Predictors of Good Clinical Outcomes, Mortality, and Successful Revascularization in Patients With Acute Ischemic Stroke Undergoing Thrombectomy

Pooled Analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Trials

Raul G. Nogueira, MD; David S. Liebeskind, MD; Gene Sung, MD; Gary Duckwiler, MD; Wade S. Smith, MD, PhD; on Behalf of the MERCI; and Multi MERCI Writing Committee

Background and Purpose—The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI trials evaluated the safety and efficacy of thrombectomy in the treatment of intracranial arterial occlusions within 8 hours of symptom onset. We sought to determine the predictors of clinical and angiographic outcomes in these patients.

Methods—The trial cohorts were combined in a data set of 305 patients. Twenty-eight baseline variables were included in univariate and multivariate analyses to define the independent predictors of good outcomes (modified Rankin Scale score ≤2), mortality, and successful revascularization (Thrombolysis In Myocardial Ischemia 2 to 3 flow).

Results—In the univariate analysis, final revascularization, baseline National Institutes of Health Stroke Scale, age, and systolic blood pressure were associated with both good outcomes and mortality at 90 days (P<0.0018 for all). In the multivariate analysis, final revascularization (OR, 20.4; 95% CI, 7.7 to 53.9; P<0.0001), baseline National Institutes of Health Stroke Scale (OR, 0.86; 95% CI, 0.81 to 0.92; P<0.0001), and age (OR, 0.96; 95% CI, 0.95 to 0.98; P=0.0004) were independent predictors of good outcome. Final revascularization (OR, 0.28; 95% CI, 0.16 to 0.50; P<0.0001), baseline National Institutes of Health Stroke Scale score (odds ratio, 1.09; 95% CI, 1.04 to 1.14; P=0.0001), age (OR, 1.05; 95% CI, 1.03 to 1.07; P<0.0001), and internal carotid artery occlusion (OR, 2.17; 95% CI, 1.22 to 3.86; P=0.0084) were the strongest predictors of mortality. Systolic blood pressure (<150 versus ≥150 mm Hg; OR, 0.42; 95% CI, 0.26 to 0.70; P=0.0007) and M2 occlusion (OR, 3.86; 95% CI, 1.28 to 11.67; P=0.0168) were independent predictors of revascularization.

Conclusion—Final recanalization status represents the strongest predictor of clinical outcomes in patients undergoing thrombectomy. The ability to remove the clot is negatively influenced by systolic blood pressure on presentation perhaps because of the hydraulic forces imposed by higher blood pressures. Although internal carotid artery occlusions are associated with increased mortality, they do not appear to influence the chances of good outcomes. This finding supports the inclusion of internal carotid artery occlusions in future efficacy trials. (Stroke. 2009;40:3777-3783.)

Key Words: acute stroke ■ endovascular treatment ■ thrombectomy

Reperfusion strategies have increasingly transformed the therapeutic approach to acute cerebral ischemia. However, despite the growing evidence linking arterial recanalization and good clinical outcomes, these 2 factors are not interchangeable and only a carefully selected patient will potentially benefit from any given reperfusion approach. Detailed knowledge about which factors are associated with desirable outcomes is therefore essential in the treatment decision process. Moreover, these variables should also be considered when designing clinical efficacy trials.

The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI trials studies were prospective, single-arm, multicenter trials designed to test the safety and efficacy of endovascular thrombectomy in the treatment of proximal intracranial arterial occlusions performed within 8 hours of stroke symptoms onset.1,2 The purpose of this study is to examine baseline factors to determine predictors of good outcome, mortality, and successful recanalization in patients undergoing thrombectomy. We hypothesized that recanalization status is one of the most powerful predictors of outcomes in these patients.
Methods

