Residual Vessel Length on Magnetic Resonance Angiography Identifies Poor Responders to Alteplase in Acute Middle Cerebral Artery Occlusion Patients

Exploratory Analysis of the Japan Alteplase Clinical Trial II

Teruyuki Hirano, MD; Makoto Sasaki, MD; Etsuro Mori, MD; Kazuo Minematsu, MD; Jyoji Nakagawara, MD; Takenori Yamaguchi, MD; for the Japan Alteplase Clinical Trial II Group

Background and Purpose—It remains unknown whether the effects of 0.6 mg/kg alteplase differ with occlusion site of the middle cerebral artery (MCA). We therefore evaluated the effects of 0.6 mg/kg intravenous alteplase in patients with different sites of MCA occlusion.

Methods—An exploratory analysis was made of 57 patients enrolled in the Japan Alteplase Clinical Trial II (J-ACT II), originally designed to evaluate 0.6 mg/kg alteplase in Japanese patients with unilateral occlusion of the MCA (M1 or M2 portion). The residual vessel length (in mm), determined by pretreatment magnetic resonance angiography, was used to reflect the occluded site. The proportions of patients with valid recanalization (modified Mori grade 2 to 3) at 6 and 24 hours and a modified Rankin Scale (mRS) score of 0 to 1 and of 0 to 2 at 3 months were compared between the groups dichotomized according to length of the residual vessel. Multiple logistic-regression models were generated to elucidate the predictors of valid recanalization, mRS 0 to 1, and mRS 0 to 2.

Results—Receiver operating characteristics analysis revealed that 5 mm was the practical cutoff length for dichotomization. In patients with an M1 length <5 mm (n=12), the frequencies of valid recanalization at 6 and 24 hours (16.7% and 25.0%) were significantly lower compared with those (62.1% and 82.8%, respectively) of the 45 patients with a residual M1 length ≥5 mm and an M2 occlusion (P=0.008 for 6 hours, P<0.001 for 24 hours). The proportions of patients who achieved an mRS of 0 to 1 and an mRS of 0 to 2 were also lower for those with an M1 length <5 mm (8.3% and 16.7%, respectively) compared with the other group (57.8% and 68.9%, respectively; P=0.003 for mRS 0 to 1, P=0.002 for mRS 0 to 2). In logistic-regression models, the site of MCA occlusion (<5 mm) was a significant predictor of valid recanalization at 6 and 24 hours and of an mRS of 0 to 1 and of mRS of 0 to 2.

Conclusions—In patients with acute MCA occlusion, a residual vessel length <5 mm on magnetic resonance angiography can identify poor responders to 0.6 mg/kg alteplase.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00412867. (Stroke. 2010;41:2828-2833.)

Key Words: acute ischemic stroke ■ middle cerebral artery occlusion ■ tissue plasminogen activator ■ recanalization ■ magnetic resonance angiography
occlusions, such as those of the internal carotid artery (ICA)\textsuperscript{14,17–20} or tandem ICA/MCA,\textsuperscript{21} carry a greater thrombus burden, whereas distal MCA occlusions are more likely to recanalize with systemic alteplase therapy. A meta-analysis revealed that recanalization, either spontaneous or related to thrombolytic or interventional therapies, is less likely with ICA occlusions.\textsuperscript{22} ICA occlusion has been shown to predict a poorer clinical outcome compared with MCA occlusion.\textsuperscript{14,17–19,20} However, little is yet known about the differences in recanalization rates and response to alteplase among patients with various sites of MCA occlusion. We therefore performed an exploratory analysis of patients with MCA occlusion enrolled in J-ACT II, giving special attention to the residual vessel length as documented on pretreatment MRA.

**Methods**

J-ACT II is a prospective, single-dose, open-label, multicenter, phase IV trial, originally designed to evaluate 0.6 mg/kg alteplase in Japanese patients with unilateral occlusion of the MCA. Details of the trial have been published previously.\textsuperscript{11} In brief, 58 patients with ischemic stroke within 3 hours of onset whose arterial occlusion was identified in the M1 or M2 segment on standardized MRA were enrolled. The results showed that the rates of early and delayed recanalization and a favorable outcome elicited by 0.6 mg/kg alteplase were comparable to the previously reported findings for the regular dose of 0.9 mg/kg.

