Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about healthcare. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and healthcare services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments and Comparative Effectiveness Reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care. Technical Briefs are the most recent addition to this body of knowledge.

A Technical Brief provides an overview of key issues related to a clinical intervention or health care service—for example, current indications for the intervention, relevant patient population and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions. The emphasis, therefore, is on providing an early objective description of the state of science, a potential framework for assessing the applications and implications of the new interventions, a summary of ongoing research, and information on future research needs. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly, while Technical Briefs will serve to inform new research development efforts.

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Executive Summary

Background

Intravenous (IV) recombinant tissue plasminogen activator (rtPA) has been approved by the United States Food and Drug Administration (FDA) for the treatment of acute ischemic stroke and is currently indicated for use within the first 3 hours of stroke onset. IV rtPA is used in less than five percent of patients with acute ischemic stroke.

In patients who are ineligible for, have contraindications to, or have failed IV rtPA use, neurothrombectomy devices (clot retrievers, aspiration/suction devices, snare-like devices, ultrasonography technologies and lasers) have been examined. Currently, two neurothrombectomy devices are FDA-approved through the FDA 510(k) process: the MERCI clot retriever and Penumbra System. Various ongoing clinical trials are currently evaluating the impact of these, as well as other "off-label" neurothrombectomy devices, for the treatment of acute ischemic stroke. The goal of this technical brief is to describe neurothrombectomy devices currently being used or actively investigated in the treatment of patients with acute ischemic stroke and to summarize the evidence supporting their use.

Methods

We developed a list of neurothrombectomy devices based on the FDA's Center for Device and Radiological Health (CDRH) guidance definition of a neurothrombectomy device, published literature, and a search of the FDA CDRH's database to identify neurothrombectomy devices that have received FDA approval (510(k) documents).

Systematic literature searches of MEDLINE, the Cochrane Central Register of Controlled Trials, SCOPUS, Web of Science, and the Cochrane Database of Systematic Reviews, from the earliest possible date through September 2009 were conducted. Grey literature searches utilizing Google, clinicaltrials.gov and manual searches were conducted.

Two investigators independently screened citations at the abstract level to identify potentially relevant studies, case series and case reports. Throughout this technical brief, our use of the terminology 'studies' will refer only to prospective, single-arm studies or retrospective studies enrolling consecutive patients. The terminology 'reports' will refer to the latter studies in addition to case series and case reports. Potentially eligible citations were retrieved for full-text review. We included human studies of any design or case series or case reports, as long as they included patients with an acute ischemic stroke, and reported at least one outcome of interest. We only included reports in English in our qualitative review of the literature.

Two investigators independently abstracted data from eligible reports, with disagreement resolved by a third. We obtained the following information from each study: author identification, year of publication, study design characteristics, study population, patient baseline characteristics, disease severity, 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 post-Thrombolysis in Myocardial Infarction (TIMI) flow grade or similar methodology, mortality, modified Rankin Scale (mRS), National Institutes of Health Stroke

Scale (NIHSS) score, Barthel Index and Glasgow Outcome Scale (GOS). Harms included: failure to deploy the device or remove the clot, device breakage or fracture, perforation, dissection, thrombus formation, vasospasm, or hemorrhage.

We used descriptive statistics and summative tables to synthesize data regarding study designs, clinical and treatment characteristics, effectiveness outcomes, and adverse events reported. We created study density figures to summarize the totality of information available on the effectiveness and safety of these devices.

Results

Key Question 1. What are the different types of neurothrombectomy devices in use or in development for treatment of acute ischemic stroke?

Table ES1 provides a list of the various neuthrombectomy classes (clot retrievers, aspiration/suction devices, snare-like devices, ultrasonography technologies, and lasers) and devices in those classes.

Neurothrombectomy devices may: (1) allow patients to avoid or reduce the use of pharmacologic thrombolysis, thereby minimizing the risk for intracerebral hemorrhage (ICH), (2) can be used beyond the short timeframe to which rtPA is limited, (3) may provide more rapid recanalization than thrombolytics, and (4) can provide a treatment option for thrombi more resistant to fibrinolytic breakdown. However, the technical difficulty of navigating mechanical devices into the intracranial circulation may result in direct trauma to the neurovasculature (including vasospasm, vessel dissection, perforation, or rupture), and fragmenting thrombi may subsequently embolize into previously unaffected vessels and cerebral territories.

Only the MERCI clot retriever and the Penumbra System are FDA approved for the treatment of patients with an acute ischemic stroke. Other devices have FDA indications ranging from retrieval of intravascular foreign bodies to infusion of fluids into the peripheral vasculature. Data on the utilization of these various devices are limited.

91 **Table ES1. Neurothrombectomy Devices in Use**

Device Class	Company Name	FDA Indication	In Clinical Use?
Aspiration/Suction			
Amplatz Thrombectomy	Ev3 Medical	Mechanical dissolution of thrombus within dialysis fistulae	No longer marketed
AngioJet	Possis	Breaking apart or removing of thrombus in peripheral veins or arterio-venous access conduits	Yes
NeuroJet	Possis	NA	No longer marketed
Oasis Thrombectomy	Boston Scientific	Removing thrombus from hemodialysis access grafts	No longer marketed
Penumbra	Penumbra, Inc	Revascularization of patients with acute ischemic stroke	Yes
Vasco +35	Balt Extrusion	NA	Not in US
Clot Retriever			
Attractor-18	Boston Scientific	NA	No longer marketed
Catch	Balt Extrusion	NA	Not in US
In-Time	Boston Scientific	Retrieval of intravascular foreign objects in peripheral vascular, neurovasculature and cardiovasculature	No longer marketed
MERCI	Concentric Medical	Restore blood flow in the neurovasculature	Yes
Phenox	Phenox GmbH	NA	Not in US
TriSpan	Boston Scientific	NA	No longer marketed
Ultrasonography			
EKOS	EKOS Corporation	Infusion of fluids into peripheral vasculature	Yes
OmniWave	OmniSonics	Removal of thrombus and infusion of fluids into peripheral vasculature	No longer marketed
Snare			
Alligator	Chestnut Medical Technologies, Inc	Peripheral and neurovasculature foreign body removal	Yes
Amplatz Gooseneck	Ev3 Medical	Retrieval and manipulation of atraumatic foreign bodies in coronary and peripheral cardiovascular system and the extra-cranial neurovascular anatomy	Yes
EnSnare Device	Merit Medical Systems, Inc.	Retrieval and manipulation of foreign objects in the cardiovascular system or hollow viscous	Yes
Neuronet	Boston Scientific	NA	No longer marketed
Soutenir	Solution	NA	Not in US
Laser			
EPAR	Endovasix Inc.	NA	No longer marketed
LaTIS	Spectranetics	Removal of thrombus from vascular grafts	No longer marketed

92 EPAR=Endovascular Photoacoustic Recanalization; FDA=Food and Drug Administration; MERCI=NA=not
93 applicable; US=United States
94

Key Question 2. From a systematic literature scan of studies on different types of neurothrombectomy devices, provide a synthesis of type(s) of devices, study design and size, patient characteristics, comparator used in comparative studies, length of follow-up, concurrent or prior therapy, outcomes measured, and adverse events, harms and safety issues reported.

A total of 1,997 citations were identified, 369 of which were retrieved for full-text review. There were 94 unique device reports encompassing 1,308 patients receiving a neurothrombectomy device for the treatment of acute ischemic stroke. Seventy-one reports (76 percent) were case series or case reports, 16 (17 percent) were prospective single-arm studies, and 7 (7 percent) were non-comparative, retrospective studies enrolling consecutive patients. These studies were published in full-text (74 percent) or abstract form (26 percent). Thirteen of 23 studies (57 percent) were published in either 2008 or 2009. Only 3 of 16 (19 percent) prospective and 1 of 7 (14 percent) retrospective studies clearly stated they utilized blinded outcome assessment.

The largest percentage of reports (38 of 94 reports, 40 percent) and prospective studies (5 of 16 reports, 31 percent) were for the MERCI clot retriever. The Penumbra System had a total of 9 reports, of which 3 were prospective. For "off-label" devices, two studies were conducted with EKOS, and one each with AngioJet, Phenox, Amplatz Gooseneck, Neuronet, EPAR and LaTIS.

The size of prospective single-arm studies ranged from 2 to 164 patients, and retrospective studies ranged from 15 to 114 patients. The largest studies evaluated the MERCI clot retriever (numbers ranged from 18 and 164 patients) and the Penumbra System (numbers ranged from 15 to 125 patients). Studies of "off label" devices ranged from 2 to 45 patients.

The remaining 71 of 94 (76 percent) reports were either case series or case reports. In total, 191 patients were evaluated with a neurothrombectomy device in case series and case reports. The combined number of patients evaluated in a case series or case report with a neurothrombectomy device ranged from 0 (EPAR and LaTIS lasers) to 75 (MERCI clot retriever). Case series and reports provide the majority of data on "off-label" use (n=109 patients) of potential neurothrombectomy devices to treat acute ischemic stroke.

Studies typically enrolled patients >18 years of age, with baseline NIHSS scores ≥8 (or ≥10), presenting within 8 hours of stroke symptom onset (or up to 24 hours for EKOS, EPAR or LaTIS if a posterior circulation occlusion was identified), and having a complete or near complete (TIMI 0-1) occlusion of a treatable large, intracranial vessel. Common exclusion criteria included advanced age, large brain infarction, abnormal hemostasis, severe or uncontrolled hypertension, hypoglycemia, and pregnancy. Studies also enrolled patients with contraindications to receive IV rtPA due to risks of adverse events, reporting outside a 3-hour window from symptom onset to IV rtPA, or who failed (target vessel not recanalized as determined by immediate angiography following the procedure) IV rtPA treatment. The one exception was the EKOS study by Tomsick in 2008. The EKOS device is designed to infuse IA thrombolytic therapy, and in this study, EKOS was used along with reduced dose IV rtPA within the first 3 hours of stroke symptoms.

The mean/median baseline NIHSS range was 15 to 23 across studies. The range for mean/median age was 42 to 68 years and studies enrolled 20 to 57 percent females. In studies where data were provided, the majority of patients had pre-device TIMI 0 or 1 flow. Mean/median time from stroke symptom to either angiography or device deployment ranged from 141 to 388 minutes, well within the 8 hour time frame suggested by the FDA CDRH

guidance. The primary embolus was most commonly in an anterior vessel (14 studies enrolled >60 percent anterior occlusion patients). However, some studies focused heavily on posterior occlusions. Only 1 of 23 studies (4 percent) reported including patients with occlusions in other areas and six studies were unclear about the location of occlusion.

A majority of case series and case reports included patients that would typically meet prospective study inclusion criteria. However, some case series and reports included both pediatric patients, those greater than 80 years of age and those with a baseline NIHSS score below or above the typical enrollment threshold of 8 to 10. Finally, some case series and reports for the Penumbra System, MERCI clot retriever, TriSpan clot retriever, In-Time clot retriever, and Neuronet and Amplatz Gooseneck snares, enrolled patients with symptom-to-angiography or device deployment times outside the 8 hour window used in prospective and retrospective studies of these devices. The location of emboli reported in case series and case reports were predominantly anterior (72 percent) and posterior circulation (24 percent).

No direct *in vivo* comparative studies were identified during our scan of the neurothrombectomy literature. All prospective and retrospective studies reported recanalization success after neurothrombectomy device deployment. The longest duration of follow-up in the majority of prospective and retrospective studies reporting effectiveness outcomes was either 30 or 90 days post-procedure. The timing of NIHSS evaluation was more variable with the longest duration of follow-up ranging from 24-hours to 90-days post-procedure. Safety endpoints were typically monitored over shorter lengths of time, such as the first 24-hours or until discharge. The reporting of follow-up outcomes in case series and case reports was variable. Of the 71 total device reports, nearly half did not report data on effectiveness or safety outcomes after patient discharge. In those reports that did, length of follow-up ranged from 6 weeks to 24 months; the most commonly reported length of follow-up was 90 days.

Prospective and retrospective neurothrombectomy studies focus on patients contraindicated to receive IV rtPA, reporting outside the recommended 3 hour window, or refractory or failing IV rtPA treatment. Consequently, the use of IV rtPA among studies ranged from 0 to 100 percent. The one exception was the aforementioned EKOS study. Concurrent or rescue therapies in identified studies, case series and reports included intra-arterial thrombolytics, cerebral artery angioplasty, and stenting.

Figure ES1 summarizes all identified reports (prospective and retrospective studies, case series and reports) of neurothrombectomy devices by device classification and the effectiveness endpoints evaluated.

Figure ES1. Effectiveness Evidence for Neurothrombectomy Devices (n=1,311)

Reported Outcomes	Devices*				
	Clot Retriever (n=748)	Aspiration/ Suction (n=383)	Snare (n=94)	Ultrasound Technology (n=50)	Laser (n=36)
Recanalization	N=744 NS=6/4/32	N=380 NS=4/3/9	N=88 NS=2/0/24	N=36 NS=1/0/1	N=36 NS=2/0/0
mRS	N=440 NS=5/1/11	N=374 NS=4/3/3	N=45 NS=2/0/9	N=15 NS=1/0/1	N=34 NS=1/0/0
Death#	N=450 NS=5/1/16	N=379 NS=4/3/6	N=65 NS=2/0/9	N=14 NS=1/0/0	N=34 NS=1/0/0
NIHSS	N=371 NS=3/0/15	N=358 NS=3/3/4	N=65 NS=2/0/11	N=14 NS=1/0/0	N=34 NS=1/0/0
BI	No Data	No Data	N=5 NS=1/0/0	N=14 NS=1/0/0	No Data
GOS	No Data	No Data	No Data	N=14 NS=1/0/0	No Data

BI=Barthel Index; GOS=Glasgow Outcome Scale; mRS=modified Rankin Scale; n=the total number of patients evaluated for any effectiveness or safety endpoint; N=number of patients evaluated; NIHSS=National Institutes of Health Stroke Scale; NS=number of evaluations categorized as Prospective/Retrospective/Case Series or Reports
#Death included if patients were followed-up for any duration of time after hospital-discharge

Narrative for Figure ES1:

This figure defines the number of patients being treated with one of five classes of neurothrombectomy device (clot retriever, aspiration/suction, snare, ultrasound technology, or laser) that were evaluated for the following effectiveness outcomes: recanalization, modified Rankin Scale, death, National Institutes of Health Stroke Scale, Barthel Index, and Glasgow

Outcome Scale. Out of 748 patients being treated with a clot retriever (including the Attractor-18, Catch, In-Time retrieval device, MERCI retrieval system, Phenox Clot Retriever, and TriSpan), 744, 440, 450, and 371 patients were evaluated for recanalization, modified Rankin Scale, death, and National Institutes of Health Stroke Scale, respectively. Out of 383 patients being treated with an aspiration/suction device [AngioJet (including Xpeedior) and Penumbra System], 380, 374, 379, and 358 patients were evaluated for recanalization, modified Rankin Scale, death, and National Institutes of Health Stroke Scale, respectively. Out of 94 patients being treated with a snare device (Alligator, Amplatz Gooseneck, Neuronet endovascular snare, and Soutenir microsnare), 88, 45, 65, 65, and 5 patients were evaluated for recanalization, modified Rankin Scale, death, National Institutes of Health Stroke Scale, and Barthel Index, respectively. Out of 50 patients being treated with an ultrasound technology device (EKOS), 36, 15, 14, 14, 14, and 14 patients were evaluated for recanalization, modified Rankin Scale, death, National Institutes of Health Stroke Scale, Barthel Index, and Glasgow Outcome Scale, respectively. Out of 36 patients being treated with a laser device (EPAR and LaTIS), 36, 34, 34, and 34 patients were evaluated for recanalization, modified Rankin Scale, death, and National Institutes of Health Stroke Scale, respectively.

