Effective Health Care Program

Technical Brief
Number 4

Neurothrombectomy Devices for Treatment of Acute Ischemic Stroke

AHRQ
Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

This report is based on research conducted by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10067-I). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

Technical Brief

Number 4

Neurothrombectomy Devices for Treatment of Acute Ischemic Stroke

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10067-I

Prepared by:
University of Connecticut/Hartford Hospital Evidence-based Practice Center (EPC)

Investigators:
William L. Baker, Pharm.D., BCPS (AQ CV)
Jennifer A. Colby, Pharm.D.
Vanita Tongbram, M.B.B.S., M.P.H.
Ripple A. Talati, Pharm.D.
Isaac E. Silverman, M.D.
C. Michael White, Pharm.D., FCP, FCCP (Co-Director of EPC)
Jeffrey Kluger, M.D., FACC
Craig I. Coleman, Pharm.D. (Co-Director of EPC)

AHRQ Publication No. 11-EHC020-EF
January 2011

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Baker WL, Colby JA, Tongbram V, Talati RA, Silverman IE, White CM, Kluger JK, Coleman CI. Neurothrombectomy Devices for Treatment of Acute Ischemic Stroke. Technical Brief No. 4. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) AHRQ Publication No. 11-EHC020-EF. Rockville, MD; Agency for Healthcare Research and Quality. January 2011. Available at: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although 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 decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future comparative effectiveness research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this Technical Brief. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Chuck Shih, M.H.S.
Task Order Officer
Evidence-Based Practice Center Program
Agency for Healthcare Research and Quality

Acknowledgments

The University of Connecticut/Hartford Hospital Evidence-based Practice Center thanks Robert Quercia, M.S., Medical Editor; Jeffrey Mather, M.S., Statistician, Database Design; and Sharon Giovenale, M.S., Medical Librarian, for their invaluable help in completing this Technical Brief.

Technical Expert Panel

Colin P. Derdeyn, M.D.
Vice-Chair, AHA Stroke Council's Scientific Statements Oversight Committee
Professor of Radiology, Neurology and Neurological Surgery
Director, Center for Stroke and Cerebrovascular Disease
Washington University School of Medicine

Anthony J. Furlan, M.D.
Gilbert Humphrey Professor
Chairman Department of Neurology
Neurological Institutes
University Hospitals Case Medical Center
Case Western Reserve University School of Medicine
Cleveland, OH

Patrick D. Lyden, M.D., FAAN
Chairman, Department of Neurology
Carmen & Louis Warschaw Chair in Neurology
Cedars-Sinai Medical Center
Los Angeles, CA

Wade S. Smith, M.D., Ph.D.
Daryl R. Gress Endowed Professor of Neurocritical Care and Stroke
Director, UCSF Neurovascular Intensive Care Unit
Department of Neurology
University of California, San Francisco School of Medicine

Contents

Tables

Figures

Appendixes

Executive Summary

Background

Acute ischemic strokes are associated with poor outcomes and high healthcare burden. In patients with occlusions of large cerebral vessels, patients with high baseline stroke severity scores as defined by the National Institute of Health Stroke Score (NIHSS), and patients unlikely to benefit or having failed treatment with intravenous (IV) recombinant tissue plasminogen activator (rtPA), there is a need for alternative methods of revascularization which can improve outcomes without increasing the risk for intracranial hemorrhage. The uses of various neurothrombectomy devices (clot retrievers, aspiration/suction devices, snare-like devices, ultrasonography technologies, and lasers) have been examined in these populations. Currently, two neurothrombectomy devices are FDA-cleared through the FDA 510(k) process: the MERCI clot retriever and the Penumbra System. Various ongoing clinical trials are currently evaluating the impact of these devices, 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 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 clearance (510(k) documents).

Systematic literature searches were conducted 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 November 2010. Grey literature searches were also conducted, utilizing Google, clinicaltrials.gov, and manual searching techniques.

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, case series, and case reports as long as they included patients with an acute ischemic stroke and reported at least one outcome of interest. We included only reports in English in our qualitative review of the literature.

Two investigators independently abstracted data from eligible reports, and disagreements were resolved by a third investigator. We obtained the following information from each report: 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 A 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: (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. In addition, the procedure itself carries risks, including the need for intubation and heavy sedation, which have been associated with worse outcomes.

Only the MERCI clot retriever and the Penumbra System are FDA cleared for use in patients with an acute ischemic stroke to restore perfusion. 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.

Recent and ongoing studies are evaluating the use of “retrievable” intracranial stents that are meant to provide immediate recanalization and then be removed along with clot trapped within the stent matrix. A recent prospective, single-center pilot study reported on the safety and efficacy of a retrievable stent in 20 acute stroke patients with a large vessel occlusion who were either refractory to or ineligible for IV rtPA therapy. The stents were deployed for from 1 to 2 minutes before retrieval, with 18 of 20 (90 percent) of patients achieving successful revascularization. Six patients (30 percent) had asymptomatic ICH while 2 patients (10 percent) experienced symptomatic ICH.

Table A. 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

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

Key Question 2. From a systematic scan of studies of different types of neurothrombectomy devices, what are the type(s) of devices, study designs and sizes, patient characteristics, comparators used in comparative studies, lengths of follow-up, concurrent or prior therapies, outcomes measured, and adverse events, harms, and safety issues reported?

A total of 2,054 citations were identified, 378 of which were retrieved for full-text review. A total of 87 articles were ultimately included in the study. Sixty-two articles (71 percent) were case series or case reports, 18 (21 percent) were prospective single-arm studies,

and 7 (8 percent) were non-comparative, retrospective studies enrolling consecutive patients. These studies were published in full-text (74 percent) or abstract form (26 percent). Fifteen of 25 studies (60 percent) were published between 2008 and 2010. Only 3 of 18 (17 percent) prospective and 1 of 7 retrospective studies clearly stated that they utilized blinded outcome assessment.

The largest percentage of overall reports (40 percent) and prospective studies (31 percent) were for the MERCI clot retriever. The Penumbra System had 10 reports, of which four were prospective. For off-label devices, two studies were conducted with EKOS, and one each with Phenox, Amplatz Gooseneck, AngioJet, EPAR, Neuronet, 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 to 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 62 of 87 (71 percent) articles 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 older than 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 25 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 timeframe 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 25 studies (3 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 was predominantly anterior (72 percent) and posterior circulation (24 percent).

No direct human 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 durations of followup in the majority of prospective and retrospective studies reporting effectiveness outcomes were either 30 days 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 followup 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 followup 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 to 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.

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

Table B. Effectiveness evidence for neurothrombectomy devices (n=1,311)
(Reported as prospective/retrospective/case series or reports)

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

Darker shading represents more frequent evaluation or larger number of patient evaluated
BI=Barthel Index; C=case report/case series; GOS=Glasgow Outcome Scale; mRS=modified Rankin Scale; n=the total number of patients evaluated for any effectiveness or safety endpoint; NIHSS=National Institutes of Health Stroke Scale; P=prospective; R=retrospective
[#]Death included if patients were followed-up for any duration of time after hospital-discharge

All prospective or retrospective studies reported recanalization results. The NIHSS score was reported in 13 of 25 (52 percent) identified studies and mRS≤2 was reported in 17 of 25 (68 percent) studies. NIHSS, mRS≤2, and mortality endpoints were reported in 20 percent, 50 percent, and 50 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.

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

Table C. Safety endpoint evidence for neurothrombectomy devices (n=1,311)
(Reported as prospective/retrospective/case series or reports)

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

Darker shading represents more frequent evaluation or larger number of patient evaluated
AICH=asymptomatic intracerebral hemorrhage; C=case report/case series; n=the total number of patients evaluated for any effectiveness or safety endpoint; P=prospective; R=retrospective; SICH=symptomatic intracerebral hemorrhage

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 50 percent, 50 percent, 30 percent, 40 percent and 20 percent of MERCI clot retriever; 100 percent, 71 percent, 29 percent, 43 percent and 43 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)?

The effects of predictor variables on select outcomes identified by researchers during neurothrombectomy studies are summarized in Table D.

Table D. Effect of various variables on post-neurothrombectomy device outcomes

Predictor Variables	Clinical Outcomes				
	Recanalization	NIHSS Improvement	Hemorrhage*	mRS≤2	Death
Recanalization	-	B	-	B	B
Older Age	-	-	-	H	H
Higher SBP	-	H	-	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	-

B=beneficial; H=harmful; I=indeterminate (no statistically significant effect); IA=intra-arterial; ICA=internal carotid artery; IV rtPA=intravenous recombinant tissue plasminogen activator; MCA=middle cerebral artery; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; SBP=systolic blood pressure

[*]including symptomatic and asymptomatic hemorrhage

[#]INR>1.7, PTT>45 and/or platelet count <100,000

Evaluated predictors of outcome (Table ES2) in these patients treated with a neurothrombectomy device include demographic, co-morbid disease, stroke severity, and stroke treatment variables. These predictors were evaluated in studies (or pooled analyses) of the MERCI clot retriever and the Penumbra System. Of particular note, recanalization was the only variable that was found to be predictive of clinical benefit (achieving a mRS≤2) as well as lower mortality. These results are similar to those found in an earlier meta-analysis as well as a pooled analysis of the IMS I and II trials, where reduced-dose IV followed by IA thrombolysis was associated with good outcomes. In addition to these variables, researchers have suggested that the presence of collateral circulation, lesion volume, and cerebral perfusion pressure have also been linked to outcomes in acute ischemic stroke patients.

In a meta-analysis by Stead and colleagues evaluating neurothrombectomy devices, younger age and lower NIHSS score at presentation had beneficial effects on achieving a mRS≤2 (p=0.001). Patients with posterior circulation occlusions were found to have higher odds of 90-day mortality compared to those with anterior occlusions (either internal carotid or middle cerebral arteries).

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. Of note, upon qualitative review, the proportion of patients recanalized in retrospective (real-world) studies did not appear to be lower than that of the prospective, single-arm studies, for either MERCI or Penumbra System studies. This suggests that practicing clinicians may be achieving outcomes similar to those clinicians involved with clinical trials, which would indicate that practicing clinicians are receiving adequate training.

Two reports have been written and approved by multiple neuroscience societies detailing the minimum training requirements for those performing neuroendovascular procedures (including neurothrombectomy devices) in patients with acute ischemic stroke, and setting out performance standards that should be adopted to assess outcomes.

Discussion

Neurothrombectomy devices are a treatment option in patients with an acute ischemic stroke. The specific population most likely to benefit from these devices is still under investigation. Current studies have involved patients with large vessel occlusions, high baseline NIHSS scores, and those either unlikely to respond or who have failed IV rtPA therapy. Only two neurothrombectomy devices, the MERCI clot retriever and the Penumbra System, are cleared by FDA to restore perfusion in patients with acute ischemic stroke. A majority of available data relates to the two cleared devices.

We did not identify any direct human comparative studies of neurothrombectomy devices 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. In this technical brief, our main objective was limited to describing neurothrombectomy devices currently being used or actively investigated in the treatment of patients with acute ischemic stroke and summarizing the evidence supporting their use. We did not draw conclusions regarding their effectiveness or safety.

A previous systematic review of neurothrombectomy devices by Stead and colleagues was identified during our literature scan. 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 than the control group to have good functional recovery. While perhaps the best "controlled" data available to date, this analysis is fraught with limitations, including the fact that the neurothrombectomy cohort was not homogeneous, the comparison was to a single-center historically concurrent cohort, and individuals were not randomly allocated.

Currently, there are eleven 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. The first of these eleven studies is estimated to end sometime in 2010. All studies 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. Seven of these studies have randomized, controlled designs with projected enrollment ranging from 20-900. The other four studies have prospective, observational designs ranging from 200-2000 projected participants. Six of the seven randomized controlled trials are allowing the use of multiple neurothrombectomy devices; most 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, similarly designed studies of these agents, these studies will enroll much larger sample sizes (n=2,000 and 3,000, respectively).

The use of advanced imaging techniques should be incorporated into future randomized controlled trials to aid in identifying those patients most likely to benefit from

neurothrombectomy devices. 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. These studies should also evaluate the impact on health-related quality-of-life of neurothrombectomy devices.

Summary

Currently available neurothrombectomy devices offer intriguing treatment options in patients with acute ischemic stroke, although a paucity of high quality research currently exists. There remains a need for further research on the topic, including randomized controlled trials to determine the optimal device(s) to use, and the patient populations most likely to benefit from their use. Additionally, studies of neurothrombectomy devices against contemporaneous controls investigating whether these devices truly treat final health outcomes associated with stroke rather than improving recanalization alone are warranted. Results of ongoing studies will likely only begin to address some of 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] The annual rate of strokes is expected to increase to 1.2 million cases by the year 2025, a troubling trend that underlines the urgency of adequate ischemic stroke treatment.[3] Stroke occurs more commonly in females than males, especially at older ages.[4] 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.[4] 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.[2,5] 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.[6] 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[7,8] 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.[2,9] 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.[10] Additionally, evidence has demonstrated the significant impact of ischemic stroke on caregiver burden and quality-of-life in caregivers.[11-13]

Natural History of Ischemic Stroke

The poor overall outcome associated with acute ischemic stroke is well recognized. A number of patient variables have been identified as being related to worse outcomes, including advancing age and stroke severity.[14,15] Fischer and colleagues demonstrated that a National Institutes of Health Stroke Score (NIHSS) of 10 or greater was predictive of angiographic findings consistent with a cerebrovascular occlusion.[14] More recent data has suggested that a higher admission NIHSS score, as well as advancing age, are independent predictors of worse neurologic outcome following an acute ischemic stroke.[15,16] Thus, early identification of patients at higher risk for poor outcome is essential to delivering effective treatment and improving long-term prognosis.

Acute ischemic stroke due to occlusions in large cerebral vessels are particularly troublesome. These ischemic events involve, but are not limited to, vertebral, basilar, and carotid terminus arteries as well as the anterior and middle cerebral arteries (MCA). Smith and colleagues reported that large vessel occlusions represented 46 percent of strokes and 13 percent of transient ischemic attacks (TIAs) in a cohort of 735 patients presenting within 24 hours of symptom onset.[16] Indeed, large vessel occlusions were predictive of higher 6-month mortality

[Odds Ratio (OR) 4.5, 95 percent Confidence Interval (CI) 2.7 to 7.3; p<0.001].[17] In addition, the likelihood of a good clinical outcome [as defined by a modified Rankin Scale (mRS) score ≤2] at 6 months was negatively predicted by the presence of a large vessel occlusion [OR 0.33, 95 percent CI 0.24 to 0.45; p<0.001]. Moreover, approximately half of patients with anterior circulation large vessel occlusions will die without revascularization and only approximately 10 percent will achieve good functional outcomes at 3 months.[15,18,19]

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.[20] If blood flow is not restored to the affected area, ischemia and eventual cell death will occur in a time-dependent fashion.[20] 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.[21] In a meta-analysis of 53 studies by Rha and Saver, successful recanalization of the occluded cerebral vessel is associated with lower 3-month mortality (OR 0.24, 95 percent CI 0.16 to 0.35) and improved functional outcomes (OR 4.43, 95 percent CI 3.32 to 5.91) than those that are not recanalized.[22] In more recent studies, final recanalization was the strongest predictor of clinical outcomes in patients being treated for acute ischemic stroke.[15] Khatri and colleagues suggest that those achieving later angiographic reperfusion experience fewer clinical benefits than those that achieve it earlier.[23]

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.[24] 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.[21] 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).[25] At 3-months, patients receiving IV rtPA had improved functional outcomes (mRS <1) vs. the group receiving placebo (39 percent vs. 29 percent; OR 1.7, 95 percent CI 1.2 to 2.6). In addition, four commonly utilized tools to assess stroke-related deficits and disabilities demonstrated superiority of IV rtPA as indicated by improvements in the Barthel Index (OR 1.6, 95 percent CI 1.1 to 2.5), mRS (OR 1.7, 95 percent CI 1.1 to 2.5), Glasgow Outcome Scale (GOS) (OR 1.6, 95 percent CI 1.1 to 2.5) and the NIHSS (OR 1.7, 95 percent CI 1.0 to 2.8).

Use of IV rtPA beyond the 3 hour timeframe has been limited. However, a pooled analysis of six randomized, placebo-controlled trials showed that patients who received IV rtPA between 3 and 4.5 hours after stroke onset were at an increased odds of a favorable outcome (a composite of stroke-related disabilities, severity of disabilities and abilities to conduct activities of daily living) as compared with placebo (OR 1.4, 95 percent CI 1.05 to 1.85).[26] The subsequently published European Cooperative Acute Stroke Study (ECASS III), which was powered based on the aforementioned meta-analysis, showed that patients receiving IV rtPA between 3 to 4.5 hours after symptom onset had significantly higher odds of a more favorable outcome (52.4 percent vs. 45.2 percent; OR 1.34, 95 percent CI 1.02 to 1.76), with no differences in mortality (p=0.68) but higher incidence of ICH seen (p=0.001).[27] In addition, two observational studies, the Safe Implementation of Thrombolysis in Stroke Monitoring Study

(SITS-MOST)[28] and the SITS-international stroke treatment registry (SITS-ISTR)[29] confirmed the benefits of rtPA use at 3 to 4.5 hours after ischemic stroke. Based on these findings, the American Heart Association and American Stroke Association issued a scientific advisory in 2009 recommending the use of IV rtPA in eligible patients presenting within 3 to 4.5 hours after the onset of stroke symptoms. This was a Class I recommendation with B level of evidence for most patients but for those older than 80 years, taking oral anticoagulants, with a baseline NIHSS score greater than 25, or with both a history of stroke and diabetes, rtPA use within 3 to 4.5 hours was a Class IIb recommendation with C level of evidence.[30]

Despite appropriate IV rtPA use, rates of recanalization remain highly variable ranging from 30 to 92 percent during the initial 6 to 24 hours after treatment.[31] Recanalization rates vary depending on the site of the occlusion: events in large cerebral vessels having particularly high clot burden may not adequately respond to IV rtPA. Early observations suggested that revascularization rates with IV rtPA ranged from 10 percent in internal cerebral artery (ICA) occlusions to less than 30 percent in MCA occlusions.[32] Reocclusion rates of 34 percent have also been shown following IV rtPA therapy, further reducing the durability of pharmacologic monotherapy in these patients.[33] In addition, delays in arriving in the emergency department and unavailability of IV rtPA in some centers make thrombolytic reperfusion therapy viable in less than five percent of patients with acute stroke.[34] Thus, patients identified as having strokes less likely to respond to IV rtPA are in need of other methods for achieving recanalization, particularly those with large vessel occlusions.

The advent of catheter-based delivery of thrombolytic agents at the site of occlusion seemed an attractive alternative. Clinical trials evaluated the use of intra-arterial (IA) rtPA in patients presenting within 6 hours of symptom onset resulting from MCA occlusions.[35] At 3-months, patients who received IA rtPA achieved significantly higher clinical success (mRS≤2) than those who received heparin control (40 percent vs. 25 percent; p=0.04). However, intracranial hemorrhage (ICH) associated with neurological deterioration occurred more frequently with IA rtPA therapy than with control (10 percent vs. 2 percent; p=0.06). Despite the safety concerns, this was the first trial that attempted to treat a large vessel occlusion ischemic stroke by endovascular means. Interestingly, Ciccone and colleagues recently performed a randomized controlled trial comparing IV rtPA with IA rtPA in 54 ischemic stroke patients with an average baseline NIHSS of 16-17.[36] Although the time from stroke onset was significantly shorter in the IV rtPA group, a trend towards improved survival in the IA rtPA group was seen (p=0.067). Thus, a treatment modality that could preserve the clinical advantages of IA rtPA over IV rtPA without the associated bleeding risk would be ideal.

Advances in Recanalization Using Neurothrombectomy Devices

Neurothrombectomy devices have been examined for use in patients presenting with acute ischemic stroke as an alternative to IV rtPA therapy either due to ineligibility, prior therapy failure, or identification of occlusions less likely to respond to IV rtPA. A neurothrombectomy device is defined by the FDA's Center for Devices and Radiological Health (CDRH) as a device intended to retrieve or destroy blood clots in the cerebral neurovasculature by mechanical, laser, ultrasound technologies, or combination of technologies.[37] These devices may offer a number of potential advantages when compared to pharmacologic thrombolysis including: more rapid achievement of recanalization vs. IV rtPA; enhanced efficacy in treating large vessel occlusions; greater efficacy with a lower risk for hemorrhagic events; and use in patients contraindicated to,

or presenting outside the appropriate window for, IV rtPA.[38] These putative advantages of neurothrombectomy devices have not been confirmed in direct comparisons against rtPA therapy. Neurothrombectomy devices employing different mechanisms including clot retrievers, aspiration/suction devices, snare-like devices, ultrasonography technologies and lasers, have been or are currently under study in patients with acute ischemic stroke. The MERCI clot 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".[39-42] 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."[42] 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 compared to contemporaneous controls.[31] 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 are not required 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 scan of studies of different types of neurothrombectomy devices, what are the type(s) of devices, study designs and sizes, patient characteristics, comparators used in comparative studies, lengths of follow-up, concurrent or prior therapies, outcomes measured, and adverse events, harms, and safety issues reported?

