Findings From the Reanalysis of the NINDS Tissue Plasminogen Activator for Acute Ischemic Stroke Treatment Trial

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Background and Purpose—Following publication of concerns about the results of the National Institute of Neurological Disorders and Stroke (NINDS) intravenous tissue plasminogen activator (t-PA) in acute stroke treatment trial, NINDS commissioned an independent committee “to address whether there is concern that eligible stroke patients may not benefit from t-PA given according to the protocol used in the trials and, whether the subgroup imbalance (in baseline stroke severity) invalidates the entire trial.”

Methods—The original NINDS trial data were reanalyzed to assess the t-PA treatment effect, the effect of the baseline imbalance in stroke severity between the treatment groups on the t-PA treatment effect, and whether subgroups of patients did not benefit from receiving t-PA.

Results—A clinically important and statistically significant benefit of t-PA therapy was identified despite subgroup imbalances in baseline stroke severity and an increased incidence of symptomatic intracerebral hemorrhage in t-PA treated patients. The adjusted t-PA to placebo odds ratio (OR) of a favorable outcome was 2.1 (95% CI, 1.5 to 2.9). Although these exploratory analyses found no statistical evidence that the t-PA treatment effect differed among patient subgroups, the study was not powered to detect subgroup treatment differences.

Conclusions—These findings support the use of t-PA to treat patients with acute ischemic stroke within 3 hours of onset under the NINDS t-PA trial protocol. Health professionals should work collaboratively to develop guidelines to ensure appropriate use of t-PA in acute ischemic stroke patients. (Stroke. 2004;35:2418-2424.)

Key Words: randomized controlled trials ■ stroke, acute ■ tissue plasminogen activator
acute ischemic stroke was insufficient to warrant its classification as a standard of care. This statement cited specific concerns regarding the risk of intracerebral hemorrhage, whether the trial results were generalizable, and whether an imbalance in baseline stroke severity between the 2 treatment groups biased the results in favor of t-PA treatment. Concerns about these issues culminated in the publication of a series of articles in March 2002 that were critical of the conduct of the trial and the subsequent development of acute stroke treatment guidelines.

In response to these criticisms, NINDS commissioned an independent committee to reanalyze the data from the trial and to address some of the concerns that had been raised. The principal charge communicated to the committee from NINDS was “to address whether there is concern that eligible stroke patients may not benefit from t-PA given according to the protocol used in the trials and whether the subgroup imbalance (in baseline stroke severity) invalidates the entire trial as claimed by some of the critics.” The committee submitted a comprehensive report to the Director of NINDS in August 2003. The present article is a summary of the committee’s methods and conclusions.

Methods
The committee restricted its analysis to the evaluation of issues defined in the NINDS charge. Full details of the methodology and the principal results of the NINDS t-PA acute stroke trial have been published previously. Full details of the independent committee’s methods, and the complete results of the reanalysis, were documented in the report that was submitted to NINDS.

Data Management
To validate the study data obtained from NINDS through an independent contractor, the committee replicated data summaries and analysis results from Tables 1 through 4 from the primary NINDS trial manuscript and one table each from several other articles. Only trivial differences were observed, indicating that the committee had access to the proper data and had defined the variables correctly.

Study Design
In their primary study the investigators described 2 studies, Parts 1 and 2, each conducted by the same investigators, following the same randomization and follow-up protocols with the investigators blinded to the outcome of Part 1 until Part 2 was complete. Randomization in each part was stratified and balanced at each center according to whether the patient was randomized within the first 90 minutes or within 91 to 180 minutes after stroke onset. Patients whose time from stroke onset exceeded 180 minutes were ineligible. Consequently, the committee treated the 2 studies as a single, large, randomized controlled trial with 3 stratification factors: study part (part 1 or 2), center (categorical variables for the clinical centers enrolling patients in the study), and time from stroke onset to treatment (OTT: 0 to 90 or 91 to 180 minutes). There were 624 patients evaluated by the NINDS investigators with 291 and 333 patients in the Part 1 and 2 studies, respectively. The committee restricted its analysis to 622 patients (310 and 322 t-PA- and placebo-treated patients, respectively) after disregarding 2 patients who were mistakenly randomized into the trial >180 minutes after stroke onset.