All prospective or retrospective studies reported recanalization results. The NIHSS score was reported in 12 of 23 (52 percent) identified studies and mRS≤2 was reported in 16 of 23 (70 percent) studies. NIHSS, mRS≤2, and mortality endpoints were reported in 22 percent, 56 percent, and 56 percent of MERCI clot retriever; 100 percent, 100 percent, and 100 percent of Penumbra System; and 50 percent, 63 percent, and 63 percent of "off-label" device studies.

Figure ES2 summarizes all identified reports of neurothrombectomy devices by device classification and the safety endpoint(s) evaluated.

Figure ES2. Safety Endpoint Evidence for Neurothrombectomy Devices (n=1,311)

Reported Adverse Events	Devices*				
	Clot Retriever (n=748)	Aspiration/ Suction (n=383)	Snare (n=94)	Ultrasound Technology (n=50)	Laser (n=36)
SICH	N=421 NS=5/0/8	N=369 NS=4/3/3	N=44 NS=1/0/10	N=49 NS=2/0/0	N=34 NS=1/0/0
AICH	N=421 NS=5/0/8	N=354 NS=4/2/3	N=44 NS=1/0/10	No Data	N=34 NS=1/0/0
Perforation/ Dissection	N=182 NS=2/0/2	N=186 NS=3/1/2	N=28 NS=1/0/4	N=49 NS=2/0/0	N=34 NS=1/0/0
Thrombus Formation	N=184 NS=2/0/4	N=176 NS=3/1/1	N=21 NS=2/0/3	No Data	No Data
Other Hemorrhage	N=191 NS=2/0/4	N=38 NS=1/1/0	N=13 NS=0/0/3	No Data	No Data

AICH=asymptomatic intracerebral hemorrhage; n=the total number of patients evaluated for any effectiveness or safety endpoint; N=number of patients evaluated; NS=number of evaluations (Prospective/Retrospective/Case Series or Reports); SICH=symptomatic intracerebral hemorrhage

Narrative for Figure ES2:

This figure defines the number of patients being treated with one of five classes of neurothrombectomy device (clot retriever, aspiration/suction, snare, ultrasound technology, or laser) that were evaluated for the following adverse events: symptomatic ICH, asymptomatic ICH, perforation/dissection, thrombus formation, or other hemorrhage. Out of 748 patients being treated with a clot retriever (including the Attractor-18, Catch, In-Time retrieval device, MERCI retrieval system, Phenox Clot Retriever, and TriSpan), 421, 421, 182, 184, and 191 patients were evaluated for symptomatic ICH, asymptomatic ICH, perforation/dissection, thrombus formation, or other hemorrhage, respectively. Out of 383 patients being treated with an aspiration/suction device [AngioJet (including Xpeedior) and Penumbra System], 369, 354, 186, 176, and 38 patients were evaluated for symptomatic ICH, asymptomatic ICH, perforation/dissection,

thrombus formation, or other hemorrhage, respectively. Out of 94 patients being treated with a snare device (Alligator, Amplatz Gooseneck, Neuronet endovascular snare, and Soutenir microsnare), 44, 44, 28, 21, and 13 patients were evaluated for symptomatic ICH, asymptomatic ICH, perforation/dissection, thrombus formation, or other hemorrhage, respectively. Out of 50 patients being treated with an ultrasound technology device (EKOS), 49 patients were evaluated for symptomatic ICH and perforation/dissection. Out of 36 patients being treated with a laser device (EPAR and LaTIS), 34, 34, and 34 patients were evaluated for symptomatic ICH, asymptomatic ICH, or perforation/dissection, respectively.

Other adverse events evaluated in the neurothrombectomy literature included, perforation/dissection, other types of hemorrhage (not intracerebral), thrombus formation proximal, adjacent or distal to the clot site, failure to deploy the device, device breakage/fracture and vasospasm. During prospective or retrospective studies, the proportion of patients per study experiencing an instance of symptomatic or asymptomatic ICH, other bleeding, perforation or dissection, or thrombus formation were reported in 56 percent, 56 percent, 22 percent, 22 percent and 22 percent of MERCI clot retriever; 100 percent, 83 percent, 33 percent, 50 percent and 50 percent of Penumbra System; and 63 percent, 38 percent, 0 percent, 63 percent and 38 percent of "off-label" device studies, respectively. Device failure-to-deploy, device fracture or breakage and vasospasm data was infrequently reported in studies.

Key Question 3: What are the variables associated with use of the devices that may impact outcomes (e.g. time to deployment, training/expertise of interventionalist, location of infarct, concurrent therapies)?

Results of univariate and multivariate analyses reported in identified prospective and retrospective studies were used to answer Key Question 3. The effects of predictor variables reported by authors of studies on select outcomes (effectiveness and adverse events) are summarized in **Table ES2.** Predictors are classified as to whether they were found to have beneficial (and statistically significant), harmful (and statistically significant) or indeterminate (not statistically significant regardless of effect direction) effects on outcomes. It is important to note that because these predictors were derived from single-arm (uncontrolled) studies, similar relationships may have been observed in these patients even if they were not treated with a neurothrombectomy device (that is to say, similar predictors are likely to be identified in a similar patient population not receiving neurothrombectomy devices).

262 **Table ES2. Effect of Various Variables on Post-Neurothrombectomy Device Outcomes**

	Clinical Outcomes				
Predictor Variables	**Recanalization**	**NIHSS Improvement**	**Hemorrhage***	**mRS≤2**	**Death**
Older Age	-	-	-	H	H
Higher SBP	-	-	-	H	H
Higher Baseline NIHSS	I	-	-	H	H
ICA Occlusion Site (vs. mostly MCA)	I	-	-	I	H
Abnormal Hemostasis#	I	-	I	H	I
Prior IV rtPA	I	-	I	I	I
Concomitant IA thrombolytics	B	-	I	I	I
Prior Stroke	-	-	-	-	H
Longer Procedure Duration	-	-	-	H	I
Right Brain Infarct	-	-	-	H	-

263 B=beneficial; H=harmful; I=indeterminate (no statistically significant effect); IA=intra-arterial; ICA=internal
264 carotid artery; IV rtPA=intravenous recombinant tissue plasminogen activator; MCA=middle cerebral artery;
265 mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; SBP=systolic blood pressure
266 *including symptomatic and asymptomatic hemorrhage
267 #INR>1.7, PTT>45 and/or platelet count <100,000
268 References: Stroke 2005;36:1432-8; Stroke 2008;39:1205-12; Stroke 2009;40:2761-8; Stroke 2009;40:E131; Stroke
269 2009;40:516-22; Stroke 2009;40:2092-7. Complete citations located in the main document starting on p.44 .
270
271
272 Evaluated predictors of outcome (**Table ES2**) in these patients treated with a
273 neurothrombectomy device include demographic, co-morbid disease, stroke severity and stroke
274 treatment variables. These predictors were evaluated in studies (or pooled analyses) of the
275 MERCI clot retriever and the Penumbra System. In addition these variables, researchers have
276 suggested that the presence of collateral circulation, lesion volume and cerebral perfusion
277 pressure have also been linked to outcomes in acute ischemic stroke patients.
278 In a meta-analysis by Stead and colleagues evaluating neurothrombectomy devices,
279 younger age and lower NIHSS score at presentation had beneficial effects on achieving a mRS≤2
280 (p=0.001). Patients with posterior circulation occlusions were found to have higher odds of 90-
281 day mortality compared to those with anterior occlusions (either internal carotid or middle
282 cerebral arteries).
283 No studies provided data assessing the relationship between the training of
284 interventionalists and outcomes in patients treated with neurothrombectomy devices. However,
285 studies of emerging technologies over the past 20 years have suggested that inadequate physician

286 training and experience can adversely affect clinical outcomes. Of note, upon qualitative review,
287 the proportion of patients recanalized in retrospective (real-world) studies did not appear to be
288 lower than that of the prospective, single-arm studies, for either MERCI or Penumbra System
289 studies.
290 In a report written and approved by multiple neuroscience societies, the minimum
291 training requirements for those performing neuroendovascular procedures (including
292 neurothrombectomy devices) in patients with acute ischemic stroke, and performance standards
293 that should be adopted to assess outcomes, have been detailed.
294

295 # Discussion

296 Neurothrombectomy devices are a treatment option in acute ischemic stroke patients
297 who have failed IV rtPA therapy or who are either ineligible for or have contraindications to IV
298 rtPA use. Only two neurothrombectomy devices, the MERCI clot retriever and Penumbra
299 System, are FDA-approved to treat patients with acute ischemic stroke. A majority of available
300 data lies with the two approved devices.
301 We did not identify any direct *in vivo* comparative studies of neurothrombectomy devices
302 to IV rtPA or each other. Instead, investigators frequently studied devices as part of prospective
303 single-arm studies, non-comparative retrospective studies enrolling consecutive patients, or case
304 series or case reports. As a technical brief, our main objective was to describe
305 neurothrombectomy devices currently being used or actively investigated in the treatment of
306 patients with acute ischemic stroke and to summarize the evidence supporting their use, not to
307 draw conclusions regarding their effectiveness or safety.
308 A previous systematic review of neurothrombectomy devices by Stead and colleagues
309 was identified during our literature scan. The literature search on which their review was based
310 extended only through March 2006 and consequently did not include the majority of the highest
311 quality data on neurothrombectomy devices (including that of the MERCI and Penumbra
312 Systems). Thus our technical brief should represent the most up-to-date review of the literature
313 at this time. Unlike our review, Stead and colleagues quantitatively compared pooled device
314 results to a control group derived from their own institution's stroke population. They found that
315 when compared with a similar matched cohort, the neurothrombectomy patients had good
316 functional recovery (mRS≤2) in 34.5 percent of patients compared with 10.7 percent of patients
317 matched for age, sex, and NIHSS score, suggesting the neurothrombectomy group was nearly 15
318 times more likely to have good functional recovery compared with the control group. While
319 perhaps the best "controlled" data available to date, this analysis is fraught with limitations,
320 including the fact that the neurothrombectomy cohort was not homogeneous, the comparison was
321 to a single-center historically concurrent cohort, and individuals were not randomly allocated.
322 Currently, there are eight ongoing studies evaluating at least one neurothrombectomy
323 device in acute ischemic stroke listed on the http://www.clinicaltrials.gov/. The first of these
324 eight studies is estimated to end sometime in 2010. All appear to be enrolling patients based
325 upon inclusion and exclusion criteria that are similar to those already used in published
326 prospective and retrospective studies. One exception is the Mechanical Retrieval and
327 Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial which will allow
328 patients to receive IV rtPA up to 4.5 hours after symptom onset. Five trials are randomized
329 controlled trials and three are prospective observational studies. Four of the five randomized
330 controlled trials are allowing the use of multiple neurothrombectomy devices; however, none

appear to be designed to compare one device to another. Instead, these studies compare the use of neurothrombectomy devices to best medical therapy (with or without IV rtPA).

Both the MERCI clot retriever and the Penumbra System have prospective observational studies in progress. Compared to previous studies of these devices of similar design, these studies will enroll much larger sample sizes (n=2,000 and 3,000, respectively).

The Pragmatic Ischemic Stroke Thrombectomy Evaluation (PISTE) randomized controlled trial (projected n>200) will be the first study to evaluate the impact of a mechanical device in acute ischemic stroke on health related quality of life and the second to evaluate treatment costs.

There appears to be a need for studies to determine the comparative effectiveness of neurothrombectomy devices and IV rtPA in patients reporting within a 3- (or 4.5-) hour window from time of stroke onset and having no contraindications to either therapy. In addition, for those patients with contraindications or who are refractory to IV rtPA, it is unclear which device is the most efficacious or safe. It would seem reasonable to conduct studies to answer such research gaps using a randomized controlled trial design, powered to show equivalency or non-inferiority of devices.

Summary

There is currently a paucity of high quality research evaluating neurothrombectomy devices in patients suffering from acute ischemic stroke. There remains a need for further research on the topic, including randomized controlled trials to determine the optimal device(s) to use, and their effectiveness and safety compared to best medical therapy. Results of ongoing studies will only begin to address these questions.

Background and Objectives for the Systematic Review

Prevalence of Ischemic Stroke

Stroke is the third leading cause of death following diseases of the heart and cancer.[1,2] A majority of strokes are classified as ischemic in nature (87 percent), with intracerebral hemorrhagic (10 percent) and subarachnoid hemorrhagic stroke (3 percent) accounting for the rest.[2] Every year in the United States, approximately 795,000 people develop a new or recurrent stroke, with 610,000 first attacks and 185,000 recurrent attacks.[2] Stroke occurs more commonly in females than males, especially at older ages.[3] Blacks have a two-fold higher risk of first-ever stroke than Caucasians, with age-adjusted incidences of 6.6 per 1000 in black men as compared with 3.6 per 1000 in Caucasian men.[3] In 2006, 43.6 deaths occurred due to stroke per 100,000 people in the Unites States, averaging out to one death due to stroke every 3 to 4 minutes.[2,4] In 2005, the overall mortality rate from stroke was approximately 44.7 per 100,000 for Caucasian males, 70.5 per 100,000 for black males, 44.0 per 100,000 for Caucasian females, and 60.7 per 100,000 for black females.[5] Lower mortality rates were seen in Hispanic, Asian and American Indian populations as compared with Caucasian populations.[2]

Stroke is the leading cause of long-term disability in the United States. Thirty percent of stroke survivors require outpatient rehabilitation services[6,7] and 15 to 30 percent of patients remain permanently disabled.[2] Costs associated with acute stroke were estimated to approach $68.9 billion in 2009, with inpatient hospital costs accounting for 70 percent of the total cost in the first year after stroke.[2,8] Significant decreases in health-related quality-of-life are also seen following a stroke.[2] Studies have shown that at-risk patients view the consequences of experiencing an ischemic stroke as being worse than death.[9] Additionally, evidence has demonstrated the significant impact of ischemic stroke on caregiver burden and quality-of-life in caregivers.[10-12]

Reperfusion Strategies for Treatment of Ischemic Stroke

The pathophysiologic basis for an acute ischemic stroke begins with the occlusion of an intracranial vessel either by an embolus or a local thrombus, reducing blood flow to the downstream brain region.[13] If blood flow is not restored to the affected area, ischemia and eventual cell death will occur in a time-dependent fashion.[13] Currently available treatment options for acute ischemic stroke focus on restoring cerebral perfusion to the affected area as quickly as possible thereby reducing or preventing brain infarction and minimizing long-term disability and stroke-related mortality.[14]