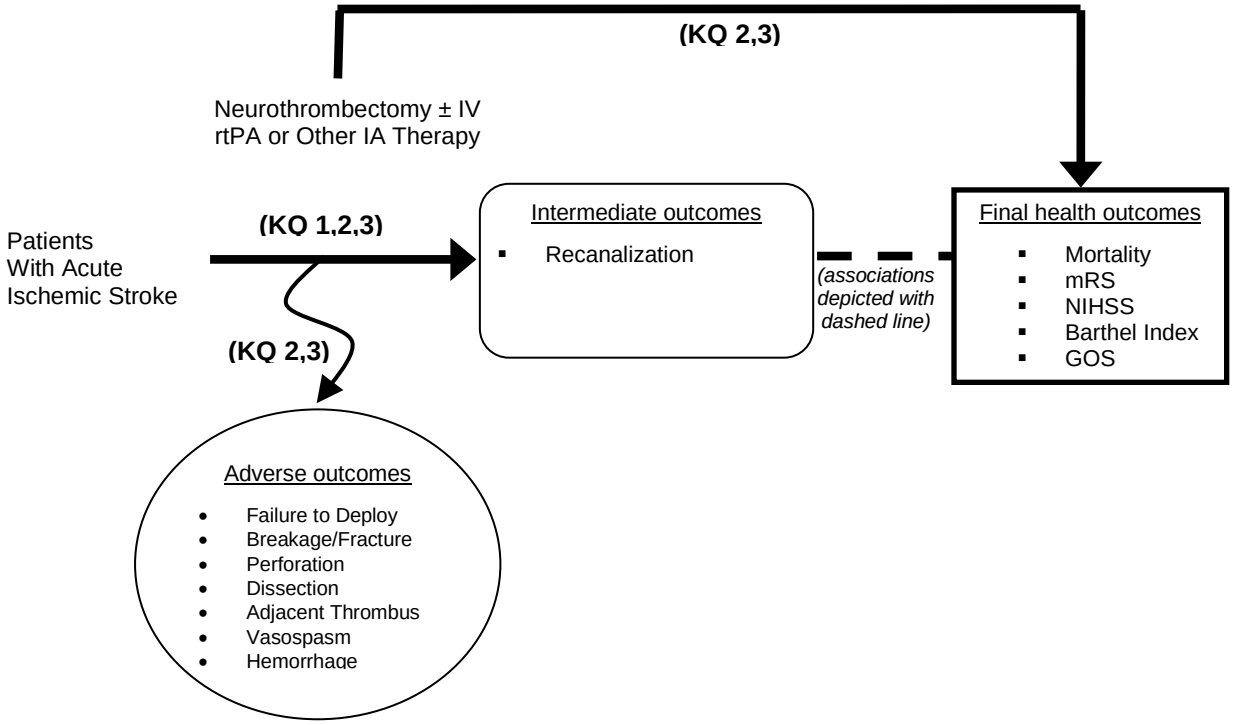
2a. Type(s) of devices
2b. Study design and size
2c. Patient characteristics
2d. Comparator used in comparative studies
2e. Length of follow-up
2f. Concurrent or prior therapy
2g. Outcomes measured
2h. Adverse events, harms and safety issues reported

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.

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 supply 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 circulation.

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,[37] published literature, and a search of the FDA CDRH's database to identify neurothrombectomy devices that have received FDA approval (510(k) documents).[42]

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 May 2010. 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),[37] 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).

Variables associated with the use of devices that may impact outcomes were identified a prior with input from our clinical experts and approved as part of the initial protocol. We evaluated each prospective or retrospective study (excluding case reports and case series) for all independent predictors of response. Data from multivariable analyses was preferentially used over univariate analyses when available. Each variable was classified as having either a beneficial ($p<0.05$ for improving the outcome), harmful ($p<0.05$ for worsening the outcome) or indeterminate (no statistically significant change regardless of direction of effect).

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.

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

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

Key Question 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.[37] As such, neurothrombectomy devices are reviewed and cleared through the 510(k) premarket notification process.[37,42] In order for a device to receive clearance 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 receive clearance based on nonclinical testing with little to no clinical data.[37] 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.[37] 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-cleared 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 clearance for the treatment of patients with an acute ischemic stroke. The MERCI retriever "is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke (who are ineligible for treatment with IV rt-PA or who fail IV rt-PA therapy)."[39,42] 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."[42]

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

Key Question 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-cleared 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.

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

The MERCI retriever and Penumbra System have FDA clearance 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.

Key Question 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.[40] 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 3-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. This includes patients with occlusions of large cerebral vessels that have been shown to respond poorly to IV rtPA use.[32] Parenthetically, providing adjunctive neurothrombolytic device treatment may be essential for accomplishing successful thrombolysis. It is possible that the use of neurothrombectomy devices would result in lower ICH rates than systemic thrombolytic therapy. This was supported by the results of the Multi-MERCI study,[43] which reported a symptomatic ICH rate of 2.4 percent as compared with the 10 percent rate seen in the PROACT-II[35] study with systemic thrombolysis although the different definitions for ICH used in these investigations may explain some of the discrepancies in event rates seen in these trials.

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.[40]

Key Question 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.[44] 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. An additional safety concern with the use of neurothrombectomy devices is the risk for ICH (both

symptomatic and asymptomatic). While early studies suggested that ICH may be a concern with device use,[45] more recent prospective study data refute these findings although differing definitions and populations limit the indirect comparison of data cross these studies.[46,47] Off-protocol use of other devices or thrombolytics in acute ischemic stroke has occurred in these non-randomized studies of neurothrombectomy devices which may increase the reported rate of symptomatic ICH.

In addition to safety concerns of the device itself, the procedure the patients undergo carries inherent risks as well. Nichols and colleagues showed that intubation and heavy sedation was associated with worse outcomes, using data from the IMS I and II trials.[48]

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

Information on the utilization of various neurothrombectomy devices is lacking. One estimate provide by the manufacturer the MERCI retriever (Concentric Medical, Inc) suggested that their device has been used more than10,000 times for the treatment of acute ischemic stroke.[49] No information regarding the time period or geographic area (e.g. Unites States only) for this data was provided. Information with other devices included in this review was not available.

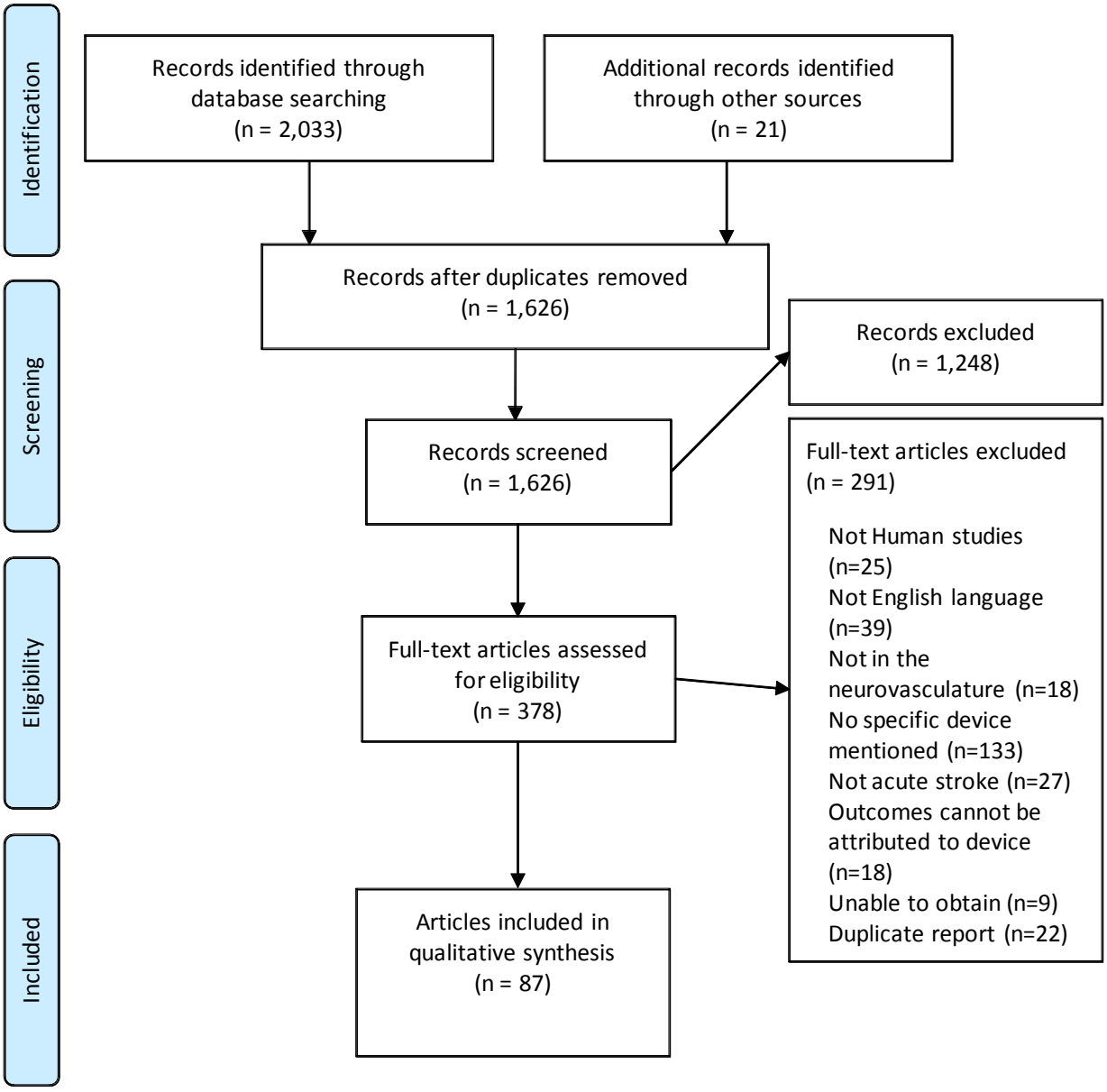
Key Question 2. From a systematic scan of studies of different types of neurothrombectomy devices, what are the type(s) of devices, study designs and sizes, patient characteristics, comparators used in comparative studies, lengths of follow-up, concurrent or prior therapies, outcomes measured, and adverse events, harms, and safety issues reported?

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 2,054 citations, 378 of which were retrieved for full-text review (Figure 2). Ultimately, 87 reports were included in the literature scan. Appendix B lists 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



Of the included reports, 18 were prospective single-arm studies, 7 were non-comparative retrospective studies enrolling consecutive patients and 59 were case series or case reports. The 62 case series and case 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 87 identified reports, we identified eleven ongoing studies evaluating at least one neurothrombectomy device in acute ischemic stroke. (Table 3)

Emerging Technologies

Two emerging technologies related to the treatment of patients with ischemic stroke include the use of intracranial stents as well as various imaging techniques. Although not

included in the main part of this review, the potential future role of these technologies deserves mention.

Intracranial stents have been evaluated as a method of providing immediate arterial recanalization which, as discussed previously, has been associated with improved clinical outcomes.[22,50] The stents achieve luminal recanalizatio n by displacing emboli toward the arterial wall, similar to their use for cardiovascular indications. However, unlike coronary vessels, intracranial arteries are more prone to vessel wall dissection and perforation resulting from their lack of an extensive external elastic lamina as well as other factors.[50] In addition, their permanent placement would necessitate long-term oral antiplatelet therapy to prevent potentially devastating restenosis. Despite these technical challenges, numerous reports have shown the benefits of stents both for salvage treatment in patients who have failed prior neurothrombectomy devices[51] or those with large vessel occlusions who cannot receive either IV or IA rtPA therapy.[52-54] In the Stent-Assisted Recanalization in Acute Ischemic Stroke (SARIS) trial, the Wingspan system (Boston Scientific) had reasonable initial safety and efficacy in 20 patients presenting within 8-hours of stroke symptom onset with a mean NIHSS of 14 and either a contraindication to IV rtPA or failure to improve 1 hour after receiving IV thrombolysis.[55] Given the permanent nature of these devices, however, they do not meet the criteria of a neurothrombectomy device in that they are not intended to retrieve or destroy blood clots.[37]

However, recent and ongoing studies are evaluating the use of 'retrievable' stents that are meant to provide immediate recanalization, and then be removed along with clot trapped within the stent matrix. A brief review of the literature identified four early case reports that describe the use of intracranial stents as salvage therapy in patients who have failed conventional neurothrombectomy treatment.[56-59] A prospective study, currently only available in abstract form, reports on the safety and efficacy of the Solitaire stent (ev3 Inc, Plymouth, MN) in 18 patients with acute ischemic stroke (Appendix Table 4C).[60] Seventy two percent of patients receiving the Solitaire system as a thrombectomy device achieved recanalization (TICI grade 2-3 flow), with three (16.7 percent) reports of ICH and one (5.6 percent) vessel perforation.[60] A more recent prospective, single-center pilot study by Castano and colleagues reported on the safety and efficacy of a retrievable stent in 20 patients with a large vessel occlusion acute ischemic stroke and were either refractory or ineligible for IV rtPA therapy (Appendix Table 4C).[61] The stents were deployed for 1-2 minutes before retrieval, with 18 of 20 (90 percent) of patients achieving successful revascularization (defined as TICI grade 2-3 flow). Six patients (30 percent) had asymptomatic ICH while 2 patients (10 percent) experienced symptomatic ICH.[61] This study used the Solitaire AB device (ev3 Inc, Plymouth, MN) which is a self-expanding stent system currently cleared by the FDA for use in treating intracranial aneurysms. This device differs from those discussed in the current Technical Brief in that it provides immediate recanalization while trapping portions of the clot within the stent matrix, which is self-expanding and fully retrievable. Most currently used devices, including the Merci and Penumbra systems remove clot as a method of recanalization. This line of products, currently being evaluated in ongoing trials, may provide a new method of restoring cerebral blood flow in patients presenting with acute ischemic stroke symptoms who are unlikely to benefit from standard therapies. The ongoing SWIFT trial is comparing the Solitaire TR device to the Merci system and will provide the first comparative effectiveness data on different neurothrombectomy treatments for acute ischemic stroke.

The use of cranial imaging techniques, including computed tomography (CT) and magnetic resonance (MR) perfusion technology, allows unique assessment of patient's

pathophysiology especially in the setting of acute large vessel occlusion. These tests may expand the breadth of eligible patients for neurothrombectomy device use.

Table 2. Number of reports for each neurothrombectomy device stratified by type of study

	Number of Reports				
Device Class	Prospective, Single-Arm (n)	Non-Comparative Retrospective* (n)	Case Series (n)	Case Reports (n)	Total (n):
Aspiration/Suction					
AngioJet	1 (12)	-	3 (10)	4 (4)	**8 (26)**
Penumbra	4 (204)	3 (173)	1 (5)	3 (3)	**11 (385)**
Clot Retriever					
Attractor-18	-	-	-	1 (1)	**1 (1)**
Catch	-	-	1 (2)	-	**1 (2)**
In-Time	-	-	1(2)	1 (1)	**2 (3)**
MERCI	6 (491)	4 (220)	12 (58)	19 (19)	**41 (788)**
Phenox	1 (45)	-	1 (2)	-	**2 (47)**
TriSpan	-	-	1(6)	-	**1 (6)**
Ultrasonography					
EKOS	2 (49)	-	-	1 (1)	**3 (50)**
Snare					
Alligator	-	-	1 (6)	2 (2)	**3 (8)**
Amplatz Gooseneck	1 (9)	-	6 (29)	4 (4)	**11 (42)**
Neuronet	1 (5)	-	1(4)	4 (4)	**6 (13)**
Soutenir	-	-	1 (2)	1 (1)	**2 (3)**
Device Not Specified	-	-	4 (27)	1 (1)	**5 (28)**
Laser					
EPAR	1 (34)	-	-	-	**1 (34)**
LaTIS	1 (2)	-	-	-	**1 (2)**
Total:	**18 (851)**	**7 (393)**	**33 (154)**	**41 (41)**	**99^(1438)**

EPAR=Endovascular Photoacoustic Recanalization

*Must have enrolled consecutive patients

^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 prospective, 7 retrospective and 59 unique case series/reports were identified.

Table 3. Summary of ongoing studies of neurothrombectomy devices for ischemic stroke

ClinicalTrials.gov Identifier	Title	Anticipated Completion Year	Device(s) evaluated	Design/ Projected N	Inclusion Criteria	Endpoint(s)
NCT01088672	Thrombectomy REvascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO)	2010	Trevo	P,O (N=50)	NIHSS: 8-30 (and mRS≤1) Symptom onset: < 8 hours Occlusion: ICA, MCA, BA, VA	mRS, death, TICI, NIHSS, SICH, SAEs
NCT00478478	Merci Registry - Real World Use of the Merci Retrieval System in Acute Ischemic Stroke	2010	MERCI	P,O (N=1000)	Revascularized with MERCI	mRS, death, TIMI, NIHSS, discharge disposition
NCT00640367	Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS EXP)	2010	Mechanical thrombolysis	RCT (N=350)	Able to initiate IV rtPA within 3 hours or IA thrombolysis within 6 hours of symptom onset	mRS, NIHSS
NCT01133223	Safety and Efficacy of the Penumbra System in Acute Middle Cerebral Artery Stroke	2010	Penumbra	RCT (N=20)	Symptom inset: ≤3.5 hours Occlusion: MCA	mRS, death, sICH
NCT01062698	Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke	2011	MERCI, Penumbra, Catch, Solitaire	RCT (N=480)	NIHSS: 10-25 Symptom onset: <3 hours Occlusion: ICA, MCA, BA	mRS, BI, HRQoL
NCT01054560	SOLITAIR FR With the Intention For Thrombectomy (SWIFT) Study	2011	Solitaire FR, MERCI	RCT (N=200)	NIHSS: 8-30 Symptom onset: <8 hours Occlusion: ICA, MCA, BA, VA IV rtPA: Ineligible/failed	mRS, death, TIMI, NIHSS, BI, ICH
NCT00963989	Imaging Guided Patient Selection for Interventional Revascularization Therapy	2011	Penumbra	P,O (N=200)	NIHSS: >10 Occlusion: ICA, MCA	mRS, death, NIHSS, TIMI, SICH, AICH, SAEs
NCT00389467	Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE)	2013	MERCI, Penumbra	RCT (N=120)	NIHSS: ≥6 Symptom onset: <8 hours Occlusion: ICA, MCA IV rtPA: Allowed <4.5 hours from symptom onset	mRS, death, NIHSS, global test statistic, hemorrhagic transformation, SAEs,
NCT00785161	Penumbra Imaging Collaborative Study (PICS)	2014	Penumbra	P,O (N=2000)	Revascularized with Penumbra	mRS, death, TIMI, NIHSS, ICH, SAEs

Table 3. Summary of ongoing studies of neurothrombectomy devices for ischemic stroke (continued)

ClinicalTrials.gov Identifier	Title	Anticipated Completion Year	Device(s) evaluated	Design/ Projected N	Inclusion Criteria	Endpoint(s)
NCT00359424	Interventional Management of Stroke (IMS) III Trial	2015	EKOS, MERCI, Penumbra	RCT (N=900)	NIHSS: ≥10 at time of IV rtPA or an NIHSS 7-10 Symptom onset: <3 hours from IV rtPA Occlusion: ICA, MCA, BA	mRS, death, NIHSS, BI, SICH, AICH
Not Registered	Pragmatic Ischemic Stroke Thrombectomy Evaluation (PISTE)	Not reported	Approved mechanical devices	RCT (N>200)	Symptom onset: <6 hours Occlusion: ICA, MCA	mRS, TIMI, infarct size, HRQoL, cost of care

AICH=asymptomatic intracerebral hemorrhage; BA=basilar artery; BI=Barthel Index; HRQoL=health-related quality-of-life; ICA=internal carotid artery; IV rtPA=intravenous recombinant tissue plasminogen activator; MCA=middle cerebral artery; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; P,O= prospective observational; RCT=randomized controlled trial; SAE=significant adverse event; SICH=symptomatic intracerebral hemorrhage; TIMI=Thrombolysis in Myocardial Infarction; VA=vertebral artery=

[c]During the peer review process of this Technical Brief, it was noted by a reviewer that the PISTE study the studies had been cancelled and was no longer recruiting patients.

Key Question 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,"[37] 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

Key Question 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 87 unique reports. Within the 87 publications/abstracts identified, a total of 100 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 (75 of 100, 75 percent) of reports identified were in the form of case series or reports. Only 18 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. Fifteen of the 25 prospective or retrospective studies (60 percent) were published between 2008 and 2010. No randomized controlled trials comparing devices to an active control (thrombolytics or other neurothrombectomy device) were identified. However, seven randomized controlled trials of neurothrombectomy devices are currently in progress. (Table 3) Of these, six 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 (40 percent) and prospective studies (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).[37] Only 3 of 18 (17 percent) prospective and 1 of 7 (14 percent) of retrospective studies clearly stated they utilized blinded outcome assessment (Appendix D, Tables 1-3). Two prospective studies used the Penumbra system while the third used the EKOS system. The single retrospective study used the Merci system.

Sample Size

Table 5 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).

Table 5. Effectiveness evidence for neurothrombectomy devices (n=1,311)
(Reported as prospective/retrospective/case series or reports)

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

Darker shading represents more frequent evaluation or larger number of patient evaluated
BI=Barthel Index; C=case report/case series; GOS=Glasgow Outcome Scale; mRS=modified Rankin Scale; n=the total number of patients evaluated for any effectiveness or safety endpoint; NIHSS=National Institutes of Health Stroke Scale; P=prospective; R=retrospective
[#]Death included if patients were followed-up for any duration of time after hospital-discharge

The size of prospective single-arm studies ranged from 2 to 164 patients, and retrospective studies ranged from 15 to 114 patients. (Table 6) 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.

Table 6. Distribution (median and range) of sample sizes for prospective and 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	7 (4/3)	29	23 to 125	53	15 to 105
Clot Retriever					
MERCI	10 (6/4)	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	-	-	-

EPAR=Endovascular Photoacoustic Recanalization, N=number of patients
*Must have enrolled consecutive patients

The remaining 74 of 99 (75 percent) identified reports, representing 59 of 82 (72 percent) unique citations, were either case series or case reports. In total, 191 patients were evaluated with a neurothrombectomy device in these case series or case reports. The number of patients receiving each neurothrombectomy device in a case series or case report as well as the combined number is depicted in Table 7. The combined number of patients evaluated in a case series or report with a neurothrombectomy device ranged from 0 (EPAR and LaTIS lasers) up to 75. As with the prospective and retrospective studies, the MERCI clot retriever was the most commonly evaluated (n=77 patients in 31 reports). Case series and reports provide the majority of data on off-label use (n=109 patients in 39 reports) of potential neurothrombectomy devices to treat acute ischemic stroke.

Table 7. 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	4 (1/3)	5	3	8
Clot Retriever				
Attractor-18	1 (0/1)	-	1	1
Catch	1 (1/0)	2	-	2
In-Time	2 (1/1)	2	1	3
MERCI	31 (12/19)	58	19	77
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

Key Question 2c. Patient characteristics

Both prospective and retrospective studies typically enrolled patients older than 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)37 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 2008.19 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 8 and 9 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.[37] 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 lesions 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 10 and 11 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).

