



USE OF THE MERCI RETRIEVER FOR THE EMERGENT TREATMENT OF ACUTE ISCHEMIC STROKE

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of the Merci Retriever device in patients with acute ischemic stroke.

BACKGROUND

Stroke

In the U.S., cerebrovascular disease is currently the third leading cause of death with more than 275,000 stroke-related fatalities per year.¹ Annually, there are more than 700,000 strokes and currently there are more than 5.7 million stroke survivors with varying degrees of disability.¹ In patients with acute stroke, angiography studies done within six hours of symptom onset have demonstrated that the majority of patients have angiographically visible occlusion of an extracranial and/or intracranial artery as the primary cause.² Studies estimate that 87% of strokes are ischemic.¹ Recanalization of the occluded artery is the only effective therapy for acute stroke. Until recently, patients were mainly treated supportively to optimize cerebral perfusion and oxygenation with antithrombotic therapy prescribed on discharge.³ In 1995, a seminal randomized clinical trial demonstrated that recanalization of the artery with intravenous (IV) administration of tissue plasminogen activator (tPA) within three hours of the onset of symptoms from acute stroke improved functional outcomes in patients and was associated with a trend towards decreased total mortality at three months.⁴ The benefits diminish rapidly with the time from symptom onset. Two large international trials are evaluating the efficacy of IV tPA in the three to six hour window (Third European Cooperative Stroke Study; International Stroke Trial), but the benefits are unlikely to be large. In trials of IV thrombolysis for stroke, there was an increase in early deaths compared to the placebo arms in the first seven to ten days following therapy, primarily due to an increase in symptomatic intracranial hemorrhage (SICH).⁵ For IV tPA there were an extra 62 cases of SICH for every 1000 patients treated (from about two percent in control patients to about eight percent with tPA).⁵ Long-term functional benefits counterbalanced these risks of early harm.

A recent meta-analysis proposed that recanalization could be used as a surrogate marker in preliminary trials evaluating interventions for the treatment of acute stroke.⁶ Recanalization does not occur universally with treatment. In the meta-analysis, spontaneous recanalization occurred in 24% of patients and in 46% of patients treated with IV thrombolytics. It has been hypothesized that large volume clots in the proximal

vessels are less likely to dissolve with intravenous tPA. Several approaches have been tested including intra-arterial thrombolytic therapy with or without systematic thrombolysis, mechanical disruption of the clot, or endovascular thrombectomy, and combinations of the above therapies.⁷ Theoretically, each of these approaches would have a greater likelihood of recanalization of the artery, a lower risk of SICH, and this should translate into better outcomes. Unfortunately, all of these approaches require angiography and intra-arterial microcatheter placement prior to treatment, which may delay the delivery of effective therapy compared to IV thrombolysis. One randomized clinical trial, the Prolyse in Acute Cerebral Thromboembolism II trial, demonstrated that intra-arterial prourokinase was associated with higher recanalization rates than medical management with IV heparin (66% versus 18%, $p < 0.001$), although the rates of SICH were also higher (10% versus 2%).⁸ Assessment of good long-term functional outcomes favored the intra-arterial thrombolysis (40% versus 25%, $p = 0.04$) with no significant difference in mortality (25% vs. 27%, p NS). It is worth noting that the FDA did not feel that these results were strong enough to support approval of the drug for this indication, despite the unequivocal increase in recanalization rates. Most other approaches have case-report level data or are being tested in ongoing clinical trials.

Merici Retriever

The Merici Retriever is the first of the endovascular mechanical devices to receive FDA approval for use in the United States. It is designed to physically trap and then remove the clot occluding an artery. Potential benefits include lower or no use of thrombolytic agent, thus lower risks of bleeding, and higher recanalization rates. These are balanced by the need for angiography and intra-arterial access which delays the time to delivery of initial therapy and can damage the vascular endothelium.

The initial models (X5, X6) of the device itself were self-expanding tapered helices made of nitinol, a nickel titanium alloy. The second generation L5 device has a somewhat different design: the coils of the helix are stronger, they no longer taper, and there are a series of filaments attached to the coils. These design changes are intended to reduce the risk of device fracture and to improve the ability of the device to capture and remove the clot.

