Clinical and Magnetic Resonance Imaging Predictors of Very Early Neurological Response to Intravenous Thrombolysis in Patients With Middle Cerebral Artery Occlusion

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Background—The early identification of patients who are unlikely to respond to intravenous recombinant tissue plasminogen activator (IV-tPA) could help select candidates for additional intra-arterial therapy or add-on antithrombotic drugs during the acute stage of stroke. Given that very early neurological improvement (VENI) is a reliable surrogate of early recanalization, we assessed the clinical and magnetic resonance imaging predictors of lack of VENI.

Methods and Results—We reviewed consecutive ischemic stroke patients with middle cerebral artery occlusion and treated within 4.5 hours by IV-tPA between 2003 and 2012 in our center, where magnetic resonance imaging is systematically implemented as first-line diagnostic workup. Lack of VENI was defined as a <40% decrease in baseline National Institutes of Health Stroke Scale (NIHSS) score 1 hour after start of IV-tPA. Poor outcome was defined as a 3-month modified Rankin scale ≥2. Associations between lack of VENI and potential determinants were assessed in logistic regression models. In all, 186 patients were included (median baseline NIHSS score, 16; median onset to treatment time, 155 minutes). One hundred forty-three patients (77%) had no VENI. The variables significantly associated with lack of VENI in multivariable analysis were baseline NIHSS (OR, 1.08; 95% CI, 1.01 to 1.16 per 1-point increase; P=0.03), onset to treatment time >120 minutes (OR, 2.94; 95% CI, 1.31 to 6.63; P=0.009) and diffusion weighted imaging—Alberta Stroke Programme Early CT Score ≤5 (OR, 3.60; 95% CI, 1.14 to 11.35; P=0.03). Patients without VENI were more likely to have a modified Rankin Scale ≥2 than those without VENI (68% versus 24%; OR, 5.01; 95% CI, 2.12 to 11.82) and less likely to have recanalization after 24 hours (OR, 0.41; 95% CI, 0.19 to 0.88).

Conclusions—Lack of VENI provides an early estimate of 3-month outcome and recanalization after IV-tPA. Baseline NIHSS, onset to treatment time, and diffusion weighted imaging—Alberta Stroke Programme Early CT Score could help to predict lack of VENI and, in turn, might help early selection of candidates for complementary reperfusion strategies. (J Am Heart Assoc. 2013;2:e000511 doi: 10.1161/JAHA.113.000511)

Key Words: acute stroke • outcome • thrombolysis

Intravenous recombinant tissue plasminogen activator (IV-tPA) is currently the most effective treatment of acute ischemic stroke. Recanalization and subsequent reperfusion are indeed essential for salvage of the at-risk tissue. However, recanalization is achieved in less than 50% of patients treated by IV-tPA only. In addition, even when achieved, it is often delayed and accordingly results in no clinical benefit. Overall, good outcome (defined as a score on the modified Rankin Scale [mRS] <2) is achieved in <40% of IV-tPA-treated patients. These considerations have prompted the development of complementary reperfusion strategies, including add-on antithrombotic drugs and intra-arterial therapies. The recent negative results of the IMS-3, SYNTHESIS Expansion, and MR-RESCEU trials have underlined the key importance of appropriately selecting patients for intra-arterial therapies. The identification of patients who are unlikely to respond to IV-tPA could help in selecting the potentially good candidates for supplementary reperfusion strategies as early as possible.

A few studies have shown that in patients with middle cerebral artery (MCA) occlusion, the majority of IV-tPA-induced recanalizations occur during the first hour after
treatment and that there is also a strong association between very early (ie, 1 or 2 hours after treatment initiation) neurological improvement (VENI) and recanalization.13 Thus, VENI could be used as a clinical surrogate of early recanalization, and in turn the identification of predictors of lack of VENI may help to select patients who should be referred for intra-arterial or other additional therapies. However, to date, it remains unknown whether initial patient characteristics can predict very early neurological outcome. We therefore assessed the clinical and magnetic resonance imaging–based factors associated with lack of VENI at 1 hour in a cohort of consecutive IV-tPA-treated patients with MCA occlusion and who had magnetic resonance imaging as first-line diagnostic workup.

