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

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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;42:00-00.)

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 interindividual 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

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the time from symptom onset to treatment initiation and clinical outcomes after intravenous recombinant tissue-type plasminogen activator (rtPA).\textsuperscript{1-7}

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.\textsuperscript{8,9} 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.\textsuperscript{10} 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.\textsuperscript{9} 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.\textsuperscript{9} 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.\textsuperscript{8,9} 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 versus >6 hours), and time to reperfusion (continuous and quartiles), as well as clinical history of hypertension, atrial fibrillation, congestive heart failure, diabetes, dyslipidemia, smoking, coronary artery disease, and peripheral artery disease. Time to reperfusion was defined as time from stroke symptom onset to procedure termination in patients with technically successful reperfusion (thrombolysis in myocardial infarction 2–3 flow). This variable was derived from the sum of 2 other variables: time from symptom onset to procedure and procedure duration time. The measurements of outcome included independent functional outcome at 90 days (prespecified as modified Rankin Scale score ≤2) and 90-day mortality.

**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 18 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 recanalization 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 nonre-
canalized 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 \( \geqslant 140 \text{ mg/dL} \)) 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 out-
comes 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 out-
comes, whereas history of atrial fibrillation showed a “trend”
toward a direct relation with mortality. The total number of
patients who had data available for all variables included in
the multivariate model-building process was 157 in the
independent outcome analysis and 163 in the mortality
analysis. Low baseline NIHSS score (odds ratio [OR], 0.84;
95% confidence interval [CI], 0.78–0.91; \( P = <0.0001 \)) and
and young age (OR, 0.97; 95% CI, 0.95–0.99; \( P = 0.014 \)) were
independent predictors of independent functional outcome.
High glucose levels demonstrated a strong trend toward
worse outcomes (OR, 0.99; 95% CI, 0.98–1.00; \( P = 0.051 \)).
Trichotomized baseline NIHSS score (OR, 5.06; 95% CI,
2.30–11.13; \( P < 0.0001 \)) and age (OR, 1.06; 95% CI, 1.02–
1.10; \( P = 0.0008 \)) were the strongest predictors of mortality.

No association was found between time to treatment and independent outcomes (continuous: OR, 1.04; 95% CI, 0.85–
1.27; \( P = 0.71 \)); trichotomized: OR, 0.91; 95% CI, 0.52–1.59;
\( P = 0.73 \)) or mortality (continuous: OR, 0.97; 95% CI, 0.78–
1.21; \( P = 0.82 \)); trichotomized: OR, 1.17; 95% CI, 0.64–2.14;
\( P = 0.61 \)) at 90 days. Similarly, there was no clear association
between time to reperfusion and independent outcomes or
mortality at 90 days in the unadjusted analysis (Table 1).
However, clinically important imbalances were noticed
across the different time to reperfusion quartiles, with early
reperfused patients tending to have older age, higher NIHSS
scores, and higher glucose levels than late reperfused patients
(Table 2). After adjustment for these variables, the relations-
ships between time to reperfusion and outcomes were mark-
edly strengthened with a strong trend toward worse outcomes
over time (Table 3, Figure 1A,B). Notably, as many as 40%
of the patients reperfused at \( \geqslant 6.9 \) hours achieved an inde-
pendent functional outcome.

### Discussion

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 intrave-
nous 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 co-
horts. The farther distal the occlusion, the lesser anatomic
opportunities for collateral flow as a compensatory mecha-
ism and, thus, the less stable is penumbral tissue over time.
A clear difference in the behavior of mismatch tissue evolu-
tion over time was seen in a recent MRI perfusion study that
separately analyzed PAO and non-PAO strokes.\(^1\)

Our study complements the findings of a recent pooled
analysis of the Interventional Management of Stroke (IMS) I
and II trials.\(^12\) 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 rep-
ervfusion (TICI 0–1) and found that after adjustments were
made for age, baseline NIHSS score, sex, and baseline
measures, 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 func-
tional outcomes (90-day modified Rankin Scale score \( \leq 2 \)).
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.\(^13\) Differences may
also exist in the nature of reperfusion achieved with slow

### Table 1. Observed Rates of 90-Day Modified Rankin Scale Score \( \leq 2 \) and Mortality by Time to Reperfusion

<table>
<thead>
<tr>
<th>Quartile of Time to Reperfusion (h)</th>
<th>1 (n=164)</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><strong>90-Day Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Rankin Scale score ( \leq 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>
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 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 between 6 and 7 hours.

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...
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).\(^\text{16,17}\) 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 that 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.\(^\text{3}\) 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.\(^\text{18}\)

**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 5 and Multi MERCI trials.

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再灌流までの時間が血栓除去療法を行った前方循環系の脳卒中臨床転帰に与える影響
— MERCI および Multi MERCI 試験の統合解析

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

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背景および目的：過去の研究により、組換え型組織プラスミノゲン活性化因子の静脈内投与の治療時間と投与後の転帰との間に強い相関が示されている。しかし、虚血の時間的変数は閉塞部位により異なると考えられ、遠位部の閉塞に比べて、閉塞が近位であるほど様々な時間的経過をたどる可能性が大きい。我々は、前方循環系の近位部動脈閉塞において、時間がどのように転帰に影響するか検討した。

方法：頭蓋内動脈または中大脳動脈（M1またはM2）部の閉塞を有する MERCI/Multi MERCI 試験の参加者の中、血行再建が成功した全患者を単変量/多変量解析の対象とし、90 日時点での機能的自立の転帰（Rankin 積度スコアが≤2）および死亡率の予測因子を特定した。再灌流までの時間の転帰に対する影響を、年齢、ベースラインの NIHSS スコア、および血液値について補正後に算出した。

結果：内頸動脈/M1/M2 の閉塞を有する患者 175 例において血行再建が成功していた。補正前の解析では、時間（治療または再灌流までの）と転帰との間に明確な関係は認められなかった。ベースラインの NIHSS スコアおよび年齢は、機能的自立の転帰および死亡率の独立予測因子であった。また、高血液値は良好な転帰に対する強い傾向を示した。年齢、ベースラインの NIHSS スコア、および血液値について補正した後、再灌流までの時間が遅れると機能的自立の転帰が減少する傾向が示された。注目すべきは、灌流までの時間が 6.9 時間以上であった患者の 40% が機能的自立の転帰を達成していたということである。

結論：時間（治療または再灌流までの）は、近位部動脈閉塞脳卒中の転帰に影響すると考えられる多くの変数の 1 つにすぎない。再灌流療法は早急に開始すべきであるが、我々の知見から、時間が経過した時点で来院した脳卒中患者に対しても有効である可能性が示唆される。

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