Emergency Medicine Journal Club
Thursday, June 11, 2015

The June emergency medicine journal club will be held during regular lecture time**.** The topic is:

Thrombolysis for Stroke

Perhaps no aspect of contemporary emergency medicine is as controversial and contentious as thrombolysis for acute stroke. The existing data can be argued both ways, there has been aggressive drug company marketing, and litigation threatens whether thrombolysis is or is not administered. Emergency physicians and neurologists couldn't be more different in their underlying chemistry and clinical approach. Bitter and personal feuds have arisen between researchers and educators, with zealous personalities enlivening both sides of the debate. This is a classic case study of critically important medical decision making in the setting of incomplete evidence.

In this journal club we will discuss: What are the benefits and risks of TPA for stroke as shown in the landmark NINDS study? What were the results of other less-publicized studies? How many stroke patients qualify for TPA therapy? What is the public health impact of this treatment? What are "stoke mimics"? How has the benefit / risk of this therapy fared in later community hospital-based trials? Why has NINDs be repeatedly re-analyzed, what why do these reanalyses disagree? Is thrombolysis effective between 3 and 4.5 hours after symptom onset? What is the nature of the litigation risk with TPA for stroke? Can it be lowered?

Page	*Presenter: Item*
2	**Andrew Johnson**. NINDS: Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333:1581. Focus on everything: methodology, results, reporting of results, relative benefits in 0-90 minute versus 91-180 minute groups.
9	**Whitney Hampton**. Chernyshev: Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia. *Neurology* 2010; 74:1340-1345. Focus on concept and accuracy of differentiation between mimics and non-mimics.
15	**Nellie Ekmekjian**. Hacke: Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke (ECASS III). *N Engl J Med* 2008; 359:1317-1329. Focus on general approach and results, and comparison with NINDS methodology.
28	**Morgaine Daniels**. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet* 2012; 379:2352-2363. Focus on general approach and results, and comparison with NINDS methodology.

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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.

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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.
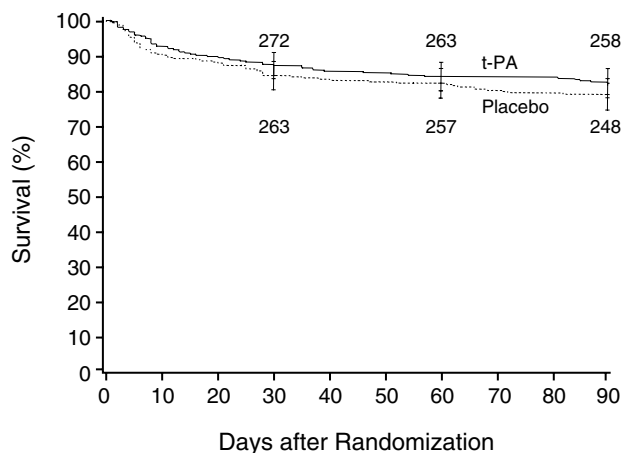

Figure 1. Mean (±SE) Survival at Three Months According to Treatment.

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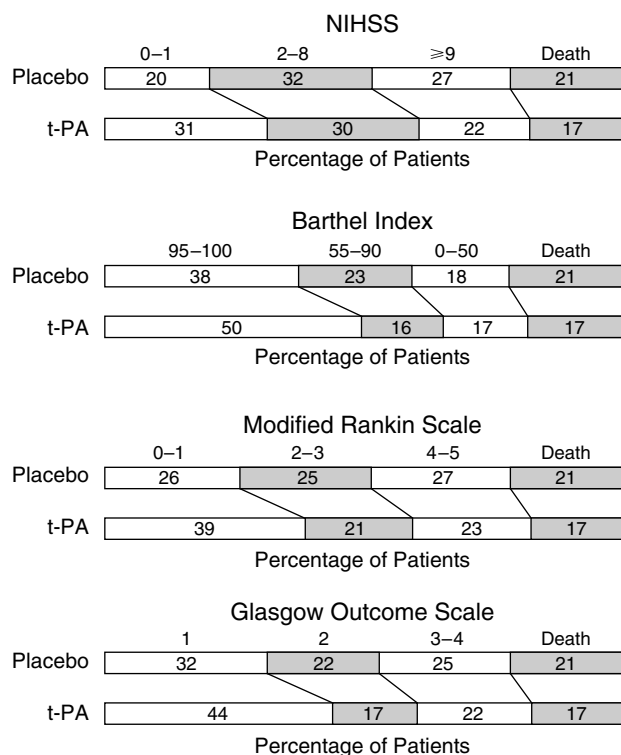
Figure 2. Outcome at Three Months in Part 2 of the Study, According to Treatment.

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.

Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia

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ABSTRACT

Background: Patients with acute neurologic symptoms may have other causes simulating ischemic stroke, called stroke mimics (SM), but they may also have averted strokes that do not appear as infarcts on neuroimaging, which we call neuroimaging-negative cerebral ischemia (NNCI). We determined the safety and outcome of IV thrombolysis within 3 hours of symptom onset in patients with SM and NNCI.

Methods: Patients treated with IV tissue plasminogen activator (tPA) within 3 hours of symptom onset were identified from our stroke registry from June 2004 to October 2008. We collected admission NIH Stroke Scale (NIHSS) score, modified Rankin score (mRS), length of stay (LOS), symptomatic intracerebral hemorrhage (sICH), and discharge diagnosis.

Results: Among 512 treated patients, 21% were found not to have an infarct on follow-up imaging. In the SM group (14%), average age was 55 years, median admission NIHSS was 7, median discharge NIHSS was 0, median LOS was 3 days, and there were no instances of sICH. The most common etiologies were seizure, complicated migraine, and conversion disorder. In the NNCI group (7%), average age was 61 years, median admission NIHSS was 7, median discharge NIHSS was 0, median LOS was 3 days, and there were no instances of sICH. Nearly all SM (87%) and NNCI (91%) patients were functionally independent on discharge (mRS 0–1).

Conclusions: Our data support the safety of administering IV tissue plasminogen activator to patients with suspected acute cerebral ischemia within 3 hours of symptom onset, even when the diagnosis ultimately is found not to be stroke or imaging does not show an infarct. *Neurology*® **2010;74:1340–1345**

GLOSSARY

AIS = acute ischemic stroke; **CI** = confidence interval; **DWI** = diffusion-weighted imaging; **ED** = emergency department; **LOS** = length of stay; **mRS** = modified Rankin score; **NIHSS** = NIH Stroke Scale; **NNCI** = neuroimaging-negative cerebral ischemia; **OR** = odds ratio; **sICH** = symptomatic intracerebral hemorrhage; **SM** = stroke mimics; **tPA** = tissue plasminogen activator.

Although there is worldwide consensus among disease experts and independent regulators regarding the utility of IV tissue plasminogen activator (tPA) for acute ischemic stroke (AIS), there is concern about administering IV tPA to patients who present with clinical features suggestive of AIS but have an alternative diagnosis.[1] AIS causes neurologic deficits that commonly occur in other disorders[2] for which tPA has no benefit and may carry an increased risk for hemorrhage. When patients present to the emergency department (ED) with acute neurologic deficits, time is important to make a rapid evaluation if IV tPA is being considered.[3] The short time window of 3 hours from symptom onset to administer tPA (per Food and Drug Administration label) may not allow physicians to make a correct diagnosis. A quick history and neurologic examination, often with the NIH Stroke Scale (NIHSS), along with a CT scan to rule out hemorrhage, comprise the main components of the evaluation. Such an approach

Supplemental data at
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may miss several other disorders that mimic stroke or cannot reliably differentiate conditions that masquerade as stroke, such as seizure, complicated migraine, or functional deficits. Does specificity matter in patients presenting with suspected stroke once a brain hemorrhage has been ruled out? Many would argue that it is wrong to give a treatment that is potentially dangerous to patients who do not have the target disease.[4] Vascular imaging with CT angiography, magnetic resonance angiography, or transcranial Doppler ultrasound can visualize large artery occlusions and diffusion-weighted imaging (DWI) is highly sensitive to detect ischemic stroke, but these modalities are not universally available at primary and community hospitals.

In the absence of additional imaging, it is estimated from studies that 3%–7% of patients treated with IV tPA for assumed acute cerebral ischemia have a stroke mimic (SM).[5,6] However, these studies collectively reported 13 patients with SMs who were treated with tPA. No large study has addressed the question of safety of thrombolysis in patients with SMs or in patients who did not have an infarct on MRI and were not found to have another diagnosis aside from stroke (i.e., averted stroke). Herein, we report a retrospective study of over 100 patients who presented to our ED with symptoms concerning for acute cerebral ischemia but who ultimately were found to have an SM or who had no supporting evidence for stroke on subsequent imaging and were discharged with an averted stroke, which we call neuroimaging-negative cerebral ischemia.

METHODS IV tPA protocol. The UT Stroke Program follows established guidelines to administer IV tPA to suspected acute stroke patients.[7] All patients who present to our ED with suspected acute cerebral ischemia are evaluated by a member of our stroke team. All patients undergo a rapid neurologic evaluation with the NIHSS and a cranial CT scan to rule out hemorrhage. Patients who, in the judgment of the treating physician, may have acute cerebral ischemia within 3 hours of symptom onset, even when other diagnoses are being considered, are treated with IV tPA as soon as possible after presentation to the ED. Our protocol follows from the National Institute of Neurological Disorders and Stroke trial,[7] in which eligibility is based on whether the patient has measurable deficits on the NIHSS scale. Any patient with a disabling deficit including mild hemiparesis, hemianopsia, or aphasia is considered for IV tPA. All treated patients are monitored either in our stroke unit with continuous cardiac monitoring or the neurointensive care unit for at least 24 hours after initiation of thrombolysis. An MRI or CT scan is routinely obtained within 24 hours after treatment.

