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Does the Merci Retriever Work?: For

Jeffrey L. Saver

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Does the Merci Retriever Work? For

Jeffrey L. Saver, MD

Technically, it works. And remarkably so. The Merci Retriever is a mechanical embolectomy device designed to reopen occluded vessels by extracting occlusive thrombi from the cerebral vasculature. In the Mechanical Embolus Removal in Cerebral Ischemia (MERCIS) trial (parts I and II combined), among 151 patients enrolled in the intention-to-treat group; partial or complete recanalization by use of the device alone was achieved in 46%.¹ This rate substantially exceeded that in the prespecified comparator group—patients enrolled in the control arm of the Prolyse in Acute Cerebral Thromboembolism (PROACT-II) trial (18%). The associated probability value of <0.0001 indicates a less than 1 in 10 000 chance that this result occurred by chance. The Merci Retriever indeed works.

And it works well where we most need it to work: on proximal occlusions for which there was previously no good therapy. Proximal carotid terminus and M1 middle cerebral artery thrombi respond poorly to IV or intra-arterial fibrinolytic therapy, likely attributable in large part to the sheer volume of the clot burden requiring enzymatic digestion. The average volume of carotid terminus thrombi (0.4 ml) is more than an order of magnitude larger than that of M2 middle cerebral artery division thrombi (0.03 ml).² Such large clot burdens resist enzymatic digestion. For example, IV tissue plasminogen activator recanalizes only 10% of carotid terminus occlusions.³ In contrast, the Merci Retriever disposes of large proximal clots with comparative ease (53% recanalization rate in the MERCI Trial).

The Merci Retriever perfectly complements lytic therapy. The device's size limits its deployment in distal vessels; it cannot currently be safely deployed beyond the proximal portion of the M2 middle cerebral artery. In contrast, lytics work best on small distal clots, in M2, M3 and higher order branches and in small penetrating arteries, inaccessible to the Retriever but highly responsive to enzymatic digestion.

Moreover, the Merci Retriever works where many a previous mechanical thrombectomy device has failed. Sus-

pending or abandoned mechanical strategies to treat cerebral thromboemboli include clot maceration and aspiration by rheolytic thrombectomy (Angiojet, too damaging to vessel walls), primary angioplasty (spongy clots spring right back), laser (too ineffective at low energies, somewhat damaging at high energies), whirling roto-rooter clot maceration (X-ciser, too damaging to vessel walls), snare retrievers (too often fail to capture clots), and nitinol capture baskets (Neuronet, too bulky to deploy easily in cerebral vessels). The technical challenge in endovascular thrombectomy is not just getting clots out, but also leaving intact vessels behind.⁴ The Merci Retriever's inwardly curved shape and avoidance of energy delivery permits it to capture thrombi without unduly injuring the delicate cerebral vasculature. Its development is a major advance in stroke care.

Does the Merci Retriever make patients better? I firmly believe that it does. The case for benefit is strong. The Merci Retriever achieves recanalization with a low rate of adverse effects. Recanalization is the single most powerful treatment for ischemic stroke.⁴ Recanalization will improve the clinical outcome of patients with persisting salvageable penumbra, albeit not patients who have already completed their infarct.⁵ As an end point, recanalization may meet criteria to serve as an acceptable surrogate end point in ischemic stroke clinical trials.^{6,7} Vessel recanalization is both biologically and statistically strongly related to stroke clinical outcomes. Across 33 studies enrolling 1094 acute cerebral ischemia patients, recanalization increased the odds of a good final functional outcome by 4.5-fold.⁸

In the MERCI Trial, recanalization was dramatically associated with improved outcomes. The Merci Retriever achieves recanalization in one-half of all treated patients, and does so more quickly after arrival on clot than intra-arterial lytics and without exposing the patient to the hemorrhagic risk, neurotoxicity, and blood-barrier disruption of fibrinolysis.

In contrast, the adverse event rate with the Merci Retriever is low. Symptomatic intracranial hemorrhage occurs, but at a rate (7.8%) lower than that associated with lytic therapy (in patients of equivalent stroke severity) and below the 10.2% rate which was compatible with substantial net clinical benefit in PROACT II. Patients who fail to recanalize with the Retriever do die frequently. However, the observed mortality rate is exactly that expected in patients who have severe strokes and persisting proximal occlusions.¹ Indeed, it is because the natural history of severe acute ischemic stroke is so dismal that the PROACT II trial identified so clear a benefit of recanalization despite its small sample size.

