Clinical Outcomes Strongly Associated With the Degree of Reperfusion Achieved in Target Mismatch Patients
Pooled Data from the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Studies

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Background and Purpose—To investigate relationships between the degree of early reperfusion achieved on perfusion-weighted imaging and clinical outcomes in the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution studies. We hypothesized that there would be a strong correlation between the degree of reperfusion achieved and clinical outcomes in target mismatch (TMM) patients.

Methods—The degree of reperfusion was calculated on the basis of the difference in perfusion-weighted imaging volumes (time to maximum of tissue residue function [Tmax] > 6 s) between the baseline MRI and the early post-treatment follow-up scan. Patients were grouped into quartiles, on the basis of degree of reperfusion achieved, and the association between the degree of reperfusion and clinical outcomes in TMM and no TMM patients was assessed. Favorable clinical response was determined at day 30 on the basis of the National Institutes of Health Stroke Scale and good functional outcome was defined as a modified Rankin Scale score ≤ 2 at day 90.

Results—This study included 121 patients; 98 of these had TMM. The median degree of reperfusion achieved was not different in TMM patients (60%) versus No TMM patients (64%; P = 0.604). The degree of reperfusion was strongly correlated with both favorable clinical response (P < 0.001) and good functional outcome (P = 0.001) in TMM patients; no correlation was present in no TMM. The frequency of achieving favorable clinical response or good functional outcome was significantly higher in TMM patients in the highest reperfusion quartile versus the lower 3 quartiles (88% versus 41% as odds ratio, 10.3; 95% confidence interval, 2.8–37.5; and 75% versus 34% as odds ratio, 5.9; 95% confidence interval, 2.1–16.7, respectively). A receiver operating characteristic curve analysis identified 90% as the optimal reperfusion threshold for predicting good functional outcomes.

Conclusion—The degree of reperfusion documented on perfusion-weighted imaging after reperfusion therapies corresponds closely with clinical outcomes in TMM patients. Reperfusion of ≥ 90% of the perfusion lesion is an appropriate goal for reperfusion therapies to aspire to. (Stroke. 2013;44:1885-1890.)

Key Words: acute stroke □ endovascular treatment □ magnetic resonance imaging □ perfusion-weighted imaging □ reperfusion

Although angiographic recanalization has been associated with favorable outcomes in numerous acute stroke studies,1–3 the association between the degree of reperfusion documented on MRI or computed tomography perfusion imaging and clinical outcomes has only been assessed in a few studies.4–6 Furthermore, there are very limited data to support the assertion that reperfusion is associated with favorable clinical outcomes only in the subgroup of patients with imaging-based evidence of salvageable tissue.7,8 Perfusion imaging has the potential advantage compared with arterial recanalization, in that it can assess tissue level flow and provide a quantitative assessment of the volume of tissue that is reperfused.

Most studies that have assessed the relationship between reperfusion and outcomes using MRI have dichotomized the degree of successful reperfusion into reperfusion versus no reperfusion using an arbitrary threshold. This prespecified threshold for successful reperfusion has varied substantially between studies. For example, 30% was used in Diffusion and Perfusion Imaging Evaluation for Understanding
Stroke Evolution (DEFUSE) 1,2 50% in DEFUSE 2 and 90% in Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET).3 It has been hypothesized that only patients with salvageable ischemic tissue are likely to benefit from early reperfusion and that patients without salvageable tissue do not.4 The DEFUSE5,6 and EPITHET1 studies have identified an MRI profile, target mismatch (TMM), that seems to identify patients who are particularly likely to have favorable clinical and radiographic responses in association with reperfusion.

In this study, we investigate the relationship between the degree of early reperfusion achieved on perfusion-weighted imaging (PWI) and clinical outcomes. We hypothesized that a strong correlation would exist between the degree of early reperfusion achieved and favorable clinical outcomes in TMM, but that there would be no relationship in patients who do not have TMM (no TMM). In addition, we explore if there is a reperfusion threshold that predicts favorable clinical outcomes in TMM patients with high specificity and good sensitivity.

