**Objective:** To evaluate whether very early neurologic improvement (VENI) after intravenous (IV) recombinant tissue plasminogen activator (rt-PA) perfusion in patients with acute ischemic stroke (AIS) predicts favorable outcome at 3 months.

**Design:** Retrospective analysis of prospective data.

**Setting:** Stroke registry at the Stroke Unit, Tenon University Hospital.

**Patients:** We analyzed consecutive patients with AIS treated with IV rt-PA between November 11, 2002, and December 24, 2007.

**Main Outcome Measures:** VENI at 1 hour was defined as a National Institute of Health Stroke Scale score of 0 at the end of rt-PA perfusion or an improvement of 5 or more points compared with baseline. Favorable outcome was defined as a modified Rankin Scale score of 1 or less at 3 months.

**Results:** Of 120 patients with AIS treated with IV rt-PA, 22 (18.3%) had VENI after IV rt-PA perfusion. Favorable outcome was observed in 15 patients with VENI (68.2%) and in 29 patients without VENI (29.6%) ($P < .001$). No symptomatic intracerebral hemorrhage occurred in patients with VENI. Mortality rates were 0% in the patients with VENI and 17.3% in patients without VENI. Baseline scores for VENI (adjusted odds ratio, 6.23; 95% confidence interval, 2.03-19.13; $P = .001$) and the National Institute of Health Stroke Scale (0.83; 0.76-0.91; $P < .001$) were the only 2 factors associated with favorable outcome (modified Rankin Scale score of $\leq 1$).

**Conclusions:** VENI at the end of IV rt-PA perfusion in patients with AIS independently predicts favorable outcome at 3 months.

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**Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) administered within 4.5 hours of symptom onset is the only effective approved therapy for acute ischemic stroke (AIS).** The efficacy of rt-PA on clinical recovery at 3 months has been proved in different randomized clinical trials, mainly in the National Institute of Neurological Disorders and Stroke (NINDS) trial for the 3-hour time window and in the European Cooperative Acute Stroke Study (ECASS III) for the 3 to 4.5-hour time window. However, not all patients respond to IV therapy; failure to respond to IV therapy is usually, but not always, associated with occlusion of large arteries and lack of recanalization. Additional IV thrombolysis therapies, such as chemical and/or mechanical intra-arterial therapy, represent a promising approach to obtaining recanalization and better recovery. In this context, the identification of very early predictors of neurologic recovery may help to improve selection of patients for bridging therapy combining IV and intra-arterial approaches.

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**For editorial comment see page 1306**

In a post hoc analysis of the NINDS trial, a neurologic improvement of 5 or more points on the National Institute of Health Stroke Scale (NIHSS) at 24 hours allowed a significant increase in the prediction of which patients would benefit from treatment with IV rt-PA for AIS at 3 months. In addition, in a Canadian single-center study, it was demonstrated that a major neurologic improvement ($\geq 8$-point improvement in NIHSS score or an
NIHSS score of 0 or 1 at 24 hours) at 24 hours after administration of IV rt-PA in patients with AIS independently predicts favorable outcome (3-month modified Rankin Scale [mRS] score of 0-1). However, to our knowledge, there are no published data about the prognosis value of clinical improvement assessed immediately after IV rt-PA administration for AIS. Our hypothesis was that a very early neurologic improvement (VENI) defined by an improvement of 5 points or more on the NIHSS 1 hour after IV rt-PA administration might predict favorable responders to IV thrombolysis with favorable outcome at 3 months (mRS score ≤1). The VENI assessment may constitute a helpful tool to rapidly estimate the efficacy of IV treatment and, consequently, could help to quickly select the patients who could benefit from a more aggressive recanalization approach after IV rt-PA.

