The Benefits of Intravenous Thrombolysis Relate to the Site of Baseline Arterial Occlusion in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET)

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Background and Purpose—In ischemic stroke, the site of arterial obstruction has been shown to influence recanalization and clinical outcomes. However, this has not been studied in randomized controlled trials, nor has the impact of arterial obstruction site on reperfusion and infarct growth been assessed. We studied the influence of site and degree of arterial obstruction patients enrolled in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET).

Methods—EPITHET was a prospective, randomized, placebo-controlled trial of intravenous tissue plasminogen activator (tPA) in the 3- to 6-hour time window. Arterial obstruction site and degree were rated on magnetic resonance angiography blinded to treatment allocation and outcomes.

Results—In 101 EPITHET patients, 87 had adequate quality magnetic resonance angiography, of whom 54 had baseline arterial obstruction. Infarct growth attenuation was greater in those with tPA treatment compared to placebo among patients with middle cerebral artery (MCA) obstruction (P = 0.037). The treatment benefit of tPA over placebo in attenuating infarct growth was greater for MCA than internal carotid artery (ICA) obstruction (P = 0.060). With tPA treatment, good clinical outcome was more likely with MCA than with ICA obstruction (P = 0.005). Most patients with ICA obstruction did not achieve good clinical outcome, whether treated with tPA (100%) or placebo (77%). The study was underpowered to prove any treatment benefit of tPA among patients with any or severe degree of arterial obstruction.

Conclusions—Arterial obstruction site strongly predicts outcomes. ICA obstruction carries a uniformly poor prognosis, whereas good outcomes with MCA obstruction are associated with tPA therapy. (Stroke. 2010;41:295-299.)

Key Words: arterial obstruction • ischemic stroke • myocardial infarction • thrombolysis
these findings, the next planned trial investigating intravenous desmoteplase (DIAS III) will utilize an inclusion criteria of arterial obstruction of higher-grade stenosis or occlusion.11

We studied the impact of the site and degree of arterial obstruction on reperfusion, recanalization, infarct growth, and clinical outcomes in ischemic stroke patients in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET). We hypothesized that the treatment benefit on imaging and clinical end points of intravenous tPA over placebo was greater among patients with MCA than ICA arterial occlusion at baseline. Second, we hypothesized that the presence and degree of arterial obstruction at baseline influenced outcomes and the treatment effect of tPA vs placebo.

Materials and Methods

The EPITHET trial was a phase II, prospective, randomized, double-blinded, placebo-controlled, multinational trial of acute ischemic stroke patients randomized to treatment with intravenous tPA or placebo 3 to 6 hours after onset and imaged with serial echoplanar MRI.12–14 EPITHET was conducted between 2001 and 2007 in 15 centers in Australia, New Zealand, Belgium, and Scotland. The study protocol and informed consent procedures were approved by Human Research and Ethics Committees at each site.

The full methodology of the EPITHET trial has been previously described.15 In brief, inclusion criteria included patients with acute hemorrhagic ischemic stroke who presented 3 to 6 hours after symptom onset, were 18 years of age or older, had a NIHSS score of >4, and had a premorbid modified Rankin score of ≤2. Patients were imaged with 1.5-Tesla echoplanar-equipped MRI scanners. Standardized diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and magnetic resonance angiography (MRA) sequences were obtained before treatment and repeated at days 3 to 5. At day 90, T2-weighted images were obtained to measure final infarct volume. For patients who died or could not be studied at day 90, the last results at day 3 to 5 were carried forward as a measure of imaging outcome.

All MRI scans were read at the coordinating center by investigators blinded to treatment assignment and clinical outcomes but not to time point. PWI-DWI mismatch was defined as PWI lesion greater than DWI lesion volume by >20% and 10 mL. At baseline and day 3 to 5, we assessed the presence, site, and degree of arterial obstruction in major intracerebral arteries on MRA. To investigate the impact of the site of arterial obstruction, we compared patients with MCA main stem and internal carotid artery obstruction. The degree of arterial obstruction was graded using an adapted thrombolysis in myocardial infarction (TIMI) grading.14 TIMI grade 0 was diagnosed when no flow signal was detected. TIMI grade 1 was diagnosed when there was minimal flow seen beyond the occlusion but not in most of the vascular bed distal to it. TIMI grade 2 was diagnosed when the flow signal was seen beyond the occlusion site and most of the distal vascular bed, and TIMI grade 3 was diagnosed when the flow signal was of normal intensity.

Recanalization was defined as an improvement of TIMI grading from baseline to day 3 to 5 by ≥2 points (TIMI 0 to 2; TIMI 0 to 3; TIMI 1 to 3).15 Reperfusion was measured as the percentage difference in perfusion lesion volumes between baseline and days 3 to 5. Infarct growth was measured as the expansion between baseline DWI and final lesions. The primary outcome measure in the main EPITHET study was the geometric mean relative growth, calculated as the exponential of mean log relative growth of the final lesion volume and baseline DWI lesion volume. Good neurological outcomes were defined as a modified Rankin score of 0 to 2 at day 90.