**Methods**

This is a post hoc analysis of the DEFUSE 1 and DEFUSE 2 studies. The design, methodology, and primary results of DEFUSE 1 and DEFUSE 2 have been reported. In DEFUSE 1, a baseline MRI scan was obtained immediately before treatment with intravenous tissue-type plasminogen activator (tPA); the median time to treatment was 5.5 hours. A follow-up MRI was obtained to assess reperfusion (median, 4.0 hours after intravenous tPA treatment). In DEFUSE 2, a baseline MRI scan was obtained just before endovascular therapy (median, 6.0 hours between symptom onset and femoral puncture). A follow-up MRI was obtained to assess reperfusion (median, 2.8 hours after endovascular treatment).

Diffusion-weighted imaging (DWI) and PWI volumes were obtained at the time of patient enrollment in DEFUSE 2 using an automated software program: RApid processing of PerfusIon and Diffusion.10 DEFUSE 1 imaging data were retrospectively analyzed using the same program. The methodology for reproprocessing of DEFUSE 1 data with RApid processing of PerfusIon and Diffusion has been previously reported.1 All imaging from DEFUSE 1 was performed on 1.5T MRI scanners; DEFUSE 2 used both 1.5T and 3T MRI systems.

The prespecified TMM criteria from DEFUSE 2 were applied to both studies for this analysis: (1) a ratio between the volume of critically hypoperfused tissue and ischemic core ≥1.8, with an absolute difference ≥15 mL; (2) ischemic core volume <70 mL; and (3) volume of tissue with a severe delay (time to maximum of tissue residue function [Tmax>10 s] <100 mL. Patients with a baseline PWI (Tmax>6 s) volume of <10 mL were excluded from this analysis because reperfusion could not be assessed in these small lesion patients. The volume of hypoperfusion on PWI (Tmax>6 s) was assessed before and after the reperfusion treatment and the degree of reperfusion was determined as follows: ([baseline PWI volume−early follow-up PWI volume]/baseline PWI volume)×100. Patients were grouped into quartiles according to the degree of reperfusion achieved and the association between the degree of reperfusion and clinical outcomes were assessed separately for patients with and without TMM.

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**Results**

Seventy-four patients were treated with tPA in DEFUSE 1 and endovascular therapy was attempted in 110 patients in DEFUSE 2. Fourteen patients with technically unsatisfactory baseline PWI scans and 30 patients (25 cases from DEFUSE 1 and 5 cases from DEFUSE 2) with baseline PWI (Tmax>6 s) volumes <10 mL were ineligible for inclusion. An additional 19 patients were excluded because the follow-up MRI was either not performed or technically unsatisfactory. Therefore, a total of 121 patients were eligible for this substudy, and of these, 98 had TMM and 23 had no TMM. Clinical characteristics are summarized in Table 1. DEFUSE 1 patients were older than DEFUSE 2 patients and hyperlipidemia was more common in DEFUSE 2. There were no statistical differences in baseline NIHSS scores or the timing of the MRI scans in relationship to symptom onset (Table 1). There was no significant difference in baseline predictors of outcome, including age, baseline NIHSS, baseline DWI, or baseline PWI, in the quartiles reflecting the degree of reperfusion achieved for either the TMM or no TMM patients (Table 2).

The median degree of reperfusion achieved did not differ between DEFUSE 1 and DEFUSE 2 (Table 1; P=0.936) or between TMM patients (median, 59.7%; interquartile range, 16.0–92.8) and no TMM patients (median, 64.1%; interquartile range, 13.6–96.9; P=0.604). The frequency of both favorable clinical response and good functional outcome was highly correlated with the degree of reperfusion (assessed by quartiles; Cochran–Armitage test for trend; P<0.001 and P=0.001) for TMM patients (Figure 1), but no correlation was present in the no TMM patients. Twenty-eight percent of the TMM patients in the lowest reperfusion quartile (<16% reperfusion) had favorable clinical response compared with 42% in the second quartile (16%–59.9% reperfusion), 52% in the third quartile (60%–93.9% reperfusion), and 88% in the highest quartile (94%–100% reperfusion; Figure 1). In this study, we investigated the relationship between the degree of early reperfusion achieved on perfusion-weighted imaging (PWI) and clinical outcomes. We hypothesized that a strong correlation would exist between the degree of early reperfusion achieved and favorable clinical outcomes in TMM, but that there would be no relationship in patients who do not have TMM (no TMM). In addition, we explored if there is a reperfusion threshold that predicts favorable clinical outcomes in TMM patients with high specificity and good sensitivity.

