

EFFECTS OF TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE AT ONE YEAR

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ABSTRACT

Background In 1995, the two-part National Institute of Neurological Disorders and Stroke (NINDS) Recombinant Tissue Plasminogen Activator Stroke Study found that patients who were treated with tissue plasminogen activator (t-PA) within three hours after the onset of symptoms of acute ischemic stroke were at least 30 percent more likely than patients given placebo to have minimal or no disability three months after the stroke. It was unknown, however, whether the benefit would be sustained for longer periods.

Methods In the NINDS trial, a total of 624 patients with stroke were randomly assigned to receive either t-PA or placebo. We collected outcome data over a period of 12 months after the occurrence of stroke. The primary outcome measure was a "favorable outcome," defined as minimal or no disability as measured by the Barthel index, the modified Rankin Scale, and the Glasgow Outcome Scale. We assessed the treatment effect using a global statistic.

Results Using an intention-to-treat analysis for the combined results of the two parts of the trial at 6 months and 12 months, we found that the global statistic favored the t-PA group (odds ratio for a favorable outcome at 6 months, 1.7; 95 percent confidence interval, 1.3 to 2.3; odds ratio at 12 months, 1.7; 95 percent confidence interval, 1.2 to 2.3). The patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at 12 months than were the placebo-treated patients (absolute increase in the proportion with a favorable outcome, 11 to 13 percentage points). There was no significant difference in mortality at 12 months between the t-PA group and the placebo group (24 percent vs. 28 percent, $P=0.29$). There was no interaction between the type of stroke identified at base line and treatment with respect to the long-term response. The rate of recurrent stroke at 12 months was similar in the two groups.

Conclusions During 12 months of follow-up, the patients with acute ischemic stroke who were treated with t-PA within three hours after the onset of symptoms were more likely to have minimal or no disability than the patients given placebo. These results indicate a sustained benefit of t-PA for such patients. (N Engl J Med 1999;340:1781-7.)

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THE National Institute of Neurological Disorders and Stroke (NINDS) Recombinant Tissue Plasminogen Activator Stroke Study was a double-blind, placebo-controlled, randomized study conducted in two parts, both of which showed a significant benefit at three months for patients with acute ischemic stroke who received treatment with intravenous tissue plasminogen activator (t-PA).¹ Despite their having a higher frequency of symptomatic intracerebral hemorrhage, the patients treated with t-PA were at least 30 percent more likely than patients given placebo to have minimal or no disability at three months. Mortality at three months among t-PA-treated patients in the two parts of the study combined (17 percent) was not significantly lower than that of the placebo group (21 percent). It was not known, however, whether the benefit found at three months would be sustained over a longer follow-up period. We analyzed data on the outcomes at 6 and 12 months.

METHODS

Patients with acute ischemic stroke who could be treated within three hours after the onset of symptoms and who had a measurable neurologic deficit according to the National Institutes of Health Stroke Scale (NIHSS)² were eligible for the study. Randomization was stratified according to the time since onset of the stroke (about half the patients were enrolled within 90 minutes after the onset of symptoms of stroke and the remainder between 90 and 180 minutes thereafter) and the clinical center. The patients were followed for 12 months. Outcome data were systematically collected 24 hours and 3, 6, and 12 months after stroke. The stroke was classified as large-vessel occlusive, small-vessel occlusive, or cardioembolic solely on the basis of the clinical and diagnostic information available to the investigator at the time of randomization. The protocols for each part of the trial were ap-

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proved by the human research committee at each site. Informed consent was obtained from all the patients.

Part 1 of the trial included 291 patients and was designed to test whether a greater proportion of patients treated with t-PA, as compared with those who received placebo, had early improvement, defined as complete resolution of the neurologic deficit or an improvement from base line of four or more points in the score on the NIHSS 24 hours after the onset of stroke. The primary hypothesis for part 2 of the trial, which included 333 patients, was that there would be a consistent and persuasive difference between the t-PA and placebo groups in terms of the proportion of patients with minimal or no neurologic deficit three months after stroke. Except for the difference in the primary hypotheses, the protocols for parts 1 and 2 were the same. The four outcome measures used in both parts of the study were the Barthel index, the modified Rankin scale, the Glasgow Outcome Scale, and the NIHSS. The NIHSS was not used in this long-term follow-up study, because the necessary data were not collected at 6 months and 12 months.

