Effect of Baseline CT Scan Appearance and Time to Recanalization on Clinical Outcomes in Endovascular Thrombectomy of Acute Ischemic Strokes

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Background and Purpose—The Penumbra Pivotal Stroke Trial reported a 25% good outcome (modified Rankin scale score ≤2) despite an 81% recanalization rate. We evaluated the association of a favorable initial noncontrast CT and a short time to recanalization in predicting good outcome.

Methods—Data were from the Penumbra Pivotal Stroke Trial. Baseline scans were evaluated by 2 experienced readers blinded to outcomes using ASPECTS. ASPECTS scores were dichotomized into >7 and ≤7 for primary analysis. Data on degree of recanalization based on thrombolysis in myocardial infarction scores, stroke onset to recanalization, and CT to recanalization times were obtained. Primary outcome was modified Rankin scale score ≤2 at 3 months.

Results—Median baseline NIHSS was 18 (range, 8–34) and median baseline ASPECTS score was 6 (range, 0–10); 81.2% achieved recanalization (thrombolysis in myocardial infarction, 2–3) and (27.7%) achieved good outcome. Good outcome was significantly higher in the ASPECTS score >7 group when compared to the ASPECTS score ≤7 group (50% vs 15%; RR, 3.3; 95% CI, 1.6–6.8; P=0.0001). No patient with an ASPECTS score ≤4 (n=28) or without recanalization (n=16) had a good outcome. There was an interaction between baseline ASPECTS score (≥7 and ≤7) and onset to recanalization time (≤300 minutes and >300 minutes) in predicting good outcome (P=0.06).

Conclusion—Patients with baseline CT ASPECTS score ≤4 do not benefit from recanalization. Fast recanalization may benefit patients with evident damage on the CT scan (ASPECTS score >4). Overall, patients benefit the most with early recanalization and a favorable baseline CT scan (ASPECTS score >7).

Key Words: injections ■ intra-arterial ■ numerical data ■ physiopathology ■ statistics ■ stroke ■ treatment outcome

Treatment of acute ischemic stroke is aimed at salvaging potentially viable ischemic brain by recanalizing the occluded artery and restoring anterograde perfusion. Final infarct size is reduced and functional outcomes are better if occluded artery and restoring anterograde perfusion. Final —Data were from the Penumbra Pivotal Stroke Trial. Baseline scans were evaluated by 2 experienced readers blinded to outcomes using ASPECTS. ASPECTS scores were dichotomized into >7 and ≤7 for primary analysis. Data on degree of recanalization based on thrombolysis in myocardial infarction scores, stroke onset to recanalization, and CT to recanalization times were obtained. Primary outcome was modified Rankin scale score ≤2 at 3 months.

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Key Words: injections ■ intra-arterial ■ numerical data ■ physiopathology ■ statistics ■ stroke ■ treatment outcome

Early CT Scale15 (ASPECTS) score >7, were 3-fold more likely to achieve independent functional outcome with endovascular treatment when compared to placebo, and patients with unfavorable scans (ASPECTS score ≤7) did not benefit, on average, from such treatment.16,17 We therefore assessed the relationship between the baseline CT scan and time to recanalization in predicting the final clinical outcome.

Materials and Methods

Data were from the Penumbra Pivotal Stroke Trial, which was a prospective, single-arm, 125-patient study designed to assess the safety and efficacy of the “Penumbra” system for removing thrombi in acute ischemic strokes.14 This study had received Institutional Review Board or Ethics Committee approval at the respective clinical centers before enrollment of any patient.

Two of the authors (M.G. and A.D.) reviewed and scored baseline CT scans while blinded to all clinical information and to follow-up scans. ASPECTS is a 10-point scale to score early ischemic changes in middle cerebral artery strokes. Baseline CT scans were scored for
early ischemic changes by consensus using the ASPECTS scoring system. Demographic data, vascular risk factors, stroke symptom onset, CT scan time and recanalization time, thrombolysis in myocardial infarction (TIMI) scores, and 3-month clinical outcome by modified Rankin scale were reported by the Penumbra trialists.

The primary outcome was modified Rankin scale score \( \leq 2 \) months. ASPECTS was dichotomized into \( >7 \) and \( \leq 7 \) for primary analysis, as has been performed previously.\(^{15,16}\) Times from stroke symptom onset to recanalization (\( \geq 300 \) minutes and \( <300 \) minutes) were analyzed as continuous and dichotomized variables dichotomized at the 25th percentile. The data are described with standard descriptive statistics and stratified analysis. A generalized linear model using the binomial distribution with log link was used with a multiplicative interaction term to assess whether an ASPECTS by time-to-recanalization interaction was present for the primary outcome. Patients who did not experience recanalization were included in the \( \geq 300 \) minute and \( <180 \) minute groups for this analysis.

