Predicting Major Neurological Improvement With Intravenous Recombinant Tissue Plasminogen Activator Treatment of Stroke

Devin L. Brown, MD; Karen C. Johnston, MD, MSc; Douglas P. Wagner, PhD; E. Clarke Haley, Jr, MD

Background and Purpose—In the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study, major neurological improvement within 24 hours (MNI) occurred significantly more frequently with recombinant tissue plasminogen activator (rtPA) treatment than with placebo. We explored the relationship between MNI and 3-month favorable outcome and sought clinical predictors of MNI.

Methods—Data from 312 rtPA-treated patients from the NINDS trial were used to assess the ability of MNI to predict favorable outcome at 3 months as defined by a modified Rankin Scale score of 0 to 1. Next, a multivariable predictive model was developed for MNI within the same data set. Clinical variables examined included age, time to treatment (TTT), diabetes, pretreatment glucose, baseline National Institutes of Health Stroke Scale score, pretreatment blood pressure, history of atrial fibrillation, weight >100 kg, and a dense artery sign. Finally, this model was used to forecast into the placebo group of the NINDS trial to assess the uniqueness of the predictors in the rtPA-treated group.

Results—MNI had a positive predictive value and negative predictive value of 0.70 for predicting favorable 3-month outcome. Only age [odds ratio (OR), 0.68; 95% confidence interval (CI), 0.47 to 0.99] and TTT (OR, 0.56; 95% CI, 0.34 to 0.91) appear to be independently associated with MNI. The model performed only moderately well (area under the receiver-operating characteristic curve, 0.66). Age (OR, 0.67; 95% CI, 0.45 to 0.99) but not TTT was associated with MNI in the placebo group.

Conclusions—MNI may be a useful surrogate for thrombolytic activity and is predictive of favorable 3-month outcome. When rates of MNI in different populations of stroke patients treated with thrombolysis are compared, adjustments for age and TTT may be necessary. (Stroke. 2004;35:147-150.)

Key Words: forecasting ■ thrombolytic therapy ■ tissue plasminogen activator ■ treatment outcome
factors would be unique to the rtPA-treated group. Although previous studies assessed predictors of deterioration in neurological status at 24 hours, previous data regarding predictors of favorable 24-hour outcome are limited.

**Subjects and Methods**

Raw data from the 624 patients treated in the NINDS trial were used for these analyses. Subjects were excluded if 24-hour NIHSS scores and/or the baseline variables used in the analysis were missing. Major neurological improvement (MNI), our measure of favorable outcome, was prespecified as improvement in NIHSS score of ≥8 points or an NIHSS score of 0 at 24 hours. This was chosen on the basis of a secondary analysis by the NINDS investigators in which an 8-point difference in 24-hour NIHSS score was found to discriminate between the treatment and placebo groups without overlap in confidence intervals (CIs).5

The ability of MNI to predict favorable outcome at 3 months, as defined by a modified Rankin Scale (mRS) score of 0 or 1, was examined. This dichotomized mRS score was used as a primary outcome measure in the NINDS trial, defining patients who had no or minimal symptoms at follow-up (excellent outcome). A 2×2 table was used to examine the relationship between MNI and excellent functional outcome by calculating the positive and negative predictive values. Using the binomial distribution, we estimated 95% CIs around these values using S-Plus 6.1 (Insightful Corp, 2002).

Next, multivariable logistic regression techniques were used to design a model to predict MNI. Clinical independent variables examined were prespecified on the basis of the literature and clinical judgment of the authors and included age,6 time from onset to treatment,7 diabetes,8 pretreatment glucose,9 pretreatment mean arterial pressure (MAP),10 history of atrial fibrillation,11 weight >100 kg, and a dense artery sign on baseline CT scan.12,13 Age, time to treatment, glucose, and baseline NIHSS scores were used as continuous variables. Diabetes, atrial fibrillation, weight >100 kg, and the presence of a dense artery sign were used as dichotomized variables. To avoid assumptions of linearity for the 4 continuous variables, restricted cubic splines with 3 knots each were used.14 This yielded a total of 13 df in the model as a whole. The clinical variables to be examined were selected on the basis of a biologically or clinically plausible relationship with either recanalization or MNI. Using S-plus 6.1, we estimated odds ratios (ORs) with 95% CIs for each variable in the multivariable model. The CIs of the predictive variables were assessed with bootstrapping. This procedure was used to generate conservative estimates of the CIs by iteratively sampling from the original sample 150 times with replacement.14 If the CIs did not include 1, a statistically significant association was inferred.

The predictive value of the model as a whole was assessed by calculating the area under the receiver-operating characteristic curve. The role of each independent variable in predicting MNI in the placebo group was determined with the identical model used in the rtPA group. S-Plus 6.1 software was used for the analysis.