**Site of MCA Occlusion**

All baseline MRA data were re-evaluated centrally by 2 reviewers, 1 expert neurologist, and 1 expert neuroradiologist (the image-reading panel), all of whom were blinded to all clinical information except the affected side. For patients with M1 occlusions, the site of occlusion was determined in an anteroposterior view on 3-dimensional time-of-flight MRA. The site of M1 occlusion was identified in the M1 or M2 segment on standardized MRA. The residual vessel length measured by 3-dimensional time-of-flight MRA. The site of M1 occlusion was determined in an anteroposterior view as the horizontal distance from the ICA bifurcation to the distal end of the flow signal. The residual vessel length (in mm) was used to reflect the occluded site in the patients with M1 occlusions (Figure 1).

**Evaluation of Recanalization**

MRA was repeated at baseline, 6 hours, and 24 hours after symptom onset. The time allowance for the 6-hour MRA was between the end of alteplase infusion and 8 hours from symptom onset, and that for the 24-hour MRA was between 24 and 36 hours after symptom onset.

Recanalization was evaluated centrally by the image-reading panel according to the modified Mori grade: grade 0, no reperfusion; grade 1, movement of thrombus not associated with any flow improvement; grade 2, partial (branch) recanalization in <50% of the branches in the occluded arterial territory; and grade 3, nearly complete recanalization with reperfusion in ≥50% of the branches in the occluded arterial territory.\textsuperscript{11} The recanalization rate was estimated by regarding grades 2 and 3 as valid recanalization, corresponding to Thrombolysis in Myocardial Infarction grades 2 and 3.

**Clinical Evaluation**

Functional outcome after 3 months was assessed by the modified Rankin Scale (mRS) score. Patients with an mRS of 0 to 1 at 3 months were regarded as having a favorable outcome. In addition, an mRS of 0 to 2 was judged to be indicative of functional independence, that is, avoiding death or dependency.

**Statistical Analysis**

The proportions of patients with valid recanalization at 6 and 24 hours after symptom onset, a favorable outcome (mRS 0 to 1), and functional independence (mRS 0 to 2) at 3 months were compared between the groups dichotomized according to length of residual vessel on MRA. Receiver operating characteristics curves were constructed for the patients with M1 occlusions to make comparisons between vessel length and clinical outcome.

The predictors of valid recanalization at 6 and 24 hours, mRS 0 to 1, and mRS 0 to 2 were assessed by multiple logistic-regression analysis. Knowledge of disease-related factors before alteplase administration, such as time from onset, presence of hypertension, diabetes mellitus, baseline National Institutes of Health Stroke Scale score, and Alberta Stroke Program Early Computed Tomography Score (ASPECTS),\textsuperscript{26} as well as MCA occlusion site, was included in a stepwise regression analysis, for which age and sex were forcibly entered into the model to adjust for their possible confounding effects.

**Table 1. Comparison of Demographic and Baseline Characteristics of the Patients (N=57) According to Site of MCA Occlusion**

<table>
<thead>
<tr>
<th></th>
<th>Total (N=57)</th>
<th>M1 &lt;5 mm (n=12)</th>
<th>M1 ≥5 mm (n=29)</th>
<th>M2 (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD age, y</td>
<td>70.7±11.2</td>
<td>74.6±9.8</td>
<td>66.4±11.7</td>
<td>75.5±8.2</td>
</tr>
<tr>
<td>Female, n</td>
<td>23 (40.4%)</td>
<td>8 (66.7%)</td>
<td>12 (41.4%)</td>
<td>3 (18.8%)</td>
</tr>
<tr>
<td>Baseline NIHSS score (range)</td>
<td>12 (5–22)</td>
<td>17 (5–22)</td>
<td>12 (6–22)</td>
<td>11 (5–21)</td>
</tr>
<tr>
<td>Stroke subtype, n</td>
<td>49 (86.0%)</td>
<td>10 (83.3%)</td>
<td>25 (86.2%)</td>
<td>14 (87.5%)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other/not</td>
<td>3 (5.3%)</td>
<td>0 (0%)</td>
<td>2 (6.9%)</td>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Concomitant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>36 (63.2%)</td>
<td>9 (75.0%)</td>
<td>13 (44.8%)</td>
<td>14 (87.5%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (17.5%)</td>
<td>2 (16.7%)</td>
<td>3 (10.3%)</td>
<td>5 (31.3%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>18 (31.6%)</td>
<td>3 (25.0%)</td>
<td>10 (34.5%)</td>
<td>5 (31.3%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>34 (59.6%)</td>
<td>9 (75.0%)</td>
<td>15 (51.7%)</td>
<td>10 (62.5%)</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>12 (21.1%)</td>
<td>1 (8.3%)</td>
<td>7 (24.1%)</td>
<td>4 (25.0%)</td>
</tr>
<tr>
<td>ASPECTS value (range)</td>
<td>9 (3–10)</td>
<td>8 (3–10)</td>
<td>9 (5–10)</td>
<td>9 (7–10)</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; TIA, transient ischemic attack. Data show the mean (SD), median (interquartile range), or No. (%).
To examine the possible interaction of MCA occlusion site with recanalization for the 3-month outcome, the following recanalization patterns were evaluated with the logistic model in addition to the disease-related factors: (1) model 1, in which recanalization on 6-hour MRA was entered; (2) model 2, in which recanalization on 24-hour MRA was entered; and (3) model 3, in which recanalization within 6 hours and delayed recanalization (that is, arterial occlusion unchanged on 6-hour MRA but recanalized on 24-hour MRA) were entered. Significance was set at $P<0.05$ in all models. The odds ratio (OR) and 95% CIs were also determined. SAS 9.1.3 was used for statistical analyses.

