**EPITHET**

Positive Result After Reanalysis Using Baseline Diffusion-Weighted Imaging/Perfusion-Weighted Imaging Co-Registration

Yoshinari Nagakane, MD, PhD; Soren Christensen, PhD; Caspar Brekenfeld, MD; Henry Ma, MBBS; Leonid Churilov, PhD; Mark W. Parsons, PhD, FRACP; Christopher R. Levi, FRACP; Kenneth S. Butcher, MD, PhD; Andre Peeters, MD; P. Alan Barber, PhD; Christopher F. Bladin, PhD; Deidre A. De Silva, MBBS, MRCP, FAMS; John Fink, FRACP; Thomas E. Kimber, PhD, FRACP; David W. Schultz, FRACP; Keith W. Muir, MD; Brian M. Tress, MD, FRANZCR, FRCR; Patricia M. Desmond, MD; Stephen M. Davis, MD, FRACP; Geoffrey A. Donnan, MD, FRACP; for the EPITHET Investigators

**Background and Purpose**—The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) was a prospective, randomized, double-blinded, placebo-controlled, phase II trial of alteplase between 3 and 6 hours after stroke onset. The primary outcome of infarct growth attenuation on MRI with alteplase in mismatch patients was negative when mismatch volumes were assessed volumetrically, without coregistration, which underestimates mismatch volumes. We hypothesized that assessing the extent of mismatch by coregistration of perfusion and diffusion MRI maps may more accurately allow the effects of alteplase vs placebo to be evaluated.

**Methods**—Patients were classified as having mismatch if perfusion-weighted imaging divided by coregistered diffusion-weighted imaging volume ratio was >1.2 and total coregistered mismatch volume was ≥10 mL. The primary outcome was a comparison of infarct growth in alteplase vs placebo patients with coregistered mismatch.

**Results**—Of 99 patients with baseline diffusion-weighted imaging and perfusion-weighted imaging, coregistration of both images was possible in 95 patients. Coregistered mismatch was present in 93% (88/95) compared to 85% (81/95) with standard volumetric mismatch. In the coregistered mismatch patients, of whom 45 received alteplase and 43 received placebo, the primary outcome measure of geometric mean infarct growth was significantly attenuated by a ratio of 0.58 with alteplase compared to placebo (1.02 vs 1.77; 95% CI, 0.33–0.99; P=0.0459).

**Conclusions**—When using coregistration techniques to determine the presence of mismatch at study entry, alteplase significantly attenuated infarct growth. This highlights the necessity for a randomized, placebo-controlled, phase III clinical trial of alteplase using penumbral selection beyond 3 hours. (*Stroke*. 2011;42:59-64.)

**Key Words:** magnetic resonance imaging ■ mismatch ■ penumbra ■ tissue plasminogen activator

Reperfusion therapies including intravenous thrombolysis with recombinant tissue plasminogen activator are based on the premise that ischemic penumbral tissue is at risk for infarction but has the potential to be salvaged by reperfusion.1 With the advent of MRI techniques, the mismatch concept defined by the perfusion-weighted imaging (PWI) lesion exceeding the diffusion-weighted imaging (DWI) lesion was postulated as a penumbral marker.2 Since then, MR PWI/DWI has become a widely used imaging research technique in the assessment of acute stroke patients.3 Mismatch volume (MV) is conventionally calculated using a volumetric method in which the DWI lesion volume is