Study design. We conducted a retrospective study of patients derived from our prospective stroke registry. We determined the safety and outcome of IV thrombolysis within 3 hours of symptom onset in patients who presented to our ED and were found, during hospitalization, not to have an ischemic stroke. Patients treated with full-dose, 0.9 mg/kg, IV tPA within 3 hours of symptom onset were identified from June 2004 to October 2008. We collected NIHSS on admission and discharge, discharge modified Rankin Scale (mRS) score, length of stay (LOS), past medical history, and symptomatic intracerebral hemorrhage (sICH), as defined in the National Institute of Neurological Disorders and Stroke trial,[7] and discharge diagnosis. Initial and follow-up neuroimaging with CT and/or MRI were performed as a part of our routine stroke evaluation. All patients who met inclusion for this study had undergone neuroimaging initially with CT upon presentation, multimodal MRI (DWI, magnetic resonance angiography, fluid-attenuated inversion recovery, and gradient echo imaging) within 24 hours of presentation, and then CT or multimodal imaging before hospital discharge. Diagnosis of SM was based on the absence of acute ischemia/infarct on pre and post IV tPA treatment neuroimaging (<24 hours from the time of onset) and follow-up neuroimaging (>24 hours from the time of onset) in addition to an alternate discharge diagnosis. Diagnosis of neuroimaging-negative cerebral ischemia (NNCI) was based on presentation of acute cerebral ischemia in the ED, the absence of acute ischemia/infarct on pre and post IV tPA treatment neuroimaging (<24 hours from the time of onset), and follow-up posttreatment neuroimaging (>24 hours from the time of onset).

Standard protocol approvals, registrations, and patient consents. This project was approved by the University of Texas–Houston Health Science Center Institutional Review Board.

Statistics. Statistical analyses were performed using SPSS 15.0 (SPSS Inc, Chicago, IL). Continuous variables were reported as mean $\pm$ SD when the distribution was normal and median with range for non-normal distributions. Categorical variables were analyzed using χ^2, Fisher exact test, or analysis of variance where appropriate.

RESULTS Over the study period, we treated 512 suspected stroke patients with full dose IV tPA (0.9 mg/kg). A total of 106 (21%) were not found to have an infarct on posttreatment DWI obtained within 1 day of hospitalization and subsequent posttreatment CT or MRI performed 24 hours after admission. Among the 106 patients, 69 had an SM (14% of the 512 patients) and 37 (7% of the 512 patients) had NNCI. Twelve patients were excluded from analysis because they did not undergo follow-up posttreatment neuroimaging. Follow-up MRI after 24 hours was done in 64% of patients, follow-up CT was done in 79%, and both a follow-up MRI and CT was done in 44% of patients.

Demographics of SM and NNCI patients. Demographics of SM and NNCI patients are detailed in

Table	Clinical characteristics, safety, and functional outcomes of patients with stroke mimics, NNCI, and acute ischemic stroke		
	Stroke mimics (n = 69)	NNCI (n = 37)	Acute ischemic stroke (n = 406)
Age, y, mean ± SD[a,c]	55 ± 15	61 ± 15	65 ± 15
Gender, male, %[a,b,c]	40	68	54
Race, white, %[c]	51	60	62
Admission NIHSS, median (range)[b,c]	7 (1–21) (IQR 4–11)	7 (1–28) (IQR 5–12) (IQR 5–12)	13 (1–40) (IQR 8–19)
Admission NIHSS 1–4, %	36.9	21.6	10.4
Hyperlipidemia, %[a,c]	55	73	72
Hypertension, %[a]	29	43	25
Diabetes mellitus, %	0	0	26
Atrial fibrillation, %[b,c]	2	6	19
Coronary artery disease, %[c]	4	12	10
Alcohol abuse, %	13	15	0.7
Prior cocaine use, %	7	12	0.4
Current tobacco use, %	36	30	24
Time from last seen normal to IV tPA, min, median (range)	156 (30–180) (IQR 126–180)	138 (47–180) (IQR 106–156)	140 (10–180) (IQR 114–161)
Symptomatic ICH, %	0	0	5.8
Angioedema, %	0	0	2.2
Discharge mRS, median (range)[b,c]	0 (0–5) (IQR 0–1)	0 (0–4) (IQR 0–0)	4 (0–6) (IQR 2–5)
Discharge mRS, %			
mRS 0[a,b,c]	74	91	8
mRS 1[a,b]	13	0	13
mRS 2	2	3	11
mRS 3	4	3	16
mRS 4	5	3	25
mRS 5	2	0	17
mRS 6	0	0	10
Length of stay, d, median (range)[b,c]	3 (2–10) (IQR 2–5)	3 (2–10) (IQR 2–5)	6 (1–50) (IQR 4–9)
Disposition, %			
Home[b,c]	81	81	31
Inpatient rehabilitation	8	6	26
Skilled nursing facility	6	8	19
Other	5	5	24

