Pretreatment Diffusion-Weighted Imaging Lesion Volume Predicts Favorable Outcome After Intravenous Thrombolysis With Tissue-Type Plasminogen Activator in Acute Ischemic Stroke

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Background and Purpose—Stroke magnetic resonance imaging with perfusion and diffusion weighting has shown its potential to select patients likely to benefit from intravenous thrombolysis with tissue-type plasminogen activator (IV-tPA). We aimed to determine the predictors of favorable outcome in magnetic resonance imaging–selected, acute stroke patients treated with IV-tPA.

Methods—We analyzed the data of acute ischemic stroke patients from a prospective, multicenter, observational study of magnetic resonance imaging–based IV-tPA treatment initiated ≤6 hours from symptom onset. Neurologic deficit on admission was assessed by the National Institutes of Health Stroke Scale. Clinical outcome was assessed after 90 days according to the modified Rankin Scale. Favorable outcome was defined as a modified Rankin Scale score of 0 to 1. Patients were compared regarding baseline parameters. Multivariate regression analysis was used to identify predictors of favorable outcome.

Results—Of 174 patients, 83 (48%) reached a favorable outcome. They were younger (median age, 62 versus 67 years; \( P = 0.001 \)), had a lower National Institutes of Health Stroke Scale score on admission (median, 11 versus 15; \( P < 0.001 \)), and had smaller diffusion-weighted imaging lesions (median, 12.9 versus 20 mL; \( P = 0.001 \)). Perfusion-weighted imaging lesion volumes and onset-to-treatment time were comparable between the groups. Age (\( P = 0.017 \)), National Institutes of Health Stroke Scale score on admission (\( P < 0.001 \)), and diffusion-weighted imaging lesion volume (\( P = 0.047 \)) were identified as independent predictors of favorable outcome.

Conclusions—A lower age, lower National Institutes of Health Stroke Scale score on admission, and smaller pretreatment diffusion-weighted imaging lesion volume were found to be associated with a favorable outcome after treatment with IV-tPA. Pretreatment perfusion lesion volume and onset-to-treatment time were not associated with outcome when patients were selected for IV-tPA by magnetic resonance imaging within 6 hours of symptom onset. (Stroke. 2011;42:00-00.)

Key Words: stroke, acute ■ outcome ■ thrombolytic therapy ■ tissue plasminogen activator ■ MRI, diffusion weighted

Thrombolytic therapy with intravenous, recombinant, tissue-type plasminogen activator (IV-tPA) improves clinical outcome after ischemic stroke.\(^1\) Magnetic resonance imaging (MRI) with perfusion- (PWI) and diffusion-weighted-imaging (DWI) is assumed to enable identification of the tissue at risk of infarction and has been suggested to be used to identify patients likely to benefit from IV-tPA treatment, even within an extended time window.\(^2\) Recently, secondary analyses of the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke study\(^3\) and the Echoplanar Imaging Thrombolytic Evaluation Trial\(^4\) have brought further insights regarding the potential of MRI to guide patient selection and to predict clinical outcome after IV-tPA. Large DWI lesion volumes as well as large and severe PWI lesions were associated with symptomatic intracerebral hemorrhage\(^3\) and poor outcome,\(^3,4\) and the exclusion of patients with very large DWI lesion volumes resulted in a significant benefit of IV-tPA treatment in the Echoplanar Imaging Thrombolytic Evaluation Trial data set, which was not the case for the whole sample.\(^5\)
We aimed to determine whether pretreatment DWI and PWI lesion volumes were associated with outcome in a large case series of patients treated with IV-tPA whose selection for such treatment was based on MRI criteria within 6 hours of symptom onset.

Methods

Patients and Treatment Protocol
We retrospectively analyzed data of acute ischemic stroke patients from a prospective, multicenter, observational study of MRI-based (including PWI and DWI) IV-tPA treatment within 6 hours from symptom onset. For those presenting within 3 hours, patients with acute ischemic stroke were treated with IV-tPA according to approved tPA protocols. For those presenting within 3 to 6 hours, treatment with IV-tPA was performed on an individual basis according to MRI findings (for a detailed description, see the original study).

MRI Protocol and Postprocessing
All MRI studies were performed on 1.5-T clinical whole-body scanners with echoplanar capabilities. The MRI protocol included an axial DWI sequence, a PWI sequence, time-of-flight MR angiography of the intracranial arteries, a T2-weighted sequence, and a T2*-weighted sequence for the exclusion of intracranial hemorrhage, as described previously in detail.

