Effect of Time to Reperfusion on Clinical Outcome of Anterior Circulation Strokes Treated With Thrombectomy
Pooled Analysis of the MERCI and Multi MERCI Trials

Raul G. Nogueira, MD; Wade S. Smith, MD, PhD; Gene Sung, MD; Gary Duckwiler, MD; Gary Walker, PhD; Robin Roberts, BSc, MSc; Jeffrey L. Saver, MD; David S. Liebeskind, MD; on Behalf of the MERCI and Multi MERCI Writing Committee

Background and Purpose—Previous studies have demonstrated a strong correlation between treatment time and outcomes after intravenous recombinant tissue-type plasminogen activator. However, the temporal profile of ischemia may vary according to the level of occlusion, and it is likely that more proximal occlusions have a more variable temporal course than their distal counterparts. We sought to establish how time influences outcomes in anterior circulation proximal arterial occlusions.

Methods—All patients from the MERCI/Multi MERCI trials with intracranial internal carotid artery and/or middle cerebral artery (M1-M2 segments) occlusions who were successfully revascularized were included in univariate/multivariate analyses to define the predictors of independent functional outcomes (modified Rankin Scale score ≤2) and mortality at 90 days. The effect of time to reperfusion on outcomes was calculated after adjustment for age, baseline National Institutes of Health Stroke Scale, and glucose levels.

Results—a total of 175 patients presenting with internal carotid artery/M1/M2 occlusions were revascularized. There was no definite association between time (to treatment or reperfusion) and outcomes in the unadjusted analysis. Baseline National Institutes of Health Stroke Scale score and age were independent predictors of independent outcome and mortality. High glucose demonstrated a strong trend toward worse outcomes. After adjustment for age, baseline National Institutes of Health Stroke Scale score, and glucose, there was a strong trend toward fewer independent outcomes with later reperfusion times. Notably, 40% of the patients reperfused at ≥6.9 hours achieved independent functional outcomes.

Conclusions—Time (to treatment or reperfusion) is only one of the many variables that may impact outcome in proximal arterial occlusions strokes. Reperfusion therapies should be started promptly, but our findings also suggest that stroke patients presenting at later time points may still benefit. (Stroke. 2011;42:3144-3149.)

Key Words: stroke outcomes ■ thrombectomy

Cerebral ischemia attributable to arterial occlusive disease is a dynamic phenomenon in which continuous growth of the infarct core occurs at the expense of the penumbral tissue until either the infarct is completed or the reperfusion is achieved. The pace of expanding cerebral ischemia is highly variable among different individuals and is likely dependent on multiple factors other than just the duration and intensity of ischemia, including the nature of collateral circulation, ischemic preconditioning, cerebral perfusion pressure, and cerebral blood volume, as well as serum glucose, body temperature, and oxygen delivery capacity. The time course of evolving infarction is largely influenced by the nature of collateral circulation compensating for a specific arterial occlusion.1 Because of greater interindvidual variation in collateral flow routes with proximal arterial occlusions, it is likely that the temporal profile of lesion expansion is more variable in proximal than in distal occlusions. Hemodynamic instability, risk of progressive ischemia, and the extent of vulnerable brain tissue may be determined by collateral perfusion; yet, such variables cannot be predicted from noncontrast CT. It therefore remains imperative that reperfusion therapies are implemented as soon as possible after symptom onset, or “time is brain.”2 Many studies have previously demonstrated a strong correlation between
the time from symptom onset to treatment initiation and clinical outcomes after intravenous recombinant tissue-type plasminogen activator (rtPA). The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) and Multi MERCI trials evaluated the safety and efficacy of endovascular thrombectomy with the Merci Retrieval System (Concentric Medical) in the treatment of intracranial proximal arterial occlusions (PAO) performed within 8 hours of stroke symptom onset. The overall patient characteristics, study methodology, and treatments were comparable in both studies. In a previous analysis, we have demonstrated that age, baseline National Institutes of Health Stroke Scale (NIHSS) score, and successful revascularization were the strongest predictors of clinical outcomes in patients undergoing thrombectomy. In that analysis, which involved 305 patients with either anterior or posterior circulation occlusions regardless of their final revascularization status, time from symptom onset to treatment was not identified as an independent predictor of good outcome or mortality. In the current analysis, we sought to establish how time from stroke symptoms onset to technically successful revascularization (time to reperfusion) affects clinical outcomes in the context of anterior circulation PAO. In addition, we investigated which baseline factors predict independent functional outcome and mortality in reperfused patients and attempted to identify any factors that may exclusively impact this patient population.

