Subject Heading terms for acute ischemic stroke. The complete search strategy is available in the **Appendix Table** (available at www.annals.org). We did not use language restrictions during the literature-identification stage. We also manually searched references from studies or reviews and searched for gray literature by using Google Scholar (Google, Menlo Park, California) and specific search terms.

Study Selection

Two independent investigators screened citations at the abstract level to identify potentially relevant studies, case series, or case reports. We retrieved and examined all potentially eligible citations for eligibility. We included human studies of any design and case series or case reports that included patients with an acute ischemic stroke and reported data on at least 1 clinical effectiveness outcome or harm. Although we did not formally include duplicate reports or subgroup analyses of previously included studies in our tallies, we did review these reports for potentially pertinent information before exclusion. We extracted and qualitatively reviewed only reports published in English.

Data Extraction and Risk for Bias

Using a standardized data abstraction tool, 2 reviewers independently extracted data, with disagreement resolved by a third reviewer. The following information was obtained from each report, where applicable: author identification, year of publication, study design characteristics, study population, patient baseline characteristics, disease severity (baseline National Institutes of Health Stroke Scale [NIHSS] and baseline Thrombolysis in Myocardial Infarction [TIMI] flow grade), location of occluded artery, time from symptom onset to device deployment or angiography, use of concurrent standard medical therapies, whether outcomes assessment was blinded, and the device used. Effectiveness outcomes included recanalization as measured by TIMI flow grade after treatment (0 to 1 = no recanalization; 2 = partial recanalization; 3 = complete recanalization) or similar method, mortality, modified Rankin Scale ($\leq$2 = good outcome; $\geq$3 = poor outcome), NIHSS score (including the $\geq$4-point decrease deemed significant by the FDA) (17), Barthel Index, and Glasgow Outcome Scale score. Harms assessed were failure to deploy the device or remove the clot (technical success); device breakage or fracture; perforation; dissection; thrombus formation proximal, adjacent, or distal to the clot site; vasospasm; or hemorrhage (including symptomatic and asymptomatic intracranial and subarachnoid hemorrhage from vessel injury and other bleeding).

We assessed the study design and classified it as a prospective, single-group study; retrospective study enrolling consecutive patients; or case series or case report. For prospective, single-group, and retrospective studies enrolling consecutive patients, we extracted data on whether outcome assessment was blinded.

Data Synthesis

The current report provides summary statistics for benefits and harms of interest. We created study density figures to summarize the information available on the effectiveness and safety of the devices. No formal quantitative synthesis (meta-analysis) was done.

Role of the Funding Source

The University of Connecticut/Hartford Hospital Evidence-based Practice Center, Hartford, Connecticut, prepared this project, with funding from the Agency for Healthcare Research and Quality. The funding source formulated the initial study questions and provided copyright release for this manuscript but did not participate in the literature search, data analysis, or interpretation of results.

Results

Neurothrombectomy Devices in Use or Development

Five broad groupings classify neurothrombectomy devices as clot retrievers, aspiration or suction devices, snare-like devices, ultrasonography technologies, or lasers. Their advantages include avoiding or reducing the use of pharmacologic thrombolysis, allowing treatment beyond the short time frame to which intravenous recombinant tissue plasminogen activator (rt-PA) is limited, and providing more rapid recanalization than thrombolytics. Potential harms associated with navigating mechanical devices into the intracranial circulation may include direct trauma to the neurovasculature (including vasospasm, vessel dissection, perforation, or rupture) and fragmenting thrombi into previously unaffected vessels and cerebral territories (18). Although intracranial hemorrhage was an early concern about device use (19), more recent data show that its incidence is similar to that with intravenous rt-PA therapy, although differing definitions and patient populations limit these conclusions (20, 21). An inherent risk of the procedure includes the need for intubation and heavy sedation, which may worsen outcomes (22).

The approval process for medical devices differs from that for pharmacologic agents. The FDA Center for Device and Radiological Health handles the regulation of medical devices both premarket and postmarket (17). As such, neurothrombectomy devices are reviewed and cleared through the 510(k) premarket notification process (15, 17). For a device to receive clearance, the manufacturer must demonstrate that the new device is equal in safety and effectiveness to a Class II device that is already on the market for a particular indication. Most commonly, devices receive clearance based on nonclinical testing with little to no clinical data (17).