Some thrombolytic agents, including recombinant tissue plasminogen activator (alteplase, rtPA), restore cerebral perfusion by activating plasminogen at the site of the occlusion, subsequently dissolving the clot.[15] Intravenous (IV) rtPA has been approved by the United States Food and Drug Administration (FDA) for the treatment of acute ischemic stroke and is currently indicated for use within the first 3 hours of onset of symptoms.[14] The National Institutes of Neurological Disorders and Stroke (NINDS) rtPA Stroke Study Group conducted a randomized, double-blind trial evaluating the benefits of IV rtPA treatment (0.9 mg/kg) administered within 3 hours of ischemic stroke onset (n=624).[16] At 3-months, patients receiving IV rtPA had more favorable results [odds ratio (OR) 1.7, 95 percent confidence interval (CI) 1.2 to 2.6] than the group receiving placebo as measured by four commonly utilized tools to assess

397 stroke-related deficits and disabilities. The global OR for improvement included improvements
398 in the Barthel Index (OR 1.6, 95 percent CI 1.1 to 2.5), modified Rankin Scale (mRS) (OR 1.7,
399 95 percent CI 1.1 to 2.5), Glasgow Outcome Scale (GOS) (OR 1.6, 95 percent CI 1.1 to 2.5) and
400 the National Institutes of Health Stroke Scale (NIHSS) (OR 1.7, 95 percent CI 1.0 to 2.8).
401 Use of IV rtPA beyond the 3 hour timeframe has been limited. However, in a pooled
402 analysis of six randomized, placebo-controlled trials evaluating IV rtPA in stroke, researchers
403 found that although better results were achieved with earliest possible use of IV rtPA, there were
404 potential benefits when used beyond the 3-hour window.[17] Patients who received IV rtPA
405 between 3 and 4.5 hours after stroke onset were at an increased odds of a favorable outcome (a
406 composite of stroke-related disabilities, severity of disabilities and abilities to conduct activities
407 of daily living) as compared with placebo (OR 1.4, 95 percent CI 1.05 to 1.85). The
408 subsequently published European Cooperative Acute Stroke Study (ECASS III), which was
409 powered based on the aforementioned meta-analysis, specifically evaluated the benefits of IV
410 rtPA administered between 3 and 4.5 hours after symptom onset.[18] When compared with
411 placebo, patients receiving IV rtPA had significantly higher odds of a more favorable outcome
412 (OR 1.34, 95 percent CI 1.02 to 1.76), with no differences in mortality (p=0.68) but higher
413 incidence of ICH seen (p=0.001).[18] In addition, two observational studies, the Safe
414 Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST)[19] and the SITS-
415 international stroke treatment registry (SITS-ISTR)[20] confirmed the benefits of rtPA use at 3-4.5
416 hours after ischemic stroke. Based on these findings, the American Heart Association and
417 American Stroke Association issued a scientific advisory in 2009 recommending the use of IV
418 rtPA in eligible patients presenting within 3 to 4.5 hours after the onset of stroke symptoms.
419 This was a Class I recommendation with B level of evidence for most patients but for those older
420 than 80 years, taking oral anticoagulants, with a baseline NIHSS score>25, or with both a history
421 of stroke and diabetes, rtPA use within 3-4.5 hours was a Class IIb recommendation with C level
422 of evidence.[21]
423 Despite appropriate IV rtPA use, rates of recanalization remain highly variable ranging
424 from 30 to 92 percent during the initial 6 to 24 hours after treatment.[22] Recanalization rates vary
425 depending on the site of the occlusion: events in large cerebral vessels having particularly high
426 clot burden may not adequately respond to IV rtPA. More importantly, delays in arriving in the
427 emergency department and unavailability of IV rtPA in some centers make thrombolytic
428 reperfusion therapy viable in less than five percent of patients with acute stroke.[23]
429 Neurothrombectomy devices have been examined in patients who are ineligible for, have
430 contraindications to, or fail IV rtPA therapy. A neurothrombectomy device is defined by the
431 FDA's Center for Devices and Radiological Health (CDRH) as a device intended to retrieve or
432 destroy blood clots in the cerebral neurovasculature by mechanical, laser, ultrasound
433 technologies, or combination of technologies.[24] These devices may offer a number of potential
434 advantages when compared to pharmacologic thrombolysis including: more rapid achievement
435 of recanalization vs. IV rtPA; enhanced efficacy in treating large vessel occlusions; greater
436 efficacy with a lower risk for hemorrhagic events; and use in patients contraindicated to, or
437 presenting outside the appropriate window for, IV rtPA.[25] These putative advantages of
438 neurothrombectomy devices have not been confirmed in direct comparisons against rtPA
439 therapy. Neurothrombectomy devices employing different mechanisms including clot retrievers,
440 aspiration/suction devices, snare-like devices, ultrasonography technologies and lasers, have
441 been or are currently under study in patients with acute ischemic stroke. The MERCI clot
442 retriever was the first neurothrombectomy device to receive FDA clearance in 2004 to "restore

blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke".[26-29] Subsequently, the Penumbra System was cleared by the FDA in 2007 "for use in the revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease within 8 hours of symptom onset."[29] These clearances through the FDA 510(k) process resulted in significant controversy given the relatively low number of patients included in the studies available at the time of clearance as well as the lack of clinical outcomes reported.[22] Various ongoing clinical trials are currently evaluating the impact of these, as well as other, neurothrombectomy devices for the treatment of acute ischemic stroke.

Statement of Work

The goal of this technical brief is to describe neurothrombectomy devices currently being used or actively investigated in the treatment of patients with acute ischemic stroke, and to summarize the evidence supporting their use.

This technical brief is based on a systematic scan of the literature. Key questions, methods, and approaches were defined by the University of Connecticut/Hartford Hospital Evidence-based Practice Center (EPC) after discussions with representatives from the Agency for Healthcare Research and Quality (AHRQ) and clinical content and technical experts.

The Key Questions

Population: The population consists of patients with acute ischemic stroke.
Intervention: The intervention is the use of a neurothrombectomy device with or without prior intravenous thrombolytics or concomitant intra-arterial therapy (thrombolytics, angioplasty or stenting).
Comparators: Studies do not have to have comparators.
Outcomes: The outcomes are separated into adverse events (e.g., failure to deploy the device or remove the clot, device breakage/fracture, perforation, dissection, thrombus formation (proximal, adjacent, or distal to the clot site), vasospasm or hemorrhage (intracerebral and other)), intermediate outcomes (e.g. recanalization), and final health outcomes (e.g. mortality and impact of therapy on the mRS, NIHSS, Barthel Index, and GOS).
Timing: The timing is not restrictive as long as the intervention was initiated within the period of the acute ischemic stroke.
Setting: The setting is not limited.

Key Question 1:
What are the different types of neurothrombectomy devices in use or in development for treatment of acute ischemic stroke?

- 1a. What are the existing FDA indications for each device?
- 1b. Which devices are being used off-label for this indication?
- 1c. What is the status of FDA approval for each device?
- 1d. What are the theoretical advantages and disadvantages of these devices compared to other treatment options?
- 1e. What are the potential safety issues and harms associated with the use of these devices?
- 1f. What is the extent of utilization of the different devices?

Key Question 2:

From a systematic literature scan of studies on different types of neurothrombectomy devices, provide a synthesis of the following variables:

- 2a. Type(s) of devices
- 2b. Study design and size
- 2c. Patient characteristics
- 2d. Comparator used in comparative studies
- 2e. Length of follow-up
- 2f. Concurrent or prior therapy
- 2g. Outcomes measured
- 2h. Adverse events, harms and safety issues reported

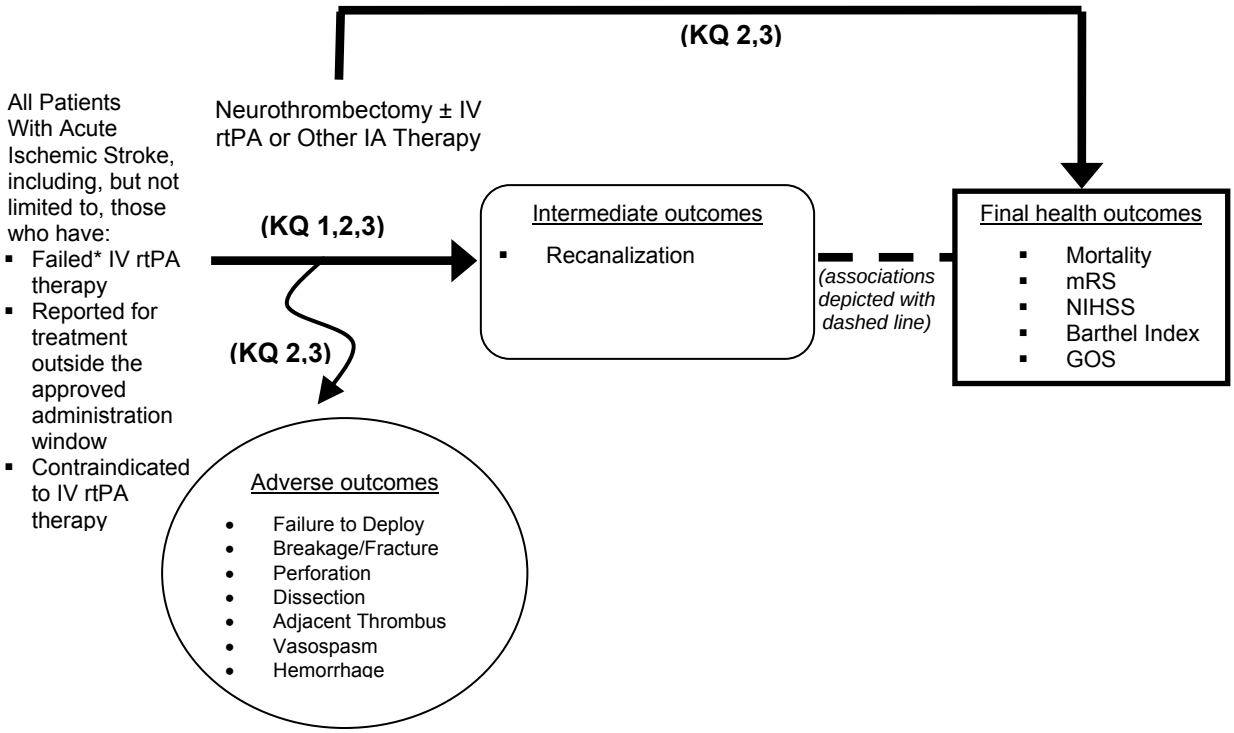
Key Question 3:

What are the variables associated with use of the devices that may impact outcomes (e.g. time to deployment, training/expertise of interventionalist, location of infarct, concurrent therapies)?

Analytic Framework

To guide our assessment of studies examining the association between neurothrombectomy devices with benefits and harms in our target population, we developed an analytic framework mapping specific linkages from comparisons to populations of interest, mechanisms of benefit, and outcomes of interest **(Figure 1)**. It is a logic chain that supports the link from the intervention to the outcomes of interest.

Figure 1. Analytic Framework for Neurothrombectomy Devices for Treatment of Acute Ischemic Stroke



Legend: GOS = Glasgow Outcome Scale; IV/IA = intravenous or intraarterial; KQ=key question; mRS = modified Rankin Scale; rtPA=recombinant tissue plasminogen activator; NIHSS = National Institutes of Health Stroke Scale. *Failure of IV rtPA refers to immediate failure to recanalize the target vessel as determined by immediate angiography following the procedure

Narrative for Figure 1:

- This analytic framework figure is intended as an overview only. The links between the use of an intervention in a population and outcomes are described. The population includes all patients experiencing an acute ischemic stroke, including, but not limited to, those who have failed IV rtPA therapy, reported for treatment outside the approved administration window or were contraindicated to receive IV rtPA therapy. The intervention is the use of a neurothrombectomy device with or without IV thrombolytic therapy or concurrent IA therapies (IA thrombolysis, angioplasty, stenting). While most studies do not have comparators, the comparator in current clinical practice would be IV thrombolytic therapy in the patient reporting within 4.5 hours of symptom onset.[16,18,21] The outcomes are separated into adverse events, intermediate outcomes, and final health outcomes. The adverse events of note include

failure of the device to employ, breakage or fracture, perforation, dissection, adjacent thrombosis, vasospasm, and hemorrhage. The intermediate outcome is recanalization. The final health outcomes include mortality and impact of therapy on the mRS, NIHSS score, Barthel Index, and GOS.

Methods

Key Terminology and Definitions

Anterior Circulation: The blood flow provided by the two internal carotid arteries, which terminate as the anterior and middle cerebral arteries.

Barthel Index (BI): A scale used to measure performance in basic activities of daily living (ADL). It uses ten variables describing ADLs and mobility. A higher number is associated with a greater likelihood of being able to live at home with a degree of independence following discharge from hospital.

Basilar Artery (BA): Artery that arises from the confluence of the two vertebral arteries at the junction between the medulla oblongata and the pons. It is one of the arteries that supplies the brain with oxygen-rich blood.

Glasgow Outcome Scale (GOS): The Glasgow Outcome Scale is a 5-point score given to victims of traumatic brain injury at some point in their recovery. It is a very general assessment of the general functioning of the person who suffered a head injury. In general, this scale is not used in the clinical management of the patient. Rather, it is used often in research to quantify the level of recovery patients have achieved.

Internal Carotid Artery (ICA): Main artery of the head and neck that helps supply blood to the brain.

Middle Cerebral Artery (MCA): One of the three major arteries that supplies blood to the cerebrum. It arises from the internal carotid and continues into the lateral sulcus where it branches and projects to many of the lateral cerebral cortex. It also supplies blood to the anterior temporal lobes and the insular cortices.

modified Rankin Scale (mRS): A commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke. It has become the most widely used clinical outcome measure for stroke clinical trials. The scale runs from 0 (perfect health without symptoms) to 6 (death).

National Institutes of Health Stroke Scale (NIHSS): A method developed by the National Institutes of Health to gauge the severity of stroke. The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss.

Neurothrombectomy Device: A device intended to retrieve or destroy blood clots in the cerebral neurovasculature by mechanical, laser, ultrasound technologies, or combination of technologies.

Posterior Circulation: The blood flow provided by the two vertebral arteries, which join together as a single basilar artery

Recanalization: The restoration of the lumen of a blood vessel following thrombotic occlusion by restoration of the channel or by the formation of new channels. Thrombolysis in Myocardial Infarction (TIMI) grade 2 represents partial recanalization. TIMI grade 3 represents complete recanalization. The TIMI grading scale was initially developed to assess coronary ciculation.

Vertebral Arteries (VA): Branches of the subclavian arteries.