### METHODS

#### PATIENTS

Data from our stroke registry at the Stroke Unit of the Department of Neurology at Tenon University Hospital were collected prospectively and analyzed retrospectively in consecutive patients treated with IV rt-PA from November 11, 2002, through December 24, 2007. The registry contains (1) demographic data, (2) baseline characteristics, (3) treatment time (onset to needle time with time of symptom onset defined by the time “last seen to be well”), (4) pretreatment CT angiographic and magnetic resonance imaging with magnetic resonance angiography in 78 patients [65.0%], (5) causative workup (12-lead electrocardiography, transcranial and carotid ultrasonography, computed tomographic angiography, magnetic resonance imaging and magnetic resonance angiography, transesophageal echocardiography and transthoracic echocardiography, 24-hour Holter monitoring, blood analysis, and, if necessary, conventional angiography). Stroke type was determined using the Trial of Org 10172 in Acute Stroke Treatment trial criteria after the diagnostic workup was completed. The decision to treat with IV rt-PA was made by a stroke-certified neurologist according to French guidelines with the following additional exceptions: age was not a contraindication for treatment by IV rt-PA and the therapeutic window was enlarged to 4.5 hours in selected patients after Hacke et al’s meta-analysis with regard to the efficacy of rt-PA in treating AIS. Treatment was initiated in the Radiological Unit or the Stroke Unit by IV rt-PA at a dose of 0.9 mg/kg (10.0% as a bolus in 1 minute, with the rest being infused during a 1-hour period. Follow-up examinations were performed in all patients according to the NIHSS and other clinical parameters at 1 (end of the infusion), 2, 3, 4, 5, 6, 7, 8, 16, and 24 hours. All NIHSSs were performed by certified stroke neurologists. Adverse effects of IV rt-PA were noted when they occurred. Every patient underwent computed tomography at 24 hours after IV rt-PA treatment to determine the presence of intracerebral hemorrhage and the characteristics of the ischemic infarction: territory involved, extension, mass effects, and brain edema.

#### OUTCOMES

The VENI was defined 1 hour after the start of IV rt-PA by an NIHSS score of 0 or an improvement of 5 or more points compared with the baseline NIHSS score, so VENI was determined at the end of rt-PA infusion. Favorable outcome at 3 months was defined as a modified mRS score of 1 or less. The predictive values of VENI on favorable outcome, mortality, and the rate of asymptomatic and symptomatic intracranial hemorrhages were analyzed.

Symptomatic intracerebral hemorrhage was defined using the ECASS III study definition: any apparently extravascular blood in the brain or within the cranium that was associated with clinical deterioration, as defined by an increase of 4 points or more in NIHSS score, or that led to death and that was identified as the predominant cause of the neurologic deterioration. The last follow-up was death or an mRS score at 3 months. Every patient except for 2 was seen at 3 months after the AIS by a certified stroke neurologist; the NIHSS and mRS scores were obtained by direct evaluation (118 patients) or by telephone interview (2 patients).

### STATISTICAL ANALYSIS

The quantitative variables were tested using the Mann-Whitney test. Nominal variables were tested using the χ² test or Fisher exact test. The significance level was 0. The association among demographic characteristics, clinical variables, radiologic data, and favorable outcome at 3 months was examined using a descending stepwise logistic regression analysis. The levels of significance were .20 for the univariate phase and .05 for the multivariate phase, respectively. Discrimination of the model was assessed by the area under the receiving operating characteristic curve. Statistical analysis was performed using StatView statistical software, version 5.0 (SAS Institute Inc, Cary, North Carolina).