Outcome Measures
The NINDS investigators used 4 outcome measures: Barthel index, modified Rankin scale, and Glasgow outcome scale, which are measures of functional status, and the National Institutes of Health Stroke Scale (NIHSS), which is a measure of neurological deficit. The primary response variable for each measure was a dichotomous indication of whether the outcome was “favorable” or “unfavorable.” The favorable definitions (Barthel, 95 or 100; Rankin, 0 or 1; Glasgow, 1; and NIHSS, 0 or 1) are associated with either normal or near normal functional status. For each measure, death was treated as an unfavorable outcome. Because the measures assess different aspects of the consequences of stroke, they are neither completely congruent nor statistically independent. The committee evaluated comparisons of the placebo and t-PA treatments for each of the measures individually and, as did the NINDS investigators, for a 4D vector of the favorable/unfavorable indicators serving as a “global” indicator of a favorable response. The investigators conducted clinical assessments in both studies at 24 hours, 90 days, and 1 year after stroke onset. The 5 patients who were “lost,” in the sense that they were known to be alive but did not provide favorable/unfavorable status information, were assigned the least favorable known level for each index. Detailed examination of outcome data at 90 days and 1 year demonstrated similar treatment effects. Therefore, the committee restricted its analysis to the outcome assessment at 90 days after stroke onset.

Analytic Methods
The baseline variable distributions of the placebo and t-PA treatment groups were compared using $\chi^2$ tests for the dichotomous and polychotomous variables and rank sum tests for the continuous variables. Missing data were handled as follows: (1) 5 variables (body mass index, prior atherosclerosis, prior hyperlipidemia, baseline fibrinogen, and prior transient ischemic attack) were eliminated from all subsequent analyses because each had missing values for >40 patients; (2) other missing values, which occurred in only a small number of patients, were imputed by sampling at random from the existing data. The imputations were replicated 5 times with no evident impact on distributions. However, it is possible that the committee’s analyses differ from the NINDS investigators’ analyses in minor ways because of different imputation strategies.

Analytic Models
To analyze the dichotomous favorable/unfavorable outcome, a generalized linear model with the logit-link function was used. Treatment comparisons were based on models that adjusted for stratification factors, potential confounding factors, and potential effect modifying factors. Conclusions are reported in both the odds ratio (OR) and probability scales.

To analyze the Global outcome measure, the committee and the investigators used a generalized estimating equation model with a logit-link function and a correlation structure estimated by the empirical correlations among the 4 indices. This analysis yields a general OR estimate comparing the odds of a (global) favorable outcome in the t-PA treated group to that in the placebo group, while adjusting for stratification and baseline factors.

With the exception of admission and baseline blood pressure (BP) measurements (reasons for the exclusions are described later), all baseline covariates were considered for initial inclusion in the models. A forward stepwise selection process ($P<0.05$ to enter and remain) was performed for each of the outcome measures, constraining the models to include the design stratification variables (study part, center, and OTT) to derive a candidate list of covariates for consideration. A covariate was considered to be in the candidate list if it entered the stepwise process for at least 1 of the 4 outcome measures. In addition, all covariates in the candidate list were reviewed for clinical relevance. The candidate covariates were then screened for pairwise interactions using the forward stepwise selection process. Any covariate or interaction (and any corresponding lower order effects) was included in the final list of covariates if it remained in the model after this second stepwise screening process for any of the 4 outcome measures. All variables in this final list were then entered in descending order of importance in the global model, and variables that were significant ($P<0.01$) in the global model were used in all analytic models.
Baseline Stroke Severity Imbalance Analysis and Subgroup Analyses

The charge from NINDS asked the committee to address the questions of whether the t-PA treatment effect might be different in subsets of patients and whether the imbalance in stroke severity in the 2 treatment arms invalidated the overall trial results. Such questions are addressed by examining interactions within the analytic models developed to compare the treatments. After developing these models by the stepwise processes described above, each subgroup of interest, and each subgroup defined by the observed imbalance in stroke severity, was examined individually. This involved entering appropriate indicator variables in the models and examining the interaction of those variables with the treatment indicator variable. The full report submitted to NINDS describes this process in detail and also provides details of the post hoc power of such tests.