Abbreviations: IQR = interquartile range; mRS = modified Rankin score; NIHSS = NIH Stroke Scale; NNCI = neuroimaging-negative cerebral ischemia; tPA = tissue plasminogen activator.
[a,b,c] Indicate significant differences in pairwise comparisons: [a] p < 0.05, difference between stroke mimics and NNCI; [b] p < 0.05, difference between NNCI and acute ischemic stroke; [c] p < 0.05, difference between stroke mimics and acute ischemic stroke.

the table. In the SM group (n = 69), the average age was 55 ± 15 years, 60% were female, and 51% were white. The median NIHSS on admission was 7. In the NNCI group (n = 37), the average age was 61 ± 15 years, 32% were female, and 60% were white. The median NIHSS on admission was 7. There were no significant differences between SM and NNCI groups except there were higher rates of hypertension and hyperlipidemia in the NNCI group and higher rates of CAD in the SM group. In comparison with the SM group, patients with AIS were older (65 ± 15 years) and had higher admission NIHSS on admission (median 13) and higher rates of hyperlipidemia, atrial fibrillation, and coronary artery disease. In comparison with the NNCI group, AIS patients had higher admission NIHSS scores and higher rates of hyperlipidemia and atrial fibrillation. There was a higher percentage of patients with NIHSS 1–4 in the SM group compared to the other groups. In fact, when compared to AIS patients, SMs were 5 times more likely to have an NIHSS of 1–4 (odds ratio [OR] 5.1, 95% confidence interval [CI] 2.8–9.2, p < 0.0001). None of the SM or NNCI patients presented with pure sensory symptoms.
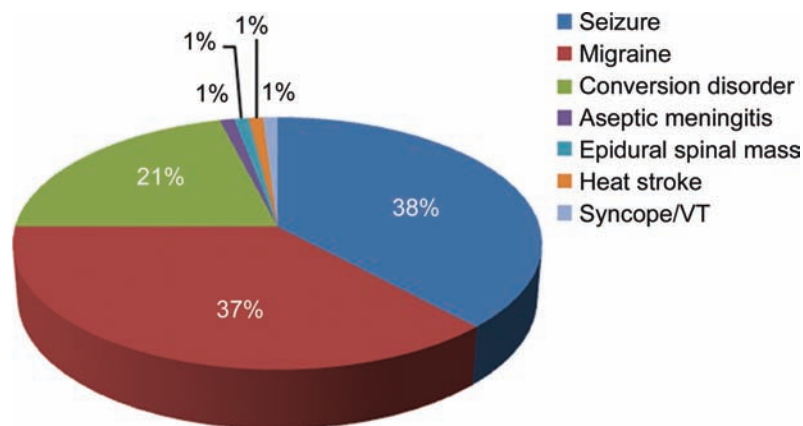
Etiologies of SM. Etiologies of SM are shown in the figure. The most common etiologies in the SM group were seizure (38%), complicated migraine (37%), and conversion disorder (21%). Case vignettes for each of these conditions are provided in appendix e-1 on the *Neurology*® Web site at www.neurology.org. In those patients diagnosed with a seizure, 2 patients presented with a history of motor activity before IV tPA administration and the rest of the patients had, during hospitalization, witnessed motor activity consistent with a seizure, an EEG showing epileptiform features explaining the presenting symptoms, or symptoms that resolved with IV Ativan but not tPA. There were single cases of aseptic meningitis, heatstroke, cardiac syncope due to arrhythmia, and spinal epidural mass.

Etiologies of NNCI. The presumptive diagnosis was either a TIA or partial/complete recanalization and reperfusion after tPA. Based on the TOAST classification, etiologies were cardioembolic (3.3%), large artery (6.7%), small artery (8.3%), cryptogenic (30%), and other (51.7%). The other category included NNCI patients who had cocaine detected on a positive urinary drug screening, leading to a presumptive clinical diagnosis of cocaine-associated vasospasm.

Safety outcomes. None of the patients with SM or NNCI had a systemic hemorrhage, intracerebral hemorrhage, or angioedema (table). One patient was found to have an epidural cervical spinal mass after tPA infusion was completed. The patient was taken for surgical decompression of the mass, which was found to be a tumor that had showed signs of hemorrhage. In comparison, patients with AIS had a 6% incidence of sICH and 2% incidence of angioedema.