Methods

Population

We reviewed all consecutive ischemic stroke patients treated within 4.5 hours by IV-tPA only (ie, without combined intra-arterial therapy) between January 2003 and September 2012 in our center, where magnetic resonance imaging is systematically implemented as first-line pretherapeutic workup. Given the specific purpose of the present study, we selected patients who had an MCA (M1 or M2) occlusion documented on time-of-flight (TOF) magnetic resonance (MR) angiography (regardless of the status of the carotid artery), and a baseline National Institutes of Health Stroke Scale (NIHSS) score $\geq 4$. Patients who had baseline computed tomography because of contraindications to MR not being included, as presence of an MCA occlusion on TOF MR angiography was a selection criterion. Decisions to treat by IV-tPA were made by stroke neurologists according to current European guidelines, except that age was not a contraindication for treatment. Diffusion-weighted imaging lesion volume or presence of microbleeds on T2* did not influence clinical decision making in our practice. The therapeutic window was extended to 4.5 hours in 2008.5,6 Treatment was initiated at a dose of 0.9 mg/kg (maximum, 90 mg). Neither heparin nor antiplatelet medications were given within the first 24 hours after IV-tPA.

Data Collection

Using a standardized medical chart, we routinely and prospectively collected baseline NIHSS score, onset to treatment time, glucose level, systolic and diastolic blood pressure before and during IV-tPA treatment, weight, current smoking ($\geq 2$ cigarettes a day), history of hypertension (systolic blood pressure $\geq 140$ mm Hg or diastolic blood pressure $\geq 90$ mm Hg or antihypertensive medication), diabetes mellitus (fasting glucose $\geq 126$ mg/dL or antidiabetic treatment), history of atrial fibrillation, past vascular diseases, concomitant drugs, and preexisting handicap (mRS). During fibrinolysis, blood pressure was monitored every 15 minutes for the first hour, then every hour during the first 24 hours. Follow-up NIHSS scores were assessed after 1 hour (end of the infusion), 24 hours, and 7 days. The 3-month mRS was assessed by a stroke neurologist either during a face-to-face visit or by phone interview, using the simplified version.14,15

We defined poor outcome as mRS $\geq 2$.

Imaging

Pretreatment imaging data was recorded. Magnetic resonance imaging was performed on a 1.5-Tesla scanner (SignaEchoSpeed, GE Healthcare) and included a diffusion-weighted imaging sequence (3 directions, b=$1000$ s/mm$^2$), FLAIR, T2*, and 3D TOF MR angiography. Acquisition time ranged between 7 and 10 minutes. Arterial occlusion was evaluated on TOF sequence. Diffusion weighted imaging—Alberta Stroke Programme Early CT Score (DWI-ASPECTS) was scored on pretreatment imaging and dichotomized into $>5$ versus $\leq 5$.16–19 However, because there is a controversy over the best DWI-ASPECTS threshold to predict clinical outcome, we performed additional analyses using a cutoff of $\leq 7$.20 Arterial recanalization was assessed on TOF MR angiography or angio–computed tomography scheduled around 24 hours after treatment, according to the Thrombolysis In Cerebral Infarction (TICI) criteria, and dichotomized into recanализed (TICI 2 to 3) or not recanalized (TICI 0 to 1).21

Outcomes

For primary analyses, we defined lack of VENI as a $<40\%$ decrease in baseline NIHSS score after IV-tPA, based on a study showing that a $\geq 40\%$ reduction in NIHSS score at 1 hour offered the best cutoff to predict early MCA recanalization.13 We also performed sensitivity analyses using alternative definitions of lack of VENI proposed in the literature: (1) improvement $<20\%$ from baseline;22 (2) improvement $<4$ points from baseline and NIHSS $>1$;23 (3) improvement $<5$ points from baseline and NIHSS $>14$; and (4) improvement $<8$ from baseline and NIHSS $>1$.22–24 At 24 hours, we defined dramatic recovery as NIHSS 0 or 1 or improvement $\geq 10$ from baseline.25

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]) and categorical variables as percentages. Continuous variables were compared using the $t$ test or Mann–Whitney $U$ test, as appropriate. Categorical variables were compared using the
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Pearson chi-square test or Fisher’s exact test, as appropriate. Associations between lack of VENI, 3-month outcome, recanalization, and potential pretherapeutic determinants were assessed by calculations of crude and adjusted odds ratios (ORs) in logistic regression models. Variables associated with VENI at a level of $P<0.20$ in univariable analysis were included into the multivariable logistic model. Statistical significance was set at $P<0.05$. Statistical analysis was performed using SAS 9.3.