Criteria for Inclusion/Exclusion of Studies in the Review

We developed a list of neurothrombectomy devices based on the FDA's guidance definition of a neurothrombectomy device,[24] published literature, and a search of the FDA CDRH's database to identify neurothrombectomy devices that have received FDA approval (510(k) documents).[29]

Two investigators independently screened citations at the abstract level to identify potentially relevant studies, case series or case reports. Throughout this technical brief, our use of the terminology 'studies' will refer only to prospective, single-arm studies or retrospective studies enrolling consecutive patients. The terminology 'reports' will refer to the latter studies in addition to case series and case reports. All potentially eligible citations were retrieved for full-text review and examined for eligibility. We included human studies of any design or case series or case reports, as long as they included patients with an acute ischemic stroke, and reported data on at least one clinical effectiveness outcome (e.g., recanalization, mortality, mRS, or outcome score including NIHSS, Barthel Index or GOS) or harm [e.g., failure to deploy the device or remove the clot, device breakage/fracture, perforation, dissection, thrombus formation proximal, adjacent, or distal to the clot site, vasospasm or hemorrhage (intracerebral and other)]. No language restrictions were used in the searching for reports; however, only reports in English were included in our qualitative review of the literature.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Two independent investigators conducted systematic literature searches of MEDLINE, the Cochrane Central Register of Controlled Trials, SCOPUS and Web of Science as well as the Cochrane Database of Systematic Reviews, from the earliest possible date until September 2009. No language restrictions were imposed during the literature identification stage. In addition, a manual search of references from identified reports or review articles was conducted. Search strategies used for MEDLINE and the Cochrane Central Register of Controlled Trials are included in **Appendix A**. Searches of Scopus and Web of Science used similar terminology. After verifying products in current clinical practice and those in development, we asked the Scientific Resource Center (SRC) at the Oregon Evidence-based Practice Center to contact the different manufacturers to obtain scientific information packets (Penumbra Inc. and EKOS Inc. were the only two manufacturers to provide information). **(Appendix B)** Finally, we conducted a grey literature search utilizing Google and specific search terms.

Data Abstraction and Data Management

Through the use of a standardized data abstraction tool, two reviewers independently collected 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 (prospective single arm study, retrospective study, randomized controlled trial, nonrandomized comparative study, case series or reports), study population (including study inclusion and exclusion criteria, duration of patient follow-up), patient baseline characteristics (age, gender), disease severity (baseline NIHSS, baseline TIMI flow), location of

occluded artery (anterior, posterior, other), time from symptom onset to device deployment or angiography, use of concurrent standard medical therapies (including prior or concurrent use of IV/IA thrombolysis, angioplasty, stents), whether outcomes assessment was blinded, and the device used. Effectiveness outcomes included: recanalization as measured by post-TIMI flow grade (0/1=no recanalization, 2=partial recanalization, 3=complete recanalization) or similar methodology, mortality, mRS (≤2=good outcome, ≥3=poor outcome), NIHSS score (including the ≥ 4 points decrease deemed significant by the FDA),[24] Barthel Index and GOS. Harms assessed included: failure to deploy the device or remove the clot (technical success), device breakage/fracture, perforation, dissection, thrombus formation proximal, adjacent, or distal to the clot site, vasospasm, or hemorrhage (including symptomatic and asymptomatic intracerebral and subarachnoid hemorrhage from vessel injury and other bleeding).

Assessment of Methodological Quality of Individual Studies

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

Data Synthesis

We utilized in-depth tables summarizing what is known about the relevant studies and case series or case reports. We created study density figures to summarize the totality of information available on the effectiveness and safety of the devices in this technical brief. No formal quantitative synthesis (meta-analysis) was undertaken.

Grading the Evidence for Each Key Question

This was deemed not applicable for this technical brief.

Future Research/Research Gaps

We searched http://www.clinicaltrials.gov/ to identify ongoing trials. Upon completion of the literature scan portion of this technical brief, we highlight areas where we feel further research is justified.

Results

Key Question 1

What are the different types of neurothrombectomy devices in use or in development for treatment of acute ischemic stroke?

1a. What are the existing FDA indications for each device?
1b. Which devices are being used off-label for this indication?
1c. What is the status of FDA approval for each device?
1d. What are the theoretical advantages and disadvantages of these devices compared to other treatment options?
1e. What are the potential safety issues and harms associated with the use of these devices?
1f. What is the extent of utilization of the different devices?

Neurothrombectomy devices are categorized into five broad classes, including clot retrievers, aspiration/suction devices, snare-like devices, ultrasonography technologies, and lasers. **Table 1** lists the various classes and devices in those classes that were identified as potentially useful for thrombus removal in the neurovasculature. It specifies those devices that have an FDA indication for acute ischemic stroke treatment and those currently available for clinical use.

The aspiration/suction devices include the Amplatz Thrombectomy, AngioJet, NeuroJet, Oasis Thrombectomy, Penumbra System, and Vasco +35. The Amplatz Thrombectomy Device (Ev3 Medical, Plymouth, MN) consists of a catheter, a small diameter impeller encased in a distal housing, and a driveshaft. The AngioJet (Possis Medical, Minneapolis, MN) contains an AngioJet catheter and a pump in one combined unit. High-pressure saline jets agitate the clot face creating clot fragments that are suctioned out through the catheter. The set includes a 3-port catheter manifold that allows for the administration of other fluids, such as contrast media, to be injected into the blood stream where the catheter is positioned. The NeuroJet (Possis Medical, Minneapolis, MN) is operated in the same manner as the AngioJet, but is a smaller catheter designed specifically for intracranial navigation. The Oasis Thrombectomy System (Boston Scientific, Natick, MA) uses high velocity saline streams to microfragment and remove thrombus. The Penumbra System (Penumbra, Alameda, CA) consists of three devices: a reperfusion catheter, a separator and aspiration tubing. Once a guide wire is passed through the clot, the separator is advanced and the aspiration pump is turned on. Continuous aspiration-debulking is facilitated by advancing and withdrawing the separator through the reperfusion catheter. If residual clot remains, a second system for direct thrombus extraction via a thrombus removal ring can be used. Of note, the latter mentioned direct thrombus extraction component of the Penumbra System was not included in the FDA clearance. The Vasco +35 (Balt Extrusion, Montmorency, France) is a dedicated aspiration device with a blunt tip.

The clot retriever devices include the Attractor-18, Catch, In-Time, MERCI, Phenox, and TriSpan devices. The Attractor-18 device (Boston Scientific, Natick, MA) is a fiber-based retriever that contains a radiopaque distal platinum coil with a wire tip. Radiolucent fibers are wound with a radiopaque distal platinum marker and attached to the distal wire tip. The Catch device (Balt Extrusion, Montmorency, France) consists of a self-expanding basket-like design that is fixed on a pusher wire. The distally closed self-expanding nitinol cage is positioned in an insertion tube and delivered through a braided 2.4-Fr microcatheter. The In-Time device

(Boston Scientific, Natick, MA) consists of a braided catheter shaft with a radiopaque basket attached to the end of the catheter. Unlike some other devices, it does not have a specific mechanism to capture the embolus. The MERCI clot retriever (Concentric Medical, Mountain View, CA) is a flexible, tapered nitinol core wire with the distal end shaped into a helix and attached with polymer filaments. The device also includes a torque device to facilitate manipulation and an insertion tool to introduce the retriever into the microcatheter. The Phenox Clot Retriever (Phenox GmbH, Bochum, Germany) consists of a highly flexible nitinol/platinum alloy compound core wire surrounded by stiff polyamide microfilaments in a conical shape. These filaments have an increasing diameter distally and are resistant to unraveling. More recent generations of this device incorporate a nitinol cage allowing it to trap thrombi with firmer consistency. The TriSpan device (Target Boston Scientific, Natick, MA) consists of three nitinol loops in a neck bridge design.

The ultrasonography devices include the EKOS and OmniWave systems. The EKOS system (EKOS, Bothell, WA) has a small ultrasound transducer at the tip of the device and a port to administer medications at the site of occlusion. The ultrasound waves increase the permeability of the clot in order to speed up the effect of IA thrombolytic agents. The OmniWave Endovascular System (Omnisonics Medical Technologies, Wilmington, MA) is a catheter-based system that directs low-power ultrasonic energy through a catheter wire creating bubbles that fracture the thrombus without damaging vessel walls.

The snare devices identified included the Alligator, Amplatz Gooseneck, EnSnare Device, Neuronet and Soutenir. The Alligator device (Chestnut Medical Technologies, Menlo Park, CA) is a retriever with grasping jaws attached to the tip of a flexible wire. It is designed to be used in conjunction with an existing microcatheter. The Amplatz Goosneck kit (Ev3 Medical, Plymouth, MN) contains a microsnare, microcatheter, a microsnare introducer and a torque device. The microsnare is constructed of a nitinol cable and gold plated tungsten loop. The catheter contains a platinum-iridium radiopaque marker band. The EnSnare system (Angiotech Technologies, Inc, Gainesville, FL) consists of three interlaced, tulip-shaped nitinol loops that open distally. The Neuronet device (Boston Scientific, Natick, MA) is a microguide-based nitinol self-expanding basket design with a crisscrossing portion that tapers to a platinum-tipped wire. The Soutenir device (Solution, Yokohama, Japan) is a basket-shaped microsnare consisting of four microwires which are 3-dimensionally configured with platinum coils on either end.

The lasers identified included the EPAR and LaTIS devices. The Endovascular Photo-Acoustic Recanalization (EPAR, Endovasix, Belmont, CA) is a mechanical clot-fragmentation device based on laser technology. Photonic energy is converted to acoustic energy at the fiberoptic tip through creation of microcavitation bubbles, emulsifying the thrombus which is then suctioned out. The LaTIS laser device (Spectanetics, Colorado Springs, CO) uses a laser at its tip to slowly inject contrast material creating a heating of the clot to the point where it breaks down.

759 **Table 1. Neurothrombectomy Devices In Use**

Device Class	Company Name	FDA Indication	In Clinical Use?
Aspiration/Suction			
Amplatz Thrombectomy	Ev3 Medical	Mechanical dissolution of thrombus within dialysis fistulae	No longer marketed
AngioJet	Possis	Breaking apart or removing of thrombus in peripheral veins or arterio-venous access conduits	Yes
NeuroJet	Possis	NA	No longer marketed
Oasis Thrombectomy	Boston Scientific	Removing thrombus from hemodialysis access grafts	No longer marketed
Penumbra	Penumbra, Inc	Revascularization of patients with acute ischemic stroke	Yes
Vasco +35	Balt Extrusion	NA	Not in US
Clot Retriever			
Attractor-18	Boston Scientific	NA	No longer marketed
Catch	Balt Extrusion	NA	Not in US
In-Time	Boston Scientific	Retrieval of intravascular foreign objects in peripheral vasculature, neurovasculature and cardiovasculature	No longer marketed
MERCI	Concentric Medical	Restore blood flow in the neurovasculature	Yes
Phenox	Phenox GmbH	NA	Not in US
TriSpan	Boston Scientific	NA	No longer marketed
Ultrasonography			
EKOS	EKOS Corporation	Infusion of fluids into peripheral vasculature	Yes
OmniWave	OmniSonics	Removal of thrombus and infusion of fluids into peripheral vasculature	No longer marketed
Snare			
Alligator	Chestnut Medical Technologies, Inc	Peripheral and neurovasculature foreign body removal	Yes
Amplatz Gooseneck	Ev3 Medical	Retrieval and manipulation of atraumatic foreign bodies in coronary and peripheral cardiovascular system and the extra-cranial neurovascular anatomy	Yes
EnSnare Device	Merit Medical Systems, Inc.	Retrieval and manipulation of foreign objects in the cardiovascular system or hollow viscous	Yes
Neuronet	Boston Scientific	NA	No longer marketed
Soutenir	Solution	NA	Not in US
Laser			
EPAR	Endovasix Inc.	NA	No longer marketed
LaTIS	Spectranetics	Removal of thrombus from vascular grafts	No longer marketed

760 EPAR=Endovascular Photoacoustic Recanalization; FDA=Food and Drug Administration; MERCI=NA=not
761 applicable; US=United States

1a. What are the existing FDA indications for each device?

The approval process for medical devices varies from that of pharmacologic agents. The FDA's CDRH handles the regulation of medical devices both premarket and postmarket.[24] As such, neurothrombectomy devices are reviewed and approved through the 510(k) premarket notification process.[24,29] In order for a device to receive approval through a 510(k) process, the manufacturer must demonstrate that the new device is substantially equivalent in safety and effectiveness to a Class II device that is already on the market for a particular indication. Most commonly, devices are approved based on nonclinical testing with little to no clinical data. The FDA does not mandate which study designs should be used, as long as the methods are scientifically sound. The FDA recommends that neurothrombectomy devices for the treatment of acute ischemic stroke assess effectiveness at 30- and 90-days postintervention using any appropriate, validated disability or neurologic impairment scale.[24] The selection of the most appropriate clinical endpoints and statistical tests varies depending on the device and study design used. The FDA also recommends reporting revascularization success using the TIMI grading of blood flow both before and after use of the specified device.

The FDA-approved indications for neurothrombectomy devices included in this review can be found in **Table 1**. The MERCI retriever and the Penumbra System are the only devices with FDA approval 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."[26,29] 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."[29]

A total of ten identified devices have FDA-approved indications through the 510(k) process but not for acute ischemic stroke. The In-Time, Alligator, Amplatz Gooseneck, and EnSnare devices are approved for the retrieval of intravascular foreign objects either in general or in the peripheral vasculature and neurovasculature. The EKOS and OmniWave systems are approved for the infusion of fluids into the peripheral vasculature. The LaTIS laser and Oasis Thrombectomy System are approved for the removal of thrombi from vascular or hemodialysis access grafts. The Amplatz Thrombectomy Device is approved for dissolution of thrombi within dialysis fistulae.

1b. Which devices are being used off-label for this indication?

A total of five devices included in this review are available for clinical use in the United States but do not have FDA-approved indications for the treatment of acute ischemic stroke. The remaining devices included in this review are either no longer marketed or are only available in countries outside of the United States.

1c. What is the status of FDA approval for each device?

The MERCI retriever and Penumbra System are currently FDA approved for acute ischemic stroke. We did not identify any other device pending FDA review for such approval at this time. Multiple generations of the MERCI retriever have received FDA approval. The first-generation devices included the X5 and X6 which used nitinol wires with a helical shaped distal tip with tapering coil loops. The second-generation devices included the L4, L5, and L6 and differed from the X-series by including a system of arcading filaments attached to a nontapering helical nitinol coil. The third-generation V-series devices incorporate features of both the X- and

L-series devices and have a more linear configuration with a slight distal taper and polymer filaments to help capture loose clot debris. The retriever is deployed distal to the clot using a microcatheter and balloon guide wire. The balloon is inflated and the retriever is slowly pulled back to capture the clot in the coil loops. The retriever and microcatheter are then slowly withdrawn to remove the clot. The Penumbra System is different in that it utilizes a unique microcatheter and separator-based thrombus debulking approach. The separator is deployed through a reperfusion catheter, then advanced and retracted at the proximal margin of the primary occlusion. This continuous motion facilitates aspiration by reducing the overall clot burden. This is followed by the use of aspiration tubing and a pump that is used in conjunction with the reperfusion catheter to remove the thrombus particles from the neurovasculature.

1d. What are the theoretical advantages and disadvantages of these devices compared to other treatment options?