Received February 4, 2010; accepted July 29, 2010.
From the National Stroke Research Institute (Y.N., C.B., H.M., L.C., G.A.D.), Florey Neuroscience Institutes, Austin Health, University of Melbourne, Australia; Department of Neurology (S.C., D.A.D.S., S.M.D.), Royal Melbourne Hospital, University of Melbourne, Australia; Institute of Interventional and Diagnostic Neuroradiology (C.B.), University of Bern, Switzerland; Department of Mathematics and Statistics (L.C.), University of Melbourne, Australia; Department of Neurology (M.W.P., C.R.L.), University of Sydney, Sydney, Australia; Department of Neurology (K.S.B.), University of Alberta, Edmonton, Alberta, Canada; University Hospital St Luc (A.P.), Brussels, Belgium; Neurology Department (P.A.B.), Auckland City Hospital, Grafton, Auckland, New Zealand; Eastern Melbourne Neurosciences (C.F.B.), Melbourne, Australia; Department of Neurology (D.A.D.S.), Singapore General Hospital campus, National Neuroscience Institute, Singapore; Department of Neurology (J.F.), Christchurch Hospital, Christchurch, New Zealand; Royal Adelaide Hospital (T.E.K.), Adelaide, Australia; Department of Neurology (D.W.S.), Finders Medical Centre, Bedford Park, Australia; Division of Clinical Neurosciences (K.W.M.), University of Glasgow, UK; Department of Radiology (B.M.T., P.M.D.), Royal Melbourne Hospital, University of Melbourne, Australia.

The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.580464/DC1.

*Correspondence to Geoffrey A. Donnan, Florey Neuroscience Institutes, University of Melbourne, Level 2 Alan Gilbert Building, 161 Barry Street, Carlton South Victoria 3053, Australia. E-mail gdonnan@unimelb.edu.au
© 2010 American Heart Association, Inc.

*Stroke* is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.110.580464
Early reperfusion of the infarct core may result in a spontaneous reperfusion and changes in collateral blood flow. However, the region of hypoperfusion fluctuates in the hours after stroke onset attributable to processes such as reperfusion and changes in collateral blood flow. Early reperfusion of the infarct core may result in a component of the DWI lesion lying outside the PWI lesion. However, the region of hypoperfusion fluctuates in the hours after stroke onset attributable to processes such as spontaneous reperfusion and changes in collateral blood flow.

The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) was a phase II, prospective, randomized, double-blinded, placebo-controlled, multinational trial of 101 patients treated between 3 and 6 hours after stroke onset. Importantly, the primary hypothesis was that patients with mismatch (defined by the standard volumetric method) who received alteplase would have attenuation of infarct growth when compared to the coregistration method.

In EPITHET, hypoperfusion volumes were defined using 1.5-T echoplanar-equipped MRI scanners before treatment and again at days 3 to 5. At day 90, T2-weighted images were obtained to document imaging outcome. Patients who died or who could not be studied at day 90, the last results at days 3 to 5 were carried forward as a measure of imaging outcome.

Definitions
All definitions were as in the main EPITHET study except for the addition of coregistered mismatch (Table 1).

Outcome Measures
The primary outcome measure was infarct growth attenuation in coregistered mismatch patients between alteplase and placebo, primarily analyzed by geometric mean and secondarily by relative growth, absolute growth, and difference in cube root lesion volumes. Secondary end points included reperfusion, clinical outcomes, recanalization, and symptomatic intracerebral hemorrhage.

Statistical Analysis
Statistical analyses were performed using Stata/IC 10 (StataCorp). The comparisons between volumetric and coregistration methods were made with Wilcoxon signed-rank test for continuous variables and with McNemar exact test for categorical variables. The agreement between the original DWI volumes and the coregistered DWI volumes was assessed by Lin’s concordance coefficient and intraclass correlation coefficient. As per the original protocol of EPITHET, the difference in means of log-relative growth between patients treated...

Figure 1. A, Coregistration of perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) allows the DWI lesion to be divided into 2 regions: DWI within (wDWI; yellow) and DWI lying outside the PWI lesion (oDWI; red). Using the volumetric technique, the mismatch volume (MV) is PWI−wDWI, whereas the coregistered MV (green) is defined as PWI−wDWI. An 82-year-old woman with baseline MR performed 325 minutes after stroke onset. The baseline DWI lesion volume was 65.3 mL (B) and PWI lesion volume was 68.8 mL (C; green areas indicate PWI abnormalities of Tmax 2 seconds or more). In EPITHET using the volumetric technique, she was classified as having no mismatch (3.5 mL); however, while coregistered (D), she was classified as having mismatch (26.2 mL; wDWI in yellow, oDWI in red, and coregistered mismatch areas in green).