Table 1. Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 120)</th>
<th>With VENI (n = 22)</th>
<th>Without VENI (n = 98)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>64.8 (14.1)</td>
<td>61.5 (13.0)</td>
<td>65.3 (14.2)</td>
<td>.40</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>77 (64.2)</td>
<td>13 (59.1)</td>
<td>64 (65.3)</td>
<td>.78</td>
</tr>
<tr>
<td>NIHSS baseline score, mean (range)</td>
<td>15 (4-25)</td>
<td>14 (6-23)</td>
<td>15 (4-25)</td>
<td>.30</td>
</tr>
<tr>
<td>Time to rt-PA, mean (SD), min</td>
<td>164 (41)</td>
<td>168 (58)</td>
<td>163 (37)</td>
<td>.79</td>
</tr>
<tr>
<td>Glucose level at admission, mean (SD), mg/dL</td>
<td>136.9 (59.4)</td>
<td>118.8 (14.4)</td>
<td>138.6 (57.6)</td>
<td>.17</td>
</tr>
<tr>
<td>Baseline systolic BP, mean (SD), mm Hg</td>
<td>146.3 (19.3)</td>
<td>141.1 (17.6)</td>
<td>146.8 (19.7)</td>
<td>.57</td>
</tr>
<tr>
<td>Baseline diastolic BP, mean (SD), mm Hg</td>
<td>76.2 (12.2)</td>
<td>74.8 (13.8)</td>
<td>76.5 (13.1)</td>
<td>.59</td>
</tr>
<tr>
<td>Frequency of risk factors, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>66 (55.0)</td>
<td>40.9</td>
<td>57 (58.2)</td>
<td>.45</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (18.3)</td>
<td>18.2</td>
<td>18 (18.4)</td>
<td>.77</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>38 (31.7)</td>
<td>36.4</td>
<td>30 (30.6)</td>
<td>.46</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>20 (16.7)</td>
<td>2 (9.1)</td>
<td>18 (18.4)</td>
<td>.86</td>
</tr>
<tr>
<td>Smoking</td>
<td>46 (38.3)</td>
<td>45.5</td>
<td>36 (36.7)</td>
<td>.62</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>16 (13.3)</td>
<td>4.5</td>
<td>15 (15.3)</td>
<td>.34</td>
</tr>
<tr>
<td>Previous use of aspirin or clopidogrel, No. (%)</td>
<td>31 (25.8)</td>
<td>9.1</td>
<td>29 (29.6)</td>
<td>.25</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; NIHSS, National Institute of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; VENI, very early neurologic improvement.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

* Determined according to Trial of Org 10172 in Acute Stroke Treatment8 classification.

statistically associated with an mRS score of 1 or less (Table 2). At logistic regression analysis, VENI (odds ratio, 6.23; 95% confidence interval, 2.03-19.13; P = .001) and baseline NIHSS score (0.83; 0.76-0.91; P < .001) were the only 2 factors associated with favorable outcome (mRS score of ≤1). No interaction was found between the 2 covariates. Patients with VENI after IV rt-PA treatment for AIS tend to have a shorter period of hospitalization (mean [SD] length of stay, 13 [7] vs 16 [12] days; P = .36).

Asymptomatic intracerebral hemorrhage was observed in 2 patients with VENI (9.1%) and in 23 patients without VENI (23.5%) (P = .15). Symptomatic intracerebral hemorrhages at 24 hours occurred in 5 patients (4.2%). All symptomatic intracerebral hemorrhages affected the patients without VENI (P = .58). The overall mortality rate at 3 months was 14.1%, 17.3% in patients without VENI and 0% in patients with VENI (P = .07) (Figure 1).

We used statistical and graphic methods to evaluate the fitness of the model. Discrimination of VENI was assessed by area under the receiver operating characteristic curve. We found an area under the curve of 0.67, indicating adequate discrimination (Figure 2). Positive and negative predictive values were 0.68 and 0.70, respectively.

We also performed analyses to explain why 32.0% of patients with VENI still had mRS scores of 2 to 6 at the 3-month mark and why 30.0% of those without VENI had a favorable outcome. The analyses are considered exploratory, so they are reported without a statistical test. The aim of our first analysis was to evaluate the outcome at 3 months according to VENI and the initial severity of stroke.
Of the patients with an early favorable response to IV rt-PA, 14.0% had clinical deterioration after initial improvement (ie, a two-point deterioration on the NIHSS after an initial two-point improvement after treatment by IV rt-PA). In our population the incidence of clinical deterioration after initial improvement was 13.6% (3/22) in patients with VENI, 7.1% (7/98) in patients without VENI, and 8.3% (10/120) in the overall population. In addition, 33.3% of patients with VENI and an mRS score greater than 1 experienced clinical deterioration after improvement at 24 hours as a possible reocclusion after recanalization, and 44.8% of patients without VENI and an mRS score of 1 or lower showed major neurologic improvement at 24 hours (ie, ≥8-point improvement in NIHSS score or an NIHSS score of 0 or 1 at 24 hours as a possible sign of delayed recanalization). Another exploratory analysis assessed the relationship among VENI, major neurologic improvement at 24 hours, and the mRS score at 3 months. The patients with VENI had greater chances to show major neurologic improvement at 24 hours, which is an independent predictor of favorable outcome at 3 months.