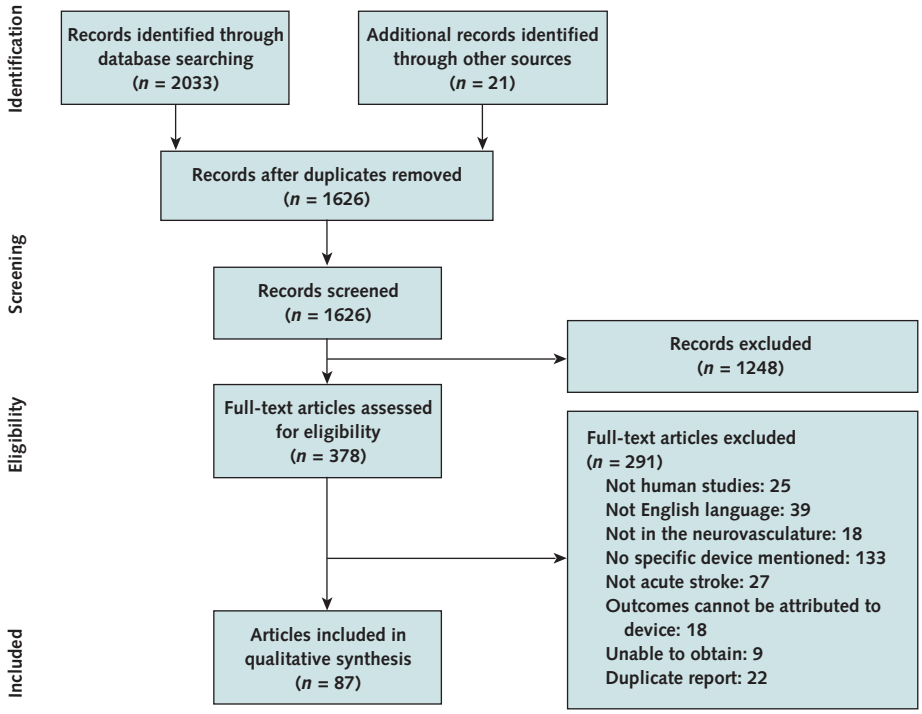
The MERCI Retriever and the Penumbra System are the only devices with FDA clearance for the treatment of patients with an acute ischemic stroke. The MERCI Retriever "is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke (who are ineligible for treatment with intravenous rtPA or who fail intravenous rtPA therapy)" (12, 15). The Penumbra System is used for the "revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease (in the internal carotid, middle cerebral—M1 and M2 segments, basilar, and vertebral arteries) within 8 hours of symptom onset" (15). Other devices have FDA clearance for indications ranging from retrieval of intravascular foreign bodies to infusion of fluids into the peripheral vasculature. The In-Time (Boston Scientific, Natick, Massachusetts), Alligator (Chestnut Medical Technologies, Menlo Park, California), Amplatz Gooseneck (ev3 Endovascular, Plymouth, Minnesota), and EnSnare (Merit Medical Systems, Gainesville, Florida) devices are cleared for the retrieval of intravascular foreign objects either in general or in the peripheral vasculature and neurovasculature. The EKOS (EKOS, Bothell, Washington) and OmniWave (OmniSonics, Wilmington, Massachusetts) systems are cleared for the infusion of fluids into the peripheral vasculature. The LaTIS laser (Spectranetics, Colorado Springs, Colorado) and Oasis Thrombectomy System (Boston Scientific) are cleared for the removal of thrombi from vascular or hemodialysis access grafts. The Amplatz Thrombectomy Device (ev3 Endovascular) is cleared for dissolution of thrombi within dialysis fistulae. Data on the use of these various devices in treating patients with acute ischemic stroke are limited.