Patients and Methods
Imaging Protocol
The study design of EPITHET, including patient eligibility, treatment allocation, and imaging protocol, has been previously reported. Briefly, patients with acute hemispheric ischemic stroke who presented 3 to 6 hours after symptom onset were assigned to intravenous alteplase or placebo and had DWI, PWI, and MRA sequences with 1.5-T echoplanar-equipped MRI scanners before treatment and again at days 3 to 5. At day 90, T2-weighted images were obtained to measure final infarct volume.

Using these coregistration techniques, the baseline DWI lesion was divided into 2 regions: DWI within and DWI outside of the PWI volume (Figure 1). Regions of interest on DWI and T2-weighted imaging (DWI) allows the DWI lesion to be divided into 2 regions: DWI within (wDWI; yellow) and DWI lying outside the PWI lesion (oDWI; red). Using the volumetric technique, the mismatch volume (MV) is PWI−wDWI, whereas the coregistered MV (green) is defined as PWI−wDWI. An 82-year-old woman with baseline MRI performed 325 minutes after stroke onset. The baseline DWI lesion volume was 65.3 mL (B) and PWI lesion volume was 68.8 mL (C; green areas indicate PWI abnormalities of Tmax 2 seconds or more). In EPITHET using the volumetric technique, she was classified as having no mismatch (3.5 mL); however, while coregistered (D), she was classified as having mismatch (26.2 mL; wDWI in yellow, oDWI in red, and coregistered mismatch areas in green).
Lesion

Infarct growth: expansion between baseline DWI and day-90 T2-weighted

10 mL

Volumetric mismatch: PWI

DWI volume

H11004

10 mL

Volumetric method

Coregistration method

Table 2. Baseline Imaging Variables for 95 Patients

<table>
<thead>
<tr>
<th></th>
<th>Alteplase (n=49)</th>
<th>Placebo (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median baseline DWI volume (mL)</td>
<td>20 (0–188)</td>
<td>21 (0–204)</td>
</tr>
<tr>
<td>Median baseline wDWI volume (mL)</td>
<td>10 (0–152)</td>
<td>16 (0–150)</td>
</tr>
<tr>
<td>Median baseline PWI volume (mL)</td>
<td>142 (0–558)</td>
<td>192 (0–428)</td>
</tr>
<tr>
<td>Median baseline mismatch volume (mL)</td>
<td>95 (–10–455)</td>
<td>136 (–93–422)</td>
</tr>
<tr>
<td>Coregistration method</td>
<td>99 (0–466)</td>
<td>152 (0–422)</td>
</tr>
<tr>
<td>Mismatch</td>
<td>40 (82)</td>
<td>41 (89)</td>
</tr>
<tr>
<td>Volumetric method</td>
<td>45 (92)</td>
<td>43 (93)</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; PWI, perfusion-weighted imaging; wDWI, diffusion-weighted imaging within the perfusion-weighted imaging lesion.

Table 1. Definitions

| Coregistered mismatch: PWI→wDWI volume > 1.2, and PWI→wDWI volume ≥ 10 mL |
|----------------------|------------------|
| Volumetric mismatch: PWI→DWI volume > 1.2, and PWI→DWI volume ≥ 10 mL |
| Infarct growth: expansion between baseline DWI and day-90 T2-weighted lesion |

Geometric mean: exponential of mean log relative growth

Relative growth: final lesion volume−baseline DWI lesion volume

Absolute growth: final lesion volume−baseline DWI lesion volume

Difference in cube root volumes: (final lesion volume)1/3−(baseline DWI lesion volume)1/3

Any growth: relative growth > 0%

Malignant profile: DWI volume and/or PWI volume with Tmax ≥ 8 seconds ≥ 100 mL

Reperfusion: >90% reduction between baseline and day-3 PWI volumes

Recanalization: improvement from baseline to day 3 to 5 in arterial obstruction by ≥ 2 points, based on an adaptation of the thrombosis in myocardial infarction grading on MRA (0 = complete occlusion, 1 = severe stenosis, 2 = mild to moderate stenosis, and 3 = normal arterial caliber)