Patients and Techniques
All patient data from the MERCI and Multi MERCI trials were combined in a single data set totaling 305 patients. 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 Ischemia (TIMI) 2 or 3 flow in all treatable vessels as adjudicated locally by nonblinded neurointerventionalists. Intra-arterial (IA) thrombolytics were used in cases of device failure to recanalize the target vessel 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 prospectively collected and included in this analysis: study (MERCI versus Multi MERCI), age (continuous and dichotomized: ≥68 years), gender, race (white versus other), baseline National Institutes of Health Stroke Scale (NIHSS) score (continuous and dichotomized: ≤10 versus 11 to 20 versus >20), site of occlusion (internal carotid artery [ICA] versus M1 versus M2 versus vertebralbasilar), side of occlusion (right versus left), systolic blood pressure (SBP, 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, IA thrombolytic use, time from symptom onset to procedure (continuous and dichotomized: <3 versus 3 to 6 versus >6 hours), final revascularization status (postretriever/postadjunctive TIMI 0 to 1 versus TIMI 2 to 3) as well as clinical history of hypertension, atrial fibrillation, congestive heart failure, diabetes, dyslipidemia, smoking, coronary artery disease, and peripheral artery disease. The measurements of outcome included good clinical outcome at 90 days (prespecified as modified Rankin Scale [mRS] score ≤2), 90-day mortality, and final revascularization status. The variable IA thrombolytic use was excluded from the recanalization analysis because it was thought to represent a surrogate of recanalization failure with the Merci Retriever and IA thrombolytics were not used as a primary therapy in the MERCI and Multi MERCI trials.

Statistical Analysis
The pooled database was interrogated by using univariate/multivariate techniques. Quantitative variables were treated in these analyses as both continuous and stratified factors dichotomized/trichotomized at clinically relevant cutoffs. For the univariate analysis, the aforementioned 19 categorical and 9 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 mRS≤2, 90-day mortality, and final TIMI 2 to 3 flow) and the degree to which the variable influenced the size of the treatment effect. The Bonferroni correction was used when assessing the significance of relationships 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. All analyses were performed by a biostatistician with the aid of SAS software (Version 8.2).

Results

Table 1 demonstrates the distribution of the different baseline variables according to good outcomes at 90 days, 90-day mortality, and final revascularization status. Data regarding revascularization status was available in all 305 patients. However, 90-day mRS and mortality data were missing in 15 of 305 (4.9%) and 6 of 305 (1.9%) patients, respectively.

Predictors of Good Clinical Outcomes and Mortality at 90 Days
Results of the univariate model, which included 290 patients in the good outcome analysis and 299 patients in the mortality analysis, are summarized in Table 2. Because we considered a total of 28 individual baseline variables, the Bonferroni correction required a probability value of 0.05/28, or 0.0018, for any one analysis to be considered “significant.” Final revascularization status, baseline NIHSS score, age, and SBP on presentation reached statistical significance by this criterion and thus demonstrated strong evidence of an influence on both good outcomes and mortality at 90 days. Other variables attained probability values close to this level and thus could only be considered to have shown a trend toward an association with outcome. History of atrial fibrillation and/or hypertension showed a trend toward a relationship with both good outcomes and mortality at 90 days. Glucose levels and history of diabetes demonstrated an inverse trend toward good outcomes. ICA occlusion showed a direct trend toward mortality.

Results of the multivariate analysis are summarized in Table 3. The total number of patients who had data available for all variables included in the model-building process was 270 in the good outcome analysis and 286 in the mortality analysis. Final revascularization (OR, 20.4; 95% CI, 7.7 to 53.9; P<0.0001), baseline NIHSS (OR, 0.86; 95% CI, 0.81 to 0.92; P<0.0001), and age (OR, 0.96; 95% CI, 0.95 to 0.98; P=0.0004) were the strongest predictors of good outcome. Final revascularization (OR, 0.28; 95% CI, 0.16 to 0.50; P<0.0001), baseline NIHSS score (OR, 1.09; 95% CI, 1.04 to 1.14; P=0.0001), age (OR 1.05; 95% CI, 1.03 to 1.07; P<0.0001), and ICA occlusion (OR, 2.17; 95% CI, 1.22 to 3.86; P=0.0084) were the strongest predictors of mortality. Di-/trichotomizing quantitative variables or treating them as continuous variables did not appreciably change the results of the multivariable analysis. A significant difference in the rates of good functional outcome and mortality was seen based on vessel recanalization (Table 1). In addition, there were more patients with mRS 0, 1, and 2 scores and less with mRS 3, 4, and 5 scores in those who achieved TIMI 2 to 3 flow (Figure 1).