Neurothrombectomy devices for the treatment of patients with acute ischemic stroke offer several advantages over pharmacologic agents.[27] Use of these devices allows patients to avoid use of pharmacologic thrombolysis agents, thereby presumably minimizing the risk for ICH. Additionally, treatment of patients with neurothrombectomy devices for acute ischemic stroke can be extended beyond the 4.5 hour window from symptom onset, beyond which thrombolytics cannot typically be used. Moreover, the uses of some devices fragment the thrombus occlusion increasing the surface area of the clot, allowing for improved accessibility of thrombolytic agents. The neurothrombectomy devices may also provide more rapid recanalization than thrombolytics as well as provide a treatment option for thrombi more resistant to fibrinolytic breakdown. As such, neurothrombectomy approaches are available as an option for patients who have either a contraindication to pharmacologic thrombolysis, such as recent surgery or abnormal hemostasis or are late in their presentation. Parenthetically, providing adjunctive neurothrombolytic device treatment may be essential for accomplishing successful thrombolysis.

The disadvantages of the neurothrombectomy devices include the technical difficulty of navigating mechanical devices into the intracranial circulation, direct trauma to the neurovasculature (including vasospasm, vessel dissection, perforation, or rupture), and fragmentation of thrombi causing distal embolization into previously unaffected vessels and cerebral territories.[27]

1e. What are the potential safety issues and harms associated with the use of these devices?

As stated above, the main safety concern with the use of neurothrombectomy devices is direct trauma to the neurovasculature as a consequence of the procedure. This can result in vasospasm, vessel dissection, perforation, or vessel rupture. Vasospasm with neurothrombectomy devices is likely secondary to vessel irritation.[30] This can lead to vessel narrowing and lower chances of achieving recanalization. Vessel dissection is caused by the passage of the catheter back and forth in the vessel lumen. This risk can be minimized when the device is advanced over a guidewire. In addition, a potential risk for thrombus fragmentation and distal embolization into previously unaffected vessels and cerebral territories exists.

One of the main safety concerns with the use of neurothrombectomy devices is the risk for ICH. A prior meta-analysis by Stead and colleagues suggested that ICH (both symptomatic and asymptomatic) occurred in 22.5 percent of patients included in their review who had received treatment with a neurothrombectomy device.[31]

1f. What is the extent of utilization of the different devices?

The MERCI retriever has been used >10,000 times for the treatment of acute ischemic stroke.[32] Information with other devices included in this review was not available.

Key Question 2

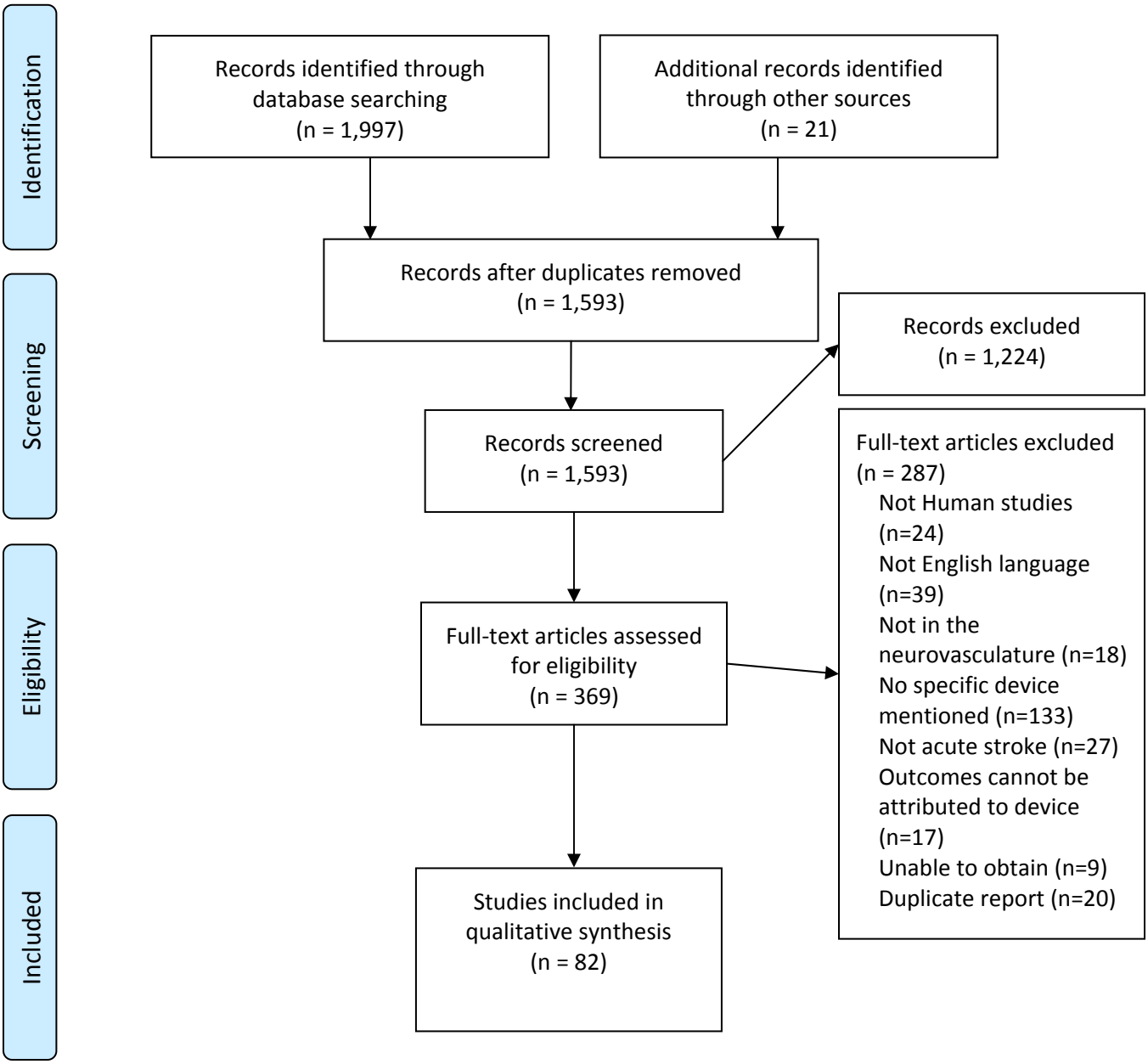
From a systematic literature scan of studies on different types of neurothrombectomy devices, provide a synthesis of the following variables:

2a. Type(s) of devices
2b. Study design and size
2c. Patient characteristics
2d. Comparator used in comparative studies
2e. Length of follow-up
2f. Concurrent or prior therapy
2g. Outcomes measured
2h. Adverse events, harms and safety issues reported

Literature Selection

Our systematic literature scan yielded a total of 1997 citations, 369 of which were retrieved for full-text review **(Figure 2)**. Ultimately, 82 reports were included in the literature scan. **Appendix C** list the citations of eligible and excluded reports (at the full-text review stage), respectively.

Figure 2. PRISMA Style Flow Chart of Report Inclusion and Exclusion



Narrative for Figure 2:

This PRISMA style flow chart delineates the dispensation of records in the technical brief. In the identification stage, 1997 records were identified through the literature search and 21 records were identified through other sources. After duplicates were removed, 1593 records were screened and 1224 subsequently excluded. Thus 369 full text articles were assessed for eligibility and 287 were excluded for the following reasons: 24 were not in humans, 39 were not in English, 18 were not in the neurovasculature, 133 did not define the specific device used, 27 were not in acute stroke, 17 were not attributable to the device, 9 full text articles could not be obtained, and 20 were duplicate reports. Thus, 82 studies were included in qualitative synthesis.

Of the included reports, 16 were prospective single-arm studies, 7 were non-comparative retrospective studies enrolling consecutive patients and 59 were case series or case reports. The 59 case series and case reports detail 71 device reports. **(Table 2)** Throughout the rest of this technical brief, we will typically discuss prospective and retrospective studies separately from case series and case reports.

In addition to 82 identified reports, we identified eight ongoing studies evaluating at least one neurothrombectomy device in acute ischemic stroke. **(Table 3)**

896 **Table 2. Number of Reports for Each Neurothrombectomy Device Stratified By Type of Study**

Device Class	Number of Reports				Total:
	Prospective, Single-Arm	Non-Comparative Retrospective*	Case Series	Case Reports	
Aspiration/Suction					
AngioJet	1	-	3	4	**8**
Penumbra	3	3	1	2	**9**
Clot Retriever					
Attractor-18	-	-	-	1	**1**
Catch	-	-	1	-	**1**
In-Time	-	-	1	1	**2**
MERCI	5	4	12	17	**38**
Phenox	1	-	1	-	**2**
TriSpan	-	-	1	-	**1**
Ultrasonography					
EKOS	2	-	-	1	**3**
Snare					
Alligator	-	-	1	2	**3**
Amplatz Gooseneck	1	-	6	4	**11**
Neuronet	1	-	1	4	**6**
Soutenir	-	-	1	1	**2**
Device Not Specified	-	-	4	1	**5**
Laser					
EPAR	1	-	-	-	**1**
LaTIS	1	-	-	-	**1**
Total:	**16**	**7**	**33**	**38**	**94^**

897 EPAR=Endovascular Photoacoustic Recanalization
898 *Must have enrolled consecutive patients
899 ^Adds up to greater than the total of 82 reports depicted in the PRISMA flow sheet, since some reports provided data on multiple devices. A total of 16
900 prospective, 7 retrospective and 59 unique case series/reports were identified.
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904
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907 **Table 3. Summary of Ongoing Studies of Neurothrombectomy Devices for Ischemic Stroke**

Name of Study ClinicalTrials.gov Identifier	Sponsor(s)	Device(s)	Study Design/ Anticipated Enrollment	Inclusion Criteria	Endpoint(s)	Start/Anticipated Completion Year
MR RESCUE NCT00389467	UCLA	MERCI or Penumbra	RCT (N=120)	18-85 years of age, NIHSS≥6, retrieval started within 8 hours of symptom onset, large vessel occlusion (ICA, MCA M1 or M2), IV rtPA within 4.5 hours of symptom onset allowed, but not required	mRS, NIHSS, global test statistic, hemorrhagic transformation, SAEs, death	2004-2013
PICS NCT00785161	Penumbra, Inc.	Penumbra	Prospective observational (N=2000)	Stroke cohort revascularized with the Penumbra system	TIMI, mRS, NIHSS, ICH, device-related SAEs, death	2009-2014
MERCI Registry NCT00478478	Concentric Medical	MERCI	Prospective observational (N=3000)	Stroke cohort revascularized with the MERCI retrieval system	TIMI, mRS, death, NIHSS, discharge disposition	2009-2014
START NCT00963989	Penumbra, Inc	Penumbra	Prospective, Single-Arm (N=200)	18-85 years of age, NIHSS>10, proximal anterior circulation large vessel (ICA/MCA) occlusion (TIMI 0-1)	mRS, TIMI, procedural SAEs, NIHSS, SICH, AICH, death	2009-2011
PISTE Not Registered	NR	Approved mechanical devices	RCT (N>200)	Acute stroke patients >17 years of age with MCA or ICA occlusion on angiography, treatment within 6 hours of symptom onset	mRS, TIMI, infarct size, HRQoL, cost of care	2009-NR
RETRIEVE Not Registered	Concentric Medical	MERCI	RCT (N=NR)	Acute stroke patients seen within 8 hours of symptom onset	NR	2009-NR

Name of Study ClinicalTrials.gov Identifier	Sponsor(s)	Device(s)	Study Design/ Anticipated Enrollment	Inclusion Criteria	Endpoint(s)	Start/Anticipated Completion Year
SYNTHESIS EXP NCT00640367	Niguarda Hospital	Mechanical thrombolysis	RCT (N=350)	Patients 18-80 years of age, with symptomatic, CT verified, acute ischemic stroke, being able to initiate IV rtPA within 3 hours and IA thrombolysis within 6 hours of stroke onset.	mRS, NIHSS	2008-2010
IMS III* NCT00359424	University of Cincinnati	EKOS or MERCI or Penumbra	RCT (N=900)	18-82 years of age, initiation of IV rtPA within 3 hours of symptom onset, NIHSS≥10 at time of IV rtPA or an NIHSS>7 and <10 with occlusion seen in M1, ICA or basilar artery on CT scan	mRS, death, SICH, AICH Barthel Index, NIHSS	2006-2015

908 AICH=asymptomatic intracerebral hemorrhage; CT=computed tomography; HRQoL=health-related quality-of-life; ICA=internal carotid artery; IMS
909 III=Interventional Management of Stroke Trial III; IV rtPA=intravenous recombinant tissue plasminogen activator; MCA=middle cerebral artery; MR
910 RESCUE=Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; mRS=modified Rankin Scale; NIHSS=National Institutes of Health
911 Stroke Scale; NR=not reported; PICS=Penumbra Imaging Collaborative Study; PISTE=Pragmatic Ischemic Stroke Thrombectomy Evaluation; RCT=randomized
912 controlled trial, RETRIEVE=Randomized Trial of Endovascular Treatment of Acute Stroke Versus Medical Management; SAE=significant adverse event;
913 SICH=symptomatic intracerebral hemorrhage; START=Clinical Outcome in Acute Stroke Treatment After Imaging Guided Patient Selection for Interventional
914 Revascularization Therapy; SYNTHESIS EXP=Intra-Arterial Versus Systematic Thrombolysis for Acute Ischemic Stroke; TIMI=Thrombolysis in Myocardial
915 Infarction; UCLA=University of California Los Angles
916 *IMS III does not directly compare the 3 neurothrombectomy devices, but rather allows operators to choose between them as options for intra-arterial treatment
917 of acute ischemic stroke

2a. Type(s) of devices

Based upon the FDA CDRH's "Guidance for Industry and FDA Staff: Pre-Clinical and Clinical Studies for Neurothrombectomy Devices"[24], a neurothrombectomy device is intended to retrieve or destroy blood clots in the cerebral neurovasculature by mechanical (clot retriever, aspiration/suction, snare-like), laser, ultrasonography technologies or combinations of these technologies. Our literature scan identified at least one report of the use of neurothrombectomy device from each of 5 distinct device classes. **(Table 4)**

Table 4. Devices By Class Evaluated in At Least One Identified Report

Clot Retriever	Aspiration/ Suction	Snare	Ultrasonography	Laser
Attractor-18	AngioJet	Alligator	EKOS	EPAR
Catch	Penumbra System	Amplatz Gooseneck		LaTIS
In-Time		Neuronet		
MERCI		Soutenir		
Phenox		Non-specific device(s)		
TriSpan				

EPAR=Endovascular Photoacoustic Recanalization

2b. Study design and size

Study design

Our literature scan identified a total of 1,308 patients receiving a neurothrombectomy device for the treatment of acute ischemic stroke as part of 82 unique reports. Within the 82 publications/abstracts identified, a total of 94 unique device reports were available since some publications/abstracts reported data on more than one type of device. **Table 2** above details the number of prospective single-arm and retrospective studies, case series and case reports identified for each neurothrombectomy device during our literature scan. The majority (71 of 94, 76 percent) of reports identified were in the form of case series or reports (59 case series or case reports providing details of 71 device reports). Only 16 were prospective, single-arm studies and 7 were non-comparative, retrospective studies enrolling consecutive patients. These studies were published in full-text (74 percent) or abstract (26 percent) form. The oldest eligible report of a neurothrombectomy device was published in 2000. Thirteen of the 23 prospective or retrospective studies (57 percent) were published in either 2008 or 2009. No randomized controlled trials comparing devices to an active control (thrombolytics or other neurothrombectomy device) were identified. However, five randomized controlled trials of neurothrombectomy devices are currently in progress. **(Table 3)** Of these, four are evaluating the use of multiple neurothrombectomy devices, albeit not one device to another. Instead, these studies compare the use of neurothrombectomy devices to best medical therapy (with or without IV rtPA). The largest percentage of overall reports (38 of 94, 40 percent) and prospective studies (5 of 16, 31 percent) were for the MERCI clot retriever. The Penumbra System had a total of nine reports describing its use, of which three (33 percent of all Penumbra reports) were

prospective in nature. For the "off-label" devices (all but MERCI and Penumbra) studied, the number of prospective studies in rank order from highest to lowest was EKOS (N=2), followed by AngioJet, Phenox, Amplatz Gooseneck, Neuronet, EPAR and LaTIS lasers (all had a N=1). The number of any type of report methodology by device (including prospective, retrospective, and case series/report) can be viewed in **Table 2**.

