Two-Hour Improvement of Patients in the National Institute of Neurological Disorders and Stroke Trials and Prediction of Final Outcome

Thomas M. Hemmen, MD, PhD; Karin Ernstrom, MS; Rema Raman, PhD

Background and Purpose—Ongoing clinical trials are using early response to intravenous tissue-type plasminogen activator (tPA) to stratify patients into endovascular therapies. Little is known about the likelihood of early recovery and its correlation with final stroke outcome.

Methods—We analyzed the National Institute of Neurological Disorders and Stroke tPA dataset for patients with early improvement (EI), a change of ≥4, or score 0 on the 2-hour National Institutes of Health Stroke Scale (NIHSS) to predict good 90-day outcome. We adjusted for multiple confounders and divided the patients by baseline NIHSS score 0 to 10, 11 to 20, >20, and stroke type to analyze if EI predicted good outcome across stroke severities and types. We analyzed different EI thresholds to identify the best level of NIHSS change to predict good 90-day outcome using a receiver-operator characteristic curve.

Results—in total, 183 of 624 (29.3%) patients had EI, 112 of 312 (35.9%) in the tPA group had EI, and 71 of 312 (22.7%) in the placebo group had EI (P<0.0001). Smokers (P=0.012) and patients treated in <90 minutes (P=0.008) were more likely to have EI; diabetic patients (P=0.023) were less likely to show EI. The baseline NIHSS (mean±SD) of patients with EI was 16.1±6.5 versus 14.3±7.4 (P=0.001). A 90-day modified Rankin Scale score of 0 to 1 was achieved in 68 of 112 (60.7%) tPA-treated patient with EI and 65 of 200 (32.5%) without (placebo groups 30 of 71 [42.3%] versus 53/241 [22.0%]). The adjusted odds ratio for good outcome was 1.71 (95% confidence interval [CI], 1.1–2.6; P=0.011) for tPA treatment and 7.69 (95% CI, 4.63–12.76; P<0.0001) for early improvement. EI predicted good outcome in patients with cardioembolic (13.6; 95% CI, 3.6–51.5) and small vessel (6.98; 95% CI, 2.86–17.03), but not large vessel stroke (1.82; 95% CI, 0.38–8.59). The receiver-operator characteristic curve showed that a threshold of 4 on the NIHSS for prediction of good outcome had a sensitivity of 84% and 36% specificity.

Conclusions—Early improvement was more common in tPA-treated patients and was associated with good 90-day outcome. Whereas 32.5% of nonresponders after tPA had a good 90-day outcome, the use of EI to predict stroke outcome shows value. (Stroke. 2011;42:00-00.)

Key Words: acute cerebral infarction ■ emergency treatment ■ stroke ■ thrombolysis

Intravenous (IV) thrombolysis (tissue-type plasminogen activator [tPA]) after stroke leads to good clinical outcome in fewer than half of those treated within 4.5 hours.1,2 Recent advances in neuroprotective and endovascular therapies are used to enhance this therapeutic effect.3 Many investigators advocate the use of a stepwise process in therapeutic decision-making: administer IV tPA and consider further therapies in patients who do not show improvement immediately after IV treatment.4

In past clinical trials of IV tPA, however, clinical response was determined during the physical examination at 3 months. The decision to add further therapies in the setting of acute stroke has to be made within minutes or hours.5

It is not known if the early clinical examination can predict outcome at 3 months. Before allowing clinical trials that make decisions based on patient examination findings within minutes or hours after IV tPA, more knowledge is needed to determine if the early response to IV tPA can reliably predict final outcome. We present data from the National Institute of Neurological Disorder and Stroke (NIINDS) tPA trials to show if the clinical response at 2 hours after IV tPA bolus predicts good clinical outcome at 3 months.