Ethics Statement

In accordance with French legislation, the study did not need approval by an institutional or ethics committee because it implied only retrospective analysis of anonymized data collected prospectively as part of routine clinical care. Because IV-tPA is part of routine care of acute stroke patients, written informed consent from patients was not deemed necessary.

Results

During the study period, a total of 293 patients were treated with IV-tPA within 4.5 hours of symptom onset, without additional endovascular therapy. We excluded 107 patients (median baseline NIHSS score, 9 [IQR, 6 to 14]) for the following reasons: NIHSS <4 ($n=5$), computed tomography as pretherapeutic imaging ($n=25$), vertebrobasilar strokes ($n=25$), isolated anterior cerebral artery stroke ($n=4$), and MCA stroke with no visible M1 or M2 occlusion on TOF MR angiography ($n=48$), leaving 186 patients for the analyses. The baseline characteristics of the population are shown in Table 1. The median baseline NIHSS score was 16 ($IQR, 11$ to 20). The median (IQR) onset to treatment time (OTT) was 155 minutes ($IQR, 120$ to 195); 40 patients (22%) were treated within 120 minutes. Occlusion was on M1 in 95 patients (51%) and on M2 in 39 patients (21%), and 52 (28%) had an internal carotid occlusion (including 45 patients with tandem internal carotid artery–MCA occlusion).

One hour after IV-tPA infusion, the median NIHSS score was 13 ($IQR, 6$ to 19) (Table 1). Recanalization was assessed at a median time of 24 hours ($IQR, 20$ to 29 hours) after treatment and was available in 167 patients (160 on TOF MR angiography and 7 on angio-CT). Three-month mRS was available in 177 patients (Figure).

The proportion of patients with lack of VENI was 77% ($n=143$) according to our primary definition and ranged from 64% to 87% according to alternative definitions (Table 2). At 24 hours, the median NIHSS score was 3 (1 to 7) in patients with and 15 (7 to 20) in those without VENI ($P<0.0001$), and dramatic recovery occurred more often in patients with than in patients without VENI (67% versus 16%, $P<0.0001$; Figure). Patients without VENI were more likely to have a mRS $\geq 2$ than those without VENI (68% versus 24%; OR, 6.55; 95% CI, 3.03 to 14.12; $P<0.0001$). This association remained strong after adjustment for OTT and baseline NIHSS (OR, 5.01; 95% CI, 2.12 to 11.82; C-statistic, 0.84). The association between lack of VENI and 3-month poor outcome was highly consistent across the alternative definitions of VENI (Table 2).

Among the 13 patients with a 3-month mRS $\geq 2$ despite VENI, 1 died on the third day from heart failure, 3 had symptomatic hemorrhagic transformation within 36 hours after IV-tPA (1 died), 1 had recurrent ischemic stroke 2 months later, 5 had secondary neurological worsening within 36 hours, and 3 had residual severe neurological deficit after 1 hour or infarct in strategic areas. NIHSS $>10$ at 1 hour was associated with a poor prognosis at 3 months (OR, 6.75; 95% CI, 3.45 to 13.19; $P<0.0001$). However, among patients with VENI, only 2 still had NIHSS $>10$ at 1 hour (both having a baseline NIHSS $\geq 20$).

Patients without VENI were less likely to have 24-hour recanalization than those without VENI (44% [57 of 149] versus 66% [25 of 38]; OR, 0.41; 95% CI, 0.19 to 0.88; $P=0.02$).