**Table 2. Univariate Analysis According to the Outcome (Modified Rankin Scale Score of ≤1)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Favorable Outcome (n = 44)</th>
<th>No Favorable Outcome (n = 76)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>62.1 (15.5)</td>
<td>66.5 (13.0)</td>
<td>.08</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>20 (45.5)</td>
<td>23 (30.3)</td>
<td>.14</td>
</tr>
<tr>
<td>Baseline NIHSS score, mean (SD)</td>
<td>12.3 (4.9)</td>
<td>16.3 (4.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VENI, No. (%)</td>
<td>15 (34.1)</td>
<td>7 (9.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline systolic BP, mean (SD), mm Hg</td>
<td>141.9 (20.2)</td>
<td>148.7 (18.4)</td>
<td>.04</td>
</tr>
<tr>
<td>Baseline diastolic BP, mean (SD), mm Hg</td>
<td>73.0 (14.1)</td>
<td>78.1 (12.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Glucose level at admission, mean (SD), mg/dL</td>
<td>122.4 (46.8)</td>
<td>140.4 (61.2)</td>
<td>.10</td>
</tr>
<tr>
<td>Time to rt-PA, mean (SD), min</td>
<td>164.4 (49.9)</td>
<td>164.3 (35.6)</td>
<td>.99</td>
</tr>
<tr>
<td>Arterial occlusion at baseline, No. (%)</td>
<td>25 (56.8)</td>
<td>56 (73.7)</td>
<td>.05</td>
</tr>
<tr>
<td>Cardioembolism–stroke subtype, No. (%)</td>
<td>14 (31.8)</td>
<td>38 (50.0)</td>
<td>.05</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; NIHSS, National Institute of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; VENI, very early neurologic improvement.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

*Defined with time-of-flight magnetic resonance imaging or computed tomographic angiogram.*

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**COMMENT**

A VENI indication at 1 hour after the start of IV rt-PA administration was observed in nearly 1 in 5 patients and was independently associated with favorable outcome (mRS score of ≤1). The VENI indication conferred a more than 6-fold increased chance of favorable outcome at 3 months. In addition, patients with VENI after IV rt-PA treatment for AIS tended to have a shorter period of hospitalization.

Different prognosis factors of favorable outcome at 3 months (mRS score of ≤1) after IV rt-PA administration in AIS had already been described: clinical, biological, or radiologic predictors. Among these prognosis factors, we can distinguish baseline characteristics (before IV rt-PA) and dynamic factors (under or after IV rt-PA) that may reflect early markers of response to treatment. Kent et al, using data from 5 randomized clinical trials (n=2184) testing IV rt-PA in the 0- to 6-hour window,
found 7 baseline variables that significantly affected the prognosis and/or the treatment effect of rt-PA: age, diabetes mellitus, stroke severity, sex, previous stroke, systolic blood pressure, and time from symptom onset. Saposnik et al⁷ showed that major neurologic improvement (≥8-point improvement in NIHSS score or an NIHSS score of 0 or 1 at 24 hours) at 24 hours after administration of IV rt-PA in AIS independently predicts favorable outcome (3-month mRS score of 0 to 1). In the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution study,¹⁴ prespecified baseline magnetic resonance imaging in patients treated with IV rt-PA for AIS can identify subgroups that are likely to benefit from treatment and subgroups that are unlikely to benefit from it and may even be harmed. Early recanalization monitored by transcranial Doppler (TCD) ultrasonography during IV rt-PA therapy has consistently been shown to predict sustained neurologic recovery and favorable outcome at 3 months.¹⁵-¹⁷