Recent and ongoing studies are evaluating the use of "retrievable" intracranial stents for managing acute ischemic stroke. They offer the ability to provide immediate recanalization, while being removable with clot trapped within the stent matrix (23–28). Initial data show promise with this technology. A recent prospective, single-center pilot study reported on the safety and efficacy of a retrievable stent in 20 patients with acute stroke and large-vessel occlusion who were either refractory or ineligible for intravenous rt-PA therapy (28). The stents were deployed for 1 to 2 minutes before retrieval, with 18 of 20 patients (90%) achieving successful revascularization. Six patients (30%) had asymptomatic intracranial hemorrhage, and 2 patients (10%) had symptomatic intracranial hemorrhage (28). Ongoing trials are evaluating this line of products, which may provide a new method of restoring cerebral blood flow in patients presenting with symptoms of acute ischemic stroke who are unlikely to benefit from standard therapies.

Literature Evaluating Neurothrombectomy Devices in Acute Ischemic Stroke

We screened 1626 abstracts and evaluated 377 full-text articles (**Figure 2**). A total of 87 articles were included. Of these, 18 were prospective, single-group studies (20, 21, 29–32, 37–40, 44–51); 7 were noncomparative retrospective studies enrolling consecutive patients (33–36, 41–43), and 62 were case series or case reports. Most of the studies (74%) were published in full text (20, 21, 29–34, 36–41, 45–50), with the remainder (26%) available only in abstract form (34, 35, 42–44, 51). Fifteen of 25 studies

Figure 2. **Study flow diagram.**



(60%) were published between 2008 and 2010 (21, 29, 33–45). Only 3 of 18 (17%) prospective (38, 40, 45) and 1 of 7 (14%) retrospective (36) studies clearly stated that they used blinded outcome assessment.

The largest percentages of overall reports (40%) and prospective studies (31%) (20, 21, 29–32) were for the MERCI Retriever. The Penumbra System was investigated in 10 reports (9%), of which 4 were prospective (37–40). For off-label devices, 2 studies used the EKOS device (45, 46) and 1 each with Phenox (Phenox, Bochum, Germany) (44), Amplatz Gooseneck (47), AngioJet (Medrad/Possis, Warrendale, Pennsylvania) (48), EPAR (EndoVasix, Belmont, California) (49), Neuronet (Guidant, Santa Clara, California) (50), and LaTIS (51).

Studies typically enrolled patients older than 18 years with baseline NIHSS scores of 8 or greater (or ≥10) who presented within 8 hours of stroke symptom onset (or up to 24 hours for EKOS, EPAR or LaTIS if posterior circulation occlusion was identified) and had a complete or near-complete (TIMI flow grade, 0 to 1) occlusion of a treatable large intracranial vessel. Common exclusion criteria included older age, large infarction in the brain, abnormal hemostasis, severe or uncontrolled hypertension, hypoglycemia, and pregnancy. Studies also enrolled patients with contraindications to intravenous rt-PA therapy because of risk for adverse events, reporting outside a 3-hour window from symptom onset to intravenous rt-PA therapy, or whose intravenous rt-PA therapy had failed (target vessel not recanalized, determined by immediate angiography after the procedure). The exception was a study by Tomsick and colleagues (45), which evaluated the EKOS device. Along with reduced-dose intravenous rt-PA therapy, the EKOS device provided an infusion of intra-arterial thrombolytic therapy to patients within the first 3 hours of stroke symptoms.

The mean or median baseline NIHSS score ranged from 15 to 23 across studies. Mean or median age ranged from 42 to 68 years, and studies enrolled 20% to 57% female patients. Mean or median time from stroke symptom onset to either angiography or device deployment ranged from 141 to 388 minutes, which is well within the 8-hour time frame suggested by the FDA Center for Device and Radiological Health (17). The primary embolus was most frequently in an anterior vessel (14 studies enrolled >60% of patients with anterior occlusion), although some studies focused on posterior occlusions. A single study (38) included patients with occlusions in other areas, whereas 6 studies (34–36, 42, 43, 45) were unclear about the location of the primary occlusion.

The guidance document from the FDA Center for Device and Radiological Health suggests assessing recanalization success by using the TIMI flow grade after treatment with a neurothrombectomy device (17). Each of the identified studies reported rates of recanalization (**Table 1**

and **Figure 3**). Recanalization success was typically defined as a TIMI flow grade of 2 (partial) or 3 (complete) within the target (or all) vessels on angiography after the procedure. Studies less frequently used a newer cerebral grading scale (the Thrombolysis in Cerebral Infarction scale), as well as neuroimaging measures (for example, final stroke lesion size and perfusion neuroimaging technologies). Rates of successful recanalization ranged from 43% to 78% with the MERCI Retriever (20, 21, 29–36), 83% to 100% with the Penumbra System (37–43), and 50% to 90% with the off-label devices (44–51).