**Results**

Of the 58 patients enrolled in the trial, 41 (70.7%) were evaluated as having an M1 occlusion. Their residual M1 length ranged from 0.0 (origin) to 17.7 mm (distal end), whereas the contralateral M1 length ranged from 19.5 to 32.1 mm (mean±SD, 26.1±3.1 mm). One patient was judged to have no occluded artery on baseline MRA by the image-reading panel and was therefore excluded from the present analysis. The remaining 16 patients (27.6%) were evaluated as having an M2 occlusion. Further analyses were therefore performed on 57 patients with MCA occlusion. Table 1 summarizes these patients’ characteristics.

The cumulative frequency of valid recanalization at 6 and 24 hours increased as the residual M1 length increased. No patient had recanalization on 6-hour MRA that subsequently disappeared on 24-hour MRA. Receiver operating characteristics analysis revealed that valid recanalization differed between the groups dichotomized by residual vessel length at both 6 (Az 0.701, $P=0.027$) and 24 (Az 0.817, $P=0.001$) hours. The optimal cutoff residual M1 lengths for predicting valid recanalization at 6 and 24 hours were the same, 5.3 mm. When the patients with M1 occlusions were divided into 2 groups (residual vessel length <5 mm or ≥5 mm), the frequency of valid recanalization was significantly lower in the patients with a residual M1 length <5 mm (n =12) compared with the combined group with an M1 length ≥5 mm (n =29) and those with M2 occlusions (n =16) ($P=0.008$ for 6 hours, $P<0.001$ for 24 hours; Fisher’s exact test; Figure 2). In logistic-regression models, the site of MCA occlusion (<5 mm) was the only significant predictor of valid recanalization at both 6 (OR =0.076; 95% CI, 0.010 to 0.573) and 24 (OR =0.023; 95% CI, 0.002 to 0.245) hours.

Similarly, receiver operating characteristics analysis demonstrated that the proportions of patients with a favorable outcome (mRS 0 to 1) and functional independence (mRS 0 to 2) were also different among patients with M1 occlusions, with an optimal cutoff length of 5.3 mm. The distribution of scores on the 3-month mRS was different among patients with M1 lengths <5 mm compared with those with an M1 length ≥5 mm and M2 occlusions (Figure 3). On logistic-

**Table 2. Predictors of Favorable Outcome and Functional Independence by Multiple Logistic Regression Analysis**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0–1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (female vs male)</td>
<td>1.011</td>
<td>0.274–3.726</td>
<td>0.9871</td>
</tr>
<tr>
<td>Age (by 1 year)</td>
<td>0.989</td>
<td>0.932–1.050</td>
<td>0.7155</td>
</tr>
<tr>
<td>Time from onset to treatment (by min)</td>
<td>0.998</td>
<td>0.971–1.027</td>
<td>0.9112</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.891</td>
<td>0.146–5.428</td>
<td>0.9006</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.872</td>
<td>0.465–7.528</td>
<td>0.3773</td>
</tr>
<tr>
<td>Baseline NIHSS (by 1 point)</td>
<td>0.878</td>
<td>0.737–1.046</td>
<td>0.1466</td>
</tr>
<tr>
<td>Occluded site (&lt;5 mm vs others)</td>
<td>0.082</td>
<td>0.008–0.812</td>
<td>0.0325</td>
</tr>
<tr>
<td>ASPECTS value (by 1 point)</td>
<td>1.429</td>
<td>0.788–2.592</td>
<td>0.2392</td>
</tr>
<tr>
<td>mRS 0–2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (female vs male)</td>
<td>0.639</td>
<td>0.152–2.689</td>
<td>0.5416</td>
</tr>
<tr>
<td>Age (by 1 year)</td>
<td>1.016</td>
<td>0.952–1.085</td>
<td>0.6290</td>
</tr>
<tr>
<td>Time from onset to treatment (by min)</td>
<td>0.978</td>
<td>0.948–1.008</td>
<td>0.1508</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.607</td>
<td>0.080–4.632</td>
<td>0.6302</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.025</td>
<td>0.235–4.473</td>
<td>0.9743</td>
</tr>
<tr>
<td>Baseline NIHSS (by 1 point)</td>
<td>0.890</td>
<td>0.746–1.061</td>
<td>0.1925</td>
</tr>
<tr>
<td>Occluded site (&lt;5 mm vs others)</td>
<td>0.125</td>
<td>0.020–0.793</td>
<td>0.0274</td>
</tr>
<tr>
<td>ASPECTS value (by 1 point)</td>
<td>2.121</td>
<td>1.082–4.158</td>
<td>0.0285</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale. Table entries in bold-faced type are statistically significant.
In the present exploratory analysis of the J-ACT II cohort, we found that a residual M1 length <5 mm on MRA was a negative predictor of early and delayed recanalizations as well as for a favorable outcome and functional independence at 3 months. Patients with residual M1 lengths <5 mm are poor responders to 0.6 mg/kg alteplase. The site of vessel occlusion was a strong predictor of outcome before systemic alteplase administration.