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contrast, no significant relationship between the degree of reperfusion and either favorable clinical response or good functional outcome was present in the no TMM group (Figure 2).

As hypothesized, the frequency of favorable clinical response was significantly greater for the highest quartile of reperfusion compared with the 3 lower quartiles (88% versus 41%; odds ratio, 10.3; 95% confidence interval, 2.8–37.5; \( P < 0.001 \)) in TMM patients. Similarly, the percentage of TMM patients with good functional outcomes was higher in the top quartile of reperfusion compared with the lower 3 quartiles (75% versus 34%; good functional outcome; odds ratio, 5.9; 95% confidence interval, 2.1–16.7; \( P \leq 0.001 \)).

In the logistic regression analysis, the degree of reperfusion was an independent predictor of both good functional outcome and favorable clinical response (\( P < 0.001 \)) for TMM patients. After adjusting for independent predictors of outcome, including age and DWI volume, each 10% increase in

### Table 1. Characteristics of Eligible Patients

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Combined (n=121)</th>
<th>DEFUSE 1 (n=34)</th>
<th>DEFUSE 2 (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, age±SD*</td>
<td>67±16</td>
<td>75±15</td>
<td>65±15</td>
</tr>
<tr>
<td>Female, %</td>
<td>53</td>
<td>59</td>
<td>51</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>78 (65)</td>
<td>20 (59)</td>
<td>58 (67)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>25 (21)</td>
<td>10 (29)</td>
<td>15 (17)</td>
</tr>
<tr>
<td>Hyperlipidemia, %†</td>
<td>57 (47)</td>
<td>9 (27)</td>
<td>48 (55)</td>
</tr>
<tr>
<td>Current or past smoker, %</td>
<td>53 (44)</td>
<td>13 (38)</td>
<td>40 (46)</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>41 (34)</td>
<td>10 (29)</td>
<td>31 (36)</td>
</tr>
<tr>
<td>NIHSS baseline (median, IQR)</td>
<td>14 (10–19)</td>
<td>14 (10–17)</td>
<td>16 (11–20)</td>
</tr>
<tr>
<td>Baseline DWI lesion volume, mL (median, IQR)</td>
<td>15.2 (5.4–32.8)</td>
<td>11 (2.9–25.5)</td>
<td>16.8 (8.0–39.5)</td>
</tr>
<tr>
<td>Baseline PWI lesion volume, mL (median, IQR)</td>
<td>81 (48.8–114.5)</td>
<td>77.5 (40.3–90.0)</td>
<td>87.1 (50.5–116.7)</td>
</tr>
<tr>
<td>Treated with IV tPA, %*</td>
<td>71 (59)</td>
<td>34 (100)</td>
<td>37 (43)</td>
</tr>
<tr>
<td>Symptom onset to baseline MR, min (median, IQR)</td>
<td>277 (194–321)</td>
<td>284 (269–307)</td>
<td>270 (162–354)</td>
</tr>
<tr>
<td>Symptom onset to IV tPA (DEFUSE 1 only), min (median, IQR)</td>
<td>327 (309–350)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom onset to femoral puncture (DEFUSE 2 only), min (median, IQR)</td>
<td></td>
<td></td>
<td>357 (238–460)</td>
</tr>
<tr>
<td>Symptom onset to follow-up MRI, min (median, IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target mismatch, %</td>
<td>98 (81)</td>
<td>29 (85)</td>
<td>69 (79)</td>
</tr>
<tr>
<td>Degree of reperfusion obtained (median %, IQR)</td>
<td>60.0 (15.5–95.3)</td>
<td>60.3 (8.0–88.0)</td>
<td>60.0 (17.0–95.5)</td>
</tr>
<tr>
<td>mRS at 90 days (median, IQR)</td>
<td>3 (1–4)</td>
<td>4 (2–4)</td>
<td>3 (1–4)</td>
</tr>
</tbody>
</table>

DEFUSE indicates Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution; DWI, diffusion-weighted imaging; IQR, interquartile range; mRS, modified Rankin Score; NIHSS, National Institutes of Health Stroke Scale; PWI, perfusion-weighted imaging; and tPA, tissue-type plasminogen activator.

