Imaging-Based Endovascular Therapy for Acute Ischemic Stroke due to Proximal Intracranial Anterior Circulation Occlusion Treated Beyond 8 Hours From Time Last Seen Well

Retrospective Multicenter Analysis of 237 Consecutive Patients

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Background and Purpose—Current selection criteria for intra-arterial therapies in the anterior circulation use time windows of 8 hours. Modern neuroimaging techniques have identified individuals with salvageable penumbra who present beyond this timeframe. We sought to assess safety, procedural, and clinical outcomes of MRI or CT perfusion imaging-based endovascular therapy in patients with anterior circulation stroke treated beyond 8 hours from time last seen well.

Methods—We conducted a multicenter retrospective review of consecutive patients meeting the following criteria: (1) acute proximal intracranial anterior circulation occlusion; (2) endovascular treatment initiated >8 hours from time last seen well; and (3) treatment selection based on MRI or CT perfusion imaging.

Results—Two hundred thirty-seven patients were identified (mean age, 63.8±16 years; mean baseline National Institutes of Health Stroke Scale, 15±5.5; mean time last seen well to treatment, 15±11.2 hours; male gender, 46%). Successful revascularization was achieved in 175 of 237 (73.84%) patients. Parenchymal hematoma occurred in 21 of 237 (8.86%) patients. The 90-day mortality rate was 21.5% (51 of 237). The rate of good outcomes was 45% (100 of 223) in the 223 patients with available modified Rankin Scale data at 90 days or time of hospital discharge. In multivariate analyses, age (OR, 0.96; 95% CI, 0.94 to 0.98; \( P < 0.002 \)), admission National Institutes of Health Stroke Scale (OR, 0.93; 0.87 to 0.98; \( P = 0.016 \)), and successful revascularization (OR, 4.32; 1.99 to 9.39; \( P < 0.0001 \)) were identified as independent predictors of good outcomes.

Conclusions—Endovascular therapy can be instituted with acceptable safety beyond 8 hours from time last seen well when selection is based on advanced neuroimaging. Successful revascularization is significantly associated with higher rates of good outcomes. The benefit of this approach compared with standard medical therapy should be assessed in a prospective randomized trial. (Stroke. 2011;42:2206-2211.)

Key Words: acute stroke ■ angiography ■ brain infarction ■ CT ■ endovascular treatment ■ interventional neuroradiology ■ MRI ■ stenting ■ thrombolysis

A concept fundamental to the rationale for instituting reperfusion therapy in acute ischemic stroke is that of mismatch between the ischemic core and penumbra. It is believed that the larger the mismatch, the higher the benefit of reperfusion. After vessel occlusion, due to progressive collateral failure, there is continuous growth of the core at the expense of the penumbra. The aim of reperfusion therapy is to reverse this process by salvaging the penumbra and thereby limit the final infarct size. Current selection criteria for reperfusion therapy use strict time windows. This is based on the assumption that the rate at which the ischemic process evolves in time is similar in all individuals. However, recent studies have shown that due to significant variability in collateral capacity, this process...
occurs at different speeds in different individuals. Consequen-
tly, the concept of a universal time window has increas-
ingly been challenged and a physiological rather than chro-
nomological approach to patient selection for acute stroke
interventions is gaining ground.5

Given the particularly dismal natural history of untreated
basilar occlusion, recanalization therapy in the posterior
circulation beyond 8 hours is an acceptable paradigm in many
centers.6 Although relatively large case series exist with
regard to endovascular therapy administered in the anterior
circulation within 8 hours of symptom onset,7 description of
this approach beyond 8 hours is limited to single-center small
case series.8–10 The aim of this study is to describe procedural
and clinical outcomes of patients with acute stroke due to
anterior circulation intracranial large vessel occlusions
treated beyond 8 hours from time last seen well (TLSW) who
were selected based on physiological data derived from
imaging studies.