**Patients and Methods**

**Patients and Techniques**

The subjects of this analysis included all patients in the MERCI and Multi MERCI studies who presented with occlusion involving the intracranial internal carotid artery and/or the middle cerebral artery (M1 and M2 segments) vessels and were successfully revascularized (postretriever/postadjunctive thrombolysis in myocardial infarction 2–3 flow). The MERCI trial was a prospective single-arm multicenter trial designed to test the safety and efficacy of the Merci Retriever to restore the patency of intracranial arteries in patients ineligible for intravenous rtPA during the first 8 hours of an acute stroke. The occlusion sites were the intracranial vertebral artery, basilar artery, internal carotid artery, or proximal middle cerebral artery branches (middle cerebral artery, M1 or M2 segments). The Multi MERCI trial was an international multicenter single-arm trial designed to explore the safety and technical efficacy of the second-generation Merci Retriever in patients who were either ineligible for intravenous rtPA or did not have recanalization after treatment with intravenous rtPA alone. Inclusion criteria and techniques were otherwise similar to the ones used in the MERCI trial. The technical details regarding the procedures used in MERCI and Multi MERCI have been previously described. Successful recanalization was defined as achieving thrombolysis in myocardial infarction 2 or 3 flow in all treatable vessels. Intra-arterial thrombolytics were only allowed in cases of unsuccessful recanalization after 6 passes with the study device or to treat distal emboli not accessible to the device after successful proximal thrombectomy.

**Clinical Variables and Measurements of Outcome**

The baseline clinical variables and the clinical, angiographic, and radiographic outcome measurements were similar in the MERCI and Multi MERCI trials. The following baseline clinical variables were included in the current analysis: study (MERCI versus Multi MERCI), age (continuous and dichotomized: 68 years or younger versus older than 68 years), gender, race (white versus other), baseline NIHSS score (continuous and dichotomized: ≤10 versus 11 to 20 versus >20), site of occlusion (internal carotid artery versus M1 versus M2), side of occlusion (right versus left), systolic blood pressure (continuous and dichotomized: <150 versus ≥150 mm Hg) and diastolic blood pressure (continuous and dichotomized: <90 versus ≥90 mm Hg) on presentation, glucose levels (continuous and dichotomized: <140 versus ≥140 mg/dL), partial thromboplastin time, prothrombin time/international normalized ratio, platelet count, intravenous thrombolytic use, intra-arterial thrombolytic use, time from symptom onset to procedure (continuous and dichotomized: ≤3 versus 3 to 6 years versus >6 hours), endovascular procedure time, and time from stroke symptom onset to procedure (continuous and dichotomized: ≤7 versus >7 days). Other variables included in the current analysis: study (MERCI versus Multi MERCI trials) involved 305 patients. Data regarding revascularization status were available in all 305 patients. However, 90-day modified Rankin Scale score and mortality data were missing in 15 of 305 (4.9%) and 6 of 305 (1.9%) patients, respectively. Thrombolysis in myocardial infarction 2 to 3 flow (postretriever/postadjunctive) was achieved in 197 out of the 305 subjects (64.6%). Twenty-two of these patients had posterior circulation occlusions. Therefore, 175 patients met the inclusion criteria for the current study (eg, successfully recanalized internal carotid artery, M1 segment, or M2 segment occlusions). A total of 164 patients were included in the independent functional outcome analysis and 170 patients were included in the mortality analysis. The rates of independent outcome and mortality at day 90 were 48.1% (79/164) and 25.9% (44/170), respectively. In contrast, the rates of

Statistical Analysis

The pooled database from MERCI and Multi MERCI was interrogated by using univariate and multivariate techniques. Quantitative variables were treated in these analyses as both continuous and stratified factors dichotomized/trichotomized at clinically relevant cut-offs. For the univariate analysis, the aforementioned 10 categorical and 10 quantitative variables that were considered possibly related to outcome were selected from pretreatment and periprocedural clinical data. A univariate analysis was first performed to assess the relation between individual baseline variables and the outcome measures (90-day modified Rankin Scale score ≥2 and 90-day mortality) and the degree to which the variable influenced the size of the treatment effect. The Bonferroni correction was used when assessing the significance of relations to allow for multiple comparisons. Only variables with P<0.20 in the univariate logistic regression analysis and present for at least 95% of the patients with the outcome variable were included in the multivariable logistic regression model-building process. Models were built using forward/backward stepwise logistic regression with variables entered into the model at the 0.05 significance level and removed at the 0.10 significance level. The observed times to reperfusion were further broken down into quartiles to look for any hidden trends. Finally, the estimated effect of time to reperfusion on clinical outcomes was calculated after adjustment for significant physiological variables including age, NIHSS score, and glucose levels. All analyses were performed by a biostatistician with the aid of SAS software (version 8.2; SAS Institute).