DWI and PWI lesion volumes were calculated at the participating centers by investigators who used locally established software that combined manual delineation and application of predefined thresholds of the apparent diffusion coefficient and maps of the time to peak or mean transit time.

Clinical Assessment and End Points
Severity of neurologic deficit on admission was assessed by the National Institutes of Health Stroke Scale (NIHSS). Clinical outcome was assessed after 90 days according to the modified Rankin Scale by telephone interview. Outcome was dichotomized, and a favorable outcome was defined as a modified Rankin Scale score of 0 to 1, whereas a poor outcome was defined as a modified Rankin Scale score of 4 to 6.

Statistical Analysis
Patients with favorable and unfavorable outcomes were compared with regard to clinical and imaging baseline parameters in nonparametric tests. To identify independent predictors of favorable outcome, we performed a multivariate binary logistic-regression analysis including all parameters with significant differences in the group comparison. Multivariate logistic-regression analysis was also performed after including the same parameters, with poor outcome and mortality as dependent variables. Receiver operating characteristic analysis identified the following thresholds for the prediction of favorable outcome: age <63 years (area under the curve = 0.651, YI = 0.248), NIHSS score on admission <13 (area under the curve = 0.739, YI = 0.364), and DWI lesion volume <16 mL (area under the curve = 0.649, YI = 0.238). The optimal cutoff for the prediction of poor outcome was a DWI lesion volume of >17.5 mL (YI = 0.244). Sensitivity, specificity, and odds ratios for these

Results
We included 174 patients with acute middle cerebral artery stroke examined by MRI and treated with IV-tPA within 6 hours of symptom onset. Of these, 83 (48%) reached a favorable outcome. Patients with a favorable outcome were younger, had a lower NIHSS score on admission, and had smaller, acute DWI lesions than did patients with an unfavorable outcome, whereas PWI lesion volumes were comparable (Table 1). Multiple-regression analysis identified age, NIHSS score on admission, and DWI lesion volume as independent predictors of a favorable outcome (Table 2). In contrast, mortality was predicted by age only, and a poor

### Table 1. Group Comparison (Favorable Versus Unfavorable Outcome)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unfavorable (n=91)</th>
<th>Favorable (n=83)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), years</td>
<td>67 (61–75)</td>
<td>62 (54–69)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>42 (46.2)</td>
<td>28 (33.7)</td>
<td>0.122†</td>
</tr>
<tr>
<td>Side of infarction on left, no. (%)</td>
<td>58 (63.7)</td>
<td>60 (72.3)</td>
<td>0.327†</td>
</tr>
<tr>
<td>NIHSS score on admission, median (IQR)</td>
<td>15 (12–18)</td>
<td>11 (7–14)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Time to tPA, median (IQR), min</td>
<td>160 (125–210)</td>
<td>170 (134–210)</td>
<td>0.286*</td>
</tr>
<tr>
<td>DWI lesion volume, median (IQR), mL</td>
<td>20 (10–48)</td>
<td>12.9 (4–27)</td>
<td>0.001*</td>
</tr>
<tr>
<td>PWI lesion volume, median (IQR), mL</td>
<td>120 (52–216)</td>
<td>99 (38–174)</td>
<td>0.147*</td>
</tr>
<tr>
<td>SICH, no. (%)</td>
<td>3 (3.3)</td>
<td>1 (1.2)</td>
<td>0.622†</td>
</tr>
</tbody>
</table>

*Fisher exact test.
†Mann-Whitney U test.

### Table 2. Predictors of Favorable Outcome Compared With Mortality and Poor Outcome: Multivariate Logistic-Regression Analysis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome (mRS score 0–1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per year</td>
<td>0.962</td>
<td>0.932–0.993</td>
<td>0.017</td>
</tr>
<tr>
<td>NIHSS score on admission, per point</td>
<td>0.861</td>
<td>0.792–0.935</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DWI lesion volume, per mL</td>
<td>0.985</td>
<td>0.970–1.000</td>
<td>0.047</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.090</td>
<td>1.019–1.166</td>
<td>0.012</td>
</tr>
<tr>
<td>NIHSS score on admission, per point</td>
<td>1.099</td>
<td>0.980–1.231</td>
<td>0.105</td>
</tr>
<tr>
<td>DWI lesion volume, per mL</td>
<td>1.001</td>
<td>0.981–1.022</td>
<td>0.888</td>
</tr>
<tr>
<td>Poor outcome (mRS score 4–6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.102</td>
<td>1.051–1.156</td>
<td>1.102</td>
</tr>
<tr>
<td>NIHSS score on admission, per point</td>
<td>1.234</td>
<td>1.108–1.375</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DWI lesion volume, per mL</td>
<td>1.014</td>
<td>1.001–1.028</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Results are shown for a multivariate binary regression analysis with favorable outcome, mortality, and poor outcome as the dependent variable. OR indicates odds ratio; CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; DWI, diffusion-weighted imaging.
parameters in the prediction of favorable outcome are given in Table 3.