**Materials and Methods**

Eleven large regional referral stroke centers participated in this
retrospective analysis of consecutive patients presenting with stroke
as the result of acute proximal anterior circulation occlusion (internal
carotid artery [ICA] and/or middle cerebral artery M1 and/or M2
segments) in whom endovascular therapy was performed beyond 8
hours from the TLSW on the basis of favorable MRI or CT perfusion
(CTP) imaging characteristics. Patients with evidence of any intracra-
nal hemorrhage or CT evidence of hypodensity involving greater
than one third of the middle cerebral artery territory were excluded
from further evaluation because they were not deemed eligible for
treatment. Time of treatment initiation was defined as the time that
the first angiographic run demonstrating the intracranial occlusion
was performed. Patients who awoke with neurological deficits after
going to sleep normal (“wake-up strokes”) or were found with an
unwitnessed stroke were included in the analysis as long as the
treatment. Time of treatment initiation was defined as the time that
the first angiographic run demonstrating the intracranial occlusion
was performed. Patients who awoke with neurological deficits after
going to sleep normal (“wake-up strokes”) or were found with an
unwitnessed stroke were included in the analysis as long as the
intra- and extracranial angioplasty and/or stenting,
mechanical embolectomy with the MERCI or Penumbra devices).

Angiographic images were analyzed and graded at each participating
center. Patients were treated between April 2001 and July 2009 with
most of the cases treated within the last 3 years. Institutional Review
Board approval at each center was obtained according to each
center’s retrospective studies Institutional Review Board policies and
data analysis was carried out in a deidentified manner.

If occlusion of an intracranial vessel was identified, various
recanalization strategies were used at the discretion of the operator
(Supplemental Figure I; http://stroke.ahajournals.org). Flow through
the previously occluded vessel was graded using the Thrombolysis in
Cerebral Ischemia or Thrombolysis in Myocardial Ischemia grading
systems at each institution. Post-treatment imaging with CT or MRI
was performed in all patients according to the local standard of care.
Primary end points included the rates of postprocedure parenchymal
hematomas (PH, including both PH-1 and PH-2 according to the
European Cooperative Acute Stroke Study [ECASS] criteria),11
successful recanalization (defined as Thrombolysis in Cerebral
Ischemia or Thrombolysis in Myocardial Ischemia score ≥2), good
functional outcome (defined as a modified Rankin Scale ≤2 at 3
months), and mortality. Functional outcomes were obtained in the
outpatient clinic at follow-up or by telephone. In cases when
outcomes after discharge were not available due to follow-up loss,
the discharge modified Rankin Scale was carried forward.

A prespecified subset of patients (Pre-DAWN Cohort) fulfilling
the following criteria: (1) baseline NIHSS score ≥10; (2) ICA or
middle cerebral artery–M1 occlusion with or without cervical occlu-
sion/severe stenosis; and (3) TLSW to treatment between 8 and 24
hours were analyzed with the intent of planning a prospective
randomized trial (DAWN [DWI and CTP Assessment in the Triage
of Wake-Up and Late Presenting Strokes Undergoing Neurointer-
vention Trial]).

**Statistical Analysis**

Statistical analysis was performed using the STATA IC-10 software
(StataCorp LP, College Station, TX). Descriptive statistics were
performed. In univariate analysis, several variables of interest were
correlated to the following binary outcome measures: good func-
tional outcome and mortality. For each end point, all covariates with
a probability value ≤0.2 were then entered into a multivariate
stepwise logistic regression model. Significant association was
considered for a probability value of <0.05.

**Results**

Two hundred thirty-seven patients were treated at 11 stroke
centers. The pertinent clinical and treatment characteristics are
summarized in Supplemental Table I. The mean age was
63.8 ± 16 years (median, 66 years; range, 19 to 91 years) and
the mean baseline NIHSS was 15.5 ± 5.5 (median, 15; inter-
quartile range, 12 to 19). Forty-nine percent (116) of the
patients were males. The mean TLSW to treatment was
15 ± 11.2 hours (median, 12 hours; interquartile range, 9.7 to
16). Information about the type of presentation was available
in 77 patients because most centers equalized TLSW to “time
of stroke onset” during data collection. Of these 77 patients,
63 (81%) had witnessed onset beyond 8 hours, 10 (13%) were
“wake-up strokes,” and 4 (5%) were “unclear time of onset
strokes.” Successful revascularization was achieved in 175 of
237 (73.8%) patients. PH occurred in 21 of 237 (8.86%) patients.
Thirteen of the 21 (62%) patients who experienced PH died with only 2 patients (9.5%) achieving a good
outcome at 3 months. The 90-day mortality rate for the
overall cohort was 21.5% (51 of 237).