* \( P < 0.001 \), † \( P = 0.005 \).

### Table 2. Baseline Characteristics of TMM and No TMM Patients

<table>
<thead>
<tr>
<th></th>
<th>First Quartile</th>
<th>Second Quartile</th>
<th>Third Quartile</th>
<th>Fourth Quartile</th>
<th>( P ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMM (n=98)</td>
<td>n=25</td>
<td>n=24</td>
<td>n=25</td>
<td>n=24</td>
<td></td>
</tr>
<tr>
<td>Age, y (mean, SD)</td>
<td>65 (17)</td>
<td>70 (15)</td>
<td>71 (17)</td>
<td>67 (15)</td>
<td>0.510</td>
</tr>
<tr>
<td>NIHSS baseline (median, IQR)</td>
<td>13 (11–19)</td>
<td>17 (10.5–20)</td>
<td>14 (9–21)</td>
<td>12 (10–16)</td>
<td>0.705</td>
</tr>
<tr>
<td>Baseline DWI lesion volume, mL (median, IQR)</td>
<td>7.7 (3.0–15.2)</td>
<td>17.5 (8.8–27.5)</td>
<td>13.5 (10.1–26.0)</td>
<td>8.1 (4.9–14.5)</td>
<td>0.095</td>
</tr>
<tr>
<td>Baseline PWI lesion volume, mL (median, IQR)</td>
<td>74.5 (38.4–89.2)</td>
<td>90.4 (50.6–115.2)</td>
<td>87.1 (60.3–107.5)</td>
<td>73.3 (56.4–101.4)</td>
<td>0.172</td>
</tr>
<tr>
<td>No TMM (n=23)</td>
<td>n=6</td>
<td>n=6</td>
<td>n=5</td>
<td>n=6</td>
<td></td>
</tr>
<tr>
<td>Age, y (mean, SD)</td>
<td>67 (17)</td>
<td>58 (13)</td>
<td>65 (19)</td>
<td>71 (12)</td>
<td>0.522</td>
</tr>
<tr>
<td>NIHSS baseline (median, IQR)</td>
<td>17 (13–18)</td>
<td>18.5 (18–19)</td>
<td>17 (13.5–19)</td>
<td>19.5 (12–25)</td>
<td>0.515</td>
</tr>
<tr>
<td>Baseline DWI lesion volume, mL (median, IQR)</td>
<td>43 (2–92)</td>
<td>55.1 (19.6–65.3)</td>
<td>45.4 (27.7–91.3)</td>
<td>79.0 (47–100.9)</td>
<td>0.548</td>
</tr>
<tr>
<td>Baseline PWI lesion volume, mL (median, IQR)</td>
<td>83.2 (21.8–167.5)</td>
<td>122.5 (76.9–134.2)</td>
<td>73.7 (52.9–170.3)</td>
<td>183.7 (37–206.9)</td>
<td>0.536</td>
</tr>
</tbody>
</table>

Quartiles are based on degree of reperfusion achieved; first quartile reflects the lowest degree of reperfusion and fourth quartile reflects the highest. DWI indicates diffusion-weighted imaging; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; PWI, perfusion-weighted imaging; and TMM, target mismatch.

*Kruskal–Wallis test.
the degree of reperfusion had an odds ratio of 1.3 (95% confidence interval, 1.13–1.49) for favorable clinical response and 1.31 (95% confidence interval, 1.14–1.50) for good functional outcome (Table 3).

The association between the degree of reperfusion achieved and favorable clinical response or good functional outcome for TMM patients in DEFUSE 1 versus DEFUSE 2 was not different; there was no significant interaction between study group (DEFUSE 1 versus DEFUSE 2) and reperfusion degree quartiles in the logistic regression analysis ($P=0.379$ for favorable clinical response; $P=0.804$ for good functional outcome). This analysis could not be performed in the no TMM cohort because of the small sample size in DEFUSE 1.

