Thrombolytic Therapy in Patients With Acute Ischemic Stroke

Judith A. Hinchey, MD; Curtis Benesch, MD

Stroke is the leading cause of disability in the United States and the third leading cause of death. Of long-term stroke survivors, 30% are dependent on others for help with activities of daily living and 15% require institutional care. Traditional care for patients with stroke has focused on treating complications and preventing recurrent strokes; the stroke itself was considered irreversible.

Recent trials of thrombolytic therapy, however, have engendered new hope for patients with acute ischemic stroke. Although studies of thrombolytic therapy for stroke were first published in 1958, only recent trials using computed tomography (CT) and shorter therapeutic time windows (defined as time from onset of stroke symptoms to treatment) have shown beneficial results. Moreover, the term brain attack defines the approach to patients with acute ischemic stroke, replacing the nihilism of an earlier era by identifying acute ischemic stroke as a medical emergency requiring urgent treatment. The impetus for this new approach has been the potential for thrombolytic therapy, but the hope is that all patients who experience stroke will benefit from more rapid assessment and initiation of treatment.

We review our understanding of the risks and benefits of thrombolytic therapy based on recent controlled trials. We also discuss evolving issues of patient selection, patient preferences for outcomes and risks, treatment outside of a controlled clinical trial, treatment by whom, and mode of delivery of treatment.

Tissue Plasminogen Activator

In the early 1990s, the first 2 randomized, controlled trials of IV recombinant tissue plasminogen activator therapy were published (Table 1). To our knowledge, these studies were the first controlled studies to establish the potential safety and efficacy of recombinant tissue plasminogen activator in patients with acute ischemic stroke.

Patients in both studies underwent a cerebral angiogram identifying the site of arterial blockage and then were given either IV recombinant tissue plasminogen activator or IV placebo. A total of 129 patients were randomized within 6 hours of symptom onset to receive IV recombinant tissue plasminogen activator or placebo, with the study by Mori et al examining 2 separate doses of recombinant tissue plasminogen activator in addition to placebo. Both studies assessed recanalization rate, which is the ability to open the blocked artery, and clinical outcome

From the Section of Cerebrovascular Disease, Department of Neurology, University of Rochester, Rochester, NY. Dr Hinchey is now with the Department of Neurology, Strong Memorial Hospital, Rochester, NY.
using the hemispheric stroke scale, hemorrhagic complications, and mortality rate. Both studies found higher recanalization rates in the recombinant tissue plasminogen activator–treated group than in the placebo group. In addition, the recanalization rate for patients with isolated middle cerebral artery (MCA) occlusion was higher than that for those with internal carotid artery occlusion. Recanalization, regardless of treatment group, was associated with a better outcome. Patients receiving thrombolytic therapy had greater improvement on the hemispheric stroke scale score than those receiving placebo. Hemorrhagic infarctions occurred more frequently in the low-dose group of patients in the study by Mori et al, but this rate was similar to that of the placebo group in the study by Yamaguchi et al (Table 1).

The largest and most recent randomized, controlled trials of IV recombinant tissue plasminogen activator included 2 studies conducted in Europe, the European Cooperative Acute Stroke Study (ECASS) I and II, and 2 in the United States, the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator trials, parts 1 and 2 (Table 2).

The ECASS I was a large, multicenter trial to evaluate the safety and efficacy of recombinant tissue plasminogen activator in patients with acute ischemic stroke. Patients were randomized within 6 hours of symptom onset to receive either IV recombinant tissue plasminogen activator or placebo. Primary outcomes assessed at 90 days were the Barthel Index (BI), a 10-item scale of activities of daily living, and the modified Rankin Scale (mRS), a 6-item scale of overall disability (Table 3). Secondary end points included the mortality rate at 30 days, the combined score of the BI and mRS at 90 days, and the stroke severity as measured by a 10-item Scandinavian Stroke Scale at 90 days. The trial did not show a statistically significant improvement in patients' ability to perform activities of daily living ($P=.99$) or their functional out-

