Results from the Merci Registry: Clinical Outcomes and Recanalization Rates

Clinical outcomes, safety, and recanalization rates using the Merci retriever embolectomy device are similar to those seen in previous prospective studies. In this study by Jovin and colleagues, investigators compared data from the Merci Registry with pooled data from the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI trials to evaluate the clinical outcomes, safety, and recanalization rates of the Merci retriever embolectomy device in a "real world" setting.

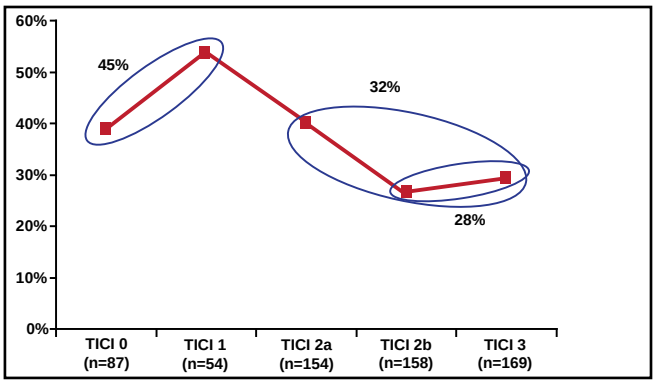
The primary endpoint was revascularization, defined as Thrombolysis in Cerebral Infarction (TICI) score of 2a or higher. The secondary endpoint was clinical outcomes at 90 days. Outcomes were evaluated at 24 hours (determined by NIH Stroke Score [NIHSS] and symptomatic intracranial hemorrhage [sICH]), discharge (determined by NIHSS and modified Rankin Scores [mRS]), and 90 days (determined by mRS). A total of 625 patients with acute ischemic stroke, large vessel intracranial occlusion, and at least one pass with the Merci retriever were included in the primary analysis. Of the 625 patients, 20% were octogenarians.

While both cohorts who were subjected to comparison presented with severe strokes, patients who were included in the pooled Merci/Multi Merci (M/MM) data had more severe strokes at presentation compared with those in the Merci Registry (mean NIHSS in the Mercy Registry 17.9 versus 19.6 in the M/MM group, p<0.0001). There was no significant difference in comorbidities or occlusion location between the two data sets. The incidence of adjuvant pharmacological thrombolysis (ie, intravenous lytic or intra-arterial lytic) was higher in the Merci Registry than in M/MM (p<0.0001).

The time from last seen at baseline to procedure onset (in hours) was higher in the Merci registry (5.72±3.28) than in M/MM (4.35±1.76; p<0.001). However, no association was found between time to procedure and clinical outcome. The majority of procedures in the Merci registry occurred between 3 and 8 hours after symptom onset (73.7%). The rate of procedures that started 8 hours or more after symptom onset was higher in the Merci registry (14.1%) than in M/MM (1.3%; p<0.001), highlighting a recent trend toward imaging rather than time-based selection for acute stroke interventions, which, in selected cases, enables expansion of the therapeutic time window beyond 8 hours. Overall, revascularization rates of TICI 2a and TICI 2b-3 were associated with lower mortality rates (32% and 28%, respectively; Figure 1) and with significantly higher rates of favorable clinical outcomes in multivariate analyses (odds ratio 2.97, p< 0.0001)

Recanalization rates were significantly better in the Merci registry (77%) versus M/MM (65%). However, successful recanalization was defined differently in the two groups, based on TICI score in the Mercy Registry versus TIMI score in the M/MM data. Modified Rankin Scores ≤2 at 90 days and 90-day mortality rates were not significantly different between the two groups. Intubated state during procedure was an adverse predictor of good clinical outcome (p=0.0004) and was associated with a higher risk of mortality (p=0.0141) at 90 days. In a multivariate analysis that looked at revascularized subjects only, baseline NIHSS, age, procedure duration, intubated state during procedures, intra-arterial lytic, and glucose ≥140 mg/dL were significant predictors of clinical outcome at 90 days.

Figure 1. Mortality Rates According to Revascularization (TICI) Score.



Reproduced with permission from T. Jovin, MD.

Tudor G. Jovin, MD, Presbyterian University Hospital, Pittsburgh, PA, pointed out two important trends that were identified during this study. First, in support of other multicenter studies that were presented at the International Stroke Conference 2010, intubated state during the procedure was shown to negatively affect clinical outcome throughout this analysis. Second, though time to procedure was not associated with better clinical outcome, procedure duration affected clinical outcome. The shorter the procedure duration, the higher the chance of a good outcome, said Dr. Jovin.