Table 8. Distribution (median and range) of patient ages, baseline NIHSS, gender and symptom-to-angiography or device 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*	7 (4/3)	62	58 to 66	18	14 to 21	48	40 to 66	180	141 to 312
Clot Retriever									
MERCI*	10 (6/4)	65	63 to 68	19	18 to 22	44	36 to 58	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	-

EPAR=Endovascular Photoacoustic Recanalization; No.=number

*Data not reported in all studies for all characteristics

[#]Must have enrolled consecutive patients

[†]Data in this table represent the range of mean/median baseline NIHSS scores from studies included for each of the states devices. This does not reflect the total range of patients from each study.

Table 9. Distribution (median and range) of emboli location for each neurothrombectomy device in prospective and 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*	7 (4/3)	80	57 to 88	20	9 to 43	0	0 to 3[‡]
Clot Retriever							
MERCI*	10 (6/4)						
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	-

EPAR=Endovascular Photoacoustic Recanalization; No.=number

[*]Data not reported in all studies for all characteristics

[#]Must have enrolled consecutive patients

†8% of occlusions were combined anterior and posterior

‡Other may include occlusions anywhere outside of the ICA, MCA, vertebral or basilar locations

Table 10. Distribution of patient ages, baseline NIHSS, gender and symptom-to-angiography or device deployment time for 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	31 (12/19)*	6 to 90	6 to 40	25 (81)	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	-	-	-	-	-

EPAR=Endovascular Photoacoustic Recanalization; n=number of patients; No.=number

*Data not reported in all studies for all characteristics

Table 11. 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*	31 (12/19)	21 (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	-	-	-	-

n=number of patients; No.=number

[*]Data not reported in all studies for all characteristics

[#]Includes only patients with reported data; 3 patients had two device types deployed during a single event

Key Question 2d. Comparator used in comparative studies

No direct human 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.[62,63] Studies are underway that are allowing the use of multiple neurothrombectomy devices; however, these studies compare the use of neurothrombectomy devices to best medical therapy (with or without IV rtPA). The ongoing SWIFT trial is prospectively examining the comparative effectiveness of two different neurothrombectomy devices in an acute ischemic stroke population. This is the first head-to-head randomized trial comparing these devices with enrollment expected to complete at the end of 2010.

Nogueira and colleagues[64] 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,[46] Multi-MERCI,[47] and Penumbra Pivotal Stroke Trial[65] as compared to 39 percent , 52 percent, and 40 percent of patients in the NINDS rtPA (IV rtPA),[25] ECASS III (IV rtPA),[27] and PROACT II (IA rtPA)[35] 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.[18] 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.

Key Question 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.[37] 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 12) 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.

Table 12. Longest duration of follow-up in prospective, single-arm or retrospective studies of neurothrombectomy 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.=7)	No.=3	No.=2	No.=2	No.=1	No.=5	No.=5	No.=3[∂]	-	-
Clot Retriever									
MERCI (No.=10)	-	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)	-	-	-	-	-	-	-	-	-

EPAR=Endovascular Photoacoustic Recanalization; mRS=modified Rankin scale; NIHSS=National Institutes of Health Stroke Scale; No.=number of studies

*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.)

∝Data provided at 24 hours

∂Data provided at hospital discharge for all three studies

Key Question 2f. Prior or concurrent therapy

Based upon the NINDS rtPA Stroke Study results,[25] 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.[30] 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 13.

The one exception was the EKOS study by Tomsick in 2008.[19] 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.

Table 13. Adjunctive thrombolysis use in prospective, single-arm or retrospective 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	7 (4/3)	88/225 (39)[#]	110/297 (37)[†]
Clot Retriever			
Attractor-18	-	-	-
Catch	-	-	-
In-Time	-	-	-
MERCI	10 (6/4)	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)

n=number of patients receiving therapy; N=number of evaluable; No.=number

[*]Must have enrolled consecutive patients

[#]One out of seven studies did not report data (PPST, 2009)

[†]One of seven studies did not report data (Frei, 2009)

[‡]Two of 10 studies did not report data (Madison, 2008; Jo, 2008)

Key Question 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.[37] 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 vs. 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).[22] Furthermore, the guidance document recommends that clinical effectiveness should be assessed using a validated neurologic impairment scale, disability measure, or handicap scale. Examples of FDA-recommended measures include the mRS, NIHSS score, Barthel Index, and GOS.[37]

Table 5, 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,[37] 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- cleared 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.[37] 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 D 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- cleared devices (Penumbra System and MERCI clot retriever) and for off-label devices.

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

Key Question 2h. Adverse events, harms, and safety issues reported

Current guidance suggests numerous different adverse event endpoints to be recorded in evaluations of neurothrombectomy devices.[37] Table 14 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 4D to 6D in Appendix D 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 7D in Appendix D 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.

Table 14. Safety endpoint evidence for neurothrombectomy devices (n=1,311)
(Reported as prospective/retrospective/case series or reports)

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

Darker shading represents more frequent evaluation or larger number of patient evaluated

AICH=asymptomatic intracerebral hemorrhage; C=case report/case series; n=the total number of patients evaluated for any effectiveness or safety endpoint; P=prospective; R=retrospective; SICH=symptomatic intracerebral hemorrhage

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 15.[15,43,46,47,65-67] 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).

Table 15. Effect of various variables on post-neurothrombectomy device outcomes

Predictor Variables	Clinical Outcomes				
	Recanalization	NIHSS Improvement	Hemorrhage*	mRS≤2	Death
Recanalization[∞43,46,59]	-	B	-	B	B
Older Age[43,46]	-	-	-	H	H
Higher SBP[43,46]	-	H	-	H	H
Higher Baseline NIHSS[43,46,59]	I	-	-	H	H
ICA Occlusion Site (vs. mostly MCA)[43,47,59]	I	-	-	I	H
Abnormal Hemostasis[#15]	I	-	I	H	I
Prior IV rtPA[47]	I	-	I	I	I
Concomitant IA thrombolytics[47,60]	B	-	I	I	I
Prior Stroke[59]	-	-	-	-	H
Longer Procedure Duration[46,59]	-	-	-	H	I
Right Brain Infarct[46]	-	-	-	H	-

B=beneficial; H=harmful; I=indeterminate (no statistically significant effect); IA=intra-arterial; ICA=internal carotid artery; IV rtPA=intravenous recombinant tissue plasminogen activator; MCA=middle cerebral artery; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; SBP=systolic blood pressure

*including symptomatic and asymptomatic hemorrhage

#INR>1.7, PTT>45 and/or platelet count <100,000

∞Revascularization as defined by achieving TIMI 2-3 flow at the site of primary occlusion.

Evaluated predictors of outcome (Table 15) in these patients treated with a neurothrombectomy device include demographic, co-morbid disease, stroke severity and stroke treatment variables. These predictors were evaluated in studies (or pooled analyses) of the MERCI clot retriever and the Penumbra System. In addition to the variables listed in Table 15, researchers have suggested that the presence of collateral circulation, lesion volume and cerebral perfusion pressure have also been linked to outcomes in acute ischemic stroke patients.[64] Of particular note, recanalization was the only variable that was found to be predictive of clinical benefit (achieving a mRS≤2) as well as lower mortality. These results are similar to those found in an earlier meta-analysis[22] as well as a pooled analysis of the IMS I and II trials were reduced-dose IV followed by IA thrombolysis was associated with good outcomes.[19]

In a meta-analysis by Stead and colleagues published in 2008 evaluating available data on neurothrombectomy devices at that time, younger age and lower NIHSS score at presentation had beneficial effects on achieving a mRS≤2 (p=0.001).[45] Conversely, patients with posterior circulation occlusions were found to have higher odds of 90-day mortality compared to those with anterior occlusions (either internal carotid or middle cerebral arteries). No other outcomes were affected by occlusion location. Time to mechanical intervention/deployment and concurrent thrombolytic administration was not associated with either mortality or attainment of 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.[68]

To date, two reports have been published by various neuroscience societies discussing training requirements for endovascular ischemic stroke interventions. Each report will be discussed individually in detail below.

The first is a report 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.[68] 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.

The Society of Interventional Radiology (SIR) has devised training guidelines which includes both physician and facility requirements.[69] These guidelines are broken up into five categories: (1) cognitive qualifications in neuroanatomy, pathophysiology, hemodynamics, and clinical correlations for ischemic and hemorrhagic stroke; (2) technical qualifications for catheter-directed pharmacologic stroke therapy; (3) technical qualifications for use of intracranial mechanical devices for stroke therapy; (4) preexisting credentials; and (5) maintenance of qualifications. At the time of the writing of these guidelines, the authors stated that intracranial mechanical devices had not been shown to improve clinical outcomes in stroke patients. Thus, definitive training requirements for these devices were not given. They do, however, acknowledge that physicians should meet the training criteria for pharmacologic lysis in ischemic strokes as well as successful completion of a training course for a specific neurothrombectomy device.

These training standard documents, although congruent in their aim, scope, and core requirements, differ in a notable way. The multi-society report by Meyers and colleagues recommends that individuals complete a 1-year endovascular surgical neuroradiology fellowship to successfully use neurothrombectomy devices.[68] Alternatively, the SIR guidelines by Connors and colleagues refute this claim stating that this level of training is not necessary for those wishing to endovascularly treat acute ischemic stroke patients.[69] They suggest that the requisite technical skills can be acquired through alternative advanced training and surrogate experience.

Discussion

The natural history and poor clinical outcomes seen in patients with acute ischemic strokes has been well documented.[15-19] The advent of neurothrombectomy devices as a method of providing adequate recanalization in these patients has created a new option for the management of these patients. The clinical utility of these technologies particularly intriguing given the data showing significantly improved outcomes with successful recanalization of an occluded cerebral vessel.[22] Most especially hopeful are the data showing the strongest benefits with those achieving recanalization as early as possible.[23] Substantial infrastructure developed in the years since the clearance of these devices support the shifts in acute ischemic stroke care, which were prompted by these endovascular advances. However, a paucity of high quality research evaluating neurothrombectomy devices exists. Currently, only two neurothrombectomy devices, the MERCI clot retriever and Penumbra System, are FDA-cleared 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 cleared devices, but the comparative effectiveness of these devices 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.[49] The extent of usage of other neurothrombectomy devices in the "real-world" setting is unknown.

Our literature scan failed to identify any direct human 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, IA rtPA.

A previous systematic review of neurothrombectomy devices by Stead and colleagues was identified during our literature scan.[45] 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 homogeneous, as 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.

A continuing area of uncertainty revolved around the patient population most likely to benefit from use of neurothrombectomy devices. Indeed, many previously published studies evaluating devices that are FDA-cleared enrolled patients who presented within 8 hours of ischemic stroke symptom onset, had high baseline NIHSS scores, and had either failed or were ineligible to receive IV rtPA.[15-19,65] In addition, many of the patients enrolled in these trials had occlusions of the large intracranial vessels which have been demonstrated to respond poorly to IV rtPA therapy.[32-33] Ongoing clinical trials are evaluating the utility of various imaging techniques to better identify which patients are most likely to benefit from neurothrombectomy device use. This emerging data should help guide clinicians in choosing the most appropriate treatment of acute ischemic strokes, although further research is warranted.

Future Research/Research Gaps

Since the literature generated to evaluate neurothrombectomy devices in acute ischemic stroke are still in their infancy, identifying gaps in current knowledge and guiding future research efforts is paramount. The general goal of future trials should be to identify appropriate patients who could most benefit from neurothrombectomy treatment and improve their chance of good functional recovery.

Currently, there are eleven 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 3).[64] The first of these eleven 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. Seven of these studies have randomized, controlled designs with projected enrollment ranging from 20-900. The other four studies have prospective, observational designs ranging from 200-2000 projected participants. Six of the seven randomized controlled trials are allowing the use of multiple neurothrombectomy devices; most 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 (HRQoL). We identified only 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 intravenous rtPA.[67] The ongoing Interventional Management of Stroke (IMS) III trial, which is designed to evaluate whether combination use of intravenous and IA strategies (including use of the MERCI or EKOS device) vs. intravenous rtPA alone, is planned to measure both HRQoL and pharmacoeconomic outcomes.[70,71]

The use of advanced imaging techniques should be incorporated into future randomized, controlled trials to aid in identifying those patients most likely to benefit from neurothrombectomy devices as well as the performance of these devices at varying levels of occlusion. In fact, a number of on-going trials are currently studying the utilization of advanced imaging techniques in acute ischemic stroke management (Table 3). The MR RESCUE trial is using multimodal CT and MRI imaging to aid in identification of patients most likely to benefit

from device use. The Penumbra Imaging Collaborative Study (PICS) is using “real world” data to determine if there is a correlation between the imaging-defined size of the ischemic penumbra at hospital admission and patient outcomes in acute ischemic stroke patients who received the Penumbra System. The Imaging Guided Patient Selection for Interventional Revascularization Therapy (START) trial is enrolling acute ischemic stroke patients with a known imaging-defined infarct volume to evaluate the impact of the Penumbra System on functional and angiographic outcomes.

The utility of studies determining the comparative effectiveness of neurothrombectomy devices and IV rtPA in patients reporting within a 3-hour window from time of stroke onset and having no contraindications to either therapy has been questioned by some. This is based on the fundamentally different patient populations at which these treatments are targeted. This further emphasizes the need for improved patient selection based on the results of neuroimaging techniques. 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. The SWIFT trial will be the first study to prospectively examine the comparative effectiveness of two different neurothrombectomy devices, the SOLITAIRE FR and MERCI. Direct head-to-head trials clinical trials comparing various neurothrombectomy devices may be limited given the wide etiology and morphology of ischemic strokes.

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. Additionally, studies focused on broadening the opportunity for patients admitted to outlying primary stroke centers to receive treatment at comprehensive centers with endovascular services are required.

Summary

Currently available neurothrombectomy devices offer intriguing treatment options in patients with acute ischemic stroke, although a paucity of high quality research currently exists. There remains a need for further research on the topic, including randomized controlled trials to determine the optimal device(s) to use, and the patient populations most likely to benefit from their use. Additionally, studies of neurothrombectomy devices against contemporaneous controls investigating whether these devices truly treat final health outcomes associated with stroke rather than improving recanalization alone are warranted. Results of ongoing studies will likely only begin to address some of these questions.

References

1. Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367:1747-1757.
2. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics 2009 update: a report from the American Heart Association statistics committee and stroke statistics subcommittee. Circulation 2009;119:480-486.
3. Broderick MD. William M. Feinberg lecture: stroke therapy in the year 2025: burden, breakthroughs, and barriers to progress. Stroke 2004;35:205-211.
4. Lisabeth LD, Ireland JK, Risser JM, et al. Stroke risk after transient ischemic attack in a population-based setting. Stroke 2004;35:1842-1846.
5. Heron MP, Hoyert DL, Xu J, et al. Preliminary Data for 2006. Hyattsvile, MD: National Center for Health Statistics; 2008. National Vital Statistics Report, Vol. 56, No. 16.
6. National Center for Health Statistics. Centers for Disease Control and Prevention. Compressed Mortality File: Underlying Cause of Death, 1979-2005. Atlanta, GA: Centers for Disease Control and Prevention; 2008. Available at: http://wonder.cdc.gov/mortSQL.html. Accessed September 22, 2009.
7. Centers for Disease Control and Prevention. Prevalence of disabilities and associated health conditions among adults: United States. 1999. MMWR Morb Mortal Wkly Rep 2001;50:120-125.
8. Centers for Disease Control and Prevention. Outpatient rehabilitation among stroke survivors: 21 stats and the District of Columbia. MMWR Morb Mortal Wkly Rep 2007;56:504-507.
9. Taylor TN, Davis PH, Torner JC, et al. Lifetime costs of stroke in the United States. Stroke 1996;27:1459-1466.
10. Samsa GP, Matchar DB, Golstein L, et al. Utilities for major stroke: results from a survey of preferences among persons at increased risk for stroke. Am Heart J 1998;136:703-713.
11. McCullagh E, Brigstocke G, Donaldson N, et al. Determinants of caregiving burden and quality of life in caregivers of stroke patients. Stroke 2005;36:2181-2186.
12. Rigby H, Gubitz G, Eskes G, et al. Caring for stroke survivors: baseline and 1-year determinants of caregiver burden. Int J Stroke 2009;4:152-158.
13. Carod-Artal FJ, Ferreira Coral L, Trizotto DS, et al. Burden and perceived health status among caregivers of stroke patients. Cerebrovasc Dis 2009;28:475-480.
14. Fischer U, Arnold M, Nedeltchev K, et al. NIHSS score and arteriographic findings in acute ischemic stroke. Stroke 2005;36:2121-2125.
15. Nogueira RG, Lielbeskind DS, Sung G, et al, MERCI Multi MERCI Writing Comm. Predictors of clinical outcomes in acute ischemic stroke patients undergoing thrombectomy: Pooled analysis of the MERCI and multi MERCI trials. Stroke 2009;40:3777-3783.
16. Smith WS, Lev MH, English JD, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. Stroke 2009;40:3834-3840.
17. Smith WS, Tsao JW, Billings ME, et al. Prognostic significance of angiographically confirmed large vessel intracranial occlusion in patients presenting with acute brain ischemia. Neurocrit Care 2006;4:14-17.
18. Josephson SA, Saver JL, Smith WS; Merci and Multi Merci Investigators. Comparison of mechanical embolectomy and intraarterial thrombolysis in acute ischemic stroke within the MCA: MERCI and Multi MERCI compared to PROACT II. Neurocrit Care 2009;10:43-49.
19. Tomsick T, Broderick J, Carrozella J, et al. Revascularization results in the interventional management of stroke II trial. AJNR Am J Neuroradiol 2008;29:582-587.
20. Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci 1999;22:391-397.
21. Albers GW, Amarenco P, Easton, et al. Antithrombotic and thrombolytic therapy for ischemic stroke. Chest 2008;133:630S-669S.
22. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke 2007;38:967-973.
23. Khatri P, Abruzzo T, Yeatts SD, et al. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology 2009;73:1066-1072.

24. Lyden PD, ed. Thrombolytic Therapy for Acute Stroke, 2nd ed. Springer-Verlag, New York, NY. 2005.
25. NINDS rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.
26. The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768-774.
27. Hacke W, Kaste M, Bluhmki E et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-1329.
28. Wahlgren N, Ahmed N, Davalos A, et al. for the SITS-MOST Investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke—Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-282.
29. Wahlgren N, Ahmed N, Davalos A, et al. for the SITS Investigators. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. Lancet 2008;372:1303-1309.
30. del Zoppo GJ, Saver JL, Jauch EC et al. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. Stroke 2009;40:2945-2948.
31. Zangerle A, Kiechl S, Spiegel M, et al. Recanalization after thrombolysis in stroke patients: predictors and prognostic implications. Neurology 2007;68:39-44.
32. Wolpert SM, Bruckmann H, Greenlee R, et al. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. Am J Neuroradiol 1993;14:3-13.
33. Alexandrov AC, Grotta JC. Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. Neurology 2002;59:862-867.
34. Brott T, Bogousslavsky J. Treatment of acute ischemic stroke. N Engl J Med 2000;343(10):710-722.
35. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in acute cerebral thromboembolism. JAMA 1999;282:2003-2011.
36. Ciccone A, Valvassori L, Ponzio M, et al. Intra-arterial or intravenous thrombolysis for acute ischemic stroke? The SYNTHESIS pilot trial. J Neurointervent Surg 2010;2:74-79.
37. Guidance for Industry and FDA Staff: Pre-Clinical and Clinical Studies for Neurothrombectomy Devices. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health. Document issued on June 18, 2007. Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071403.htm. Accessed December 21, 2009.
38. Thomassen L, Bakke SJ. Endovascular reperfusion therapy in acute ischaemic stroke. Acta Neurol Scand 2007;115(Suppl 187):22-29.
39. Becker KJ, Brott TG. Approval of the MERCI Clot Retriever: a critical review. Stroke 2005;36:400-403.
40. Nogueira RG, Schwamm LH, Hirsch JA. Endovascular approaches to acute stroke, part 1: drugs, devices, and data. Am J Neuroradiol 2009;30:649-661.
41. Lutsep HL. Mechanical endovascular recanalization therapies. Curr Opin Neurol 2008;21:70-75.
42. United States Food and Drug Administration. 510(k) Premarket Notification. Available at: http://www.accessdata.fda.gov/scrIpts/cdrh/cfdocs/cfPMN/pmn.cfm. Accessed December 21, 2009.
43. Safety and efficacy of endovascular thrombectomy in patients with abnormal hemostasis pooled analysis of the MERCI and multi MERCI trials. Stroke 2009;40:516-522.
44. Gupta R. Arterial vasospasm during mechanical thrombectomy for acute stroke. J Neuroimaging 2009;19:61-64.
45. Stead LG, Gilmore RM, Bellolio MF, et al. Percutaneous clot removal devices in acute ischemic stroke: a systematic review and meta-analysis. Arch Neurol 2008;65:1024-1030.
46. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: Results of the MERCI trial. Stroke 2005;36:1432-1438.
47. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. Stroke 2008;39:1205-1212.