The univariable relationships between clinical and radiological variables and lack of VENI are shown in Table 1. Baseline NIHSS score (OR, 1.08; 95% CI, 1.02 to 1.15 per 1-point increase; $P=0.01$), OTT $>120$ minutes (OR, 3.41; 95% CI, 1.60 to 7.27; $P=0.001$), and DWI-ASPECTS score $\leq 5$ (OR, 4.62; 95% CI, 1.56 to 13.72; $P=0.003$) were significantly associated with lack of VENI. In multivariable analysis, lack of VENI was independently associated with baseline NIHSS (OR, 1.08; 95% CI, 1.01 to 1.16 per 1-point increase; $P=0.03$), OTT $>120$ minutes (OR, 2.94; 95% CI, 1.31 to 6.63; $P=0.009$), DWI-ASPECTS $\leq 5$ (OR, 3.60; 95% CI, 1.14 to 11.35; $P=0.03$) after adjusting for site of occlusion and current smoking (c-statistic, 0.74). In an alternative model using the $<7$ DWI-ASPECTS cutoff, the adjusted OR for DWI-ASPECTS was 2.54 (95% CI, 1.16 to 5.57). Using other definitions of lack of VENI, the results were similar except for NIHSS, where the association disappeared or was inverted when VENI was defined as an absolute change in NIHSS score instead of a relative decrease (Table 3).

Discussion

We have shown that, irrespective of the definition of VENI, more than two thirds of patients with MCA occlusion on TOF MR angiography had no VENI 1 hour after start of IV-tPA infusion. Lack of VENI was strongly associated with lack of improvement at 24 hours and poor outcome at 3 months. In this population of patients with MCA occlusion, only baseline NIHSS, OTT, and DWI-ASPECTS were significantly associated with lack of VENI.
Table 1. Characteristics of the Population and Relationships With Lack of Very Early Neurological Improvement at 1 Hour

| Characteristic | All Patients (n=186) | Lack of VENI (n=143) | VENI (n=43) | OR (95% CI) | P Value |
|----------------|----------------------|-----------------------|-------------|-------------|---------|
| **Patient history** |                       |                       |             |             |         |
| Age, mean±SD, y | 67.4±16.2            | 67.6±15.4             | 66.8±18.8   | 1.03 (0.84 to 1.27)* | 0.78    |
| ≥80            | 39 (21)              | 29 (20)               | 10 (23)     | 0.85 (0.34 to 2.14) | 0.91    |
| 65 to 79       | 81 (44)              | 63 (44)               | 18 (42)     | 1.03 (0.47 to 2.24) | 0.003   |
| <65            | 66 (35)              | 51 (36)               | 15 (35)     | 1.00        |         |
| Male sex       | 98 (53)              | 72 (50)               | 26 (60)     | 0.66 (0.33 to 1.33) | 0.24    |
| Hypertension   | 102 (55)             | 77 (54)               | 25 (58)     | 0.84 (0.42 to 1.67) | 0.62    |
| Diabetes mellitus | 22 (12)             | 16 (11)               | 6 (14)      | 0.78 (0.28 to 2.13) | 0.62    |
| Current smoking | 35 (19)              | 23 (16)               | 12 (28)     | 0.49 (0.22 to 1.10) | 0.08    |
| Atrial fibrillation | 55 (30)          | 42 (29)               | 13 (30)     | 0.96 (0.46 to 2.02) | 0.91    |
| History of antiplatelet use | 53 (29)     | 40 (28)               | 13 (30)     | 0.90 (0.43 to 1.91) | 0.79    |
| History of statin use | 58 (31)      | 45 (32)               | 13 (30)     | 1.07 (0.51 to 2.24) | 0.86    |
| Prestroke mRS >1 | 8 (4)                | 7 (5)                 | 1 (2)       | 2.16 (0.26 to 18.08) | 0.46    |
| **Pretreatment characteristics** |                         |                       |             |             |         |
| NIHSS, median (IQR) | 16 (11 to 20)     | 17 (12 to 21)         | 12 (9 to 18) | 1.08 (1.02 to 1.15)† | 0.01    |
| >15             | 102 (55)             | 85 (59)               | 17 (17)     | 2.41 (1.04 to 5.59) | 0.07    |
| 10 to 15        | 44 (24)              | 31 (22)               | 13 (30)     | 1.15 (0.45 to 2.90) |         |
| <10             | 40 (21)              | 27 (19)               | 13 (33)     | 1.00        |         |
| OTT, median (IQR), min | 155 (120 to 195) | 160 (132 to 198)      | 130 (100 to 175) | 1.05 (0.99 to 1.11)‡ | 0.10    |
| OTT, min        |                       |                       |             |             |         |
| >120            | 146 (78)             | 120 (84)              | 26 (60)     | 3.41 (1.60 to 7.27) | 0.001   |
| ≤120            | 40 (22)              | 23 (16)               | 17 (40)     | 1.00        |         |
| >180            | 66 (35)              | 56 (39)               | 10 (23)     | 4.48 (1.02 to 19.62) | 0.01 to 0.003† |
| 121 to 180      | 80 (43)              | 64 (45)               | 16 (37)     | 3.20 (0.77 to 13.30) |         |
| 90 to 120       | 31 (17)              | 18 (13)               | 13 (30)     | 1.11 (0.25 to 4.94) |         |
| ≤90             | 9 (5)                | 5 (3)                 | 4 (1)       | 1.00        |         |
| **Blood pressure** |                       |                       |             |             |         |
| Systolic BP, mean±SD, mm Hg | 152.9±23.2         | 153.5±23.9            | 150.7±21.1  | 1.06 (0.91 to 1.23)§ | 0.48    |
| Diastolic BP, mean±SD, mm Hg | 83.0±16.4         | 83.0±17.0             | 83.1±14.6   | 0.99 (0.81 to 1.23)§ | 0.96    |
| Serum glucose, mean±SD, mmol/L | 6.8±2.2          | 6.9±2.2               | 6.5±2.3     | 1.10 (0.92 to 1.31)§ | 0.31    |
| >8              | 28 (15)              | 24 (17)               | 4 (9)       | 1.97 (0.64 to 6.02) | 0.23    |
| ≤8              | 158 (85)             | 119 (83)              | 39 (91)     | 1.00        |         |
| **Site of occlusion** |                       |                       |             |             |         |
| Internal carotid artery | 52 (28)           | 42 (29)               | 10 (23)     | 1.08 (0.38 to 3.06) | 0.57    |
| M1 segment      | 95 (51)              | 70 (49)               | 25 (58)     | 0.72 (0.29 to 1.78) |         |
| M2 segment      | 39 (21)              | 31 (22)               | 8 (19)      | 1.00        |         |
| **Imaging** |                       |                       |             |             |         |
| DWI-ASPECTS, median (IQR) | 7 (5 to 8)       | 7 (5 to 8)            | 8 (7 to 9)  | 1.38 (1.12 to 1.70)† | 0.003   |
| DWI-ASPECTS ≤5 | 50 (27)              | 46 (32)               | 4 (9)       | 4.62 (1.56 to 13.72) | 0.003   |
| >5              | 136 (73)             | 97 (68)               | 39 (91)     | 1.00        |         |
| ≤7              | 120 (65)             | 100 (70)              | 20 (47)     | 2.67 (1.33 to 5.37) | 0.005   |
| >7              | 66 (35)              | 43 (30)               | 23 (53)     | 1.00        |         |