Symptomatic ICH: ICH with significant clinical deterioration of ≥ 4 NIHSS points within 36 hours of treatment and parenchymal hemorrhage of grade 2 on CT (blood clots in >30% of the infarcted area with substantial space-occupying effect) adjudicated by a blinded committee (SITS-MOST definition)9

Good neurological outcome: NIHSS at day 90 of 0 or 1 or improvement ≥ 8 from baseline

Good functional outcome: modified Rankin scale at day 90 of 0 to 2

Results

Ninety-nine of 101 patients enrolled in EPITHET had baseline DWI and PWI and were included in this study. Automatic coregistration of baseline DWI and PWI succeeded in 95 of 99 patients, with 5 patients requiring initialization by manual landmarks. Coregistration failed in 4 (4%) patients because of artifact (3 had severe ghost artifacts of PWI and 1 had DWI motion artifacts), and these patients were excluded from subsequent analysis.

Table 2 shows baseline imaging variables for the 95 patients. Transformation of DWI into PWI space during the coregistration process resulted in baseline DWI volume increasing slightly from 20 mL (range, 0–197) to 21 mL (range, 0–204), and the agreement on the DWI volumes between original and after coregistration was confirmed by both intraclass correlation coefficient of 1.00 (95% CI, 0.98–1.00) and Lin concordance coefficient of 0.996 (0.995–0.998). After coregistration, median baseline DWI within and DWI outside the PWI lesion volumes were 13 mL (range, 0–152) and 5 mL (range, 0–119), respectively. Median baseline coregistered MV was significantly larger than baseline volumetric MV (128 mL vs 118 mL), with median difference of 5 mL (interquartile range, 3–12; 95% CI, 4–6; P<0.0001). Because 7 patients with no mismatch by the volumetric method had mismatch by the coregistration method (Figure 1B), the prevalence of mismatch increased from 85% (81/95) by the volumetric method to 93% (88/95) by the coregistration method (P=0.0156).

Figure 2 shows the study profile and Table 3 shows baseline characteristics for mismatch patients with valid imaging outcomes. Of the 101 enrolled patients, 91 patients had baseline PWI and DWI with a day-90 T2-weighted image or with a surrogate day-3 to day-5 DWI for the final lesion. Because of coregistration failure in 4 patients (2 each in the alteplase and placebo groups), 87 patients were assessed for mismatch between PWI and DWI and 80 had mismatch (38 received alteplase and 42 received placebo). Baseline variables of patients with mismatch did not significantly differ (P≥0.1) between alteplase and placebo groups (Table 3), and no statistical correction was needed.

For the primary outcome measure using the originally prespecified analytic method (geometric mean growth), the coregistered mismatch patients showed significant infarct growth attenuation with alteplase compared to placebo (1.02 vs 1.77; ratio, 0.58; 95% CI, 0.33–0.99; P=0.0459; Table 4). When the geometric mean growth was compared among the volumetric mismatch patients without coregistration, infarct growth attenuation did not differ between the treatment groups (1.06 vs 1.79; ratio, 0.59; 95% CI, 0.32–1.06; P=0.0779). This was confirmed by significant attenuation in infarct growth by the secondary analytical methods: relative growth (P=0.0139), absolute growth (P=0.0332), and difference in cube root lesion volume (P=0.0204). Further additional analytical methods including the proportion of patients who had any growth (P=0.0216), ratio of geometric mean (P=0.0113), and median relative growth (P=0.0038)
in patients with a baseline lesion of $>$5 mL (33 patients in the alteplase group and 36 in the placebo group) also showed a positive effect of alteplase compared to placebo.

For secondary outcome measures, 76 of the 88 coregistered mismatch patients had a valid PWI volume at days 3 to 5 to assess reperfusion, and all 88 had assessment of clinical outcome (Tables 4 and the online-only supplemental Table, available at http://stroke.ahajournals.org). Both the incidence of reperfusion ($\geq 90\%$) and the median percentage of reperfusion were significantly higher in patients with coregistered mismatch who received alteplase. Reperfusion was significantly associated with infarct growth attenuation, good neurological outcome, and good functional outcome in patients with coregistered mismatch. As with the original EPITHET analysis, which was not powered for a clinical outcome, the difference in good neurological and functional outcomes between the alteplase and placebo groups was not significant in patients with coregistered mismatch. Recanalization could be assessed with adequate MRA scans in 43 patients with coregistered mismatch, and it occurred in 27 (63\%) of these patients (Table 4). The proportion of recanalization did not differ between treatment arms.