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So, there is every reason to believe that the Merci Retriever works clinically, as well as technically—that it improves patient final outcomes just as it reopens occluded arteries and restores blood flow to ischemic but salvageable neural tissue.

Is a randomized trial of the Merci device needed? Absolutely. I have never had a stronger belief that a therapy helps acute ischemic stroke patients. Firmly grounded in physiology, surrogate end point data, and remarkable clinical experiences, my belief in the benefit of the device approaches absolute conviction. I feel disappointed when a patient of mine is randomized to supportive medical care rather than Merci Retriever intervention. However, belief is not knowledge and conviction is not proof. If there is one trait my generation of stroke researchers has acquired, it is a sense of humility.⁹ Over the course of my career, I have participated in trials of numerous promising treatments for acute ischemic stroke, each launched with high hopes and strong beliefs. My personal record for success is 1 win (aspirin) and roughly 39 losses. I have learned the hard way the difference between belief and knowledge. A first in class device like the Merci Retriever requires a randomized, controlled trial with a clinical end point to demonstrate benefit. Technical end point, uncontrolled trials are appropriate for 2nd, 3rd, and later in class devices that modify proven treatment strategies, but not for the first-ever test of a new treatment strategy.

Accordingly, it is imperative that randomized clinical trials of the Merci Retriever be performed. The ongoing National Institutes of Health (NIH)-funded MR RESCUE (Merci Retrieval versus conventional supportive care) and IMS 3 (IV tPA+endovascular intervention versus IV tPA alone) trials

must receive the support and referrals of neurologists and neurointerventionalists. Only then will we know what I (and you, dear Reader) already believe—that the Merci Retriever works clinically as well as technically.

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KEY WORDS: acute stroke ■ brain ischemia ■ clinical trials ■ embolectomy ■ therapeutics

Does the Merci Retriever Work? Against

Lawrence R. Wechsler, MD

In a decade after approval of IV rt-PA for acute stroke, treatment leads to good outcomes in less than half of patients, and hemorrhage rates have not been reduced. Recanalization improves outcome¹ but is often delayed and incomplete. Devices offer the promise of rapid recanalization with a greater proportion of good outcomes and fewer hemorrhages. The Merci retrieval system was introduced with hopes of fulfilling this promise. The FDA recently approved this device for removal of thrombus from intracranial

arteries in patients with stroke. Despite this approval, the question of whether the device works remains unsettled.

The recently published Mechanical Embolus Removal in Cerebral Ischemia (MERCi) trial² using the Merci retriever claims efficacy based on a recanalization rate that is greater than the spontaneous recanalization rate observed in the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial control group.³ Recanalization may result in a variety of outcomes depending on timing, depth and duration of ischemia.⁴ These include improvement, no clinical change, reperfusion hemorrhage or massive cerebral edema resulting in neurological worsening or death. Thus, the most important measure of efficacy for any acute stroke treatment is not recanalization, but clinical outcome. On this score, evidence that the Merci Retriever works is lacking. In the MERCI trial, only 28% of patients reached a mRS score of ≤ 2 at 90 days. This is only slightly greater than the 25% of control patients reaching this outcome in the PROACT II study and does not compare

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favorably with the 40% of patients achieving mRS ≤ 2 in the treatment group. In the MERCI trial, treatment was associated with a 44% mortality. Mortality in PROACT II was considerably lower at 27%. Although inclusion of distal internal carotid artery and basilar occlusions possibly biases the MERCI study toward worse outcomes, when considering only the patients with middle cerebral artery occlusion (similar to PROACT II) only 29% had good outcomes and mortality was 39%. Overall, these results certainly do not provide any signal suggesting the device improves outcome.