Materials and Methods

We analyzed data from the NINDS tPA trials, the only clinical trials of IV tPA after acute ischemic stroke with a placebo arm and clinical outcome measures in the acute phase (2 hours after IV tPA or placebo bolus). We compared the basic demographics between placebo-treated and tPA-treated patients regarding age, sex, race, weight, blood pressure, baseline National Institutes of Stroke Scale (NIHSS) score, history of diabetes, previous stroke/transient ische-
Results

We analyzed 312 IV tPA-treated patients and 312 placebo-treated patients across the 2 NINDS trials. Aspirin use was more common \((P=0.002)\), weight (kg) was lower \((76.2\pm15.7 \text{ versus } 80.0\pm19.2; P=0.009)\) and age (years) was older \((68.0\pm11.3 \text{ versus } 65.9\pm11.9; P=0.023)\) in tPA-treated patients when compared to placebo-treated patients.\(^{1}\)

Of the total 624 patients, 125 had cardioembolic stroke, 241 had small vessel occlusive disease, and 61 had large vessel atherosclerosis. The rate of tPA use was similar in each stroke type group. The baseline NIHSS was 0 to 10 in 209 patients, 11 to 20 in 275, and >20 in 140.

We identified 183 patients with and 441 without early improvement (Figure 1). Patients with early improvement were more likely to have a higher baseline NIHSS score \((16.1\pm6.5 \text{ versus } 14.3\pm7.4; P=0.001)\), less likely to have diabetes \((15.3\% \text{ versus } 23.6\%; P=0.023)\), more likely to smoke \((42.6\% \text{ versus } 31.7\%; P=0.012)\), and more likely to be treated between 0 and 180 minutes versus 91 to 180 minutes \((56.8\% \text{ versus } 44.9\%; P=0.008)\) (Table 1).

Patients treated with tPA were more likely to have EI compared to nontreated patients. In the placebo arm, 71 of 312 \((22.8\%\) had improvement at 2 hours versus 112 of 312 \((35.9\%\) in the tPA-treated groups \((P<0.0001)\).

In the group of patients with early improvement, 98 of 183 \((53.6\%\) had a 90-day mRS score of 0 to 1 versus 118 of 441 \((26.8\%\) without early improvement. Within the tPA-treated groups, 68 of 112 \((60.7\%\) patients with early improvement versus 65 of 200 \((32.5\%\) without early improvement had a 90-day mRS of 0 to 1. In the placebo groups, 30 of 71 \((42.3\%)\) with and 53 of 241 \((22.0\%)\) without early improvement had a 90-day mRS of 0 to 1 (Table 2).

The multivariable logistic regression analysis found a significant effect of IV tPA treatment (odds ratio [OR], 1.71; 95% confidence interval [CI], 1.27 to 2.34) on early improvement. Patients treated with tPA were more likely to have an improved NIHSS score \((P=0.001)\).

### Table 1. Baseline Characteristics Between Patients With and Without Early Improvement (National Institutes of Health Stroke Scale Score ≥4 or 0 at 2 Hours)

<table>
<thead>
<tr>
<th></th>
<th>Early Improvement ((n=183))</th>
<th>No Early Improvement ((n=441))</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline National Institutes of Health Stroke Scale score</td>
<td>16.1±6.5</td>
<td>14.3±7.4</td>
<td>0.001*</td>
</tr>
<tr>
<td>Male (%)</td>
<td>60.1</td>
<td>57.1</td>
<td>0.533</td>
</tr>
<tr>
<td>Race (%) white</td>
<td>66.7</td>
<td>63.7</td>
<td>0.567</td>
</tr>
<tr>
<td>Age, y (±SD)</td>
<td>65.8±11.5</td>
<td>67.4±11.7</td>
<td>0.104</td>
</tr>
<tr>
<td>Weight kg (±SD)</td>
<td>77.8±17.7</td>
<td>78.2±17.6</td>
<td>0.073</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>30.6</td>
<td>32.7</td>
<td>0.639</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>63.7</td>
<td>67.1</td>
<td>0.456</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>15.3</td>
<td>23.6</td>
<td>0.023*</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>42.6</td>
<td>31.7</td>
<td>0.012*</td>
</tr>
<tr>
<td>Aspirin use (%)</td>
<td>30.1</td>
<td>36.5</td>
<td>0.139</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>14.4</td>
<td>20.3</td>
<td>0.089</td>
</tr>
<tr>
<td>Time to treatment in 0–90 min (%)</td>
<td>56.8</td>
<td>44.9</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

SD indicates standard deviation.

*P<0.05.