During the first 24 hours after randomization, patients were monitored closely in an intensive care setting. Blood pressure was managed according to an algorithm, and antithrombotic and antiplatelet agents were not allowed by the protocol.³ After this initial period, treatment was directed by the patient's physician and not dictated by the protocol.

Clinical investigators remained unaware of the results of part 1 until part 2 was completed and the data were analyzed. Although the outcome data at 6 and 12 months were prospectively collected in accordance with the protocol, these outcomes were not specified as secondary outcomes in the protocol. Thus the analyses presented here are considered post hoc and exploratory.

Certified nurse coordinators or study physicians telephoned the patients or their care givers to determine the vital status of the patients; their ability to perform daily activities (measured with the Barthel index)⁴; and the degree of functional disability (measured with the modified Rankin scale⁵ and the Glasgow Outcome Scale⁶). The evaluators were unaware of the treatment assignments when the 6- and 12-month outcomes were assessed, and the patients and their care givers were also unaware of the treatment assignments. Several studies have validated telephone assessment of the outcome of stroke.⁷⁻⁹ Data were also collected on the causes of death and serious medical events, including intracerebral hemorrhage and recurrent stroke.

A favorable outcome was defined as minimal or no disability, as measured by scores of 95 or 100 on the Barthel index (range of scores, 0 to 100), 0 or 1 on the modified Rankin scale (range of scores, 0 to 5), and 1 on the Glasgow Outcome Scale (range of scores, 1 to 5). Using an intention-to-treat analysis, we assigned the patients who died before the specified follow-up the most unfavorable scores for each of the outcome measures. Patients for whom data were missing on an outcome measure were given the most unfavorable score for that measure. To increase the ability of the study to detect differences in long-term outcomes, we combined data from parts 1 and 2, since the methods for both parts, including those used for recruitment, treatment, and follow-up, were identical.

In this study, as in the original study of this cohort, favorable outcomes were determined with the use of a global statistic (the Wald test) derived from a general linear model with logit-link function, computed with the use of generalized estimating equations.¹⁰ The global test incorporated simultaneously the proportion of patients with minimal or no disability on the Barthel index, the modified Rankin scale, and the Glasgow Outcome Scale at 6 and 12 months. If the global tests indicated a significant difference at the 0.05 level, a Mantel-Haenszel test was used to compare the scores of the patients treated with t-PA and those of the patients who received placebo for each of the three scales.¹¹

To describe the treatment effects across the range of outcomes, outcomes were classified into one of four categories: minimal or no disability (score on Barthel index, 95 or 100; score on modified Rankin scale, 0 or 1; and score on Glasgow Outcome Scale, 1),

moderate disability (Barthel index, 55 to 90; modified Rankin scale, 2 or 3; and Glasgow Outcome Scale, 2), severe disability (Barthel index, 0 to 50; modified Rankin scale, 4 or 5; and Glasgow Outcome Scale, 3 or 4), and death.

Log-rank tests were conducted to compare survival in the two groups 6 months and 12 months after the onset of stroke. The incidence of recurrent stroke and intracerebral hemorrhage was reported according to treatment group and time after randomization (≤ 3 months, >3 to 6 months, and >6 to 12 months).

The cause of death was determined independently by a panel of three investigators who were unaware of the patients' treatment assignments. The patients' files and pertinent computed tomographic (CT) scans were reviewed. The causes of death were classified into one of the following five categories: cerebrovascular cause, in which death was due to intracerebral hemorrhage, severe infarction, or extensive cerebral edema; cardiovascular cause, which included congestive heart failure and pulmonary edema, acute myocardial infarction, ventricular arrhythmia, and pulmonary embolism; infection, primarily aspiration pneumonia and sepsis; cancer; and other, if the cause of death could not be classified into one of the preceding categories. All discrepancies regarding classification among the investigators were adjudicated by the panel until a consensus was reached.

After the cause of death was determined, its relation to the index stroke was assessed according to whether it was definitely related, possibly related, or not related. Although all base-line CT scans had to show no evidence of intracerebral hemorrhage for a patient to be included in this study, subsequent CT scans could show intracerebral hemorrhage or infarction without evidence of hemorrhage. For all causes of death that were judged to be definitely related to the index stroke, the underlying pathophysiologic feature of the stroke deemed to have been related to the patient's death was categorized as intracerebral hemorrhage, cerebral edema, or cerebral infarction. To allow comparisons between deaths due to severe or extensive ischemic infarction and those due to intracerebral hemorrhage, the categories of edema and infarction were combined. Deaths thought to be due to the severity of the index stroke could then be compared with deaths judged to be due to intracerebral hemorrhage.