Predictors of Final Revascularization Status
Results of the univariate model, which included 305 patients, are summarized in Table 4. A total of 26 individual baseline variables were considered requiring a probability value of 0.05/26, or 0.0019, for any one analysis to be considered “significant.” Both SBP (dichotomized: <150 versus ≥150 mm Hg) and diastolic blood pressure (continuous and dichotomized: <90 versus ≥90 mm Hg) on presentation reached statistical significance by this criterion and thus
Table 1. Relationships Between Outcomes and Baseline Characteristics

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Overall</th>
<th>Successful Revascularization</th>
<th>90-Day mRS=2</th>
<th>90-Day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of subjects (n/N)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>305</td>
<td>64.6% (197/305)</td>
<td>35.4% (108/305)</td>
<td>32.4% (94/290)</td>
</tr>
<tr>
<td>Age, median years</td>
<td>72</td>
<td>71</td>
<td>72</td>
<td>67.5</td>
</tr>
<tr>
<td>[IQR]</td>
<td>[58–80]</td>
<td>[58–80]</td>
<td>[59–80]</td>
<td>[47–76]</td>
</tr>
<tr>
<td>Baseline NIHSS median (n)</td>
<td>19 (304)</td>
<td>18 (196)</td>
<td>20 (108)</td>
<td>16 (94)</td>
</tr>
<tr>
<td>[IQR]</td>
<td>[15–23]</td>
<td>[15–23]</td>
<td>[16–24]</td>
<td>[13–19]</td>
</tr>
<tr>
<td>Successful revascularization (n/N)</td>
<td>64.6% (197/305)</td>
<td>100% (197/197)</td>
<td>0% (0/0)</td>
<td>47.3% (88/186)</td>
</tr>
<tr>
<td>Failed revascularization (n/N)</td>
<td>35.4% (108/305)</td>
<td>0% (0/0)</td>
<td>100% (108/108)</td>
<td>5.8% (6/104)</td>
</tr>
<tr>
<td>Male gender (n/N)</td>
<td>47.9% (146/305)</td>
<td>69.9% (102/146)</td>
<td>30.1% (44/146)</td>
<td>33.3% (47/141)</td>
</tr>
<tr>
<td>Female gender (n/N)</td>
<td>52.1% (159/305)</td>
<td>30.7% (47/159)</td>
<td>69.3% (112/159)</td>
<td>31.5% (47/149)</td>
</tr>
<tr>
<td>Stroke onset to treatment, median hours, n</td>
<td>4.3 (303)</td>
<td>4.2 (195)</td>
<td>4.4 (108)</td>
<td>4.1 (94)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.

demonstrated strong evidence of an influence on final recanalization status. M2 occlusion (P=0.049), male gender (P=0.066), and history of diabetes (P=0.095) showed a positive trend toward recanalization. History of hypertension (P=0.066) and M1 occlusion (P=0.099) showed a negative trend toward recanalization.

Results of the multivariate analysis are summarized in Table 5. The diastolic blood pressure variables were removed from model consideration because they were highly correlated to SBP and SBP entered the model first. A total of 290 patients had data available for all variables included in the model-building process. Dichotomized SBP (<150 versus ≥150 mm Hg; OR, 0.42; 95% CI, 0.26 to 0.70; P=0.0007) and M2 segment occlusion (OR, 3.86; 95% CI, 1.28 to 11.67; P=0.0168) were independent predictors of successful revascularization.

Discussion

In this large cohort of patients treated with thrombectomy for proximal intracranial arterial occlusions within 8 hours of...
symptom onset, achievement of TIMI 2 to 3 recanalization, younger age, and lower NIHSS scores were directly associated with good clinical outcomes and inversely associated with mortality at 90 days. ICA occlusion was a strong predictor of mortality. Our findings are for the most part consistent with the outcomes analysis derived from prior acute stroke treatment studies. Among the 141 patients enrolled in the MERCI trial, age, baseline NIHSS score, and recanalization status had already been found to be independent predictors of both good clinical outcome and mortality.1 The expansion of the analysis cohort to 305 patients further strengthened the relationships between good outcome/mortality and revascularization status and minimally weakened the relationships between good outcome/mortality to age and baseline NIHSS score. Interestingly, right brain infarct, which demonstrated an inverse association with good outcomes in the MERCI trial, was not found to be an independent predictor of outcomes in the current analysis. On the other hand, ICA occlusion, which was not related to clinical outcomes in the MERCI trial, was demonstrated to independently predict mortality in this larger analysis.