**Results**

Three hundred twelve patients were treated with rtPA in the NINDS trial. One subject was excluded because of missing 24-hour outcome data. Of the 311 remaining patients, 101 had MNI, and 133 had an excellent outcome at 3 months (mRS, 0 or 1). MNI predicted excellent 3-month outcome with a positive predictive value of 0.70 (95% CI, 0.64 to 0.76) and a negative predictive value of 0.70 (95% CI, 0.61 to 0.78). The association between MNI and excellent 3-month outcomes was statistically significant ($\chi^2$=42.65, $P<0.0001$). There were 63 patients who had a favorable outcome at 3 months without having achieved MNI. Their median NIHSS score at 24 hours was 4 (range, 1 to 19; 25th percentile, 2; 75th percentile, 7).

Of the 311 rtPA-treated patients with available data on 24-hour outcome, 26 were missing a baseline variable used in the multivariable predictive model, leaving 285 patients for analysis. Eighty-nine of these patients (31%) had MNI. Table 1 shows the number of patients with each baseline variable and the number of patients for whom data on that variable was present. The only 2 variables independently and significantly related to MNI were age and time from onset to treatment (Table 2 and the Figure). Shorter time from onset to treatment and lower age were positively associated with MNI. The model in its entirety was only a moderate predictor of MNI in the rtPA-treated group with an area under the receiver-operating characteristic curve of 0.66.

There were 312 patients in the placebo group. Twelve were omitted because of missing data. Fifty-two (17%) had MNI. When the model was used to forecast into the placebo group, age, but not time from onset to treatment, was significantly related to MNI (Table 2). Baseline NIHSS score and glucose were also predictors of MNI in the placebo group.

**Table 1. Baseline Variables in the Model and Their Presence in the rtPA-Treated Group of the NINDS Stroke Trial**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With Data Available, n</th>
<th>Patients With Variable Present, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight &gt;100 kg</td>
<td>312</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>308</td>
<td>58 (19)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>310</td>
<td>68 (30)</td>
</tr>
<tr>
<td>Dense artery sign</td>
<td>307</td>
<td>37 (12)</td>
</tr>
<tr>
<td>Age</td>
<td>312</td>
<td>312 (100)</td>
</tr>
<tr>
<td>Time to treatment</td>
<td>312</td>
<td>312 (100)</td>
</tr>
<tr>
<td>Baseline glucose</td>
<td>310</td>
<td>310 (100)</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>312</td>
<td>312 (100)</td>
</tr>
<tr>
<td>MAP</td>
<td>297</td>
<td>297 (100)</td>
</tr>
</tbody>
</table>

**Table 2. Multivariable Model: Association of Individual Baseline Variables With MNI While Other Variables Are Held Constant in the rtPA and Placebo Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR Estimates</th>
<th>95% CI</th>
<th>OR Estimates</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to treatment</td>
<td>0.56</td>
<td>0.34–0.91†</td>
<td>1.05</td>
<td>0.50–2.21</td>
</tr>
<tr>
<td>Age*</td>
<td>0.68</td>
<td>0.47–0.99†</td>
<td>0.67</td>
<td>0.45–0.99†</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.59</td>
<td>0.23–1.55</td>
<td>0.83</td>
<td>0.29–2.43</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.82</td>
<td>0.45–1.47</td>
<td>0.39</td>
<td>0.19–0.79†</td>
</tr>
<tr>
<td>Baseline NIHSS score*</td>
<td>1.55</td>
<td>0.85–2.84</td>
<td>2.43</td>
<td>1.16–5.12†</td>
</tr>
<tr>
<td>MAP*</td>
<td>0.95</td>
<td>0.63–1.45</td>
<td>0.73</td>
<td>0.44–1.22</td>
</tr>
<tr>
<td>Dense artery sign</td>
<td>0.52</td>
<td>0.16–1.64</td>
<td>0.69</td>
<td>0.08–6.08</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.81</td>
<td>0.38–1.73</td>
<td>1.11</td>
<td>0.43–2.90</td>
</tr>
<tr>
<td>Weight &gt;100 kg</td>
<td>0.51</td>
<td>0.05–5.20</td>
<td>0.39</td>
<td>0.00–67.99</td>
</tr>
</tbody>
</table>

All ORs are calculated for the favorable outcome, MNI.

*OR estimates for the continuous variables are calculated comparing the 75th and 25th percentiles (treatment time, 157 and 89 min; age, 76 and 61 years; glucose, 167 and 105; NIHSS score, 19 and 8). ORs for the dichotomous variables are based on the presence vs absence of the risk factor.