Results

Baseline Balance

The balance between the placebo and t-PA groups was assessed for 64 baseline variables. As in the NINDS trial, a number of statistically significant imbalances were identified. Patients randomized to placebo were slightly younger, weighed slightly more, and were less likely to be on a daily regimen of aspirin. Although the 2 groups did not have different median baseline NIHSS values (15 versus 14; \(P=0.10\)), when the patients were categorized as NIHSS 0 to 5, 6 to 10, 11 to 15, 16 to 20, and >20, a significant imbalance was identified (\(P=0.005\)) as presented in detail below. This latter imbalance was specifically mentioned in the charge to the committee, and our analysis of its impact will be discussed later.

Covariates

The stepwise process described in the methods section was applied to see which, if any, of the baseline variables were related to outcome and, thus, should be included in the analytic models. Age, baseline NIHSS (as a continuous variable), and an interaction between them were collectively highly significant for each outcome variable and for the global analysis (\(P<0.0001\)). A history of diabetes (\(P<0.003\)) and the existence of a disability before the stroke (\(P<0.0001\)) were also significantly related to the outcome measures. These variables were included, along with the stratification variables, in all analytic models.

Primary Analysis

The global analysis resulted in an unadjusted t-PA to placebo OR of a favorable outcome estimate of 1.9 (95% CI, 1.4 to 2.5) and an adjusted t-PA to placebo OR of 2.1 (95% CI, 1.5 to 2.9), both implying a statistically significant benefit of t-PA treatment at 3 months (Table 1). The latter analysis was adjusted for study part, center, OTT, age, baseline NIHSS, diabetes, and preexisting disability. Older age, more severe stroke (as measured by baseline NIHSS), a history of diabetes, and preexisting disability were all associated with a decreased likelihood of having a favorable clinical outcome at 3 months. The adjusting variables were examined for effect modification and there was no statistically compelling evidence that any variable modified the t-PA treatment effect.

### Absolute Treatment Benefit

The observed percentage point differences between the favorable outcome rates for the t-PA and placebo treatment groups were 14.1, 16.3, 14.4, and 13.7 for the Barthel, Rankin, Glasgow, and NIHSS outcome measures, respectively (Table 1). Using the adjusted OR estimates for each of the outcome measures, the adjusted estimated percentage point differences were 19.3, 20.2, 17.9, and 15.6, respectively for the Barthel, Rankin, Glasgow, and NIHSS outcome measures (Table 1). Thus, after taking into account the modeling process, which led to slightly larger adjusted OR estimates, the adjusted estimated differences were also greater than the observed differences.

### Analysis of Baseline Stroke Severity Imbalance

When patients were grouped into 5 strata (approximate quintiles [Q]) according to baseline NIHSS (Q<sub>1</sub>, 0 to 5; Q<sub>2</sub>, 6 to 10; Q<sub>3</sub>, 11 to 15; Q<sub>4</sub>, 16 to 20; and Q<sub>5</sub>, >20), there was a statistically significant difference in the distribution of patients between the t-PA and placebo treatment groups. This imbalance is demonstrated in Table 2, which shows that of...
the 58 patients in Q₁, 72% were randomized to t-PA treatment versus only 28% randomized to placebo treatment. This imbalance was compensated in Q₂ and Q₅ where the percentages of patients in the t-PA and placebo groups were 45% and 55%, respectively. Q₃ and Q₄ were balanced. As seen in Table 2, the majority of the baseline stroke severity imbalance occurred among patients randomized in the 91- to 180-minute OTT stratum. However, the committee’s analysis did not demonstrate that the difference in baseline stroke severity distributions between the OTT strata contributed in any substantial way to the results. Subsequent analyses make no further reference to the relation of the baseline NIHSS categorical variable to OTT.

For each of the 4 outcome measures, both placebo and t-PA treated patients in Q₁ had an excellent chance for a favorable outcome, and the percentage of favorable outcomes for both treatment groups decreased with increasing NIHSS score (Table 3). For patients in Q₅, with the highest NIHSS scores