In a previous magnetic resonance imaging–based, open-label, nonrandomized study, the German Stroke Excellence Network Initiative,16 the reported recanalization rate of proximal MCA occlusions was comparable with distal MCA and M2 occlusions (76.7% for the proximal MCA, 60.0% for the distal MCA, and 87.5% for M2) in the 76 patients treated with thrombolysis. On the other hand, the difference in recanalization rate was significant between an MCA origin and other sites of MCA occlusion in our study. In addition to the different alteplase doses between Europe and Japan, the lack of a clear definition of “proximal” and “distal” MCA might have led to this discrepancy. In our study, cumulative analysis of a clear definition of “proximal” and “distal” MCA might have led to this discrepancy. In our study, cumulative analysis of a clear definition of “proximal” and “distal” MCA might have led to this discrepancy. In our study, cumulative analysis of a clear definition of “proximal” and “distal” MCA might have led to this discrepancy. In our study, cumulative analysis of a clear definition of “proximal” and “distal” MCA might have led to this discrepancy.

Possible interactions between the pretreatment residual vessel length and patterns of recanalization were evaluated by multiple logistic-regression analysis (Table 3). Among the models for favorable outcome, recanalization in model 1, recanalization and baseline National Institutes of Health Stroke Scale score in model 2, and 6-hour and delayed recanalization in model 3 were significant predictors. Among the models for functional independence, recanalization and ASPECTS score in model 1, recanalization and ASPECTS score in model 2, and 6-hour recanalization and ASPECTS score in model 3 were significant predictors.

**Discussion**

In the present exploratory analysis of the J-ACT II cohort, we found that a residual M1 length <5 mm on MRA was a negative predictor of early and delayed recanalizations as well as for a favorable outcome and functional independence at 3 months. Patients with residual M1 lengths <5 mm are poor responders to 0.6 mg/kg alteplase. The site of vessel occlusion was a strong predictor of outcome before systemic alteplase administration.

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Our results paralleled those of Saqqur et al,15 who examined the effects of alteplase by transcranial Doppler. They showed that patients with distal MCA occlusions were more likely to recanalize and were twice as likely to achieve an

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**Table 3. Predictors of Favorable Outcome and Functional Independence by Multiple-Logistic Regression Analysis in 3 Different Models of Posttreatment Recanalization**

<table>
<thead>
<tr>
<th></th>
<th>Model 1: 6-Hour Recanalization Model</th>
<th>Model 2: 24-Hour Recanalization Model</th>
<th>Model 3: 6-Hour and Delayed Recanalization Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>mRS 0–1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (female vs male)</td>
<td>0.846 0.138–3.245</td>
<td>0.989 0.605–1.823</td>
<td>0.814 0.138–3.245</td>
</tr>
<tr>
<td>Age (by 1 year)</td>
<td>1.066 0.138–3.245</td>
<td>0.456 0.138–3.245</td>
<td>1.914 0.138–3.245</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.341 0.138–3.245</td>
<td>2.919 0.138–3.245</td>
<td>2.011 0.138–3.245</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.976 0.138–3.245</td>
<td>1.976 0.138–3.245</td>
<td>1.976 0.138–3.245</td>
</tr>
<tr>
<td>Recanalization within 6 h</td>
<td></td>
<td>3.110 0.138–3.245</td>
<td>3.110 0.138–3.245</td>
</tr>
<tr>
<td>Recanalization within 24 h</td>
<td></td>
<td>3.572 0.138–3.245</td>
<td>3.572 0.138–3.245</td>
</tr>
<tr>
<td>Delayed recanalization</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IHSS indicates National Institutes of Health Stroke Scale. Table entries in bold-faced type are statistically significant.
mRS of 0 to 1 than were those with proximal MCA occlusions. Their transcranial Doppler–based definitions of the occluded site in the MCA and of complete recanalization differed from ours, however. The proportions of patients achieving an mRS of 0 to 1 decreased with more proximal occlusions: distal MCA, 52%; proximal MCA, 25%; tandem ICA/MCA, 21%; and terminal ICA, 18%.