For studies, we also collected data on whether key effectiveness and/or safety data were assessed by a blinded investigator or in a core laboratory (as recommended in the FDA CDRH's guidance document).[24] Only 3 of 16 (19 percent) prospective and 1 of 7 (14 percent) of retrospective studies clearly stated they utilized blinded outcome assessment.

Sample size

Figure 3 summarizes all identified reports of neurothrombectomy devices by device classification. It provides the total number of patients treated with each device class as well as the study design utilized and endpoint(s) evaluated.

In rank order by total number of patients evaluated from highest to lowest, clot retrievers (n=748) were the most common device classification studied, followed by aspiration or suction devices (n=383), snare-like devices (n=94), ultrasonography technologies (n=50) and lasers (n=36).

Figure 3. Effectiveness Evidence for Neurothrombectomy Devices (n=1,311)

	Devices*				
Reported Outcomes	Clot Retriever (n=748)	Aspiration/ Suction (n=383)	Snare (n=94)	Ultrasound Technology (n=50)	Laser (n=36)
Recanalization	N=744 NS=6/4/32	N=380 NS=4/3/9	N=88 NS=2/0/24	N=36 NS=1/0/1	N=36 NS=2/0/0
mRS	N=440 NS=5/1/11	N=374 NS=4/3/3	N=45 NS=2/0/9	N=15 NS=1/0/1	N=34 NS=1/0/0
Death#	N=450 NS=5/1/16	N=379 NS=4/3/6	N=65 NS=2/0/9	N=14 NS=1/0/0	N=34 NS=1/0/0
NIHSS	N=371 NS=3/0/15	N=358 NS=3/3/4	N=65 NS=2/0/11	N=14 NS=1/0/0	N=34 NS=1/0/0
BI	No Data	No Data	N=5 NS=1/0/0	N=14 NS=1/0/0	No Data
GOS	No Data	No Data	No Data	N=14 NS=1/0/0	No Data

BI=Barthel Index; GOS=Glasgow Outcome Scale; mRS=modified Rankin Scale; n=the total number of patients evaluated for any effectiveness or safety endpoint; N=number of patients evaluated; NIHSS=National Institutes of Health Stroke Scale; NS=number of evaluations categorized as Prospective/Retrospective/Case Series or Reports
#Death included if patients were followed-up for any duration of time after hospital-discharge

Narrative for Figure 3:

This figure defines the number of patients being treated with one of five classes of neurothrombectomy device (clot retriever, aspiration/suction, snare, ultrasound technology, or laser) that were evaluated for the following effectiveness outcomes: recanalization, modified Rankin Scale, death, National Institutes of Health Stroke Scale, Barthel Index, and Glasgow

Outcome Scale. Out of 748 patients being treated with a clot retriever (including the Attractor-18, Catch, In-Time retrieval device, MERCI retrieval system, Phenox Clot Retriever, and TriSpan), 744, 440, 450, and 371 patients were evaluated for recanalization, modified Rankin Scale, death, and National Institutes of Health Stroke Scale, respectively. Out of 383 patients being treated with an aspiration/suction device [AngioJet (including Xpeedior) and Penumbra System], 380, 374, 379, and 358 patients were evaluated for recanalization, modified Rankin Scale, death, and National Institutes of Health Stroke Scale, respectively. Out of 94 patients being treated with a snare device (Alligator, Amplatz Gooseneck, Neuronet endovascular snare, and Soutenir microsnare), 88, 45, 65, 65, and 5 patients were evaluated for recanalization, modified Rankin Scale, death, National Institutes of Health Stroke Scale, and Barthel Index, respectively. Out of 50 patients being treated with an ultrasound technology device (EKOS), 36, 15, 14, 14, 14, and 14 patients were evaluated for recanalization, modified Rankin Scale, death, National Institutes of Health Stroke Scale, Barthel Index, and Glasgow Outcome Scale, respectively. Out of 36 patients being treated with a laser device (EPAR and LaTIS), 36, 34, 34, and 34 patients were evaluated for recanalization, modified Rankin Scale, death, and National Institutes of Health Stroke Scale, respectively.

The size of prospective single-arm studies ranged from 2 to 164 patients, and retrospective studies ranged from 15 to 114 patients. **(Table 5)** The largest studies were those evaluating the MERCI clot retriever (numbers ranged from 18 and 164 patients) and the Penumbra System (numbers ranged from 15 to 125 patients). Both these devices had relatively large (>100 patients) clinical studies and "real-world" (retrospective) evaluations. Ongoing prospective observational studies plan to collect data on 2,000 to 3,000 additional patients utilizing each these two devices. Eight prospective studies (no retrospective studies) of various "off-label" neurothrombectomy devices were identified. Two evaluated an EKOS ultrasonography technology (numbers ranging from 14 to 35 patients). The six remaining studies each evaluated a different "off-label" device. The largest of these studies enrolled 45 patients and the smallest study enrolled only two.

1026 **Table 5. Distribution (Median and Range) of Sample Sizes for Prospective and**
1027 **Retrospective Studies for Each Neurothrombectomy Device**

		Study Design			
		Prospective, Single-Arm		Non-Comparative Retrospective*	
Device Class	No. of Reports (Prospective, Single-Arm/ Non-Comparative Retrospective*)	Median N	Range of N	Median N	Range of N
Aspiration/Suction					
AngioJet	1 (1/0)	12	-	-	-
Penumbra	6 (3/3)	29	23 to 125	53	15 to 105
Clot Retriever					
MERCI	9 (5/4)	30	24 to 164	44	18 to 114
Phenox	1 (1/0)	45	-	-	-
Ultrasonography					
EKOS	2 (2/0)	25	14 to 35	-	-
Snare					
Amplatz Gooseneck	1 (1/0)	9	-	-	-
Neuronet	1 (1/0)	5	-	-	-
Laser					
EPAR	1 (1/0)	34	-	-	-
LaTIS	1 (1/0)	2	-	-	-

1028 EPAR=Endovascular Photoacoustic Recanalization, N=number of patients
1029 *Must have enrolled consecutive patients
1030
1031 The remaining 71 of 94 (76 percent) identified reports, representing 59 of 82 (72 percent)
1032 unique citations, were either case series or case reports. In total, 191 patients were evaluated
1033 with a neurothrombectomy device in these case series or case reports. The number of patients
1034 receiving each neurothrombectomy device in a case series or case report as well as the combined
1035 number is depicted in **Table 6**. The combined number of patients evaluated in a case series or
1036 report with a neurothrombectomy device ranged from 0 (EPAR and LaTIS lasers) up to 75. As
1037 with the prospective and retrospective studies, the MERCI clot retriever was the most commonly
1038 evaluated (n=75 patients in 29 reports). Case series and reports provide the majority of data on
1039 "off-label" use (n=109 patients in 39 reports) of potential neurothrombectomy devices to treat
1040 acute ischemic stroke.
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Table 6. Distribution of Sample Sizes (Total number of patients and Range) in Case Series and Reports for Each Neurothrombectomy Device

		Study Design		
		Case Series	Case Reports	
Device Class	No. Reports (Case Series/ Case Reports)	Total Patients N	Total Patients N	Combined Total N
Aspiration/Suction				
AngioJet	7 (3/4)	10	4	14
Penumbra	3 (1/2)	5	2	7
Clot Retriever				
Attractor-18	1 (0/1)	-	1	1
Catch	1 (1/0)	2	-	2
In-Time	2 (1/1)	2	1	3
MERCI	29 (12/17)	58	17	75
Phenox	1 (1/0)	2	-	2
TriSpan	1 (1/0)	6	-	6
Ultrasonography				
EKOS	1 (0/1)	-	1	1
Snare				
Alligator	3 (1/2)	6	2	8
Amplatz Gooseneck	10 (6/4)	29	4	33
Neuronet	5 (1/4)	4	4	8
Device Not Specified	5 (4/1)	27	1	28
Soutenir	2 (1/1)	2	1	3
Laser				
EPAR	-	-	-	-
LaTIS	-	-	-	-

EPAR=Endovascular Photoacoustic Recanalization, N=number of patients, No.=number

2c. Patient characteristics

Both prospective and retrospective studies typically enrolled patients >18 years of age, with baseline NIHSS scores≥8 (or ≥10), presenting within 8 hours of stroke symptom onset (or up to 24 hours for EKOS, EPAR or LaTIS laser if a posterior circulation occlusion was identified) and having a complete or near complete (TIMI 0-1)[24] occlusion of a treatable large, intracranial vessel. Common exclusion criteria included advanced age (>80 years of age), large brain infarction, high risk of bleeding (including prothrombin time>15 seconds, hemorrhagic diathesis, coagulation factor deficiency, oral anticoagulation with international normalized ratio (INR)>3, use of heparin with partial thromboplastin time >2 times normal, platelets <30,000), severe or uncontrolled hypertension, glucose <50 mg/dL, and pregnancy. Studies also enrolled patients with contraindications to receive IV rtPA due to risks of adverse events (i.e., ICH), those reporting outside a 3-hour window (standard for studies at that time) from symptom onset to IV rtPA, or who failed (target vessel not recanalized as determined by immediate angiography following the procedure) IV rtPA treatment. The one exception was the EKOS study by Tomsick in 2008. The EKOS device is designed to infuse IA thrombolytic therapy, and in this study, the EKOS (Primo) device was used along with reduced dose IV rtPA within the first 3-

hours of stroke symptoms. **Tables 1D to 3D** can be found in **Appendix D** and detail study-specific inclusion and exclusion criteria for prospective and retrospective studies.

Tables 7 and 8 below summarize key patient characteristics including age, gender, baseline NIHSS, symptom-to-angiography or device time and location of embolus/occlusion for studies which provided data. As a result of these inclusion/exclusion criteria, the mean/median baseline NIHSS range was fairly narrow across studies, ranging from 15 to 23. The range for mean/median age was 42 to 68 years, and studies enrolled between 20 percent and 57 percent females. In studies where data were provided, the majority of patients had pre-device TIMI 0 or 1 flow. Mean/median stroke symptom-to either angiography or device deployment time ranged from 141 to 388 minutes; all studies had a mean/median intervention time within the 8 hour time frame suggested by the FDA CDRH guidance for deploying a neurothrombectomy device.[24] The location of the primary embolus was most commonly in an anterior vessel (14 studies enrolled >60 percent anterior occlusion patients. However, some studies focused heavily on posterior (vertebral and/or basilar) occlusions (two studies enrolled 100 percent vertebral or basilar occlusions). While we characterized studies by the proportion of anterior and posterior circulation lesions, it is important to note that not all anterior or posterior circulation leasuions pose the same risk of stroke severity (e.g., while both classified as anterior, a more proximal occlusion in the distal ICA (carotid 'T') generally poses a higher risk than a smaller, more peripheral MCA-branch lesion). Six studies were unclear about the location of occlusion. A limited number of patients with occlusions in other areas of the cerebral circulation were included in studies. Only 1 of 23 (4 percent) studies reported including patients with occlusions in these other areas.

Summarized in **Tables 9 and 10** are baseline characteristics and location of embolic occlusions for patients studied in case series and case reports. While the majority of case series and case reports included patients that would typically meet prospective study inclusion criteria, a few enrolled patients outside these norms. Case series and reports included both pediatric patients and those greater than 80 years of age (case series/report age range: 6 to 90 years), both which were excluded in prospective and retrospective studies. Furthermore, a small number of case series and reports enrolled patients with baseline NIHSS scores below the typical enrollment threshold of 8 to 10 (case series/report NIHSS range: 0 to 42). Finally, some case series and reports for the Penumbra System, MERCI clot retriever, TriSpan clot retriever, In-Time clot retriever, and Neuronet and Amplatz Gooseneck snares, enrolled patients with symptom-to-angiography or device deployment times outside the 8 hour (480 minute) window used in prospective and retrospective studies of these devices (maximum time range was 1,200 minutes). Only studies of the EKOS, EPAR or LaTIS laser devices have utilized a device in patients with such prolonged symptom times (up to 24 hours from symptom onset), and only in patients with posterior occlusions.

The location of emboli reported in evaluable patients (n=156) assessed in case series and case reports was predominantly in the anterior circulation (72 percent), followed by the posterior circulation (24 percent), and in other parts of the neurovasculature (4 percent).