The number of patients with a favorable outcome was clearly higher in those with an acute DWI lesion volume <16 mL (59.8% versus 37.0%, \(P = 0.004\); see Figure 1). Dividing the sample by quartiles of DWI lesion volume showed comparable numbers of patients with a favorable outcome within the first 3 quartiles but a clearly decreased proportion of patients with a favorable outcome in the fourth quartile (patients with a DWI lesion >36 mL; see Figure 2).

To test for a potential differential effect of DWI lesion volume with regard to outcome prediction for patients treated at ≤3 or after 3 to 6 hours, we performed an additional multivariate regression analysis including onset to treatment time ≤3 hours or 3 to 6 hours. This analysis revealed no significant effect of onset to treatment time (\(P = 0.288\)).

Discussion

In this large sample of acute stroke patients treated with IV-tPA based on MRI criteria, lower age, less neurologic deficit on admission, and smaller DWI lesion volume predicted a favorable outcome at 90 days. The clinical predictors of favorable outcome are in line with those reported in previous studies.\(^1\)\(^,\)\(^9\) DWI allows the detection of acute ischemic lesions within minutes with high contrast\(^10\) and is assumed to represent mostly already irreversibly damaged tissue.\(^2\) Thus, an association between the amount of already infarcted tissue before initiation of thrombolysis appears quite straightforward. There are previous reports of MRI lesion volumes in patients treated with IV-tPA\(^5\)\(^,\)\(^11\); however, the numbers of IV-tPA–treated patients in those studies were small. In addition, a relation between infarct volume and long-term functional outcome after treatment with IV-tPA\(^12\) was pointed out. Of note, in our study, poor outcome, like favorable outcome, was predicted by DWI lesion volume and NIHSS score on admission, whereas mortality was predicted by age only.

In our sample, a DWI lesion volume threshold of <16 mL performed best with regard to the identification of patients likely to reach a favorable outcome. This threshold is quite similar to the result from a recently published secondary analysis of Echoplanar Imaging Thrombolytic Evaluation Trial data, which showed that the effect of IV-tPA was clearly increased in patients with acute DWI lesion volumes <18 mL, whereas no clear benefit was seen in patients with DWI lesions exceeding 25 mL.\(^5\) However, on the basis of these findings, we cannot designate a definite DWI lesion volume threshold above which thrombolysis appears to be futile or dangerous. The division of our sample by quartiles of DWI lesion volume gives the impression that only in the quartile of patients with the largest DWI lesion volumes (>36 mL) was a clearly decreased proportion of patients with favorable outcomes found. Previous reports also found that large DWI lesions were associated with poor outcomes (the so-called “malignant profile” in the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke study).\(^3\) Accordingly, in the subgroup of patients with a DWI lesion >100 mL, not a single patient had a favorable outcome.

Pretreatment PWI lesion volume was not related to outcome after IV-tPA treatment. This might in large part be explained by the fact that we studied patients treated with IV-tPA. Treatment with thrombolysis is supposed to alter, via reperfusion, the fate of tissue involved in the initial PWI lesion. In line with this, PWI lesions showed a much stronger correlation with clinical outcome in patients without thrombolysis compared with patients treated with IV-tPA.\(^13\)

The outcome after IV thrombolysis is strongly associated with onset-to-treatment time in patients selected on the basis of clinical criteria and noncontrast computed tomography.\(^1\) However, in patients selected for IV-tPA based on PWI and