The procedure is similar to other angiographic procedures. An introducer is placed in the femoral artery and a catheter threaded into the extracranial artery leading to the affected artery. A microcatheter is threaded through the guiding catheter and positioned immediately proximal to the clot. The Merici retriever device is deployed through the clot and pulled back into the clot. A balloon at the tip of the guiding catheter is inflated



to block blood flow. With the balloon inflated, the Merci Retriever and the clot are withdrawn into the positioning catheter and out of the patient's body.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The Merci Retriever models X5 and X6 were approved through the FDA 510(k) process in August 2004 as substantially equivalent to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976. Modifications to the Merci Retriever were also approved through the FDA 510(k) process in April 2007 and August 2007.

Per the FDA: "The Merci Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke. Patients who are ineligible for treatment with intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy are candidates for treatment. The Merci Retriever is also indicated for use in the retrieval of foreign bodies misplaced during interventional radiological procedures in the neuro, peripheral and coronary vasculature."

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words **embolectomy** and **thrombectomy**. These were cross-referenced with the keywords **cerebrovascular accident** and human. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in

full. The search performed for the period from 1966 through September 2007 identified 66 references, of which three presented primary data from two case series evaluating the Merci retriever device⁹⁻¹¹. The remainder were either review articles, editorials, or studies of unrelated devices and procedures. The



bibliographies of systematic reviews and key articles were manually searched for additional references and references were requested from the device manufacturers. We also reviewed “related articles” in PubMed for each of the key clinical trials. This identified one additional reference presenting data on the first 30 patients in the first case series.¹²

The search thus identified four publications describing two case series: the MERCI trial and the Multi-MERCI trial. The first study performed simple comparisons with some of the results from the control arm of the PROACT II trial that was briefly described above and thus could be considered a comparative trial with historical controls. However, the study populations were differed in the arterial distribution for the strokes included in the trials and no patient level data were available from the PROACT II trial.

The most important outcomes to consider in acute stroke trials are death from all causes, SICH, and poor functional outcome, usually measured by the modified Rankin Scale. The most commonly reported scales used in stroke studies are described below:

Key measurement tools for stroke outcomes

National Institutes of Health Stroke Survey (NIHSS)

The NIHSS is a 15-item scale used to evaluate the severity of acute stroke.¹³ It can be completed reproducibly in approximately ten minutes by trained, non-specialist observers. The scale assesses level of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensation. The scale ranges from 0 for normal to 31 for a stroke patient with complete hemiparesis, hemianopia, hemineglect, and aphasia. The examination requires between five and eight minutes to complete. Studies have demonstrated excellent reliability of the scale in multiple settings.¹³⁻¹⁵ The NIHSS score correlates well with the size of the stroke on CT scan at one week¹³ and with three month clinical outcomes assessed by standard measures like the modified Rankin Scale or the Barthel Index.¹⁶

Modified Rankin Scale (mRS)

The modified Rankin scale, a measure of global disability, is widely applied for evaluating stroke patient outcomes and as an end point in randomized clinical trials. All recent large scale stroke clinical trials use a mRS score ≤ 2 as the primary measurement defining a good clinical outcome. The scale is defined below:

Table 1: Modified Rankin Scale

Score	Definition
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.
3	Moderate disability requiring some help, but able to walk without assistance
4	Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention.
6	Dead

TIMI Flow Grading System

The TIMI flow grading has been used for more than 20 years to assess the quality of arterial blood flow, particularly following interventions to restore flow.¹⁷ The score has been widely applied to angiographic-based studies:

Table 2: TIMI Flow

Grade	Description
0	Complete occlusion of the infarct-related artery
1	Some penetration of contrast material beyond the point of obstruction but without perfusion of the distal coronary bed
2	Perfusion of the entire infarct vessel into the distal but with delayed flow compared with a normal artery
3	Full perfusion of the infarct vessel with normal flow



The two published studies of the Merci Retriever device are both prospective case series. At least two ongoing randomized trials, the MR and Recanalization of Stroke Clots Using Embolectomy trial (MR

Rescue) and the International Management of Stroke Trial 3 (IMS III) are further evaluating the role of the Merci Retriever system. Given that only Level 5 evidence is available, TA criterion 2 is not met.

