TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

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Abstract *Background.* Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke after recent pilot studies suggested that t-PA was beneficial when treatment was begun within three hours of the onset of stroke.

Methods. The trial had two parts. Part 1 (in which 291 patients were enrolled) tested whether t-PA had clinical activity, as indicated by an improvement of 4 points over base-line values in the score of the National Institutes of Health stroke scale (NIHSS) or the resolution of the neurologic deficit within 24 hours of the onset of stroke. Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at three months, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS.

Results. In part 1, there was no significant difference between the group given t-PA and that given placebo in the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed (global odds ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA but only 0.6 percent of patients given placebo (P<0.001). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group (P=0.30).

Conclusions. Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. (N Engl J Med 1995;333:1581-7.)

ISCHEMIC stroke affects over 400,000 people in the United States annually,[1] and there is no direct treatment to reduce the extent of neurologic injury. Cerebral angiography conducted soon after the onset of stroke demonstrates arterial occlusions in 80 percent of acute infarctions.[2,3] Thrombolytic canalization of occluded arteries may reduce the degree of injury to the brain if it is done before the process of infarction has been completed. Since intracerebral hemorrhage was a frequent major complication reported in early trials of thrombolytic therapy,[4,5] the use of recombinant human tissue plasminogen activator (t-PA) for cerebral arterial thrombolysis requires a careful evaluation of both the risks and the potential benefits.

The safety of intravenous t-PA for the treatment of acute cerebral ischemia was previously tested in two open-label, dose-escalation studies,[6,7] which emphasized very early treatment — within 90 and 180 minutes of the onset of the stroke — to reduce the risk of hemorrhage and to maximize the potential for recovery. These studies suggested that doses of less than 0.95 mg of t-PA per kilogram of body weight were relatively safe and resulted in early neurologic improvement in a substantial proportion of patients. These results were enough to justify further investigation in the form of a larger, randomized, placebo-controlled trial.

METHODS

The trial was carried out in two parts. Part 1 assessed changes in neurologic deficits 24 hours after the onset of stroke as a measure of the activity of t-PA. Part 2, the pivotal study, used four outcome measures representing different aspects of recovery from stroke to assess whether treatment with t-PA resulted in sustained clinical benefit at three months. To provide a comprehensive evaluation of t-PA as a treatment for acute ischemic stroke, the results of the two parts were combined and stratified according to the length of time from the onset of stroke to the initiation of treatment.

Hypotheses and Design

Part 1 was designed to test whether t-PA had clinical activity — specifically, whether a greater proportion of patients treated with t-PA, as compared with those given placebo, had early improvement. Early improvement was defined as complete resolution of the neuro-

logic deficit or an improvement from base line in the score on the National Institutes of Health stroke scale (NIHSS) by 4 or more points 24 hours after the onset of stroke. Each group was assessed according to the time from the onset of stroke to the beginning of treatment: 0 to 90 minutes, 91 to 180 minutes, and 0 to 180 minutes after the onset of stroke. The primary hypothesis for part 2 was that there would be a consistent and persuasive difference between the t-PA and placebo groups in terms of the proportion of patients who recovered with minimal or no deficit three months after treatment. Except for the difference in the primary hypotheses, the protocols for parts 1 and 2 were the same. To prevent premature extrapolation of the results of part 1 to part 2, investigators remained unaware of the results of part 1 until the completion of part 2. The Data and Safety Monitoring Committee reviewed data from part 1 before approving the protocol for part 2 and designating the primary end point. Both protocols were approved by the Human Research Committee at each site.

In part 1, with the inclusion of 70 patients per time stratum (0 to 90 minutes or 91 to 180 minutes) and treatment group (total, 280 patients), the power was 0.90 to detect an absolute difference of 24 percentage points in outcome given a rate of 16 percent in the placebo group (alpha level of 0.05 by a two-sided test). In part 2, with the inclusion of 160 patients per treatment group, the power was 0.95 to detect a difference of 20 percentage points between groups in a single measure. The power of the global test is equal to or greater than that of a single measure.[8]