Clinical effectiveness, defined as the proportion of patients having a "good" outcome (modified Rankin Scale score, 0 to 2), was available in 17 of the 25 studies (68%). Individual rates ranged from 21% to 36% with the MERCI Retriever (20, 21, 30–32), 20% to 48% with the Penumbra System (37–43), and 15% to 60% with the off-label devices (46–50). Seventeen of 25 studies (68%) reported mortality rates ranging from 29% to 44% with the MERCI Retriever (20, 21, 30–32), 11% to 45% with the Penumbra System (37–43), and 0% to 38% with the off-label devices (46–50).

Table 1. **Published Studies of Neurothrombectomy Devices for Acute Ischemic Stroke***

Author, Year (Reference)	Design	Participants, *n*	Efficacy, *n/N (%)*			Harms, *n/N (%)*		
			Recanalization	mRS ≤2	Death	SICH	AICH	Perforation or Dissection
MERCI Retriever								
Loh et al, 2010 (29)	Prospective	97	71/97 (73)	NR	NR	NR	NR	NR
Smith et al, 2008 (21)	Prospective	164	90/164 (55)	59/164 (36)	56/164 (34)	16/164 (10)	50/164 (31)	NR
Devlin et al, 2007 (30)	Prospective	25	14/25 (56)	6/25 (24)	9/25 (36)	1/25 (4)	7/25 (28)	0/25 (0)
Kim et al, 2006 (31)	Prospective	24	13/24 (54)	6/24 (25)	7/24 (29)	2/24 (8)	9/24 (38)	0/24 (0)
Smith et al, 2005 (20)	Prospective	151	68/141 (48)	36/130 (28)	60/138 (44)	11/141 (8)	39/141 (28)	10/141 (7)
Gobin et al, 2004 (32)	Prospective	30	12/28 (43)	6/28 (21)	10/28 (36)	0/28 (0)	12/28 (43)	NR
Lin et al, 2009 (33)	Retrospective	34	24/34 (71)	NR	NR	NR	NR	NR
Jo et al, 2008 (34)	Retrospective	114	75/114 (66)	NR	NR	NR	NR	NR
Madison et al, 2008 (35)	Retrospective	54	28/54 (52)	NR	NR	NR	NR	NR
Kidwell et al, 2008 (36)	Retrospective	18	14/18 (78)	NR	NR	NR	NR	NR
Penumbra System								
Kulcsár, 2010 (37)	Prospective	27	25/27 (93)	13/27 (48)	3/27 (11)	0/27 (0)	NR	NR
PPST, 2009 (38)	Prospective	125	102/125 (82)	25/125 (20)	33/125 (26)	14/125 (11)	21/125 (17)	6/125 (5)
Grunwald et al, 2009 (39)	Prospective	29	25/29 (86)	11/29 (38)	4/29 (14)	2/29 (7)	3/29 (10)	NR
Bose et al, 2008 (40)	Prospective	23	20/20 (100)	7/20 (35)	9/20 (45)	2/10 (10)	6/20 (30)	0/20 (0)
Struffert et al, 2009 (41)	Retrospective	15	15/15 (100)	5/15 (33)	3/15 (20)	0/15 (0)	NR	0/15 (0)
Tarr et al, 2009 (42)	Retrospective	105	87/105 (83)	34/105 (32)	22/105 (21)	5/105 (5)	1/105 (1)	NR
Frei and Bellon, 2009 (43)	Retrospective	53	44/53 (83)	19/53 (36)	19/53 (36)	3/53 (6)	5/53 (9)	NR
Phenox								
Liebig et al, 2008 (44)	Prospective	45	24/45 (53)	NR	NR	NR	NR	NR
EKOS Primo								
Tomsick et al, 2008 (45)	Prospective	35	18/29 (62)	NR	NR	7/29 (24)	NR	0/29 (0)
EKOS MicroLysUS								
Mahon et al, 2003 (46)	Prospective	14	10/14 (71)	5/14 (36)	5/14 (36)	2/14 (14)	NR	0/14 (0)
Amplatz Goosneck								
González et al, 2007 (47)	Prospective	9	7/9 (78)	2/7 (29)	2/7 (29)	1/7 (14)	1/7 (14)	0/7 (0)
AngioJet								
Mayer et al, 2005 (48)	Prospective	12	9/10 (90)	4/12 (33)	3/10 (30)	3/12 (25)	2/12 (17)	0/12 (0)
EPAR								
Berlis et al, 2004 (49)	Prospective	34	14/34 (41)	5/34 (15)	13/34 (38)	2/34 (6)	2/34 (6)	0/34 (0)
Neuronet								
Mayer et al, 2002 (50)	Prospective	5	3/5 (60)	3/5 (60)	0/5 (0)	NR	NR	NR
LaTIS								
Clark et al, 2010 (51)	Prospective	2	1/2 (50)	NR	NR	NR	NR	NR