Level of Evidence: 5

TA Criterion 2 is not met.

TA Criterion 3: The technology must improve net health outcomes.

Case series

The primary clinical data used for FDA approval of the Merci retriever device came from the Mechanical Embolus Removal in Cerebral Ischemia (MERICI) trial.¹¹ The study was multi-center prospective case-series with two parts. In Part I, 55 patients were enrolled and followed for 30 days. In Part II, an additional 96 patients were enrolled and followed for 90 days. The study enrolled patients 18 years and older who had symptoms of acute stroke between three and eight hours or between zero and three hours if the patient had a contraindication to intravenous tPA, a NIHSS score ≥ 8 , and a CT scan of the brain that excluded hemorrhage. Patients were required to have arterial occlusion of one of the following “treatable” vessels: the intracranial vertebral artery, basilar artery, intracranial carotid artery (ICA), the ICA terminal bifurcation, or the first division (M1) of the middle cerebral artery (MCA). Part II of the study allowed enrollment of patients with occlusion of the second division (M2) of the MCA. Patients were ineligible if they had a known bleeding disorder, oral anticoagulant use (INR >1.7 in Part I; INR >3.0 in Part II), pregnancy, severe hypoglycemia, recent heparin use, thrombocytopenia, allergy to IV contrast media, uncontrolled hypertension, tortuous or stenotic target arteries, or CT scan evidence of significant mass effect.

The primary outcome variables were the rate of target vessel recanalization and the rate of device related complications, which included vascular perforation, arterial dissection, or embolization. Other important complications included SICH defined as a decline of at least four points in the NIHSS associated with any bleeding seen on CT scan of the brain. Secondary outcomes included the NIHSS and mRS scores at one and three months. A good neurologic outcome was defined as mRS ≤ 2 or NIHSS score improvement of at least ten points.

A summary of key patient characteristics and outcomes is described in Table 3 below. The author's benchmark for comparison of their primary outcome was the recanalization rate of 18% seen in the control arm of the PROACT II study. The recanalization rate with the Merci Retriever was 48%, which was significantly greater than that seen in the control arm of the PROACT II study ($p < 0.0001$). There are several issues with this comparison. For the statistical analysis used (exact binomial), the 18% control rate in PROACT has to be the true absolute rate, even though that arm of the trial included only 59 patients and the inclusion and exclusion criteria of the PROACT trial differ greatly from that of the MERCI trial. Furthermore, the authors did not present the comparison with the active arm of the PROACT II trial. The recanalization rate was 66% ($p < 0.0001$ by exact binomial test vs. the recanalization rate in the MERCI trial). Additionally, mortality in the MERCI trial was much higher than that in either arm of the PROACT II trial with neurologic outcomes that were similar to the control arm and significantly worse than those in the PROACT II active arm. These differences likely represent differences in the patients enrolled: patients in the MERCI trial were older and had higher NIHSS scores, so their outcomes would be predicted to be worse. Furthermore, the MERCI trial included strokes outside the MCA circulation and allowed enrollment of patients up to 8 hours after symptom onset compared with 6 hours in the PROACT II trial. However, these differences between the patients in the two trials call into question the validity of **any** direct comparison between them due to significant selection bias. It is also important to note that adjuvant intra-arterial thrombolytics were used in 51/141 cases in which the Merci Retriever device was used including 17 patients that recanalized with the device and an additional 17 patients with successful recanalization only after thrombolytic therapy. As expected recanalization was associated with good neurologic outcome ($p < 0.001$) and reduced mortality ($p < 0.01$).