Selection of Patients

To be eligible for the study, patients had to have had an ischemic stroke with a clearly defined time of onset, a deficit measurable on the NIHSS, and a base-line computed tomographic (CT) scan of the brain that showed no evidence of intracranial hemorrhage. Patients did not undergo randomization if they had had another stroke or serious head trauma within the preceding 3 months; had undergone major surgery within 14 days; had a history of intracranial hemorrhage; had a systolic blood pressure above 185 mm Hg or diastolic blood pressure above 110 mm Hg; had rapidly improving or minor symptoms; had symptoms suggestive of subarachnoid hemorrhage; had gastrointestinal hemorrhage or urinary tract hemorrhage within the previous 21 days; had arterial puncture at a noncompressible site within the previous 7 days; or had a seizure at the onset of stroke. Patients who were taking anticoagulants or who had received heparin within the 48 hours preceding the onset of stroke and had an elevated partial-thromboplastin time were excluded, as were those with prothrombin times greater than 15 seconds, platelet counts below 100,000 per cubic millimeter, or glucose concentrations below 50 mg per deciliter (2.7 mmol per liter) or above 400 mg per deciliter (22.2 mmol per liter). Patients were also excluded if aggressive treatment was required to reduce their blood pressure to the specified limits. Informed consent was obtained for all patients.

Randomization and Treatment

A permuted-block design with blocks of various sizes was used for randomization, with patients stratified according to clinical center and time from the onset of stroke to the start of treatment (0 to 90 or 91 to 180 minutes). Patients received placebo or alteplase (Activase, Genentech, South San Francisco), a recombinant t-PA, in a dose of 0.9 mg per kilogram of body weight (maximum, 90 mg), 10 percent of which was given as a bolus followed by delivery of the remaining 90 percent as a constant infusion over a period of 60 minutes. Genentech supplied and distributed both the t-PA and the placebo and monitored the clinical sites.

The protocol required that no anticoagulants or antiplatelet agents be given for 24 hours after treatment and that blood pressure be maintained within prespecified values. The medical monitor reviewed each patient's compliance with the protocol throughout the trial.

Outcome Measures

Four outcome measures were selected on the basis of their reliability, familiarity to the neurologic community, adaptability for use in patients

Table 1. The Medical Histories of the Patients in the Study.

VARIABLE	PART 1		PART 2	
	t-PA (N=144)	PLACEBO (N=147)	t-PA (N=168)	PLACEBO (N=165)
	percent			
Stroke	17	17	12	9
Transient ischemic attack	22	14	13	19
Aspirin therapy	41	31	40	26
Diabetes	24	21	20	20
Hypertension	66	64	67	67
Myocardial infarction	25	21	22	20
Atrial fibrillation	18	20	20	16
Angina pectoris	18	22	24	24
Congestive heart failure	14	17	16	19
Valvular heart disease	11	7	6	6
Smoking in year before stroke	43	37	27	35
No preexisting disability	90	91	95	93

who have had a stroke, and comparability to end points used in other trials of thrombolytic therapy. The Barthel index[9] is a reliable and valid measure of the ability to perform activities of daily living such as eating, bathing, walking, and using the toilet. Patients able to perform all activities with complete independence are given a score of 100. The Barthel index has been used to evaluate outcome in patients who have had a stroke.[10] The modified Rankin scale[11] is a simplified overall assessment of function in which a score of 0 indicates the absence of symptoms and a score of 5, severe disability. The Glasgow outcome scale[12] is a global assessment of function in which a score of 1 indicates a good recovery; a score of 2, moderate disability; a score of 3, severe disability; a score of 4, survival but in a vegetative state; and a score of 5, death. It has been used in a trial of treatment for stroke caused by subarachnoid hemorrhage.[13] The NIHSS,[14] a serial measure of neurologic deficit, is a 42-point scale that quantifies neurologic deficits in 11 categories. For example, a mild facial paralysis is given a score of 1, and complete right hemiplegia with aphasia, gaze deviation, visual-field deficit, dysarthria, and sensory loss is given a score of 25. Normal function without neurologic deficit is scored as zero. In part 1, the NIHSS was expected to be sensitive to and reliably detect a change in neurologic deficit in patients who had had a stroke. In part 2, the NIHSS was dichotomized to identify clearly patients with minimal or no neurologic deficit. This use for the NIHSS is new but consistent with its purpose and capability. Scores of 95 or 100 on the Barthel index, ≤1 on the NIHSS and the modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favorable outcome.

Data Collection

According to the protocol, the outcome was determined at 24 hours and three months by certified examiners who had not performed the base-line examination and had not been present during the initial treatment. The reliability and reproducibility of the Barthel index and the NIHSS certification process have been reported.[14-16] Classification of the subtypes of the strokes was based only on information available before randomization.

CT Scans

During the study, third- or fourth-generation CT scanners had to be available 24 hours a day. CT quality standards were established before the trial started. Each scan was reviewed centrally for compliance by a radiologist blinded to all clinical information, including treatment group.

