Intravenous Tissue-Type Plasminogen Activator for Treatment of Acute Stroke
The Standard Treatment with Alteplase to Reverse Stroke (STARS) Study

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Tissue-type plasminogen activator (tPA) is the only medication approved for treatment of acute ischemic stroke. This therapy was approved by the Food and Drug Administration in June 1996 for selected patients who can be treated within 3 hours of stroke onset. The approval was based on the results of a clinical trial sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) that randomized a total of 624 patients to treatment with intravenous tPA (0.9 mg/kg, maximum of 90 mg) vs placebo within 3 hours of stroke onset.1,2 This study demonstrated substantial and statistically significant benefits in neurologic outcomes at 3 and 12 months, despite a 6.4% rate of symptomatic intracerebral hemorrhage (ICH) within 36 hours of tPA treatment.

Use of intravenous tPA for appropriately selected patients with acute ischemic stroke has been strongly endorsed (Grade A recommendations) by the American Academy of Neurology, the American Heart Association, and the American Stroke Association. The modified Rankin Scale score was used to assess clinical outcomes at 30 days.

Context Tissue-type plasminogen activator (tPA) is the only therapy for acute ischemic stroke approved by the Food and Drug Administration.
Objective To assess the safety profile and to document clinical outcomes and adverse events in patients treated with intravenous tPA for acute stroke in clinical practice.
Design and Setting Prospective, multicenter study of consecutive patients enrolled between February 1997 and December 1998 at 57 medical centers in the United States (24 academic and 33 community).
Intervention Intravenous tPA (recombinant alteplase).
Patients Three hundred eighty-nine patients with a mean age of 69 years (range, 28-100 years); 55% were men.
Main Outcome Measures Time intervals between stroke symptom onset, hospital arrival, and treatment with tPA; pretreatment computed tomographic scan results, intracerebral hemorrhage, and major systemic bleeding. The modified Rankin Scale score was used to assess clinical outcomes at 30 days.
Results Median time from stroke onset to treatment was 2 hours 44 minutes, and the median baseline National Institutes of Health Stroke Scale score was 13. The 30-day mortality rate was 13%. At 30 days after treatment, 35% of patients had very favorable outcomes (modified Rankin score, 0-1) and 43% were functionally independent (modified Rankin score, 0-2). Thirteen patients (3.3%) experienced symptomatic intracerebral hemorrhage, including 7 who died. Twenty-eight patients (8.2%) had asymptomatic intracerebral hemorrhage within 3 days of treatment with tPA.

Protocol violations were reported for 127 patients (32.6%), and included treatment with tPA more than 3 hours after symptom onset in 13.4%, treatment with anticoagulants within 24 hours of tPA administration in 9.3%, and tPA administration despite systolic blood pressure exceeding 185 mm Hg in 6.7%. A multivariate analysis found predictors of favorable outcome to be a less severe baseline National Institutes of Health Stroke Scale score, absence of specific abnormalities (effacement or hypodensity of >33% of the middle cerebral artery territory or a hyperdense middle cerebral artery) on the baseline computed tomographic scan, an age of 85 years or younger, and a lower mean arterial pressure at baseline.

Conclusions This study, conducted at multiple institutions throughout the United States, suggests that favorable clinical outcomes and low rates of symptomatic intracerebral hemorrhage can be achieved using tPA for stroke treatment.

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See also pp 1151 and 1189.

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American College of Chest Physicians.3,5 Despite these endorsements, only a small fraction of eligible stroke patients currently receive tPA therapy.6,7 One of the greatest concerns regarding the use of tPA for stroke treatment is the belief that the risk of symptomatic ICH may be higher in routine clinical use than it was in the NINDS-sponsored research study.8

Standard Treatment with Alteplase to Reverse Stroke (STARS) was a large phase 4 study, mandated by the Food and Drug Administration, and designed to assess the safety profile and clinical outcomes obtained following intravenous tPA therapy for acute stroke patients in clinical practice. This prospective, monitored, multicenter study followed the clinical course of nearly 400 patients with acute ischemic stroke consecutively treated at 57 medical centers in the United States.