Values are numbers unless otherwise indicated. BP indicates blood pressure; CI, confidence interval; DWI-ASPECTS, diffusion weighted imaging—Alberta Stroke Programme Early CT Score; IQR, interquartile range; mRS, modified Rankin Scale; OR, odds ratio; OTT, onset to treatment; SD, standard deviation; VENI, very early clinical improvement.

*Per 10-year increase. †Per 1-point increase. ‡Per 10-minute increase. §Per 10 mm Hg increase. ¶Per 1 mmol/L increase. kP for trend.

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The proportion of patients with lack of VENI after IV-tPA is currently uncertain because of the small number of dedicated studies and of the heterogeneity in the definitions used. However, the proportion found in our population (77%) was similar to that observed in the few previous studies focusing on lack of VENI 1 or 2 hours after IV-tPA infusion (ranging from 62% to 88%).23–27 Like others, we showed that lack of VENI was independently associated with 3-month poor outcome.24 The positive predictive value of lack of VENI to predict 3-month poor outcome was 76% in our population, making it a potentially interesting prognostic marker. However, 24% of patients had a good 3-month outcome despite lack of VENI, which might be explained by low baseline NIHSS score, delayed recanalization rescuing persistent penumbra, or delayed neurological improvement despite early recanalization (“stunning of the brain”).23 In addition, 32% of patients had a poor 3-month outcome despite VENI, in line with a previous study.26 As a matter of fact, the majority of patients with VENI and poor 3-month outcome had either a delayed complication (hemorrhagic transformation, stroke recurrence, or extraneurological complications) or a persistent severe or strategic neurological deficit despite VENI (ie, mainly patients with very high NIHSS at admission).