Variables were chosen for the model based on clinical knowledge and univariate analysis. Statistical analyses were conducted with STATA version 10. All tests were 2-tailed. Conventional \( P<0.05 \) was considered significant. In multivariable analysis, interaction effects were considered significant at \( P<0.10. \(^{17}\)

### Results

Of 125 patients in the Penumbra Pivotal Stroke Trial, 85 were included in this study. Forty patients were excluded as follows: 18 had incomplete patient data or missing baseline scans, 6 had posterior circulation strokes, 5 had unreadable CT scans, and 11 had missing interval time information. Two patients with missing clinical follow up at 3 months were excluded from clinical outcome analysis only. Median baseline NIHSS score was 18 (range, 8–34) and median baseline ASPECTS score was 6 (range, 0–10); 81.2% of patients in this cohort achieved recanalization (TIMI, 2–3) and (27.7%) achieved good clinical outcome (Table).

There was no difference in baseline characteristics between the groups with ASPECTS score \( >7 \) and \( \leq 7 \) except in history of hypertension (more common in the \( \leq 7 \) group; \( P=0.01 \)). No difference in recanalization (TIMI, 2–3) or interval times was noted between these 2 groups. Good clinical outcome was significantly greater in the \( >7 \) group when compared to the \( \leq 7 \) group (RR, 3.3; 95% CI, 1.6–6.8; Table). No patient with an ASPECTS score \( \leq 4 \) (n=28) had good clinical outcome (Figure 1). Good clinical outcome was significantly higher in the early recanalizer (\( \geq 300 \) minutes) group when compared to a combined late recanalizer (\( <300 \) minutes) or

### Table. Baseline Characteristics, Reperfusion Rates, Treatment Times, and Clinical Outcomes Stratified by Baseline CT ASPECTS Score >7 and \( \leq 7 \)

<table>
<thead>
<tr>
<th></th>
<th>Total (n=85)</th>
<th>ASPECTS Score &gt;7 (n=31)</th>
<th>ASPECTS Score ( \leq 7 ) (n=54)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>64.1 (31–88)</td>
<td>67 (31–88)</td>
<td>69 (33–79)</td>
<td>0.1</td>
</tr>
<tr>
<td>Male (%)</td>
<td>43 (50.6)</td>
<td>12 (38.7)</td>
<td>31 (57.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>18 (14–20)</td>
<td>17 (13–20)</td>
<td>18 (15–22)</td>
<td>0.6</td>
</tr>
<tr>
<td>Baseline ASPECTS, median (IQR)</td>
<td>6 (3–9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (n=83)</td>
<td>55 (66.3%)</td>
<td>14 (45.2%)</td>
<td>41 (75.9%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (27.7%)</td>
<td>7 (22.5%)</td>
<td>16 (29.6%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>34 (40.9%)</td>
<td>10 (32.2%)</td>
<td>24 (44.4%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Site of occlusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid</td>
<td>19 (22.4%)</td>
<td>6 (19.3%)</td>
<td>13 (24.1%)</td>
<td></td>
</tr>
<tr>
<td>M1 MCA</td>
<td>54 (63.5%)</td>
<td>19 (61.3%)</td>
<td>35 (64.8%)</td>
<td></td>
</tr>
<tr>
<td>M2 MCA</td>
<td>12 (14.1%)</td>
<td>6 (19.3%)</td>
<td>6 (11.1%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Thrombolysis in myocardial infarction (2–3)</td>
<td>69 (81.2%)</td>
<td>26 (83.9%)</td>
<td>43 (79.6%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Onset to CT time (min, median (IQR)</td>
<td>97.9 (62–167)</td>
<td>96 (69–166)</td>
<td>98.3 (59.4–179)</td>
<td>0.9</td>
</tr>
<tr>
<td>Onset to recanalization time (min, median (IQR)</td>
<td>365.5 (292.5–432)</td>
<td>390 (283–463)</td>
<td>359 (295–420)</td>
<td>0.6</td>
</tr>
<tr>
<td>CT to recanalization time (min, median (IQR)</td>
<td>216.1 (168–284)</td>
<td>223.8 (177–359)</td>
<td>208 (160–257)</td>
<td>0.6</td>
</tr>
<tr>
<td>Modified Rankin scale score (0–2) at 3 mo (n=83)</td>
<td>23 (27.7%)</td>
<td>15 (50%)</td>
<td>8 (15%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; MCA, middle cerebral artery. N=85.