48. Nichols C, Carrozella J, Yeatts S, et al. Is periprocedural sedation during acute stroke therapy associated with poorer functional outcomes? J Neurointervent Surg 2010;2:67-70.
49. The Merci Retrieval System.® Available at: http://www.concentric-medical.com/webpage.php?ln_id=53. Accessed December 21, 2009.
50. Velat GJ, Hoh BL, Levy EI, et al. Primary intracranial stenting in acute ischemic stroke. Curr Cardiol Rep 2010;12:14-9.
51. Mocco J, Hanel RA, Sharma J, et al. Use of a vascular reconstruction device to salvage acute ischemic occlusions refractory to traditional endovascular recanalization methods. J Neurosurg 2010;112:557-562.
52. Zaidat OO, Wolfe T, Hussain SI, et al. Interventional acute ischemic stroke therapy with incracranial self-expanding stent. Stroke 2008;39:2392-2395.
53. Levy EI, Mehta R, Gupta R, et al. Self-expanding stents for recanalization of acute cerebrovascular occlusions. AJNR Am J Neuroradiol 2007;28:816-822.
54. Brekenfeld C, Schroth G, Mattle HP, et al. Stent placement in acute cerebral artery occlusion. Use of a self-expandable intracranial stent for acute stroke treatment. Stroke 2009;40:847-852.
55. Levy EI, Siddiqui AH, Crumlish A, et al. First Food and Drug Administration-approved prospective trial of primary intracranial stenting for acute stroke. SARIS (Stent-Assisted Recanalization in acute Ischemic Stroke). Stroke 2009;40:3552-3556.
56. Kelly ME, Furlan AJ, Fiorella D. Recanalization of an acute middle cerebral artery occlusion using a self-expanding, reconstrainable, intracranial microstent as a temporary endovascular bypass. Stroke 2008;39:1770-1773.
57. Suh SH, Lee KY, Hong CK, et al. Temporary stenting and retrieval of the self-expandable, intracranial stent in acute middle cerebral artery occlusion. Neuroradiology 2008;51:541-544.
58. Hauck EF, Mocco J, Snyder KV, et al. Temprary endovascular bypass: a novel treatment for acute stroke. Am J Neuroradiol 2009;30:1532-1533.
59. Castano C, Serena J, Davalos A. Use of the new Solitaire™ AB device for mechanical thrombectomy when Merci clot retriever has failed to remove the clot. A case report. Intervent Neuroradiol 2009;15:209-214.
60. Henkes H, Liebig T, Miloslavski E, et al. Endovascular acute ischemic stroke treatment using the self-expanding and fully retrievable Solitaire stent. Stroke 2009;40:E247-E248. Abstract P410.
61. Castano C, Dorado L, Guerrero C, et al. Mechanical thrombectomy with the Solitaire AB device in large artery occlusions of the anterior circulation. A pilot study. Stroke 2010 June 10 [Epub ahead of print].
62. Liebig T, Reinartz J, Hannes R, et al. Comparative *in vitro* study of five mechanical embolectomy systems: effectiveness of clot removal and risk of distal embolization. Neuroradiology 2008;50:43-52.
63. Gralla J, Schroth G, Remonda L, et al. Mechanical thrombectomy for acute ischemic stroke: thrombus-device interaction, efficiency, and complications *in vivo*. Stroke 2006;37:3019-3024.
64. Nogueira RG, Yoo AJ, Buonanno FS, et al. Endovascular approaches to acute stroke, part 2: a comprehensive review of studies and trials. AJNR Am J Neuroradiol 2009;30:859-875.
65. PPST Investigators. The penumbra pivotal stroke trial: Safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. Stroke 2009;40:2761-2768.
66. Lin R, Vora N, Zaidi S, et al. Mechanical approaches combined with intra-arterial pharmacological therapy are associated with higher recanalization rates than either intervention alone in revascularization of acute carotid terminus occlusion. Stroke 2009;40:2092-2097.
67. Patil CG, Long EF, Lansberg MG. Cost-effectiveness analysis of mechanical thrombectomy in acute ischemic stroke. J Neurosurg 2009;110:508-513.
68. Meyers PM, Schumacher HC, Alexander MJ, et al. Performance and training standards for endovascular ischemic stroke treatment. J Neurosurg 2010;113:149-152.
69. Connors JJ, Sacks D, Black CM, et al. Training guidelines for intra-arterial catheter-directed treatment of acute ischemic stroke: a statement from the special writing group of the Society of Interventional Radiology. J Vasc Interv Radiol 2009;20:1507-1522.
70. Khatri P, Hill MD, Palesch YY, et al. Methodology of the International Management of Stroke III Trial. Int J Stroke 2008;3:130-137.

71. Mauldin PD, Simpson KN, Palesch YY, et al. Design of the economic evaluation for the International Management of Stroke (III) trial. Int J Stroke 2008;3:138-144.

Appendix A. MEDLINE and CENTRAL Search Strategies

MEDLINE (OVID)

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

CENTRAL (OVID)

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

18. cerebral ischemia
19. acute ischemic stroke
20. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 11 and 20

Appendix B. Citations for Included and Excluded Reports

Citations for Included Reports

1. Abelson M, Roos J, Rymer M. Mechanical thrombo-embolectomy in acute ischaemic stroke: A local experience. Cardiovasc J Afr 2008;19:204-7.
2. Abou-Chebl A, Bajzer CT, Krieger DW, et al. Multimodal therapy for the treatment of severe ischemic stroke combining GPIIb/IIIa antagonists and angioplasty after failure of thrombolysis. Stroke 2005;36:2286-8.
3. Agner C, Deshaies EM, Bernardini GL, et al. Coronary AngioJet catheterization for the management of dural venous sinus thrombosis: Technical note. J Neurosurg 2005;103:368-71.
4. Bellon RJ, Putman CM, Budzik RF, et al. Rheolytic thrombectomy of the occluded internal carotid artery in the setting of acute ischemic stroke. Am J Neuroradiol 2001;22:526-30.
5. Bergui M, Stura G, Daniele D, et al. Mechanical thrombolysis in ischemic stroke attributable to basilar artery occlusion as first-line treatment. Stroke 2006;37:145-50.
6. Berlis A, Lutsep H, Barnwell S, et al. Mechanical thrombolysis in acute ischemic stroke with endovascular photoacoustic recanalization. Stroke 2004;35:1112-6.
7. Bose A, Henkes H, Alfke K, et al. The penumbra system: A mechanical device for the treatment of acute stroke due to thromboembolism. Am J Neuroradiol 2008;29:1409-13.
8. Buck BH, Saver JL. A case of acute ischemic stroke: Optimizing management with penumbra and vessel imaging. Nat Clin Pract Neurol 2007;3:465-9.
9. Burns TC, Rodriguez GJ, Patel S, et al. Endovascular interventions following intravenous thrombolysis may improve survival and recovery in patients with acute ischemic stroke: A case-control study. Am J Neuroradiol 2008;29:1918-24.
10. Bush RL, Bhama JK, Lin PH, et al. Transient ischemic attack due to early carotid stent thrombosis: Successful rescue with rheolytic thrombectomy and systemic abciximab. J Endovasc Ther 2003;10:870-4.
11. Castaño C, Serena J, Dávalos A. Use of the new solitaire™ AB device for mechanical thrombectomy when merci clot retriever has failed to remove the clot: A case report. Interv Neuroradiol 2009;15:209-14.
12. Chapot R. First experience with the catch, a new device for cerebral thrombectomy. Interv Neuroradiol 2005(Suppl. 2):58.
13. Chapot R, Wassef M, Bisdorff A, et al. Occlusion of the middle cerebral artery due to synthetic fibers. Am J Neuroradiol 2006;27:148-50.
14. Chiam PT, Samuelson RM, Mocco J, et al. Navigability trumps all: Stenting of acute middle cerebral artery occlusions with a new self-expandable stent. AJNR Am J Neuroradiol 2008;29:1956-8.
15. Chopko BW, Kerber C, Wong W, et al. Transcatheter snare removal of acute middle cerebral artery thromboembolism: Technical case report. Neurosurgery 2000;46:1529-31.
16. Clarençon F, Blanc R, Gallas S, et al. Thrombectomy for acute basilar artery occlusion by using double merci retriever devices and bilateral temporary vertebral artery flow reversal: Technical note. J Neurosurg 2009;111:53-6.

17. Clark WM, Buckley LA, Nesbit GM, et al. Intraarterial laser thrombolysis therapy for clinical stroke: A feasibility study. Stroke 2000;31:307.
18. Dabus G, Nogueira RG. Empty microcatheter technique for the deployment of a self-expanding stent to treat refractory middle cerebral artery occlusion in the setting of severe proximal tortuosity. J Neuroimaging 2009;19:164-8.
19. Devlin TG, Baxter BW, Feintuch TA, et al. The merci retrieval system for acute stroke: The southeast regional stroke center experience. Neurocrit Care 2007;6:11-21.
20. DeVries JT, White CJ, Cunningham MC, et al. Catheter-based therapy for acute ischemic stroke: A national unmet need. Catheter Cardiovasc Interv 2008;72:705-9.
21. Drake B, Redekop G. Middle cerebral artery embolectomy after failed mechanical clot removal. Can J Neurol Sci 2010;37:408-11.
22. du Mesnil de Rochemont R, Sitzer M, Neumann-Haefelin T, et al. Endovascular recanalization of acute atherothrombotic carotid artery occlusion holds up progressive stroke. Neuroradiology 2004;46:583-6.
23. Feng L, Mangla S, Pile-Spellman J. Rheolytic thrombectomy of acute stent thrombosis of cervical vertebral artery: Case report and literature review. Interv Neuroradiol. 2002;8:305-11.
24. Frei D, Bellon R. Mechanical thrombectomy in acute stroke patients who were refractory to intravenous thrombolytic therapy. Stroke 2009;40:E250.
25. Gobin YP, Starkman S, Duckwiler GR, et al. MERCI 1: A phase 1 study of mechanical embolus removal in cerebral ischemia. Stroke 2004;35:2848-54.
26. González A, Mayol A, Martínez E, et al. A. Mechanical thrombectomy with snare in patients with acute ischemic stroke. Neuroradiology 2007;49:365-72.
27. Grunwald IQ, Bose A, Struffert T, et al. Images in neurology. Liposuction in mind. Arch Neurol 2009;66:800-1.
28. Grunwald IQ, Walter S, Papanagiotou P, et al. Revascularization in acute ischaemic stroke using the penumbra system: The first single center experience. Eur J Neurol 2009;16:1210-6.
29. Gupta R. Arterial vasospasm during mechanical thrombectomy for acute stroke. J Neuroimaging 2009;19:61-4.
30. Harrigan MR, Levy EI, Bendok BR, et al. Bivalirudin for endovascular intervention in acute ischemic stroke: Case report. Neurosurgery 2004;54:218-23.
31. Henkes H, Reinartz J, Lowens S, et al. A device for fast mechanical clot retrieval from intracranial arteries (phenox clot retriever). Neurocrit Care 2006;5:134-40.
32. Huded V, Saraf R, Limaye U. Mechanical device the penumbra system in the management of acute stroke: Report of five cases. Neurol India 2009;57:310-2.
33. Hui FK, Narayanan S, Cawley CM. Posterior-to-anterior circulation access using the penumbra stroke system for mechanical thrombectomy of a right middle cerebral artery thrombus. World Neurosurg 2010;73:17-21.
34. Imai K, Mori T, Izumoto H, et al. Successful thrombectomy in acute terminal internal carotid occlusion using a basket type microsnare in conjunction with temporary proximal occlusion: A case report. Am J Neuroradiol 2005;26:1395-8.
35. Ionita CC, Yamamoto J, Tummala RP, et al. MRI assessment followed by successful mechanical recanalization of a complete tandem (internal carotid/middle cerebral artery) occlusion and reversal of a 10-hour fixed deficit. J Neuroimaging 2008;18:93-5.

36. Jo KD, Saver JL, Starkman S, et al. Predictors of recanalization with mechanical thrombectomy for acute ischemic stroke. Stroke 2008;39:599.
37. Kawamura A, Tilem M, Gossman DE. Rheolytic thrombectomy for thromboembolic occlusion of the internal carotid artery complicating coronary intervention. J Invasive Cardiol 2006;18:E108-10.
38. Kerber CW, Barr JD, Berger RM, et al. Snare retrieval of intracranial thrombus in patients with acute stroke. J Vasc Interv Radiol 2002;13:1269-74.
39. Kerber CW, Wanke I, Bernard Jr. J, et al. Rapid intracranial clot removal with a new device: The alligator retriever. Am J Neuroradiol 2007;28:860-3.
40. Kidwell CS, Latour L, Saver JL, et al. Thrombolytic toxicity: Blood brain barrier disruption in human ischemic stroke. Cerebrovasc Dis 2008;25:338-43.
41. Kim D, Jahan R, Starkman S, et al. Endovascular mechanical clot retrieval in a broad ischemic stroke cohort. Am J Neuroradiol 2006;27:2048-52.
42. Kim D, Liebeskind D, Starkman S, Ovbiagele B, et al. Time to recanalization for acute endovascular stroke therapies. Neurology 2006;66:A159.
43. Kobayashi A, Czepiel W, Dowzenko A, et al. Mechanical embolectomy in acute ischaemic stroke - report of the first two cases. Neurol Neurochir Pol 2008;42:451-7.
44. Kulcsar Z, Bonvin C, Pereira VM, et al. Penumbra system: A novel mechanical thrombectomy device for large-vessel occlusions in acute stroke. Am J Neuroradiol 2010;31:628-33.
45. Kuruvilla A, Norris GM, Manjila S, et al. Factor v leiden mutation in reocclusion after intra-arterial thrombolysis. Stroke 2009;40:660-2.
46. Lansberg MG, Fields JD, Albers GW, et al. Mechanical thrombectomy following intravenous thrombolysis in the treatment of acute stroke. Arch Neurol 2005;62:1763-5.
47. Layton KF, White JB, Cloft HJ, et al. Use of the perclose ProGlide device with the 9 french merci retrieval system. Neuroradiology 2006;48:324-6.
48. Layton KF, White JB, Cloft HJ, et al. Expanding the treatment window with mechanical thrombectomy in acute ischemic stroke. Neuroradiology 2006;48:402-4.
49. Liebeskind DS, Kim D, Starkman S, et al. Collateral failure? Late mechanical thrombectomy after failed intravenous thrombolysis. J Neuroimaging 2010;20:78-82.
50. Liebig T, Reinartz J, Guethe T, et al. Early clinical experiences with a new thrombectomy device for the treatment of ischemic stroke. Stroke 2008;39:608-9.
51. Lin R, Vora N, Zaidi S, et al. Mechanical approaches combined with intra-arterial pharmacological therapy are associated with higher recanalization rates than either intervention alone in revascularization of acute carotid terminus occlusion. Stroke 2009;40:2092-7.
52. Loh Y, Jahan R, McArthur DL, et al. Recanalization rates decrease with increasing thrombectomy attempts. Am J Neuroradiol 2010;31:935-9.
53. Madison MT, Goddard JK. III, Lassig JP, et al. Single center experience with combined (thrombolytics and mechanical thrombectomy) intra-arterial intervention in 112 consecutive patients with angiographically confirmed large vessel thromboembolic ischemic stroke (1-6 hours post symptom onset) from 2003 to 2007. Stroke 2008;39:547.
54. Mahon BR, Nesbit GM, Barnwell SL, et al. North american clinical experience with the EKOS MicroLysUS infusion catheter for the treatment of embolic stroke. AJNR Am J Neuroradiol 2003;24:534-8.

55. Marden FA, Putman CM. Cement-embolic stroke associated with vertebroplasty. AJNR Am J Neuroradiol 2008;29:1986-8.
56. Mayer TE, Hamann GF, Brueckmann HJ. Treatment of basilar artery embolism with a mechanical extraction device: Necessity of flow reversal. Stroke 2002;33:2232-5.
57. Mayer TE, Hamann GF, Schulte-Altedorneburg G, et al. Treatment of vertebrobasilar occlusion by using a coronary waterjet thrombectomy device: A pilot study. Am J Neuroradiol 2005;26:1389-94.
58. Mayer TE, Hmann GF, Brueckmann HJ. Mechanical extraction of a basilar-artery embolus with the use of flow reversal and a microbasket. N Engl J Med 2002;347:769-70.
59. Mocco J, Tawk RG, Jahromi BS, et al. Endovascular intervention for acute thromboembolic stroke in young patients: An ideal population for aggressive intervention? J Neurosurg 2009;110:30-4.
60. Nesbit GM, Luh G, Tien R, Barnwell SL. New and future endovascular treatment strategies for acute ischemic stroke. J Vasc Interv Radiol 2004;15:S103-10.
61. Newman CB, Pakbaz RS, Nguyen AD, et al. Endovascular treatment of extensive cerebral sinus thrombosis. J Neurosurg 2009;110:442-5.
62. Nogueira RG, Schwamm LH, Buonanno FS, et al. Low-pressure balloon angioplasty with adjuvant pharmacological therapy in patients with acute ischemic stroke caused by intracranial arterial occlusions. Neuroradiology 2008;50:331-40.
63. Noufal M, Schmidley JW, Erdem E, et al. Basilar artery occlusion treated with mechanical thrombectomy beyond eight hours with successful recanalization and good functional outcomes. Cerebrovasc Dis 2009;27:614-5.
64. Olson SE, Pakbaz RS, Kerber CW. Rapid clot removal for acute stroke therapy: Technical case report. Neurosurgery 2007;61:E86.
65. Oomura M, Hayakawa M, Sadato A, et al. Thrombectomy with soutenir for acute ischemic stroke patients unresponsive to intravenous recombinant tissue plasminogen activator. JNET 2009;3:10-6.
66. Phillips S, Stanley L, Nicoletto H, et al. Use of emergency department transcranial doppler assessment of reperfusion after intravenous tPA for ischemic stroke. J Emerg Med 2008 [Epub ahead of print].
67. PPST Investigators. The penumbra pivotal stroke trial: Safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. Stroke 2009;40:2761-8.
68. Qureshi AI, Janjua N, Kirmani JF, et al. Mechanical disruption of thrombus following intravenous tissue plasminogen activator for ischemic stroke: Clinical investigation study. J Neuroimaging 2007;17:124-30.
69. Qureshi AI, Siddiqui AM, Kim SH, et al. Reocclusion of recanalized arteries during intra-arterial thrombolysis for acute ischemic stroke. Am J Neuroradiol 2004;25:322-8.
70. Qureshi AI, Siddiqui AM, Suri MFK, et al. Aggressive mechanical clot disruption and low-dose intra-arterial third-generation thrombolytic agent for ischemic stroke: A prospective study. Neurosurgery 2002;51:1319-29.
71. Schumacher HC, Meyers PM, Yavagal DR, et al. Endovascular mechanical thrombectomy of an occluded superior division branch of the left MCA for acute cardioembolic stroke. Cardiovasc Intervent Radiol 2003;26:305-8.

72. Shah QA, Georgiadis A, Suri MFK, et al. Preliminary experience with intra-arterial nicardipine in patients with acute ischemic stroke. Neurocrit Care 2007;7:53-7.
73. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: Final results of the Multi MERCI trial. Stroke 2008;39:1205-12.
74. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: Results of the MERCI trial. Stroke 2005;36:1432-8.
75. Struffert T, Köhrmann M, Engelhorn T, et al. Penumbra stroke system as an "add-on" for the treatment of large vessel occlusive disease following thrombolysis: First results. Eur Radiol 2009;19:2286-93.
76. Sugrue PA, Hage ZA, Surdell DL, et al. Basilar artery occlusion following C1 lateral mass fracture managed by mechanical and pharmacological thrombolysis. Neurocrit Care 2008:1-6.
77. Suzuki S, Kidwell CS, Starkman S, et al. Use of multimodal MRI and novel endovascular therapies in a patient ineligible for intravenous tissue plasminogen activator. Stroke 2005;36:e77-9.
78. Tarr R, Alfke K, Stingele R, et al. Initial post-market experience of the penumbra system: Revascularization of large vessel occlusion in acute ischemic stroke in the united states and europe. Stroke 2009;40:e151.
79. Tomsick T, Broderick J, Carrozella J, et al. Revascularization results in the interventional management of stroke II trial. AJNR Am J Neuroradiol 2008;29:582-7.
80. Tsivgoulis G, Horton JA, Ness JM, et al. Intravenous thrombolysis followed by intra-arterial thrombolysis and mechanical thrombectomy for the treatment of pediatric ischemic stroke. J Neurol Sci 2008;275:151-3.
81. Versnick EJ, Do HM, Albers GW, et al. Mechanical thrombectomy for acute stroke. Am J Neuroradiol 2005;26:875-9.
82. Wikholm G. Transarterial embolectomy in acute stroke. Am J Neuroradiol 2003;24:892-4.
83. Wikholm G. Mechanical intracranial embolectomy. Interv Neuroradiology 1998;4:159-64.
84. Yin NS, Benavides S, Starkman S, et al. Autopsy findings after intracranial thrombectomy for acute ischemic stroke: A clinicopathologic study of 5 patients. Stroke 2010;41:938-47.
85. Yu W, Binder D, Foster-Barber A, et al. Endovascular embolectomy of acute basilar artery occlusion. Neurology 2003;61:1421-3.
86. Zaidat OO, Tolbert M, Smith TP, et al. Primary endovascular therapy with clot retrieval and balloon angioplasty for acute basilar artery occlusion. Pediatr Neurosurg 2005;41:323-7.
87. Zhang A, Collinson RL, Hurst RW, et al. Rheolytic thrombectomy for cerebral sinus thrombosis. Neurocrit Care 2008;9:17-26.

Citations for Excluded Reports

1. AbuRahma AF, Hayes JD, Deel JT, et al. Complications of diagnostic carotid/cerebral arteriography when performed by a vascular surgeon. Vasc Endovasc Surg 2006;40:189-95.
2. Aburahma AF, Robinson PA, Short YS. Management options for post carotid endarterectomy stroke. J Cardiovasc Surg 1996;37:331-6.