Statistical Analysis

All analyses were based on the intention to treat.[17] The critical level for a two-sided test of each primary hypothesis was 0.05. Clinical cen-

Table 2. Base-Line Characteristics of the Patients in the Two Parts of the Study, According to Treatment Group.*

CHARACTERISTIC	PART 1		PART 2	
	t-PA (N = 144)	PLACEBO (N = 147)	t-PA (N = 168)	PLACEBO (N = 165)
Age (yr)	67±10	66±11	69±12	66±13
Race or ethnic group (%)				
White, non-Hispanic	62	61	69	66
Black	29	31	23	26
Hispanic	8	5	5	7
Asian	1	0	3	1
Other	0	3	1	1
Female sex (%)	42	40	43	42
Weight (kg)	76±15	80±18	76±16	80±21
NIHSS score				
Median	14	14	14	15
Minimum	1	1	2	2
Maximum	37	32	37	33
Stroke subtype (%)				
Small-vessel occlusive	19	11	14	9
Cardioembolic	42	44	45	44
Large-vessel occlusive	35	42	39	45
Other	3	3	2	3
Blood pressure (mm Hg)				
Systolic	155±22	153±20	153±22	152±21
Diastolic	85±12	85±13	85±14	86±15
Fibrinogen (mg/dl)	332±94	349±106	311±102	316±86
Glucose (mg/dl)†	149±76	152±78	149±66	149±78
CT findings (%)				
Edema	5	3	4	6
Mass effect	3	2	3	4

*Plus–minus values are means ±SD. Because of rounding, not all columns total 100 percent.

†To convert values for glucose to millimoles per liter, multiply by 0.05551.

ter and, where appropriate, time from the onset of the stroke were used to stratify the data.

Primary Outcome in Part 1

For each primary hypothesis, Mantel–Haenszel tests were used to compare the proportion of patients with improvement in the NIHSS 24 hours after the onset of stroke. There was no adjustment for multiple comparisons, since the three hypotheses were prespecified. Pa-

tients who for some reason were not assessed with the NIHSS at 24 hours were considered to have had no improvement.

Primary Outcome in Part 2

The primary hypothesis was tested with a global statistic (the Wald test) derived from a general linear model with logit-link function, computed with the use of generalized estimating equations.[18,19] This global test statistic simultaneously tests for effect in all four outcome measures specified in the primary hypothesis. Patients who died before the three-month assessment were given the worst possible score for all outcomes. In cases of surviving patients with missing outcome data, outcome data obtained after three months were used; if there were none, the data from the measurement closest in time, but at least seven days after randomization, were used. Otherwise, the worst possible score was assigned. Mantel–Haenszel tests comparing the differences in each of the four measures were planned only if the global-test results were significant at the 0.05 level. Each univariate test used a critical level of 0.05 as a guideline to interpretation. An additional global test was performed after adjustment for the stratifying variables and for covariates that differed significantly at base line between the two groups ($P<0.05$).

Secondary Analyses

Intention-to-treat analysis was used for the secondary outcomes at three months in part 1 and for the NIHSS measurement at 24 hours in part 2. These secondary analyses were considered descriptive. For binary outcomes, Mantel–Haenszel tests were used to compare individual variables between groups, and global tests were used to compare sets of variables. Analysis of covariance was used for post hoc comparisons of median NIHSS scores on the ranked data.

Monitoring for Efficacy

Interim analyses with adjusted critical levels for the primary outcomes were performed once during part 1 and once during part 2.[20,21]

Monitoring for Safety

Intracranial hemorrhage, serious systemic bleeding, death, and new stroke were the primary adverse events monitored. To detect intracranial hemorrhage, CT scans were required at 24 hours and 7 to 10 days after the onset of stroke and when any clinical finding suggested hemorrhage. A hemorrhage was considered symptomatic if it was not seen on a previous CT scan and there had subsequently been either a suspicion of hemorrhage or any decline in neurologic status. All CT

Table 3. Scores on the NIHSS 24 Hours after the Onset of Stroke.