Multivariable analyses were carried out to test the association of selected base-line variables, including the type of stroke, and favorable outcome at one year. Variables for inclusion in the models were selected with the use of procedures described previously.¹² A multivariable model was also fitted to identify base-line variables associated with survival at one year with the use of Cox proportional-hazards regression analysis. An interaction with a P value of less than 0.1 was considered to indicate significance. Variables with a P value of less than 0.05 or interactions between variables with a P value of less than 0.1 were retained in the final model. The effect of treatment on outcome at 12 months was tested again, with adjustments for base-line covariates and interactions remaining in the final model.

RESULTS

A total of 624 patients were randomly assigned to treatment. Only 15 of the surviving patients (2.4 percent of the original 624; 7 in the t-PA group and 8 in the placebo group) were not available for the 6-month follow-up assessment for all three outcome scales, and 26 (4.2 percent; 14 in the t-PA group and 12 in the placebo group) were unavailable for the follow-up assessment at 12 months for all three scales. According to the intention-to-treat analysis, these patients were considered to have an unfavorable outcome for each missing scale.

Like the data at 3 months, the 6-month and 12-month data showed that the patients treated with t-PA

were more likely to have a favorable outcome than those who received placebo. The odds ratio for a favorable outcome at 6 months in the t-PA group as compared with the placebo group was 1.7 (95 percent confidence interval, 1.3 to 2.3) and at 12 months was 1.7 (95 percent confidence interval, 1.2 to 2.3) (Table 1). A similar pattern is evident in the results of the univariate tests for the Barthel index, the modified Rankin scale, and the Glasgow Outcome Scale (Table 1). At 12 months, the range of the absolute increase in the proportion of patients with a favorable outcome was 11 to 13 percentage points, and the range of the relative increase in favorable outcome was 32 to 46 percent for the three outcome scales.

Figure 1 shows the outcomes at 12 months. The six-month data (not shown) were very similar. The greater proportion of patients in the t-PA group with a favorable outcome at 12 months, as compared with those in the placebo group, was not accompanied by an increase in severe disability or mortality. In addition, when we compared the outcomes at 3 months and 12 months, the rate of agreement in results for patients with respect to a favorable outcome was 88 percent on the Barthel index and 91 percent on the modified Rankin scale and the Glasgow Outcome Scale, suggesting the stability of these outcomes over the 12-month period.

In the t-PA group, there were 23 symptomatic intracerebral hemorrhages during the first three months after the stroke, 20 of which occurred within the first 36 hours. Six of the 23 patients (26 percent) were alive at 12 months. In the placebo group,

four symptomatic intracerebral hemorrhages occurred within three months, two of which occurred within the first 36 hours after the stroke. One of these four patients was alive at 12 months. Between 3 months and 12 months two additional patients had symptomatic hemorrhages in the t-PA group, one of whom was alive at 12 months. In the placebo group, one additional patient had symptomatic hemorrhage between 3 months and 12 months; this patient did not survive.

Thirty-four of the 624 patients had symptomatic recurrent strokes by 12 months, including 2 patients with two recurrences. Twenty-four events occurred within 3 months after treatment (12 in the t-PA group, and 12 in the placebo group), 7 between 3 and 6 months (4 in the t-PA group, and 3 in the placebo group), and 3 between 6 months and 12 months (1 in the t-PA group and 2 in the placebo group). Of the 34 recurrent strokes, 2 (6 percent) were classified as small-vessel disease, 16 (47 percent) as cardioembolic, 9 (26 percent) as large-vessel disease, and 7 (21 percent) as of unknown cause. There was no significant difference in the incidence of recurrent stroke between patients in the t-PA group and those in the placebo group ($P=0.89$ at 6 months, and $P=0.96$ at 12 months).

The mortality rate 6 months after stroke was not significantly lower in the t-PA group than in the placebo group (21 percent vs. 23 percent, $P=0.31$) or at 12 months (24 percent vs. 28 percent, $P=0.29$) (Fig. 2).