METHODS
Consecutive patients who presented with an acute ischemic stroke and who received intravenous tPA were eligible for participation in the study. Patients treated with tPA at the participating centers were approached just prior to, or immediately following, tPA therapy and asked to participate in this study. Investigators were instructed to attempt to enroll every patient they treated with intravenous tPA for acute stroke at each participating center. Data regarding the number of potentially eligible patients who refused tPA therapy were not collected. The protocol was approved by the human subjects committee at each participating center. Informed consent was obtained from the patient (or the responsible family member if the patient was not capable of understanding the study).

Information regarding patient demographics, associated medical problems, time intervals between stroke symptom onset, hospital arrival, and treatment with tPA was collected. A cranial computed tomographic (CT) scan was performed prior to tPA treatment in all patients; the initial CT interpretation was performed by the investigator or a radiologist, or both, or a neuroradiologist. The patients’ clinical course was followed closely by the investigators during hospitalization. If significant neurologic deterioration occurred, an urgent CT scan was obtained to assess the presence of ICH. Any major systemic bleeding or requirement for a blood transfusion was recorded. At the time of treatment, the baseline National Institutes of Health Stroke Scale (NIHSS) score was obtained. Information regarding the findings on the baseline CT scan was collected based both on the investigator’s reading of the study and the final radiology report.

Patient follow-up (either by telephone or in person) occurred 30 days after therapy. The patient or caregiver provided information regarding any significant adverse effects following the acute hospitalization and a modified Rankin Scale score10 was obtained to assess functional outcome. For patients who died, the cause of death was determined. In addition, if any clinically significant neurologic deterioration occurred following the acute hospitalization, an attempt was made to determine the cause based on review of the medical record. All follow-up data were collected by one of the principal investigators or study coordinators; these individuals were all trained in the administration of both the NIHSS and the modified Rankin Scale.

All 83 active centers that were participating in an ongoing randomized clinical trial (the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS] study),11 which was evaluating the benefits of intravenous tPA therapy administered between 3 and 5 hours after stroke symptom onset, were invited to participate in the STARS study. Fifty-seven medical centers (24 academic and 33 community) agreed to participate (listed at the end of this article). Nearly all of the principal investigators were neurologists who had previous experience treating patients with stroke with tPA or placebo in the setting of a clinical trial. Patients were enrolled between February 1997 and December 1998.

A preplanned multivariate analysis was carried out to assess predictors of recovery (modified Rankin Scale score, ≤1) and independence (modified Rankin Scale score, ≤2). Potential predictors of favorable outcome were identified in advance by members of the STARS publication committee. It was specified in advance that any variable with more than 10% missing values would not be used in this analysis.

Data in this study were collected on standardized case report forms that were audited by study monitors at onsite visits. Data were double-entered and checked for consistency at a centralized data management center (Genentech Inc, San Francisco, Calif). Errors and inconsistencies were resolved by contacting study site personnel.

Violations of the protocol for tPA administration used for the NINDS tPA Stroke Trial were assessed. The following were considered to be protocol violations: dose of tPA administered of more than 10% the calculated dose requirement, treatment initiated more

### Table 1. Patient Characteristics (N = 389)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), y</td>
<td>69 (28-100)</td>
</tr>
<tr>
<td>Men</td>
<td>55</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
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<tr>
<td>Black</td>
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<tr>
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<tr>
<td>Hispanic</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Previous stroke</td>
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<tr>
<td>Congestive heart failure</td>
<td>13</td>
</tr>
<tr>
<td>Previous transient ischemic attack</td>
<td>12</td>
</tr>
<tr>
<td>Cancer</td>
<td>11</td>
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<tr>
<td>Baseline computed tomographic scan results</td>
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<tr>
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<td>42</td>
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<tr>
<td>Acute hypodensity</td>
<td>15</td>
</tr>
<tr>
<td>≤1⁄3 middle cerebral artery</td>
<td>13</td>
</tr>
<tr>
<td>&gt;1⁄3 middle cerebral artery</td>
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</tr>
<tr>
<td>Hyperdense middle cerebral artery</td>
<td>9</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>6</td>
</tr>
<tr>
<td>Mass effect</td>
<td>2</td>
</tr>
<tr>
<td>Baseline National Institutes of Health Stroke Scale score</td>
<td>8</td>
</tr>
<tr>
<td>1-4</td>
<td>1</td>
</tr>
<tr>
<td>5-10</td>
<td>8</td>
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<tr>
<td>11-15</td>
<td>31</td>
</tr>
<tr>
<td>16-20</td>
<td>22</td>
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<tr>
<td>&gt;20</td>
<td>20</td>
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than 3 hours after symptom onset, evidence of ICH on the baseline CT scan, blood pressure higher than 185/110 mm Hg at the time of tPA treatment, baseline international normalized ratio of more than 1.7, elevation of the baseline partial thromboplastin time, treatment with antiplatelet agents or anticoagulants within 24 hours of tPA administration, and prior medical history contraindication (known bleeding diathesis, intracerebral neoplasm, arteriovenous malformation, or cerebral aneurysm).