What are the potential reasons for different outcomes between patients with residual M1 lengths <5 mm and others? In terms of thrombus size and the association of thrombi with atherosclerosis, clot size is bigger in patients with a residual M1 length <5 mm, and there may be differences in clot composition between proximal and distal M1 occlusions. A greater propensity for lysis by alteplase compared with platelet-rich clots. Relative to other stroke subtypes, the rate of complete recanalization has been reported to be higher in patients with cardioembolic stroke. Although there was no statistical difference, atherosclerotic occlusion was found more frequently in patients with proximal M1 occlusions (16.7% in M1 <5 mm; 6.7% in M1 ≥5 mm and M2, \( P = 0.281 \)).

Another possible explanation concerns the number of perforating arteries originating from the M1 portion. Patients with a residual M1 length <5 mm seldom spare perforators that allow a continuous blood stream. Effective delivery and distribution of alteplase into the clot may thus become severely disturbed. Experimental studies have demonstrated that the fibrinolytic rate is dependent on the pressure gradient to which the clot is exposed.

In our first logistic-regression model including only pretreatment factors, the site of vessel occlusion (M1 <5 mm or other) was a strong predictor of 3-month outcome. Once important posttreatment factors, like early and/or delayed recanalization, were included in the second of the 3 different models, the site of vessel occlusion no longer remained as significant. This is reasonable, because the site of vessel occlusion before treatment with alteplase was strongly correlated to posttreatment recanalization. To achieve an mRS of 0 to 1, the key is recanalization immediately after thrombolysis, as repeatedly reported. Using the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register database, Karthonova et al also noted that disappearance of a hyperdense MCA signs, an indirect marker of recanalization on computed tomography, was significantly related to functional independence and survival.

On the other hand, an mRS of 0 to 2 might be achieved independently of recanalization if the patient has good collateral flow, indicated by a high ASPECTS value. Regarding the influence of pretreatment ASPECTS, the PRO-UKRINASE for Acute Cerebral Thromboembolism II trial demonstrated that patients with ASPECTS scores >7 were 3 times more likely to achieve an mRS of 0 to 2.

It might be reasonable to modify our treatment strategy according to the MRA information concerning the site of pretreatment vessel occlusion. We speculate that patients with M1-origin occlusions (residual vessel length <5 mm) as well as those with ICA occlusions may be potential candidates for rescue interventional therapies, such as intra-arterial thrombolysis and mechanical thrombectomy, should intravenous thrombolysis fail to achieve recanalization and reperfusion.

The present study has several limitations. First, the number of patients was relatively small because the target population was strictly limited to MRA-documented M1 or M2 occlusions. Second, we could not evaluate collateral status because MRA was the only required modality for imaging. Good collateral flow up to the distal end of the clot might have accelerated recanalization. Third, the alteplase dose was 0.6 mg/kg, which is the specified dose in the Japanese license.

The recanalization rate in patients with a residual M1 length <5 mm could have been improved with the 0.9 mg/kg dose of alteplase, although J-ACT II demonstrated efficacy in terms of vascular and clinical outcomes.

In conclusion, the effect of 0.6 mg/kg intravenous alteplase differs according to the MRA-documented site of MCA occlusion. In patients with acute MCA occlusions, a residual M1 length <5 mm on MRA can identify poor responders to 0.6 mg/kg alteplase.

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用磁共振血管造影残留血管长度确定急性大脑中动脉闭塞患者
阿替普酶治疗的预后
日本阿替普酶临床试验Ⅱ的探索性分析

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背景和目的：目前还不清楚阿替普酶(0.6 mg/kg)的作用效果是否会因大脑中动脉闭塞位置的不同而有差异，本试验对大脑中动脉闭塞部位不同的患者进行阿替普酶(0.6 mg/kg)静脉溶栓治疗，评估其疗效是否不同。