### Table 1. Trials of Intravenous Thrombolytic Therapy After Visualization of the Clot by a Cerebral Angiogram

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Patients</th>
<th>Partial or Total Recanalization, %</th>
<th>Recanalization of MCA Only, %*</th>
<th>Hemorrhagic Infarctions, %</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mori et al,3 1992</td>
<td>Recombinant tissue plasminogen activator, mg/kg</td>
<td>1.17</td>
<td>10</td>
<td>50</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.73</td>
<td>9</td>
<td>44</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>12</td>
<td>17</td>
<td>13</td>
<td>33</td>
</tr>
<tr>
<td>Yamaguchi et al,4 1993</td>
<td>Recombinant tissue plasminogen activator, 0.73 mg/kg</td>
<td>47</td>
<td>57</td>
<td>NA</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>46</td>
<td>24</td>
<td>NA</td>
<td>47</td>
</tr>
</tbody>
</table>

* The time to treatment was 6 hours for all trials. MCA indicates middle cerebral artery; NA, data not available.

### Table 2. Intravenous Recombinant Tissue Plasminogen Activator Thrombolytic Trials*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type of Therapy</th>
<th>Time to Treatment, h</th>
<th>No. of Patients</th>
<th>Dose of Recombinant Tissue Plasminogen Activator, mg/kg</th>
<th>Initial Stroke Severity (NIHSS Score)</th>
<th>Minimal to No Disability, %</th>
<th>Slight to No Disability, %</th>
<th>Symptomatic ICH, %</th>
<th>Mortality Due to ICH, %</th>
<th>Mortality at 90 d, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS7</td>
<td>Recombinant tissue plasminogen activator</td>
<td>3</td>
<td>312</td>
<td>0.9</td>
<td>14</td>
<td>43</td>
<td>NA</td>
<td>6</td>
<td>2.90</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>3</td>
<td>312</td>
<td>0.9</td>
<td>15</td>
<td>26</td>
<td>NA</td>
<td>1</td>
<td>0.30</td>
<td>21</td>
</tr>
<tr>
<td>ECASS I6</td>
<td>Recombinant tissue plasminogen activator</td>
<td>6</td>
<td>313</td>
<td>1.1</td>
<td>12</td>
<td>36</td>
<td>47</td>
<td>NA</td>
<td>6.30</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6</td>
<td>307</td>
<td>1.1</td>
<td>13</td>
<td>29</td>
<td>39</td>
<td>NA</td>
<td>2.40</td>
<td>16</td>
</tr>
<tr>
<td>II6</td>
<td>Recombinant tissue plasminogen activator</td>
<td>6</td>
<td>409</td>
<td>0.9</td>
<td>11</td>
<td>40</td>
<td>54</td>
<td>9</td>
<td>3.00†</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6</td>
<td>391</td>
<td>0.9</td>
<td>11</td>
<td>37</td>
<td>46</td>
<td>3</td>
<td>&lt;1.00†</td>
<td>11</td>
</tr>
</tbody>
</table>

* NIHSS indicates National Institute of Health Stroke Scale; ICH, intracerebral hemorrhage; NINDS, National Institute of Neurological Disorders and Stroke; ECASS, European Cooperative Acute Stroke Study; and NA, data not available.
† Data only available for the first 7 days.

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Table 3. Modified Rankin Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>2</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>3</td>
<td>Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderate disability: requiring some help but able to walk without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability: bedridden, incontinent, and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Death</td>
</tr>
</tbody>
</table>

comes (P=.41), but there was a statistically significant (P=.003) difference in favor of the recombinant tissue plasminogen activator–treated group for the combined BI and mRS score. However, 109 patients (17.4% of the total enrolled) should not have been enrolled based on unintended departures from the protocol, such as patients who had an abnormal head CT scan result showing evidence of early infarction or the presence of blood. An analysis of the research cohort excluding these 109 patients showed recombinant tissue plasminogen activator–related improvements in the functional outcome of patients and in the Scandinavian Stroke Scale and the combined BI and mRS scores. There was a 3-fold higher rate of brain hemorrhage in the recombinant tissue plasminogen activator–treated group, and a significant (P = .02) increase in deaths due to ICH in this group. However, the overall mortality rate at 90 days was not significantly (P = .04) different between the recombinant tissue plasminogen activator and placebo groups (Table 2). The researchers concluded that recombinant tissue plasminogen activator was effective in patients with acute ischemic stroke when administered to those who do not have early radiographic signs of cerebral infarction or other significant departures from the protocol.