3. Ade-Ajayi N, Hall NJ, Liesner R, et al. Acute neonatal arterial occlusion: Is thrombolysis safe and effective? J Pediatr Surg 2008;43:1827-32.
4. Adovasio R, Visintin E. The subclavian-carotid bypass as a method for treating obstruction of the common carotid. Ann Ital Chir 1999 discussion 250-1;Mar-Apr;70:247-50.
5. Agrawal D, Mahapatra AK, Mishra NK. Fusiform aneurysm of a persistent trigeminal artery. J Clin Neurosci 2005;12:500-3.
6. Ahn JY, Han IB, Chung SS, et al. Endovascular thrombolysis and stenting of a middle cerebral artery occlusion beyond 6 hours post-attack: Special reference to the usefulness of diffusion-perfusion MRI. Neurol Res 2006;28:881-5.
7. Alfke K, Janssens U. Endovascular intervention in cases of impending stroke. Journal fur Anasthesie und Intensivbehandlung 2006;13:274.
8. Aljama Perez De La Lastra PJ, Garcia Villanueva A, Higuero Moreno F. Acute arterial obstruction. Angiologia 1975;27:78-82.
9. AlKawi A, Kirmani JF, Nazli JN, et al. Management of recurrent cerebral arterial occlusion in a patient with cardiac decompensation. Neurocrit Care 2007;6:139-45.
10. Anand N, Chan C, Wang NE. Cerebral venous thrombosis: A case report. J Emerg Med 2009;36:132-7.
11. Anda T, Suyama K, Kawano T, et al. Shotgun pellet embolus in the cerebral circulation via the internal carotid artery in the neck; a case report. No Shinkei Geka 1992;20:457-61.
12. Arboix A. Thrombolytic treatment in acute cerebral infarction. Neurol India 2007;55:8-9.
13. Armonda RA. Rapid clot removal for acute stroke therapy: Technical case report - commentary. Neurosurgery 2007;61.
14. Arnold M, Steinlin M, Baumann A, et al. Thrombolysis in childhood stroke: Report of 2 cases and review of the literature. Stroke 2009;40:801-7.
15. Assadian A, Senekowitsch C, Assadian O, et al. Combined open and endovascular stent grafting of internal carotid artery fibromuscular dysplasia: Long term results. Eur J Vascular Surg 2005;29:345-9.
16. Balzer K. Treatment of carotid stenosis: Carotid surgery or stent? in favor of operation. Herz 2004;29:90-103.
17. Bang OY, Saver JL, Buck BH, et al. Impact of collateral flow on tissue fate in acute ischaemic stroke. J Neurol Neurosur PS 2008;79:625-9.
18. Bang OY, Saver JL, Liebeskind DS, et al. Cholesterol level and symptomatic hemorrhagic transformation after ischemic stroke thrombolysis. Neurology 2007;68:737-42.
19. Barreto AD, Albright KC, Hallevi H, et al. Thrombus burden is associated with clinical outcome after intra-arterial therapy for acute ischemic stroke. Stroke 2008;39:3231-5.
20. Baumgartner RW, Georgiadis D, Nedeltchev K, et al. Stent-assisted endovascular thrombolysis versus intravenous thrombolysis in internal carotid artery dissection with tandem internal carotid and middle cerebral artery occlusion. Stroke 2008;39:e27-e28.
21. Belkin M, Mackey WC, Pessin MS, et al. Common carotid artery occlusion with patent internal and external carotid arteries: Diagnosis and surgical management. J Vasc Surg 1993;17:1019-28.
22. Berthet JP, Marty-Ané CH, Picard E, et al. Acute carotid artery thrombosis: Description of 12 surgically treated cases. Ann Vasc Surg 2005;19:11-8.

23. Bhatt A, Vora NA, Thomas AJ, et al. Lower pretreatment cerebral blood volume affects hemorrhagic risks after intra-arterial revascularization in acute stroke. Neurosurgery 2008;63:874-8.
24. Bicknell CD, Cheshire NJW. The relationship between carotid atherosclerotic plaque morphology and the embolic risk during endovascular therapy. Eur J Vasc Endovasc Surg 2003;26:17-21.
25. Bielecki D, Goracy J, Lewandowski M, et al. Acute thrombosis during carotid artery stenting treated with percutaneous embolectomy in a patient resistant to heparin. Kardiol Pol 2008;66:559-62,discussion 563
26. Biggs KL, Chiou AC, Hagino RT, et al. Endovascular repair of a spontaneous carotid artery dissection with carotid stent and coils. J Vasc Surg 2004;40:170-3.
27. Blanchi C, Ballard JL, Bergan JH, et al. Vascular reconstruction and major resection for malignancy. Arch Surg 1999;134:P851-5.
28. Borioni R, Garofalo M, Actis Dato GM, et al. Kinking of internal carotid artery: Is it a risk factor for cerebro-vascular damage in patients undergoing cardiac surgery? J Cardiovasc Surg 1994;35:325-6.
29. Bose A, Jansen O, PS Trial Investigators. The penumbra system: A new generation of mechanical device for clot removal by aspiration and extraction in acute stroke. Stroke 2007;38:603.
30. Brautaset NJ. Endovascular treatment in brain infarction. Tidsskr Nor Laegeforen 2008; 128:1074.
31. Brekenfeld C, Remonda L, Nedeltchev K, et al. Endovascular neuroradiological treatment of acute ischemic stroke: Techniques and results in 350 patients. Neurol Res. 2005;27(SUPPL. 1).
32. Brekenfeld C, Schroth G, Mattle HP, et al. Stent placement in acute cerebral artery occlusion: Use of a self-expandable intracranial stent for acute stroke treatment. Stroke 2009;40:847-52.
33. Brunner U, Schneider E, Largiader J, et al. Acute arterial occlusion: Surgical thrombectomy versus local fibrinolysis. Vasa-J Vascular Dis 1986;15:158-61.
34. Bulsara KR. Advances in mechanical devices for the treatment of stroke in patients with diabetes and impaired glucose tolerance. J Cardiometabl Syndr 2007;2:131-2.
35. Carrillo EH, Osborne DL, Spain DA, et al. Blunt carotid artery injuries: Difficulties with the diagnosis prior to neurologic event. J Trauma 199;46:1120-5.
36. Chaikof EL, Campbell BE, Smith III RB, et al. Paradoxical embolism and acute arterial occlusion: Rare or unsuspected? J Vasc Surg 1994;20:377-84.
37. Chapot R, Houdart E, Rogopoulos A, et al. Thromboaspiration in the basilar artery: Report of two cases. AJNR Am J Neuroradiol 2002;23:282-4.
38. Charvát F, Lacman J, Mašková J, et al. Mechanical embolectomy by means of the merci retriever in patients with acute occlusion of brain arteries. Cesk slov Neurol N. 2008;71:69-74.
39. Chen YJ, Chen WL, Tsai WC, Tsao YT. Sentinel central retinal artery occlusion: A forme fruste of idiopathic renal infarction. Am J Emerg Med 2009; 27:253.e1-2.
40. Choi JH, Bateman BT, Mangla S, et al. Endovascular recanalization therapy in acute ischemic stroke. Stroke 2006;37:419-24.
41. Chun JY, Smith W, Van Halbach V, et al. Current multimodality management of infectious intracranial aneurysms. Neurosurgery 2001;48:1203-14.

42. Ciostek P, Myrcha P, Grochowicz Ł, et al. Surgical treatment of common carotid artery occlusion by means of the cervical approach. Pol Przegl Chir. 2004;76:1231-44.
43. Cohen JE, Lylyk P, Ferrario A, et al. Carotid stent angioplasty: The role of cerebral protection devices. Neurol Res 2003;25:162-8.
44. Comeaux ME, Harkrider WW. Color doppler imaging versus angiography in near-total occlusion of the internal carotid artery. J Vasc Technol 1994;18:85-7.
45. Coward LJ, McCabe DJ, Ederle J, et al. Long-term outcome after angioplasty and stenting for symptomatic vertebral artery stenosis compared with medical treatment in the carotid and vertebral artery transluminal angioplasty study (CAVATAS): A randomized trial. Stroke 2007;38:1526-30.
46. Coward L, Featherstone R, Brown MM. Percutaneous transluminal angioplasty and stenting for vertebral artery stenosis. Cochrane Database Syst Rev 2005;(2):CD000516.
47. Cox MW, Whittaker DR, Martinez C, et al. Traumatic pseudoaneurysms of the head and neck: Early endovascular intervention. J Vasc Surg 2007;46:1227-33.
48. Cryer PE, Kissane J. Multiple arterial occlusions in a young woman. Am J Med 1975;59:837-43.
49. Dai C, Wang S, Zhang X, et al. Stent placement in acute cerebral artery occlusion. Stroke 2009;40.
50. Davis SM, Donnan GA. Merci retriever does it work? Stroke 2006;37:1342-3.
51. Delgado MG, Gil A, Mateos V, et al. Perfusion computed tomography-guided subacute endovascular reperfusion in a patient with carotid occlusion. Ann Vasc Surg 2008;22:465-8.
52. Deshmukh VR, Fiorella DJ, Albuquerque FC, et al. Intra-arterial thrombolysis for acute ischemic stroke: Preliminary experience with platelet glycoprotein IIb/IIIa inhibitors as adjunctive therapy. Neurosurgery 2005;56:46-54,discussion 54-5
53. DeVries JT, White CJ, Collins TJ, et al. Acute stroke intervention by interventional cardiologists. Catheter Cardio Inte 2009;73:692-8.
54. Diederich KW, Tuebler T, Schuler G, et al. In: First clinical experience in 42 patients with the mo.ma device, a novel endovascular clamping system for prevention of embolic stroke during percutaneous carotid stenting. Am J Cardiol;2002:TCT136.
55. Dorrler J, Maurer PC, Holzmann T, et al. Surgical treatment of acute arterial and venous occlusion. Hefte Unfallheilkd 1984;164:383-9.
56. Duckwiler G, MERCI Trial Investigators. Results of the combined MERCI (mechanical embolus removal in cerebral ischemia) trials I-II. J Neurosurg 2004;100:A180.
57. Ecker RD, Tummala RP, Levy EI, et al. "Internal cross-clamping" for symptomatic internal carotid artery thrombus: Report of two cases. J Neurosurg. 2007;107:1223-7.
58. Ederle J, Featherstone R, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev 2007;(4):CD000515..
59. Edgell RC, Yavagal DR, Agner C, et al. Recanalization of a symptomatic extracranial internal carotid artery near occlusion with proximal and distal protection: Technical case report. Neurosurgery 2007;61:E174
60. Egashira Y, Ikegame Y, Aki T, et al. Surgical treatment of a ruptured traumatic anterior cerebral artery aneurysm: Report of two cases. Jpn J Neurosurg 2005;14:635-40.
61. Emanuelli G, Marina R, Bizzi U, et al. Endovascular therapy versus surgery in carotid stenosis: Personal experience. Ital J Vasc Endovasc 2005;12:47-54.

62. Eskioglu E, Burry MV, Mericle RA. Transradial approach for neuroendovascular surgery of intracranial vascular lesions. J Neurosurg 2004;101:767-9.
63. Fearn SJ, Parry AD, Picton AJ, et al. Should heparin be reversed after carotid endarterectomy? A randomised prospective trial. Eur J Vasc Endovasc 1997;13:394-7.
64. Feist RM, Emond TL. Translumenal nd:Yag laser embolysis for central retinal artery occlusion. Retina 2005;25:797-9.
65. Feiwell RJ, Besmertis L, Sarkar R, et al. Detection of clinically silent infarcts after carotid endarterectomy by use of diffusion-weighted imaging. Am J Neuroradiol 2001;22:646-9.
66. Felberg RA, Burgin WS, Shaw S, et al. Patients who received thrombolysis for acute stroke and required mechanical ventilation: Outcome and analysis. Stroke 2000;31:138.
67. Feng W, Caplan M, Matheus MG, et al. Meningovascular syphilis with fatal vertebrobasilar occlusion. Am J Med Sci 2009;338:169-71.
68. Fiehler J, Boor S, Dörbecker R, et al. Table for optimization and monitoring of cerebral aneurysm therapy (TOMCAT): Results and implications of the lead-in phase. Clin Neuroradiol 2008;18:168-76.
69. Findlay JM, Ashforth R, Dean N. "Malignant" carotid artery dissection. Can J Neurol Sci 2002;29:378-85.
70. Findlay JM, Lougheed WM, Hamilton MG, et al. Carotid microendarterectomy. Neurosurgery 1993;32:792-8.
71. Flint AC, Duckwiler GR, Budzik RF, et al, MERCI and Multi MERCI Writing Committee. Mechanical thrombectomy of intracranial internal carotid occlusion: Pooled results of the MERCI and multi MERCI part I trials. Stroke 2007;38:1274-80.
72. Gada HG, Ali MJ, Graziano K, et al. Carotid embolectomy in the treatment of a paradoxical embolus. Ann Vasc Surg 2003;17:456-60.
73. Gagliardi R, Benvenuti L, Guizzardi G. Acute operation in cases of middle cerebral artery occlusion. Neurosurgery 1983;12:636-9.
74. Gandini R, Spinelli A, Fabiano S, et al. Carotid artery stenting with filter protection in high-risk patients showing severe electroencephalographic alterations during carotid endarterectomy. J Endovasc Surg 2006;13:451-6.
75. Gansera B, Schmidtler F, Angelis I, et al. Simultaneous carotid endarterectomy and cardiac surgery-additional risk factor or safe procedure? Z Kardiol 2004;93:49-57.
76. Gao Z, Miao Z, Ling F. Correlation of risk factors and therapeutic options with the unfavorable results in young patients with intra- and extracranial artery stenosis. Chinese Journal of Cerebrovascular Diseases 2008;5:10-4.
77. García-Arumí J, Martinez-Castillo V, Boixadera A, et al. Surgical embolus removal in retinal artery occlusion. Br J Ophthalmol 2006;90:1252-5.
78. Georgiadis AL, Hussein HM, Wright EJ, et al. Current statin use is associated with higher recanalization rates among patients treated with endovascular procedures for acute ischemic stroke. Stroke 2007;38:506.
79. Gibbons RJ, Miller TD. Tc-99m sestamibi infarct size as a surrogate endpoint. J Nucl Cardiol 2005;12:12-9.
80. Gobin A. Result of the MERCI (mechanical embolus removal in cerebral ischemia) trial. Am J Cardiol 2004;94(Suppl.1):128E.
81. Goldstein LB. Acute ischemic stroke treatment in 2007. Circulation 2007;116:1504-14.

82. Gomez-Beldarrain M, Telleria M, Garcia-Monco JC. Peripheral arterial embolism during thrombolysis for stroke. Neurology 2006;67:1096-7.
83. Green DW, Sanchez LA, Parodi JC, et al. Acute thromboembolic events during carotid artery angioplasty and stenting: Etiology and a technique of neurorescue. J Endovasc Ther 2005;12:360-5.
84. Greiner C, Wassmann H, Palkovic S, et al. Revascularization procedures in internal carotid artery pseudo-occlusion. Acta Neurochir 2004;146:237-43.
85. Grigoriadis S, Gomori JM, Grigoriadis N, et al. Clinically successful late recanalization of basilar artery occlusion in childhood: What are the odds? case report and review of the literature. J Neurol Sci 2007;260:256-60.
86. Grobelny TJ, Akhtar N, Rymer M, et al. Intracranial thrombolysis outcome analysis in the mechanical embolus removal in cerebral ischemia (MERCI) trial. J Neurosurg 2004;100:A191-2.
87. Gross BA, Hurley MC, Bernstein R, et al. Endovascular recanalization for subacute symptomatic intracranial arterial occlusion: A report of two cases. Clin Neurol Neurosurg 2008;110:1058-63.
88. Gubitz G, Lip G, Sudlow C, et al. Secondary prevention of stroke. Vasa-J Vascular Dis 2004;33:110-4.
89. Hagendorff A, Hertfelder HJ, Fehske W, et al. Recurrent arterial thromboembolism in hereditary hypoplasminogenaemia. Dtsch Med Wochenschr 1996;121:263-8.
90. Halse O, Clifton A, Cloud GC. Endovascular intervention for symptomatic bilateral carotid artery stenosis in an octogenarian. Age Ageing 2007;36:102-4.
91. Hamann GF. PTCA and STENT in acute brain infarction. Internist 1999;40:1333.
92. Hankey GJ. The BASICS of treating symptomatic basilar artery thrombosis. Lancet Neurol 2009;8:695-7.
93. Hanoa R. Carotid surgery for the prevention of stroke. Tidsskr Nor Laegeforen 2003;123:767.
94. Hellier KD, Hampton JL, Guadagno JV, et al. Perfusion CT helps decision making for thrombolysis when there is no clear time or onset. J Neurol Neurosur PS 2006;77:417-9.
95. Hepgul KT, Canbolat AT, Hamamcioglu MK, et al. Microsurgical removal of a balloon embolus from the middle cerebral artery caused during endovascular treatment of carotid-cavernous fistula: Case report. Turkish Neurosurgery 1994;4:88-92.
96. Higashida RT. Recent advances in the interventional treatment of acute ischemic stroke. Cerebrovasc Dis 2005;20:140-7.
97. Hirschl M, Kundi M, Blazek G. Five-year follow-up of patients after thromboendarterectomy of the internal carotid artery: Relevance of baroreceptor sensitivity. Stroke 1996;27:1167-72.
98. Ho J, Mah JK, Hill MD, Pacaud D. Pediatric stroke associated with new onset type 1 diabetes mellitus: Case reports and review of the literature. Pediatr Diabetes 2006;7:116-21.
99. Hoh DJ, Larsen DW, Elder JB, et al. Novel use of an endovascular embolectomy device for retrograde suction decompression-assisted clip ligation of a large paraclinoid aneurysm: Technical case report. Neurosurgery 2008;62(5 Suppl.2):ONSE412-3;discussion ONSE 413-4.
100. Horiuchi T, Nitta J, Sakai K, et al. Emergency embolectomy for treatment of acute middle cerebral artery occlusion. J Neurosurg 2007;106:257-62.

101. Huang Y, Chen Y, Wang Y, et al. Cervicocranial arterial dissection: Experience of 73 patients in a single center. Surg Neurol 2009;72:S2:20-7.
102. Hulusi M, Basaran M, Yilmaz AT. Carotid and coronary artery occlusion in a patient with takayasu arteritis. J Card Surg 2007;22:352-5.
103. Inagaki T, Saito K, Okuyama T, et al. Indication of thrombolysis for middle cerebral artery occlusion using MR diffusion - weighted image. Interv Neuroradiol 1999;5:137-44.
104. Iskander A, Nayak A, Chauhan MS. Submassive pulmonary embolism and paradoxical embolic stroke treated with percutaneous rheolytic thrombectomy and closure of the patent foramen ovale. Catheter Cardio Inte 2005;64:356-60.
105. Iwata T, Mori T, Tajiri H. Successful removal of clots embolic carotid occlusion by aspiration with a syringe - case report. Brain Nerve 2008;60:1067-72.
106. Jacobsen EA. Stroke--endovascular treatment methods. Tidsskr Nor Laegeforen 2008;128:698-702.
107. Jacobson II JH, Wallman LJ, Schumacher GA. Microsurgery as an aid to middle cerebral artery endarterectomy. Microsurgery 1992;13:112-8.
108. Janjua N, Alkawi A, Suri MF, et al. Impact of arterial reocclusion and distal fragmentation during thrombolysis among patients with acute ischemic stroke. AJNR Am J Neuroradiol 2008;29:253-8.
109. Jicking G, Scozzafava J, Mouradian M, et al. A cool-handed patient with a right hemispheric stroke. Can J Neurol Sci 2008;35:655-7.
110. Johnston SC, Hauser SL. Neurology and medical devices. Ann Neurol 2006;60.
111. Josephson SA, Saver JL, Smith WS. Comparison of mechanical embolectomy and intraarterial thrombolysis in acute ischemic stroke within the MCA: MERCI and multi MERCI compared to PROACT II. Neurocrit Care 2009;10:43-9.
112. Jost JO, Ruehland D, Pircher W. Acute arterial occlusion. Z Allgemeinmed 1981;57:765-71.
113. Jung YA, In BH, Sang SC, et al. Endovascular thrombolysis and stenting of a middle cerebral artery occlusion beyond 6 hours post-attack: Special reference to the usefulness of diffusion-perfusion MRI. Neurol Res 2006;28:881-5.
114. Kai Y, Hamada J, Morioka M, et al. Successful treatment of a ruptured dissecting basilar artery aneurysm: Case report. J Neurosurg 2004;100:1072-5.
115. Kakinuma K, Ezuka I, Takai N, et al. The simple indicator for revascularization of acute middle cerebral artery occlusion using angiogram and ultra-early embolectomy. Surg Neurol 1999;51:332-41.
116. Kakinuma K, Ezuka I, Takai N, et al. The simple indicator for revascularization of acute middle cerebral artery occlusion using angiogram and ultra-early embolectomy. Surg Neurol 1999;51:332-41.
117. Kao HL, Lin MS, Wang CS, et al. Feasibility of endovascular recanalization for symptomatic cervical internal carotid artery occlusion. J Am Coll Cardiol 2007;49:765-71.
118. Kao H, Lin M. Feasibility ad safety of endovascular recanalization for chronic cervical internal carotid artery occlusion. Am J Cardiol 2008;102(Suppl.1):103I.
119. Karam C, Koussa S. Cerebral dural sinus thrombosis following cisplatin chemotherapy. J Clin Neurosci 2008;15:1274-5.