In univariate analyses, increasing age, history of atrial
fibrillation, history of hypertension, lack of vessel recanal-
zation, ICA terminus occlusion, and the development of PH
were significantly associated with mortality. In multivariate
analysis age (OR, 1.03; 95% CI, 1.00 to 1.05; \( P = 0.005 \)), vessel recanalization (OR, 0.35; 0.14 to 0.64; \( P = 0.002 \)), ICA terminus occlusion (OR, 2.16; 1.04 to 4.30; \( P = 0.047 \)), and development of PH (OR, 8.41; 2.99 to 23.67; \( P = 0.0001 \)) remained significantly associated with mortality (Table 1). In 14 of 237 cases (5.5%), information regarding 90-day or discharge modified Rankin Scale was not available. The rate of good outcome was 45% (100 of 223) in the 223 patients with available modified Rankin Scale data at 90 days or time of hospital discharge and 47% (93 of 198) in the 198 patients with available modified Rankin Scale data at 90 days. In univariate analysis, age, gender, history of atrial fibrillation, admission NIHSS, successful recanalization, smoking, and the presence of ICA terminus occlusion were significantly associated with a good outcome (Supplemental Table I). In multivariate analyses, age (OR, 0.96; 0.94 to 0.98; \( P = 0.002 \)), admission NIHSS (OR, 0.93; 0.87 to 0.98; \( P = 0.016 \)), and successful revascularization (OR, 4.32; 1.99 to 9.39; \( P < 0.0001 \)) were identified as independent predictors of good outcomes (Table 1).

A significant difference in the rates of good functional outcome and mortality was seen based on recanalization status. Fifty-two percent of the recanalized patients versus only 23% of the nonrecanalized patients achieved a good functional outcome at 90 days (\( P < 0.0001 \)). Mortality rate at 90 days was 16% in the recanalized patients versus 38% in the nonrecanalized patients (\( P < 0.0001 \); Figure). We were not able to detect an association between good outcomes or PH and imaging selection modality (MRI versus CTP). Good outcomes were observed in 47% of patients selected based on CTP, 42% of patients selected based on MRI, and 53% of patients selected based on both modalities (\( P = \) nonsignificant). PH was observed in 9.1% of patients selected based on CTP, 11.3% of patients selected based on MRI, and 7.6% in patients selected based on both modalities (\( P = \) nonsignificant). Similarly, there was no significant association between presentation with “witnessed onset stroke beyond 8 hours” and good outcome or postprocedure PH.

A total of 169 patients fulfilled the pre-DAWN criteria. Pre-DAWN patients had similar age and baseline NIHSS scores as the patients in Pro-Urokinase (r-proUK) for Acute Cerebral Thromboembolism (PROACT) II and achieved similar rates of good outcome and mortality to the PROACT-II IA r-prouk-treated patients despite having more severe occlusions (ICA terminus and tandem occlusions included and M2 occlusions excluded) and significantly longer TLSW to treatment. In addition, the rates of symptomatic hemorrhage were also similar in the pre-DAWN and intra-arterial-treated PROACT-II patients (Table 2).

### Table 1. Multivariate Predictors of Good Outcome and Mortality at 90 Days

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>( P )</th>
<th>OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revascularization</td>
<td>4.32 (1.99–9.39)</td>
<td>&lt;0.0001</td>
<td>0.35 (0.14–0.64)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.96 (0.94–0.98)</td>
<td>0.002</td>
<td>1.03 (1.00–1.05)</td>
<td>0.005</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>0.93 (0.87–0.98)</td>
<td>0.016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA occlusion</td>
<td>2.16 (1.04–4.30)</td>
<td>0.047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PH</td>
<td>8.41 (2.99–23.67)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; PH, parenchymal hematoma; CI, confidence interval; OR, odds ratio.