†Statistically significant results.
In the current analysis, the presence of MNI, suggesting successful recanalization, was found to be a marker for favorable 3-month outcome. The positive and negative predictive values achieved support a predictive relationship between MNI and favorable 3-month outcome, which is consistent with the previous suggestion that NIHSS scores after 2 hours from stroke onset correlate with 3-month outcome. Additionally, a recent study demonstrated that early recanalization of the middle cerebral artery after thrombolysis, as demonstrated by transcranial Doppler, is associated with a favorable 3-month outcome.

One of the predictor variables, baseline NIHSS score, was confounded in both the placebo- and rtPA-treated group for mathematical reasons. The dependent variable in the logistic regression predictive model, MNI, was determined by a calculation that included baseline NIHSS score, thereby creating a definition of the dependent variable that involved an independent variable. Therefore, although baseline NIHSS score appeared to be predictive of favorable outcome in the placebo group and had a similar OR in the rtPA group, these findings are difficult to interpret.

As hypothesized, clinical factors identified at baseline were associated with MNI in the rtPA group, specifically age and time to treatment. Earlier time to treatment with thrombolysis has been shown to be associated with a greater chance of favorable 3-month outcome. The association between time to treatment and MNI seems biologically plausible because earlier treatment should result in earlier recanalization and a greater salvage of tissue at risk of infarction. As would be expected if the effect were related to recanalization, the association between time to treatment and MNI was unique to the rtPA-treated group.

Age was predictive of MNI in both the rtPA- and placebo-treated groups. This relationship is likely a biological effect, as supported by previous findings that age is related to long-term outcome in patients with and without thrombolytic treatment. Glucose was found to be a predictor of MNI in the placebo group but not in the rtPA-treated group. Given the plausibility of this finding based on basic science research and previous clinical studies, this may represent a biological effect. It may be that glucose has a differential effect on reperfused and nonreperfused tissue. If this was the case, there may be an effect of glucose in the placebo group that is not evident in the rtPA group given the higher rates of presumed recanalization in the latter group.

There were significant differences in the factors that predicted 24-hour favorable outcome in this study and those known to predict 3-month favorable outcome. Many of the factors known to predict 3-month outcome did not predict 24-hour outcome in this analysis. In the final multivariable model of the NINDS trial, treatment with rtPA, diabetes, age-by-NIHSS score, admission MAP-by-age, and thrombus or hypodensity/mass effect on baseline CT scan were independently associated with 3-month favorable outcome in both rtPA- and placebo-treated patients. Age and time from onset to treatment are therefore predictors of both MNI at 24 hours and 3-month favorable outcome in rtPA-treated patients.

This study has several limitations. The analysis was an exploratory post hoc analysis that was intended to be hypothesis generating. There were small numbers of subjects in each
of the predictive variable subgroups, lowering the power to detect predictive relationships with MNI. Although we used 13 rather than 9 df, as would be suggested by the rule of 10 (which requires at least 10 least-frequent outcomes for each 1 df used in the model), this minimal excess was considered permissible, given the exploratory nature of this analysis. The use of restricted cubic splines, allowing the possibility of nonlinear relationships, increased explanatory power somewhat but not enough to compensate for the extra degrees of freedom. Given the limited degrees of freedom available for use, only a limited number of prespecified variables could be used. Because the overall model worked only moderately well as a predictor of MNI, it is possible that important variables that would have added to the value of the model were not included. In a larger data set, more variables could have been explored.

Given the few extra degrees of freedom used, it is possible that our model was overfit. Traditional validation techniques could validate the model as a whole but would not specifically validate the relationship between particular variables and MNI. Because the purpose of this exploratory analysis was to identify baseline characteristics that may affect 24-hour outcome, not to develop a model to be used for future predictions, we did not validate the model as a whole. In an attempt to avoid finding spurious associations, CIs were estimated very conservatively with bootstrapping, limiting assumptions made about the underlying distribution of our data. Additionally, the original model was forecasted into the placebo group to see whether the predictors of MNI found were unique to the rtPA-treated group. Despite these methods to reduce the likelihood of finding spurious relationships, these data need to be validated in an outside data set of patients treated with intravenous thrombolytics within 3 hours of stroke onset.

To estimate the thrombolytic activity of a novel agent, consideration of risk adjustment, especially in small data sets, is important. This study suggests that it may be necessary to adjust for age and time from stroke onset to treatment. Although this study did not demonstrate other baseline characteristics that predicted MNI with statistical significance, further studies may demonstrate other baseline characteristics for which adjustments should be made when different populations of stroke patients treated with intravenous thrombolytics within a 3-hour window are compared.

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References

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