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 score 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.

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Key Words: acute ischemic stroke • middle cerebral artery occlusion • tissue plasminogen activator • recanalization • magnetic resonance angiography

Intravenous thrombolysis with recombinant tissue plasminogen activator is effective in carefully selected patients with acute ischemic stroke. Among patients treated with intravenous alteplase, stroke severity, systolic hypertension, early ischemic changes on computed tomography, persistent arterial occlusion, stroke subtype, and time to thrombolytic treatment have been repeatedly demonstrated as independent predictors of poor outcome. Previous angiographic, transcranial Doppler, and MRA studies have demonstrated that recanalization of the occluded artery represented the most powerful predictor of a favorable outcome at 3 months in selected patients with magnetic resonance angiography (MRA)–documented middle cerebral artery (MCA) occlusions. Information concerning early predictors of recanalization resistance may thus be useful for selecting patients to receive more aggressive reperfusion strategies.

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occlusions, such as those of the internal carotid artery (ICA) or tandem ICA/MCA, 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. ICA occlusion has been shown to predict a poorer clinical outcome compared with MCA occlusion. 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. 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 IV trial, originally designed to evaluate 0.6 mg/kg alteplase.

**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 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. 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 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), 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>Site of MCA Occlusion</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>5 (8.8%)</td>
<td>2 (16.7%)</td>
<td>2 (6.9%)</td>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>3 (5.3%)</td>
<td>0 (0%)</td>
<td>2 (6.9%)</td>
<td>1 (6.3%)</td>
</tr>
</tbody>
</table>

**Concomitant diseases**

- Hypertension, n 36 (63.2%) 9 (75.0%) 13 (44.8%) 14 (87.5%)
- Diabetes 10 (17.5%) 2 (16.7%) 3 (10.3%) 5 (31.3%)
- Dyslipidemia 18 (31.6%) 3 (25.0%) 10 (34.5%) 5 (31.3%)
- Arrial fibrillation 34 (59.6%) 9 (75.0%) 15 (51.7%) 10 (62.5%)
- Previous stroke/TIA 12 (21.1%) 1 (8.3%) 7 (24.1%) 4 (25.0%)
- ASPECTS value (range) 9 (3–10) 8 (3–10) 9 (5–10) 9 (7–10)

NIHSS indicates National Institutes of Health Stroke Scale; TIA, transient ischemic attack. Data show the mean (SD), median (interquartile range), or No. (%).

**Figure 1. Measurement of residual vessel length in patients with M1 occlusions. Examples are shown of 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.**
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 imagerading 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. The distribution of the rate of valid recanalization was significantly lower in patients with a residual M1 length \(<5\) mm compared with those with an M1 length \(\geq 5\) mm. Similar results were obtained when the frequency of functional independence, ie, an mRS of 0 to 2, was investigated. Data were not obtained in 1 patient each with a residual M1 length \(<5\) mm and M2. These patients were assigned an mRS \(\geq 3\).

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Rate of valid recanalization at 6 and 24 hours by site of vessel occlusion. The rate of valid recanalization was significantly lower in patients with a residual M1 length \(<5\) mm at both 6 and 24 hours.

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 \(\geq 5\) mm and M2 occlusions (Figure 3). On logistic-

![Figure 3](http://stroke.ahajournals.org/)

**Figure 3.** Distribution of scores at 3 months on the mRS scale by site of vessel occlusion. The proportion of patients with a favorable outcome, ie, an mRS score of 0 to 1, was significantly lower in patients with a residual M1 length \(<5\) mm. Similar results were obtained when the frequency of functional independence, ie, an mRS of 0 to 2, was investigated. Data were not obtained in 1 patient each with a residual M1 length \(<5\) mm and M2. These patients were assigned an mRS \(\geq 3\).

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**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><strong>mRS 0–1</strong></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>0.9096</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><strong>mRS 0–2</strong></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, 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 followed by receiver operating characteristics analysis demonstrated that <5 mm was the practical cutoff length between proximal and distal sites within the M1 portion.

Our results paralleled those of Saqqur et al, 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
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.23 Fibrin-rich clots have been shown to display a greater propensity for lysis by alteplase compared with platelet-rich clots.19 Relative to other stroke subtypes, the rate of complete recanalization has been reported to be higher in patients with cardioembolic stroke.10 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.24

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 25–29 Using the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry database, Kharitonova et al20 also noted that disappearance of a hyperdense MCA sign, 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.31 Regarding the influence of pretreatment ASPECTS, the Pro-Urokinase 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 2.32 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.33 Third, the alteplase dose was 0.6 mg/kg, which is the specified dose in the Japanese license.34 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.11

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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Eploratory 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

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)。M1 段患者分为两组 : 残留血管长度 <5 mm 的患者 (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 段阻塞在内的确诊患者的有效再通。M1 段残留血管长度 <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 评分达到 0-1 和 0-2 分的比例 (P=0.003; mRS 评分 0-2 组, P=0.002), 总体回归模型表明，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 评分能否达到 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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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述 [11]。简言之，对发病 3 小时内标准 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的水平距离来确定阻塞位置，用残留血管长度（以 mm 计）来反应 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阻塞部位对患者 (N=57) 进行人口学和基线特征的比较