TIME TO TREATMENT AFTER STROKE ONSET	t-PA		PLACEBO		RELATIVE RISK (95% CI)†	P VALUE‡	NIHSS SCORE	
	NO. OF PATIENTS	NO. WITH IMPROVEMENT (%)*	NO. OF PATIENTS	NO. WITH IMPROVEMENT (%)*			t-PA	PLACEBO
min							median (range)§	
Part 1								
0–90	71	36 (51)	68	31 (46)	1.1 (0.8–1.6)	0.56	9 (3–17)	11 (5–17)¶
91–180	73	31 (42)	79	26 (33)	1.3 (0.9–1.9)	0.23	8 (3–17)	12 (8–20)‖
0–180	144	67 (47)	147	57 (39)	1.2 (0.9–1.6)	0.21	8 (3–17)	12 (6–19)‖
Part 2								
0–90	86	51 (59)	77	30 (39)	1.5 (1.1–2.1)	0.02	9 (2–18)	12 (8–20)‖
91–180	82	29 (35)	88	35 (40)	0.9 (0.6–1.3)	0.52	9 (3–20)	14 (6–19)¶
0–180	168	80 (48)	165	65 (39)	1.2 (0.9–1.5)	0.19	9 (3–20)	14 (7–19)‖
Combined results								
0–90	157	87 (55)	145	61 (42)	1.3 (1.0–1.7)	0.02	9 (2–17)	12 (6–18)‖
91–180	155	60 (39)	167	61 (37)	1.1 (0.8–1.4)	0.73	8 (3–19)	13 (7–19)‖
0–180	312	147 (47)	312	122 (39)	1.2 (1.0–1.4)	0.06	8 (3–18)	12 (6–19)‖

*Improvement was defined as a 4-point improvement in the NIHSS score from base-line values or complete resolution of the neurologic deficit.

†CI denotes confidence interval.

‡The Mantel–Haenszel test was used with stratification according to clinical center and, for analyses of 0-to-180-minute groups, the time to treatment after the onset of stroke (0 to 90 minutes or 91 to 180 minutes).

§Interquartile range.   ¶P>0.18 by analysis of covariance.   ‖P<0.02 by analysis of covariance.

Table 4. Outcomes at Three Months According to the Time to Treatment after the Onset of Stroke.

Assessment Instrument	Percentage with Favorable Outcome*		Odds Ratio (95% CI)†	Relative Risk (95% CI)†	P Value
	t-PA	PLACEBO			
Part 2, 0–180 min‡					
No. of patients	168	165			
Global test	—	—	1.7 (1.2–2.6)	—	0.008
Barthel index	50	38	1.6 (1.1–2.5)	1.3 (1.0–1.7)	0.026
Modified Rankin scale	39	26	1.7 (1.1–2.6)	1.5 (1.1–2.0)	0.019
Glasgow outcome scale	44	32	1.6 (1.1–2.5)	1.4 (1.0–1.8)	0.025
NIHSS	31	20	1.7 (1.0–2.8)	1.5 (1.0–2.2)	0.033
Part 1, 0–180 min‡§					
No. of patients	144	147			
Global test	—	—	2.1 (1.3–3.2)	—	0.001
Barthel index	54	39	1.8 (1.1–2.8)	1.4 (1.1–1.8)	0.012
Modified Rankin scale	47	27	2.3 (1.4–3.6)	1.7 (1.3–2.3)	<0.001
Glasgow outcome scale	47	31	2.0 (1.2–3.1)	1.5 (1.1–2.0)	0.005
NIHSS	38	21	2.2 (1.3–3.7)	1.8 (1.2–2.6)	0.002
Combined results§					
0–90 min‡					
No. of patients	157	145			
Global test	—	—	1.9 (1.2–2.9)	—	0.005
Barthel index	53	38	1.8 (1.2–2.9)	1.4 (1.1–1.8)	0.010
Modified Rankin scale	40	28	1.7 (1.0–2.6)	1.4 (1.0–1.9)	0.035
Glasgow outcome scale	43	32	1.6 (1.0–2.5)	1.3 (1.0–1.8)	0.057
NIHSS	34	20	2.0 (1.2–3.4)	1.7 (1.1–2.5)	0.008
91–180 min‡					
No. of patients	155	167			
Global test	—	—	1.9 (1.3–2.9)	—	0.002
Barthel index	51	38	1.6 (1.1–2.5)	1.3 (1.0–1.7)	0.026
Modified Rankin scale	45	25	2.4 (1.5–3.7)	1.8 (1.3–2.4)	<0.001
Glasgow outcome scale	47	30	2.0 (1.3–3.2)	1.6 (1.2–2.1)	0.002
NIHSS	34	21	2.0 (1.2–3.2)	1.6 (1.1–2.3)	0.008

*Scores of 95 or 100 on the Barthel index, ≤1 on the NIHSS and modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favorable outcome in this intention-to-treat analysis.

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

‡Time to treatment after the onset of stroke.