Symptomatic intracerebral hemorrhage was seen in 8.0\% (4/50) of patients treated with alteplase. All patients had mismatch by the coregistration method, whereas 3 out of 4 had mismatch by the volumetric method. Median baseline DWI volume did not differ between patients with symptomatic intracerebral hemorrhage (43 mL; interquartile range, 31–101) and those without symptomatic intracerebral hemorrhage (15 mL; interquartile range, 7–37; $P=0.058$).

Primary outcome could be assessed in 7 patients without coregistered mismatch. Infarct growth did not differ significantly between the alteplase and placebo groups (geometric mean growth 0.93 vs 1.03; ratio, 0.91; 95\% CI, 0.31–2.66; $P=0.8283$). Between mismatch and nonmismatch patients in the alteplase group, infarct growth, reperfusion rate, and clinical outcomes did not differ significantly.

### Discussion

The efficacy analysis in EPITHET, although negative on the prespecified primary outcome, provided strong support for further investigation of the use of PWI/DWI mismatch in the identification of favorable reperfusion outcomes with alteplase. By applying the coregistration method to assess MV...
by guest on April 13, 2017 http://stroke.ahajournals.org/ Downloaded from

at study entry, we found that the prevalence of mismatch patients was increased and resulted in a positive outcome of EPITHET for the primary end point of infarct growth attenuation with alteplase in mismatch patients. As in EPITHET, we also found a strongly positive relationship between reperfusion and both attenuation of infarct growth and good clinical outcome in the coregistered mismatch group. These results emphasize the concept that selecting patients with PWI/DWI mismatch beyond 3 hours might be a useful approach to extend the time window for thrombolytic therapy.10,11 Our findings can now be put in the context of useful approach to extend the time window for thrombolytic therapy.10,11 Our findings can now be put in the context of a more sensitive selection criterion, with all measures of infarct growth showing significant attenuation with alteplase in patients included in EPITHET using this approach.

The great advantage of coregistration of PWI and DWI is that it allows a more precise estimate of the spatial relationship between these imaging modalities to occur and, hence, a better understanding of the dynamic nature of the evolving ischemia and reperfusion process. In particular, it becomes clear that portions of the DWI lesions have already reperfused at the time of imaging and, under these circumstances, the volumetric method does underestimate the true proportion of mismatch.7 This is illustrated in Figure 1A, in which the coregistered MV is greater than the volumetric MV by the differences of average or percentage for alteplase minus that for placebo, unless indicated as a ratio or median difference.