Functional outcomes. SM and NNCI patients had a median NIHSS on discharge of 0 and the median

Figure Etiologies of stroke mimics

- Seizure 38%
- Migraine 37%
- Conversion disorder 21%
- Aseptic meningitis 1%
- Epidural spinal mass 1%
- Heat stroke 1%
- Syncope/VT 1%

LOS was 3 days (table). The majority were functionally independent on discharge (mRS 0–1) and the median discharge mRS was 0 in both groups. A total of 81% were discharged home and the remaining patients had baseline neurologic deficits or functional weakness for which a neuroanatomic etiology could not be found. They were transferred to other services: inpatient rehabilitation, skilled nursing facility, or an inpatient medical floor. In comparison, patients with AIS had a median 6-day LOS and 21% were functionally independent on discharge (mRS 0–1).

Excluded patients. We also analyzed the 12 patients excluded from this study and found an average age of 48 ± 13 years, median admission NIHSS 9, no instances of sICH, and median discharge mRS 0. There were no significant differences in stroke severity or other baseline characteristics compared with the SM or NNCI group.

DISCUSSION It is of paramount importance to study the safety of IV tPA in patients with suspected acute cerebral ischemia who are ultimately found on hospital workup not to have a stroke. Within 3 hours after the onset of symptoms, it may be difficult to determine whether acute neurologic signs are due to stroke or to another cause. ED physicians are uncomfortable differentiating a hemiplegic migraine, for example, from stroke.[4] The concern is that exposing patients who do not have ischemic stroke to an added risk of hemorrhage with tPA is inappropriate.[4]

Over a 4-year period, we discovered that 21% of our patients who had presented to our ED with symptoms suggestive of acute cerebral ischemia and had received Food and Drug Administration–approved IV tPA did not have a confirmed infarct on subsequent DWI. Among all treated patients, the incidence of SM was 14% and NNCI was 7%. Our stroke center has a wide referral base and a high vol-

ume of hyperacute patients with neurologic problems requiring emergency stroke workup to consider administration of standard of care IV tPA. The incidence of SM in our patient population is higher than other reported studies, which might reflect a greater number of patients referred and evaluated for thrombolysis, and possibly a lower threshold to treat with IV tPA at our center. Our treatment approach is to consider any patient for thrombolysis with a measurable deficit that is disabling such as a mild hemiparesis. In addition, we used serial monitoring of patients with imaging as part of the definition of SM and NNCI groups. All SM and NNCI patients had follow-up posttreatment neuroimaging. Previous studies did not consistently use posttreatment imaging as a selection criterion for SM.[5,6,8] Our method to define SM may be a limiting factor to determine the actual SM rate among hospitals without primary stroke centers.

To our knowledge, this is the largest reported series of patients with SM treated with tPA. In contrast to patients with AIS, they were younger, were more often women, and had significantly lower admission NIHSS scores. SM patients had a more favorable functional status and disposition at discharge compared with AIS patients. Other studies with a smaller sample number have not found demographic differences between AIS and SM patients.[5] SM patients were diagnosed with a variety of territorial syndromes: right and left MCA, posterior circulation, and subcortical presentations. A prior study of 7 treated SM patients found mainly left MCA symptoms. Consistent with prior studies,[5,6,8] the main SM etiologies were seizures, migraine, and conversion disorder. However, we also treated patients with tPA who were subsequently diagnosed with aseptic meningitis, a cervical epidural mass, and cardiac syncope.

Neuroimaging before and after treatment in the absence of an alternative diagnosis other than acute cerebral ischemia allowed us to distinguish an NNCI group from the SM group. Rapid, sometimes dramatic recovery from stroke-like syndromes within 24 hours after IV thrombolysis has previously been reported.[6,9] As per the WHO criteria, acute focal deficits resolving after treatment might be described as TIAs. Such patients may have recanalized rapidly after tPA before imaging could show damage. These patients have also been described as having an averted stroke.[10] Our findings are in agreement with a recent study showing that tPA was safe to administer in 23 patients with suspected cerebral ischemia who were found not to have an infarct and were diagnosed with TIA.[10] Alternatively, small strokes may not be detected on neuroimaging, including DWI.

False negative DWI studies have been described in acute ischemic stroke within the first 24 hours of symptom onset in which follow-up studies confirmed the "missing" infarct.[11] However, in our dataset, all patients had imaging not only before treatment but at least 24 hours after treatment. Given the absence of an infarct and that no diagnosis other than averted stroke could be found, we believed this condition merited its own category separate from SM. Pretreatment vascular studies and perfusion imaging would have been helpful to better define if NNCI patients had evidence for ischemia or evidence for recanalization after thrombolysis. It is also possible that some patients in this group had a nonischemic etiology that was not found during hospitalization.