120. Kelly ME, Furlan AJ, Fiorella D. Recanalization of an acute middle cerebral artery occlusion using a self-expanding, reconstrainable, intracranial microstent as a temporary endovascular bypass. Stroke 2008;39:1770-3.
121. Kidwell C, Jahan R, Starkman S, et al. Merci retriever and recanalization of stroke clots using embolectomy. International Stroke Conference 2009(Ongoing Clinical Trials Abstract):2009.
122. Kidwell CS. Embolectomy for clot removal after acute stroke. In: Cochrane Central Register of Controlled Trials, 2005: CN-00603486.
123. Kidwell CS, Jahan R, Starkman S, et al. MR and REcanalization of stroke clots using embolectomy (MR RESCUE). International Stroke Conference. 2006(Ongoing Clinical Trials Abstracts):2006.
124. Kidwell CS, Jahan R, Starkman S, et al. MR and recanalization of stroke clots using embolectomy (MR RESCUE). International Stroke Conference. 2005(Ongoing Clinical Trials Abstracts):2005.
125. Kidwell CS, Saver JL, Latour LL, et al. Reduced incidence of HARM following mechanical thrombectomy compared to intra-arterial thrombolysis in acute stroke. Stroke 2004;35:236.
126. Kim DJ, Kim DI, Byun JS, et al. Simple microwire and microcatheter mechanical thrombolysis with adjuvant intraarterial urokinase for treatment of hyperacute ischemic stroke patients. Acta Radiol 2008;49:351-7.
127. Kim I, Inada Y, Kim F. Surgical treatment of extracranial internal carotid occulusion. A case of thrombo-endarterectomy using fogarty catheter. Neurol Surg Tokyo 1978;6:913-7.
128. Kirton A, Wong JH, Mah J, et al. Successful endovascular therapy for acute basilar thrombosis in an adolescent. Pediatrics 2003;112:e248-51.
129. Klisch J. Acute simultaneous occlusion of the distal common carotid artery and middle cerebral artery: Endovascular recanalization. Klinische Neuroradiologie 2004;14:216-22.
130. Kniemeyer HW, Aulich A, Schlachetzki F, et al. Pseudo- and segmental occlusion of the internal carotid artery: A new classification, surgical treatment and results. Eur J Vasc Endovasc 1996;12:310-20.
131. Kobayashi M, Takayama H, Mihara B, et al. Severe vasospasm caused by repeated intraventricular haemorrhage from small arteriovenous malformation. Acta Neurochir 2002;144:405-6.
132. Koch P, Desal HA, Auffray-Calvier E, et al. Natural history and management of mycotic intracranial aneurysm. J Neuroradiology 2005;32:258-65.
133. Koenigsberg RA, Gul N, Thomas C, et al. Emergency treatment of anterior circulation cerebral arterial thrombosis within the 6- to 9-h window. Emer Radiol 2000;7:129-34.
134. Koide M, Abe M, Kodera K, et al. Thromboembolism originated from the pulmonary artery stump after fontan operation. Jpn J Thorac Cardiovasc Surg 1999;47:346-9.
135. Kole MK, Pelz DM, Lee DH, et al. Intra-arterial thrombolysis of embolic middle cerebral artery using collateral pathways. Can J Neurol Sci 2005;32:257-60.
136. Kollár L, Kasza G, Rozsos I, et al. Internal carotid stent implantation with angioscopic control. Acta Chir Hung 1997;36:168-9.
137. Konovalov AN, Serbinenko FA. A case of successful removal of a middle cerebral artery thrombus developing after occlusion with balloons of the afferent vessels of an

arteriovenous aneurysm (russian). Zhurnal Voprosy Nejrokhirurgii Imeni N.N.Burdenko 1973;37:29-34.
138. Koren MJ, Bryant B, Hilton TC, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. N Engl J Med 1995;332:1237-8.
139. Krajina A, Krajíčková D, Špriňar Z, et al. Mechanical percutaneous extraction of embolus in acute stroke: A case report and review of the literature. Ceska a Slovenska Neurologie a Neurochirurgie 2005;68:51-7.
140. Kraus GE, Herman JM, Marciano F, et al. Ruptured giant aneurysm of an occluded middle cerebral artery in a severe- grade patient: Case report. Neurosurgery 1995;36:169-72.
141. LaMuraglia GM, Fabian RL, Brewster DC, et al. The current surgical management of carotid body paragangliomas. J Vasc Surg 1992;15:1038-45.
142. Lanfranconi S, Bersano A, D'Adda E, et al. Safety of carotid stenting for stroke prevention: Need of an independent outcome assessor. Neurol Sci 2009 Apr;30:93-7.
143. Lawton MT, Quinones-Hinojosa A, Chang EF, et al. Thrombotic intracranial aneurysms: Classification scheme and management strategies in 68 patients. Neurosurgery 2005;56:441-54.
144. Le BHC, Williams DS, Gibbs P. Acute arterial ischaemia secondary to multiple tumour emboli. Intern Med J 2006;36:475-6.
145. Leary MC, Gobin YP, Jahan R, et al. Thrombolysis following attempted mechanical embolectomy in acute stroke treatment (MERCI trial). Stroke 2003:34:311.
146. Leary MC, Saver JL, Gobin YP, et al. Beyond tissue plasminogen activator: Mechanical intervention in acute stroke. Ann Emerg Med 2003;41:838-46.
147. Lee VH, Samuels S, Herbst TJ, et al. Histopathologic description of wingspan stent in acute ischemic stroke. Neurocrit Care 2009. doi 10.1007/s12028-009-9258-0.
148. Leischker AH, Kolb G. Patients over 75 with symptomatic carotid stenosis profit more from carotid thromboendarterectomy than younger patients. European Journal of Geriatrics. 2001;3:205-7.
149. Levy EI, Ecker RD, Hanel RA, et al. Acute M2 bifurcation stenting for cerebral infarction: Lessons learned from the heart: Technical case report. Neurosurgery 2006;58.
150. Liebeskind D, Duckwiler G, Starkman S, et al. No reflow: Open arteries without tissue perfusion in acute ischemic stroke. Stroke 2009;40:e122.
151. Lilja A, Holtås S. Nya tekniker för säker diagnos och terapi vid stroke. Lakartidningen 2008;105:3424-9.
152. Lin M, Kao H. Safety of endovascular recanalization for symptomatic cervical internal carotid artery occlusion. Am J Cardiol 2008:AS221.
153. Lin M, Wang C, Lin L, et al. Feasibility and safety of endovascular recanalization for symptomatic cervical internal carotid artery occlusion. Circulation 2006;114:684-5.
154. Lin PH, Bush RL, Peden E, et al. What is the learning curve for carotid artery stenting with neuroprotection? analysis of 200 consecutive cases at an academic institution. Perspect Vasc Surg Endovasc Ther. 2005;17:113-25.
155. Lin PH, Bush RL, Peden EK, et al. Carotid artery stenting with neuroprotection: Assessing the learning curve and treatment outcome. Am J Surg 2005;190:850-7.
156. Lin PH, Kougias P, Huynh TT, et al. Endovascular repair of ascending aortic pseudoaneurysm: Technical considerations of a common carotid artery approach using the zenith aortic cuff endograft. J Endovasc Ther 2007;14:794-8.

157. Linfante I, Llinas RH, Selim M, et al. Clinical and vascular outcome in internal carotid artery versus middle cerebral artery occlusions after intravenous tissue plasminogen activator. Stroke 2002;33:2066-71.
158. Linskey ME, Sekhar LN, Hecht ST. Emergency embolectomy for embolic occlusion of the middle cerebral artery after internal carotid artery balloon test occlusion. case report. J Neurosurg 1992;77:134-8.
159. Linskey ME, Stephanian E, Sekhar LN. Emergent middle cerebral artery embolectomy: A useful technique for cranial base surgery. Skull Base Surg. 1993;3:80-6.
160. Lord RSA, Raj TB, Stary DL, et al. Comparison of saphenous vein patch, polytetrafluoroethylene patch, and direct arteriotomy closure after carotid endarterectomy. part I. perioperative results. J Vasc Surg 1989;9:521-9.
161. Lovblad KO. Intracerebral interventions other than lysis in acute stroke. Cardiovasc Intervent Radiol 2005;28(SUPPL. 1).
162. Lutsep HL, Clark WM, Nesbit GH, et al. Intra-arterial suction thrombectomy in acute stroke. Stroke 1999;30:P13.
163. Lutsep HL, Clark WM, Nesbit GM, et al. Intraarterial suction thrombectomy in acute stroke. Am J Neuroradiol 2002;23:783-6.
164. Lutsep HL, Rymer MM, Nesbit GM. Vertebrobasilar revascularization rates and outcomes in the MERCI and multi-MERCI trials. J Stroke Cerebrovasc Dis 2008;17:55-7.
165. Mangiafico S, Cellerini M, Nencini P, et al. Intravenous glycoprotein IIb/IIIa inhibitor (tirofiban) followed by intra-arterial urokinase and mechanical thrombolysis in stroke. AJNR Am J Neuroradiol 2005;26:2595-601.
166. Mangiafico S, Cellerini M, Nencini P, et al. Intravenous tirofiban with intra-arterial urokinase and mechanical thrombolysis in stroke: Preliminary experience in 11 cases. Stroke 2005;36:2154-8.
167. Marder V, Chute D, Starkman S, et al. Histology of thrombi retrieved from acute ischemic stroke patients by endovascular embolectomy. Stroke 2005;36:516.
168. Marder VJ, Chute DJ, Starkman S, et al. Analysis of thrombi retrieved from cerebral arteries of patients with acute ischemic stroke. Stroke 2006;37:2086-93.
169. Martinez H, Zoarski GH, Obuchowski AM, et al. Mechanical thrombectomy of the internal carotid artery and middle cerebral arteries for acute stroke by using the retriever device. Am J Neuroradiol 2004;25:1812-5.
170. Martínez-Fernández E, González García A, Gil Peralta A, et al. Outcome of intraarterial procedures in acute ischemic stroke. Neurologia 2008;23:21-8.
171. Massano J, Ferreira D, Toledo T, et al. Stroke and multiple peripheral thrombotic events in an adult with varicella. Eur J Neurol 2008;15:e90-1.
172. Mazighi M, Serfaty J-, Labreuche J, et al. Comparison of intravenous alteplase with a combined intravenous-endovascular approach in patients with stroke and confirmed arterial occlusion (RECANALISE study): A prospective cohort study. Lancet Neurol 2009;8:802-9.
173. McCormick PW, Spetzler RF, Bailes JE, et al. Thromboendarterectomy of the symptomatic occluded internal carotid artery. J Neurosurg 1992;76:752-8.
174. McKinney WB, O'Hara W, Sreeram K, et al. The successful surgical treatment of a paradoxical embolus to the carotid bifurcation. J Vasc Surg 2001;33:880-2.

175. McLaughlin MR, Jho H, Kwon Y. Acute subdural hematoma caused by a ruptured giant intracavernous aneurysm: Case report. Neurosurgery 1996;38:388-92.
176. Meyer FB. Emergency embolectomy for treatment of acute middle cerebral artery occlusion. J Neurosurg 2007;106:255.
177. Meyer FB, Friedman JA, Nichols DA, et al. Surgical repair of clinoidal segment carotid artery aneurysms unsuitable for endovascular treatment. Neurosurgery 2001;48:476-86.
178. Meyer FB, Piepgras DG, Sundt Jr. TM, et al. Emergency embolectomy for acute occlusion of the middle cerebral artery. J Neurosurg 1985;62:639-47.
179. Mohammad Y, Hussein HM, Christoforidis G, et al. In: The effect of mechanical disruption of thrombus during intra-arterial thrombolysis for patients with acute ischemic stroke. Neurology 2008;70(Suppl.1):A358.
180. Morgan T, Zuccarello M, Narayan R, et al. Preliminary findings of the minimally-invasive surgery plus rtPA for intracerebral hemorrhage evacuation (MISTIE) clinical trial. Act Neur S 2008;105:147-51.
181. Mudra H, Ziegler M, Haufe MC, et al. Percutaneous carotid angioplasty with stent implantation and protection device against embolism--a prospective study of 100 consecutive cases. Dtsch Med Wochenschr 2003;128:790-6.
182. Mullen MT, Sansing LH, Hurst RW, et al. Obstructive hydrocephalus from venous sinus thrombosis. Neurocrit Care 2009;10:359-62.
183. Müllges W. Acute cerebral ischemia and its treatment. Journal fur Anasthesie und Intensivbehandlung 2007;14.
184. Muramoto M, Kim F, Kim I. Thrombectomy of the middle cerebral artery. Neurol Surg Tokyo 1981;9:733-8.
185. Mussa FF, Aaronson N, Lamparello PJ, Maldonado TS, Cayne NS, Adelman MA, et al. Outcome of carotid endarterectomy for acute neurological deficit. Vasc Endovasc Surg 2009;43:364-9.
186. Myers SI, Valentine RJ, Estrera A, et al. The intra-aortic balloon pump, a novel addition to staged repair of combined symptomatic cerebrovascular and coronary artery disease. Ann Vasc Surg 1993;7:239-42.
187. Nagaraja D, Sarma GRK. Treatment of cerebral sinus/venous thrombosis. Neurol India 2002;50:114-6.
188. Nakamura K, Murata K, Kawakami T, et al. Percutaneous transluminal angioplasty for stenosis of the posterior cerebral artery in progressive stroke - case report. Neurol Med 2009;49:351-3.
189. Nanjudappa A, Dieter RS. How would you treat this patient? VDM 2008;5:96.
190. Natali J. The surgical treatment of stenoses and occlusions of the internal carotid artery. Ann Chir 1973;27:297-304.
191. Nazliel B, Starkman S, Liebeskind D, et al. Impact of endovascular recanalization upon functional outcome in acute ischemic stroke. Neurology 2007;68:A88.
192. Nedeltchev K, Brekenfeld C, Remonda L, et al. Internal carotid artery stent implantation in 25 patients with acute stroke: Preliminary results. Radiology 2005;237:1029-37.
193. Nemati MN, Dietz H. Regional cerebral blood circulation and cerebrovascular reserve capacity as indications for in vascular reconstructive surgery. Fortschr Neurol Psychiatr 1996:515-21.

194. Nikas D, Reimers B, Elisabetta M, et al. Percutaneous interventions in patients with acute ischemic stroke related to obstructive atherosclerotic disease or dissection of the extracranial carotid artery. J Endovasc Ther 2007;14:279-88.
195. Nogueira RG, Smith WS. Safety and efficacy of endovascular thrombectomy in patients with abnormal hemostasis pooled analysis of the MERCI and multi MERCI trials. Stroke 2009;40:516-22.
196. Nogueira RG, Liebeskind DS, Smith WS. Systolic blood pressure is a strong predictor of vessel recanalization in acute ischemic stroke patients undergoing thrombectomy: Pooled analysis of the MERCI and multi MERCI trials. Neurology 2009;72(Suppl.3):A4.
197. Nogueira RG, Lielbeskind DS, Sung G, et al, MERCI Multi MERCI Writing Comm. Predictors of clinical outcomes in acute ischemic stroke patients undergoing thrombectomy: Pooled analysis of the MERCI and multi MERCI trials. Stroke 2009;40:E131.
198. Nowierski LW,Jr. Embolectomy following major artery occlusion. Northwest Med 1956;55:955-8.
199. Ohanian AG, Saver JL, Starkman S, et al. Successful endovascular recanalization predicts modest reduction of reactive hypertension in acute ischemic stroke. Stroke 2008;39:725-6.
200. Opremcak E, Rehmar AJ, Ridenour CD, et al. Restoration of retinal blood flow via translumenal nd:YAG embolysis/embolectomy (TYL/E) for central and branch retinal artery occlusion. Retina 2008;28:226-35.
201. Ozdemir O, Bussière M, Leung A, et al. Intra-arterial thrombolysis of occluded middle cerebral artery by use of collateral pathways in patients with tandem cervical carotid artery/middle cerebral artery occlusion. Am J Neuroradiol 2008;29:1596-600.
202. Panagotacos JJ, Bang OY, Saver JL, et al. Multimodal MRI predicts outcome of mechanical thrombectomy for acute cerebral ischemia. Ann Neurol 2008;64(Suppl.12):S18.
203. Parodi JC, Rubin BG, Azizzadeh A, et al. Endovascular treatment of an internal carotid artery thrombus using reversal of flow: A case report. J Vasc Surg 2005;41:146-50.
204. Patel RK, Fasan O, Arya R. Thrombolysis in pregnancy. Thromb Haemost 2003;90:1216-7.
205. Patil CG, Long EF, Lansberg MG. Cost-effectiveness analysis of mechanical thrombectomy in acute ischemic stroke. J Neurosurg 2009;110:508-13.
206. Peiper C, Nowack J, Ktenidis K, et al. Eversion endarterectomy versus open thromboendarterectomy and patch plasty for the treatment of internal carotid artery stenosis. Eur J Vasc Endovasc 1999;18:339-43.
207. Peterson BG, Resnick SA, Morasch MD, et al. Aortic arch vessel stenting: A single-center experience using cerebral protection. Arch Surg. 2006;141:560-3.
208. Peyman GA, Gremillion Jr. CM. Surgical removal of a branch retinal artery embolus: A case report. Int Ophthalmol 1990;14:295-8.
209. Pfefferkorn T, Mayer TE, Dichgans M. Telephone-guided intravenous thrombolysis followed by mechanical recanalisation therapy for acute basilar artery occlusion. J Neurol 2007;254(Suppl.3):52.
210. Pfefferkorn T, Mayer TE, Opherk C, et al. Staged escalation therapy in acute basilar artery occlusion: Intravenous thrombolysis and on-demand consecutive endovascular

mechanical thrombectomy: Preliminary experience in 16 patients. Stroke 2008;39:1496-500.
211. Prabhakaran S, Chen M, Choi JH, et al. Major neurologic improvement following endovascular recanalization therapy for acute ischemic stroke. Cerebrovasc Dis 2008;25:401-7.
212. Pride Jr. GL, Horowitz MB, Purdy PD. Endovascular problem solving with intravascular stents. Am J Neuroradiol 2000;21:532-40.
213. Qureshi AI, Alkawi A, Hussein HM, et al. Angiographic analysis of intravascular thrombus volume in patients with acute ischemic stroke. J Endovasc Ther 2007;14:475-82.
214. Qureshi AI, Kirmani JF, Janjua N, et al. Mechanical thrombectomy following intravenous thrombolysis for ischemic stroke is safe and promotes recanalization. Stroke 2006;37:658.
215. Reimers B, Tübler T, De Donato G, et al. Endovascular treatment of in-stent restenosis after carotid artery stenting: Immediate and midterm results. J Endovasc Ther 2006;13:429-35.
216. Restrepo L, Bang OY, Ovbiagele B, et al. Impact of hyperlipidemia and statins on ischemic stroke outcomes after intra-arterial fibrinolysis and percutaneous mechanical embolectomy. Cerebrovasc Dis 2009;28:384-90.
217. Restrepo L, Bang OY, Ovbiagele B, et al. Safety and potential benefits of statins in stroke patients undergoing intra-arterial thrombolysis and percutaneous mechanical embolectomy. Stroke 2008;39:691.
218. Reynard M, Hanscom TA. Neodymium:Yttrium-aluminum-garnet laser arteriotomy with embolectomy for central retinal artery occlusion. Am J Ophthalmol 2004;137:196-8.
219. Ringer AJ, Qureshi AI, Fessler RD, et al. Angioplasty of intracranial occlusion resistant to thrombolysis in acute ischemic stroke. Neurosurgery 2001;48:1282-90.
220. Rose SC. Mechanical devices for arterial occlusion and therapeutic vascular occlusion utilizing steel coil technique: Clinical applications. Am J Roentgenol 2009;192:321-4.
221. Russman AN, Frost N, Katzan IL, et al. Antithrombotic therapy and thrombectomy for stroke complicating cerebral venous thrombosis: The cleveland clinic experience. Stroke 2006;37:662.
222. Russo MJ, Chaer RA, Lin SC, et al. Percutaneous endovascular treatment of acute sequential systemic emboli. J Vasc Surg 2006;43:388-92.
223. Safian RD, Bacharach JM, Ansel GM, et al. Carotid stenting with a new system for distal embolic protection and stenting in high-risk patients: The carotid revascularization with ev3 arterial technology evolution (CREATE) feasibility trial. Catheter Cardio Inte. 2004;63:1-6.
224. Sakai K, Nitta J, Horiuchi T, et al. Emergency revascularization for acute main-trunk occlusion in the anterior circulation. Neurosurg Rev 2008;31:69-76.
225. Santoro A, Bristot R, Paolini S, et al. Radiation injury involving the internal carotid artery: Report of two cases. J Neurosurg Sci 2000;44:159-64.
226. Santoro A, Paolini S, Piattella MC, et al. Spontaneous thrombosis of a giant carotid-ophthalmic aneurysm and of the ipsilateral internal carotid. case report. Nuova Rivista di Neurologia 1997;7:147-50.
227. Sartipy U, Malmstedt J, Holm P, et al. Aorto-carotid bypass for cerebral malperfusion after aortic dissection surgery: A case report. Heart Surg Forum 2006;9:342-3.

228. Sauvageau E, Samuelson RM, Levy EI, et al. Middle cerebral artery stenting for acute ischemic stroke after unsuccessful merci retrieval. Neurosurgery 2007;60:701-6.
229. Schlangen C, Kosinski CM, Mull M, et al. Management of an occluding macro-embolus at the carotid bifurcation. J Neurol 2008;255:446-7.
230. Schneiderman J, Feinberg MS, Schwammenthal E, et al. Protruding aortic arch thrombus: Treatment with minimally invasive surgical approach. J vasc Surg 2004;40:1083-8.
231. Schonewille WJ, Wijman CA, Michel P, et al. Treatment and outcomes of acute basilar artery occlusion in the basilar artery international cooperation study (BASICS): A prospective registry study. Lancet Neurol 2009;8:724-30.
232. Schulte-Altedorneburg G. The effectivity of intraarterial thrombolysis in acute occlusion of the proximal middle cerebral artery. Radiologe 2008;48:228.
233. Schulte-Altedorneburg G, Bruckmann H, Hamann GF, et al. Ischemic and hemorrhagic complications after intra-arterial fibrinolysis in vertebrobasilar occlusion. AJNR Am J Neuroradiol 2007;28:378-81.
234. Sekhar LN, Iwai Y, Wright DC, et al. Vein graft replacement of the middle cerebral artery after unsuccessful embolectomy: Case report. Neurosurgery 1993;33:723-7.
235. Selaru D, Radocea R, Stanca H. Inferior temporal branch arterial occlusion--acute form. Oftalmologia 2008;52:64-71.
236. Setacci C, de Donato G, Chisci E, et al. Rationale and design of Emergent/Urgent carotid artery stenting (EUCAS) registry. J Cardiovasc Surg 2008;49:737-42.
237. Setacci C, de Donato G, Setacci F, et al. In-stent restenosis after carotid angioplasty and stenting: A challenge for the vascular surgeon. Eur J Vasc Endovasc 2005;29:601-7.
238. Shah QA, Memon MZ, Tummala RP, et al. Combined surgical and endovascular approach to treat symptomatic in-stent occlusion of the left common carotid artery origin: Technical note. J Neurosurg 2009;110:935-8.
239. Sheehan MK, Greisler HP, Littooy FN, et al. The effect of intraoperative duplex on the management of postoperative stroke. Surgery 2002;132:761-6.
240. Shhadeh A, Sarkar A, Hassan A, et al. Predictors of recanalization and outcome of multimodal endovascular therapy for acute ischemic stroke: Early treatment versus modality. Neurology 2009;11(Suppl.3):A290.
241. Shi Y, Meng X, Cai T, et al. Intracranial arterial thrombolysis and mechanical fragmentation in patients with acute infarction. J Intervent Radiol 2008;17:309-12.
242. Shi Z, Liebeskind DS, Saver JL, et al. Subarachnoid hemorrhage in acute stroke is more common with mechanical revascularization than intra-arterial thrombolysis. Stroke 2009;40:E272.
243. Silver B, Gulka I, Nicolle M, et al. Idiopathic free-floating thrombus of the common carotid artery. Can J Neurol Sci 2002;29:97-9.
244. Silverman IE, Beland DK, Bohannon RW, et al. Expanding the range of therapies for acute ischemic stroke: The early experience of the regional stroke center at hartford hospital. Conn Med 2004;68:419-29.
245. Skelly CL, Gallagher K, Fairman RM, Carpenter, et al. Risk factors for restenosis after carotid artery angioplasty and stenting. J Vasc Surg 2006;4:1010-5.
246. Smith WS. Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke. results of the multi mechanical embolus removal in cerebral ischemia (MERCI) trial, part I. Am J Neuroradiol 2006;27:1177-82.