By contrast with previous studies, our results identified an easy and very early dynamic factor assessed at the patient’s bedside with a clinical routine tool (NIHSS), which may predict favorable outcome. To define VENI, we used at least a 5-point improvement of NIHSS score at 1 hour. The definition might be considered as arbitrary; however, this variable was consistent with the effects of IV treatment on AIS at 24 hours according to the NINDS.⁶ On part 1 of the NINDS the clinical activity of IV rt-PA at 24 hours was tested; early improvement at 24 hours was defined as complete resolution of a neurologic deficit or an improvement from baseline in the NIHSS score of 4 or more points.² The originally posited 4-point threshold was too easy a target in the placebo group, so the observed differences of early improvement at 24 hours were not statistically significant between the rt-PA–treated group (47.1%) and the placebo-treated group (39.1%). In a post hoc analysis of NINDS, a 5-point or more improvement from baseline in the NIHSS score at 24 hours is statistically significant in rt-PA patients compared with placebo-treated patients.⁶

Favorable recovery (mRS score of ≤1) at 3 months after IV rt-PA treatment in patients with AIS was observed in 122 patients (39.1%) on the NINDS (3-hour time window) and in 219 patients (52.4%) on the ECASS III (4.5-hour time window).³,⁴ Favorable outcome in our study was achieved in 15 patients with VENI (68.2%) and in 29 patients without VENI (29.6%). Our predictable model has a significant discrimination with an area under the receiver operating characteristic curve of 0.67, a positive predictive value at 0.68, and a negative predictive value at 0.70. Bad outcome at 3 months in patients with VENI was observed especially in patients with a high baseline NIHSS score, which is strongly associated with prognosis.¹⁸-²¹ Another hypothesis concerning the poor outcome in some patients with VENI may be the occurrence of reocclusion after recanalization within 24 hours after IV rt-PA, which occurs in up to 15% of patients.¹²

The present study has some limitations. It is a single-center study without external validation; therefore, our results need to be confirmed in another data set. Another limitation of our study is the lack of data with regard to early recanalization. It has been proved that recanalization assessed by TCD ultrasonography is a powerful predictor of favorable outcome after thrombolysis.¹⁵-¹⁷ We did not perform TCD ultrasonography–enhanced thrombolysis, and we did not monitor patients with TCD ultrasonography to assess the rate of very early recanalization. We do not contend that VENI might be the only predictor of favorable outcome, but our results show for the first time, to our knowledge, that a dynamic clinical factor under therapy assessed at the end of IV rt-PA infusion can predict favorable outcome at 3 months.

A promising new approach in the treatment of AIS is bridging therapy with a dual approach: IV thrombolysis by rt-PA followed by chemical or mechanical endovascular therapy.³,²²-²⁷ Our results suggest that VENI, as determined by a clinical routine tool (NIHSS) at a patient’s bedside, might help to rapidly select patients who will not respond to IV rt-PA but who could be candidates for bridging therapy. The value of this dynamic clinical factor alone and in combination with the rate of recanalization by TCD needs to be confirmed in a large prospective study of patients undergoing IV thrombolysis.

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Author Contributions: Drs Muresan and Alamowitch had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Muresan and Alamowitch. Acquisition of data: Muresan and Marro. Analysis and interpretation of data: Muresan, Favrole, Levy, Andreux, and Alamowitch. Drafting of the manuscript: Muresan, Favrole, Levy, Andreux, Marro, and Alamowitch. Critical revision of the manuscript for important intellectual content: Muresan and Alamowitch. Statistical analysis: Levy. Administrative, technical, and material sup-

Figure 4. Favorable outcomes (modified Rankin scale [mRS] scores of ≤1) at 3 months according to major neurologic improvement at 24 hours in patients with and without very early neurologic improvement (VENI). Major neurologic improvement (MNI) at 24 hours was defined by an 8-point or greater improvement in National Institute of Health Stroke Scale (NIHSS) score or an NIHSS score of 0 or 1 at 24 hours.

REFERENCES