A total of 169 patients fulfilled the pre-DAWN criteria. Pre-DAWN patients had similar age and baseline NIHSS scores as the patients in Pro-Urokinase (r-proUK) for Acute Cerebral Thromboembolism (PROACT) II and achieved similar rates of good outcome and mortality to the PROACT-II IA r-prouk-treated patients despite having more severe occlusions (ICA terminus and tandem occlusions included and M2 occlusions excluded) and significantly longer TLSW to treatment. In addition, the rates of symptomatic hemorrhage were also similar in the pre-DAWN and intra-arterial-treated PROACT-II patients (Table 2).

### Discussion

The main finding of our study is that MRI or CTP imaging-based endovascular therapy in patients with acute ischemic stroke treated beyond 8 hours from TLSW can be performed with a safety profile that is similar to that observed in patients treated within 8 hours. Another observation is that the rate of favorable clinical outcomes with this approach appears to be similar to that seen when endovascular therapy is administered within 8 hours in patients selected based only on noncontrast CT.
The advent of CTP in addition to diffusion-weighted imaging and MRI perfusion has triggered significant debate with regard to the optimal modality for patient selection. An important advantage of modern imaging technologies is the ability to more reliably outline the ischemic core, the most powerful imaging predictor of outcome in acute stroke due to large vessel occlusion.\(^1\)\(^2\) Although core threshold values that predict favorable outcomes have not been prospectively established, retrospective studies indicate that a volume \(\leq 70\) mL on diffusion-weighted imaging or Alberta Stroke Program Early CT Score \(\leq 8\) on CTP–cerebral blood volume maps is predictive of favorable outcomes.\(^1\)\(^3\)\(^4\) Studies investigating the use of MRI or CTP as a selection tool to extend the time window for intravenous thrombolysis have been typically based on visual inspection of the pretreatment imaging revealing a substantial mismatch between irreversibly injured brain and brain that is threatened but still viable. De facto this translates into determining a small core in the presence of a large perfusion deficit. Despite its strong foundation, this physiological approach to patient selection has not yet been validated by randomized clinical trials. Indeed, a recent pooled analysis of the Desmoteplase in Acute Ischemic Stroke Trial (DIAS), DIAS II, Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS), Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE), and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) trials involving a total of 502 mismatch patients who were thrombolyzed beyond 3 hours failed to confirm a benefit of mismatch-based delayed intravenous thrombolysis.\(^1\)\(^5\) Several factors might have contributed to these findings. First, mismatch is not equal to penumbra because it often incorporates a region of “benign oligemia” that will not evolve into core even in the absence of reperfusion.\(^1\)\(^6\) Second, the aforementioned studies included patients with both distal and proximal arterial occlusions. This represents a challenge on both ends. Intravenous thrombolysis recanalizes only 10% to 30% of the proximal arterial occlusions.\(^6\) Patients with distal occlusions on pretreatment imaging likely have a high rate of spontaneous reperfusion and/or good outcomes even in the absence of any intervention. Finally, thrombolysis carries the risk of symptomatic intracranial hemorrhage, which may further attenuate the benefits of reperfusion therapy. The reasons these studies may have limited relevance to our results are related to the fact that we only included patients with large vessel occlusion as well as to the fact that we used a treatment modality that is associated with higher rates of reperfusion.\(^7\) Indeed, the aforementioned meta-analysis of the mismatch-based delayed thrombolysis trials demonstrated that favorable outcomes were greater for mismatch patients who were