### Table 2. Day 90 Modified Rankin Scale Score and Early Improvement (≥4 or 0) for All Patients, Patients Treated and Not Treated With Intravenous Tissue-Type Plasminogen Activator

<table>
<thead>
<tr>
<th></th>
<th>Early Improvement</th>
<th>No Early Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>183</td>
<td>441</td>
</tr>
<tr>
<td>90-d mRS 0–1 (%) and 2–6 (%)</td>
<td>98 (53.6)</td>
<td>118 (26.8)</td>
</tr>
<tr>
<td>tPA patients</td>
<td>112</td>
<td>200</td>
</tr>
<tr>
<td>90-d mRS 0–1 (%) and 2–6 (%)</td>
<td>68 (60.7)</td>
<td>65 (32.5)</td>
</tr>
<tr>
<td>Placebo patients</td>
<td>71</td>
<td>241</td>
</tr>
<tr>
<td>90-d mRS 0–1 (%) and 2–6 (%)</td>
<td>44 (39.3)</td>
<td>135 (67.5)</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale; tPA, tissue-type plasminogen activator.

For statistical significance, please see multivariate analysis.
95% confidence interval, 1.1–2.6; \( P = 0.011 \), early improvement (OR, 7.69; 95% CI, 4.63–12.76; \( P < 0.0001 \)), age (OR, 0.98; 95% CI, 0.96–0.99; \( P = 0.012 \)), and baseline NIHSS score (OR, 0.8; 95% CI, 0.76–0.83; \( P < 0.0001 \)) on the 90-day mRS score of 0 to 1.

Examining the effect of EI in relationship to baseline NIHSS score and stroke subtype, we found that an EI of \( \geq 4 \) points or NIHSS score of 0 on the NIHSS at 2 hours predicted good outcome for patients with a baseline NIHSS score 0 to 10, 11 to 20, and \( \geq 20 \). The OR for a 90-day mRS of 0 to 1 was 4.46 (95% CI, 1.85–10.73), 10.5 (95% CI, 5.36–20.56), and 6.99 (95% CI, 1.3–37.59). EI predicted good outcome in patients with cardioembolic stroke (OR, 13.59; 95% CI, 3.59–51.45) and small vessel occlusive disease (OR, 6.98; 95% CI, 2.86–17.03), but not large vessel atherosclerosis (OR, 1.82; 95% CI, 0.38–8.59; Table 3).

The receiver-operator characteristic curve to examine the threshold of EI that best predicts good outcome is shown in Figure 2. Using a threshold of \( \geq 4 \) or NIHSS score of 0 (alternative 2 or 8), the sensitivity for predicting good outcome was 84% and the specificity was 36% (alternative 70% and 52% or 94% and 15%). Further analysis of receiver-operator characteristic curve for EI in patients across 3 levels of baseline NIHSS score and stroke types is shown in Figures 3 and 4.

### Discussion

Analyzing the only trials that included a placebo group and measured neurological status before and 2 hours after IV tPA bolus, we find that EI is more common in tPA-treated patients. Despite this association, 1 out of 3 (32.5%) patients who received IV tPA and did not show improvement at 2 hours had a good 90-day clinical outcome.

The approval of IV tPA after stroke was based on 3-month outcome measures.\(^1\) Our study strengthens the recommendation that caution should be used extrapolating early treatment response to final stroke outcome. Most studies that have examined early response to tPA focused on clinical findings 24 hours after stroke.\(^6\) In clinical practice, however, decisions regarding additional therapies after stroke must be made within minutes to a few hours when additional neuroprotection or tissue salvage is still possible.\(^7\) Imaging surrogates to predict final clinical outcome are still lagging proven validity, reliability, and are not readily available at most medical centers.\(^8\)

Limitations of our study include that the data were from clinical trials concluded in 1995 and current medical therapy and changes in risk factor distribution may have changed the treatment responses. A recent smaller and prospective study, however, showed similar findings.\(^9\) Another limitation is the definition of clinical improvement requiring a change of \( \geq 4 \) points on the NIHSS. As illustrated in Figure 1, patients with low baseline NIHSS score may have been less likely to meet this criterion. Therefore, patients with low baseline NIHSS score may not have been captured in our analysis as improved unless they reached an NIHSS score of 0 at 2 hours. We addressed this concern by analyzing EI across different ranges of baseline NIHSS and found that an EI of \( \geq 4 \) or NIHSS score of 0 predict good outcome across the range of NIHSS (Table 3).