AICH = asymptomatic intracranial hemorrhage; mRS = modified Rankin Scale; NR = not reported; PPST = Penumbra Pivotal Stroke Trial; SICH = symptomatic intracranial hemorrhage.

* Brand-name devices evaluated were MERCI Retriever (Concentric Medical, Mountain View, California), Penumbra System (Penumbra, Alameda, California), Phenox (Phenox, Bochum, Germany), EKOS Primo and EKOS MicroLysUS (EKOS, Bothell, Washington), Amplatz Goosneck (Ev3 Medical, Plymouth, Minnesota), AngioJet (Medrad/Possis, Warrendale, Pennsylvania), EPAR (EndoVasix, Belmont, California), Neuronet (Guidant, Santa Clara, California), and LaTIS (Spectranetics, Colorado Springs, Colorado).

Figure 3. **Effectiveness evidence for neurothrombectomy devices.**

Reported Outcomes		Devices														
		Clot Retriever (*n* = 847)			Aspiration/ Suction (*n* = 411)			Snare (*n* = 94)			Ultrasonography Technology (*n* = 50)			Laser (*n* = 36)		
		P	R	C	P	R	C	P	R	C	P	R	C	P	R	C
Recanalization	Studies	7	4	34	5	3	10	2	0	24	1	0	1	2	0	0
	Patients	524	220	98	211	173	24	14	0	74	29	0	7	36	0	0
mRS	Studies	5	1	11	5	3	4	2	0	9	1	0	1	1	0	0
	Patients	440	18	11	213	173	16	12	0	33	14	0	1	34	0	0
Death*	Studies	5	1	16	5	3	7	2	0	9	1	0	0	1	0	0
	Patients	450	18	38	184	173	23	12	0	53	14	0	0	34	0	0
NIHSS	Studies	3	0	15	4	3	5	2	0	11	1	0	0	1	0	0
	Patients	371	0	31	211	173	12	12	0	53	14	0	0	34	0	0
BI	Studies							1	0	0	1	0	0			
	Patients							5	0	0	14	0	0			
GOS	Studies										1	0	0			
	Patients										14	0	0			

Darker shading represents more frequent evaluation or larger number of patients evaluated. BI = Barthel Index; C = case report or case series; GOS = Glasgow Outcome Scale; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; P = prospective; R = retrospective.
* Death was included if patients were followed after hospital discharge.

Incidences of intracranial hemorrhage, both symptomatic and asymptomatic, and vessel perforation or dissection were the most commonly reported potential harms (**Figure 4**). Symptomatic intracranial hemorrhage was reported in 16 of 25 studies (64%). Rates ranged from 0% to 10% with the MERCI Retriever (20, 21, 30–32), 0% to 11% with the Penumbra System (38–43), and 6% to 25% with the off-label devices (45–49). Thirteen studies (52%) reported the incidence of asymptomatic intracranial hemorrhage. Rates ranged from 28% to 43% with the MERCI Retriever (20, 21, 30–32), 1% to 30% with the Penumbra System (38–43), and 6% to 17% with the off-label devices (47–49). Incidence of target vessel perforation or dissection was documented less often, with only 11 of 25 studies (44%) reporting data. Rates ranged from 0% to 7% with the MERCI Retriever (20, 30, 31) and 0% to 5% with the Penumbra System (38, 40, 41), and no events occurred in the 5 off-label studies that reported the outcome (45–49).