RESULTS

Three hundred eighty-nine consecutive patients were enrolled at 57 medical centers. The median number of patients enrolled per center was 5 (range, 1-24). Demographic characteristics of the patient population are shown in Table 1. The median time from stroke onset to tPA treatment was 2 hours 44 minutes (25th–75th percentiles, 2 hours 14 minutes–2 hours 56 minutes). The median time from presentation to the emergency department (ED) and tPA treatment was 1 hour and 36 minutes (25th–75th percentiles, 1 hour 15 minutes–2 hours 4 minutes). Most patients (82.3%) were treated with tPA between 91 and 180 minutes after stroke onset, 4.1% were treated within 90 minutes, and 13.4% were treated after 180 minutes.

Patients who arrived at the ED soon after stroke onset typically had longer delays between ED arrival and tPA treatment (Figure). On average, every 30-minute delay between stroke onset and ED arrival was associated with a 15-minute decrease in the time between arrival and initiation of tPA therapy (regression coefficient, −0.56; P < .001). The median NIHSS score at baseline was 13 (mean, 14 [range, 1-38]). Stroke severity ranged from mild (NIHSS score, ≤4) in 8% to severe (NIHSS score, >20) in 19% (Table 1). All 389 patients had a baseline CT scan prior to tPA treatment (Table 1). Three hundred forty-two patients (88%) had a follow-up head CT scan during their hospitalization.

Symptomatic ICH occurred within 3 days of treatment in 13 patients (3.3% [95% confidence interval, 1.8%-5.6%]). Seven (54%) of the 13 patients with symptomatic ICH died. Two (29%) of the 7 patients who had hypodensity involving more than one third of the middle cerebral artery (MCA) territory on the baseline CT scan had a symptomatic ICH compared with 11 (3%) of the 382 patients who had no hypodensity or hypodensity in less than one third of the MCA territory (P = .02). Asymptomatic ICH within 3 days of treatment occurred in 28 patients (8.2% [95% confidence interval, 5.2%-11.1%]). Major systemic bleeding occurred in 6 patients (1.5% [95% confidence interval, 0.3%-2.8%]).

Protocol violations occurred in 127 patients (32.6%) (Table 2). Symptomatic ICH occurred in 3.9% of the patients with protocol violations (time-to-treatment >3 hours [n = 3]; blood pressure >185/110 mm Hg at time of treatment [n = 1]; >10% overdose of tPA [n = 1]) compared with a rate of 3.1% in patients without protocol violations (P = .70).

Thirty-day follow-up data were available for 382 (98%) of the 389 enrolled patients. The 30-day mortality rate was 13%; 51 patients died. A total of 132 patients (35%) had a very favorable clinical outcome (modified Rankin Scale score, 0-1) and 165 (43%) were functionally independent (modified Rankin Scale score, ≤2). Moderate disability (modified Rankin Scale score, 3) was present in 47 (12%), and 119 (31%) had moderate-to-severe or severe disability (modified Rankin score, 4-5).

Because of the low incidence of symptomatic ICH, it was not possible to perform a multiple logistic regression to assess predictors of ICH. The results of the multiple regression model to determine predictors of recovery (Rankin score, 0-1) or independence (Rankin score, 0-2) at 30 days are shown in Table 3. Predictors of favorable clinical outcome were a baseline NIHSS score of 10 or less, absence of specific abnormalities (hyperdense MCA, hypodensity, or effacement of >one third of the MCA territory) on the baseline CT scan, age 85 years and younger, and lower mean arterial pressure at baseline.

For every 5-point increase in baseline NIHSS score, patients had a 22% decrease in the odds of recovery (P = .16), and patients with baseline NIHSS scores greater than 10 had a 75% decrease in the odds of recovery.