The causes of death at one year are summarized in Table 2. For the three major categories (cerebrovas-

TABLE 1. OUTCOMES SIX MONTHS AND ONE YEAR AFTER THE ONSET OF STROKE.

TIME POINT AND ASSESSMENT INSTRUMENT	PERCENTAGE OF PATIENTS WITH FAVORABLE OUTCOMES*		ODDS RATIO (95% CI)†	RELATIVE RISK (95% CI)†	P VALUE
	t-PA (N=312)	PLACEBO (N=312)			
6 Months after stroke					
Global test‡	—	—	1.7 (1.3–2.3)	—	<0.001
Barthel index	50	37	1.7 (1.2–2.4)	1.4 (1.1–1.6)	0.001
Modified Rankin scale	41	29	1.8 (1.3–2.5)	1.4 (1.2–1.8)	0.001
Glasgow Outcome Scale	43	31	1.6 (1.2–2.3)	1.4 (1.1–1.7)	0.004
12 Months after stroke					
Global test‡	—	—	1.7 (1.2–2.3)	—	0.001
Barthel index	50	38	1.6 (1.1–2.1)	1.3 (1.1–1.5)	0.005
Modified Rankin scale	41	28	1.8 (1.3–2.5)	1.5 (1.2–1.8)	0.001
Glasgow Outcome Scale	43	32	1.6 (1.1–2.2)	1.3 (1.1–1.6)	0.006

*Scores of 95 or 100 on the Barthel index, 0 or 1 on the modified Rankin scale, and 1 on the Glasgow Outcome Scale were considered to indicate a favorable outcome.

†The Mantel–Haenszel test was used for univariate analyses, with groups stratified according to clinical center and the time to treatment (0 to 90 minutes and 91 to 180 minutes). For the global tests (which used logit-link function), the same stratifying variables were included as covariates. CI denotes confidence interval.

‡There is no published method by which to compute relative risk.