**Results**

The entire patient cohort from the MERCI and Multi MERCI trials involved 305 patients. Data regarding revascularization status were available in all 305 patients. However, 90-day modified Rankin Scale score and mortality data were missing in 15 of 305 (4.9%) and 6 of 305 (1.9%) patients, respectively. Thrombolysis in myocardial infarction 2 to 3 flow (postretriever/postadjunctive) was achieved in 197 out of the 305 subjects (64.6%). Twenty-two of these patients had posterior circulation occlusions. Therefore, 175 patients met the inclusion criteria for the current study (eg, successfully recanalized internal carotid artery, M1 segment, or M2 segment occlusions). A total of 164 patients were included in the independent functional outcome analysis and 170 patients were included in the mortality analysis. The rates of independent outcome and mortality at day 90 were 48.1% (79/164) and 25.9% (44/170), respectively. In contrast, the rates of
independent outcome and mortality at 90 days in the nonrevascularized patients were 6.1% (6/98) and 57.4% (58/101), respectively.

Because we considered a total of 28 individual baseline variables in the univariate model, the Bonferroni correction required \( P = 0.05/28 \), or \( P = 0.0018 \), for any one analysis to be considered “significant.” Baseline NIHSS score, age, and glucose levels (<140 versus ≥140 mg/dL) reached statistical significance by this criterion and, thus, demonstrated strong evidence of an influence on both independent functional outcomes and mortality at 90 days. Other variables attained \( P \) values close to this level and, thus, could only be considered to have shown a “trend” toward an association with outcome. History of diabetes and systolic blood pressure levels showed a “trend” toward an inverse relation with independent outcomes and a direct relation with mortality at 90 days. History of coronary artery disease and hypertension demonstrated a “trend” toward an inverse relation with independent outcomes and a direct relation with mortality at 90 days. History of atrial fibrillation showed a “trend” toward an inverse relation with independent outcomes (90-day modified Rankin Scale score ≤2 and mortality by time to reperfusion).

Table 1. Observed Rates of 90-Day Modified Rankin Scale Score ≤2 and Mortality by Time to Reperfusion

<table>
<thead>
<tr>
<th>Quartile of Time to Reperfusion (h)</th>
<th>1</th>
<th>2 (n=164)</th>
<th>3 (n=164)</th>
<th>4 (n=164)</th>
<th>( P ), Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin Scale score ≤2</td>
<td>19/41 (46.3%)</td>
<td>25/41 (61.0%)</td>
<td>19/42 (45.2%)</td>
<td>16/40 (40.0%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Mortality (n=170)</td>
<td>9/43 (20.9%)</td>
<td>10/42 (23.8%)</td>
<td>14/43 (32.6%)</td>
<td>11/42 (26.2%)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

In this large cohort of patients who were selected for treatment on the basis of noncontrast CT evaluation and who underwent thrombectomy for anterior circulation PAO within 8 hours of symptoms, time from onset to reperfusion had a relatively modest impact on clinical outcomes, with many of the late reperfused patients achieving independent outcomes, suggesting that the association between time from stroke onset to treatment and functional outcomes may not be as strong for late endovascular therapy as it is for early intravenous thrombolysis. Likely, this is partly attributable to the fact that virtually all patients who undergo endovascular therapy have occlusions in proximal large arteries in contrast to the mixture of proximal, distal, and even perforator arterial occlusions typically seen in intravenous thrombolysis cohorts. The farther distal the occlusion, the lesser anatomic opportunities for collateral flow as a compensatory mechanism and, thus, the less stable is penumbral tissue over time. A clear difference in the behavior of mismatch tissue evolution over time was seen in a recent MRI perfusion study that separately analyzed PAO and non-PAO strokes.

Our study complements the findings of a recent pooled analysis of the Interventional Management of Stroke (IMS) I and II trials. The IMS I–II investigators compared 54 cases of anterior circulation PAO (intracranial internal carotid artery, \( n = 8 \); middle cerebral artery M1, \( n = 46 \)) that were successfully reperfused (thrombolysis in cerebral infarction (TICI) 2–3) by intra-arterial rtPA within 7 hours of stroke onset (range, 208–395 minutes) with 38 cases without reperfusion (TICI 0–1) and found that after adjustments were made for age, baseline NIHSS score, sex, and baseline glucose, only time from symptom onset to reperfusion (OR, 0.982; 95% CI, 0.969–0.996) and age (OR, 0.945; 95% CI, 0.899–0.993) independently predicted independent functional outcomes (90-day modified Rankin Scale score ≤2).