§The results for part 1 were considered hypothesis-generating. The definition of favorable outcomes was derived from part 1 data and required testing in part 2.
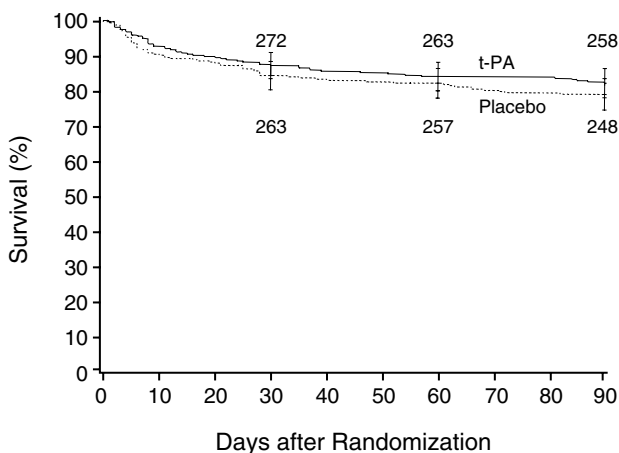

Figure 1. Mean (±SE) Survival at Three Months According to Treatment.

The combined results of parts 1 and 2 are shown. There were 312 patients in each group, and no patient had missing data on mortality. Error bars represent the standard errors of the point estimates of survival at 30, 60, and 90 days. The number of patients surviving at each interval is shown.

scans were made available to treating physicians while a patient was receiving care. Later, each CT scan was examined for evidence of hemorrhage by a neuroradiologist at the CT-reading center who was blinded to clinical information. The medical monitor independently reviewed the clinical reports to detect any unreported adverse events.

Interim analyses were required after every 3 symptomatic intracranial hemorrhages and after every 10 deaths. A lower boundary ($z = -2.0$) was set to allow the trial to be stopped if t-PA was found to be harmful.[22,23] For deaths, a direct comparison of the survival curves was made with a log-rank test. For symptomatic intracranial hemorrhage, the rate among patients treated with t-PA was compared with the rate of 8 percent estimated from pilot studies using similar doses and times of treatment.

RESULTS

From January 1991 through October 1994, 624 patients underwent randomization. The treatment groups were well matched with respect to all base-line characteristics except weight in part 1 of the trial and age and aspirin use in part 2 (Tables 1 and 2).

Compliance with the protocol was excellent in this trial. In part 1, 90 percent of the t-PA group and 92 percent of the placebo group received the full dose (±5 percent) of the study medication, whereas in part 2, 93 percent of both groups received the full dose (±5 percent). Of the primary outcome measures for the 291 patients in part 1, data were missing for 1. Of the 1332 primary outcome measures in part 2 (333 patients), data were missing for 7 (4 patients). Twenty-four hours after the onset of stroke, only 2 percent of the patients given placebo had no neurologic deficit, as measured by the NIHSS.

In part 1 no statistically significant differences were detected between groups in the primary outcome (improvement by 4 or more points in the NIHSS score or a complete resolution of the neurologic deficit) (Table 3). However, post hoc comparisons of median NIHSS scores showed improvement in the condition of patients treated with t-PA as compared with those given placebo in most time strata in parts 1 and 2 and in the combined analysis.

In part 2 the number of patients with favorable outcomes for each of the four primary outcome measures three months after stroke was higher in the t-PA group than in the placebo group (Table 4). As evaluated by the global test statistic, the odds ratio for a favorable outcome in the t-PA group was 1.7 (95 percent confidence interval, 1.2 to 2.6; P=0.008). As compared with the placebo group, there was a 12 percent absolute (32 percent relative) increase in the number of patients with
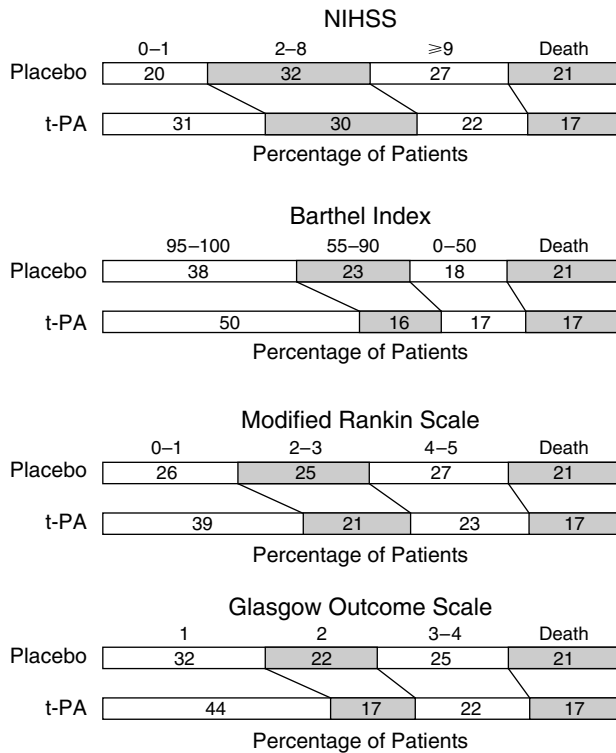
NIHSS