Patients with a hyperdense MCA sign or hypodensity or effacement of more than 33% of the MCA territory on the baseline CT scan had an 87% decrease in odds of recovery. Only 5% of the patients with these early CT signs...
recovered compared with 38% of those who did not have these findings. Every 10-point increase in baseline mean arterial pressure decreased the odds of recovery by 19%.

The results of the multivariate model to predict independence were similar to those of the model developed to predict recovery (Table 3). The only significant differences were that age of 85 years and younger was a predictor of independence and baseline mean arterial pressure was not.

**COMMENT**

The STARS study is the largest prospective, monitored, postapproval trial with intravenous tPA for treatment of acute ischemic stroke. The most important difference between STARS and the NINDS clinical trial is that STARS did not include a control group to allow an assessment of the efficacy of tPA therapy. In addition, clinical outcomes were assessed 30 days after treatment in STARS, and at 90 days in the NINDS study. Furthermore, the methods for assessment of ICHs differed slightly between the 2 studies. These differences significantly limit any direct comparison of the results of these 2 studies. Despite these limitations, the STARS results provide compelling evidence that the NINDS protocol can be applied safely by physicians at a wide variety of medical centers throughout the United States.

The most important finding of this study is that the symptomatic ICH rate was 3.3% at 3 days, which is lower than the rate (6.4%) observed in the NINDS tPA Stroke Trial. This finding demonstrates that use of tPA for treatment of acute ischemic stroke in clinical practice by properly trained physicians can be as safe as it was in the NINDS-sponsored clinical trial.

This low rate of symptomatic hemorrhage is unlikely to be explained by major differences between the patient populations enrolled in STARS and the NINDS study. Independent predictors of symptomatic ICH in the NINDS study were baseline stroke severity and the presence of brain edema on the baseline CT. The median NIHSS score was only slightly lower in the STARS study than the NINDS trial (13 vs 14), while the number of patients with very severe strokes (NIHSS score, >20), 19% in STARS and 20% in NINDS, was similar. Cerebral edema on the baseline CT scan was reported in 4% of the NINDS study patients and 6% of the STARS patients. The NINDS trial required a repeat CT scan 24 hours after treatment for all patients. In STARS, a repeat CT was only required for patients who experienced clinical deterioration; however, 88% of the patients in STARS had follow-up CT scans during their hospitalization. The rates of asymptomatic plus symptomatic ICH (11.3% in STARS and 10.9% in the NINDS study) were similar. It is possible that some of the hemorrhages considered to be asymptomatic by STARS investigators might have been rated symptomatic in the NINDS study.

Although 5 of the 13 patients with symptomatic ICH in STARS had protocol violations, this was not a significant increase when compared with patients who did not have protocol violations. Several smaller trials have documented higher rates of symptomatic ICH in patients with violations of the NINDS protocol. Further study is required to determine which protocol violations are most closely associated with ICH.

Very favorable clinical outcomes at 30 days (modified Rankin score, ≤1) occurred in 35% of the STARS patients; 43% were functionally independent (modified Rankin score, ≤2). These clinical outcomes cannot be directly compared with the NINDS trial results because 30-day modified Rankin scores were not obtained in the NINDS trial. At 90 days, 39% of the tPA-treated patients in part 2 of the NINDS study had a modified Rankin score of 1 or less. A larger percentage of highly favorable outcomes is typically expected at 90 days compared with the 30-day rates. For example, among 272 patients treated with intravenous tPA between 3 to 5 hours after stroke onset in the ATLANTIS trial, 36.5% had a modified Rankin score of 1 or less at 30 days, whereas 42.3% achieved this level of recovery at 90 days. Therefore, the percentage of patients with 90-day modified Rankin scores of 1 or less in STARS is likely comparable with the results obtained in the NINDS study.