Does the device actually improve recanalization? Perhaps it does compared with spontaneous recanalization rates but not in comparison to other stroke treatments. In the PROACT II study, intra-arterial prourokinase recanalized 66% of arteries. Recanalization was achieved in 56% of patients treated with combined intravenous and intra-arterial rt-PA in the Interventional Management of Stroke (IMS) study.⁵ In the MERCI study, recanalization was achieved in 46% of all patients and 45% of middle cerebral arteries. Given the small sample size of these studies the differences may not be significant. However, there is no indication that the MERCI device is superior to these other interventional approaches which, unlike the Merci Retriever, are not FDA approved. Another potential advantage of a clot removal device is more rapid recanalization compared with the 2-hour infusion in PROACT II and IMS. Unfortunately, the report of the MERCI trial gives no information about time to recanalization. It is also unfortunate that recanalization was assessed by unblinded local investigators rather than by central blinded adjudication because this might have resulted in overestimation of recanalization.

The MERCI trial investigators point out that in patients with recanalization, good outcomes were greater (36%) with lower mortality (32%). However, these results remain unimpressive compared with outcomes with other acute stroke therapies and do not consider the possibility that patients may have been harmed by the device if recanalization did not occur.⁶

Another way the device could work is by reducing complications. By this criteria, the Merci Retriever again fails. Symptomatic hemorrhage occurred in 7.8% of patients, not different from the 10% rate in PROACT II and 6.3% in IMS. In addition, other complications such as perforation, dissection, embolization, groin hematoma and device fractures occurred in 13% of patients, and 7.1% were considered clinically significant. When added to the symptomatic hemorrhages, 14.9% of patients experienced clinically significant complications, a sobering figure for a treatment with unproven efficacy.

In summary, the MERCI study does not provide any evidence of improved outcomes or greater recanalization rates compared with other acute stroke therapies. In addition, both clinically significant complications and mortality are higher than the results of other interventional trials. Even acknowledging the hazards of comparing disparate studies, the results do not support the proposal that the Merci retrieval device works by any definition.

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KEY WORD: acute stroke

Merci Retriever Does it Work?

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The central theme of this controversy is not controversial! We all agree that recanalization is the most important target for therapy in acute ischemic stroke because it undoubtedly improves outcomes. The caveats are that recanalization

needs to be performed within a time window to salvage significant penumbral tissue and that safety (hemorrhagic transformation and maintenance of vascular integrity) is within reasonable limits. So where does this place mechanical recanalization with the Merci Retriever?

Since the introduction of IV thrombolysis a decade ago, we have improved our understanding significantly of the processes involved in site and responsiveness to therapy. For example, we now know that the recanalization rate for large proximal vessels is poor.¹ Also, all clots are not the same. As pointed out by Saver, there is an order of magnitude difference in the volume of proximal and distal thrombi in the internal carotid/middle cerebral axis, correlating with the likelihood of successful recanalization

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zation. It, therefore, appears rational to us that decision algorithms for individual patients (IV versus intra-arterial thrombolysis versus mechanical recanalization) should be based on an understanding of individual patient pathophysiology.

Although the focus of the discussion of our protagonists has been on arterial recanalization, we would also suggest that a broader imaging strategy should include identification of the presence and extent of the ischemic penumbra.² Clearly, expensive therapeutic efforts to recanalize vessels is probably not warranted if there is no penumbra to salvage. Hence, in the future, we will be moving toward a total evaluation of arterial and tissue status in individual patients, regardless of time of stroke onset, with the aim of individualizing therapy.

To return to our controversy, does the Merci Retriever work? In spite of his passion, Saver quite rightly tempers his comments, echoed by Wexler, that these are early days, and that large clinical trials are needed to determine the clinical safety and efficacy of this exciting technology. Even with mechanical retrieval using the Merci device, recanalization was only achieved in 46% of patients, mortality was 44%, and symptomatic intracerebral hemorrhage occurred in 7.8% of patients, comparable to IV tPA.³ Early days indeed!

An issue not raised in this controversy is the resource implication of a successful translation of this technology into practice. Obviously, few patients are likely to have access to

facilities where this procedure could be used. Generalizeability will, therefore, become a real issue if further clinical trials prove that the Merci device does work with an acceptable safety profile. Stroke clinicians should be aware that primary coronary angioplasty is superior to thrombolysis for acute coronary syndromes and is routine in many centers around the world.⁴ We should not resile from our responsibility to our patients in pushing this technology forward.

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