The NINDS recombinant tissue plasminogen activator trials compared IV recombinant tissue plasminogen activator, 0.9 mg/kg (maximum, 90 mg), with placebo administered within 3 hours of symptom onset. The NINDS study comprised 2 trials (n = 291 in part 1 and n = 333 in part 2); part 1 measured outcomes at 24 hours, and part 2 measured outcomes at 90 days. Because part 1 also measured outcome at 90 days, the overall results were combined by the investigators and are summarized in Table 2. The primary outcomes assessed for these trials were the BI and the mRS, the same as those for the ECASS I. In addition, 2 other outcomes were measured. The first was the National Institute of Health Stroke Scale (NIHSS) score, which is an 11-item (+2-point) neurologic examination that tests cognition, level of consciousness, eye movements, visual fields, motor ability, sensation, and ataxia. It is most often used to grade the stroke severity at onset. Scores of 14 or higher are considered a moderate to large stroke. The initial NIHSS score is often compared with a follow-up score at 90 days to categorize improvement. An NIHSS score of 0 or 1 at follow-up is considered an excellent result. Another outcome measure was the Glasgow Outcome Scale, a 5-point global outcome scale with 1 representing death and 5 representing good recovery.

The primary efficacy outcome for part 1 was a 4-point improvement on the NIHSS score or the resolution of symptoms within 24 hours of stroke onset. The results demonstrated no significant (P = .21) improvement in the NIHSS score at 24 hours.

In part 2, the primary efficacy outcome was the percentage of patients with minimal or no deficit at 90 days measured by the 4 separate scales: the NIHSS, the BI, the mRS, and the Glasgow Outcome Scale. Because part 1 measured these 4 scales at 90 days as a secondary outcome, the results are often combined in the final report (n = 624). Patients treated with recombinant tissue plasminogen activator had a significantly (P = .008) better functional recovery at 90 days compared with the placebo group. Overall, there was an 11% to 13% absolute difference favoring recombinant tissue plasminogen activator in the number of patients with minimal or no deficits at 90 days. In other words, patients treated with recombinant tissue plasminogen activator were 30% more likely to have an excellent recovery than patients receiving placebo. The benefits of treatment with recombinant tissue plasminogen activator were sustained at 1 year. There were more patients with symptomatic hemorrhages and fatal ICHs in the recombinant tissue plasminogen activator–treated group than in the placebo group. However, there were no significant (P = .30) differences in early or 3-month mortality between groups (Table 2). This study showed that neurologic outcome was improved by the use of IV recombinant tissue plasminogen activator for patients with acute ischemic stroke.

Although there are case reports and nonrandomized trials that show the benefit of thrombolytic therapy, the NINDS study remains the only placebo-controlled, double-blind study to report a statistically significant (P = .008) benefit of IV thrombolytic therapy for acute ischemic stroke.

Because of the excessive protocol departures in the ECASS I and the positive results of the NINDS trial, the ECASS II (n = 800) was designed using a lower dosage of recombinant tissue plasminogen activator and requiring stricter adherence to the protocol, especially exclusion of patients with early infarct signs on a CT scan, and the NINDS studies’ guidelines for blood pressure control. The time window for treatment remained 6 hours. However, the ECASS II failed to demonstrate a significant (P = .28) difference between treatment groups in the primary outcome measure, minimal or no deficit (mRS score of 0 or 1) at 90 days (Table 2). When mRS scores were dichotomized for independence (mRS scores of 0, 1, or 2) and death or dependence (mRS score of ≥3), there was a significant (P = .02) benefit for recombinant tissue plasminogen activator–treated patients, with more patients having slight to no disability in the recombinant tissue plasminogen activator–treated arm (Table 2). The investigators found no treatment differences between patients treated within 3 hours and those treated from 3 to 6 hours after onset. Symptomatic ICH occurred more often in the recombinant tissue plasminogen activator–
treated patients than in the placebo-treated patients, but mortality at 90 days was the same in both groups. The lack of benefit of recombinant tissue plasminogen activator–treated patients in the ECASS II may be attributed to the observation that patients enrolled in the ECASS II had less severe strokes, as shown by the lower admission stroke severity scores and by the lower mortality rates in the placebo-treated group compared with mortality rates in other trials (Table 2). Thirty seven percent of the placebo-treated patients had a favorable outcome at 90 days, which is similar to the positive responses for the recombinant tissue plasminogen activator–treated patients in the ECASS I (36%) and in the NINDS (39%) trials. Also, the mortality rate in the ECASS II was roughly half that observed in the other 2 trials. Nevertheless, the researchers concluded that the trend supported a beneficial effect of recombinant tissue plasminogen activator, especially if the results were considered along with the positive results of the NINDS trial.