Several predictors of favorable outcome were identified in the multiple regression analysis. Patients who were most likely to achieve favorable outcomes were younger, had milder base-

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**Table 3. Predictors of Neurologic Recovery and Independence**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Neurologic Recovery</th>
<th>Neurologic Independence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>0.55 (0.3-1.1)</td>
<td>0.41 (0.20-0.84)</td>
</tr>
<tr>
<td>&lt;65</td>
<td>1.25 (0.7-2.2)</td>
<td>1.32 (0.74-2.34)</td>
</tr>
<tr>
<td>Mean arterial pressure per 10 mm Hg</td>
<td>0.81 (0.68-0.98)</td>
<td>0.81 (0.71-1.01)</td>
</tr>
<tr>
<td>National Institutes of Health Stroke Scalea</td>
<td>0.78 (0.54-1.1)</td>
<td>0.77 (0.55-1.07)</td>
</tr>
<tr>
<td>Score per 5 points</td>
<td>.16</td>
<td>.003</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0.25 (0.10-0.63)</td>
<td>0.24 (0.10-0.58)</td>
</tr>
<tr>
<td>Early computed tomographic signs†</td>
<td>0.13 (0.03-0.58)</td>
<td>0.13 (0.04-0.46)</td>
</tr>
<tr>
<td>Off-label usage‡</td>
<td>0.94 (0.53-1.67)</td>
<td>0.87 (0.49-1.53)</td>
</tr>
</tbody>
</table>

*aIndicates baseline values.
†Indicates overdose of more than 10%, treatment lasting longer than 3 hours, evidence of blood on baseline computed tomographic scan, anticoagulant or antiplatelet medications within 24 hours after treatment, blood pressure higher than 185/110 mm Hg at the time of treatment, international normalized ratio of more than 1.7, partial thromboplastin time elevated at baseline, or prior medical history contraindication.

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line stroke severity (NIHSS score, ≤10), were less likely to have certain abnormalities on their baseline CT scan, and had lower mean arterial pressure at baseline. These same clinical features were identified in the NINDS trial as important predictors of clinical outcome. However, in the NINDS study, the presence of these features did not predict a differential clinical response to tPA therapy. Although older patients with severe baseline neurologic deficits generally have a poor prognosis, tPA therapy may result in more of these patients having a mild-to-moderate disability rather than a severe disability. Therefore, the presence of these poor prognostic features does not indicate that tPA should be withheld from these patients. Rather, these patients and their family members can be informed that very favorable outcomes are unlikely, however, tPA treatment may result in a lower rate of severe disability.

Evidence on baseline CT scan of acute hypodensity involving greater than one third of the MCA territory was found to be a predictor of poor response to intravenous tPA therapy in a post-hoc analysis of a study (European Cooperative Acute Stroke Study 1) that treated patients with a higher dose of tPA (1.1 mg/kg) up to 6 hours after stroke onset. Only 2% of the STARS patients had acute hypodensity greater than one third of the MCA territory, and these patients had an increased rate of symptomatic ICH. This finding supports current recommendations that tPA therapy should be withheld in patients with evidence of major early infarction on the baseline CT scan.

In the NINDS trial, half of the patients were treated within 90 minutes of symptom onset. Recently, the NINDS investigators concluded that the benefits of treatment declined significantly toward the end of the 3-hour treatment window. In the STARS study, the median time from stroke onset to tPA treatment was 2 hours and 44 minutes, indicating that only half the patients were treated prior to the last 15 minutes of the therapeutic window. In addition, 13.4% of the patients were treated beyond 3 hours after stroke onset. The relatively long median time from ED arrival to tPA treatment (1 hour 36 minutes) suggests that considerably more effort is required to expedite the emergency evaluation of these patients. The inverse relationship between the time from symptom onset to ED arrival and treatment delays in the ED indicates that patients arriving early after symptom onset were not evaluated as rapidly as patients arriving later after symptom onset. This discrepancy should be a focus of future educational efforts.

The symptomatic ICH rates and favorable outcome rates in STARS are similar to those reported in several smaller phase 4 studies. We believe the STARS data is reliable and accurate because case report forms were monitored prospectively during the course of the study, data were checked and verified, and consecutive patients were enrolled.

In summary, the STARS study is the largest prospective, monitored, post-approval trial with intravenous tPA for treatment of acute ischemic stroke. The results of this study suggest that favorable outcomes and low rates of symptomatic ICH can be achieved in clinical practice at multiple medical centers across the United States.

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INTRAVENTOUS tPA FOR TREATMENT OF STROKE

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REFERENCES

Learning is not attained by chance, it must be sought for with ardor and attended to with diligence.
—Abigail Adams (1744-1818)