There is currently no consensual definition of VENI, as various absolute or relative reductions in baseline NIHSS 1, 2, or 24 hours after IV-tPA have been used across studies.13,22,24,26,27 Although some patients without 1-hour clinical improvement may improve later, 1 hour is probably a good time to assess early neurological response because it is compatible with decision making at the hyperacute stage.13 Unlike relative reductions, absolute reductions in NIHSS score have been found to have a different sensitivity for predicting recanalization between low- and high-baseline NIHSS score patients.13 Thus, absolute reductions in NIHSS are potentially less accurate than relative reductions to predict early response after IV-tPA. In line with these results, we observed that the direction of the association between baseline NIHSS score and VENI varied depending on the definition of VENI, namely, absolute or relative reduction in NIHSS (Table 3). This apparent paradox is explained by the fact that the higher the baseline NIHSS score is, the easier it is to

### Table 2. Association Between Lack of VENI and 3-Month Outcome According to Different Definitions of VENI

| Definition of Lack of VENI | OR (95% CI) for 3-Month mRS ≥2 | P Value | OR (95% CI) for 3-Month mRS ≥3 | P Value |
|---------------------------|--------------------------------|---------|--------------------------------|---------|
| Improvement <40% from baseline NIHSS (n=143, 77%) | 6.54 (3.03 to 14.12) | <0.0001 | 4.76 (2.16 to 10.47) | <0.0001 |
| <20% From baseline NIHSS (n=119, 64%) | 8.64 (4.25 to 17.55) | <0.0001 | 4.86 (2.50 to 9.44) | <0.0001 |
| Improvement <4 points from baseline and NIHSS >1 (n=130, 70%) | 4.89 (2.44 to 9.76) | <0.0001 | 3.28 (1.67 to 6.45) | <0.0004 |
| Improvement <5 points from baseline and NIHSS >1 (n=143, 77%) | 4.53 (2.14 to 9.58) | <0.0001 | 3.86 (1.79 to 8.35) | 0.0003 |
| Improvement <8 points from baseline and NIHSS >1 (n=162, 87%) | 4.15 (1.63 to 10.56) | 0.002 | 3.64 (1.36 to 9.72) | 0.007 |

CI indicates confidence interval; mRS, modified Rankin Scale; OR, odds ratio; VENI, very early clinical improvement.
reach an absolute 4- or 5-point reduction, without necessarily reaching the specified relative reduction threshold. However, this is not true when higher thresholds are required.

Unlike others, we found a significant association between OTT and lack of VENI. However, our results are consistent with an increased efficiency of IV-tPA toward recent (ie, less organized) thrombi. Furthermore, although longer OTT is strongly associated with larger ischemic lesions, the association between OTT and lack of VENI remained after adjustment for DWI-ASPECTS. We also find that DWI-ASPECTS ≤5 or ≤7 is associated with lack of VENI in multivariable analysis, consistent with studies reporting that DWI-ASPECTS ≤7 is an independent predictor of 24-hour neurological improvement in patients with MCA occlusion.

Lack of VENI is a very straightforward and cost-free assessment that, combined with arterial status evaluation, could potentially be used to screen patients for randomized trials comparing bridging therapy with IV-tPA alone. However, VENI depends not only on the thrombolytic action of IV-tPA, which itself depends not only on thrombus burden, but also on the ability of the brain to recover after recanalization, which depends on the amount of salvageable tissue. In practice, it would be even more useful if patients unlikely to have VENI could be identified before treatment decision. Along this line, the present study identified 3 easily available factors that might help in identifying patients who will not rapidly improve. However, it is clear that these factors are still insufficient to categorize individual patients accurately. Additional factors such as thrombus burden and composition, collateral circulation, and extent of penumbral tissue may have significance in adding value to predict early response to IV-tPA. In addition to the potential use of predicting lack of VENI for trials of bridging therapy, our data also could suggest that lack of VENI might help the clinician to quickly estimate the patient’s long-term prognosis after IV-tPA treatment.