Several factors likely contribute to the stronger association of onset to recanalization time with clinical outcome in the IMS trials than in the MERCI trials. The longer time from symptom onset to endovascular treatment initiation in the MERCI trials as compared to the IMS trials may have led to the exclusion of patients with larger strokes due to poor collateral compensation since areas of ischemia would have become more obvious over time. The potential neurotoxicity of rtPA could have attenuated the benefit of reperfusion at the later time epochs in the IMS I–II trials. Differences may also exist in the nature of reperfusion achieved with slow...
catheter infusion of fibrinolytics versus more abrupt device thrombectomy.

However, likely the greatest factor contributing to the discrepancy in the strength of the association between time to reperfusion and clinical outcomes among the IMS and the MERCI/Multi MERCI analyses is the differences in the time distribution seen in the 2 studies. Patients in IMS I–II were treated at considerably earlier time windows because they were required to undergo intravenous thrombolysis within 3 hours from symptoms onset. The IMS I–II analysis was limited to patients who were successfully reperfused within the first 7 hours from stroke onset, whereas the MERCI combined trials analysis included patients who were reperfused and had treatment initiation (as opposed to reperfusion) within 8 hours from stroke onset. The IMS trials median time to reperfusion was 300 minutes versus 351 minutes in the MERCI trials. The IMS I–II analysis included 15 patients who were reperfused between 6 and 7 hours. This obviously limited the evaluation of the effects of reperfusion at the later time epochs. In contrast, the current study included 82 patients who were reperfused and had treatment initiation (as opposed to reperfusion) within 8 hours from stroke onset. The IMS trials median time to reperfusion was 300 minutes versus 351 minutes in the MERCI trials. The IMS I–II analysis included <15 patients who were reperfused between 6 and 7 hours. This obviously limited the evaluation of the effects of reperfusion at the later time epochs. In contrast, the current study included 82 patients who were reperfused ≥5.8 hours, 40 of whom were reperfused ≥6.9 hours. This allowed us to better define the relationships between time to reperfusion and outcomes at the later time windows.

Another interesting finding of this study is that in this analysis specifically focused on successfully reperfused patients, high glucose levels showed a strong trend toward worse outcomes, whereas no association between glucose levels and outcomes was found in a previous analysis involving the overall MERCI and Multi MERCI population (reperfused and nonreperfused patients). These findings are consonant with a previous study that showed that admission glucose >140 mg/dL was an independent predictor of poor outcome in reperfused but not in nonreperfused patients treated with intravenous rtPA. These studies further support the notion that hyperglycemia plays an important role in the mechanism of reperfusion injury.

Our analysis has limitations. The lack of a control arm in the MERCI and Multi MERCI trials makes it difficult to

<table>
<thead>
<tr>
<th>Baseline Factor</th>
<th>mRS ≤2 (n=79)</th>
<th>mRS&gt;2 (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean</td>
<td>63.4</td>
<td>72.5</td>
</tr>
<tr>
<td>Median</td>
<td>69</td>
<td>77</td>
</tr>
<tr>
<td>NIHSS Mean</td>
<td>16.7</td>
<td>20.8</td>
</tr>
<tr>
<td>Median</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>Glucose (mg/L)</td>
<td>Mean</td>
<td>122</td>
</tr>
<tr>
<td>Median</td>
<td>114</td>
<td>131</td>
</tr>
</tbody>
</table>

NHSS indicates National Institutes of Health Stroke Scale.

<table>
<thead>
<tr>
<th>Baseline Factor</th>
<th>Alive (n=126)</th>
<th>Dead (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean</td>
<td>65.7</td>
<td>75.9</td>
</tr>
<tr>
<td>Median</td>
<td>71</td>
<td>79</td>
</tr>
<tr>
<td>NIHSS Mean</td>
<td>17.9</td>
<td>21.8</td>
</tr>
<tr>
<td>Median</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>Glucose (mg/L)</td>
<td>Mean</td>
<td>126</td>
</tr>
<tr>
<td>Median</td>
<td>115</td>
<td>135</td>
</tr>
</tbody>
</table>