### Table 2. Comparison of Baseline Characteristics and Outcomes in the Pre-DAWN Cohort Versus the PROACT-II Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-DAWN ((n=169))</th>
<th>PROACT-II Treated Arm ((n=121))</th>
<th>PROACT-II Control Arm ((n=59))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±16</td>
<td>64±14</td>
<td>64±14</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Range</td>
<td>(10–29)</td>
<td>(5–27)</td>
<td>(4–28)</td>
</tr>
<tr>
<td>Gender, % (no.)</td>
<td>54% (91)</td>
<td>42%</td>
<td>39%</td>
</tr>
<tr>
<td>TLSWT, h</td>
<td>12.6±3.7</td>
<td>4.7 (4.0–5.3)*</td>
<td>5.1 (4.2–5.5)</td>
</tr>
<tr>
<td>Site of occlusion (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA-M2</td>
<td>0%</td>
<td>35%</td>
<td>37%</td>
</tr>
<tr>
<td>MCA-M1</td>
<td>54% (91/169)</td>
<td>61%</td>
<td>63%</td>
</tr>
<tr>
<td>ICA-T</td>
<td>22% (38/169)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Tandem ICA/MCA</td>
<td>17% (26/169)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Tandem ICA/ICA-T</td>
<td>7% (12/169)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>TIMI 2–3 revascularization</td>
<td>74% (125/169)</td>
<td>66%</td>
<td>18%</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>10% (17)</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>90-d mRS (\geq 2)</td>
<td>40% (57/142)*</td>
<td>40%</td>
<td>25%</td>
</tr>
<tr>
<td>90-d mRS (\geq 3)</td>
<td>58% (82/142)*</td>
<td>52%</td>
<td>47%</td>
</tr>
<tr>
<td>90-d mortality</td>
<td>25% (42/167)*</td>
<td>25%</td>
<td>27%</td>
</tr>
</tbody>
</table>

DAWN indicates DWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention Trial; PROACT, Pro-Urokinase (r-proUK) for Acute Cerebral Thromboembolism; NIHSS, National Institutes of Health Stroke Scale; TLSWT, time last seen well time; IQR, interquartile range; MCA, middle cerebral artery; ICA, internal carotid artery; TIMI, Thrombolysis in Myocardial Ischemia; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; SD, standard deviation.
successively reperfuscated. Nonetheless, nonstandardized visual inspection of diffusion-weighted images or perfusion scans is subject to highly variable interpretation with regard to the presence and extent of mismatch, especially because thresholds that define reversible and irreversible ischemia both on MRI and (to a greater extent) on CTP have not been clearly established. Future prospective studies addressing these questions should use core and penumbra thresholds obtained quantitatively and validated by prospective studies.

A recent study investigating the benefit of intra-arterial thrombolytic therapies in acute ischemic stroke has established a clear relationship between time from stroke onset to angiographic reperfusion and good outcomes. To that regard, at a first glance, our results seem to contradict these findings. We do, however, believe that this is not the case because this study enrolled only patients presenting very early (within 3 hours). Furthermore, the only imaging selection criterion for this study was a noncontrast head CT ruling out intracranial hemorrhage or a large hypodensity. Therefore, when patients are treated very early in the course of a stroke, and selection of patients occurs on the basis of a plain CT, there is a strong association between time to reperfusion and outcome. However, this does not discard the fact that at later points in time, there are patients with favorable physiology who may benefit from reperfusion. It has been shown that the earlier the time point in the course of acute cerebral ischemia, the higher the likelihood of mismatch. However, in the setting of large vessel occlusion, many patients will have a significant mismatch even in the 9- to 24-hour window. From that standpoint, in the ultraearly stages of ischemia (within 3 hours), a noncontrast head CT as imaging selection criteria may be sufficient because the majority of patients will have favorable physiology and the additional time requirement to obtain more sophisticated imaging studies may not be justified. As patients present further out in time with respect to symptoms onset, the likelihood of favorable physiology diminishes and therefore advanced MR/CTP techniques may become necessary. At later time windows, therefore, time appears to diminish its relevance as a selection tool. Although there is general consensus that information regarding tissue viability is required for appropriate patient selection, the superiority of the more expensive and time-consuming MRI or CTP techniques over expertly interpreted plain CT in conjunction with the clinical examination (CT–clinical mismatch) as a selection tool for endovascular therapy is not yet proven and still a matter of debate.