**Streptokinase**

Several trials of streptokinase for acute ischemic stroke were terminated prematurely due to excessive early mortality in the treatment groups. These trials administered 1.5 × 10^6 U of IV streptokinase over 1 hour to patients who presented within 4 to 6 hours of symptom onset. Mortality rates for the streptokinase-treated patients ranged from 27% to 36% compared with 12% to 20% for the placebo group. Consequently, enthusiasm for thrombolytic treatment with streptokinase has waned. However, these trials were not preceded by dose escalation studies; streptokinase was often combined with aspirin; and doses of streptokinase used were those used for myocardial infarction and may have been too high. In addition, the researchers in one of the trials have noted that the mortality rates for patients treated within 4 to 6 hours of symptom onset. The lack of benefit of recombinant tissue plasminogen activator–treated patients in the ECASS II may be attributed to the observation that patients enrolled in the ECASS II had less severe strokes, as shown by the lower admission stroke severity scores and by the lower mortality rates in the placebo-treated group compared with mortality rates in other trials (Table 2). Thirty seven percent of the placebo-treated patients had a favorable outcome at 90 days, which is similar to the positive responses for the recombinant tissue plasminogen activator–treated patients in the ECASS I (36%) and in the NINDS (39%) trials. Also, the mortality rate in the ECASS II was roughly half that observed in the other 2 trials. Nevertheless, the researchers concluded that the trend supported a beneficial effect of recombinant tissue plasminogen activator, especially if the results were considered along with the positive results of the NINDS trial.

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**CONTROLLED TRIALS OF INTRA-ARTERIAL (IA) THROMBOLYSIS**

Intra-arterial thrombolysis is an alternative approach to the use of IV thrombolytic therapy involving a cerebral angiogram to identify the site of occlusion, and delivery of thrombolytic therapy directly into the clot. There have been 2 randomized, controlled trials of IA thrombolytic therapy for the treatment of stroke due to angiographically documented occlusion of the MCA. Both trials used recombinant prourokinase, a precursor of urokinase with high fibrin specificity (ie, “clot specific”), administered along with the positive results of the NINDS trial.

<table>
<thead>
<tr>
<th>Baseline NIHSS Score</th>
<th>Recombinant Prourokinase</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-10</td>
<td>10/16</td>
<td>5/8</td>
</tr>
<tr>
<td>11-20</td>
<td>34/75</td>
<td>9/37</td>
</tr>
<tr>
<td>21-30</td>
<td>4/30</td>
<td>1/14</td>
</tr>
</tbody>
</table>

*Data from Furlan et al.12 Values are given as number (percentage) of patients. PROACT indicates Prolyse in Acute Cerebral Thromboembolism; NIHSS, National Institute of Health Stroke Scale.*

The PROACT II trial was a safety and efficacy study comparing 6 mg of IA recombinant prourokinase with placebo; both treatment groups received heparin, a 2000-IU bolus and a 500-IU/h infusion for 4 hours.13 One hundred eighty patients were enrolled (121 received recombinant prourokinase and 59 received placebo). Patients were stratified by enrollment NIHSS score into 1 of 3 severity categories (4-10, mild; 11-20, moderate to severe; and 21-30, severe) to ensure a balance of stroke severity between the treated and placebo groups. The primary outcome measure was the mRS score at 90 days, with a favorable outcome defined as an mRS score of 2 or less. Secondary outcomes were percentage of patients with an NIHSS score of 1 or less at 90 days, recanalization rates, mortality, BI, and percentage of patients with a 50% decrease in NIHSS score.

Overall, patients treated with recombinant prourokinase had a significantly (P = .04) better functional recovery (mRS score of ≤2) at 90 days compared with the placebo group. Patients with an intermediate severity stroke with an NIHSS score between 11 and 20 had the greatest difference in functional outcome between the recombinant prourokinase–treated group and the placebo group (Table 4). In those patients with a mild stroke (NIHSS score, 4-10), there was no difference in the pro-
portion attaining a good functional status. Across all 3 groups of stroke severity, there was a 15% absolute difference favoring treatment with IA recombinant prourokinase. Patients treated with recombinant prourokinase were 60% more likely to have slight or no significant disability compared with the placebo-treated group.