### Table 3. Sensitivity, Specificity, and Odds Ratios (ORs) for the Prediction of Favorable Outcome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;63 years</td>
<td>0.58 (0.47–0.69)</td>
<td>0.67 (0.56–0.77)</td>
<td>2.789 (1.504–5.169)</td>
</tr>
<tr>
<td>NIHSS score on admission &lt;13</td>
<td>0.64 (0.53–0.74)</td>
<td>0.73 (0.62–0.81)</td>
<td>4.664 (2.454–8.864)</td>
</tr>
<tr>
<td>DWI lesion volume &lt;16 mL</td>
<td>0.59 (0.48–0.70)</td>
<td>0.64 (0.53–0.74)</td>
<td>2.533 (1.374–4.669)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NIHSS, National Institutes of Health Stroke Scale; and DWI, diffusion-weighted imaging.
of recanalization with regard to the prediction of outcome. Thus, we cannot report on the potential impact of vessel occlusion in this sample. We also did not assess a covariate influencing the predictive value of lesion volume, moreover, the location of vessel occlusion might be a relation between small DWI lesions and better outcome. Acute stroke MRI with PWI and DWI lesions on pretreatment MRI are less likely to reach a very large DWI lesions (which are supposed to be associated with poor outcome) from IV-tPA treatment in our study might affect the results. However, the a priori exclusion of patients with large DWI volumes in our treatment protocol did not seem to be an independent predictor of outcome. In patients selected angiographically by the presence of a middle cerebral artery trunk occlusion, the effect of local thrombolysis with pro-urokinase also was not related to the time from symptom onset.14 Patient selection based on vessel or tissue status might overrule onset-to-treatment time with regard to the effect of thrombolysis.

There are limits to our model. The use of MRI to select patients might result in a certain bias, and the exclusion of patients with large DWI volumes in our treatment protocol might affect the results. However, the a priori exclusion of very large DWI lesions (which are supposed to be associated with poor outcome) from IV-tPA treatment in our study would most likely result in an underestimation of a possible relation between small DWI lesions and better outcome. Moreover, the location of vessel occlusion might be a covariate influencing the predictive value of lesion volume, which we cannot judge, as we did not systematically study vessel occlusion in this sample. We also did not assess recanalization; thus, we cannot report on the potential impact of recanalization with regard to the prediction of outcome.

Conclusions
To summarize, our study provides further evidence from a large case series for the association of pretreatment DWI lesion volume and outcome after IV thrombolysis. Patients with small, initial DWI lesion volumes are likely to reach a favorable outcome when treated with IV-tPA, even if the PWI lesion is large. On the other hand, patients with already large DWI lesions on pretreatment MRI are less likely to reach a favorable outcome. Acute stroke MRI with PWI and DWI adds valuable information, which should be considered when thrombolysis is debated, and which may help guide treatment decisions in individual patients with acute ischemic stroke.

Disclosures
None.

References
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治療前の拡散強調画像の病変体積は急性虚血性脳卒中における組織プラスミノゲン活性化因子による静脈内血栓溶解療法後の良好な転帰を予測する

Pretreatment Diffusion-Weighted Imaging Lesion Volume Predicts Favorable Outcome After Intravenous Thrombolysis With Tissue-Type Plasminogen Activator in Acute Ischemic Stroke

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背景および目的: 灌流および拡散強調による脳卒中の磁気共鳴画像（MRI）は、組織プラスミノゲン活性化因子による静脈内血栓溶解療法（IV-tPA）が有益である可能性の高い患者を選別する可能性を示している。本研究は、MRIにて選択した、IV-tPAによる治療を受けた急性脳卒中患者の良好な転帰の予測因子を特定することを目的とした。

方法: 症状発現から6時間以内にMRIに基づいて開始したIV-tPA療法の前向き多施設共同観察研究に参加した急性虚血性脳卒中患者のデータを分析した。入院時の神経障害をNIHSSスコアにより評価した。臨床転帰を90日後に改変Rankin尺度（mRS）により評価して、mRSスコアが0〜1を良好な転帰と定義した。ベースラインのパラメータに関して患者の比較を行い、多変量回帰分析を用いて良好な転帰の予測因子を同定した。

結果: 174例のうち83例（48％）が良好な転帰に達した。これらの患者は年齢が若く（年齢の中央値、62歳対67歳、p = 0.001）、入院時のNIHSSスコアが低く（中央値、11対15、p < 0.001）、拡散強調画像の病変が小さかった（中央値、12.9mL対20mL、p = 0.001）。灌流強調画像の病変体積および発症から治療までの時間は両群で同程度であった。年齢（p = 0.017）、入院時のNIHSSスコア（p < 0.001）、および拡散強調画像の病変体積（p = 0.047）が良好な転帰の独立予測因子として同定された。

結論: 年齢が低いこと、入院時のNIHSSスコアが低いこと、および治療前の拡散強調画像の病変体積が小さいこと、IV-tPAによる治療後の良好な転帰と関連していることが判明した。症状発現から6時間以内にMRIによりIV-tPA療法の対象とする患者を選択した場合、治療前の灌流強調画像の病変体積および発症から治療までの時間と転帰には関連がなかった。

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