Figure 1. Unadjusted clinical outcomes (modified Rankin scale score at 3 months) stratified into 3 groups (n=83): good scan (ASPECTS score \( 0–4 \)), intermediate scan (ASPECTS score \( 5–7 \)), and poor scan (ASPECTS score \( 8–10 \)).
nonrecanalizer (TIMI, 0–1) group (RR, 2.3; 95% CI, 1.2–4.4). No patient without recanalization (TIMI, 0–1; n = 16) fared well (Figure 2).

In the ASPECTS score >7 group, 62.5% of patients with onset to recanalization time ≤300 minutes had good clinical outcome when compared to 45.5% patients with either onset to recanalization time >300 minutes or no recanalization. In the ASPECTS score ≤7 group, the corresponding figures are 33.3% with onset to recanalization time ≤300 minutes vs 7.9% in the >300-minute group or no recanalization group (Figure 3). After adjusting for baseline stroke severity, there was evidence of an ASPECTS by onset-to-recanalization time interaction (P = 0.066) in the multivariable model. The direction of interaction was such that among patients with ASPECTS score >7, the relative effect of onset to recanalization time (≤300 minutes or >300 minutes) in predicting outcome was small. Among patients with ASPECTS score ≤7, only those with an onset to recanalization time ≤300 minutes had some chance of achieving a functional outcome. Patients with an unfavorable scan (ASPECTS score ≤7) with late recanalization fared poorly.

Discussion

Concordant with previous data,16,18 we show that patients with favorable baseline CT scan (ASPECTS score >7) have better clinical outcomes when compared to those with baseline CT scan ASPECTS score ≤7 with an effect size of 35%. We also note that no patient with a poor baseline CT scan (ASPECTS score ≤4) achieves good clinical outcome. We further refine the use of the baseline CT information by showing effect modification by time. Patients treated early (<5-hour onset-to-recanalization time), even with evident damage on the baseline CT scan (ASPECTS score 5–7), can still benefit. Patients treated early (<5-hour onset-to-recanalization time) with a favorable scan (ASPECTS score >7) achieve the best outcomes. Only patients with favorable baseline CT scan appearance (ASPECTS score >7) are more likely, on average, to have a good clinical outcome when treated in a later time window (>5 hours from onset to recanalization). Patients with unfavorable scans (ASPECTS score ≤7) treated late and those who do not experience recanalization fare poorly.

An analysis of data from PROACT-2 showed that patients with a baseline ASPECTS score >7 were 3-times more likely to achieve good clinical outcomes with intra-arterial thrombolytic treatment.16 In a comparison of the IMS-1 patient cohort with historical NINDS IV tissue plasminogen activator cohort,18 only patients with ASPECTS score ≥7 fare well with IV and intra-arterial treatment when compared to IV tissue plasminogen activator. Patients with ASPECTS score <7 were harmed by IV and intra-arterial therapy. The effect size, an absolute risk increase of 10%, is large. These results suggest that ASPECTS score on baseline CT could be used to select patients who will particularly benefit from endovascular management of acute ischemic strokes.

The best outcomes are achieved among patients with favorable scans and fast recanalization times. This is biologically intuitive and time has been shown to be an important modifier of the intravenous thrombolytic treatment effect in randomized trials.2 Further, the evidence of the interaction between baseline CT scan and onset-to-recanalization time is particularly appealing given our understanding of modern imaging. Early treatment works best and late treatment is futile among patients with unfavorable changes on CT scan. At any treatment time point, if there are extensive changes on CT scan (ASPECTS ≤4), then endovascular therapy simply does not help.

An endovascular approach to acute stroke treatment is expensive, resource-intensive, and sometimes has significant procedural risks. We therefore suggest that proper patient selection using baseline CT scan, allied to efficient strategies aimed at faster recanalization, will result in better clinical outcomes in patients with acute ischemic strokes treated using endovascular techniques. Although some have argued for the use of multimodal MRI in selecting patients for acute
ischemic strokes,19–22 this modality has not yet achieved widespread acceptance and use. Noncontrast CT with CT angiography is a widely available and fast technique that can be used in acute ischemic strokes without any major contra-indications. As a result, many of the recent endovascular studies have used noncontrast CT and clinical assessment (NIHSS) to triage patients.

The limitations of this analysis include the small sample size. Other unmeasured factors such as the effect of leptomeningeal collaterals,23 clot burden,24 and clot characteristics in modifying the effect of time to recanalization on clinical outcome could be relevant. The ASPECTS scoring system imperfectly accounts for brain eloquence, is limited to the middle cerebral artery territory, is dependent on attention to scan quality and technique, and takes practice to learn and use well. The Penumbra Pivotal Stroke Study used TIMI grades scan quality and technique, and takes practice to learn and use.