Recanalization rates were higher in the group treated with recombinant prourokinase but so were rates of symptomatic and asymptomatic hemorrhages. Despite the higher rate of early symptomatic hemorrhages in the recombinant prourokinase arm, mortality rates at 90 days were no different between the groups. Interestingly, 476 patients underwent angiography for possible participation in the PROACT II trial; 62% were excluded before treatment because they did not have an occlusion of the stem or first branch of the MCA. Of the 62% excluded, an internal carotid artery occlusion was found in 20%, no occlusion was identified in 19%, and 23% had either a more distal MCA occlusion or some other arterial occlusion.

Intra-arterial thrombolysis was efficacious in patients with an angiographically documented MCA occlusion of less than 6 hours’ duration. Even when using a functional outcome score similar to that used in the NINDS trial (mRS score of ≤1), more patients receiving recombinant prourokinase had a favorable outcome compared with the placebo group (Table 5).

### UNANSWERED QUESTIONS

The results from the ECASS II and the PROACT II trial raise important questions. If some milder strokes improve without treatment, should we be treating such patients with thrombolytic agents? Half the patients enrolled into the ECASS II had a stroke severity score of less than 11 (relatively mild). Thirty-seven percent of all patients had minimal to no deficit at 3 months without any thrombolytic treatment; we do not know if the improvement was seen only in those with milder stroke. In the PROACT II trial, there was no difference in outcome between drug- and placebo-treated patients with NIHSS scores between 4 and 10. Are these patients with low NIHSS scores (4-10) better candidates for IV recombinant tissue plasminogen activator therapy or should thrombolytic agents be avoided entirely? To answer these questions, we need more studies to assess the benefits and risks of treatment according to the initial stroke severity. Patients with milder strokes who may do well without thrombolytic treatment should be able to weigh the chance of increased improvement with treatment vs the risk of worsening or dying from ICH. On the other hand, patients with severe strokes who may have an increased risk of hemorrhage from recombinant tissue plasminogen activator therapy may consider risking treatment to lessen the chance of being permanently disabled or dependent on others. A recent trial of a heparinoid in patients with acute stroke by Adams and colleagues suggested that 46% of patients who present with a low NIHSS score between 7 and 10 will have an excellent outcome without any short-term therapy. Like this trial by Adams et al, most stroke trials should be designed to randomize patients according to their initial stroke severity to help address the relation between initial stroke severity and impact of therapy.

Another question raised by the results of the ECASS II and the PROACT II trial is how much improvement must occur following a stroke to be considered a meaningful outcome? Thrombolytic trials are considered “positive” if the patients have minimal to no deficit (mRS score of ≤1). Although the ECASS II found that significantly (P = .02) more patients treated with thrombolytic agents became functionally independent compared with placebo, it was not considered a successful trial because there were no treatment differences in patients for the primary outcome of minimal to no deficit. Being functionally independent is an excellent result for most patients with stroke who most fear their loss of independence. Whereas full recovery is a laudable outcome, we may be striving for too much. The PROACT II trial was considered positive because it chose as the primary outcome functional independence (mRS score of ≤2). Nevertheless, this was based on a small sample size insufficient for regulatory approval in the United States. Further work is needed to address patients’ definition of quality of life so they can help us determine what outcome they most prefer. We advocate more outcome studies that address patient preferences, expanding on work done by Matchar and colleagues that showed patients would rather be dead than dependent on others, so the added benefit of moving from an mRS score of 3 to 2 may be worthwhile to the patient population we are treating.

Based on the results of the NINDS trials, the Food and Drug Administration approved the use of IV recombinant tissue plasminogen activator therapy for the treatment of acute ischemic stroke in June 1996. Several studies have since been published showing the safety and effectiveness of recombinant tissue plasminogen activator therapy in the community. The Standard Treatment