### TABLE 2. Baseline Stroke Severity Imbalance

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Treatment Group</th>
<th>0–5 (Q₁)</th>
<th>6–10 (Q₂)</th>
<th>11–15 (Q₃)</th>
<th>16–20 (Q₄)</th>
<th>&gt;20 (Q₅)</th>
<th>Total</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Placebo</td>
<td>16 (28%)</td>
<td>83 (55%)</td>
<td>66 (50%)</td>
<td>70 (49%)</td>
<td>77 (55%)</td>
<td>312 (50.2%)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>t-PA</td>
<td>42 (72%)</td>
<td>67 (45%)</td>
<td>65 (50%)</td>
<td>73 (51%)</td>
<td>63 (45%)</td>
<td>310 (49.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>58</td>
<td>150</td>
<td>131</td>
<td>143</td>
<td>140</td>
<td>622</td>
<td></td>
</tr>
<tr>
<td>OTT† 0–90 minutes</td>
<td>Placebo</td>
<td>9 (41%)</td>
<td>37 (55%)</td>
<td>31 (44%)</td>
<td>37 (48%)</td>
<td>31 (47%)</td>
<td>145 (48.0%)</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>t-PA</td>
<td>13 (59%)</td>
<td>30 (45%)</td>
<td>39 (56%)</td>
<td>40 (52%)</td>
<td>35 (53%)</td>
<td>157 (52.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>22</td>
<td>67</td>
<td>70</td>
<td>77</td>
<td>66</td>
<td>302</td>
<td></td>
</tr>
<tr>
<td>OTT 91–180 minutes</td>
<td>Placebo</td>
<td>7 (19%)</td>
<td>46 (55%)</td>
<td>35 (57%)</td>
<td>33 (50%)</td>
<td>46 (62%)</td>
<td>167 (52.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>t-PA</td>
<td>29 (81%)</td>
<td>37 (45%)</td>
<td>26 (43%)</td>
<td>33 (50%)</td>
<td>28 (38%)</td>
<td>153 (47.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>36</td>
<td>83</td>
<td>61</td>
<td>66</td>
<td>74</td>
<td>320</td>
<td></td>
</tr>
</tbody>
</table>

*P for test for imbalance.
†OTT = time from stroke onset to treatment.

### TABLE 3. Analysis of Baseline Stroke Severity Imbalance and Likelihood of Favorable Outcome

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Baseline NIHSS Quintiles</th>
<th>Test for Equal ORs</th>
<th>χ²</th>
<th>P</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–5 (Q₁)</td>
<td>6–10 (Q₂)</td>
<td>11–15 (Q₃)</td>
<td>16–20 (Q₄)</td>
<td>&gt;20 (Q₅)</td>
<td>χ²(4 df)</td>
</tr>
<tr>
<td>Barthel index</td>
<td>t-PA Placebo</td>
<td>83.3</td>
<td>93.8</td>
<td>79.1</td>
<td>55.4</td>
<td>52.3</td>
</tr>
<tr>
<td>Modified Rankin scale</td>
<td>OR* in favor of t-PA</td>
<td>0.3</td>
<td>3.0</td>
<td>1.6</td>
<td>1.6</td>
<td>0.8–3.2</td>
</tr>
<tr>
<td>Glasgow outcome scale</td>
<td>95% CI for OR</td>
<td>0.04–3.0</td>
<td>1.5–6.3</td>
<td>0.8–3.2</td>
<td>0.8–3.3</td>
<td>0.6–3.3</td>
</tr>
<tr>
<td>NIHSS</td>
<td>Favorable outcome (%)</td>
<td>81.0</td>
<td>76.5</td>
<td>71.6</td>
<td>53.0</td>
<td>46.2</td>
</tr>
<tr>
<td></td>
<td>OR* in favor of t-PA</td>
<td>0.6</td>
<td>2.2</td>
<td>2.3</td>
<td>1.6</td>
<td>0.7–3.4</td>
</tr>
<tr>
<td></td>
<td>95% CI for OR</td>
<td>0.1–3.2</td>
<td>1.1–4.4</td>
<td>1.1–4.7</td>
<td>0.7–3.4</td>
<td>0.5–4.6</td>
</tr>
</tbody>
</table>

*Unadjusted odds ratios.
†χ² for the test for equal odds ratios adjusted for center, study part, and time from stroke onset to treatment.
‡χ² for the test for equal odds ratios adjusted for center, study part, time from stroke onset to treatment, preexisting disability, history of diabetes, age, baseline NIHSS, and age times baseline NIHSS.
indicating more severe strokes, the likelihood of a favorable outcome was poor, and the absolute difference in favorable outcome was much smaller than in Q2 through Q4.