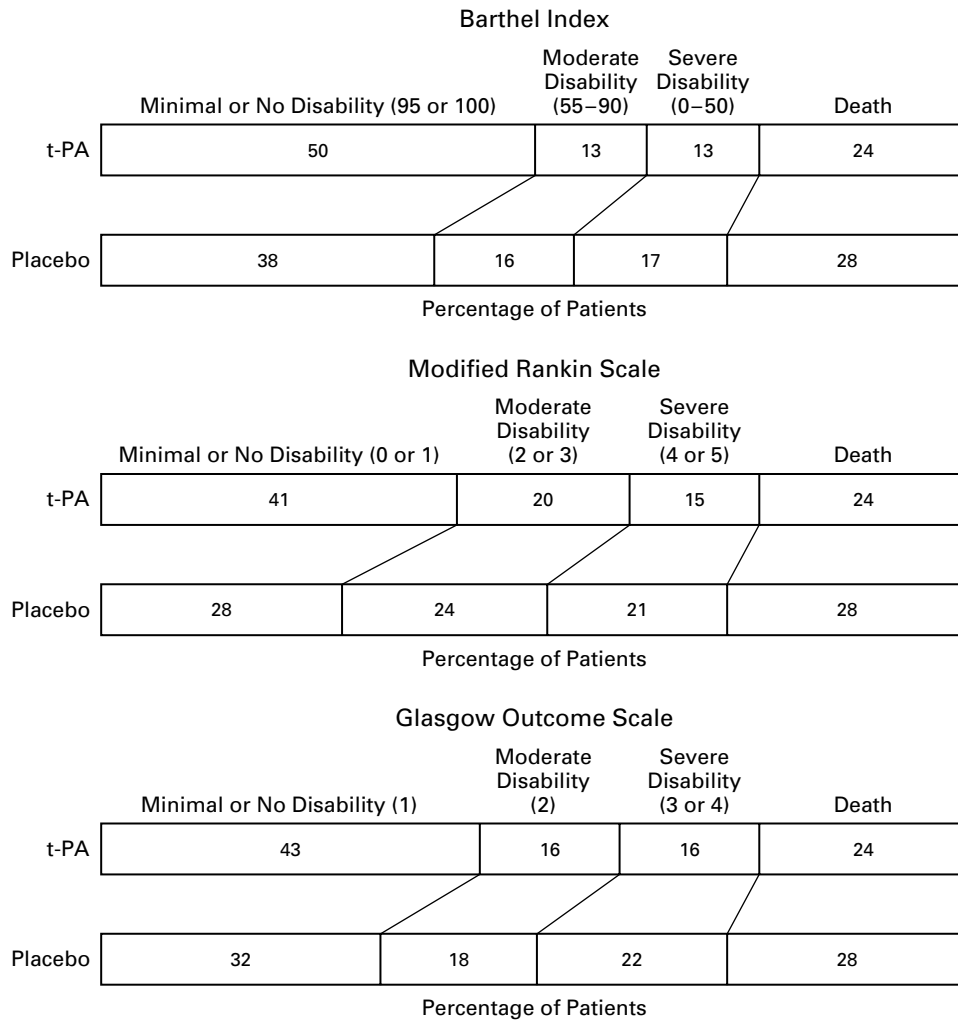


Figure 1. Outcome at 12 Months, According to Treatment Group. Scores of 95 or 100 on the Barthel index, 0 or 1 on the modified Rankin scale, and 1 on the Glasgow Outcome Scale were considered to indicate a favorable outcome. Percentages do not always total 100 because of rounding.

cular cause, cardiovascular cause, and infection), there was no significant difference between the t-PA group and the placebo group ($P=0.47$). For the t-PA group, 47 percent of the deaths were judged to be definitely related to the index stroke, 21 percent possibly related, and 32 percent not related. For the placebo group, 41 percent of the deaths were considered to be definitely related to the index stroke, 26 percent possibly related, and 32 percent not related. Among the patients whose deaths were judged to be definitely related to the index stroke, a larger percentage of such patients died of intracerebral hemorrhage in the t-PA group than in the placebo group (28 percent vs. 6 percent); a greater majority of patients in the placebo group died of severe ischemic stroke (94 percent vs. 72 percent).

The base-line variables retained in the final 12-

month multivariable model of favorable outcomes were the presence or absence of diabetes, age, NIHSS score, and the interaction of age and NIHSS score. Patients who were older, who had diabetes, or who had higher base-line NIHSS scores were less likely to have a favorable outcome at 12 months. The benefit of treatment with t-PA remained significant after adjustment for these variables. No interactions between treatment and base-line variables were detected. Table 3 shows the percentages of patients with favorable outcomes at 12 months according to base-line NIHSS score. In all but one subgroup (patients with NIHSS scores of more than 20 at base line, with use of only the Glasgow scale as the outcome measure), the proportion of patients with a favorable outcome was greater in the t-PA group than in the placebo group. As was the case for the three-month assess-

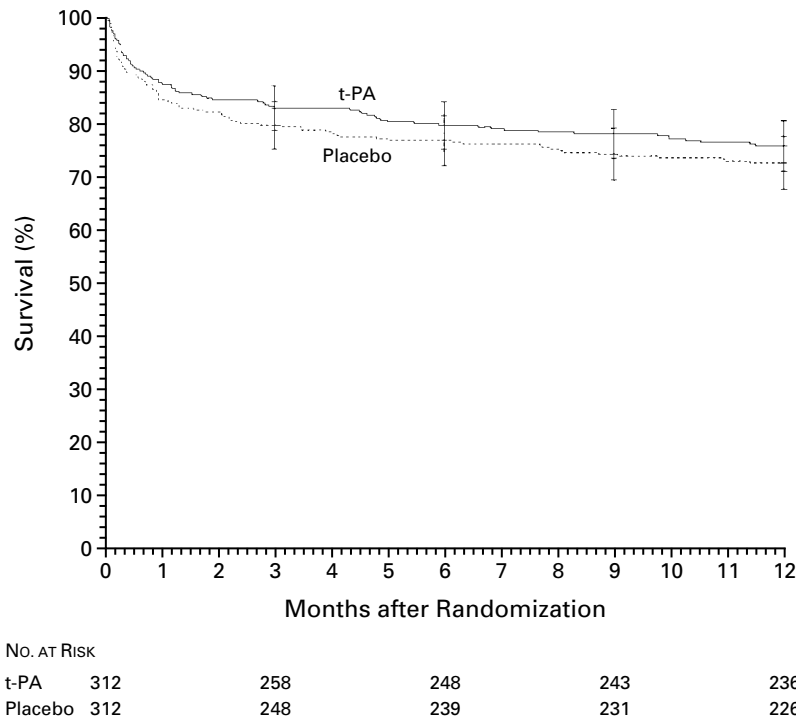


Figure 2. Kaplan-Meier Estimate of Survival after Stroke in the t-PA and Placebo Groups. I bars represent the standard errors of the point estimates of survival at 3, 6, 9, and 12 months.

