Assessing Reperfusion and Recanalization as Markers of Clinical Outcomes After Intravenous Thrombolysis in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET)

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Background and Purpose—Reperfusion and recanalization have both been used as surrogate markers of clinical outcome in trials of stroke thrombolysis. We aimed to prove that the beneficial impact of recanalization with intravenous tissue plasminogen activator on clinical outcomes is attributable to reperfusion in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET).

Methods—EPITHET was a prospective, randomized, placebo-controlled trial of intravenous tissue plasminogen activator in the 3- to 6-hour window. Reperfusion was defined as >90% reduction in magnetic resonance perfusion-weighted imaging lesion volume and recanalization as improvement of MR angiographic Thrombolysis In Myocardial Infarction grading by ≥2 points from baseline to Day 3 to 5.

Results—At Day 3 to 5, reperfusion and recanalization with intravenous tissue plasminogen activator were strongly correlated. Reperfusion was associated with improved clinical outcome independent of whether recanalization occurred. In contrast, recanalization was not associated with clinical outcome when reperfusion was included as a covariate in regression analyses.

Conclusion—Reperfusion is a surrogate marker of clinical outcomes independent of recanalization based on the criteria applied in EPITHET. The impact of recanalization on clinical outcomes was attributable to reperfusion. (Stroke. 2009;40:2872-2874.)

Key Words: clinical outcomes ■ ischemic stroke ■ recanalization ■ reperfusion ■ thrombolysis

In proof-of-concept Phase II trials such as the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET), imaging surrogates of clinical outcome provide evidence for biological plausibility of stroke thrombolysis with smaller numbers required to prove statistical efficacy and earlier time-point assessments that reduce study duration. Reperfusion has been confirmed as a good surrogate end point in response to intravenous tissue plasminogen activator (tPA) in both the EPITHET1 and the Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study.2 Recanalization of obstructed arteries within 24 hours also correlates with clinical outcome.3 Recanalization and subsequent reperfusion of the ischemic penumbra are closely linked phenomena. Reperfusion of the microcirculation is influenced not only by recanalization, but also by factors such as cerebral perfusion pressure, hemorheological variables, and collateral flow patterns.

There has been only one previous study comparing recanalization and reperfusion in response to therapy. Post hoc analysis of the Interventional Management of Stroke I trial investigating combined intravenous and intra-arterial thrombolysis found there was no difference in predicting clinical outcomes between recanalization (graded by the arterial occlusion lesion score first described in this study) and reperfusion (graded by the Thrombolysis In Myocardial Infarction [TIMI] score) based on angiographic assessment.4 However, this study did not investigate whether the associations of reperfusion and recanalization with clinical outcomes were independent of each other. In this post hoc analysis of EPITHET, we hypothesized that tissue reperfusion influences...
outcomes independent of vessel recanalization, and the benefcial effects of recanalization are attributable to reperfusion.

Materials and Methods
EPITHET was a Phase II prospective, randomized, double-blinded, placebo-controlled, multinational trial in patients with acute ischemic stroke randomized to treatment with intravenous tPA or placebo 3 to 6 hours after symptom onset. Participants were imaged with serial echoplanar MRI before study medication (baseline), at Day 3 to 5, and Day 90. The full methodology of the EPITHET trial has been previously described. We measured the percentage difference of perfusion lesion volumes using a Tmax delay threshold of ≥2 seconds assessed by a single reader blinded to treatment arm, clinical data, and arterial status between baseline and Day 3 to 5 and defined reperfusion as >90% reduction. At baseline and Day 3 to 5, the presence and degree of arterial obstruction in major intracerebral arteries (internal carotid, middle cerebral, and anterior cerebral arteries) on time-of-flight or phase-contrast MR angiography were assessed by 2 readers and rated by consensus using an adapted TIMI grading as used in the Desmoteplase In Acute ischemic Stroke (DIAS) II trial. Recanalization was defined as an improvement of TIMI grading from baseline to Day 3 to 5 of ≥2 points. Good neurological outcome was defined as National Institutes of Health Stroke Scale score of 0 to 1 at Day 90 or improvement >8 from baseline. Good functional outcome was defined as modified Rankin Score at Day 90 of 0 to 2.

Statistical analyses were performed with SPSS Version 15.0. Fisher exact test was used for comparison of categorical variables and Wilcoxon test for continuous variables. Binary logistic regression in view of their strong correlation with each other. The study protocol and informed consent procedures were approved by human research and ethics committees at each site.