	0–1	2–8	≥9	Death
Placebo	20	32	27	21
t-PA	31	30	22	17

Percentage of Patients

Barthel Index

	95–100	55–90	0–50	Death
Placebo	38	23	18	21
t-PA	50	16	17	17

Percentage of Patients

Modified Rankin Scale

	0–1	2–3	4–5	Death
Placebo	26	25	27	21
t-PA	39	21	23	17

Percentage of Patients

Glasgow Outcome Scale

	1	2	3–4	Death
Placebo	32	22	25	21
t-PA	44	17	22	17

Percentage of Patients

Figure 2. Outcome at Three Months in Part 2 of the Study, According to Treatment.

Scores of ≤1 on the NIHSS, 95 or 100 on the Barthel index, ≤1 on the modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favorable outcome. Values do not total 100 percent because of rounding.

minimal or no disability (a score of 95 or 100 on the Barthel index) in the t-PA group. There was also an 11 percent absolute (55 percent relative) increase in the number of patients with an NIHSS score of 0 or 1 in this group. A similar magnitude of effect was seen with respect to the absolute and relative improvement in the t-PA group with the use of the modified Rankin scale and the Glasgow outcome scale. The inclusion of variables that differed between the two groups at base line (aspirin use, weight, and age) as covariates in addition to the clinical center and time to treatment after the onset of stroke in the global test increased the odds ratio to 2.0 (95 percent confidence interval, 1.3 to 3.1). Secondary outcomes for part 1 and data from the combined analysis for both time strata are also shown in Table 4 and indicate the same pattern of benefit for t-PA. There were no significant differences in mortality between the groups (Fig. 1). By 90 days after the onset of stroke, 54 of the 312 t-PA–treated patients had died (17 percent), as compared with 64 of the 312 placebo-treated patients (21 percent) (P=0.30).

Figure 2 shows the outcome at three months in part 2 of the study. The results of all four outcome measures favor the t-PA group. The greater proportion of pa-

tients left with minimal or no deficit three months after t-PA therapy, as compared with placebo treatment, was not accompanied by an increase in severe disability or mortality. The results were similar in part 1. The positive effect of t-PA on all outcome measures at three months was seen consistently in subgroups categorized according to age, base-line classification of the stroke subtype (Table 5), severity of the stroke, and use of aspirin before the stroke.

Symptomatic intracerebral hemorrhage during the first 36 hours occurred more commonly in t-PA–treated patients (P<0.001 for the combined analysis) (Table 6). Patients with symptomatic intracranial hemorrhage had more severe deficits at base line (median NIHSS score, 20; range, 3 to 29) than the study population as a whole (median NIHSS score, 14; range, 1 to 37). Nine percent of the patients with intracranial hemorrhage had CT evidence of cerebral edema at base line, as compared with 4 percent of the study population as a whole. Another six patients had symptomatic intracranial bleeding (four given t-PA and two given placebo) between 36 hours and three months after the start of treatment. Eleven deaths were attributed to intracerebral hemorrhage. At three months, 17 of the 28 patients with symptomatic hemorrhage (61 percent) had died.

The rate of asymptomatic intracerebral hemorrhage was similar in the two groups. The percentage of patients with serious systemic bleeding during the first 10 days was similar in part 1 (two patients in the t-PA group and none in the placebo group) and part 2 (three patients in the t-PA group and none in the placebo group). Minor external bleeding during the first 10 days was more common with t-PA than placebo (23 percent vs. 3 percent).

In part 1 of the study, new ischemic strokes occurred

Table 5. Outcome at Three Months According to the Classification of the Stroke Subtype at Base Line.

STROKE SUBTYPE*	t-PA		PLACEBO	
	NO. OF PATIENTS	% WITH FAVORABLE OUTCOME†	NO. OF PATIENTS	% WITH FAVORABLE OUTCOME†
Small-vessel occlusive	51		30	
Barthel index		75		50
Modified Rankin scale		63		40
Glasgow outcome scale		63		43
NIHSS		47		33
Large-vessel occlusive	117		135	
Barthel index		49		36
Modified Rankin scale		40		22
Glasgow outcome scale		45		28
NIHSS		33		18
Cardioembolic	136		137	
Barthel index		46		37
Modified Rankin scale		38		28
Glasgow outcome scale		39		31
NIHSS		29		20

*Eighteen patients (2.9 percent) with other stroke subtypes were excluded from the analysis.