247. Soleau SW, Schmidt R, Stevens S, et al. Extensive experience with dural sinus thrombosis. Neurosurgery 2003;52:534-44.
248. Sosa T, Erdelez L, Macina AS, et al. Carotid endarterectomy in asymptomatic patients. Acta Clin Croat, Supplement 1998;37:69.
249. Spengel FA, Ruthlein VM, Kuffer GV. Percutaneous transluminal catheter thrombectomy. An additional method to local catheter lysis. Vasa-J Vascular Dis 1988;17:168-l69.
250. Spetzger U, Reul J, Thron A, et al. Microsurgical embolectomy and removal of a migrated coil from the middle cerebral artery. Cerebravasc Dis 1997;7:226-31.
251. Starkman S, MERCI Investigators. Results of the combined MERCI (R) I-II (mechanical embolus removal in cerebral ischemia) trials. Stroke 2004;35:240.
252. Stead LG, Gilmore RM, Bellolio MF, et al. Percutaneous clot removal devices in acute ischemic stroke: A systematic review and meta-analysis. Arch Neurol 2008;65:1024-30.
253. Sturm JT, Toro C, Snyder BD. Emergency carotid artery thrombectomy for postpartum hemiplegia. Am J Emerg Med 1987;5:291-3.
254. Sugg RM, Malkoff MD, Noser EA, et al. Endovascular recanalization of internal carotid artery occlusion in acute ischemic stroke. AJNR Am J Neuroradiol 2005;26:2591-4.
255. Sugg RM, Malkoff MD, Shaltoni HM, et al. Endovascular recanalization of internal carotid occlusion in acute ischemic stroke. Neurology 2005;64(Suppl.1):A111.
256. Suh SH, Lee KY, Hong CK, et al. Temporary stenting and retrieval of the self-expandable, intracranial stent in acute middle cerebral artery occlusion. Neuroradiology 2009;51:541-4.
257. Sunder Plassmann L, Hildebrandt U. Arterial embolectomy and venous thrombectomy in the old patient: Risks and results. Aktuelle Gerontol 1983;13:136-8.
258. Syrek JR, Calligaro KD, Dougherty MJ, et al. Five-step protocol for carotid endarterectomy in the managed health care era. Surgery 1999;125:96-101.
259. Takach TJ, Reul Jr. GJ, Round ME, et al. Preocclusive carotid artery thrombosis: Pathogenesis and management. Vasc Surg 1999;33:691-6.
260. Tanne D, Levine SR. Safer thrombolysis for acute ischemic stroke: Is early recanalization the key? Neurology 2008;71:1300-1.
261. Taoka T, Yuh WT, Chaloupka JC, et al. Assessing reperfusion by angiogram and immediate post-contrast CT in acute stroke treated with endovascular recanalization. Radiology 2000;217:776.
262. Tenser MS, Liebeskind DS, Starkman S, et al. In: Deterioration following improvement in acute stroke patients after endovascular recanalization therapy. Stroke 2009;40:E249.
263. Terada T, Yamaga H, Tsumoto T, et al. Use of an embolic protection system during endovascular recanalization of a totally occluded cervical internal carotid artery at the chronic stage. J Neurosurg 2005;102:558-64.
264. Theiss W, Hermanek P, Mathias K, et al. Pro-CAS: A prospective registry of carotid angioplasty and stenting. Stroke 2004;35:2134-9.
265. Topaz O. Focus on the infarct-related artery: A thrombus runs through it. Catheter Cardio Inte 2002;57:340-1.
266. Touho H, Morisako T, Hashimoto Y, et al. Embolectomy for acute embolic occlusion of the internal carotid artery bifurcation. Surg Neurol 1999;51:313-20.

267. Toyoda K, Uda K, Shirakawa A, et al. Combined and staged endovascular recanalization of cervical and intracranial arteries in hyperacute ischemic stroke. Intern Med 2007;46:1935-6.
268. Turnbull RG, Tsang VT, Teal PA, et al. Successful innominate thromboembolectomy of a paradoxic embolus. J Vasc Surg 1998;28:742-5.
269. Vallee JN, Crozier S, Guillevin R, et al. Acute basilar artery occlusion treated by thromboaspiration in a cocaine and ecstasy abuser. Neurology 2003;61:839-41.
270. Van Damme H, Sakalihasan N, Limet R. Fibromuscular dysplasia of the internal carotid artery. personal experience with 13 cases and literature review. Acta Chir Belg 1999:163-8.
271. Van Der Hoek C, Van Groenendael JHLM, Gratama S. Disseminated cholesterol-emboli, renal failure and eosinophilia. Ned Tijdschr Geneeskd 1979;123:1017-20.
272. Vázquez-Barquero A, Quintana F, Austin O, et al. Emergency embolectomy of middle cerebral artery occlusion due to microcoil migration: Case report. Surg Neurol 1994;42:135-7.
273. Vora NA, Gupta R, Thomas AJ, et al. Factors predicting hemorrhagic complications after multimodal reperfusion therapy for acute ischemic stroke. Am J Neuroradiol 2007;28:1391-4.
274. Weis-Muller BT, Huber R, Spivak-Dats A, et al. Indication for emergent revascularisation of acute carotid occlusion. Chirurg 2007;78:1041-8.
275. Wen H, Du J, Li J. Comparison of the therapeutic effect between interventional treatment and anticoagulation therapy alone in patients with intracranial venous sinus thrombosis. Chinese Journal of Cerebrovascular Diseases 2009;6:24-8.
276. Willis SL, Welch TS, Scally JP, et al. Impending paradoxical embolism presenting as a pulmonary embolism, transient ischemic attack, and myocardial infarction. Chest 2007;132:1358-60.
277. Xu G, Cheng S, Liu X. Focus on endovascular solutions for cerebrovascular diseases: Report of the fourth international stroke summit, nanjing, china, july 25-27, 2008. Cerebrovasc Dis 2008;26:667-8.
278. Xu GF, Dae CS, Choong GC, et al. Aspiration thrombectomy of acute complete carotid bulb occlusion. J Vasc Interv Radiol 2005;16:539-42.
279. Xv J, Qiao X, Chen J, et al. Exploration of the cause and treatment of recurrent traumatic carotid cavernous fistula after endovascular embolization. Chin J Contemp Neurol Neurosurg 2009;9:50-4.
280. Yano T, Sakai N, Yamagami H, et al. Revascularization procedure mainly by suction thrombectomy for acute cervical carotid occlusion. Interv Neuroradiol 2007;13:174-8.
281. Yassa AS, Bellolio MF, Dajani N, et al. In: TIMI flow obtained after mechanical embolectomy for acute ishemic stroke and its impact on functional outcome. Ann Emerg Med 2007;50(Suppl.1):104.
282. Yousaf M, Atherton ME, Culp WC. Incomplete modeling of the thromboembolectomy technique. Stroke 2008;39:e127.
283. Yu W, Kostanian V, Fisher M. Endovascular recanalization of basilar artery occlusion 80 days after symptom onset. Stroke 2007;38:1387-9.
284. Zarins CK, Shaver DM, Arko FR, et al. Introduction of endovascular aneurysm repair into community practice: Initial results with a new food and drug administration - approved device. J Vasc Surg 2002;36:226-33.

285. Zhou W, Lin PH, Bush RL, et al. Carotid artery aneurysm: Evolution of management over two decades. J Vasc Surg 2006;43:493-6.
286. Zlotnik EI. Thrombectomy of the middle cerebral artery. case report. J Neurosurg 1975;42:723-5.
287. Zlotnik EI. Thrombectomy in occlusion of the middle cerebral artery (russian). Zhurnal Voprosy Nejrokhirurgii Imeni N.N.Burdenko 1973;37:25-8.

Appendix C. Tables of Included Study Characteristics, Inclusion and Exclusion Criteria

Table C1. Characteristics of prospective, single-arm or retrospective studies of the Penumbra System (Penumbra, Alameda, CA)

Study, yr N	Device	Design	Inclusion Criteria	Exclusion Criteria	Baseline Characteristics (mean/median)	Location of Emboli (%)
Kulcsar, 2010 N=27	Penumbra	Prospective	Patients not responding to initial IV rtPA or presenting >4 hours from symptom onset	NR	NIHSS: 14 Age: 66 Female %: 48 TICI 0/1 %: 100 ST: 266 minutes	ICA/ICA-T: 19 MCA: 66 VB = 15
PPST, 2009 N=125	Penumbra	Prospective	NIHSS≥8, presentation <8 hours from symptoms onset, angiographic TIMI 0/1 occlusion of a treatable large, intracranial vessel, ineligible or refractory to IV rtPA if presenting <3 hours from symptom onset	Infarction greater than one-third of the MCA, severe edema, intracerebral hemorrhage and pregnancy	NIHSS: 18 Age: 64 Female %: 49 TIMI 0/1 %: 100 ST: 258 minutes	ICA/ICA-T: 18 MCA: 70 VB: 9 Other: 3
Grunwald, 2009 N=29	Penumbra	Prospective	NIHSS≥8, >18 years of age, presentation <8 hours from symptom onset, TIMI 0/1 occlusion of a treatable large, intracranial vessel, ineligible or refractory to IV rtPA if presenting <3 hours from symptom onset	Brain edema or intracerebral hemorrhage	NIHSS: 20 Age: 58 Female %: 48 TIMI 0/1%: 100 ST: 312 minutes	ICA/ICA-T: 28 MCA: 52 VB: 21 Other: 0
Bose, 2008 N=23	Penumbra	Prospective	>18 years of age, presentation <8 hours from symptoms onset, angiographic TIMI 0/1 occlusion of a treatable large, intracranial vessel, ineligible or refractory to IV rtPA if presenting <3 hours from symptom onset	Risk of bleeding, vessels deemed too tortuous for Penumbra system, uncontrolled hypertension and pregnancy	NIHSS: 21 Age: 60 Female %: 40 TIMI 0/1%: 100 ST: 50% > 3 hours from symptoms	ICA/ICA-T: 33 MCA: 24 VB: 43 Other: 0
Struffert, 2009 N=15	Penumbra	Retrospective	Consecutive patients with large vessel occlusion (ICA, MCA, BA). Inclusion and exclusion criteria of Bose, 2009 (see above) followed except IV rtPA allowed between 3-9 hours if perfusion imaging mismatch is visible on MRI	NR	NIHSS: 15 Age: 60 Female %:40 TIMI 0%: 100 ST: 151 minutes	ICA/ICA-T: 33 MCA: 47 VB: 20 Other: 0
Tarr, 2009 N=105 (Abstract Only)	Penumbra	Retrospective	NIHSS≥8, presentation <8 hours from symptom onset, TIMI 0/1 occlusion of a treatable large, intracranial vessel (consistent with device approval indication)	NR	NIHSS: 17 Age: 64 Female %: NR TIMI 0/1%: 96 ST: 141 minutes	NR

Table C1. Characteristics of prospective, single-arm or retrospective studies of the Penumbra System (Penumbra, Alameda, CA)

Study, yr N	Device	Design	Inclusion Criteria	Exclusion Criteria	Baseline Characteristics (mean/median)	Location of Emboli (%)
Frei, 2009 N=53 (Abstract Only)	Penumbra	Retrospective	Failed IV rtPA prior to therapy	NR	NIHSS: 18 Age: 66 Female %:55 TIMI 0/1 %: 100 ST: NR	NR

BA=basilar artery; ICA=internal carotid artery; ICA-T=internal carotid artery terminus; IV rtPA=intravenous recombinant tissue plasminogen activator; MCA=middle cerebral artery; N=total number of patients evaluated; NIHSS=National Institutes of Health Stroke Scale; NR=not reported; PPST=Penumbra Pivotal Stroke Trial; TIMI=Thrombolysis in Myocardial Infarction; ST=symptom time (to angiography or device deployment); VB=vertebrobasilar

Table C2. Characteristics of prospective, single-arm or retrospective studies of the MERCI retrieval system (Concentric Medical Inc., Mountain View, CA)

Study, yr N	Device	Design	Inclusion Criteria	Exclusion Criteria	Baseline Characteristics (mean/median)	Location of Emboli (%)
Loh, 2010 N=97	MERCI	Prospective	Consecutive patients undergoing MERCI retrieval for large cerebral artery occlusion acute ischemic strokes.	NR	NIHSS: NR Age: 65-68 Female %: 58 TIMI 0/1 %: NR ST: 403-417 minutes	NR
Smith, 2008 N=164	MERCI	Prospective	NIHSS≥8, >18 years of age, presentation <8 hours from symptoms onset, angiographic TIMI 0/1 occlusion of a treatable large, intracranial vessel (ICA, ICA-T, MCA M1 or M2), ineligible or refractory to IV rtPA if presenting <3 hours from symptom onset, otherwise similar to Smith, 2005	Excessive tortuosity of vessels, pregnancy, allergy to contrast media, life expectancy < 3months, >50% stenosis of the artery proximal to target vessel, glucose <50 mg/dL, prothrombin time>2 times normal, hemorrhagic diathesis, coagulation factor deficiency, oral anticoagulation with INR>3, use of heparin with partial thrombplastin time >2 times normal, platelets <30,000, severe hypertension, CT scan showing significant mass effect with midline shift	NIHSS: 19 Age: 68 Female %: 57 TIMI 0/1 %: NR ST: 258 minutes	ICA/ICA-T: 32 MCA: 60 VB: 8 Other: 0
Devlin, 2007 N=25	MERCI	Prospective	NIHSS≥8, >18 years of age, presentation <8 hours from symptoms onset, occlusion of a treatable large, intracranial vessel (ICA, ICA-T, MCA M1 or M2), ineligible or refractory to IV rtPA if presenting <3 hours from symptom onset (n=9 were treated with IV rtPA after 3-hours, n=8 were treated for 50% stenosis of proximal carotid)	Hypodensity >one-third of MCA on CT, glucose <50 mg/dL, hemorrhagic diathesis, coagulation factor deficiency, oral anticoagulation with INR>3, use of heparin in past 48 hours with partial thrombplastin time >2 times normal, platelets <30,000, severe hypertension, CT scan showing significant mass effect with midline shift, life expectancy <3 months	NIHSS: 18 Age: 63 Female %: 36 TIMI 0/1 %: 96 ST: 312 minutes	ICA/ICA-T: 12 MCA: 48 VB: 8 Tandem ICA/MCA: 32
Kim, 2006 N=24	MERCI	Prospective	NIHSS≥8, presentation <8 hours from symptoms onset, angiographic TIMI 0/1 occlusion of a treatable large, intracranial vessel, ineligible or refractory to IV rtPA if presenting <3 hours from symptom onset, otherwise similar to Gobin, 2004 and Smith, 2005	No large mismatch between core infarct and salvageable penumbra, enrolled in Gobin, 2004 and Smith, 2005	NIHSS: 21 Age: 64 Female %: 42 TIMI 0/1 %: NR ST: 303 minutes	ICA/ICA-T: 38 MCA: 58 VB: 4 Other: 0

Table C2. Characteristics of prospective, single-arm or retrospective studies of the MERCI retrieval system (Concentric Medical Inc., Mountain View, CA)

Study, yr N	Device	Design	Inclusion Criteria	Exclusion Criteria	Baseline Characteristics (mean/median)	Location of Emboli (%)
Smith, 2005 N=151	MERCI	Prospective	NIHSS≥8, >18 years of age, presentation <8 hours from symptoms onset, angiographic TIMI 0/1 occlusion of a treatable large, intracranial vessel, ineligible for IV rtPA if presenting <3 hours from symptom onset	Excessive tortuosity of cervical vessels, pregnancy, allergy to contrast media, life expectancy < 3months, >50% stenosis of the artery proximal to target vessel, glucose <50 mg/dL, prothrombin time >2 times normal, hemorrhagic diathesis, coagulation factor deficiency, oral anticoagulation with INR>1.7 in part 1 and >3.0 in part 2, use of heparin within 48 hours and a partial thromboplastin time >2 times normal, platelets <50,000 (<30,000 in part 2), severe hypertension, CT scan showing significant mass effect with midline shift, < one-third of the MCA region with hypodensity, life expectancy < 3 months	NIHSS: 20 Age: 67 Female %: 46 TIMI 0/1 %: NR ST: 258 minutes	ICA/ICA-T: 33 MCA: 57 VB: 10 Other: 0
Gobin, 2004 N=30	MERCI	Prospective	NIHSS≥10, >18 years of age, presentation <8 hours from symptoms onset, angiographic TIMI 0/1 occlusion of a treatable large, intracranial vessel, ineligible for IV rtPA if presenting <3 hours from symptom onset	Hypodensity >one-third of MCA on CT, glucose <50 mg/dL, seizure at stroke onset, prothrombin time >15 seconds, hemorrhagic diathesis, coagulation factor deficiency, oral anticoagulation with INR >3, use of heparin with partial thrombplastin time >2 times normal, platelets <50,000, severe hypertension, CT scan showing significant mass effect with midline shift, severe arterial stenosis proximal to thrombus precluding thrombus removal	NIHSS:22 Age: 68 Female %: 50 TIMI 0/1 %: NR ST: 301 minutes	ICA/ICA-T: 18 MCA: 64 VB: 7 Tandem ICA/MCA: 11
Lin, 2009 N=34	MERCI	Retrospective	Consecutive patients with acute ischemic stroke, occlusion of the ICA with or without extension into the MCA, ineligible or refractory to IV rtPA if presenting <3 hours from symptom onset	NR	NIHSS: NR Age: NR Female %: NR TIMI 0/1 %: NR ST: NR	ICA/MCA: 100
Jo, 2008 N=114 (Abstract Only)	MERCI	Retrospective	Consecutive patients with acute ischemic stroke	NR	NIHSS: 19 Age: 65 Female %: NR TIMI 0/1 %: NR ST: NR	NR

Table C2. Characteristics of prospective, single-arm or retrospective studies of the MERCI retrieval system (Concentric Medical Inc., Mountain View, CA)

Study, yr N	Device	Design	Inclusion Criteria	Exclusion Criteria	Baseline Characteristics (mean/median)	Location of Emboli (%)
Madison, 2008 N=54 (Abstract Only)	MERCI	Retrospective	Consecutive patients with acute ischemic stroke with angiographically confirmed large vessel occlusion treated with intra-arterial intervention within 6 hours of symptom onset	NR	NIHSS: NR Age: NR Female %: NR TIMI 0/1 %: NR ST: NR	NR
Kidwell, 2008 N=18	MERCI	Retrospective	Patients within 8 hours of symptom onset and having a baseline MRI scan, FLAIR MRI within 7-days and endpoint data recorded out to 90-days.	Receiving adjunctive thrombolysis	NIHSS: 19 Age: 63 Female %: 39 TIMI 0/1 %: NR ST: NR	NR

BA=basilar artery; FLAIR=fluid attenuated inversion recovery; ICA=internal carotid artery; ICA-T=internal carotid artery terminus; IV rtPA=intravenous recombinant tissue plasminogen activator; MCA=middle cerebral artery; MRI=magnetic resonance imaging; N=total number of patients evaluated; NIHSS=National Institutes of Health Stroke Scale; NR=not reported; PPST=Penumbra Pivotal Stroke Trial; TIMI=Thrombolysis in Myocardial Infarction; ST=symptom time (to angiography or device deployment); VB=vertebrobasilar

Table C3. Characteristics of prospective, single-arm or retrospective studies of off-label neurothrombectomy devices

Study, yr N	Device	Design	Inclusion Criteria	Exclusion Criteria	Baseline Characteristics (mean/median)	Location of Emboli (%)
Liebig, 2008 N=45 (Abstract Only)	Phenox	Prospective	Patients with ischemic stroke	NR	NIHSS: NR Age: NR Female %: NR TIMI 0/1 %: NR ST: NR minutes	ICA/ICA-T: 27 MCA: 38 VB: 27 Other: 8
Tomsick, 2008* N=35	EKOS Primo	Prospective	NIHSS≥10, <81 years of age, presenting <3 hours from symptom onset	NR	NIHSS: NR Age: NR Female %: NR TIMI 0/1 %: NR ST: NR	NR
Mahon, 2003 N=14	EKOS MicroLysUS	Prospective	Patients between 18-77 years with a treatable artery, NIHSS≥8, time from symptom onset of <6 hours for anterior circulation or <24 hours for posterior circulation occlusions, exclusion from IV thrombolysis protocol	Confounding prior neurologic event or hemorrhage on CT scan	NIHSS: 18 Age: 64 Female %: 50 TIMI 0/1 %: NR ST: 331 minutes	ICA/ICA-T: 36 MCA: 36 VB/Other: 28
Gonzalez, 2007 N=9	Amplatz Gooseneck	Prospective	NIHSS≥8, ineligible for IV rtPA, <8 hours since symptoms for anterior and <24 hours for posterior occlusions	CT scan showing hemorrhage or hypoattenuation involving more than one-third of the MCA, history of chronic severe illness, previous disabling stroke, and/or dementia	NIHSS: 16 Age: 55 Female %: NR TIMI 0/1 %: NR ST: 251 minutes	ICA/ICA-T: 11 MCA: 56 VB: 33 Other: 0
Mayer, 2005 N=12	AngioJet	Prospective	Consecutive patients with VB occlusion confirmed by angiography, diameter >2mm in vessel to be treated	Coma >8 hours, >80 years of age, acute intracerebral hemorrhage and extensive brain stem or thalamic infarction by CT or MRI	NIHSS: 20 Age: 56 Female %: 25 TIMI 0/1 %: 100 ST: 5-216 hours	ICA/ICA-T: 0 MCA: 0 VB: 100 Other: 0
Berlis, 2004 N=34	EPAR	Prospective	Patients 18-85 years, NIHSS >3, stroke <7 hours from projected EPAR use if anterior and ≤24 hours if posterior occlusion, occlusion of the ICA, MCA, PCA, basilar or vertebral arteries, diameter >2mm, TIMI 0-1 flow	Pregnancy, evidence of aneurysm or dissection, uncontrolled bleeding diathesis, blood pressure >200 mmHg systolic, 120 mmHg diastolic, intracranial tumor or massive infarct, markedly increasing improvement of neurologic symptoms by time of treatment initiation, evidence of intracranial hemorrhage	NIHSS: 19 Age: 68 Female %: 50 TIMI 0/1 %: 100 ST: 382 minutes	ICA/ICA-T: 29 MCA: 35 VB: 32 Other: 3

