Are Some Patients Likely to Benefit From Recombinant Tissue-Type Plasminogen Activator for Acute Ischemic Stroke Even Beyond 3 Hours From Symptom Onset?

David M. Kent, MD, MS; Robin Ruthazer, MPH; Harry P. Selker, MD, MSPH

Background and Purpose—Recombinant tissue plasminogen activator (rtPA) has been demonstrated to improve outcomes in acute ischemic stroke when delivered within 3 hours of symptom onset. However, the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS B) trial, in which patients were treated mostly between 3 and 5 hours after symptom onset, found no overall benefit from rtPA. We hypothesized that a subgroup of patients at low risk for thrombolysis-related intracranial hemorrhage, identifiable on the basis of pretreatment clinical variables, may benefit even when treated after 3 hours, despite the overall results of the trial.

Methods—Using an independently derived multivariate model that predicts the risk of thrombolysis-related intracranial hemorrhage in patients receiving tPA for acute myocardial infarction (based on 6 easily obtainable clinical characteristics), we stratified patients in the ATLANTIS B trial into low-, intermediate-, and high-risk tertiles. We examined outcomes in the prespecified low-risk subgroup using a global test of significance across 4 outcome scales.

Results—Despite having a similar average baseline stroke severity and median time to treatment (270 minutes), patients in the prespecified low-risk group (n = 194) were significantly less likely to have a symptomatic intracranial hemorrhage than other patients in the trial (2.2% versus 9.2%, P = 0.03). Although there was no treatment effect for rtPA in the overall trial, a consistent trend favoring rtPA therapy (a 5% to 12% absolute treatment benefit) was found across 4 different stroke scales in the prespecified low-risk group (P = 0.10). The treatment-benefit-by-risk interaction was significant (P = 0.03).

Conclusions—Use of a multivariate index based on clinical variables is a promising approach to assist in the selection of patients with a favorable risk-benefit profile for thrombolytic therapy beyond 3 hours. (Stroke. 2003;34:lll–lll.)

Key Words intracerebral hemorrhage ▪ risk assessment ▪ stroke, acute ▪ stroke, ischemic ▪ thrombolytic therapy ▪ time factors

The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study demonstrated that recombinant tissue plasminogen activator (rtPA) improves outcomes in acute ischemic stroke when delivered within 3 hours of symptom onset. Yet despite the overall positive outcome, a significant risk of thrombolysis-related intracranial hemorrhage remains. Additionally, the very narrow therapeutic time window of 3 hours, in which the benefits of therapy are felt to outweigh these risks, has severely limited the number of eligible patients because treatment must be preceded by symptom recognition, transport, and clinical and radiological evaluation. Registry data indicate that <2% of patients with acute ischemic stroke currently receive thrombolytic therapy.

The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS B) trial, conducted immediately after the NINDS trial, tested whether rtPA might be beneficial if initiated 3 to 5 hours after symptom onset. This trial found no benefit for rtPA treatment compared with placebo as measured by the primary outcome, the proportion of patients with minimal or no residual symptoms 90 days after stroke. The rate of symptomatic intracranial hemorrhage was significantly higher in the rtPA group (1.1% versus 7.0%, P = 0.001).

We reasoned that the lack of overall benefit in patients treated beyond the 3-hour time window may obscure the fact that some carefully selected patients, especially those at lower risk of thrombolysis-related intracranial hemorrhage, might still benefit at these later times. Furthermore, we hypothesized that an independently derived model may be able to identify such patients on the basis of pretreatment clinical characteristics.

Methods

To test our hypothesis, we sought an independently derived model that would select patients at low risk of intracranial hemorrhage who...
may benefit from thrombolytic therapy. Previous modeling on the NINDS database indicated that only stroke severity and the presence of CT scan findings predicted the risk of thrombolysis-related symptomatic intracranial hemorrhage.\(^5\) According to this model, only patients with low-severity strokes would be at low risk for intracranial hemorrhage, and such patients have relatively good outcomes whether they receive thrombolytic therapy or not. Patients with higher-severity strokes, on the other hand, who might stand to gain most from therapy would be classified by such a model as at high risk for treatment.

Thus, we sought a model that might indicate a patient’s propensity for intracranial hemorrhage independently of the stroke severity. To do so, we used a model derived from 71,073 patients who received tPA for acute myocardial infarction, of whom 673 experienced a thrombolysis-related intracranial hemorrhage.\(^3\) This model uses 6 baseline clinical characteristics (age, sex, race, systolic blood pressure, diastolic blood pressure, and history of prior stroke) to predict a patient’s likelihood of thrombolysis-related intracranial hemorrhage. We hypothesized that patients with a low score on this risk index would be less likely to have a thrombolysis-related intracranial hemorrhage when treated for stroke and may be more likely to benefit from thrombolytics, even when treated after the 3-hour time window.

Based on a prior analysis of the NINDS data suggesting a substantial decrease in the risk of thrombolysis-related intracranial hemorrhage in the low-risk tertile, we stratified patients in the ATLANTIS B trial into low-, medium- and high-risk tertiles. Then we examined the proportion of patients with minimal or no residual deficit were used as the outcome, and the global test for significance indicated a consistent trend across the 4 stroke scales toward greater treatment benefit for low-risk compared with high-risk patients.