The present study has several potential limitations. First, the single-center design may weaken the generalizability of our results. However, the patients’ baseline characteristics were similar to those of previous studies in patients with MCA stroke treated by IV-tPA. Second, our sample size was modest, and we may have lacked statistical power to show associations between some baseline variables and lack of VENI (especially sex and current smoking). Furthermore, many of our analyses lacked precision, with wide confidence intervals for the odds ratios. Third, MCA occlusion was mostly assessed using TOF magnetic resonance angiography, which may have led to misclassifying high-grade MCA stenosis as occlusion. However, a susceptibility vessel sign on T2*, confirming the existence of a thrombus, was present in about 80% patients in our population, as we previously reported. Fourth, the arterial status was assessed 24 hours after IV-tPA infusion, and we therefore were unable to assess whether VENI is associated with recanalization within the first 2 hours. It is possible that some patients without VENI had late recanalization, which could be observed after 24 hours, without clinical significance. Despite this limitation, we found an association between VENI after 1 hour and recanalization assessed after 24 hours. Fifth, VENI remains an imperfect surrogate of early recanalization. Baseline NIHSS is strongly correlated with brain infarct extent, and patients with high NIHSS are less likely to recover completely even though they recanalize. Conversely, ≤30% of patients with VENI still have MCA occlusion despite persistent occlusion, potentially because they have good collateral blood supply. However, in our study among patients with VENI, only 2 still had NIHSS >10 one hour after thrombolysis. Finally, the extent of ischemic penumbra, which could be an important determinant of lack of VENI, was not assessed in this study.

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Disclosures
None.
References

1. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintemark M, Yonas H. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:870–947.

2. Vivien D, Gauberti M, Montagne A, Defer G, Touze E. Impact of tissue plasminogen activator on the neurovascular unit: from clinical data to experimental evidence. J Cereb Blood Flow Metab. 2011;31:2119–2134.

3. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke. 2007;38:967–973.

4. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med. 1995;333:1561–1587.

5. Hacke W, Kastrup J, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Morgenstern L, Nitisoraphanakul P, von Kummer R, Wahlgren N, Toni D. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–1329.

6. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, Tilley BC, Davis SM, Donnan GA, Hacke W; ECASS III Study Group. Early neurologic improvement after intravenous thrombolysis: a pooled analysis of ECASS I, ECASS II, and ECASS III trials. Lancet. 2010;375:1695–1703.

7. Wahlgren N, Ahmed N, Davalos A, Hacke W, Miller M, Muir K, Raine RO, Toni D, Lees KR; SITS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke (SITS-ISTR): an observational study. Lancet. 2008;372:1303–1309.

8. Baker WL, Colby JA, Tongbram V, Talati R, Silverman IE, White CM, Kluger J, Coleman CI. Neurothrombectomy devices for the treatment of acute ischemic stroke: state of the evidence. Ann Intern Med. 2011;154:243–252.

9. Mazighi M, Serfaty JM, Labreuche J, Laissy JP, Meseguer E, Lavalle EC, Cabrejo L, Siaou T, Goudou C, Lapergue B, Klein IF, Olivot JM, Aboud H, Simon O, Niclot P, Niffie T, Touboul PJ, Raphaeli G, Gohin C, Claey S, Amarenco P. RECANALISE investigators. Comparison of intravenous alteplase with a combined intravenous-endovascular approach in patients with stroke and confirmed arterial occlusion (RECANALISE study): a prospective cohort study. Lancet Neurol. 2009;8:802–809.

10. Mazighi M, Meseguer E, Labreuche J, Amarenco P. Bridging therapy in acute ischemic stroke: a systematic review and meta-analysis. Stroke. 2012;43:1302–1308.

11. Barreto AD, Alexandrov AV, Tyshavanov AE, Lin C, Close B, Davis K, Baute V, Aryal T, Brooks D, Hess DC, Switzer JA, Nichols FT. Simplified modified Rankin Scale questionnaire: reproducibility over the telephone and validation with quality of life. Stroke. 2011;42:2276–2279.

12. Bruno A, Shah N, Lin C, Close B, Hess DC, Davis K, Baute V, Switzer JA, Waller JL, Nichols FT. Improving modified Rankin Scale assessment with a simplified questionnaire. Stroke. 2010;41:1048–1050.

13. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolysis therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet. 2000;355:1670–1674.