Despite finding that we gave IV tPA to 14% of patients with suspected acute cerebral ischemia who were ultimately diagnosed with an SM, we found no instances of symptomatic or systemic hemorrhage despite a range of nonstroke diagnoses. It may not be surprising to have found no instances of sICH in these patients since they did not have a stroke. Patients treated with IV tPA for acute myocardial infarction have less than 1% incidence of intracerebral hemorrhage, and the tPA dose for stroke is lower.[12] The patient who presented with a cervical epidural mass and acute focal deficits required surgery, during which it was found that the mass had bled after tPA. However, we believe the patient's symptoms did not worsen because of the hemorrhage. Most patients with SM and NNCI had shorter hospital stays, significant improvement on the NIHSS score, and excellent functional outcomes.

This study has important limitations including its retrospective design and single center experience from a comprehensive stroke center. Therefore, extrapolating the results to community hospitals with lower volumes of stroke patients must be done with caution. The small sample size may possibly introduce sample and selection bias. In the National Institute of Neurological Disorders and Stroke trial,[7] the rate of ICH in the treated group was 6.41% (95% CI 3.69%–9.13%). Thus, the margin of error with a 95% CI was 2.72%. The sample size needed to obtain this rate is 312. Thus, while our sample of 405 AIS patients is adequate to observe the same rate of ICH as in the National Institute of Neurological Disorders and Stroke trial with at least 95% confidence, the sample size in our study of SM and NNCI patients was not powered to detect such a difference. Thus, this retrospective study is vulnerable to type II error. Certain patients were excluded from our analysis if they were unable to undergo MRI secondary to large body size or presence of implants. While our study suggests that the safety risk is low in patients who later turn out to have an SM, our data should not be used to excuse a less than thorough evaluation. All patients enrolled in this study and treated with tPA met published Food and Drug Administration and American Heart Association guidelines for treatment, and we do not advocate that these criteria should be shortcut. However, even if these criteria are followed, the diagnosis of stroke will remain based on clinical judgment. Our data would support that if the clinician thinks that the patient may be experiencing a stroke, and the patient meets accepted guidelines, the patient should be treated.

Overall, our data together with others[5,6,10] support administering IV tPA to patients presenting in the 3-hour window with suspected AIS, even when alternate etiologies are being considered. Taken collectively, the preponderance of data from this study and the literature suggests that delaying IV tPA administration in the ED in order to obtain further investigations beyond cranial CT in the form of imaging or EEG may not be warranted, even if the diagnosis ultimately is not AIS. However, some centers are able to rapidly obtain additional testing such as CT angiography with CT or even an MRI in the ED setting. Because the risk of emergently treating SMs such as migraine are low, and there is loss of potential benefit in withholding treatment if the patient is indeed having a stroke, we favor IV tPA treatment if the patient meets Food and Drug Administration and American Heart Association criteria for thrombolysis. Subsequent studies after tPA initiation can be performed to better clarify the etiology in cases where the diagnosis is uncertain. Further prospective investigations are needed to establish the safety of thrombolysis in SM and NNCI.

REFERENCES

1. D'Addesio JP. Should thrombolytic therapy be the first-line treatment for acute ischemic stroke? N Engl J Med 1998;338:762; author reply 762–763.

2. Hemmen TM, Meyer BC, McClean TL, Lyden PD. Identification of nonischemic stroke mimics among 411 code strokes at the University of California, San Diego, Stroke Center. J Stroke Cerebrovasc Dis 2008;17:23–25.

3. Saver JL. Time is brain: quantified. Stroke 2006;37:263–266.

4. Caplan LR, Mohr JP, Kistler JP, Koroshetz W. Should thrombolytic therapy be the first-line treatment for acute ischemic stroke? Thrombolysis: not a panacea for ischemic stroke. N Engl J Med 1997;337:1309–1310; discussion 1313.

5. Winkler DT, Fluri F, Fuhr P, et al. Thrombolysis in stroke mimics: frequency, clinical characteristics, and outcome. Stroke 2009;40:1522–1525.

6. Scott PA, Silbergleit R. Misdiagnosis of stroke in tissue plasminogen activator-treated patients: characteristics and outcomes. Ann Emerg Med 2003;42:611–618.

7. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581–1587.

8. Vroomen PC, Buddingh MK, Luijckx GJ, De Keyser J. The incidence of stroke mimics among stroke department admissions in relation to age group. J Stroke Cerebrovasc Dis 2008;17:418–422.

9. Alexandrov AV, Molina CA, Grotta JC, et al. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med 2004;351:2170–2178.

10. Uchino K, Massaro L, Hammer MD. Transient ischemic attack after tissue plasminogen activator: aborted stroke or unnecessary stroke therapy? Cerebrovasc Dis 2009;29:57–61.