1112 **Table 7. Distribution (Median and Range) of Patient Ages, Baseline NIHSS, Gender and Symptom-to-Angiography or Device**
1113 **Deployment Time for Each Neurothrombectomy Device in Prospective and Retrospective Studies**

Device Class	No. of Reports (Prospective, Single-Arm/ Non-Comparative Retrospective#)	Mean or Median Age		Mean or Median NIHSS		Mean or Median Female (percent)		Mean or Median Symptom-to-Angiography or Device Deployment Time (minutes)	
		Median	Range	Median	Range	Median	Range	Median	Range
Aspiration/Suction									
AngioJet	1 (1/0)	56	-	20	-	25	-	-	-
Penumbra*	6 (3/3)	62	58 to 66	18	15 to 21	48	40 to 55	180	141 to 312
Clot Retriever									
MERCI*	9 (5/4)	65	63 to 68	19	18 to 22	44	36 to 57	301	258 to 312
Phenox*	1 (1/0)	-	-	-	-	-	-	-	-
Ultrasonography									
EKOS*	2 (2/0)	64	-	18	-	50	-	331	-
Snare									
Amplatz Gooseneck	1 (1/0)	55	-	16	-	-	-	251	-
Neuronet	1 (1/0)	42	-	20	-	20	-	388	-
Laser									
EPAR	1 (1/0)	68	-	19	-	50	-	382	-
LaTIS*	1 (1/0)	-	-	23	-	-	-	375	-

1114 EPAR=Endovascular Photoacoustic Recanalization; No.=number
1115 *Data not reported in all studies for all characteristics
1116 #Must have enrolled consecutive patients

1117 **Table 8. Distribution (Median and Range) of Emboli Location for Each Neurothrombectomy Device in Prospective and**
1118 **Retrospective Studies[#]**

Device Class	No. of Reports (Prospective, Single-Arm /Non-Comparative Retrospective[#])	Anterior Circulation Occlusion (percent)		Posterior Circulation Occlusion (percent)		Other Occlusion (percent)	
		Median	Range	Median	Range	Median	Range
Aspiration/Suction							
AngioJet	1 (1/0)	0	-	100	-	0	-
Penumbra*	6 (3/3)	80	57 to 88	20	9 to 43	0	0 to 3[‡]
Clot Retriever							
MERCI*	9 (5/4)						
Phenox*	1 (1/0)	65	-	27[†]	-	-	-
Ultrasonography							
EKOS*	2 (2/0)	71	-	29	-	0	-
Snare							
Amplatz Gooseneck	1 (1/0)	67	-	33	-	0	-
Neuronet	1 (1/0)	0	-	100	-	0	-
Laser							
EPAR	1 (1/0)	65	-	35	-	0	-
LaTIS*	1 (1/0)	100	-	0	-	0	-

1119 EPAR=Endovascular Photoacoustic Recanalization; No.=number
1120 *Data not reported in all studies for all characteristics
1121 #Must have enrolled consecutive patients
1122 [†]8% of occlusions were combined anterior and posterior
1123 [‡]Other may include occlusions anywhere outside of the ICA, MCA, vertebral or basilar locations
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1133 **Table 9. Distribution of Patient Ages, Baseline NIHSS, Gender and Symptom-to-Angiography or Device Deployment Time for**
1134 **Each Neurothrombectomy Device in Case Series and Case Reports**

Device Class	No. of Reports (Case Series/Case Reports)	Age (years)	Baseline NIHSS	Female	Symptom-to-Angiography or Device Deployment Time (minutes)
		Range	Range	n (percent)	Range
Aspiration/Suction					
AngioJet	7 (3/4)*	14 to 84	19 to 25	8 (62)	10 to 270
Penumbra	3 (1/2)	28 to 59	15 to 42	2 (29)	120 to 780
Clot Retriever					
Attractor-18	1 (0/1)	72 to 72	12 to 12	0 (0)	380 to 380
Catch	1 (1/0)	-	-	-	-
In-Time	2 (1/1)*	16 to 72	14 to 28	1 (33)	300 to 720
MERCI	29 (12/17)*	6 to 90	6 to 40	24 (60)	120 to 1020
Phenox	1 (1/0)	70 to 78	-	0 (0)	-
TriSpan	1 (1/0)	43 to 72	20 to 28	3 (50)	240 to 1200
Ultrasonography					
EKOS	1 (0/1)	19 to 19	15 to 15	1 (100)	-
Snare					
Alligator	3 (1/2)*	50 to 84	0 to 25	2 (100)	60 to 480
Amplatz Gooseneck	10 (6/4)	37 to 90	10 to 30	16 (48)	60 to 600
Neuronet	5 (1/4)*	7 to 48	13 to 24	3 (75)	360 to 600
Device Not Specified	5 (4/1)*	33 to 79	7 to 27	4(40)	240 to 354
Soutenir	2 (1/1)	49 to 78	19 to 33	0 (0)	190 to 230
Laser					
EPAR	-	-	-	-	-
LaTIS	-	-	-	-	-

1135 EPAR=Endovascular Photoacoustic Recanalization; n=number of patients; No.=number
1136 *Data not reported in all studies for all characteristics
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1143 **Table 10. Distribution of Emboli Location for Each Neurothrombectomy Device in Case Series and Case Reports**

Device Class	No. of Reports (Case Series/ Case Reports)	Anterior Circulation Occlusion n (percent)#	Posterior Circulation Occlusion n (percent)#	Other Occlusion n (percent)#
Aspiration/Suction				
AngioJet	7 (3/4)	14 (50)	1 (7)	6 (43)
Penumbra	3 (1/2)	4 (57)	3 (43)	0
Clot Retriever				
Attractor-18	1 (0/1)	1 (100)	0	0
Catch	1 (1/0)	2 (100)	0	0
In-Time	2 (1/1)	0	3 (100)	0
MERCI*	29 (12/17)	50 (82)	10 (16)	1 (2)
Phenox	1 (1/0)	1 (50)	1 (50)	0
TriSpan	1 (1/0)	0	6 (100)	0
Ultrasonography				
EKOS	1 (0/1)	1 (100)	0	0
Snare				
Alligator	3 (1/2)	8 (100)	0	0
Amplatz Gooseneck*	10 (6/4)	14 (58)	10 (42)	0
Neuronet*	5 (1/4)	2 (50)	2 (50)	0
Device Not Specified*	5 (4/1)	12 (92)	1 (8)	0
Soutenir	2 (1/1)	3 (100)	0 (0)	0
Laser				
EPAR	-	-	-	-
LaTIS	-	-	-	-

1144 n=number of patients; No.=number
1145 *Data not reported in all studies for all characteristics
1146 # Includes only patients with reported data; 3 patients had two device types deployed during a single event
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2d. Comparator used in comparative studies

No direct *in vivo* comparative studies were identified during our scan of the neurothrombectomy literature. Existing direct device-to-device comparisons have come in the form of *in vitro* or animal studies and are outside the scope of this technical brief.[33,34] Ongoing studies are underway that are allowing the use of multiple neurothrombectomy devices; however, none appear to be designed to compare one device to another. Instead, these studies compare the use of neurothrombectomy devices to best medical therapy (with or without IV rtPA).

Nogueira and colleagues[35] compared the percentage of patients experiencing a good outcome (defined using the mRS) in several neurothrombectomy studies to those of IV or IA rtPA arms of other studies. Good outcomes occurred in 28 percent, 36 percent, and 25 percent of patients receiving neurothrombectomy therapy (mRS≤2) in the MERCI[36], Multi-MERCI[37], and Penumbra Pivotal Stroke Trial[38] as compared to 39 percent , 52 percent, and 40 percent of patients in the NINDS rtPA[16], ECASS III[18], and PROACT II[39] studies (mRS<2), respectively, despite higher rates of successful recanalization as compared to those receiving IV or IA rtPA. Patients receiving neurothrombectomy device therapy also exhibited higher rates of mortality. The authors postulated, however, that differences between patient populations across studies such as clot location and burden, baseline stroke severity, and time from symptom onset to treatment may have driven these differences, not the inferiority of neurothrombectomy devices. Moreover, changes in standards of stroke care over time may have played a role as well.

In one study, patients (n=121) from the IA thrombolytic arm of the PROACT II trial were compared only to patients (n=142) in the neurothrombectomy arms of the MERCI and Multi-MERCI trials who would have been eligible had they enrolled in PROACT II.[40] By selecting and analyzing only comparable patients, similar rates of good outcome and mortality resulted. This supports the hypothesis that differences in study design and baseline patient characteristics between rtPA and neurothrombectomy trials account for differences in outcomes. Based upon findings such as these, we caution reviewers or decision makers against making indirect comparisons between studies of different recanalization strategies in an attempt to determine their comparative effectiveness or safety.

2e. Length of follow-up

The FDA CDRH guidance document for neurothrombectomy devices suggests that recanalization success should be assessed following the procedure, and that clinical effectiveness should be assessed at 30- and 90-days.[24] All studies reported recanalization success after neurothrombectomy device deployment. The longest duration of follow-up in the majority of studies reporting effectiveness outcomes (i.e., mRS or death) was either 30- or 90-days post-procedure. **(Table 11)** The timing of NIHSS evaluation was more variable with the longest duration of follow-up ranging from 24-hour to 90-days post-procedure. Safety endpoints were typically monitored over shorter lengths of time, such as the first 24-hours or until discharge.

The reporting of follow-up outcomes in case series and case reports was variable. Of the 71 total device reports, nearly half did not report data on effectiveness or safety outcomes after patient discharge. In those reports that did, length of follow-up ranged from 6 weeks to 24 months; the most commonly reported length of follow-up was 90-days.

1192 **Table 11. Longest Duration of Follow-Up in Prospective, Single-Arm or Retrospective Studies of Neurothrombectomy**
1193 **Devices**

Device	Outcome Reporting at 30-Days			Outcome Reporting at 90-Days			Outcome reporting at Other Times		
	NIHSS*	mRS≤2	Death	NIHSS	mRS≤2	Death	NIHSS	mRS≤2	Death
Aspiration/Suction									
AngioJet (No.=1)	-	-	-	-	No.=1	No.=1	-	-	-
Penumbra (No.=6)	No.=3	No.=2	No.=2	-	No.=4	No.=4	No.=3	-	-
Clot Retriever									
MERCI (No.=9)	-	No.=1	No.=1	No.=1	No.=4	No.=4	No.=1	-	-
Phenox (No.=1)	-	-	-	-	-	-	-	-	-
Ultrasonography									
EKOS (No.=2)	-	-	-	No.=1	No.=1	No.=1	-	-	-
Snare									
Amplatz Gooseneck (No.=10)	-	-	-	No.=1	No.=1	No.=1	-	-	-
Neuronet (No.=1)	-	-	-	No.=1	No.=1	No.=1	-	-	-
Laser									
EPAR (No.=1)	No.=1	No.=1	No.=1	-	-	-	-	-	-
LaTIS (No.=1)	-	-	-	-	-	-	-	-	-

1194 EPAR=Endovascular Photoacoustic Recanalization; mRS=modified Rankin scale; NIHSS=National Institutes of Health Stroke Scale; No.=number of studies
1195 *Includes any method of reporting of NIHSS (i.e., NIHSS decrease ≥4, 50% drop, NIHSS 0-1 or improved by at least 10-points at discharge, etc.)
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2f. Prior or concurrent therapy

Based upon the NINDS rtPA Stroke Study results[16], IV rtPA treatment has become the standard-of-care treatment for those with acute ischemic stroke presenting within 3 hours (up to 4.5 hours in some patients) of symptom onset.[21] Neurothrombectomy studies identified have thus focused, through inclusion and exclusion criteria, on either patients contraindicated to receive IV rtPA due to risks of adverse events (i.e., ICH), those presenting outside the recommended 3 hour window, or who were refractory or failed IV rtPA treatment. Consequently, the use of IV rtPA among studies ranged from 0 percent (studies required patients be ineligible) to 100 percent (studies required patients to have failed IV rtPA therapy prior to enrollment). The adjunctive use of thrombolysis in prospective or retrospective studies of neurothrombectomy devices is depicted in **Table 12.**

The one exception was the EKOS study by Tomsick in 2008.[41] The EKOS device is designed to infuse IA thrombolytics and in this study, the EKOS (Primo) device was used along with reduced dose IV rtPA within the first 3 hours of stroke symptoms.

Concurrent or rescue therapies in identified studies, case series and reports included IA thrombolytics, cerebral artery angioplasty and stenting. In most studies, the decision to use these strategies was left to the discretion of the investigator/treating neurologist.

1242 **Table 12. Adjunctive Thrombolysis Use in Prospective, Single-Arm or Retrospective**
1243 **Studies of Neurothrombectomy Devices**

Device Class	No. of Reports (Prospective, Single-Arm/ Non-Comparative Retrospective*)	Intravenous Thrombolysis n/N (percent)	Intra-arterial Thrombolysis n/N (percent)
Aspiration/Suction			
AngioJet	1 (1/0)	0/12 (0)	5/12 (42)
Penumbra	6 (3/3)	88/225 (39)#	110/297 (37)†
Clot Retriever			
Attractor-18	-	-	-
Catch	-	-	-
In-Time	-	-	-
MERCI	9 (5/4)	53/446 (12)‡	95/614 (15)
Phenox	1 (1/0)	NR	NR
TriSpan	-	-	-
Ultrasonography			
EKOS	2 (2/0)	35/49 (71)	49/49 (100)
Snare			
Alligator	-	-	-
Amplatz Gooseneck	1 (1/0)	0/9 (0)	4/9 (44)
Neuronet	1 (1/0)	0/5 (0)	3/5 (60)
Soutenir	-	-	-
Device Not Specified	-	-	-
Laser			
EPAR	1 (1/0)	1/34 (3)	16/34 (47)
LaTIS	1 (1/0)	0/2 (0)	0/2 (0)

1244 n = number of patients receiving therapy; N = number of evaluable; No.=number
1245 * Must have enrolled consecutive patients
1246 # One out of six studies did not report data (PPST, 2009)
1247 † One of six studies did not report data (Frei, 2009)
1248 ‡ Two of nine studies did not report data (Madison, 2008; Jo, 2008)
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2g. Effectiveness outcomes measured

The FDA CDRH guidance document suggests that recanalization success be assessed using TIMI grading of flow after treatment with a neurothrombectomy device.[24] While recanalization is considered an intermediate outcome, there is an abundance of data demonstrating that achieving recanalization results in favorable final health outcomes. In a meta-analysis of 53 studies encompassing over 2,000 patients, Rha and colleagues demonstrated that at 3 months, favorable functional outcomes were more frequent in recanalized versus non-recanalized patients (OR 4.43, 95 percent CI 3.32 to 5.91), and mortality was reduced (OR 0.24, 95 percent CI 0.16 to 0.35).[42] Furthermore, the guidance document recommends that clinical effectiveness should be assessed using a validated neurologic impairment scale, disability measure, or handicap scale. Examples of appropriate measures include the mRS, NIHSS score, Barthel Index, and GOS.[24]

Figure 3, previously referenced and provided above, summarizes all identified reports of neurothrombectomy devices by device classification and the effectiveness endpoint(s) evaluated. The figure uses a density-shading scheme, so that the most common effectiveness endpoints have the greatest degree of shading. The figure demonstrates that recanalization, mRS, NIHSS, and death are the most commonly assessed endpoints. Despite being listed in the CDRH's guidance document,[24] few reports assessed the Barthel Index or GOS.

Recanalization success was typically defined as establishment of TIMI grade II (partial) or III (complete) flow within the target (or all) vessels upon angiography following the procedure. A newer cerebral grading scale (the Thrombolysis in Cerebral Infarction or TICI scale) was used far less frequently, as were neuroimaging measures (e.g., final stroke lesion size and perfusion neuroimaging technologies). All prospective or retrospective studies reported recanalization results. **Figures 1E to 3E** in **Appendix E** depict the proportion of patients achieving partial or complete recanalization in these studies. The figures are stratified by device, with separate figures for each of the FDA-approved devices (Penumbra System and MERCI clot retriever) and for "off-label" devices.

The NIHSS score was often assessed in reports of neurothrombectomy devices, with a decrease of 4 points commonly defined as a clinically important improvement in neurological outcome.[24] NIHSS outcome data, in some form, was presented in 12 of 23 (52 percent) identified prospective or retrospective studies. For studies assessing clinical effectiveness using mRS, successful treatment was typically defined as the proportion of patients having a 'good' outcome (score of 0-2). Individual study achievement of mRS≤2 was presented in 16 of 23 (70 percent) studies. **Tables 1E to 3E** in **Appendix E** depict the results of prospective or retrospective studies for the NIHSS, mRS≤2, as well as mortality after discharge endpoints. These effectiveness endpoints were reported in 22 percent, 56 percent and 56 percent of MERCI clot retriever, 100 percent, 100 percent and 100 percent of Penumbra System, and 50 percent, 50 percent and 63 percent of "off-label" device studies. As with recanalization, results are stratified by device, with separate figures for each of the FDA-approved devices (Penumbra System and MERCI clot retriever) and for "off-label" devices.