In our general analysis, we used a threshold of \( \geq 4 \) or NIHSS score of 0 to define EI. To examine if other thresholds

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**Table 3. Odds Ratios (95% Confidence Interval) for a 90-Day Modified Rankin Scale Score of 0 to 1 From a Multivariable Logistic Regression Model**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n=624)</th>
<th>NIHSS Score 0–10 (n=209)</th>
<th>NIHSS Score 11–20 (n=275)</th>
<th>NIHSS &gt;20 (n=140)</th>
<th>CES (n=125)</th>
<th>SVD (n=241)</th>
<th>LVA (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPA treatment</td>
<td>1.71 (1.13, 2.6)</td>
<td>1.46 (0.77, 2.78)</td>
<td>1.71 (0.88, 3.3)</td>
<td>2.26 (0.45, 11.44)</td>
<td>2.33 (0.85, 6.35)</td>
<td>0.95 (0.44, 2.01)</td>
<td>1.90 (0.58, 6.24)</td>
</tr>
<tr>
<td>EI (( \geq 4 ) or 4)</td>
<td>7.69 (4.63, 13.76)</td>
<td>6.91 (1.85, 10.73)</td>
<td>6.91 (1.59, 14.75)</td>
<td>13.59 (2.6–70.8)</td>
<td>6.91 (2.6–70.8)</td>
<td>6.91 (2.6–70.8)</td>
<td>6.91 (2.6–70.8)</td>
</tr>
<tr>
<td>Age</td>
<td>0.98 (0.96, 0.99)</td>
<td>0.94 (0.92, 0.97)</td>
<td>0.94 (0.92, 0.97)</td>
<td>0.97 (0.92, 1.02)</td>
<td>0.96 (0.93, 0.99)</td>
<td>1.00 (0.96, 1.05)</td>
<td>1.00 (0.96, 1.05)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.97 (0.49, 1.35)</td>
<td>0.63 (0.30, 1.32)</td>
<td>0.94 (0.43, 2.06)</td>
<td>1.32 (0.21, 8.22)</td>
<td>0.63 (0.20, 1.97)</td>
<td>0.85 (0.33, 2.23)</td>
<td>0.92 (0.22, 3.8)</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>0.80 (0.76, 0.83)</td>
<td>0.71 (0.60, 0.83)</td>
<td>0.83 (0.73, 0.94)</td>
<td>1.03 (0.82, 1.28)</td>
<td>0.79 (0.71, 0.87)</td>
<td>0.74 (0.68, 0.80)</td>
<td>0.84 (0.71, 1.00)</td>
</tr>
</tbody>
</table>
Figure 3. Receiver-operator characteristic curve of the neurological improvement using different National Institutes of Health Stroke Scale (NIHSS) thresholds for early improvement (EI) at 2 hours in patients with baseline NIHSS score <10, 11 to 20, and >20.

Figure 4. Receiver-operator characteristic curve of the neurological improvement using different National Institutes of Health Stroke Scale (NIHSS) thresholds for early improvement (EI) at 2 hours in patients with cardioembolic stroke (CES), small vessel occlusive disease (SVD), and large vessel atherosclerosis (LVA).
may have predicted good outcome (90-day mRS score, 0–1) better, we performed a receiver-operator characteristic curve of EI thresholds. This analysis showed that a threshold with ≥4 improvement or NIHSS score of 0 showed a high sensitivity (84%) but low specificity (34%) to predict good 90-day outcomes. Using a cutoff of 2 or 8 would have either lowered specificity to 70% in the former or lowered sensitivity to 15% in the latter (Figure 2). The receiver-operator characteristic analysis, however, demonstrates that no single definition for EI has high specificity and sensitivity for the prediction of good final outcome. This limits the use of any certain definition for good EI to predict good final stroke outcome.

Although in the analysis of all patients a cut-off of ≥2 or NIHSS score of 0 had sensitivity and specificity of 50% to predict good outcome (Figure 2). Patients with a baseline NIHSS score of 11 to 20 had a 70% sensitivity and specificity for good outcome; patients with a baseline NIHSS >20 had 65% sensitivity and 90% specificity. Based on these data, caution must be used before basing the decision about additional therapies after ischemic stroke after IV tPA administration on changes in NIHSS at 2 hours.

Conclusions
In conclusion, we found that early improvement is associated with final clinical outcome, but caution should be used before clinical decisions are based on early therapeutic responses to therapies that were reviewed by regulatory agencies based on 3-month treatment responses. Further analysis is required to better-understand and define an early treatment response after stroke that is likely to benefit from additional interventions.

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None.

References
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