The receiver operating characteristic curve identified 87% and 90% as the optimal degree of reperfusion by Youden index for predicting favorable clinical outcomes in TMM patients: reperfusion of 87% of the hypoperfused Tmax>6 lesion had a sensitivity of 55% and specificity of 89% for predicting a favorable clinical response; 90% reperfusion had a 52% sensitivity and 87% specificity for predicting good functional outcome.

**Discussion**

The results of this study suggest that for patients with the TMM profile on baseline MRI, the degree of early reperfusion attained on PWI is strongly associated with the probability of achieving favorable clinical outcomes. No relationship between the degree of reperfusion and clinical outcomes was apparent in no TMM patients. Furthermore, the TMM patients who had complete or nearly complete reperfusion (the highest quartile of reperfusion, 94%–100%) had substantially better outcomes than patients who achieved lesser degrees of reperfusion. The receiver operating characteristic analysis identified 90% as the optimal degree of reperfusion to predict good functional outcome with high specificity and good sensitivity. TMM patients who achieved this high degree of reperfusion had exceptional clinical outcomes, including favorable clinical response frequency of $\approx90\%$ and a Rankin 0 to 2 rate at 90 days of $\approx75\%$. Therefore, obtaining reperfusion of $\geq90\%$ of the perfusion lesion may be an appropriate benchmark for reperfusion therapies to aspire to.

Most previous studies that have assessed the relationship between the degree of reperfusion and clinical outcomes have used angiographic approaches, such as Thrombolysis in Cerebral Infarction scores,2,3,11 to assess recanalization/reperfusion. These studies have typically demonstrated that patients with reperfusion have better clinical outcomes than patients with no reperfusion.12,13 In the recent Interventional Management of Stroke III14 trial, the frequency of good functional outcome (modified Rankin Scale, 0–2) in the endovascular group correlated strongly with the degree of reperfusion obtained on the Thrombolysis in Cerebral Infarction score ($P<0.001$); however, even among patients with a Thrombolysis in Cerebral Infarction score of 2b (reperfusion of 50%–99% of the vascular distribution of the occluded artery), only 48% had good functional outcome.
Assessing reperfusion with perfusion imaging has some advantages compared with angiographic assessments at the end of the endovascular procedure. Recanalization of an arterial occlusion does not necessarily result in capillary reperfusion because of the no-reflow phenomenon and tissue reperfusion can occur, despite lack of angiographic recanalization, via recruitment of collateral flow. Furthermore, assessing reperfusion after completion of the procedure allows for visualization of perfusion changes that occur shortly after completion of the procedure (such as reperfusion related to administration of intra-arterial thrombolytic or improved collaterals).

Our study has some limitations. DEFUSE 1 and 2 used different therapeutic approaches to achieve reperfusion; intravenous tPA alone in the DEFUSE 1 study and endovascular therapy (often after initial intravenous tPA treatment) in the DEFUSE 2 study. Despite this, the studies did not differ in the degree of reperfusion attained and the relationship between the degree of reperfusion and clinical outcomes in TMM patients was consistent between studies. Furthermore, the multivariate analysis demonstrated that the degree of reperfusion achieved was an independent predictor of clinical outcomes in TMM analysis demonstrated that the degree of reperfusion achieved was consistent between studies. Furthermore, the multivariate analysis demonstrated that the degree of reperfusion achieved was an independent predictor of clinical outcomes in TMM patients. There were relatively few no TMM patients enrolled in the DEFUSE studies. Therefore, studies with larger numbers of no TMM patients are required to clarify the association between reperfusion and clinical outcomes in these patients.

The frequency of favorable clinical response did not correlate well with the frequency of good functional outcome in the no TMM group. This may be because of the small number of patients or the fact that an 8-point improvement in NIHSS score is often inadequate to produce a nondisabled outcome in patients with a high baseline NIHSS score.

We think that the current study is the first to report the association between the degree of PWI-documented reperfusion and clinical outcomes. We demonstrate that TMM patients who achieved complete or nearly complete reperfusion had exceptional clinical outcomes. Furthermore, every 10% of additional reperfusion achieved in TMM patients was associated with a 30% increase in the odds of favorable clinical response and a 31% increase in good functional outcome. The contrasting results of this study for TMM versus no TMM patients suggest that optimizing patient selection for reperfusion therapies is likely to have an important effect on the clinical outcomes of these interventions.

### Sources of Funding

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### References


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