Results
Arterial patency was analyzed for 87 of the 101 patients enrolled in EPITHET (6 had no baseline MR angiography performed and in 7, baseline MR angiography was of poor quality). The frequency of baseline arterial obstruction was 62% (54 of 87), 44% with TIMI 0, 12% with TIMI 1, and 6% with TIMI 2. Recanalization at Day 3 to 5 could be assessed in 48 of these 54 patients, 20 in the tPA group and 28 in the placebo group. The frequency of recanalization was 62% (30 of 48). There was no statistically significant difference in the frequency of recanalization between tPA- and placebo-treated participants (70% versus 57%, P=0.364). Among the 95 patients with baseline perfusion deficit, 82 had adequate perfusion imaging at Day 3 to 5, of whom 32 (39%) achieved reperfusion.

Neurological and functional status at Day 90 was not ascertained for one patient treated with tPA. Both recanalization and reperfusion were associated with improved clinical outcomes (Table 1). Reperfusion was associated with good neurological (OR, 2.77; P<0.001) and functional (OR, 2.19; P=0.003) outcome independent of recanalization. However, recanalization was no longer associated with good neurological (OR, 0.15; P=0.865) and functional (OR, 1.32; P=0.141) outcome when reperfusion was included as a covariate.

Among the 20 tPA-treated patients in whom recanalization was able to be assessed, 18 also had adequate assessment of reperfusion. Recanalization correlated with the presence and extent of reperfusion among patients treated with tPA (Table 2). Recanalization also correlated with the presence (P=0.053) and extent for reperfusion (P<0.001) among the 18 placebo-treated patients with both recanalization and reperfusion assessed.

Discussion
Vessel recanalization assessed at Day 3 to 5 is strongly associated with tissue reperfusion determined at Day 3 to 5. This is consistent with the DEFUSE study’s findings of an association between vessel recanalization and tissue reperfusion determined at 3 to 6 hours. In EPITHET, both of these surrogate markers of reperfusion and recanalization predicted clinical outcomes. We confirmed our hypotheses that reperfusion predicts clinical outcome independent of recanalization, and the beneficial clinical impact of recanalization is attributable to reperfusion. The ongoing Phase III trial of intravenous desmoteplase (DIAS 3) selects patients by arterial status, does not include perfusion imaging, and thus will not be able to conduct any post hoc analysis of improved reperfusion with treatment.

The main limitation of this study is the delayed time point of assessment of reperfusion and recanalization at Day 3 to 5. Recanalization and reperfusion rates decrease with time from intravenous tPA. However, later recanalization occurring between 6 and 24 hours is associated with improved clinical outcomes. Although we have used the prespecified EPITHET definitions, there are other criteria for recanalization and reperfusion. Interpretation of these data are therefore limited to these definitions of recanalization and reperfusion. Although patients with TIMI 2 obstruction cannot achieve recanalization by our definition, we included them in the

### Table 1. Associations With Clinical Outcomes Among Patients Treated With Intravenous tPA

<table>
<thead>
<tr>
<th></th>
<th>Recanalization (n=14)</th>
<th>No Recanalization (n=5)</th>
<th>P</th>
<th>Reperfusion (n=21)</th>
<th>No Reperfusion (n=16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good neurological outcome</td>
<td>64% (9)</td>
<td>0% (0)</td>
<td>0.033*</td>
<td>81% (17)</td>
<td>25% (4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Good functional outcome</td>
<td>57% (8)</td>
<td>0% (0)</td>
<td>0.045*</td>
<td>67% (14)</td>
<td>31% (5)</td>
<td>0.049*</td>
</tr>
</tbody>
</table>

*Fisher exact test.
†Wilcoxon test.
IQR indicates interquartile range.

### Table 2. Relationship Between Recanalization and Reperfusion After Intravenous tPA Treatment

<table>
<thead>
<tr>
<th></th>
<th>Recanalization (n=9)</th>
<th>No Recanalization (n=9)</th>
<th>Median Reperfusion Percentage (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recanalization</td>
<td>69% (9)</td>
<td>31% (4)</td>
<td>94 (52 to 99)</td>
</tr>
<tr>
<td>No recanalization</td>
<td>0% (0)</td>
<td>100% (5)</td>
<td>−29 (−37 to 44)</td>
</tr>
<tr>
<td>P</td>
<td>0.029*</td>
<td>0.004†</td>
<td></td>
</tr>
</tbody>
</table>
multivariate analysis because they can possibly achieve reperfusion. A small proportion of patients had ungradable MR angiography (7%, 11%) or perfusion imaging (2%, 5%) at baseline and Day 3 to 5. These results should be considered with caution in view of the study’s post hoc analysis and small sample size and the results need to be confirmed in larger studies with earlier assessment times and varying definitions of recanalization and reperfusion.

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References
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