ment, there was no interaction between the type of stroke at base line (i.e., small-vessel occlusive, large-vessel occlusive, or cardioembolic) and treatment. The base-line variables that were associated with survival at 12 months included age, NIHSS score, diabetes, and the interaction of diabetes and age. Patients who were younger, had lower NIHSS scores at base line, or did not have diabetes had a higher rate of survival than the other patients. As was true for the univariate analysis, after adjustment for these variables, no difference in survival between the t-PA and placebo groups could be detected ($P=0.29$).

DISCUSSION

We previously reported that treatment with intravenous t-PA within three hours after the onset of symptoms of an acute ischemic stroke improved the clinical outcome at three months.¹ We now report that the magnitude of this benefit was sustained at 6 months and 12 months. In addition, patients treated with t-PA were less likely to be severely disabled 12 months after the stroke. These findings indicate that the beneficial effect of t-PA is sustained and that the primary benefit of t-PA is seen early after treatment.

The rates of recurrent stroke were similar in the t-PA group and the placebo group during the 12 months of follow-up and were similar to those found in previous population-based studies of stroke.¹³⁻¹⁵

Although our patients were carefully selected, the similarity in the rates of recurrent stroke suggests that they may be representative of patients with ischemic stroke. The mortality rates were also similar between the two groups at 6 months (21 percent in the t-PA group and 23 percent in the placebo group) and at 12 months (24 percent and 28 percent, respectively).

In our earlier study we found that despite the increased risk of intracerebral hemorrhage in patients treated with t-PA, there was no difference in overall mortality between those receiving t-PA and those

TABLE 2. PRIMARY CAUSES OF DEATH AT 12 MONTHS.

CAUSE OF DEATH	t-PA GROUP	PLACEBO GROUP
	no. (%) of deaths	
Cerebrovascular cause	28 (37)	26 (30)
Cardiovascular cause	28 (37)	39 (45)
Infection	18 (24)	18 (21)
Cancer	1 (1)	2 (2)
Other	1 (1)	2 (2)
Total	76 (100)	87 (100)

TABLE 3. ASSOCIATION OF BASE-LINE NIHSS SCORE WITH OUTCOME AT 12 MONTHS.*

TREATMENT GROUP AND NIHSS SCORE	NO. OF PATIENTS	BARTHEL INDEX	MODIFIED RANKIN SCALE	GLASGOW OUTCOME SCALE
		percentage with favorable outcome†		
t-PA				
≤9	99	75	68	73
10–14	63	59	51	51
15–20	87	38	28	31
>20	63	17	6	5
Placebo				
≤9	78	72	62	62
10–14	73	40	23	33
15–20	84	27	21	25
>20	77	16	4	10

*The possible range of scores is 0 to 42, with a higher score reflecting more severe disability. NIHSS denotes National Institutes of Health Stroke Scale.

†Scores of 95 or 100 on the Barthel index, 0 or 1 on the modified Rankin scale, and 1 on the Glasgow Outcome Scale were considered to indicate a favorable outcome.

receiving placebo. Our current results suggest that the explanation for this finding is that patients who die from causes related to the index stroke are likely to die regardless of whether intracerebral hemorrhage occurs. This explanation reflects the often fatal consequences of severe ischemic stroke even in the absence of intracerebral hemorrhage.¹⁶

The results of multivariable analyses of variables related to a favorable outcome at 12 months were similar to those reported at 3 months.¹² The absence of diabetes and the interaction between younger age and lower base-line NIHSS score remained in both models. In addition, younger age and a lower NIHSS score at base line were independently associated with a favorable outcome at 12 months. The base-line variables of younger age, lower NIHSS score, absence of diabetes, and the interaction of the absence of diabetes and younger age were also predictors of survival at 12 months. However, none of these variables associated with a favorable outcome or survival interacted with treatment. Therefore, even though patients who are older, have diabetes, or have higher base-line NIHSS scores are less likely to have a favorable outcome or survive 12 months after a stroke, they should not be selected for treatment solely on the basis of these features.¹² For example, it would be fallacious to select a single subgroup with a high NIHSS score from those listed in Table 3 and draw the conclusion that t-PA is not beneficial for that subgroup.¹⁷ The broader trend of benefit with t-PA treatment that was demonstrable among all subgroups makes a single isolated aberration within one category of a subgroup more likely to be a random occurrence related

to the small size of the sample than a clinically meaningful biologic trend.