The quintile-specific OR estimates for each of the outcome measures, as well as those for the global analysis, are also documented in Table 3. For each outcome measure, the ORs favor t-PA except in Q1, where 4 of the ORs are <1. Even in Q4, the ORs are in favor of t-PA therapy. The Figure illustrates both the quintile-specific ORs favoring t-PA treatment and the decreasing trend in favorable outcome percentages across the 5 quintiles for the modified Rankin scale. Tests of the hypothesis that the ORs were equal across the quintiles, adjusting for the stratification factors, were not statistically significant (Table 3). However, when adjusting for all covariates, these tests are complicated by the presence of a highly significant interaction between age and baseline NIHSS. In this context, such tests involve a complex interaction with 9 degrees of freedom. Table 3 documents the results of the χ² tests for models including both the 4 and 9 degrees of freedom tests. These analyses demonstrate that for each of the 4 outcome measures and the global analysis there was insufficient evidence to declare a difference in treatment effects (ORs) across the 5 quintiles. However, the study has low power for these exploratory analyses and the individual OR estimates in Table 3 are based on sample sizes ∼20% as large as the whole study estimates. Consequently, many of the 25 CIs in Table 3 include 1.0, suggesting that the issue of whether the use of t-PA is associated with either benefit or harm is undecided in those subgroups. These subgroup analyses must be interpreted very cautiously, because the erroneous identification of differential subgroup effects may lead to inappropriate provision or withholding of treatment.

Ten of the 15 tests had χ² values <3.8, the 5% critical level for a 1 degree of freedom test, and the others had values <6.6, the 1% critical level. Such results suggest that the estimates of “interaction effect” size are very small. Thus, this study does not support the presence of a clinically important interaction between baseline NIHSS and t-PA, and the baseline imbalance in NIHSS plays a very minor role in the estimated benefit of t-PA. The committee concludes that there was no evidence that the imbalance in the distribution of baseline NIHSS between the treatment groups had either a statistically or clinically significant effect on the trial results.

Blood Pressure Assessment and Management

The committee performed an extensive evaluation of BP, and several problems were identified regarding pre- and postrandomization BP measurement and management: 112 patients (18%) were found to have identical admission and baseline BP readings; 22 patients had missing baseline BP data; an unknown number of patients had high BP treated both before arrival in the Emergency Department and in the Emergency Department by nonstudy physicians; no data were recorded to indicate whether patients had high BP treated after randomization. Based on these observations, the committee concludes that the effect of BP and its management on clinical outcome in acute ischemic stroke patients treated in the NINDS trial could not be assessed. Consequently, BP variables were excluded from statistical models.

Exploratory Analyses

The committee’s report documents the results from a wide range of exploratory analyses. Analysis of stroke subtype, preexisting disability, history of diabetes, clinical centers, and the interaction of age and baseline stroke severity showed no statistically significant evidence of any subgroup of patients that responded differently to t-PA. Time from stroke onset to treatment was analyzed separately and no evidence was found of a differential effect of t-PA treatment based on the time elapsed between stroke onset and treatment.

There were 22 cases of symptomatic intracerebral hemorrhage (ICH) in this study (20 among t-PA–treated patients.
The committee found that there was a statistically significant, and clinically important, benefit of t-PA treatment, despite an increased incidence of symptomatic intracerebral hemorrhage in t-PA–treated patients and subgroup imbalances in baseline stroke severity. There was a higher likelihood of having a favorable clinical outcome at 3 months of follow-up when t-PA was administered to patients with acute ischemic stroke according to the study protocol. The difference between the 2 treatment groups in the percentage of patients achieving a favorable clinical outcome at 3 months was statistically significantly in favor of t-PA for each of the 4 outcome measures (Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS). After adjusting for center, time from stroke onset to treatment, and study part, 4 patient attributes were found to be related to the probability of a favorable clinical outcome 3 months after stroke onset. Increasing age, increasing stroke severity, a history of diabetes, and preexisting disability were all associated with a decreased likelihood of having a favorable clinical outcome at 3 months. However, these analyses found no evidence that any of these variables modified the t-PA treatment effect to either a statistically or clinically significant degree.