方法：以日本阿替普酶临床试验II(J-ACT II)中的57名患者为研究对象进行探索性分析研究，评估阿替普酶(0.6 mg/kg)对单侧大脑中动脉闭塞(M1或M2段)患者的治疗效果。在治疗前先用磁共振血管造影(MRA)检查残留血管长度(以毫米计)以反应血管闭塞的位置，然后根据残留血管长度将病人分为两组，比较两组在6小时和24小时的有效再通率(改良Mori评分2-3级)，及其3个月时改良Rankin量表(mRS)评分达到0-1和0-2的患者比例，并用多重逻辑回归模型来阐明mRS评分达到0-1和0-2时有效再通的预测因子。

结果：受试者操作特征(ROC)分析显示，区分阿替普酶治疗临床预后的残留血管长度界值为5 mm。在M1段残留血管长度<5 mm的患者中(n=12)，6小时和24小时的有效再通率(16.7%和25.0%)明显低于其余45名包括M1段残留血管长度≥5 mm以及M2段阻塞在内的患者的相应再通率(分别为62.1%和82.8%，6小时P=0.008；24小时P=0.001)。M1段残留长度<5 mm的患者中，mRS评分达到0-1和0-2分的比例(分别为8.3%和16.7%)也低于其余患者的比例(分别为57.8%和68.9%；mRS评分0-1组，P=0.003；mRS评分0-2组，P=0.002)。逻辑回归模型表明，大脑中动脉闭塞位置(<5 mm)是评估6小时和24小时能否有效再通，mRS评分能达到0-1和0-2的重要预测因子。

结论：在急性大脑中动脉闭塞的患者中，阿替普酶(0.6 mg/kg)对MRA残留血管长度<5 mm的患者溶栓效果不佳。

关键字：急性缺血性卒中，大脑中动脉闭塞，组织型纤溶酶原激活剂，再通，磁共振血管造影

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急性缺血性卒中患者能否进行重组组织型纤溶酶原激活剂静脉溶栓治疗，需经过严格的筛选。在阿替普酶静脉溶栓治疗中，卒中严重程度、收缩压水平、CT中早期缺血性改变、持续性动脉闭塞、卒中亚型和溶栓治疗的时间等因素已被反复证明是预示不良预后的独立预测因子。而日本阿替普酶II期临床试验(J-ACT II)也清楚表明：对于磁共振血管造影(MRA)诊断出的脑中动脉闭塞患者，闭塞动脉的再通情况是评估3个月时阿替普酶疗效最有力的预测因子。因此有关再通阻力的早期预测因子可能是决定患者能否进行进一步再灌注溶栓治疗的筛选指标。

前期血管造影、经颅多普勒和MRA的研究结果也表明，越是近端的阻塞，如颈内动脉、颈内动脉和大脑中动脉相连处的阻塞，血栓负荷越大，更不易再通；而大脑中动脉远
端闭塞的患者经阿替普酶系统治疗后更容易再通。一项 meta 分析显示无论是自发性再通还是药物溶栓或介入治疗后的再通 [22]，都很少出现在颈内动脉阻塞的再通上。试验表明：颈内动脉阻塞的临床预后比大脑中动脉阻塞的临床预后更差 [14,17,19,20]。但是，对于大脑中动脉各种阻塞位置的患者，阿替普酶的溶栓疗效及再通率的差异性仍然知之甚少。因此，我们对 J-ACT II 试验中大脑中动脉闭塞的患者进行了探索性分析，重点观察其治疗前的 MRA 显示的残留血管长度。

方法

J-ACT II 是一个前瞻性、单剂量、开放的、多中心的 IV 期试验，用于评估阿替普酶 (0.6 mg/kg) 对单侧大脑中动脉阻塞患者的治疗效果。有关该试验的细节已有详细 [11]。简言之，对发病 3 小时内标准化 MRA 上显示阻塞部位为 M1 或者 M2 段的 58 名缺血性卒中患者进行研究分析，结果显示，阿替普酶 (0.6 mg/kg) 的早期或延迟再通率和预后良好率不低于以前用常规剂量 0.9 mg/kg 的研究结果。

大脑中动脉闭塞的位置

由一位知名的神经科专家和一位神经放射科专家组成阅片专家组，对所有病人的 MRA 影像数据进行重新评估。两人对所有病人的临床信息均不了解，以排除偏倚。对于 M1 段阻塞的患者，用三维时间飞跃法 MRA(3D-TOF-MRA) 的前后视图中颈内动脉转折处到远端流动信号的终止点作为水平距离来确定 M1 段阻塞位置。用残留血管长度（以 mm 计）来反映 M1 段阻塞患者的阻塞位置（图 1）。

血栓再通的评估

患者在症状出现时、症状出现后 6 小时和 24 小时分别做 MRA。6 小时 MRA 的时间范围为阿替普酶灌注结束到症状出现后的 8 小时之间，24 小时 MRA 的时间范围为症状出现后的 24 小时与 36 小时之间。