In addition, after adjusting for the other base-line variables, we could not detect an association between the type of stroke identified at base line and the outcome over the long term. The type of stroke at base line may not correspond to the type of stroke that is ultimately identified, as determined by a complete diagnostic workup. However, the constraints of a very narrow therapeutic window mandate that a determination of the type of stroke be made at the time of clinical presentation. With these limitations in mind, our findings support the conclusion that the selection of patients for treatment with t-PA cannot be based solely on the mechanism of stroke, as determined at base line on the basis of clinical impression.

Other large studies of thrombolysis for the treatment of acute ischemic stroke have shown either no benefit¹⁸⁻²⁰ or equivocal benefit²¹ from intravenous streptokinase or t-PA and high rates of early mortality and intracerebral hemorrhage. Reasons for the disparity between the results of these studies and ours may include differences in the time from the onset of symptoms to the initiation of treatment (zero to three hours in our study as compared with zero to four or six hours in the other trials), the choice and dose of thrombolytic agent, and the concomitant use or non-use of heparin or aspirin.²²⁻²⁴ In addition, we used a strict algorithm for the management of blood pressure after beginning treatment with t-PA. A more recent trial of intravenous t-PA given within six hours after the onset of symptoms, but whose protocol was otherwise similar to ours, failed to show a benefit for t-PA in the primary analysis.²⁵ This finding further supports the recommendation that treatment of acute ischemic stroke with intravenous t-PA be limited to patients who can be treated within three hours after the onset of stroke.

The results of this long-term follow-up study have potential implications for public health. For example, for every 100 patients treated with t-PA according to the selection criteria and management guidelines of this study, at least 11 additional patients will have a favorable outcome during the subsequent year. In addition, a cost-effectiveness analysis has demonstrated net cost savings to the health care system and improved quality of life for patients treated with t-PA.²⁶

In conclusion, patients who received t-PA within three hours after the onset of symptoms were more likely to have minimal or no disability 3, 6, and 12 months later. Similar results may be attainable in everyday practice if guidelines for treatment and management are followed closely.^{24,27}

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Drs. Kwiatkowski, Libman, Frankel, Morgenstern, Broderick, Lewandowski, and Levine have been members of a speakers' bureau sponsored by Genentech. Dr. Morgenstern has also served on a Genentech advisory panel.