Identified ongoing studies appear to be collecting data on effectiveness/efficacy endpoints recommended in the FDA CDRH guidance document and similar to those assessed in completed studies.

2h. Adverse events, harms and safety issues reported

Current guidance suggests numerous different adverse event endpoints to be recorded in evaluations of neurothrombectomy devices.[24] **Figure 4** below summarizes all identified reports of neurothrombectomy devices by device classification and the safety endpoint(s) evaluated. As with the effectiveness figure above, this figure uses a density-shading scheme so that the most common endpoints have the greatest degree of shading. The figure demonstrates that ICH, either symptomatic or asymptomatic, was the most commonly assessed adverse event, harm or safety issue. Other safety endpoints evaluated in the neurothrombectomy literature included: perforation/dissection, other types of hemorrhage (not intracerebral), thrombus formation proximal, adjacent or distal to the clot site, failure to deploy the device, device breakage/fracture and vasospasm. **Tables 4E to 6E** in **Appendix E** depict the proportion of patients per study experiencing an instance of symptomatic or asymptomatic ICH, other bleeding, perforation or dissection or thrombus formation in prospective or retrospective studies. These safety endpoints were reported in 56 percent, 56 percent, 22 percent, 22 percent and 22 percent of MERCI clot retriever, 100 percent, 83 percent, 33 percent, 50 percent and 50 percent of Penumbra System, and 63 percent, 38 percent, 0 percent, 63 percent and 38 percent of "off-label" device studies, respectively. In addition, **Table 7E** in **Appendix E** provides data on the rate of device failure-to-deploy and device fracture or breakage in these same studies. These were infrequently reported in device reports, as were data on vasospasm.

Identified ongoing studies appear to be collecting data on adverse event endpoints similar to those assessed in completed studies.

Figure 4. Safety Endpoint Evidence for Neurothrombectomy Devices (n=1,311)

Reported Adverse Events	Devices*				
	Clot Retriever (n=748)	Aspiration/ Suction (n=383)	Snare (n=94)	Ultrasound Technology (n=50)	Laser (n=36)
SICH	N=421 NS=5/0/8	N=369 NS=4/3/3	N=44 NS=1/0/10	N=49 NS=2/0/0	N=34 NS=1/0/0
AICH	N=421 NS=5/0/8	N=354 NS=4/2/3	N=44 NS=1/0/10	No Data	N=34 NS=1/0/0
Perforation/ Dissection	N=182 NS=2/0/2	N=186 NS=3/1/2	N=28 NS=1/0/4	N=49 NS=2/0/0	N=34 NS=1/0/0
Thrombus Formation	N=184 NS=2/0/4	N=176 NS=3/1/1	N=21 NS=2/0/3	No Data	No Data
Other Hemorrhage	N=191 NS=2/0/4	N=38 NS=1/1/0	N=13 NS=0/0/3	No Data	No Data

AICH=asymptomatic intracerebral hemorrhage; n=the total number of patients evaluated for any effectiveness or safety endpoint; N=number of patients evaluated; NS=number of evaluations (Prospective/Retrospective/Case Series or Reports); SICH=symptomatic intracerebral hemorrhage

Narrative for Figure 4:

This figure defines the number of patients being treated with one of five classes of neurothrombectomy device (clot retriever, aspiration/suction, snare, ultrasound technology, or laser) that were evaluated for the following adverse events: symptomatic ICH, asymptomatic ICH, perforation/dissection, thrombus formation, or other hemorrhage. Out of 748 patients being treated with a clot retriever (including the Attractor-18, Catch, In-Time retrieval device, MERCI retrieval system, Phenox Clot Retriever, and TriSpan), 421, 421, 182, 184, and 191 patients were evaluated for symptomatic ICH, asymptomatic ICH, perforation/dissection, thrombus formation, or other hemorrhage, respectively. Out of 383 patients being treated with an aspiration/suction device [AngioJet (including Xpeedior) and Penumbra System], 369, 354, 186, 176, and 38 patients were evaluated for symptomatic ICH, asymptomatic ICH, perforation/dissection,

thrombus formation, or other hemorrhage, respectively. Out of 94 patients being treated with a snare device (Alligator, Amplatz Gooseneck, Neuronet endovascular snare, and Soutenir microsnare), 44, 44, 28, 21, and 13 patients were evaluated for symptomatic ICH, asymptomatic ICH, perforation/dissection, thrombus formation, or other hemorrhage, respectively. Out of 50 patients being treated with an ultrasound technology device (EKOS), 49 and 49 patients were evaluated for symptomatic ICH and perforation/dissection. Out of 36 patients being treated with a laser device (EPAR and LaTIS), 34, 34, and 34 patients were evaluated for symptomatic ICH, asymptomatic ICH, or perforation/dissection, respectively.

Key Question 3

What are the variables associated with use of the devices that may impact outcomes (e.g. time to deployment, training/expertise of interventionalist, location of infarct, concurrent therapies)?

Results of univariate and multivariate analyses reported in identified prospective and retrospective studies were used to answer Key Question 3. The effects of predictor variables reported by authors of studies on select outcomes (effectiveness and adverse events) are summarized in **Table 13**.[36-38,43-45,47] Predictors are classified as to whether they were found to have beneficial (and statistically significant), harmful (and statistically significant) or indeterminate (not statistically significant regardless of effect direction) effects on outcomes. It is important to note that because these predictors were derived from single-arm (uncontrolled) studies, similar relationships may have been observed in these patients even if they were not treated with a neurothrombectomy device (that is to say, similar predictors are likely to be identified in a similar patient population not receiving neurothrombectomy devices).

1390 **Table 13. Effect of Various Variables on Post-Neurothrombectomy Device Outcomes**

	Clinical Outcomes				
Predictor Variables	**Recanalization**	**NIHSS Improvement**	**Hemorrhage***	**mRS≤2**	**Death**
Older Age[36,43]	-	-	-	H	H
Higher SBP[36,43]	-	-	-	H	H
Higher Baseline NIHSS[36,38,43]	I	-	-	H	H
ICA Occlusion Site (vs. mostly MCA)[37,38,43]	I	-	-	I	H
Abnormal Hemostasis[44#]	I	-	I	H	I
Prior IV rtPA[37]	I	-	I	I	I
Concomitant IA thrombolytics[37,45]	B	-	I	I	I
Prior Stroke[38]	-	-	-	-	H
Longer Procedure Duration[36,38]	-	-	-	H	I
Right Brain Infarct[36]	-	-	-	H	-

1391 B=beneficial; H=harmful; I=indeterminate (no statistically significant effect); IA=intra-arterial; ICA=internal
1392 carotid artery; IV rtPA=intravenous recombinant tissue plasminogen activator; MCA=middle cerebral artery;
1393 mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; SBP=systolic blood pressure
1394 *including symptomatic and asymptomatic hemorrhage
1395 #INR>1.7, PTT>45 and/or platelet count <100,000
1396
1397 Evaluated predictors of outcome (**Table 13**) in these patients treated with a
1398 neurothrombectomy device include demographic, co-morbid disease, stroke severity and stroke
1399 treatment variables. These predictors were evaluated in studies (or pooled analyses) of the
1400 MERCI clot retriever and the Penumbra System. In addition to the variables listed in **Table 13**,
1401 researchers have suggested that the presence of collateral circulation, lesion volume and cerebral
1402 perfusion pressure have also been linked to outcomes in acute ischemic stroke patients.[35]
1403 In a meta-analysis by Stead and colleagues published in 2008 evaluating available data
1404 on neurothrombectomy devices at that time, younger age and lower NIHSS score at presentation
1405 had beneficial effects on achieving a mRS≤2 (p=0.001).[31] Conversely, patients with posterior
1406 circulation occlusions were found to have higher odds of 90-day mortality compared to those
1407 with anterior occlusions (either internal carotid or middle cerebral arteries). No other outcomes
1408 were affected by occlusion location. Time to mechanical intervention/deployment and
1409 concurrent thrombolytic administration was not associated with either mortality or attainment of
1410 mRS≤2.

No studies provided data assessing the relationship between the training of interventionalists and outcomes in patients treated with neurothrombectomy devices. However, studies of emerging technologies over the past 20 years have suggested that inadequate physician training and experience can adversely affect clinical outcomes.[46] Of note, upon qualitative review, the proportion of patients recanalized in retrospective studies did not appear to be lower than that of the prospective, single-arm studies, for either MERCI or Penumbra System studies. These findings may be, at least partially, a result of some of the prospective, investigational studies not requiring interventionalists to have treated patients outside of the trial before being able to enroll patients within the trial.[37]

A report was written and approved by multiple neuroscience societies (including the Society of NeuroInterventional Surgery; American Academy of Neurology; American Association of Neurological Surgeons, Cerebrovascular Section; and Society of Vascular & Interventional Neurology) representing practitioners involved in the medical, surgical, and endovascular care of patients with acute stroke. In this report the minimum training requirements for those performing neuroendovascular procedures (including the use of neurothrombectomy devices) in patients with acute ischemic stroke and performance standards that should be adopted to assess outcomes have been detailed.[46] Specifically, in regards to neurothrombectomy devices, they suggest the operator: (1) Completes an accredited [Accreditation Council for Graduate Medical Education (ACGME)] residency program which includes at least six months of documented cerebrovascular training, training in the diagnosis and management of acute stroke, and the interpretation of cerebral arteriography and brain imaging under the supervision of a board-certified neurologist, neurosurgeon, or neuroradiologist with the American Board of Medical Speciality (ABMS) eligibility or certification during a 4-year residency program. (2) Completes one year of graduate medical education in endovascular surgical neuroradiology. An ACGME-approved program is preferred but not required. (3) Have documented prior training and experience in catheter arteriography, including 100 cerebral arteriograms. Clinical outcomes must meet or exceed the American College of Radiology (ACR) benchmarks for technical success and complications. (4) Have documented prior training and experience in intracranial microcatheter (3-French) and microguidewire (0.014 inch) navigation under the supervision of fellowship-trained and credentialed neurointerventionalist(s). (5) Have documented prior experience in assessment and performance of endovascular stroke interventional procedures as the primary operator in 10 patients under the supervision of fellowship-trained and credentialed neurointerventionalists(s). (6) Previously credentialed physicians who perform IA catheter-directed stroke procedures at their local institutions should have documented procedural and clinical outcomes that meet national standards and published evidence-based guidelines. (7) Successfully complete a training course for use of any specific device.

Discussion

There is currently a paucity of high quality research evaluating neurothrombectomy devices in patients suffering from acute ischemic stroke. Whether neurothrombectomy devices should be used preferentially over IV rtPA remains unstudied. Currently, only two neurothrombectomy devices, the MERCI clot retriever and Penumbra System, are FDA-approved to treat patients with acute ischemic stroke, with a plethora of other neurothrombectomy devices studied in an “off-label” capacity. A strong majority of available

data lies with the two approved devices, but which device is better (most effective and/or safe) in any given acute ischemic stroke patient, again, remains unstudied.

Little data exist regarding the current usage of such devices. Data from Concentric Medical suggests that >10,000 patients have been treated with the MERCI clot retriever.[32] The extent of usage of other neurothrombectomy devices in the "real-world" setting is unknown.

Our literature scan failed to identify any direct *in vivo* comparative studies of neurothrombectomy devices, either to IV rtPA or each other. Instead, investigators frequently studied devices as part of prospective single-arm studies, non-comparative retrospective studies enrolling consecutive patients, or case series or case reports. Based upon the expected paucity of comparative data, this report was assigned to be a technical brief by AHRQ. Consequently, our main objective was to describe neurothrombectomy devices currently being used or actively investigated in the treatment of patients with acute ischemic stroke and to summarize the evidence supporting their use, not to draw conclusions regarding the effectiveness or safety compared to each other or the chief medical intervention, IV rtPA, or this drug delivered via an endovascular approach, intra-arterial rtPA.

A previous systematic review of neurothrombectomy devices by Stead and colleagues was identified during our literature scan.[31] Similar to our technical brief, this systematic review identified and qualitatively synthesized only non-comparative studies and case series and reports. However, the literature search on which their review was based extended only through March 2006, and consequently did not include the majority of the highest quality data on neurothrombectomy devices (including that of the MERCI and Penumbra Systems). Thus our technical brief should represent the most up-to-date review of the literature at this time. Unlike our review, Stead and colleagues quantitatively compared pooled device results to a control group derived from their own institution's stroke population. They found that when compared with a similar matched cohort, the neurothrombectomy patients had good functional recovery (mRS≤2) in 34.5 percent of patients compared with 10.7 percent of patients matched for age, sex, and NIHSS score, suggesting the neurothrombectomy group was nearly 15 times more likely to have good functional recovery compared with the control group. While, perhaps the best "controlled" data available to date, this analysis is fraught with limitations, including the fact that the neurothrombectomy cohort was not a homogeneous one, the comparison was to a single-center historically concurrent cohort (albeit matched for important variables), and individuals were not randomly allocated to treatment, thus allowing the influence of confounding variables.

Future Research/Research Gaps

Currently, there are eight on-going studies evaluating at least one neurothrombectomy device in acute ischemic stroke listed on the http://www.clinicaltrials.gov/ Web site or mentioned in previous review articles **(Table 13)**.[35] The first of these eight studies is estimated to end sometime in 2010. All appear to be enrolling patients based upon inclusion and exclusion criteria that are similar to those already used by the prospective and retrospective studies detailed throughout this report. One exception is the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial which will allow patients to receive IV rtPA up to 4.5 hours after symptom onset. Five trials are randomized controlled trials and three are prospective observational studies. Four of the five randomized controlled trials are allowing the use of multiple neurothrombectomy devices; however, none appear to be designed to compare

one device to another. Instead, these studies compare the use of neurothrombectomy devices to best medical therapy (with or without IV rtPA).

Both the MERCI clot retriever and the Penumbra System have prospective observational studies in progress. Compared to previous studies of these agents of similar design, these studies will enroll much larger sample sizes (n=2,000 and 3,000, respectively).

Our literature scan did not identify any reports of neurothrombectomy devices evaluating their impact on health-related quality-of-life. The Pragmatic Ischemic Stroke Thrombectomy Evaluation (PISTE) randomized controlled trial (projected n>200) will be the first to do so in a study of mechanical devices to treat acute ischemic stroke. It will also evaluate treatment costs associated with these devices.[35] Our literature scan only identified one previous 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 IV rtPA.[47]

There appears to be a need for studies to determine the comparative effectiveness of neurothrombectomy devices and IV rtPA in patients reporting within a 3- (or 4.5-) hour window from time of stroke onset and having no contraindications to either therapy. In addition, for those patients with contraindications or who are refractory to IV rtPA, it is unclear which device is the most efficacious or safe.

It would seem reasonable to conduct studies to answer such research gaps using a randomized controlled trial design, powered to show equivalency or non-inferiority of devices. Future trials should focus on accepted efficacy and safety endpoints, but also consider collecting data on health-related quality-of-life and treatment costs.

Summary

There is currently a paucity of high quality research evaluating neurothrombectomy devices in patients suffering from acute ischemic stroke. There remains a need for further research on the topic, including randomized controlled trials to determine the optimal device(s) to use, and their effectiveness and safety compared to best medical therapy. Results of on-going studies will likely only begin to address some of these questions.

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