### Table 5. Intra-arterial Recombinant Prourokinase Trials*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type of Therapy</th>
<th>No. of Patients</th>
<th>Initial Stroke Severity (NIHSS Score)</th>
<th>Minimal to No Disability, %</th>
<th>Slight to No Disability, %</th>
<th>Symptomatic ICH, %</th>
<th>Mortality Due to ICH, %</th>
<th>Mortality at 90 d, %</th>
<th>Recanalization, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROACT I</td>
<td>Recombinant prourokinase</td>
<td>26</td>
<td>17 NA</td>
<td>NA</td>
<td>15</td>
<td>4</td>
<td>27</td>
<td>58</td>
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<tr>
<td>Placebo</td>
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<td>14</td>
<td>19 NA</td>
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<td>43</td>
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<tr>
<td>PROACT II</td>
<td>Recombinant prourokinase</td>
<td>121</td>
<td>17 26</td>
<td>40</td>
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<td>25</td>
<td>66</td>
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<tr>
<td>Placebo</td>
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<td>59</td>
<td>17</td>
<td>17</td>
<td>25</td>
<td>4</td>
<td>NA</td>
<td>27</td>
<td>18</td>
</tr>
</tbody>
</table>

*PROACT indicates Prolyse in Acute Cerebral Thromboembolism; NIHSS, National Institute of Health Stroke Scale; ICH, intracerebral hemorrhage; and NA, data not available.
with Alteplase to Reverse Stroke study\(^9\) prospectively collected data on 389 patients treated with recombinant tissue plasminogen activator from 24 academic and 33 community centers. All principal investigators in this study were neurologists who had experience in treating patients with stroke who received recombinant tissue plasminogen activator. The study reported a 30-day mortality rate of 13\% and an ICH rate of 10\% (3\% symptomatic and 7\% asymptomatic). Deviations from the NINDS protocol occurred in 27\% of patients.\(^9\) The most common protocol violation was treatment beyond the 3-hour time window, and the next most common violations were treatment with anticoagulants within 24 hours of receiving a thrombolytic drug and an elevated blood pressure just before treatment. Tanne and colleagues\(^8\) performed a retrospective survey of hospitals that have organized stroke triage systems and experience giving recombinant tissue plasminogen activator. They found that symptomatic ICH occurred in 6\% of treated patients. Deviations from the NINDS protocol occurred in 30\% of patients.\(^9\) The Stroke Treatment in the Community project voluntarily collects data from 18 hospitals in Minnesota. So far, they have collected information on approximately half of all patients treated with recombinant tissue plasminogen activator and have a 10\% combined symptomatic and asymptomatic ICH rate.\(^9\)

Many of these reports published since approval of recombinant tissue plasminogen activator involved stroke centers experienced in the administration of thrombolytic agents. Many also used voluntary reporting of cases that may be biased.\(^8,9,21\) A citywide audit of 27 Cleveland, Ohio, area hospitals prospectively collected cases of patients treated with IV recombinant tissue plasminogen activator and compared the results with patients not treated with thrombolytic therapy.\(^22\) In this study, Katz and colleagues found a higher symptomatic ICH rate (15.7\%) and a higher mortality rate (15.7\%) in the thrombolytic-treated group compared with those found in the NINDS trial. The researchers also found that 50\% of patients treated with thrombolytic agents had deviations from national treatment guidelines.\(^2,3\) The most common deviations involved the use of antiplatelet agents or anticoagulants within 24 hours of recombinant tissue plasminogen activator administration and treatment beyond the 3-hour limit. The explanation for the higher rates of ICH and mortality is unknown. The researchers speculate that hospitals with less experience in the administration of recombinant tissue plasminogen activator may have had higher symptomatic hemorrhage rates. They also note that the high rate of departures from the national recommendations for treatment with recombinant tissue plasminogen activator may be a surrogate marker for lack of familiarity with thrombolysis and acute stroke management. Others\(^8,9,21\) have also found higher complication rates when strict adherence to the guidelines was not followed, although the Standard Treatment with Alteplase to Reverse Stroke study\(^9\) did not find a correlation.