Variables That May Affect Clinical Outcomes

We determined the association between predictor variables and selected outcomes (effectiveness and harms) by using multivariate data from prospective and retrospective studies (7, 20, 21, 26, 27, 52). We classified predictors by whether they were suggested to have beneficial (and statistically significant), harmful (and statistically significant), or indeterminate (not statistically significant regardless of effect direction) associations with outcomes. These include various demographic, comorbid disease, stroke severity, and stroke treatment variables. Studies reporting these predictors were limited to those investigating the MERCI Retriever and Penumbra System.

Achievement of successful recanalization was the only variable that was predictive of good outcomes, although concomitant use of intra-arterial thrombolytics was predictive of achieving recanalization (20, 26, 52). Variables that predicted worse outcomes included older age (20, 52), higher baseline systolic blood pressure (20, 52), higher baseline NIHSS scores (20, 26, 52), history of stroke (26), longer procedure duration (20, 26), and documented occlusions of the internal cerebral artery (20, 26, 52). Variables linked to outcomes in patients with acute ischemic stroke included the presence of collateral circulation, lesion volume, and cerebral perfusion pressure (53). Of note, recanalization was the only variable found to be predictive of clinical benefit as well as lower mortality.

We did not identify studies assessing the relationship between the training of interventionalists and outcomes in patients treated with neurothrombectomy devices. However, studies of other emerging stroke technologies from the past 20 years have suggested that inadequate physician training and experience can adversely affect clinical outcomes (54). Two reports detail the minimum training requirements for persons performing neuroendovascular procedures (including neurothrombectomy devices) in patients with acute

ischemic stroke and the performance standards that should be adopted to assess outcomes (54, 55).

Discussion

The natural history and poor clinical outcomes seen in patients with acute ischemic strokes have been well documented (3, 7, 47). The advent of neurothrombectomy devices to provide adequate recanalization has created a new option for managing these patients. These technologies are particularly intriguing given the data showing significantly improved outcomes with successful and early recanalization of an occluded cerebral vessel (7, 56). Currently, only 2 neurothrombectomy devices, the MERCI Retriever and Penumbra System, are cleared by the FDA to treat patients with acute ischemic stroke. The comparative effectiveness of these devices remains unstudied.

Our report is the most up-to-date review of the literature on neurothrombectomy devices. A prior meta-analysis, which included studies published up to 2006, found that more patients who received neurothrombectomy devices (34.5%) had good functional recovery (modified Rankin Scale score ≤2) compared with a patient cohort matched for age, sex, and NIHSS score (10.7%) (19). Although intriguing, this analysis is fraught with limitations, including significant heterogeneity within the neurothrombectomy cohort, comparison with a historical control (albeit matched for important variables), and lack of participant randomization.

A continuing area of uncertainty is the patient population that is most likely to benefit from use of neurothrombectomy devices. Indeed, many published studies evaluating FDA-cleared devices have enrolled patients who presented within 8 hours of onset of ischemic stroke symptoms, had high baseline NIHSS scores, and were ineligible to receive intravenous rt-PA therapy or in whom intravenous rt-PA therapy had failed (3, 7, 47, 57, 58). In addition, many of the patients had occlusions of the large intracranial vessels, which respond poorly to intravenous rt-PA therapy (10, 59). Future randomized, controlled trials should incorporate advanced imaging techniques to better identify patients who are most likely to benefit from neurothrombectomy devices, as well as to evaluate the performance of these devices at varying levels of occlusion. Ongoing clinical trials, including the MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy) study, are evaluating the utility of various imaging techniques to better identify which patients are most likely to benefit from neurothrombectomy device use. These emerging data should help guide clinicians in choosing the most appropriate treatment of acute ischemic strokes.