<table>
<thead>
<tr>
<th>总数 (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>年龄，均值±</td>
<td>70.7±11.2</td>
<td>74.6±9.8</td>
<td>66.4±11.7</td>
</tr>
<tr>
<td>标准差，岁</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>性别:人数</td>
<td>23 (40.4%)  8 (66.7%) 12 (41.4%) 3 (18.8%)</td>
<td>21 (72.4%)  6 (20.7%) 9 (31.0%) 1 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>基线 NIHSS 评分 (范围)</td>
<td>12 (5–22) 17 (5–22) 12 (6–22) 11 (5–21)</td>
<td>12 (5–22) 17 (5–22) 12 (6–22) 11 (5–21)</td>
<td></td>
</tr>
<tr>
<td>发生率</td>
<td>49 (86.0%) 10 (83.3%) 25 (86.2%) 14 (87.5%)</td>
<td>49 (86.0%) 10 (83.3%) 25 (86.2%) 14 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>心源性梗塞</td>
<td>5 (8.8%) 2 (16.7%) 2 (6.9%) 1 (6.3%)</td>
<td>5 (8.8%) 2 (16.7%) 2 (6.9%) 1 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>动脉粥样硬化</td>
<td>3 (5.3%) 0 (0%) 2 (6.9%) 1 (6.3%)</td>
<td>3 (5.3%) 0 (0%) 2 (6.9%) 1 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>其它 / 原因不明</td>
<td>36 (63.2%) 9 (75.0%) 13 (44.8%) 14 (87.5%)</td>
<td>36 (63.2%) 9 (75.0%) 13 (44.8%) 14 (87.5%)</td>
<td></td>
</tr>
<tr>
<td>糖尿病</td>
<td>10 (17.5%) 2 (16.7%) 3 (10.3%) 5 (31.3%)</td>
<td>10 (17.5%) 2 (16.7%) 3 (10.3%) 5 (31.3%)</td>
<td></td>
</tr>
<tr>
<td>血脂异常</td>
<td>18 (31.6%) 3 (25.0%) 10 (34.5%) 5 (31.3%)</td>
<td>18 (31.6%) 3 (25.0%) 10 (34.5%) 5 (31.3%)</td>
<td></td>
</tr>
<tr>
<td>房颤</td>
<td>34 (59.6%) 9 (75.0%) 15 (51.7%) 10 (62.5%)</td>
<td>34 (59.6%) 9 (75.0%) 15 (51.7%) 10 (62.5%)</td>
<td></td>
</tr>
<tr>
<td>既往卒中/TIA</td>
<td>12 (21.1%) 1 (8.3%) 7 (24.1%) 4 (25.0%)</td>
<td>12 (21.1%) 1 (8.3%) 7 (24.1%) 4 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>ASPECTS 分值 (范围)</td>
<td>9 (3–10) 8 (3–10) 9 (5–10) 9 (7–10)</td>
<td>9 (3–10) 8 (3–10) 9 (5–10) 9 (7–10)</td>
<td></td>
</tr>
</tbody>
</table>
| 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) 和中位数 (四分位距)。
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。

用多重逻辑回归分析法来评估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(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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### 表2 用多重逻辑回归分析法进行良好预后和功能独立的预测因子

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>性别(女性 vs 男性)</td>
<td>1.011</td>
<td>0.274–3.726</td>
<td>0.9871</td>
</tr>
<tr>
<td>年龄(以岁计)</td>
<td>0.989</td>
<td>0.932–1.050</td>
<td>0.7155</td>
</tr>
<tr>
<td>从发病到治疗的时间(以分钟计)</td>
<td>0.998</td>
<td>0.971–1.027</td>
<td>0.9112</td>
</tr>
<tr>
<td>糖尿病</td>
<td>0.891</td>
<td>0.146–5.428</td>
<td>0.9066</td>
</tr>
<tr>
<td>高血压</td>
<td>1.872</td>
<td>0.465–7.528</td>
<td>0.3773</td>
</tr>
<tr>
<td>基线NIHSS(以分计)</td>
<td>0.878</td>
<td>0.737–1.046</td>
<td>0.1466</td>
</tr>
<tr>
<td>梗塞位置(&lt;5 mm vs 其它情况)</td>
<td>0.082</td>
<td>0.008–0.812</td>
<td>0.0325</td>
</tr>
<tr>
<td>ASPECTS值(以分计)</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>性别(女性 vs 男性)</td>
<td>0.639</td>
<td>0.152–2.689</td>
<td>0.5416</td>
</tr>
<tr>
<td>年龄(以岁计)</td>
<td>1.016</td>
<td>0.952–1.085</td>
<td>0.6290</td>
</tr>
<tr>
<td>从发病到治疗的时间(以分钟计)</td>
<td>0.978</td>
<td>0.948–1.008</td>
<td>0.1508</td>
</tr>
<tr>
<td>糖尿病</td>
<td>0.860</td>
<td>0.080–4.632</td>
<td>0.6302</td>
</tr>
<tr>
<td>高血压</td>
<td>1.025</td>
<td>0.235–4.473</td>
<td>0.9743</td>
</tr>
<tr>
<td>基线NIHSS(以分计)</td>
<td>0.890</td>
<td>0.746–1.061</td>
<td>0.1925</td>
</tr>
<tr>
<td>梗塞位置(&lt;5 mm vs 其它情况)</td>
<td>0.125</td>
<td>0.020–0.793</td>
<td>0.0274</td>
</tr>
<tr>
<td>ASPECTS值(以分计)</td>
<td>2.121</td>
<td>1.082–4.158</td>
<td>0.0285</td>
</tr>
</tbody>
</table>