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

Table 6. Incidence of Intracranial Hemorrhage within 36 Hours of Treatment for Stroke.

Type of Intracranial Hemorrhage	t-PA	Placebo
	no. (%)	
Part 1	144	147
Symptomatic	8 (6)	0
Fatal*	4	0
Nonfatal	4	0
Asymptomatic	5 (3)	3 (2)
Part 2	168	165
Symptomatic	12 (7)	2 (1)
Fatal*	5	1
Nonfatal	7	1
Asymptomatic	9 (5)	6 (4)

*Values include all deaths attributed to hemorrhage.

in 8 percent of t-PA–treated patients and 7 percent of those given placebo. In part 2, new ischemic stroke occurred in 4 percent of t-PA–treated patients and 4 percent of those given placebo.

DISCUSSION

This study found a benefit of intravenous t-PA therapy for patients with ischemic stroke when treatment was initiated within three hours of the onset of symptoms. As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months, as measured by the outcome scales (absolute increase in favorable outcome, 11 to 13 percent). This benefit was not associated with any increase in mortality.

Treatment with t-PA resulted in a more favorable outcome than treatment with placebo regardless of the subtype of stroke diagnosed at base line. Even though the diagnosis of these subtypes was based on the limited information obtained before treatment was started, the distribution of the subtypes was similar in both groups. Because treatment was started so early, some patients with transient ischemic attacks could have been enrolled despite the exclusion of patients whose symptoms rapidly improved. Since so few patients given placebo (2 percent) were free of neurologic deficits at 24 hours on the basis of the NIHSS scores, it is unlikely that the benefit seen with t-PA was due to the spontaneous resolution of stroke symptoms.

In part 2 of our study, our intent was to consider the balance between risk and benefit. To justify the serious risks of thrombolytic therapy, we required a meaningful increase in the number of patients who recovered with minimal or no disability after treatment with t-PA as compared with placebo. To increase our confidence in this outcome, we required that the results of all four outcome measures be similar. The modified Rankin scale, Barthel index, and Glasgow outcome scale represent the entire range of function from death and severe disability to complete recovery. The NIHSS measures neurologic deficit and not functional outcome. As used here, it ensured that complete recovery also meant complete neurologic recovery regardless of function.

Two previous small, randomized studies of intravenous t-PA for stroke found no conclusive evidence of efficacy.[24,25] In a recently completed large, placebo-controlled European trial in which 1.1 mg of t-PA per kilogram was given intravenously within six hours of hemispheric ischemia, the investigators reported no benefit in the population analyzed according to the intention to treat.[26] Two other large, randomized trials of intravenous streptokinase were stopped early because of an unacceptable rate of symptomatic intracranial hemorrhage.[27,28] These large trials treated most patients more than three hours after the onset of stroke and used different drugs, dosing regimens, and methods of outcome measurement from those used in our study. The most obvious difference between our study and the other large trials is the extent to which we focused on minimizing the time to treatment. For 302 patients, symptom recognition, transport to the hospital, triage, neurologic evaluation including CT scanning, laboratory studies, informed consent, and randomization were accomplished within 90 minutes of the onset of stroke. Trials in patients with myocardial infarction have shown increased benefit with early treatment.[29] Such a benefit from early treatment is consistent with our understanding of the process of infarction and the narrow window of opportunity for effective intervention.[30]

There were more intracranial hemorrhages in t-PA–treated patients than in those given placebo, but the proportion with hemorrhage was lower in our trial than in other randomized trials of streptokinase[27,28] and t-PA.[26] These differences may be due to the earlier initiation of treatment[3] and lower doses used in our study.[26,31] Post-treatment elevation in blood pressure may also increase the risk of hemorrhage.[31] In our trial, treating physicians used an algorithm to manage blood pressure after treatment began. Accordingly, the safety of t-PA given later than three hours after the onset of stroke, in doses higher than 0.9 mg per kilogram, and without careful blood-pressure management is not clear.

In conclusion, despite an increased incidence of intracerebral hemorrhage, an improvement in clinical outcome at three months was found in patients treated with intravenous t-PA within three hours of the onset of acute ischemic stroke.