Table C3. Characteristics of prospective, single-arm or retrospective studies of off-label neurothrombectomy devices

Study, yr N	Device	Design	Inclusion Criteria	Exclusion Criteria	Baseline Characteristics (mean/median)	Location of Emboli (%)
Mayer, 2002 N=5	Neuronet	Prospective	NR	NR	NIHSS: 20 Age: 42 Female %: 20 TIMI 0/1 %: 100 ST: 388 minutes	ICA/ICA-T: 0 MCA: 0 VB: 100 Other: 0
Clark, 2000 N=2 (Abstract Only)	LaTIS	Prospective	NIHSS >5, treated within 8 hours for anterior and <24 for posterior occlusion, TIMI 0, and a vessel diameter of 2-5 mm.	NR	NIHSS: 20/26 Age: NR Female %: NR TIMI 0/1 %: 100 ST: 479/270 minutes	ICA/ICA-T: 0 MCA: 100 VB: 0 Other: 0

CT=computed tomography; EPAR=Endovascular Photoacoustic Recanalization; ICA=internal carotid artery; ICA-T=internal carotid artery terminus; IV rtPA=intravenous recombinant tissue plasminogen activator; MCA=middle cerebral artery; N=total number of patients evaluated; N=total number of patients evaluated; NIHSS=National Institutes of Health Stroke Scale; NR=not reported; PCA=posterior cerebral artery; PPST=Penumbra Pivotal Stroke Trial; TIMI=Thrombolysis in Myocardial Infarction; ST=symptom time (to angiography or device deployment); VB=vertebrobasilar

*Data from Tomsick, 2008 publication of Interventional management of Stroke (IMS)-II Trial. Data for EKOS Primo only

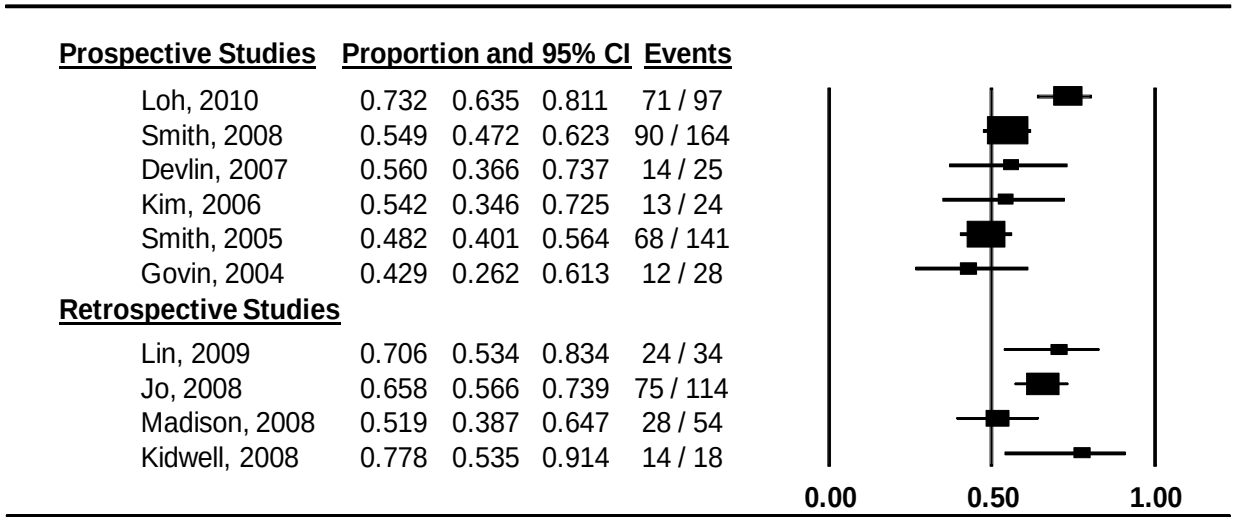
Table C4. Characteristics of prospective, single-arm or retrospective studies of stent retriever devices

Study, yr N	Device	Design	Inclusion Criteria	Exclusion Criteria	Baseline Characteristics (mean/median)	Location of Emboli (%)
Castano, 2010 N=20	Solitaire AB	Prospective	NIHSS≥8, refractory or ineligible for IV rtPA, <8 hours since symptoms for anterior, absence of large signs of ischemia, angiographically proven arterial circulation occlusion	NR	NIHSS: 19 Age: 65 Female %: 50 TIMI 0/1 %: 90 ST: 352 minutes	ICA/ICA-T: 25 MCA: 55 VB: 0 Other: 20
Mocco, 2009 N=18 (Abstract Only)	Solitaire	Prospective	NR	NR	NIHSS: NR Age: NR Female %:NR TIMI 0/1 %: NR ST: NR	ICA/ICA-T: 11 MCA: 67 VB: 0 Other: 22

ICA=internal carotid artery; ICA-T=internal carotid artery terminus; IV rtPA=intravenous recombinant tissue plasminogen activator; MCA=middle cerebral artery; N=total number of patients evaluated; N=total number of patients evaluated; NIHSS=National Institutes of Health Stroke Scale; NR=not reported; PCA=posterior cerebral artery; TIMI=Thrombolysis in Myocardial Infarction; ST=symptom time (to angiography or device deployment); VB=vertebrobasilar

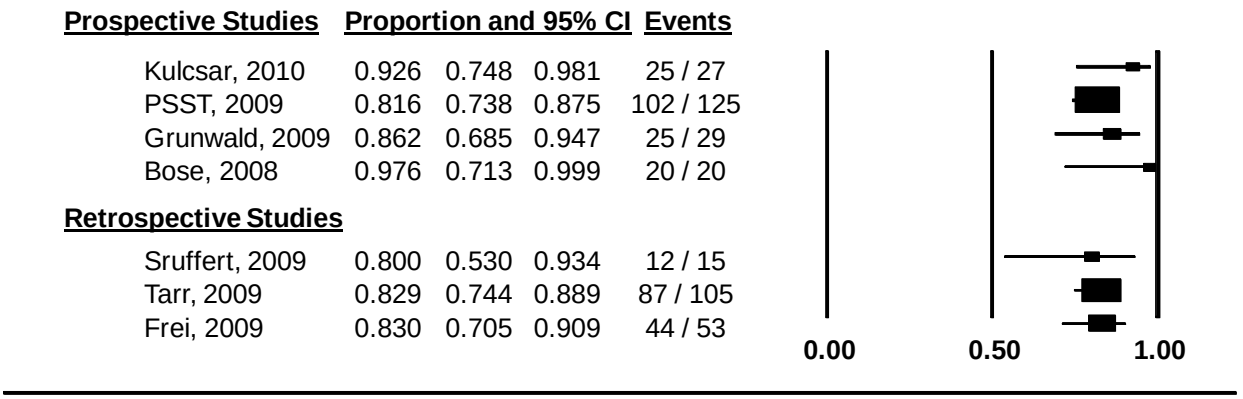
Appendix D. Summary Figures and Tables

Figure D1. Proportion of patients achieving recanalization with MERCI retriever



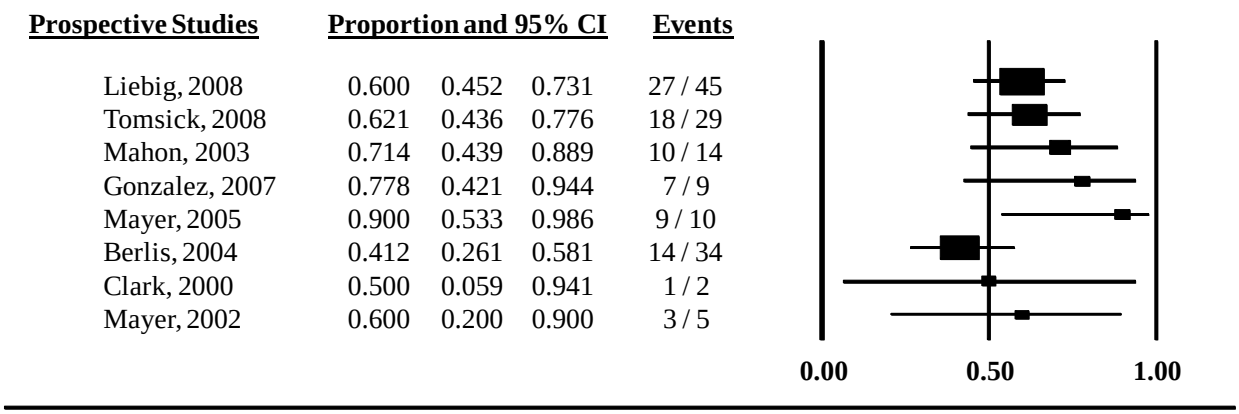
CI=confidence interval; n=number of patients with outcome; N=total number of patients evaluated

Figure D2. Proportion of patients achieving recanalization with Penumbra System



CI=confidence interval; n=number of patients with outcome; N=total number of patients evaluated

Figure D3. Proportion of patients achieving recanalization with off-label neurothromectomy devices



CI=confidence interval; n=number of patients with outcome; N=total number of patients evaluated

Table D1. Key efficacy endpoint results of prospective, single-arm or retrospective studies of the Penumbra System (Penumbra, Alameda, CA)

Study, yr	Device	Design	Blinded Outcome Assessment	Outcome, n/N (%)			
				TIMI II/III	NIHSS decrease ≥4[#]	mRS≤2*	Death^
Kulcsar, 2010	Penumbra	Prospective	Unclear/No	25/27 (93)	15/27 (56)	13/27 (48)	3/27 (11)
PPST, 2009	Penumbra	Prospective	Yes	102/125 (81.6)	27/125 (21.6)	25/125 (20.0)	33/125 (26.4)
Grunwald, 2009	Penumbra	Prospective	Unclear/No	25/29 (86.2)	19/29 (65.5)	11/29 (37.9)	4/29 (13.8)
Bose, 2008	Penumbra	Prospective	Yes	20/20 (100)	9/20 (45.0)	7/20 (35.0)	9/20 (45.0)
Struffert, 2009	Penumbra	Retrospective	Unclear/No	12/15 (80.0)	11/15 (73.3)	5/15 (33.3)	3/15 (20.0)
Tarr, 2009	Penumbra	Retrospective	Unclear/No	87/105 (82.9)	59/105 (56.2)	34/105 (32.4)	22/105 (21.0)
Frei, 2009	Penumbra	Retrospective	Unclear/No	44/53 (83.0)	30/53 (56.6)	19/53 (35.8)	19/53 (35.8)

mRS=modified Rankin Scale; n=number of patients with outcome; N=total number of patients evaluated; NIHSS=National Institutes of Health Stroke Scale; PPST=Penumbra Pivotal Stroke Trial; TIMI=Thrombolysis in Myocardial Infarction
#NIHSS decrease of at least 4-points at 30-days except PPST, 2009 (NIHSS 0-1 or improved by at least 10-points at discharge); Tarr, 2009 and Frei, 2009 (each assessed only at discharge).
*mRS at 90-days except Grunwald, 2009 and Bose, 2008 (30-day)
^Death at 90-days except Grunwald, 2009 and Bose, 2008 (30-day)

Table D2. Key efficacy endpoint results of prospective, single-arm or retrospective studies of the MERCI Retrieval System (Concentric Medical Inc., Mountain View, CA)

Study, yr	Device	Design	Blinded Outcome Assessment	Outcome, n/N (%)			
				TIMI II/III	NIHSS decrease ≥4[#]	mRS≤2*	Death^
Loh, 2010	MERCI	Prospective	Unclear/No	71/97 (73)	-	-	-
Smith, 2008	MERCI	Prospective	Unclear/No	90/164 (54.9)	38/146 (26.0)	59/164 (36.0)	56/164 (34.1)
Devlin, 2007	MERCI	Prospective	Unclear/No	14/25 (56.0)	-	6/25 (24.0)	9/25 (36.0)
Kim, 2006	MERCI	Prospective	Unclear/No	13/24 (54.2)	-	6/24 (25.0)	7/24 (29.2)
Smith, 2005	MERCI	Prospective	Unclear/No	68/141 (48.2)	46/141 (32.6)	36/130 (27.7)	60/138 (43.5)
Gobin, 2004	MERCI	Prospective	Unclear/No	12/28 (42.9)	-	6/28 (21.4)	10/28 (35.7)
Lin, 2009	MERCI	Retrospective	Unclear/No	24/34 (70.6)	-	-	-
Jo, 2008	MERCI	Retrospective	Unclear/No	75/114[@] (65.8)	-	-	-
Madison, 2008	MERCI	Retrospective	Unclear/No	28/54 (51.9)	-	-	-
Kidwell, 2008	MERCI	Retrospective	Yes	14/18 (77.8)	-	-	-

mRS=modified Rankin Scale; n=number of patients with outcome; N=total number of patients evaluated; NIHSS=National Institutes of Health Stroke Scale; TIMI=Thrombolysis in Myocardial Infarction
#NIHSS decrease of at least 4-points at 30-days except Smith, 2008 (NIHSS improved by at least 10-points or 0 score at 24-hours); Smith, 2005 (NIHSS improved by at least 10-points at 90-days)
@TICI II/III not TIMI II/III for Jo, 2008
*mRS at 90-days except Gobin, 2004 (30-day)
^Death at 90-days except Gobin, 2004 (30-day)

Table D3. Key efficacy endpoint results of prospective, single-arm or retrospective studies of off-label neurothrombectomy devices

Study, yr	Device	Design	Blinded Outcome Assessment	Outcome, n/N (%)			
				TIMI II/III	NIHSS decrease ≥4[#]	mRS≤2*	Death^
Liebig, 2008	Phenox	Prospective	Unclear/No	27/45 (60.0)	-	-	-
Tomsick, 2008	EKOS Primo	Prospective	Yes	18/29[@] (62.1)	-	-	-
Mahon, 2003	EKOS MicroLysUS	Prospective	Unclear/No	10/14 (71.4)	8/14 (57.1)	5/14 (35.7)	5/14 (35.7)
Gonzalez, 2007	Amplatz Gooseneck	Prospective	Unclear/No	7/9 (77.8)	3/7 (42.9)	2/7 (28.6)	2/7 (28.6)
Mayer, 2005	AngioJet	Prospective	Unclear/No	9/10 (90.0)	-	4/12 (33.3)	3/10 (30.0)
Berlis, 2004	EPAR	Prospective	Unclear/No	14/34 (41.2)	7/34 (20.6)	5/34 (14.7)	13/34 (38.2)
Mayer, 2002	Neuronet	Prospective	Unclear/No	3/5 (60.0)	4/5 (80.0)	3/5 (60.0)	0/5 (0)
Clark, 2000	LaTIS	Prospective	Unclear/No	1/2 (50.0)	-	-	-

EPAR=Endovascular Photoacoustic Recanalization; mRS=modified Rankin Scale; n=number of patients with outcome; N=total number of patients evaluated; NIHSS=National Institutes of Health Stroke Scale; TIMI=Thrombolysis in Myocardial Infarction
@TICI II/III not TIMI II/III for Tomsick, 2008
#NIHSS decrease of at least 4-points at 90-days except Berlis 2004 (30-day, NIHSS ≥ 50% decrease)
*mRS at 90-days except Berlis, 2004 (30-day)
^Death at 90-days except Berlis, 2004 (30-day)

Table D4. Key safety endpoint results of prospective, single-arm or retrospective studies of the Penumbra System (Penumbra, Alameda, CA)

Study, yr	Device	Design	Outcome, n/N (%)				
			SICH	AICH	Other Hemorrhage	Perforation/ Dissection	Thrombus Formation
Kulcsar, 2010	Penumbra	Prospective	0/27 (0)	-	-	-	-
PPST, 2009	Penumbra	Prospective	14/125 (11.2)	21/125 (16.8)	-	6/125 (4.8)	1/125 (0.8)
Grunwald, 2009	Penumbra	Prospective	2/29 (6.9)	3/29 (10.3)	-	-	-
Bose, 2008	Penumbra	Prospective	2/20 (10.0)	6/20 (30.0)	2/20 (10.0)	0/20 (0)	0/20 (0)
Struffert, 2009	Penumbra	Retrospective	0/15 (0)	-	0/15 (0)	0/15 (0)	0/15 (0)
Tarr, 2009	Penumbra	Retrospective	5/105 (4.8)	1/105 (1.0)	-	-	-
Frei, 2009	Penumbra	Retrospective	3/53 (5.7)	5/53 (9.4)	-	-	-

AICH=asymptomatic intracerebral hemorrhage; n=number of patients with outcome; N=total number of patients evaluated; PPST=Penumbra Pivotal Stroke Trial; SICH=symptomatic intracerebral hemorrhage

Table D5. Key safety endpoint results of prospective, single-arm or retrospective studies of the MERCI Retrieval System (Concentric Medical Inc., Mountain View, CA)

Study, yr	Device	Design	Outcome, n/N (%)				
			SICH	AICH	Other Hemorrhage	Perforation/ Dissection	Thrombus Formation
Loh, 2010	MERCI	Prospective	-	-	16/27 (59)	2/27 (7)	-
Smith, 2008	MERCI	Prospective	16/164 (9.8)	50/164 (30.5)	-	-	-
Devlin, 2007	MERCI	Prospective	1/25 (4.0)	7/25 (28.0)	2/25 (8.0)	0/25 (0)	-
Kim, 2006	MERCI	Prospective	2/24 (8.3)	9/24 (37.5)	-	0/24 (0)	0/24 (0)
Smith, 2005	MERCI	Prospective	11/141 (7.8)	39/141 (27.7)	7/141 (5.0)	10/141 (7.1)	3/141 (2.1)
Gobin, 2004	MERCI	Prospective	0/28 (0)	12/28 (42.9)	-	-	-
Lin, 2009	MERCI	Retrospective	-	-	-	-	-
Jo, 2008	MERCI	Retrospective	-	-	-	-	-
Madison, 2008	MERCI	Retrospective	-	-	-	-	-
Kidwell, 2008	MERCI	Retrospective	-	-	-	-	-

AICH=asymptomatic intracerebral hemorrhage; n=number of patients with outcome; N=total number of patients evaluated; SICH=symptomatic intracerebral hemorrhage

Table D6. Key safety endpoint results of prospective, single-arm or retrospective studies of off-label neurothrombectomy devices

Study, yr	Device	Design	Outcome, n/N (%)				
			SICH	AICH	Other Hemorrhage	Perforation/ Dissection	Thrombus Formation
Liebig, 2008	Phenox	Prospective	-	-	-	-	-
Tomsick, 2008	EKOS Primo	Prospective	7/29 (24.1)	-	-	0/29 (0)	-
Mahon, 2003	EKOS MicroLysUS	Prospective	2/14 (14.3)	-	-	0/14 (0)	-
Gonzalez, 2007	Amplatz Gooseneck	Prospective	1/7 (14.3)	1/7 (14.3)	-	0/7 (0)	0/7 (0)
Mayer, 2005	AngioJet	Prospective	3/12 (25.0)	2/12 (16.7)	-	0/12 (0)	1/12 (8.3)
Berlis, 2004	EPAR	Prospective	2/34 (5.9)	2/34 (5.9)	-	0/34 (0)	-
Mayer, 2002	Neuronet	Prospective	-	-	-	-	2/5 (40.0)
Clark, 2000	LaTIS	Prospective	-	-	-	-	-

AICH=asymptomatic intracerebral hemorrhage; EPAR=Endovascular Photoacoustic Recanalization; n=number of patients with outcome; N=total number of patients evaluated; SICH=symptomatic intracerebral hemorrhage

Table D7. All device failure to-deploy or breakage/fracture

Study, yr	Design	Device	Outcome, n/N (%)	
			Failure to Deploy	Breakage/ Fracture
Kulcsar, 2010	Penumbra	Prospective	-	-
PPST, 2009	Penumbra	Prospective	0/125 (0)	-
Grunwald, 2009	Penumbra	Prospective	0/29 (0)	-
Bose, 2008	Penumbra	Prospective	3/23 (13.0)	-
Struffert, 2009	Penumbra	Retrospective	0/15 (0)	0/15 (0)
Tarr, 2009	Penumbra	Retrospective	-	0/7 (0)
Frei, 2009	Penumbra	Retrospective	-	-
Loh, 2010	MERCI	Prospective	-	-
Smith, 2008	MERCI	Prospective	13/177 (7.3)	1/164 (0.6)
Devlin, 2007	MERCI	Prospective	-	1/25 (4.0)
Kim, 2006	MERCI	Prospective	-	3/24 (12.5)
Smith, 2005	MERCI	Prospective	10/151(6.6)	11/341* (3.2)
Gobin, 2004	MERCI	Prospective	2/30 (6.7)	1/30 (3.3)
Lin, 2009	MERCI	Retrospective	-	-
Jo, 2008	MERCI	Retrospective	-	-
Madison, 2008	MERCI	Retrospective	-	-
Kidwell, 2008	MERCI	Retrospective	-	-
Liebig, 2008	Phenox	Prospective	3/45 (6.7)	-
Tomsick, 2008	EKOS Primo	Prospective	6/35 (17.1)	-
Mahon, 2003	EKOS MicroLysUS	Prospective	-	1/14 (7.1)
Gonzalez, 2007	Amplatz Gooseneck	Prospective	2/9 (22.2)	-
Mayer, 2005	AngioJet	Prospective	2/12 (16.7)	-
Berlis, 2004	EPAR	Prospective	16/34 (47.1)	-
Mayer, 2002	Neuronet	Prospective	1/5 (20.0)	-
Clark, 2000	LaTIS	Prospective	-	-

EPAR=Endovascular Photoacoustic Recanalization; n=number of patients with outcome; N=total number of patients evaluated; PPST=Penumbra Pivotal Stroke Trial

*Refers to number of breakages/fractures divided by total number of devices used.