11. Oppenheim C, Stanescu R, Dormont D, et al. False-negative diffusion-weighted MR findings in acute ischemic stroke. AJNR Am J Neuroradiol 2000;21:1434–1440.

12. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673–682.

New Guideline Addresses Issue of Driving with Dementia

A new evidence-based clinical guideline published by the American Academy of Neurology in the April 20, 2010, edition of the journal *Neurology*® urges people with dementia who drive to proceed with caution and prepare to give up their keys eventually. Accepting the driving risks associated with dementia requires careful thought by all involved. In time, however, nearly all people with dementia will have to give up driving. It is important for doctors to discuss this with patients and caregivers soon after diagnosis. Physicians should consider multiple information sources to evaluate driving safety (e.g., cognitive tests, on-road driving tests). It is important that the decision to stop driving be directed by a doctor trained and experienced in working with people with dementia and their families. Visit *www.aan.com/go/practice/guidelines* for more information.

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Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

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ABSTRACT

BACKGROUND

Intravenous thrombolysis with alteplase is the only approved treatment for acute ischemic stroke, but its efficacy and safety when administered more than 3 hours after the onset of symptoms have not been established. We tested the efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of a stroke.

METHODS

After exclusion of patients with a brain hemorrhage or major infarction, as detected on a computed tomographic scan, we randomly assigned patients with acute ischemic stroke in a 1:1 double-blind fashion to receive treatment with intravenous alteplase (0.9 mg per kilogram of body weight) or placebo. The primary end point was disability at 90 days, dichotomized as a favorable outcome (a score of 0 or 1 on the modified Rankin scale, which has a range of 0 to 6, with 0 indicating no symptoms at all and 6 indicating death) or an unfavorable outcome (a score of 2 to 6 on the modified Rankin scale). The secondary end point was a global outcome analysis of four neurologic and disability scores combined. Safety end points included death, symptomatic intracranial hemorrhage, and other serious adverse events.

RESULTS

We enrolled a total of 821 patients in the study and randomly assigned 418 to the alteplase group and 403 to the placebo group. The median time for the administration of alteplase was 3 hours 59 minutes. More patients had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; P=0.04). In the global analysis, the outcome was also improved with alteplase as compared with placebo (odds ratio, 1.28; 95% CI, 1.00 to 1.65; P<0.05). The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 27.0% vs. 17.6%; P=0.001; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%; P=0.008). Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; P=0.68). There was no significant difference in the rate of other serious adverse events.

CONCLUSIONS

As compared with placebo, intravenous alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; alteplase was more frequently associated with symptomatic intracranial hemorrhage. (ClinicalTrials.gov number, NCT00153036.)

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*The European Cooperative Acute Stroke Study (ECASS) investigators are listed in the Appendix.

INTRAVENOUS THROMBOLYTIC TREATMENT with alteplase, initiated within 3 hours after the onset of symptoms, is the only medical therapy currently available for acute ischemic stroke. In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) study group reported that patients with acute ischemic stroke who received alteplase (0.9 mg per kilogram of body weight) within 3 hours after the onset of symptoms were at least 30% more likely to have minimal or no disability at 3 months than those who received placebo.[1] Two European trials, the European Cooperative Acute Stroke Study (ECASS) and ECASS II, investigated a time window of up to 6 hours but failed to show the efficacy of thrombolytic treatment, as defined by each trial.[2,3]

A subsequent analysis of the NINDS study[4] and the combined analysis[5] of data from six randomized trials,[1-3,6,7] which investigated thrombolysis treatment for ischemic stroke in a total of 2775 patients, showed a clear association between treatment efficacy and the interval between the onset of symptoms and administration of the thrombolytic agent. In the pooled analysis, a favorable outcome was observed even if treatment was given between 3 and 4.5 hours, with an odds ratio of 1.4 for a favorable outcome with alteplase treatment as compared with placebo. This analysis also suggested that the longer time window, as compared with the shorter window, was not associated with higher rates of symptomatic intracranial hemorrhage or death.[5] International guidelines recommend alteplase as a first-line treatment for eligible patients when administered within 3 hours after the onset of stroke.[8-10] Despite this recommendation, alteplase is underused; it is estimated that fewer than 2% of patients receive this treatment in most countries, primarily because of delayed admission to a stroke center.[11]

Thrombolysis with alteplase has been approved in most countries. In Europe, the European Medicines Agency (EMEA) granted approval of alteplase in 2002 but included two requests. One request was that an observational safety study be initiated; subsequently, the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS–MOST) was undertaken. This study confirmed that alteplase is as safe and effective in routine clinical practice as it is in randomized trials.[12] The second request was that a randomized trial be conducted in which the therapeutic time window was extended beyond 3 hours.