Many authors have previously investigated the predictors of outcomes in intravenous thrombolysis. A subgroup analysis of the National Institute of Neurological Diseases and Stroke rt-PA Stroke Trials concluded that although no pre-treatment information significantly affected patients’ response to recombinant tissue plasminogen activator (rtPA), interactions between age and NIHSS scores, age and mean arterial pressure, diabetes, and early CT findings (edema, hypodensity, or intravascular thrombus) were independent predictors of good outcomes.2 The Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST) investigators found that age, complete recanalization, baseline NIHSS score, and time from symptom onset to rtPA bolus were independent predictors of 3-month outcome.3 An analysis of 2184 patients enrolled in 5 major randomized clinical trials testing rtPA in the 0- to 6-hour window demonstrated that age, diabetes, NIHSS score, gender, previous stroke, SBP, and time from symptom onset significantly affected the likelihood of normal/near-normal outcomes (mRS=1) and/or the treatment effect of rtPA, whereas age, NIHSS score, and serum glucose were significantly associated with catastrophic outcomes (mRS=5).4

Similar factors appear to play a role in the outcomes of patients undergoing IA thrombolysis. Ueda et al reported on the 6-month outcome predictors in 76 patients treated with IA urokinase within 6 hours of stroke onset.6 Pretreatment single photon emission CT residual cerebral blood flow (P<0.0001), NIHSS score at baseline and the following day (P<0.0001), infarct etiology (P=0.0014), age (P=0.0074), and recanalization grade (P=0.007) were significant independent predictors of outcome. Arnold et al analyzed the clinical and radiological findings of 100 consecutive patients with acute stroke treated with IA urokinase and found that age <60 years (P=0.04), low NIHSS score at admission (P<0.00001), and vessel recanalization (P=0.0004) were independent predictors of favorable outcome, whereas diabetes was associated with a poor outcome (P=0.002). In this analysis, gender, hypertension, smoking, stroke etiology, early CT signs, CT hyperdense middle cerebral artery sign, time to treatment, and collateral flow were not independently associated with outcome.7 In a subsequent analysis of 350 patients with acute stroke treated with IA urokinase at this same institution, low NIHSS at admission (P<0.001), good collaterals (P<0.001), and successful endovascular recanalization (P<0.001) were found to be predictors of favorable outcome, whereas diabetes (P<0.001) and symptomatic hem-

Table 3. Multivariate Predictors of Good Outcome and Mortality at 90 Days

<table>
<thead>
<tr>
<th>Variable</th>
<th>mRS≤2 (OR [95% CI])</th>
<th>P Value</th>
<th>Mortality (OR [95% CI])</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revascularization</td>
<td>20.43 (7.74–53.92)</td>
<td>&lt;0.0001</td>
<td>0.28 (0.16–0.50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>0.86 (0.81–0.92)</td>
<td>&lt;0.0001</td>
<td>1.09 (1.04–1.14)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.96 (0.95–0.98)</td>
<td>0.0004</td>
<td>1.05 (1.03–1.07)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICA occlusion</td>
<td></td>
<td></td>
<td>2.17 (1.22–3.86)</td>
<td>0.0084</td>
</tr>
</tbody>
</table>

Figure 1. Clinical outcome at 90 days by mRS. Although successful recanalization is linked to higher rates of good functional outcome and lower rates of mortality, it does not appear to increase the chances of high-disability survival.

*mRS available in 186 of 197 patients. †mRS available in 104 of 108 patients.
The presence of tandem extracranial carotid occlusion was inversely correlated with recanalization rates in a series of 64 intravenous rtPA-treated patients with occlusion of the intracranial ICA or middle cerebral artery.16 In another study, Ribo et al evaluated 139 consecutive patients with stroke with documented intracranial artery occlusion who were treated with intravenous rtPA. Serum glucose >158 mg/dL (OR, 7.3; 95% CI, 1.3 to 42.3; P = 0.027), proximal middle cerebral artery occlusion (OR, 2.6; 95% CI, 1.1 to 6.5; P = 0.034), and platelet count <219 000/mL (OR, 2.6; 95% CI, 1.1 to 6.1; P = 0.029) were independent predictors of recanalization failure.17 The data on predictors of revascularization after endovascular treatment are limited to fewer studies. Jovin et al identified mean ipsilateral cerebral blood flow measurements on xenon CT as the only predictor of recanalization (OR, 1.25; 95% CI, 1.01 to 1.54; P = 0.035) in a multivariate analysis of 23 patients with stroke who presented with M1 or ICA terminus occlusion and underwent endovascular treatment within 6 hours of symptoms onset.18 Gupta et al described an inverse correlation between ICA terminus occlusion and revascularization (OR, 0.34; 95% CI, 0.16 to 0.73; P = 0.006) in a retrospective analysis of 168 consecutive patients with stroke treated with a multimodal endovascular approach.19 Finally, baseline angiographic characteristics, including the extent of collateral flow,20 the presence of a clot outline sign (antegrade contrast opacification of the occluded cerebral artery distal to the thrombus),21 and the initial angiographic appearance of intracranial vascular occlusion,22 have also been shown to correlate with the chances of successful revascularization.