The retrospective nature represents the major limitation of our study. However, the validity of our results is supported by the fact that factors predicting good outcomes in our study are similar to the ones observed in trials enrolling patients within 8 hours in which successful revascularization, age, and baseline stroke severity were found to be the most powerful predictors of favorable outcomes. Information about the distinct types of presentation was only available in a limited number of patients. Although we could not find any significant difference in our analysis, it is likely that patients with “unclear time of onset strokes” and “wake-up strokes” will behave differently from patients with “witnessed onset stroke beyond 8 hours” because in the first 2 categories, the true time of onset may be significantly closer to the time point at which the treatment was administered. However, it may also be the case that in the setting of similar physiological imaging signatures, the type of presentation is less relevant in defining outcomes after successful reperfusion. As discussed, the lack of standardization of the imaging protocol represents another important limitation of the current analysis. These limitations should be addressed in future prospective studies. Another major shortcoming of our study with respect to its ability to assess efficacy of the intervention used is the lack of a control group. Although outcomes obtained in our group of patients compare favorably with historical controls from randomized intra-arterial trials (eg, PROACT-II and Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial [MELT] trials) as well as prospective nonrandomized studies (eg, Mechanical Embolus Removal in Cerebral Ischemia [MERCI], Multi MERCI, and Penumbra Trials), the natural history of stroke due to large vessel occlusion in patients with small ischemic core volumes presenting beyond 8 hours from TLSW is unknown. Because lower core volumes at presentation are known to carry a more favorable prognosis both in patients who recanalize and in those who do not recanalize, it is likely that outcomes in this group of patients may be more benign than in patients presenting with same vascular occlusion site within shorter time windows. Nevertheless, the presence of a severe clinical deficit as evidenced by a median NIHSS of 15 in our group of patients coupled with the presence of significant perfusion deficit suggest that in most of the patients described here, stroke progression with consequent worsening neurological status or lack of improvement would have constituted the more likely outcome as illustrated by the highly significant differences in the rates of clinical outcomes according to revascularization status in our cohort (Supplemental Figure II). The comparison of the Pre-DAWN Cohort with the PROACT-II Trial further supports our hypothesis. However, given the uncertainties with regard to the fate of nontreated patients who have a similar clinical and imaging presentation to the patients described in the present study, it is imperative that prospective, randomized data are generated before this approach can be recommended as a matter of routine clinical care. Therefore, our results should be interpreted as hypothesis-generating and may aid in the design of a randomized trial comparing recanalization therapies with conservative management, which is necessary to prove superiority of this approach over medical therapy alone.