### Table 4. Trial Outcomes for Patients With Coregistered Mismatch

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alteplase</th>
<th>Placebo</th>
<th>Difference or Ratio (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct growth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary analytical method</td>
<td>1.02</td>
<td>1.77</td>
<td>0.58† (0.33–0.99)</td>
<td>0.0459</td>
</tr>
<tr>
<td>Secondary analytical methods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median relative growth (mL)</td>
<td>1.00 (0.50–1.80)</td>
<td>1.70 (1.00–3.10)</td>
<td>0.57† (0.36–0.88)</td>
<td>0.0139</td>
</tr>
<tr>
<td>Median absolute growth (mL)</td>
<td>−0.2 (−5.7–32.1)</td>
<td>27.4 (−0.2–55.6)</td>
<td>−12.2† (−31.8–0.7)</td>
<td>0.0332</td>
</tr>
<tr>
<td>Mean difference in cube root volumes (cm)</td>
<td>0.27 (1.19)</td>
<td>0.71 (1.06)</td>
<td>−0.43 (−0.94–0.06)</td>
<td>0.0855</td>
</tr>
<tr>
<td>Median difference in cube root volumes (cm)</td>
<td>0.0 (−0.4–0.7)</td>
<td>0.5 (0.0–1.2)</td>
<td>−0.5‡ (−0.9 to −0.1)</td>
<td>0.0204</td>
</tr>
<tr>
<td>Additional analytical methods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth &gt;0%</td>
<td>18 (47%)</td>
<td>31 (74%)</td>
<td>−26% (−47% to −6%)</td>
<td>0.0216</td>
</tr>
<tr>
<td>Baseline DWI lesions &gt;5 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean growth§</td>
<td>1.04</td>
<td>2.01</td>
<td>0.52‡ (0.31–0.86)</td>
<td>0.0113</td>
</tr>
<tr>
<td>Median relative growth§</td>
<td>1.00 (0.50–1.80)</td>
<td>1.85 (1.30–3.20)</td>
<td>0.53† (0.33–0.77)</td>
<td>0.0038</td>
</tr>
<tr>
<td>Reperfusion assessed</td>
<td>n=34</td>
<td>n=42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reperfusion ≥90%</td>
<td>20 (59%)</td>
<td>11 (26%)</td>
<td>33% (11%–54%)</td>
<td>0.0052</td>
</tr>
<tr>
<td>Median percentage reperfusion</td>
<td>93% (68–100)</td>
<td>53% (16 to 93)</td>
<td>18% (3%–53%)</td>
<td>0.0088</td>
</tr>
<tr>
<td>Recanalization assessed</td>
<td>n=17</td>
<td>n=26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recanalization</td>
<td>13 (76%)</td>
<td>14 (54%)</td>
<td>22% (−5%–50%)</td>
<td>0.1994</td>
</tr>
<tr>
<td>Good neurological outcome</td>
<td>23 (51%)</td>
<td>16 (37%)</td>
<td>14% (−7%–34%)</td>
<td>0.2056</td>
</tr>
<tr>
<td>mRS 0–2</td>
<td>20 (44%)</td>
<td>17 (40%)</td>
<td>5% (−16%–26%)</td>
<td>0.6712</td>
</tr>
<tr>
<td>mRS 0–1</td>
<td>16 (36%)</td>
<td>9 (21%)</td>
<td>15% (−4%–33%)</td>
<td>0.1591</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; mRS, modified Rankin Scale.
Data are mean (SD), N (%) of patients, or median (interquartile range).
*Difference of average or percentage for alteplase minus that for placebo, unless indicated as a ratio or median difference.
†Ratios.
‡Median difference estimated by Hodges-Lehman shift parameter (95% CI).
techniques as the original EPITHET were used, apart from the addition of the coregistration components.

There are some limitations to this study. First, some patients were excluded from the analysis because of coregistration failure, mainly attributable to inadequate imaging quality. Therefore, the altered trial results cannot be attributed exclusively to the inclusion of additional patients. There is a constant improvement occurring in the quality of DWI and PWI imaging techniques with software and MR hardware developments. In the clinical trial setting, imaging quality is better-controlled and may allow the support of successful coregistration procedures (including manual adjustment when required), whereas in a clinical setting, volumetric mismatch would seem to be a realistic “fall-back” option in cases in which registration fails. Second, the coregistration method here was only used to select patients and not to assess infarct growth, which requires the presence of follow-up MR images. Coregistration is possible but less reliable at later time points because of the structural changes associated with later infarct volumes, hemorrhagic transformation, and shrinkage. Although it seems likely that automated coregistration software without manual quality control may become a reality in the near future, its clinical use is likely to be restricted to the acute assessment only as it was in the current study. Third, this study was a post hoc analysis and, therefore, does not provide any change in interpretation of the original results of EPITHET. Despite these limitations, this study provided a more ideal mismatch analysis approach for selecting eligible candidates for thrombolytic therapy beyond the 3-hour time window. This suggests that there is a need to develop appropriate software to provide rapid coregistered image analysis.

Sources of Funding
National Health and Medical Research Council, Australia; National Stroke Foundation, Australia; and Heart Foundation of Australia.

Disclosures
None.