NIHSS，国立卫生研究院卒中量表，表中的黑体字有统计学意义。
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已经显示：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) 与高 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）。

本文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。

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### 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
多项研究表明，要达到最优预后的有力因素。但是，一旦有重要的治疗后遗症，立即再通的可能^性大，获得 mRS 评分 0-1 的患者也是后者的两倍。然而，该研究发现，多数患者对大脑中动脉梗塞位置和完全再通的定义与本研究不同，使得达到 mRS 评分 0-1 的患者比例降低，近端梗塞的患者比例增多，大脑中动脉远端梗塞占 52%；大脑中动脉近端梗塞占 25%；颈内动脉/大脑中动脉相连接处占 21%；颈内动脉末端占 18%。

M1 段残留长度 <5 mm 的患者与其他患者治疗效果不同的原因有哪些呢？从血栓大小和血栓与动脉粥样硬化的联系上讲，M1 段 <5 mm 的患者血栓更大，M1 段近端梗塞和远端梗塞的血栓成分与可能不同^21]。研究发现用阿替普酶溶栓，富含纤维蛋白的血栓比富含血小板的血栓更易于溶解^10]。据报道，心源性卒中患者比其它亚型的卒中患者的完全再通率高^10]。虽然没有统计学差异，但是研究发现近端 M1 梗塞患者中，动脉粥样硬化梗塞的比率较高 (M1 段 <5 mm 占 16.7%；M1 段 ≥5 mm 和 M2 占 6.7%，P=0.281)。

另外，治疗效果的不同还可能与源自 M1 段的穿通支动脉的数量有关。M1 段残留 <5 mm 的患者很少有穿通支动脉使血液流畅，从而不能够手术的阿替普酶输送和分配到凝块位置。而且试验结果显示，血栓溶栓率与凝块所在处的压力梯度有关^24]

在脑部包括治疗前因素的逻辑回归分析中，血管梗塞的位置 (M1 段 <5 mm 或其他情况) 是预测 3 个月预后的重要因素。但是，一旦有重要的治疗后因素，如早期和(或)延迟再通(包括在模式 2 中)，血管梗塞的位置便不再重要。这是因为阿替普酶治疗前血管梗塞的位置与治疗后的再通有很大的联系。多项研究显示，要达到 mRS 评分 0-1，关键是溶栓后能够立即再通^25-29]。Kharitonova 等人^10] 对国际卒中溶栓治疗登记数据库的数据进行研究，结果表明 CT 上高密度信号 (血栓再通的一个间接指标) 的消失，与治疗后功能独立和存活率有密切联系。

另一方面，如果病人有良好的侧支循环，即 ASPECTS 值较高，即使梗塞血管不能再通，mRS 评分也可以达到 0-2^31]。前尿激酶治疗急性脑梗塞的 II 期试验涉及对治疗前 ASPECTS 值的影响，结果表明 ASPECTS 得分 >7 的患者 mRS 评分达到 0-2 的可能性比其他患者高三倍^32]。因此，根据治疗前 MRA 显示的血管梗塞位置来调整治疗策略是可行的。我们推断，M1 起始端梗塞 (残留血管长度 <5 mm) 和颈内动脉梗塞的患者可能适合进行介入治疗，例如动脉内溶栓和机械性溶栓，静脉溶栓不能达到再通和再灌注的效果。

本研究也存在一定的局限性。第一，由于研究人群严格限制在 MRA 影像记录为 M1 或 M2 梗塞的患者，所以受试者的数量相对较小。第二，由于 MRA 是唯一的一种影像学检查，所以我们无法评估侧支循环的情况，而较好的侧支循环可以使血流达到血栓的远端，这可能会加速血管的再通^33]。第三，J-ACT II 试验中阿替普酶的剂量仍然是日本许可的指定剂量 0.6 mg/kg^34]。虽然本试验表明了血管再通和临床预后的关系，但用 0.9 mg/kg 的阿替普酶剂量可以使残留 M1 段 <5 mm 患者的再通率提高^11]

总之，0.6 mg/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：在急性脑中动脉梗塞的患者中，MRA 显示 M1 段残留长度 <5 mm 的患者对 0.6 mg/kg 剂量的阿替普酶反应不佳。

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