APPENDIX

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REFERENCES

1. Division of Chronic Disease Control and Community Intervention. Cardiovascular disease surveillance: stroke, 1980-1989. Atlanta: Centers for Disease Control and Prevention, 1994.
2. Fieschi C, Argentino C, Lenzi GL, Sacchetti ML, Toni D, Bozzao L. Clinical and instrumental evaluation of patients with ischemic stroke within the first six hours. J Neuro Sci 1989;91:311-22.
3. del Zoppo GJ, Poeck K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol 1992;32:78-86.
4. Fletcher AP, Alkjaersig N, Lewis M, et al. A pilot study of urokinase therapy in cerebral infarction. Stroke 1976;7:135-42.
5. Meyer JS, Gilroy J, Barnhart J. Therapeutic thrombolysis in cerebral thromboembolism: randomized evaluation of intravenous streptokinase. In: Siekert W, Whisnant JP, eds. Cerebral vascular diseases. New York: Grune & Stratton, 1965:200-13.
6. Brott TG, Haley EC Jr, Levy DE, et al. Urgent therapy for stroke. I. Pilot study of tissue plasminogen activator administered within 90 minutes. Stroke 1992;23:632-40.
7. Haley EC Jr, Levy DE, Brott TG, et al. Urgent therapy for stroke. II. Pilot study of tissue plasminogen activator administered 91-180 minutes from onset. Stroke 1992;23:641-5.
8. Pocock SJ, Geller NL, Tsiatis AA. The analysis of multiple endpoints in clinical trials. Biometrics 1987;43:487-98.
9. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. Md State Med J 1965;14(2):61-5.
10. The American Nimodipine Study Group. Clinical trial of nimodipine in acute ischemic stroke. Stroke 1992;23:3-8. [Erratum, Stroke 1992;23:615.]
11. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-7.
12. Teasdale G, Knill-Jones R, van der Sande J. Observer variability in assessing impaired consciousness and coma. J Neurol Neurosurg Psychiatry 1978; 41:603-10.
13. Haley EC Jr, Kassell NF, Torner JC, et al. A randomized controlled trial of high-dose nicardipine in aneurysmal subarachnoid hemorrhage. J Neurosurg 1993;78:537-47.
14. Lyden P, Brott T, Tilley B, et al. Improved reliability of the NIH Stroke Scale using video training. Stroke 1994;25:2220-6.
15. Albanese MA, Clarke WR, Adams HP Jr, Woolson RF. Ensuring reliability of outcome measures in multicenter clinical trials of treatments for acute ischemic stroke: the program developed for the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Stroke 1994;25:1746-51.
16. Lyden PD, Broderick J, Mascha E. Reliability of the Barthel Index used for the NINDS t-PA Stroke Trial. In: Yamaguchi T, Mori E, Minematsuk K, del Zoppo GJ, eds. Thrombolytic therapy in acute stroke III. Tokyo, Japan: Springer-Verlag (in press).
17. Friedman LM, Furberg CD, DeMets DL. Fundamentals of clinical trials. 2nd ed. Littleton, Mass.: PSG Publishing, 1985.
18. Lefkopoulou M, Moore D, Ryan L. The analysis of multiple correlated binary outcomes: application to rodent teratology experiments. J Am Stat Assoc 1989;84:810-5.
19. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121-30.
20. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.
21. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
22. DeMets DL, Ware JH. Group sequential methods for clinical trials with a one-sided hypothesis. Biometrika 1980;67:651-60.
23. *Idem.* Asymmetric group sequential boundaries for monitoring clinical trials. Biometrika 1982;69:661-3.
24. Haley EC Jr, Brott TG, Sheppard GL, et al. Pilot randomized trial of tissue plasminogen activator in acute ischemic stroke. Stroke 1993;24:1000-4.
25. Mori E, Yoneda Y, Tabuchi M, et al. Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. Neurology 1992; 42:976-82.
26. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. JAMA 1995;274:1017-25.
27. Hommel M, Boissel JP, Cornu C, et al. Termination of trial of streptokinase in severe acute ischaemic stroke. Lancet 1995;345:57.
28. Donnan GA, Hommel M, Davis SM, McNeil JJ. Streptokinase in acute ischaemic stroke. Lancet 1995;346:56.
29. Fibrinolytic Therapists Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994;343:311-22. [Erratum, Lancet 1994;343:742.]
30. Zivin JA, Fisher M, DeGirolami U, Hemenway CC, Stashak JA. Tissue plasminogen activator reduces neurological damage after cerebral embolism. Science 1985;230:1289-92.
31. Levy DE, Brott TG, Haley EC Jr, et al. Factors related to intracranial hematoma formation in patients receiving tissue-type plasminogen activator for acute ischemic stroke. Stroke 1994;25:291-7.