Procedural complications occurred in 18 patients (13%). These included three cases of embolization to previously uninvolved vascular territories, four cases of vascular dissection, six cases of intracranial vascular perforation, three additional subarachnoid hemorrhages without identifiable perforation, and three groin hemorrhages requiring transfusions or surgical repair. Of the 341 devices used in the trial, 11 fractured. Two of these fractured devices were thought to contribute to the patients' deaths. As a result of these events, training for use of the device was revised and the device design was modified to increase its strength.

Table 3: Comparison of MERCI and Multi-MERCI trials with PROACT II

Study	N*	Age	Baseline NIHSS	SICH	RR 1	RR 2	90 day mRS≤2	90 day Mortality
MERCI	141	67	20	8	48	60	28	44
Multi-MERCI	111	66	19	9	54	69	34	31
PROACT active	121	64	17	10	66	NA	40	25
PROACT control	59	64	17	2	18	NA	25	27

* Per protocol for MERCI studies, intention to treat for PROACT II

RR 1: Recanalization Rate following initial therapy; RR 2: Recanalization Rate with MERCI device plus intra-arterial thrombolytic; NA: Not applicable.

Initial data from a second case series, the Multi-MERCI trial, has been published.¹⁰ This trial was a multi-center study designed to further evaluate the safety and efficacy of the Merci Retriever. The study initially used the first generation X5 and X6 models, followed by the second generation L5 device with design changes prompted by device failures in the original MERCI trial. Inclusion and exclusion criteria for the trial were identical to the original MERCI trial except that patients could be pretreated with IV tPA.

The study enrolled 123 patients and treated 111 of the patients with the Merci Retriever. Thirty of the 111 patients were initially treated with IV tPA. The primary results are presented in Table 3 above. The overall recanalization rate among patients who were treated with the device was 54% and this increased to 69% after additional intra-arterial therapy. At 90 day follow-up mortality was 31% and good neurologic outcome, defined by a mRS ≤ 2, was 34%. These results were better than those observed in the MERCI trial, though not as good as those observed in the active arm of the PROACT II trial. The newer L5 model was associated with slightly better recanalization rates (45/78 patients, 58%) compared with the older X5 and X6 devices (46%).

Harms were similar to those observed in the first case series. The rate of SICH was nine percent. An additional 30% of patients (33/111) were noted to have asymptomatic intracranial hemorrhage. Procedural complications included one case of embolization to previously uninvolved vascular territories, three cases of vascular dissection, and three cases of intracranial vascular perforation.

Major protocol violations were identified by the investigators in 38 patients (34%). These included the use of abciximab, the simultaneous use of multiple Merci Retriever devices, the use of intra-arterial thrombolytics



before and between passes of the retriever device, the use of intra-arterial tPA more than six hours after stroke onset, and the initiation of treatment more than eight hours after symptom onset. The procedure related adverse event rate was higher in cases with major protocol violations (18.4% vs. 5.5%, $p=0.044$). The analyses suggested that the use of abciximab and the use of intra-arterial tPA before and between passes of the Merci Retriever device were associated with subarachnoid hemorrhage.

In summary, there are two prospective case-series reporting on the safety and efficacy of two generations of the Merci Retriever devices. Recanalization rates appear to be somewhat higher than expected without intervention, although mortality rates in the two studies were also somewhat higher than might be expected. It is difficult to make valid conclusions comparing outcomes from these trials to other trials because neurologic and mortality outcomes are highly dependant on the characteristics of patients at the time of presentation. Furthermore, there were a significant number of device and procedure related adverse events as well as major protocol violations in these initial trials. Further data is needed to clarify the appropriate use of this device in the management of acute stroke.

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The established therapy for patients presenting with an acute stroke within three hours of symptom onset is IV tPA. There is no established alternative outside the three hour window. Ongoing randomized studies are evaluating the use of tPA between three and six hours after symptom onset. One randomized trial (PROACT II) found that intra-arterial prourokinase improved neurologic outcomes in patients presenting with middle cerebral artery strokes up to six hours after symptom onset.⁸ However, the FDA has requested additional studies before approving the use of intra-arterial thrombolytics for this indication. Many other approaches are under active investigation. There have been no direct patient level comparisons between the outcomes of the Merci Retriever devices against any of the potential alternatives. It is impossible to conclude at this time that the Merci Retriever device is as effective as the alternatives.