These outcomes for both the overall trial and the prespecified low-risk group are shown in the Figure. The range of absolute treatment benefit seen across scales in the overall trial was \(-1\%\) to \(1\%\), indicating that any benefit of thrombolysis was completely offset by the harm of thrombolysis. However, in the prespecified low-risk subgroup, a consistent trend favoring rtPA therapy (a 5% to 12% absolute treatment benefit) was found across all stroke scales (\(P=0.10\)).

### Discussion

Our results demonstrate that a subgroup of patients with acute ischemic stroke, identifiable on the basis of easily obtainable pretreatment clinical characteristics, may be likely to benefit from rtPA therapy even when treated \(>3\) hours after symptom onset. Because this trial was not powered to find treatment effects in patient subgroups, the benefit found among the 195 patients classified as low risk did not reach statistical significance. However, the observed effect is potentially clinically significant so that, assuming a true treat-

### Results

Patient characteristics of the prespecified low-risk tertile compared with other patients in the trial are shown in Table 1. As expected, the average values for several variables are different between the risk groups, especially those variables that define risk in the model. For example, on average, low-risk patients are younger, are more frequently male, and have lower systolic blood pressure. However, the values for each variable have significant overlap between risk groups. Importantly, there was no difference in baseline stroke severity between risk groups and the median time from symptom onset to therapy was \(\approx4.5\) hours in both groups.

### Table 1. Patient Characteristics of Low-Risk Tertile Compared With Other Trial Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low-Risk (n=194)</th>
<th>Medium- to High-Risk (n=395)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>55.4 (±9.4)</td>
<td>70.6 (±8.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percent male</td>
<td>72.2%</td>
<td>53.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percent Caucasian</td>
<td>82.0%</td>
<td>84.6%</td>
<td>0.4223</td>
</tr>
<tr>
<td>Weight (SD)</td>
<td>83.4 (±19.9)</td>
<td>76.9 (±17.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smokers</td>
<td>39.7%</td>
<td>22.8%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47.7%</td>
<td>67.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.1%</td>
<td>22.4%</td>
<td>0.5264</td>
</tr>
<tr>
<td>Systolic blood pressure (SD)</td>
<td>145.6 (±19.6)</td>
<td>155.6 (±20.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure (SD)</td>
<td>81.5 (±13.4)</td>
<td>81.7 (±13.8)</td>
<td>0.8383</td>
</tr>
<tr>
<td>Symptom onset to treatment time</td>
<td>270 (240–290)*</td>
<td>275 (241–294)*</td>
<td>0.3025</td>
</tr>
<tr>
<td>NIHSS at baseline (SD)</td>
<td>11.1 (±5.5)</td>
<td>11.0 (±5.6)</td>
<td>0.7670</td>
</tr>
</tbody>
</table>

*Interquartile range in minutes.

NIHSS indicates National Institutes of Health Stroke Scale.

### Table 2. Symptomatic Intracranial Hemorrhage Rate by Treatment Group and Risk Strata

<table>
<thead>
<tr>
<th>Risk Strata</th>
<th>tPA</th>
<th>Placebo</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Risk</td>
<td>2/90 (2.2%)</td>
<td>0/103(0%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Medium- to High-Risk</td>
<td>19/204 (9.3%)</td>
<td>3/189(1.6%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Outcomes in the overall ATLANTIS B trial (A) compared with outcomes in the low-risk subgroup (B). There was no benefit for rtPA therapy in the ATLANTIS B trial overall, with the absolute percent benefit ranging from −1% to 1% across 4 different stroke scales. However, for patients identified by the independently derived model as being at relatively low risk of intracranial hemorrhage, there was a consistent benefit, ranging from 5% to 12% across the 4 stroke scales. For patients at moderate to high risk, there was a commensurate trend toward harm. NIH indicates National Institutes of Health Stroke Scale.

When therapies have both significant risks and benefits, the average results of a clinical trial may be misleading for some patients in the trial.14 Therapies that demonstrate overall benefit may be useless in many and harmful in some12; conversely, a therapy that shows no overall benefit may provide considerable benefit to many patients. Traditional subgrouping by single clinical variables in isolation may be unlikely to reveal these subgroups with significantly different treatment effects because individual patients have multiple characteristics simultaneously that might influence the outcome of treatment. For thrombolytic therapy in acute ischemic stroke, although time from symptom onset to therapy is critical, other clinical factors also influence the response to therapy and should be taken into account in the design of future clinical trials. Because the opportunity for benefit and harm is so finely balanced in this case, formal risk-benefit profiling with multivariate models may be especially useful.12,13

Our analysis suggests that a subgroup of patients, identifiable from pretreatment information, may receive substantial benefit from rtPA therapy even when treated >3 hours after symptom onset. Models to optimize patient selection should be refined on prior stroke trial databases, and methods of real-time risk scoring should be developed for future clinical trials.
Acknowledgment
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References
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