14. Barber PA, Hill MD, Eliasziw M, Demchuk AM, Fuxman JH, Hudon ME, Tomasek A, Frayne R, Buchan AM; ASPECTS Study Group. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. J Neurol Neurosurg Psychiatry. 2005;76:1528–1533.

15. Kimura K, Iuchi Y, Shibazaki K, Terasawa Y, Ioue T, Uemura J, Aoki J. Large ischemic lesions on diffusion-weighted imaging done before intravenous tissue plasminogen activator thrombolysis predicts a poor outcome in patients with acute stroke. Stroke. 2008;39:2388–2391.

16. Barreto AD, Rajan S, Roque J, Demchuk AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolysis therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet. 2000;355:1670–1674.

17. Barber PA, Hill MD, Eliasziw M, Demchuk AM, Fuxman JH, Hudon ME, Tomasek A, Frayne R, Buchan AM; ASPECTS Study Group. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. J Neurol Neurosurg Psychiatry. 2005;76:1528–1533.

18. Kimura K, Iuchi Y, Shibazaki K, Terasawa Y, Ioue T, Uemura J, Aoki J. Large ischemic lesions on diffusion-weighted imaging done before intravenous tissue plasminogen activator thrombolysis predicts a poor outcome in patients with acute stroke. Stroke. 2008;39:2388–2391.

19. Turc G, Aipoil M, Nagarra O, Calvet D, Lamy C, Tataru AM, Méder JF, Mas JL, Baron JC, Oppenheim C, Touzé E. Magnetic Resonance Imaging-DRAGON score: 3-month outcome prediction after intravenous thrombolysis for anterior circulation stroke. Stroke. 2013;44:1323–1328.

20. Nezu T, Koga M, Kimura K, Shikagawa Y, Nakagawa J, Furui E, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Naganuma M, Minematsu K, Toyoda K. Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA: SAMURAI rt-PA Registry. Neurology. 2010;75:555–561.

21. Labeyrie MA, Turc G, Hess A, Hervo P, Mas JL, Meder JF, Baron JC, Touzé E, Oppenheim C. Diffusion lesion reversal after thrombolysis: a MR correlate of early neurological improvement. Stroke. 2012;43:2986–2991.

22. Khairtonova T, Mikulik R, Roine RO, Soine L, Ahmed N, Wahlgren N. Association of early National Institutes of Health Stroke Scale improvement with vessel recanalization and functional outcome after intravenous thrombolysis in ischemic stroke. Stroke. 2011;42:1638–1643.

23. Alexandrov AV, Hall CE, Labiche LA, Wojner AW, Grotta JC. Ischemic stunning of the brain: early recanalization without immediate clinical improvement in acute ischemic stroke. Stroke. 2004;35:449–452.

24. Muresan IP, Favrole P, Levy P, Andreux F, Marro B, Alamowitch S. Very early neurologic improvement after intravenous thrombolysis. Arch Neurol. 2010;67:1323–1328.

25. Felberg RA, Okon NJ, El-Mitwalli A, Burgin WS, Grotta JC, Alexandrov AV. Early dramatic recovery during intravenous tissue plasminogen activator infusion: clinical pattern and outcome in acute middle cerebral artery stroke. Stroke. 2002;33:1301–1307.

26. Bodenat M, Debette S, Cordier C, Dumont F, Henon H, Bordet R, Leys D. A very early neurological improvement after intravenous thrombolysis for acute cerebral ischaemia does not necessarily predict a favourable outcome. Acta Neurol Belg. 2013;113:67–72.

27. Labiche LA, Al-Senani F, Wojner AW, Grotta JC, Malkoff M, Alexandrov AV. Is the benefit of early recanalization sustained at 3 months? A prospective cohort study. Stroke. 2003;34:695–698.

28. Aoki J, Kimura K, Shibazaki K, Sakamoto Y. DWI-ASPECTS as a predictor of dramatic recovery after intravenous recombinant tissue plasminogen activator administration in patients with middle cerebral artery occlusion. Stroke. 2013;44:534–537.

29. Legrand L, Nagarra O, Turc G, Mellerio C, Rocca P, Calvet D, Labeyrie MA, Baron JC, Mas JL, Meder JF, Touze E, Oppenheim C. Clot burden score on admission T2*-MRI predicts recanalization in acute stroke. Stroke. 2013;44:1878–1884.