TA Criterion 4 is not met.



TA Criterion 5: The improvement must be attainable outside of the investigational setting.

In order to successfully use the Merci Retriever System, physicians must have training and experience in both intra-arterial catheter manipulation and neuroradiology. In addition, the manufacturer, Concentric Medical, has developed a program to train physicians with the appropriate skill set, to use the device. Initial recommendations for credentialing include a requirement for physicians to perform at least five procedures annually with the device.¹⁸ There is no literature yet on a learning curve for the device.

As the utility of the Merci Retriever System has not yet been demonstrated in the investigational setting, no conclusions can be reached about the effectiveness of the device in a community setting.

TA Criterion 5 is not met.

CONCLUSION

The prospect of opening up occluded intracerebral arteries with endovascular devices is promising and has precedent in the coronary artery vasculature where primary PTCA has become first line therapy over thrombolysis at centers where endovascular treatments can be deployed rapidly. The data from the two case series using the Merci retriever device suggest that it may be used safely and with modest success, though the high mortality rates are concerning and there were a significant number of procedure and device related complications. Experts suggest that there are stroke locations, like the ICA terminus, where thrombectomy should be more efficacious than potential alternatives such as intra-arterial prourokinase. However there are no data directly comparing the efficacy of the Merci Retriever device to other approaches in any settings and thus no data supporting its superiority in particular subgroups of patients.

As the principal investigator for the two case series wrote in a review, “The MERCI and Multi-MERCI trials were single-armed studies using historical controls, and therefore do not establish the clinical efficacy of the device. It is likely, however, that mechanical recanalization of vessels does improve outcome.”¹⁹ Further clinical trial data are needed to establish clear indications for use of this promising new technology device.



RECOMMENDATION

It is recommended that the use of the Merci retriever does not meet Technology Assessment Criteria 2 through 5 for safety, effectiveness and improvement in health outcomes when used to treat acute ischemic stroke.

The CTAF panel voted nine in favor and three opposed to the recommendation.

October 17, 2007



RECOMMENDATIONS OF OTHERS

BLUE CROSS BLUE SHIELD ASSOCIATION (BCBSA)

The BCBSA Technology Evaluation Center has not conducted a review of this device.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

In 2006, CMS approved a new ICD-9 Procedure Code for ischemic stroke patients treated with the Merci Retriever. Neither a National Coverage Decision nor a Local Coverage Decision was found.

ASSOCIATION OF CALIFORNIA NEUROLOGISTS (ACN)

A representative of the ACN attended the meeting and participated in the discussion regarding this technology. The ACN does not have a formal position on the use of the Merci Retriever.

CALIFORNIA ASSOCIATION OF NEUROLOGICAL SURGEONS

CANS was invited to provide an opinion regarding the use of this technology and to have a representative participate at the meeting.

AMERICAN HEART ASSOCIATION/AMERICAN STROKE ASSOCIATION

The AHA/ASA updated their Guidelines for the Early Management of Adults with Ischemic Stroke in 2007.

The guideline is available at this web address:

<http://stroke.ahajournals.org/cgi/reprint/STROKEAHA.107.181486>

ABBREVIATIONS USED IN THIS REVIEW

IV	Intravenous
tPA	Tissue plasminogen activator
SICH	Symptomatic intracranial hemorrhage
DARE	Database of Abstracts of Reviews of Effects
NIHSS	National Institutes of Health Stroke Survey
mRS	Modified Rankin Scale
MR Rescue	MR and Recanalization of Stroke Clots Using Embolectomy trial
IMS III	International Management of Stroke Trial 3
MERCI	Mechanical Embolus Removal in Cerebral Ischemia
ICA	Intracranial carotid artery
M1	First division
MCA	Middle cerebral artery
M2	Second division
PTCA	Percutaneous Transluminal Coronary Angioplasty

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