Table 3. Estimated Effect of Time to Reperfusion

<table>
<thead>
<tr>
<th>Effect of Time to Reperfusion</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin Score ≤2</td>
<td>Quartiles Unadjusted* 0.87 (0.66–1.15)</td>
<td>0.33</td>
</tr>
<tr>
<td>Continuous Unadjusted</td>
<td>0.73 (0.52–1.01)</td>
<td>0.055</td>
</tr>
<tr>
<td>Continuous Adjusted</td>
<td>0.93 (0.77–1.13)</td>
<td>0.49</td>
</tr>
<tr>
<td>Mortality Quarters Unadjusted*</td>
<td>0.82 (0.65–1.02)</td>
<td>0.073</td>
</tr>
<tr>
<td>Continuous Unadjusted</td>
<td>1.14 (0.84–1.55)</td>
<td>0.41</td>
</tr>
<tr>
<td>Continuous Adjusted</td>
<td>1.38 (0.96–1.96)</td>
<td>0.081</td>
</tr>
<tr>
<td>Continuous Adjusted</td>
<td>1.09 (0.89–1.34)</td>
<td>0.38</td>
</tr>
<tr>
<td>Continuous Adjusted</td>
<td>1.29 (1.01–1.64)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

*Odds ratio per quarter.
†Odds ratio per hour.
establish the actual natural history of PAO at these different time epochs. However, comparison with historical controls from the PROACT-II trial suggests that MERCI/Multi MERCI patients who were reperfused at the later quartiles (≥5.8 hours, n=82) may have benefited from treatment because they achieved higher rates of good outcomes as compared to the PROACT-II control patients (n=59) despite having slightly older ages and higher baseline NIHSS scores (90-day modified Rankin Scale score ≤2: 42.7% versus 25%; P=0.034).

Analyzed baseline prognostic factors did not include all predictor variables that previous studies have linked to clinical outcome, including the degree of angiographic collateral flow and the extent of established core infarction visualized on the baseline CT (eg, ASPECTS score). Other limitations, including retrospective nature, constraints of selective inclusion criteria, and lack of advanced imaging beyond noncontrast CT, also limit generalization of our findings to a broader stroke population. Nevertheless, PAO in the anterior circulation is commonly encountered and non-contrast CT remains the most common initial diagnostic study. It is often argued that narrow time windows preclude advanced multimodal CT or MRI; however, perhaps the severe time restrictions that fail to consider pathophysiology in a given case may cause treatment to be withheld from those who may benefit. Variability likely exists across patients in the neurological impact caused by the degree and duration of flow compromise before therapeutic reperfusion. Patient-specific factors relating to collateral flow may be delineated with more advanced multimodal CT or MRI may reveal why time alone is inconsequential. Strict time windows may increase the chance of therapeutic success in a clinical trial, yet adherence to time constraints without consideration of underlying pathophysiology may incorrectly deny treatment to later patients in clinical practice. Even with the use of noncontrast CT to carefully select cases, the ECASS-3 investigators were able to demonstrate that stroke patients may benefit from intravenous thrombolysis up to 4.5 hours after symptom onset. Unfortunately, stroke patients presenting between 3 and 4.5 hours after symptom onset around the world were denied the only approved drug for stroke for 14 years after the 3-hour time window was declared irrefutable.

Conclusions

In conclusion, baseline NIHSS score and age are the strongest predictors for both independent functional outcomes and mortality at 90 days in anterior circulation stroke patients who are successfully revascularized with endovascular retriever-based therapy within 8 hours from symptoms onset. Time (to treatment or reperfusion) is only 1 of the many variables that may impact the outcomes of PAO stroke patients, and it appears to have a more modest effect during the later phases of stroke evolution. Reperfusion therapies should be started promptly, but our findings also suggest that stroke patients presenting at later time points may still benefit from intervention.

Disclosures

R.G.N., W.S.S., G.S., G.D., J.L.S., and D.S.L. are on the Scientific Advisory Board for Concentric Medical Inc. R.G.N., J.L.S., and D.S.L. are on the Scientific Advisory Board for CoAxia Inc. R.G.N. and J.L.S. are on the Scientific Advisory Boards for ev3 Neurovascular. W.S.S., G.D., J.L.S., and D.S.L. are employees of University of California, which holds the patent on the Merci retriever. J.L.S. is on the Scientific Advisory Board for Talecris and is funded by NIH-NINDS awards P50 NS044378/U01 NS 44364. W.S.S. and G.D. have stock ownership in Concentric Medical. G.W. is an employee of Concentric Medical. W.S.S. was the Principal Investigator in the MERCI and Multi MERCI trials.

References

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