References
EPITHET: Positive Result After Reanalysis Using Baseline Diffusion-Weighted Imaging/Perfusion-Weighted Imaging Co-Registration
for the EPITHET Investigators

Stroke. 2011;42:59-64; originally published online December 2, 2010;
doi: 10.1161/STROKEAHA.110.580464
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/42/1/59

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2010/12/02/STROKEAHA.110.580464.DC1
http://stroke.ahajournals.org/content/suppl/2012/02/26/STROKEAHA.110.580464.DC2
http://stroke.ahajournals.org/content/suppl/2012/03/12/STROKEAHA.110.580464.DC3

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
(Online-only) Table. Effect of reperfusion on radiological, neurological, and functional outcomes for co-registered mismatch patients

<table>
<thead>
<tr>
<th></th>
<th>Reperfusion</th>
<th>No reperfusion</th>
<th>Difference or ratio (95% CI)*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct growth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean</td>
<td>0.79</td>
<td>1.99</td>
<td>0.40† (0.23 to 0.69)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Median relative growth</td>
<td>0.80 (0.30 to 1.70)</td>
<td>1.70 (1.20 to 3.30)</td>
<td>0.38† (0.23 to 0.65)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Median absolute growth (mL)</td>
<td>−2.2 (−8.7 to 9.9)</td>
<td>40.1 (1.4 to 76.7)</td>
<td>−36.9‡ (−57.5 to −18.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean difference in cube root</td>
<td>−0.13 (0.77)</td>
<td>0.95 (1.16)</td>
<td>−1.07 (−1.55 to −0.60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median difference in cube root</td>
<td>−0.1 (−0.7 to 0.5)</td>
<td>0.7 (0.2 to 1.5)</td>
<td>−1.0‡ (−1.4 to −0.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clinical outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good neurological outcome</td>
<td>23 (74%)</td>
<td>13 (29%)</td>
<td>45% (25 to 66%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Good functional outcome</td>
<td>20 (65%)</td>
<td>15 (33%)</td>
<td>31% (9 to 53%)</td>
<td>0.0101</td>
</tr>
</tbody>
</table>

Data are mean (SD), number (%) of patients, or median (IQR).

*Difference of average or percentage for reperfusion minus that for no reperfusion, unless indicated as a ratio or median difference. †Ratios.

‡Median difference estimated by Hodges-Lehman shift parameter (95%CI).
EPITHET — ベースラインの拡散強調画像／灌流強調画像のコレジストレーションによる再分析で得られた肯定的な結果

Yoshinari Nagakane, MD, PhD*; Soren Christensen, PhD‡; Caspar Brekenfeld, MD*,#; Henry Ma, MBBS‡;
Leonid Churilov, PhD‡,*; Mark W. Parsons, PhD, FRACP‡; Christopher R. Leve, FRACP‡; Kenneth S.
Butcher, MD, PhD‡; Andre Peeters, MD‡; P. Alan Barber, PhD‡; Christopher F. Bladin, PhD‡; Deidre A. De
Silva, MBBS, MRCP, FAMS*,#; John Tink, FRACP‡; Thomas E. Kimber, PhD, FRACP‡; David W. Schultz,
FRACP*; Keith W. Mair, MD‡; Brian M. Tress, MD‡; FRANZCR, FRCR; Patricia M. Desmond, MD‡; and
Stephen M. Davis, MD, FRACP‡; Geoffrey A. Donnan, MD, FRACP‡; for the EPITHET Investigators