Because the literature base of evaluations of neurothrombectomy devices in acute ischemic stroke is still in its infancy, identifying gaps in current knowledge and guiding future research efforts are paramount. Currently, 11 ongoing studies evaluating at least 1 neurothrombectomy device in acute ischemic stroke are listed in ClinicalTrials.gov or are mentioned in previous review articles (53) (**Table 2**). Seven of these studies have randomized, controlled designs, with projected enrollment ranging from 20 to 900 partic-

Figure 4. **Safety end point evidence for neurothrombectomy devices.**

Reported Adverse Events		Devices														
		Clot Retriever (*n* = 847)			Aspiration/ Suction (*n* = 411)			Snare (*n* = 94)			Ultrasonography Technology (*n* = 50)			Laser (*n* = 36)		
		P	R	C	P	R	C	P	R	C	P	R	C	P	R	C
SICH	Studies	5	0	8	5	3	3	1	0	10	2	0	0	1	0	0
	Patients	382	0	39	213	173	10	7	0	37	49	0	0	34	0	0
AICH	Studies	5	0	8	5	2	3	1	0	10				1	0	0
	Patients	382	0	39	213	158	10	7	0	37				34	0	0
Perforation/ Dissection	Studies	3	0	2	3	1	2	1	0	4	2	0	0	1	0	0
	Patients	190	0	17	157	15	14	7	0	21	49	0	0	34	0	0
Thrombus Formation	Studies	2	0	5	3	1	1	2	0	3						
	Patients	165	0	20	157	15	4	12	0	9						
Other Hemorrhage	Studies	2	0	4	1	1	0	0	0	3						
	Patients	166	0	25	20	15	0	0	0	13						

Darker shading represents more frequent evaluation or larger number of patients evaluated. AICH = asymptomatic intracranial hemorrhage; C = case report or case series; P = prospective; R = retrospective; SICH = symptomatic intracranial hemorrhage.

Table 2. **Summary of Ongoing Studies of Neurothrombectomy Devices for Ischemic Stroke**

ClinicalTrials.gov Identification Number	Title	Anticipated Completion Year	Device Evaluated*	Design (Projected Enrollment Number)	Inclusion Criteria	End Points
NCT01088672	TREVO (Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke)	2010	Trevo	P,O (50)	NIHSS: 8–30 (and mRS ≤1) Symptom onset: <8 h Occlusion: ICA, MCA, BA, VA	mRS, death, TIMI, NIHSS, SICH, SAEs
NCT00478478	Merci Registry—Real World Use of the Merci Retrieval System in Acute Ischemic Stroke	2010	MERCI Retriever	P,O (1000)	Revascularized with MERCI Retriever	mRS, death, TIMI flow grade, NIHSS, discharge disposition
NCT00640367	SYNTHESIS EXP (Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke)	2010	Mechanical thrombolysis	RCT (350)	Able to initiate IV rt-PA within 3 h or IA thrombolysis within 6 h of symptom onset	mRS, NIHSS
NCT01133223	Safety and Efficacy of the Penumbra System in Acute Middle Cerebral Artery Stroke	2010	Penumbra System	RCT (20)	Symptom inset: ≤3.5 h Occlusion: MCA	mRS, death, SICH
NCT01062698	Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke	2011	MERCI Retriever, Penumbra System, Catch, Solitaire	RCT (480)	NIHSS: 10–25 Symptom onset: <3 h Occlusion: ICA, MCA, BA	mRS, BI, HRQoL
NCT01054560	SWIFT (SOLITAIRE FR With the Intention for Thrombectomy) Study	2011	Solitaire FR, MERCI Retriever	RCT (200)	NIHSS: 8–30 Symptom onset: <8 h Occlusion: ICA, MCA, BA, VA IV rt-PA: ineligible or failed	mRS, death, TIMI flow grade, NIHSS, BI, SICH
NCT00963989	Imaging Guided Patient Selection for Interventional Revascularization Therapy	2011	Penumbra System	P,O (200)	NIHSS: >10 Occlusion: ICA, MCA	mRS, death, NIHSS, TIMI flow grade, SICH, AICH, SAEs
NCT00389467	MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy)	2013	MERCI Retriever, Penumbra System	RCT (120)	NIHSS: ≥6 Symptom onset: <8 h Occlusion: ICA, MCA IV rt-PA: allowed <4.5 h from symptom onset	mRS, death, NIHSS, global test statistic, hemorrhagic transformation, SAEs,
NCT00785161	PICS (Penumbra Imaging Collaborative Study)	2014	Penumbra System	P,O (2000)	Revascularized with Penumbra System	mRS, death, TIMI flow grade, NIHSS, ICH, SAEs
NCT00359424	IMS (Interventional Management of Stroke) III Trial	2015	EKOS, MERCI Retriever, Penumbra System	RCT (900)	NIHSS: ≥10 at time of IV rt-PA, or 7–10 Symptom onset: <3 h from IV rt-PA Occlusion: ICA, MCA, BA	mRS, death, NIHSS, BI, SICH, AICH
Not registered	PISTE (Pragmatic Ischemic Stroke Thrombectomy Evaluation)	Not reported	Approved mechanical devices	RCT (>200)	Symptom onset: <6 h Occlusion: ICA, MCA	mRS, TIMI flow grade, infarct size, HRQoL, cost of care