The association between SBP and response to thrombectomy is particularly noteworthy because blood pressure (BP) is frequently elevated in the setting of acute cerebral ischemia. Theoretically, this hypertensive response may protect the brain by increasing perfusion pressure to the penumbral tissue through collateral or partially occluded arteries. Pharmacological BP augmentation has been proposed as a potential therapeutic strategy in patients with acute stroke.23 Although there is some logic to this approach, higher SBP levels have been associated with lower rates of complete recanalization in patients treated with intravenous rtPA.4 In concurrence with our findings, the previously mentioned study also demonstrated that successful revascularization, but not pretreatment SBP, was an independent predictor of good clinical outcomes at 3 months. Conversely, an analysis involving 149 patients with stroke undergoing IA thrombolysis demonstrated that the temporal course of elevated SBP, but not pretreatment SBP itself, was inversely related to revascularization rates.24 In another words, SBP tended to remain elevated longer when recanalization failed.
than when it succeeded despite the similarly high baseline SBP levels. Although our study is the first to show a direct correlation between SBP and recanalization in thrombectomy-treated patients, indirect evidence to support such an association also exists. Liebeskind et al have shown that a greater degree of collateral circulation on pretreatment angiography is associated with higher recanalization rates after mechanical thrombectomy with the Merci Retriever. In the same patient cohort, higher pretreatment SBP levels were found to be strongly associated with poorer degrees of collateral flow. One could then conclude that higher pretreatment SBP is related to poorer collateral flow, which is also linked with lower revascularization rates. The exact mechanisms underlying these findings have yet to be elucidated. Tsivgoulis et al hypothesized that the inverse relationship between pretreatment SBP and revascularization was potentially related to an impairment in the endogenous capacity for fibrinolysis. We would contend that this phenomenon might simply reflect the effects of stronger hydromechanical forces in the setting of higher arterial BP levels (Figure 2). These forces would result in higher impaction of the clot and therefore more difficult mechanical retrieval. Conversely, the retrograde leptomeningeal collateral flow would theoretically exert hydromechanical forces with an inversely directed vector. As such, higher collateral flow would lower the degree of thrombus impaction and facilitate clot retrieval and/or thrombolysis. A complex interaction and overlap of these factors may therefore influence recanalization. In cases of high SBP and poor collaterals, the pressure gradient across the clot would be maximal leading to more clot impaction and likely more difficult clot removal. Alternatively, normal SBP and good collaterals would lead to a lesser pressure gradient across the clot and likely easier thrombectomy. It is also possible that greater clot impaction leads to vascular spasm that further hampers clot removal. In thrombolysis cases, the higher impaction of the thrombus would prevent penetration of the plasminogen activator into the thrombus and decrease the influx of new plasminogen into the clot matrix, both of which would result in failure to thrombolyze. Our observation in this pooled analysis that acute hypertension is a potent inverse predictor of recanalization underscores the need to refine our understanding about the underlying physiology before broader BP management guidelines can be established.

In conclusion, final recanalization status represents one of the strongest predictors of clinical outcomes in patients with acute stroke undergoing thrombectomy. Although ICA occlusions are associated with increased rates of mortality, they do not appear to decrease the chances of good outcomes after thrombectomy. This finding supports the rationale of including ICA occlusions in future efficacy trials. Finally, this study provides further evidence that higher BP on presentation hampers arterial recanalization making decisions difficult about BP management in patients with stroke who are potential candidates for endovascular therapy.

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Disclosures
R.G.N. is a member of the Scientific Advisory Boards for Concentric Medical Inc, ev3 Neurovascular Inc, and Coaxia Inc. D.S.L. is a consultant for Coaxia Inc. D.S.L. and G.S. are consultants for Concentric Medical Inc. G.D. and W.S.S. have stock ownership in Concentric Medical Inc.

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