These observations raise an important question of whether the community experience with recombinant tissue plasminogen activator can match that of a controlled trial run by experienced stroke investigators. The results of the ECASS I have shown us the perils of protocol violations. More prospective studies will be needed to follow the outcome of patients treated with thrombolytic therapy outside of a randomized, controlled trial. These studies may also provide insight into other questions regarding widespread use of thrombolytic therapy. For instance, what is the appropriate level of clinical expertise needed for administration of thrombolytic therapy? Does a neurologist need to be present or simply available by telephone? On a larger scale, should thrombolytic treatment be available in all emergency department settings? These answers can only be provided by ongoing surveillance of recombinant tissue plasminogen activator use and carefully planned surveillance studies. The Stroke Treatment in the Community project is still ongoing and, although this is a voluntary project with inherent biases, should provide important insights into the community experience with thrombolytic agents. Further analysis is under way to compare outcomes between patients treated at academic, metropolitan, and rural hospitals. Another ongoing study\(^26\) is a prospective comparison of the outcome of treatment with IV recombinant tissue plasminogen activator by emergency department physicians with telephone consultation of a neurologist vs treatment by a stroke neurologist. A preliminary report suggested there was no difference in outcomes, although there was an initial disparity between protocol violations among the emergency department physicians (33\%) vs the neurologists (5\%). An educational program was supplied and the disparity lessened, but further results are pending.\(^26\)

Extensive diagnostic testing may limit the application of recombinant tissue plasminogen activator because a certain level of expertise would need to be quickly available in all emergency departments. Do we need to know the cause of stroke before we administer thrombolytic therapy? Since IV thrombolytic therapy must be administered within 3 hours of symptom onset, many patients receive treatment before the cause of stroke can be fully evaluated. The PROACT II trial has shown that 19\% of patients who are thought to have a blood clot do not have an arterial occlusion by angiography. Caplan et al\(^2\) advocated using IV recombinant tissue plasminogen activator therapy only when arterial occlusive lesions can be demonstrated by vascular imaging studies. While this approach will treat only patients with ischemic stroke due to identifiable arterial blockage, it also delays treatment and limits thrombolytic intervention to specialized centers with readily available imaging technology. Conversely, James Grotta, MD, recommends more widespread use of IV recombinant tissue plasminogen activator therapy for patients with acute ischemic stroke in strict accordance with published guidelines, emphasizing reducing time to treatment over establishing a definitive diagnosis.\(^2\) In this approach, some patients with transient ischemic attacks or nonischemic conditions may receive thrombolytic therapy. Both viewpoints illustrate the need for ongoing research to better define the indications for thrombolysis and identify new ones.

There are no recent, large, randomized, controlled studies that directly compare thrombolytic agents in the treatment of acute ischemic stroke. In the United States,
IV recombinant tissue plasminogen activator therapy is the only approved agent for this indication. Based on recent controlled trials, streptokinase cannot be recommended for the treatment of ischemic stroke. Recent studies have demonstrated that IA prourokinase may be a new thrombolytic option in selected patients with stroke. Although the recalibration rate for IA therapy is higher than that for IV administration, and recalibration is associated with improved outcome, until we have more conclusive evidence, we cannot recommend one route over the other. Location of clot, severity of stroke, and institutional and community capabilities may eventually dictate the most appropriate routes. Studies need to be done that compare IA with IV therapy in patients with acute ischemic stroke.

It is our opinion that IV recombinant tissue plasminogen activator therapy can at once be the standard of care for acute ischemic stroke and a source of comparison in prospective, randomized trials of new diagnostic and treatment alternatives. For example, these trials may investigate the role of imaging technologies, such as diffusion-weighted magnetic resonance imaging, magnetic resonance angiography, CT angiography, and transcranial Doppler ultrasonography, in identifying optimal candidates for thrombolysis. Prospective, randomized trials using IV recombinant tissue plasminogen activator therapy as the standard of care also provide the most powerful and efficient means of investigating new treatment alternatives, such as variations in thrombolytic delivery (dose, time window, mode of administration, and type of agent) and combination therapy with cytoprotective agents or platelet inhibitors.

In summary, thrombolytic therapy for ischemic stroke exemplifies the delicate balance between risk and benefit. Data from randomized, controlled trials have provided indications when the benefits of thrombolytic therapy clearly outweigh the risks. These trials also provide insight into clinical situations when the risk is too high for intervention. Unsettled issues requiring controlled investigation include the following: (1) identifying subgroups of patients based on initial stroke severity who will derive particular benefit or who are at special risk; (2) determining whether knowledge of site of occlusion should influence mode of delivery; (3) measuring health-related quality of life and patient preferences to determine what is the optimal outcome from the patients’ perspective; and (4) assessing the effectiveness of thrombolytic therapy in the community.

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Reprints: Judith A. Hinchey, MD, Strong Memorial Hospital, Box 681, 601 Elmwood Ave, Rochester, NY 14620 (e-mail: Judith_Hinchey@urmc.rochester.edu).

REFERENCES