Results of this large, prospective study of mechanical embolectomy with the MERCI device were similar to those found in previous studies with regard to clinical outcome, safety, and recanalization rates. These data

confirm that successful recanalization is associated with better clinical outcome. This study also shed some light on the effect of intubation, procedure duration, and time to treatment on clinical outcome. However, this analysis was based on nonrandomized, self-reported data in the absence of a control. Therefore, efficacy of this treatment approach compared with standard medical therapy was not addressed by this study, and further randomized controlled studies are warranted.

Perlecan Domain V is a Novel Stroke Treatment

Perlecan domain V (DV) may improve functional stroke outcome. Boyeon Lee, PhD, Texas A&M College of Medicine, College Station, TX, presented findings from a study that investigated the effect of the extracellular matrix (ECM) fragment perlecan domain V on angiogenesis and neurogenesis in poststroke rats and mice.

Neurovascular coupling of angiogenesis and neurogenesis has been shown to involve ECM remodeling and ECM fragment initiation [Ohab JJ et al. *J Neuroscience* 2006]. Additionally, DV has been shown to interact with the ECM and promote angiogenesis [Segev A et al. *Cardiovasc Res* 2004; Mongiat M et al. *J Biol Chem* 2003]. In this study by Lee and colleagues, sham surgery control was performed or transient middle cerebral artery occlusive stroke was induced by using sterotactic injection of endothelin-1 in rats or tandem ipsilateral common carotid artery and middle cerebral artery occlusion in mice. All subjects received either intraperitoneal injections of human recombinant DV 0.5-1 mg/kg or phosphate-buffered saline control at Days 1, 3, 5, and 7 poststroke (n=15 for each group). Functional use of the affected limb was determined by the vibrissae-elicited paw placement reflex in mice and the cylinder test in rats. Concurrent brain microvascular endothelial cell *in vitro* studies were also performed to evaluate the effect of DV on angiogenesis.

Brain immunohistochemistry (von Willebrand factor) demonstrated that perlecan DV homed to the stroke and peri-infarct vasculature. DV was significantly higher in the stroked cerebral hemisphere at Days 1, 3, 5, and 7 poststroke compared with corresponding contralateral hemisphere levels (Day 1 p=0.0001; Day 3 p=0.0007; Day 5 p=0.007; Day 7 p=0.005). Additionally, subjects that were treated with DV had more neurons with normal morphology and lower incidence of TUNEL-positive cells or shrunken and misshapen cells, suggesting a neuroprotective component that was associated with DV. DV treatment was associated with increased poststroke neurogenesis and poststroke angiogenesis. Significant increases were observed in stroke peri-infarct vasculature in subjects that were treated with DV on poststroke Days 3, 5, and 7 versus control (p=0.001; p<0.00001; p<0.00001 for Days 3, 5, and 7, respectively). DV treatment also resulted in significantly more doublecortin-positive pixels on poststroke Days 3, 5, and 7 versus control (Day 3, p=0.00001; Day 5, p<0.00001; Day 7, p<0.00001, resulting in enhanced poststroke neurogenesis.

Functional stroke outcome was significantly better in stroked subjects that were treated with DV versus control, and improvement in contralateral paw use was observed at Days 3 (p=0.03) and 7 (p=0.009) poststroke. While significant contralateral forelimb improvement was noted in those that were treated with DV, PBS control subjects remained significantly impaired at poststroke Days 3 (p=0.008), 5 (p=0.006), and 7 (p=0.005).

The *in vitro* analysis that was included in this study revealed possible mechanisms by which DV affects angiogenesis. At 3 days poststroke, an increase in α5β1 levels was noted in those that were treated with DV. DV enhances brain endothelial cell formation, which may be inhibited via α5β1. In α5β1 and DV coimmunohistochemistry of brain endothelial cells, colocalization of DV and α5β1 was identified. DV also induces brain endothelial cell VEGF synthesis and release via the α5β1 integrin. A DV dose-dependent VEGF response was noted *in vitro*.

Dr. Lee concluded that DV is neuroprotective and promotes poststroke angiogenesis and neurogenesis, thus, contributing to improved functional stroke outcome. DV-induced VEGF release via the α5β1 integrin pathway plays a role in the DV angiogenesis and neurogenesis. However, the extent of their involvement remains unclear. Results from this study are promising and suggest that perlecan DV may provide a viable treatment option for stroke in the future.

Failure to Validate Association Between Variants on 12p13 and Ischemic Stroke

A meta-analysis of genomewide association studies (GWAS) did not validate findings that associated the single-nucleotide polymorphisms rs12425791 and rs11833579 with stroke. Representing the members of the International Stroke Genetics Consortium, Jonathan Rosand, MD, MSc, Massachusetts General Hospital, Boston, MA, detailed findings from this meta-analysis.

A previous GWAS found that two intergenic single-nucleotide polymorphisms (SNPs), rs12425791 and