The effect of the imbalance in baseline stroke severity between the 2 treatment groups was a key issue leading to this reanalysis. After detailed analyses, the committee concludes that this imbalance did not invalidate the results of the trial. The committee’s analysis identified a number of problems regarding pre- and postrandomization BP measurement and management, including noncompliance with the defined protocol and uncertainty regarding the number of people treated with antihypertensive medication either according to or in violation of the protocol. Based on these observations, it was not possible to assess the effect of either pretreatment BP measurements or hypertension management on clinical outcome in the NINDS trial, so BP variables were not included in the statistical models. However, the committee concludes that adjusting for BP would be unlikely to have an impact on the relation between use of t-PA and the likelihood of a favorable outcome or a symptomatic ICH. This conclusion is based on the finding that outcome following an ischemic stroke is not related to BP at the time of the stroke in the majority of studies that have evaluated predictors of outcome following stroke,28 and that the study we evaluated was not designed to have sufficient statistical power to assess whether BP and its management had an impact on the likelihood of having either a favorable outcome or a symptomatic ICH.

The committee concludes that the inconsistent documentation of BP readings and hypertension management seriously undermines the NINDS investigators’ statement that BP management contributed to the success of the trial.29 However, it is biologically plausible that hypertension management could affect clinical outcome in patients with acute ischemic stroke treated with t-PA. Data from the cardiology literature has already demonstrated that in patients with acute myocardial infarction treated with thrombolytic medication, the risk of having an intracerebral hemorrhage is related to pretreatment BP.30–32 Therefore, the committee recommends that BP management, as defined in the NINDS trial protocol29 or comparable rigorous approaches to the control and monitoring of BP, should be included in protocols for treating acute ischemic stroke patients with t-PA. However, further clinical studies will be needed to assess whether BP management is related to better clinical outcomes in patients with acute ischemic stroke treated with t-PA.

The committee was charged with addressing whether eligible stroke patients may not benefit from t-PA given according to the protocol used in the trials. Multiple exploratory analyses performed to address this question did not identify any subgroup of acute ischemic stroke patients who would be more likely either to benefit from or be harmed by receiving t-PA. The committee assessed time from stroke onset to treatment, stroke subtype, preexisting disability, history of diabetes, center, and the interaction of age and baseline stroke severity, and found no evidence of any subgroup of patients that responded differently to t-PA. Although a number of clinical features were associated with the occurrence of symptomatic intracerebral hemorrhage, there was no statistically significant evidence of the existence of any subgroup of acute ischemic stroke patients in whom the risk, and consequences, of having a symptomatic ICH clearly outweighed the potential beneficial effects of t-PA. However, neither the Part 1 nor Part 2 study was powered to detect clinically important subgroup effects or treatment interaction effects. The combined studies still have low power for these investigations. Consequently, subgroup analyses and evaluations of interactions operate in a low-power, exploratory context. As discussed by Brookes et al,27 such analyses must be interpreted very cautiously, because they may have “potentially serious implications because erroneous identification of differential subgroup effects may lead to inappropriate provision or withholding of treatment.” Using the stroke subtype analysis as an example, although the exploratory analysis found no evidence of a statistically significant differential t-PA treatment effect among stroke subtypes, it is incorrect to conclude that these results imply t-PA was equally effective in all stroke subtypes. Further
studies are needed that are powered to address these important clinical practice issues.

Our findings support the use of t-PA to treat patients with acute ischemic stroke within 3 hours of the onset of symptoms under the protocol specified by these studies. Importantly, the clinical experience gained since 1996 has shown that the drug is most effective when administered within stroke care systems that adhere strictly to the study protocol. Therefore, the committee recommends that professional organizations representing health professionals who are involved in treating acute stroke patients work collaboratively to develop guidelines on the resources necessary for institutions to treat all acute stroke patients effectively, administering t-PA when appropriate. Finally, new studies are needed that are designed to identify subgroups of acute ischemic stroke patients that are more likely either to benefit from or be harmed by receiving t-PA.

Acknowledgments
The National Institute of Neurological Disorders and Stroke (NINDS) provided funding to conduct this review. The funds were administered through an independent contractor, which also provided the committee with the data from the original NINDS-funded t-PA for the acute ischemic stroke treatment trial. The review was conducted independently of NINDS. None of the committee members had any connection with NINDS, the original t-PA for acute ischemic stroke trial, or the manufacturers of the study drug, alteplase (Activesave, Genentech Inc, San Francisco, Calif).

References
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