Statistical analyses were performed with SPSS version 15.0. Fisher exact test was used for comparison of categorical variables, Student t test was used for comparison of parametric continuous variables, and Wilcoxon test was used for comparison of nonparametric continuous variables. Interactions between variables were tested with binary logistic regression for dichotomous outcomes and 2-way ANOVA for continuous outcomes.

Results

There were 100 of 101 patients in EPITHET who received study medication.12 Acute MRA scans were of adequate quality to assess baseline arterial obstruction in 87 patients (median age, 75 years; 53% male) and these patients are the subject of this report. Baseline MRA was not performed for 6 patients and was not of adequate quality for interpretation for another 7 patients. Of the 87 patients with adequate baseline MRA scans, 54 (62%) had arterial obstruction of varying degrees; 38 (44%) had TIMI 0, 11 (12%) had TIMI 1, and 5 (6%) had TIMI 2. Baseline arterial obstruction involved the ICA in 22 patients, MCA (main stem) in 27 patients, and MCA branch occlusion in 5 patients. There were no significant differences in age, hypertension, diabetes, NIHSS score, time to treatment, and baseline DWI lesion volume between patients with ICA and MCA stem obstruction (Table 1). There was a higher proportion of women with MCA obstruction (P=0.097). Baseline PWI lesion (P=0.015) and PWI-DWI mismatch lesion (P=0.009) volumes were larger with ICA than MCA obstructions. All patients with MCA obstruction and 91% with ICA obstruction fulfilled the prespecified criteria of PWI-DWI mismatch.

Among the patients with MCA obstruction, tPA significantly attenuated infarct growth compared to placebo (0.60 vs 1.87; P=0.037; Table 2). However, there was no infarct growth attenuation with tPA among patients with ICA obstruction. Treatment with tPA did not significantly affect the extent of reperfusion, likelihood of recanalization, and clinical outcomes compared to placebo for patients with either MCA or ICA obstruction.
The extent of reperfusion was greater and recanalization was more likely with MCA than ICA obstruction, in both the tPA (median reperfusion, 94% vs 19%; P=0.003; recanalization rate, 90% vs 38%; P=0.043) and placebo (median reperfusion, 82% vs 17%; P=0.004; recanalization rate, 80% vs 25%; P=0.007) treatment groups. With tPA treatment, infarct growth was significantly lower with MCA than ICA obstruction (0.60 vs 5.12; P=0.037) and placebo (median reperfusion, % (IQR) 5.12 3.49 0.528). Among patients treated with tPA, there was no difference in infarct growth between patients with TIMI 0 to 1 and TIMI 2 to 3 (P=0.811), nor between patients with TIMI 0 to 2 vs TIMI 3 (P=0.315). The presence of any arterial obstruction (TIMI 0–2 vs TIMI 3; P=0.478) and severe arterial obstruction (TIMI 0–1 vs TIMI 2–3; P=0.288) did not influence the treatment benefit of intravenous tPA over placebo in attenuating infarct growth.

**Discussion**

This is the first randomized, placebo-controlled study to our knowledge investigating the impact of the site of arterial obstruction in patients treated with intravenous tPA. Whereas concurring with published data that MCA obstruction has a better prognosis than ICA obstruction,6,11 this study advances current knowledge by showing the superior benefits of intravenous tPA over placebo among patients with MCA compared to ICA obstruction. This study provides evidence that the site of arterial obstruction is an important factor in stratification of outcome after intravenous tPA. With tPA treatment, patients with MCA obstruction are more likely to achieve recanalization and reperfusion than those with ICA obstruction, leading to infarct growth attenuation and improved clinical outcomes after tPA treatment. We hypothesize that patients with MCA obstruction may benefit from intravenous tPA up to 6 hours from onset.

Patients with ICA obstruction had poor clinical outcomes with or without intravenous tPA. However, patient numbers were relatively small and there remains insufficient evidence to exclude these patients from intravenous tPA treatment. Patients with ipsilateral ICA obstruction are excluded from the DIAS III trial investigating intravenous desmoteplase in
the 3- to 9-hour time window.\textsuperscript{11} We speculate that patients with ICA obstruction may be potential candidates for trials of other reperfusion strategies, such as the combined intravenous and intra-arterial thrombolysis in the Interventional Management of Stroke (IMS) III trial\textsuperscript{16} and intra-arterial thrombolysis in the SYNTHESIS trial.\textsuperscript{17} Alternatively, patients with ICA obstruction may be more suitable for rescue interventional therapies, such as intra-arterial thrombolysis and mechanical thrombectomy, should intravenous thrombolysis fail to achieve recanalization and reperfusion.

What are the potential reasons for the differential outcomes between patients with MCA and ICA obstruction? First, the clot size is smaller with MCA than ICA obstruction,\textsuperscript{18} and clot burden has been shown to predict clinical outcome.\textsuperscript{19} Second, there may be differences in clot composition between MCA and ICA obstruction. Fibrin-rich clots have been shown to have a greater propensity for lysis with tPA compared to platelet-rich clots.\textsuperscript{20} Although clots extracted by the MERCI retrieval device from MCA and ICA obstructions were shown to be histologically similar,\textsuperscript{18} there may have been selection bias as only clots that could be retrieved were analyzed.