APPENDIX

The following persons and institutions participated in the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group: **Clinical Centers — University of Cincinnati** (150 patients): T. Brott, J. Broderick, R. Kothari, M. O'Donoghue, W. Barsan, T. Tomsick, J. Spilker, R. Miller, and L. Sauerbeck; Affiliated sites: *St. Elizabeth Hospital (South)*, J. Farrell, J. Kelly, T. Perkins, and R. Miller; *University Hospital, T. McDonald*; *Bethesda North Hospital, M. Rorick* and C. Hickey; *St. Luke Hospital (East)*, J. Armitage and C. Perry; *Providence Hospital, K. Thalinger* and R. Rhude; *Christ Hospital, J. Armitage* and J. Schill; *St. Luke Hospital (West)*, P.S. Becker, R.S. Heath, and D. Adams; *Good Samaritan Hospital, R. Reed* and M. Klei; *St. Francis/St. George Hospital, A. Hughes* and R. Rhude; *Bethesda Oak Hospital, J. Anthony* and D. Baudendistel; *St. Elizabeth Hospital (North)*, C. Zadicoff and R. Miller; *St. Luke Hospital—Kansas City, M. Rymer, I. Bettinger*, and P. Laubinger; *Jewish Hospital, M. Schmerler* and G. Meirose; **University of California, San Diego** (146 patients): P. Lyden, K. Rapp, T. Babcock, P. Daum, D. Persona, M. Brody, C. Jackson, S. Lewis, J. Liss, Z. Mahdavi, J. Rothrock, T. Tom, R. Zweifler, J. Dunford, and J. Zivin; Affiliated sites: *Sharp Memorial Hospital, R. Kobayashi, J. Kunin, J. Licht, R. Rowen*, and D. Stein; *Mercy Hospital, J. Grisolia* and F. Martin; *Scripps Memorial Hospital, E. Chaplin, N. Kaplitz, J. Nelson, A. Neuren*, and D. Silver; *Tri-City Medical Center, T. Chippendale, E. Diamond, M. Lobatz, D. Murphy, D. Rosenberg, T. Ruel, M. Sadoff, J. Schim, and J. Schleimer*; *Mercy General Hospital, Sacramento, R. Atkinson, D. Wentworth, R. Cummings, R. Frink*, and P. Heublein; **University of Texas Medical School, Houston** (104 patients): J. Grotta, T. DeGraba, M. Fisher, A. Ramirez, S. Hanson, L. Morgenstern, C. Sills, W. Pasteur, F. Yatsu, K. Andrews, C. Villar-Cordova, P. Pepe, P. Bratina, L. Greenberg, S. Rozek, and K. Simmons; Affiliated sites: *Houston Fire Department Emergency Medical Services, Hermann Hospital, St. Luke's Episcopal Hospital, Lyndon Baines Johnson General Hospital, Memorial Northwest Hospital, Memorial Southwest Hospital, Heights Hospital, Park Plaza Hospital, and Twelve Oaks Hospital*; **Long Island Jewish Medical Center** (72 patients): T. Kwiatkowski, S. Horowitz, R. Libman, R. Kanner, R. Silverman, J. LaMantia, C. Mealie, R. Duarte, R. Donnarumma, M. Okola, V. Cullen, and E. Mitchell; **Henry Ford Hospital** (62 patients): S. Levine, C. Lewandowski, G. Tokarski, N. Ramadan, P. Mitsias, M. Gorman, B. Zarowitz, J. Kokinos, J. Dayno, P. Verro, C. Gymnopoulos, R. Dafer, L. D'Olhaberriague, K. Sawaya, S. Daley, and M. Mitchell; **Emory University School of Medicine** (39 patients): M. Frankel, B. Mackay, C. Barch, J. Braimah, B. Flaherty, J. MacDonald, S. Sailor, A. Cook, H. Karp, B. Nguyen, J. Washington, J. Weissman, M. Williams, and T. Williamson; Affiliated sites: *Grady Memorial Hospital, Crawford Long Hospital, Emory University Hospital, South Fulton Hospital, M. Kozinn* and L. Hellwick; **University of Virginia Health Sciences Center** (37 patients): E. Haley, Jr., T. Bleck, W. Cail, G. Lindbeck, M. Granner, S. Wolf, M. Gwynn, R. Mettetal, Jr., C. Chang, N. Solenski, D. Brock, G. Ford, G. Kongable, K. Parks, S. Wilkinson, and M. Davis; Affiliated site: *Winchester Medical Center*; G. Sheppard, D. Zontine, K. Gustin, N. Crowe, and S. Massey; **University of Tennessee** (14 patients): M. Meyer, K. Gaines, A. Payne, C. Bales, J. Malcolm, R. Barlow, and M. Wilson; Affiliated sites: *Baptist Memorial Hospital, C. Cape*; *Methodist Hospital Central, T. Bertorini*; *Jackson Madison County General Hospital, K. Misulis*; *University of Tennessee Medical Center, W. Paulsen* and D. Shepard; **Coordinating Center — Henry Ford Health Sciences Center**: B. Tilley, K. Welch, S. Fagan, M. Lu, S. Patel, S. Li, J. Verter, J. Boura, J. Main, L. Gordon, N. Maddy, and T. Chociemski; *Computed tomography reading centers*: Part 1 — *Henry Ford Health Sciences Center*; J. Windham and H. Soltanian Zadeh; Part 2 — *University of Virginia Medical Center, W. Alves, M. Keller, and J. Wenzel*; *Central Laboratory: Henry Ford Hospital, N. Raman* and L. Cantwell; *Drug Distribution Center*: A. Warren, K. Smith, and E. Bailey; **Committees — Executive**: K. Welch, B. Tilley, and J. Marler; *Steering*: K. Welch, T. Brott, P. Lyden, J. Grotta, T. Kwiatkowski, S. Levine, M. Frankel, E. Haley, Jr., M. Meyer, B. Tilley, and J. Marler; *Participants from Genentech*: J. Froehlich and J. Breed; *Data and Safety Monitoring Committee*: J. Easton, J. Hallenbeck, G. Lan, J. Marsh, and M. Walker; **Project Office — NINDS**: J. Marler.

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