Disclosures

References


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Table 1. Baseline Clinical Variables, Treatment Modalities, and Univariate Analysis for Predictors of Good Outcome and Mortality at 90 Days.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>Median(IQR)</th>
<th>mRS ≤ 2* OR</th>
<th>P value</th>
<th>95% CI</th>
<th>Mortality* OR</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>66 (53-76)</td>
<td>0.96 (0.001)</td>
<td>0.95-0.98</td>
<td>1.03</td>
<td>0.003</td>
<td>1.01-1.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>15 (12-19)</td>
<td>0.92 (0.002)</td>
<td>0.87-0.97</td>
<td>1.01</td>
<td>0.51</td>
<td>0.96-1.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to Procedure (hrs)</td>
<td>12 (9.7-16)</td>
<td>1.05 (0.26)</td>
<td>1.01-1.09</td>
<td>0.96</td>
<td>0.16</td>
<td>0.91-1.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>121 (51)</td>
<td>0.56 (0.034)</td>
<td>0.33-0.95</td>
<td>1.34</td>
<td>0.14</td>
<td>0.72-2.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>153 (64.8)</td>
<td>1.42 (0.21)</td>
<td>0.81-2.48</td>
<td>1.51</td>
<td>0.016</td>
<td>0.76-3.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>47 (19.92)</td>
<td>0.69 (0.28)</td>
<td>0.35-1.35</td>
<td>0.85</td>
<td>0.059</td>
<td>.38-1.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afib</td>
<td>68 (28.8)</td>
<td>0.49 (0.023)</td>
<td>0.26-0.90</td>
<td>1.91</td>
<td>0.051</td>
<td>0.99-3.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>77 (33)</td>
<td>1.96 (0.019)</td>
<td>1.11-3.45</td>
<td>0.59</td>
<td>0.15</td>
<td>0.28-1.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>14 (100)</td>
<td>0.6 (0.14)</td>
<td>0.31-1.17</td>
<td>1.66</td>
<td>0.15</td>
<td>0.82-3.36</td>
<td></td>
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</tr>
<tr>
<td>Hyperlipidemia</td>
<td>79 (33.4)</td>
<td>1.3 (0.94)</td>
<td>0.74-2.29</td>
<td>1.03</td>
<td>0.92</td>
<td>0.53-1.99</td>
<td></td>
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</tr>
<tr>
<td>PH</td>
<td>21 (8.9)</td>
<td>0.12 (0.005)</td>
<td>0.27-0.53</td>
<td>7.61</td>
<td>&lt;0.0001</td>
<td>2.95-19.6</td>
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</tr>
<tr>
<td>ICAT</td>
<td>47 (19.8)</td>
<td>0.38 (0.004)</td>
<td>0.20-0.73</td>
<td>2.35</td>
<td>0.01</td>
<td>1.21-4.56</td>
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<tr>
<td>Tandem</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tandem ICA/M1</td>
<td>31 (13)</td>
<td>1.46 (0.24)</td>
<td>0.77-2.77</td>
<td>0.49</td>
<td>0.19</td>
<td>0.17-1.42</td>
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</tr>
<tr>
<td>Tandem ICA/M2</td>
<td>6 (2.5)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tandem ICA/ICAT</td>
<td>13 (5.4)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>M1</td>
<td>114 (48.5)</td>
<td>1.56 (0.1)</td>
<td>0.9-2.7</td>
<td>0.7</td>
<td>0.26</td>
<td>0.37-1.31</td>
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<tr>
<td>M2</td>
<td>25 (10.5)</td>
<td>1.95 (0.1)</td>
<td>0.86-4.43</td>
<td>0.35</td>
<td>0.098</td>
<td>0.10-1.21</td>
<td></td>
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<tr>
<td>TIMI≥ 2</td>
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</tr>
<tr>
<td>IA lytic (t-PA, urokinase, retevase)</td>
<td>109 (47)</td>
<td>1.66 (0.059)</td>
<td>.98-2.84</td>
<td>0.77</td>
<td>0.43</td>
<td>0.41-1.46</td>
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<tr>
<td>MERCI embolectomy</td>
<td>147 (62)</td>
<td>0.8 (0.42)</td>
<td>0.46-1.38</td>
<td>1.15</td>
<td>0.65</td>
<td>0.60-2.20</td>
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<tr>
<td>GPIIb/IIIa inhibitors (i.v .or i.a.)</td>
<td>78 (33)</td>
<td>1.91 (0.022)</td>
<td>1.09-3.34</td>
<td>0.72</td>
<td>0.35</td>
<td>0.36-1.41</td>
<td></td>
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<tr>
<td>Other mechanical interventions (penumbra, stent, angioplasty)</td>
<td>85 (35.9)</td>
<td>1.24 (0.79)</td>
<td>0.72-2.15</td>
<td>0.86</td>
<td>0.67</td>
<td>0.45-1.66</td>
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</tr>
</tbody>
</table>

* Significant Associations are Outlined in Bold
**Figure 1.** Example of a patient included in the study: 67 year-old woman presenting with a NIHSS of 20 in the setting of acute cervical and intracranial tandem occlusions. Treatment was initiated 11 hours after TLSW. CT angiography demonstrated complete occlusion of the left supraclinoid ICA and proximal MCA (1.A. large arrow). Note the reconstitution of the distal MCA branches (1.A. small arrows) reflecting collateral flow. MRI DWI demonstrated changes involving the basal ganglia and peri-insular area consistent with infarct core (1.B. white arrow). MRI Mean Transient Time (MTT, 1.C.) maps demonstrated a large area of “tissue at risk”. The overall picture was consistent with “failing” collateral flow resulting in large penumbral tissue as evident by the relatively small DWI lesion in the setting of a large clinical deficit (NIHSS) and MTT lesion. The patient was taken for endovascular treatment based on the favorable imaging physiology. Angiogram demonstrated a complete occlusion of the cervical left ICA (1.D. black arrow) which was successfully treated with angioplasty and stenting (1.E. white arrow). The intracranial ICA occlusion (1.E. black arrow) was treated with balloon angioplasty and IA infusion of urokinase resulting in reperfusion with TICI 2b flow (1.F. white arrow). Follow-up MRI 24 hours post-treatment demonstrated expected evolution of the deep infarct (1.G. white arrow) with complete sparing of the previously described territory at risk. At 90 days post-treatment, the NIHSS was down to 4 and the mRS was 2.