This study was underpowered to prove any benefit of intravenous tPA over placebo for patients with arterial obstruction grade TIMI 0 to 1 or TIMI 0 to 2. However, the lack of infarct growth attenuation with tPA treatment among patients without any (TIMI 3) or severe degree (TIMI 2 to 3) arterial obstruction lends some support to the DIAS III inclusion criterion of high-grade arterial stenosis or occlusion. Both arterial obstruction and PWI-DWI mismatch are targets of thrombolytic treatment via recanalization and reperfusion. In EPITHET, only two-thirds of patients who fulfilled the PWI-DWI mismatch criteria were found to have arterial obstruction of major intracerebral arteries. This may be attributable to obstruction in smaller arteries below the resolution of MRA. Alternatively, these patients may have had the “no reflow phenomenon,” which is downstream microvascular obstruction despite recanalization of the large supplying artery.\textsuperscript{21} We are currently investigating whether selection of patients with both arterial obstruction and PWI-DWI mismatch is a feasible approach for thrombolytic treatment stratification.

### Conclusion

Strengths of this study include its randomized, placebo-controlled nature, which allowed for assessment of interaction effects between treatment group and baseline arterial obstruction factors, as well as blinded objective assessment of arterial obstruction, recanalization, and reperfusion using prespecified criteria. In addition, we assessed multiple outcome parameters including imaging (recanalization, reperfusion, and infarct growth) and clinical (neurological and functional) outcomes. Our study also has some limitations. First, MRA overestimates the degree of arterial obstruction. Conversely, MRA provides a rapid technique for assessing arterial obstruction. It is useful in patient selection for acute stroke treatment and in triage for recruitment for some acute stroke trials. Second, the assessment of recanalization and reperfusion at days 3 to 5 includes early and late recanalization and possibly re-obstruction. Recanalization up to 24 hours after stroke onset has been found to be associated with clinical course and functional outcome.\textsuperscript{22} Reperfusion assessed at days 3 to 5 has been shown to be strongly correlated with infarct growth attenuation and better clinical outcomes in the main EPITHET study.\textsuperscript{12} Third, the high rate of recanalization (80%) with MCA obstruction in the placebo group may be attributable to late spontaneous recanalization. Despite this, patients with MCA obstruction treated with tPA had greater infarct growth attenuation compared to the placebo group, possibly because of earlier recanalization. Fourth, with the recanalization definition used (improvement of TIMI by $\geq 2$ points) it is not possible for patients with baseline TIMI grade 2 to fulfill the criterion for recanalization even if flow improves to TIMI grade 3. In view of the post hoc nature of these analyses and small sample size involved,

### Table 4. Treatment Effects Based on Arterial Obstruction Degree

<table>
<thead>
<tr>
<th></th>
<th>tPA</th>
<th>Placebo</th>
<th>$P$</th>
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<tbody>
<tr>
<td>TIMI grade 0, 1 (n=49), n</td>
<td></td>
<td></td>
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<tr>
<td>Infarct growth, n</td>
<td>21</td>
<td>28</td>
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<tr>
<td>Geometric mean growth</td>
<td>1.25</td>
<td>2.38</td>
<td>0.129</td>
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<tr>
<td>Clinical outcomes, n</td>
<td>21</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Good neurological outcome</td>
<td>52% (11)</td>
<td>32% (9)</td>
<td>0.154</td>
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<tr>
<td>Good functional outcome</td>
<td>48% (10)</td>
<td>36% (10)</td>
<td>0.401</td>
</tr>
<tr>
<td>TIMI grade 2, 3 (n=38), n</td>
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<tr>
<td>Geometric mean growth</td>
<td>1.26</td>
<td>1.15</td>
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<tr>
<td>Clinical outcomes, n</td>
<td>24</td>
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<td></td>
</tr>
<tr>
<td>Good neurological outcome</td>
<td>58% (14)</td>
<td>39% (5)</td>
<td>0.313</td>
</tr>
<tr>
<td>Good functional outcome</td>
<td>50% (12)</td>
<td>39% (5)</td>
<td>0.731</td>
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<tr>
<td>Good neurological outcome</td>
<td>46% (11)</td>
<td>31% (9)</td>
<td>0.394</td>
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<tr>
<td>Good functional outcome</td>
<td>35% (10)</td>
<td>42% (10)</td>
<td>0.776</td>
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<tr>
<td>TIMI grade 3 (n=33), n</td>
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<td>0.95</td>
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<td>12</td>
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<tr>
<td>Good neurological outcome</td>
<td>67% (14)</td>
<td>42% (5)</td>
<td>0.273</td>
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<tr>
<td>Good functional outcome</td>
<td>57% (12)</td>
<td>42% (5)</td>
<td>0.481</td>
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these results should be interpreted with caution and replicated in larger studies.

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