AICH = asymptomatic intracranial hemorrhage; BA = basilar artery; BI = Barthel Index; HRQoL = health-related quality of life; IA = intra-arterial; ICA = internal carotid artery; ICH = intracranial hemorrhage; IV-intravenous; MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; P,O = prospective, observational; RCT = randomized, controlled trial; rt-PA = recombinant tissue plasminogen activator; SAE = significant adverse event; SICH = symptomatic intracranial hemorrhage; TIMI = Thrombolysis in Myocardial Infarction; VA = vertebral artery.
* Brand-name devices evaluated include Trevo and MERCI Retriever (Concentric Medical, Mountain View, California), Penumbra System (Penumbra, Alameda, California), Catch (Balt Extrusion, Montmorency, France), Solitaire and Solitaire FR (ev3 Endovascular, Plymouth, Minnesota), and EKOS (EKOS, Bothell, Washington).

ipants. The other 4 studies have prospective, observational designs, with enrollment ranging from 200 to 2000 projected participants. Of note, the SWIFT (SOLITAIR FR With the Intention for Thrombectomy) Study will be the first to evaluate the comparative effectiveness of 2 different technologies, the SOLITAIRE FR (ev3 Endovascular) and the MERCI Retriever, by using a prospective, randomized method in patients with acute ischemic stroke.

Our literature search did not identify any reports evaluating the effect of neurothrombectomy devices on health-related quality-of-life outcomes. We identified only 1 economic evaluation of neurothrombectomy devices: a Markov model that evaluated the cost and effectiveness of mechanical thrombectomy compared with standard medical therapy in patients who were ineligible to receive intravenous rt-PA therapy (60). The ongoing IMS (Interventional Management of Stroke) III Trial, which is designed to evaluate combination use of intravenous and intra-arterial strategies (including use of the MERCI Retriever or EKOS device) versus intravenous rt-PA therapy alone, plans to measure both health-related quality-of-life and pharmacoeconomic outcomes (61, 62).

Currently available neurothrombectomy devices offer intriguing treatment options in patients with acute ischemic stroke, although a paucity of high-quality research currently exists. Further research is needed on the topic, including randomized, controlled trials to determine the

optimal device to use and the patient populations that are most likely to benefit from its use. The results of ongoing studies, some of which are using randomized, controlled designs, are eagerly anticipated. In addition, future studies should investigate whether neurothrombectomy devices affect final health outcomes associated with stroke rather than improving recanalization alone when compared with contemporary controls.

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Appendix Table. Search Strategies for MEDLINE and Cochrane Central Register of Controlled Trials

MEDLINE (Ovid)

1. thrombectomy
2. embolectomy
3. endovascular recanalization
4. endovascular embolectomy
5. mechanical thrombolysis
6. mechanical embolus removal
7. mechanical thrombus removal
8. endovascular intervention
9. endovascular device
10. mechanical device
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. stroke
13. acute stroke
14. cerebrovascular accident
15. cva
16. vascular accident
17. artery occlusion
18. cerebral ischemia
19. acute ischemic stroke
20. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 11 and 20

Cochrane Central Register of Controlled Trials (Ovid)

1. thrombectomy
2. embolectomy
3. endovascular recanalization
4. endovascular embolectomy
5. mechanical thrombolysis
6. mechanical embolus removal
7. mechanical thrombus removal
8. endovascular intervention
9. endovascular device
10. mechanical device
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. stroke
13. acute stroke
14. cerebrovascular accident
15. cva
16. vascular accident
17. artery occlusion
18. cerebral ischemia
19. acute ischemic stroke
20. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 11 and 20