根据改良 Mori 评分等级，阅片专家组对血栓再通情况进行集中分级：0 级，不能再灌注；1 级，血栓的运动与血流增加无关；2 级，部分再通，<50% 动脉阻塞部位分支再灌注；3 级，几乎完全再通，≥50% 动脉阻塞部位分支再灌注 [11]。将 2 级和 3 级视为有效再通，并据此评估再通率，这与心肌梗塞溶栓分级的 2 级与 3 级类似。

临床评估

用改良 Rankin 量表 (mRS) 评分评估 3 个月后的恢复效果，3 个月 mRS 评分为 0-1 的患者视为预后良好。mRS 评分为 0-2 视为功能独立，即已脱离生命风险或依赖。

统计分析

根据 MRA 中残留血管长度将患者分为两组，表 1 根据大脑中动脉不同梗塞部位对患者（N=57）进行人口学和基线特征的比较

<table>
<thead>
<tr>
<th>总数</th>
<th>M1&lt;5 mm</th>
<th>M1≥5 mm</th>
<th>M2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=57)</td>
<td>(n=12)</td>
<td>(n=29)</td>
<td>(n=16)</td>
</tr>
<tr>
<td>年龄，均值±标准差，岁</td>
<td>70.7±11.2</td>
<td>74.6±9.8</td>
<td>66.4±11.7</td>
</tr>
<tr>
<td>女性，人数</td>
<td>23 (40.4%)</td>
<td>8 (66.7%)</td>
<td>12 (41.4%)</td>
</tr>
<tr>
<td>基线 NIHSS 评分 (范围)</td>
<td>12 (5–22)</td>
<td>17 (5–22)</td>
<td>12 (6–22)</td>
</tr>
<tr>
<td>卒中亚型，人数</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>心源性梗塞</td>
<td>49 (86.0%)</td>
<td>10 (83.3%)</td>
<td>25 (86.2%)</td>
</tr>
<tr>
<td>动脉粥样硬化</td>
<td>5 (8.8%)</td>
<td>2 (16.7%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>其它 / 原因未明</td>
<td>3 (5.3%)</td>
<td>0 (0%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>伴发病</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>高血压，人数</td>
<td>36 (63.2%)</td>
<td>9 (75.0%)</td>
<td>13 (44.8%)</td>
</tr>
<tr>
<td>糖尿病</td>
<td>10 (17.5%)</td>
<td>2 (16.7%)</td>
<td>3 (10.3%)</td>
</tr>
<tr>
<td>血脂异常</td>
<td>18 (31.6%)</td>
<td>3 (25.0%)</td>
<td>10 (34.5%)</td>
</tr>
<tr>
<td>房颤</td>
<td>34 (59.6%)</td>
<td>9 (75.0%)</td>
<td>15 (51.7%)</td>
</tr>
<tr>
<td>既往卒中 / TIA</td>
<td>12 (21.1%)</td>
<td>1 (8.3%)</td>
<td>7 (24.1%)</td>
</tr>
<tr>
<td>ASPECTS 分值 (范围)</td>
<td>9 (3–10)</td>
<td>8 (3–10)</td>
<td>9 (5–10)</td>
</tr>
<tr>
<td>NIHSS，国立卫生研究院卒中量表；TIA，短暂性脑缺血发作；数据为均值 (标准差)、中位数 (四分位距)、或人数 (%).</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
比较两组在症状出现后6小时和24小时的有效再通率，统计在3个月时预后良好(mRS为0-1)与功能独立(mRS为0-2)的患者比例。对M1段梗塞患者构建受试者操作特征(ROC)曲线，研究残留血管长度和临床预后之间的关系。

用多重逻辑回归法来评估6小时和24小时有效再通的预测因子：mRS评分0-1和mRS评分0-2。对阿替普酶治疗前已知的疾病相关因素，诸如发作时间、高血压、糖尿病、以国立卫生研究院卒中量表(NIHSS)基线评分和Alberta卒中项目早期CT评分(ASPECTS)基线得分[6]，以及大脑中动脉梗塞位置进行逐步回归分析，所选患者的性别和年龄也强制进入模型中来修正其可能产生的混杂。

为了检测大脑中动脉梗塞位置是否与3个月时的预后有关，本研究利用去除疾病相关因素的逻辑模型对以下再通模式进行评估：
1. 模式1，6小时MRA显示大脑中动脉再通；
2. 模式2，24小时MRA显示大脑中动脉再通；
3. 模式3，MRA显示6小时内延迟再通(也就是说，大脑中动脉梗塞在6小时没有变化但是在24小时再通)。所有的模式设定在P<0.05时有意义。计算优势比(OR)值及95%可信区间(CI)，用SAS 9.1.3软件进行统计学分析。