*National Stroke Research Institute, Florey Neuroscience Sciences, Austin Health, University of Melbourne, Australia; ‡Department of Neurology, Royal Melbourne Hospital, University of Melbourne, Australia; §Institute of International and Diagnostic Neuroanatomy, University of Bern, Switzerland; †Department of Mathematics and Statistics, University of Melbourne, Australia; #Department of Neurology, Hunter Medical Research Institute, John Hunter Hospital, University of Newcastle, Australia; &Department of Neurology, University of Alberta, Edmonton, Alberta, Canada; ‡University Hospital St Luc, Brussels, Belgium; #Neuropathology Department, Auckland City Hospital, Grafton, Auckland, New Zealand; 4Department of Neurology, Rizzoli Medical Centre, Bologna, Italy; 5Division of Clinical Neurosciences, University of Glasgow, UK; 6Department of Radiology, Royal Melbourne Hospital, University of Melbourne, Australia; 7Department of Neurology, Canberra Hospital, ACT, Australia; 8Department of Neurology, Flinders Medical Centre, Bedford Park, Australia; 9Division of Clinical Neurosciences, University of Glasgow, UK; 10Department of Radiology, Royal Melbourne Hospital, University of Melbourne, Australia.
Se cree que la discrepancia de difusión-perfusión en las imágenes de RM aporta una aproximación de la penumbra isquémica, que se considera el objetivo de las estrategias actuales de reperfusión, incluida la trombólisis con activador de plasminógeno tisular (tPA). El estudio Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) fue un ensayo multinacional de fase II, prospectivo, aleatorizado, doble ciego y controlado con placebo, en el que se evaluó la hipótesis de que la trombolisis con tPA en un plazo de 3 a 6 horas tras el inicio del síntoma pudiera atenuar el crecimiento del infarto observado en la RM. Aunque se observó una tendencia a la atenuación del crecimiento del infarto, esta no alcanzaba significancia estadística. Nagakane y colaboradores presentan un reanálisis de los datos del EPITHET utilizando técnicas de registro conjunto de las imágenes de ponderación de difusión-imágenes de ponderación de perfusión (DWI-PWI) para mejorar la identificación de los pacientes con una discrepancia agradable, así como los efectos posteriores de tPA sobre la atenuación del crecimiento del infarto. El registro conjunto indicó una prevalencia significativamente superior de la discrepancia en comparación con la evaluación volumétrica simple (93% frente a 83%, \( p = 0.0156 \)). La media geométrica del crecimiento (variable de valoración primaria) se vio atenuada de forma significativa en el grupo de tPA en comparación con el grupo control al utilizar el método de registro conjunto (\( p = 0.0459 \)) pero no en el análisis volumétrico simple (\( p = 0.0799 \)). Se obtuvieron resultados similares con el empleo de diversos métodos analíticos secundarios y adicionales (en los pacientes con una lesión basal < 5 mL en las imágenes de DWI). Con el empleo del conjunto de datos de registro conjunto, los parámetros de valoración secundarios indicaron una incidencia más elevada de reperfusión ≥ 90% (\( p = 0.0032 \)), así como de la mediana de porcentaje de reperfusión (\( p = 0.0080 \)). La reperfusión se asoció significativamente a la atenuación del crecimiento del infarto, una buena evolución neurológica y un buen resultado funcional en los pacientes con una discrepancia en el registro conjunto. El estudio EPITHET no tuvo la potencia estadística suficiente para la evaluación de resultados clínicos, y no hubo una diferencia significativa entre el grupo de alteplasa y el grupo placebo en cuanto a la buena evolución neurológica y funcional. Con el empleo de técnicas sofisticadas de registro conjunto puede obtenerse una delimitación más sensible y precisa de la penumbra isquémica. Es de esperar que esto se traduzca en una selección adecuada mediante RM de los pacientes en los que es más probable la obtención de un efecto beneficioso con estrategias de perfusión después de la ventana temporal establecida para el tratamiento. (Comentario al artículo EPITHET: Positive Result After Reanalysis Using Baseline Diffusion-Weighted Imaging/Perfusion-Weighted Imaging Co-Registration. Yoshinari Nagakane, Soren Christensen, Caspar Brekenfeld, Henry Ma, Leonid Chaulov, Mark W. Parsons, Christopher R. Levi, Kenneth S. Butcher, Andre Peeters, P. Alan Barber, Christopher F. Eladain, Deidre A. De Silva, John Fink, Thomas E. Kimber, David W. Schultz, Keith W. Mui, Brian M. Tress, Patricia M. Desmond, Stephen M. Davis, Geoffrey A. Donnan for the EPITHET Investigators. Stroke. 2011;42:S5–S4.)