Nevertheless, our data are consistent with previous assessments of the PROACT-2 study, the IMS-1 study, and the IV thrombolysis trials. We believe that optimal selection of patients requires attention to the baseline noncontrast CT scan and delivering and achieving recanalization as rapidly as possible.

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Disclosures

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SUPPLEMENTAL MATERIAL

Methods

Measurement of Infarct Volume. Following 24 hours of reperfusion, the mice were killed and transcardially perfused with heparinized saline (1U/mL). The brains were removed and post-fixed in 4% paraformaldehyde for 1 week. The cerebrum was then cut into 1 mm thick serial coronal sections. 10 μm paraffin embedded sections were stained with hematoxylin and eosin and the cerebral infarct volume was quantified using NIH image analysis software (Image J ver 1.43). Infarct volume was corrected for brain edema.

Immunohistochemistry. Microglia and macrophage activation and localization were determined after 24 hours of reperfusion with the microglia/macrophage selective antibody ionized calcium-binding adapter protein 1 (Iba1) (Abcam) at a 1:300 dilution using standard staining protocols on paraffin embedded sections. Iba1+ cells were quantified and expressed as number of cells/field (40X objective). Two 40X fields were counted per anatomical region and averaged to obtain the number of Iba1+ microglia and macrophages.

Quantitative real-time RT-PCR. mRNA expression was measured after 24 hours reperfusion. Total RNA was extracted from frozen whole cerebral hemispheres using TRIzol reagent and then purified with the RNeasy Mini Kit (Qiagen). Purified RNA (1μg) was reverse transcribed to cDNA using an Applied Biosystems kit. QRT-PCR was performed using a Bio-Rad iCycler. The relative mRNA expression was quantified using the comparative method and mRNA was normalized to β-actin.

Laser Doppler Flowmetry and Blood Gas. Cortical perfusion in the MCA territory was measured used laser Doppler flowmetry and was determined before and during occlusion of the
MCA. For measurement of pH, PO$_2$, and PCO$_2$, a catheter was implanted into the femoral artery and arterial blood was collected during pre-ischemic and ischemic periods.

**Microglia Isolation and Culture.** Isolation of cerebral microglia was performed as described elsewhere$^1$. Briefly, 10-12 wk old mice FC and MyMRKO mice were euthanized and transcardially perfused with heparinized saline (1U/mL). The cerebrum was homogenized in ice cold PBS in a Tenbroeck homogenizer. The homogenate was then filtered through a 50 μm strainer and then resuspended in 70% isotonic Percoll. A 0/40/70% Percoll gradient was set up and centrifuged at 1200 x g for 45 min at 20°C. The microglia containing fraction was then collected, resuspended in RPMI + 10% FBS and plated at a density of 2 x 10$^5$ cells/mL/well. Cells were washed with PBS (+ calcium chloride, + magnesium chloride) after 2 hours to remove non-adherent cells and then incubated for 24 hours at 37 °C, 5% CO$_2$. 
Figure Legend

S2. Expression of MR in cultured microglia. Microglia were isolated from the cerebrum of FC and MyMRKO mice and cultured for 24 hours. No significant change in MR expression was detected between FC and MyMRKO mice. N = 5 per group.
Table S1. Cerebral blood flow and arterial blood gas measurements.

<table>
<thead>
<tr>
<th></th>
<th>CBF (%)</th>
<th>pH</th>
<th>P\textsubscript{O2}, mm Hg</th>
<th>P\textsubscript{CO2}, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-Ischemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FC</td>
<td>100</td>
<td>7.34 ± 0.04</td>
<td>19.3 ± 3.9</td>
<td>158.7 ± 17.4</td>
</tr>
<tr>
<td>MyMRKO</td>
<td>100</td>
<td>7.36 ± 0.06</td>
<td>17.6 ± 2.5</td>
<td>149.0 ± 14.8</td>
</tr>
<tr>
<td><strong>Ischemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FC</td>
<td>46.1 ± 0.9</td>
<td>7.28 ± 0.06</td>
<td>20.8 ± 4.1</td>
<td>138.6 ± 17.0</td>
</tr>
<tr>
<td>MyMRKO</td>
<td>46.6 ± 3.8</td>
<td>7.39 ± 0.05</td>
<td>20.9 ± 4.6</td>
<td>140.7 ± 12.3</td>
</tr>
</tbody>
</table>

Values represent mean ± S.E. The ischemic cerebral blood flow (CBF) is represented as the percentage of the pre-ischemic, baseline CBF. There were no significant differences between FC and MyMRKO mice (N = 4 per group). FC = Floxed Control, MyMRKO = myeloid MR knockout.
Figure S2.
Supplemental References