结果

在58例受试患者中，41例(70.7%)属于M1位置的梗塞，他们残留的M1段长度从0.0(起始端)到17.7 mm(远端)，对侧的M1段长度从19.5到32.1 mm(均值±标准差，26.1±3.1 mm)。根据MRA结果，阅片专家组发现有一位患者没有发生动脉梗塞，因此该患者被排除在当前分析外。剩余的16例(27.6%)为M2位置的梗塞。对57例大脑中动脉梗塞的患者进行进一步的分析，患者的特征见表1。

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进行比较，残留血管长度M1<5 mm(n=12)患者组的有效再通率明显低于M1长度≥5 mm(n=29)和M2段梗塞患者组(n=16)的再通率(6小时P=0.008，24小时P<0.001；Fisher’s精确检验；图2)。逻辑回归分析表明：大脑中动脉阻塞位置(<5 mm)是预测6小时(OR=0.076；95% CI, 0.010-0.573)和24小时(OR=0.023；95% CI, 0.002-0.245)能否有效再通的唯一有统计学意义的因素。

同样，ROC分析显示：在M1段梗塞的患者中，患者预后良好(mRS为0-1)和功能独立(mRS为0-2)的比例也不同，最适临界长度也是5.3 mm。M1长度<5 mm患者与M1长度≥5 mm和M2段梗塞患者，在3个月时的mRS评分分布也不同(图3)。在包括了阿替普酶治疗前已存在疾病相关因素的逻辑回归分析结果显示：残留M1长度<5 mm是预测良好预后的唯一有统计学差异的预测因素(OR=0.082；95% CI, 0.008-0.812；表2)。残留M1长度<5 mm (OR=0.125；95% CI, 0.020-0.793)伴高ASPECTS值(OR=2.121；95% CI, 1.082-4.158)与3个月时功能独立有显著性关联(表2)。

本试验用多重逻辑回归分析法研究治疗前的残留血管长度与再通模式之间可能的相关性(表3)，在预后良好的模型中，模式1的再通、模式2的再通和NIHSS基线评分、模式3的6小时延迟再通，均为有统计学意义的预测因素。在功能独立的模型中，模式1的再通和ASPECTS得分、模式2的再通和ASPECTS得分、模式3的6小时延迟再通和ASPECTS得分，也均为有统计学意义的预测因素。

### 讨论

目前，根据J-ACT II探索性分析，我们发现MRA中残留M1长度<5 mm对于早期或延迟再通以及3个月时良好预后和功能独立来说是一个负向预测因子。残留M1长度<5 mm患者对阿替普酶(0.6 mg/kg)的反应不佳。在阿替普酶系统治疗前，血管阻塞的位置是评估其疗效的一个有力预测因子。

在之前的以MRI为基础的、开放的、非随机试验——德国卒中精英网络倡议计划(German Stroke Excellence Network Initiative)[16]中，结果表明在用溶栓治疗的76名患者中，大脑中动脉近端梗塞的再通
率与远端大脑中动脉和M2段梗塞的再通率相似（大脑中动脉近端为76.7%，远端大脑中动脉为60.0%，M2段为87.5%）。但是本研究中大脑中动脉起始部和大脑中动脉其他位置梗塞的再通率不同，且有统计学意义。这种差异除了与欧洲和日本阿替普酶使用剂量和时间有关外，还可能与对“近端”和“远端”大脑中动脉的定义不同有关。本研究中，ROC分析的累计分析表明M1段近端和远端的临界长度是5mm。

本试验的结果与Saqqur等人[15]的研究结果一致，该研究通过经颅多普勒分析阿替普酶的疗效，结果表明大脑中动脉远端梗塞患者比近端梗塞患者再通的可能性大，获得mRS评分0-1的患者也是后者的两倍。然而，该试验表明大脑中动脉起始部和大脑中动脉其他位置梗塞的再通率不同，且有统计学意义。这种差异除了与欧洲和日本阿替普酶使用剂量不同有关外，还可能与对“近端”和“远端”大脑中动脉的定义不同有关。本研究中，ROC分析的累计分析表明M1段近端和远端的临界长度是5mm。

总的来说，0.6mg/kg阿替普酶治疗大脑中动脉梗塞的疗效因MRA影像上梗塞位置的不同而有所差异。而且可以确定的是：在急性大脑中动脉梗塞的患者中，MRA显示M1段残留长度<5mm的患者对0.6mg/kg剂量的阿替普酶反应不佳。

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