We describe the results of ECASS III, a randomized, placebo-controlled, phase 3 trial designed to test the hypothesis that the efficacy of alteplase administered in patients with acute ischemic stroke can be safely extended to a time window of 3 to 4.5 hours after the onset of stroke symptoms.

METHODS

PATIENT POPULATION AND STUDY DESIGN

ECASS III was a double-blind, parallel-group trial that enrolled patients from multiple centers across Europe (see the Appendix). Patients were eligible for inclusion in the study if they were 18 to 80 years of age, had received a clinical diagnosis of acute ischemic stroke, and were able to receive the study drug within 3 to 4 hours after the onset of symptoms. A cerebral computed tomographic (CT) scan was required before randomization to exclude patients who had an intracranial hemorrhage or major ischemic infarction. In some cases, magnetic resonance imaging (MRI) was performed instead of CT (Fig. 1). The inclusion and exclusion criteria are summarized in Table 1. In May 2005, after 228 patients had been enrolled, the study protocol was amended, and the time window of 3 to 4 hours was extended by 0.5 hour (3 to 4.5 hours). There were two reasons for the extension of the time window: the publication of the pooled analysis, which suggested that patients may benefit from thrombolytic treatment administered up to 4.5 hours after the onset of symptoms,[5] and a slow rate of patient recruitment. The trial protocol and the amendments were accepted by the EMEA and were approved by the institutional review boards of the participating centers. All patients or legally authorized representatives gave written informed consent before enrollment.

RANDOMIZATION AND TREATMENT

Eligible patients were randomly assigned, in a 1:1 ratio, to receive 0.9 mg of alteplase (Actilyse, Boehringer Ingelheim) per kilogram, administered intravenously (with an upper limit of 90 mg), or placebo. An interactive voice-randomization system was used, with randomization at centers performed in blocks of four to ensure a balanced
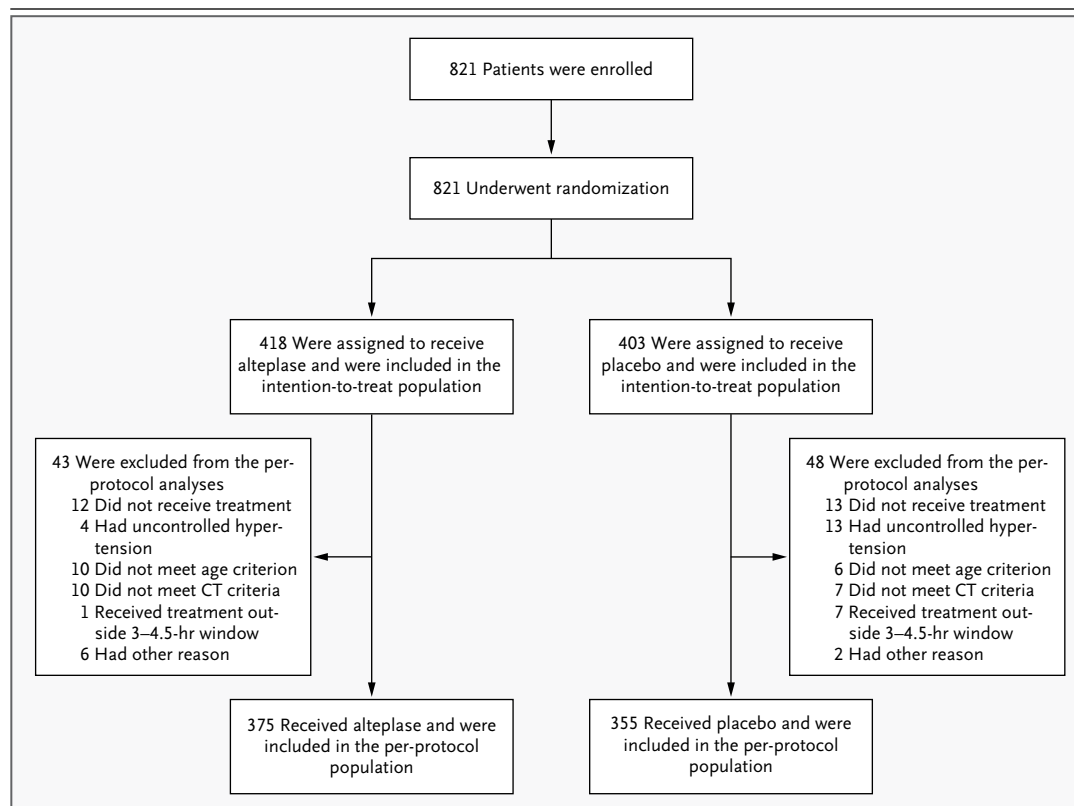
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                          ┌─────────────────────────┐
                          │ 821 Patients were enrolled │
                          └─────────────────────────┘
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                          │ 821 Underwent randomization │
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                ┌──────────────────────┴──────────────────────┐
    ┌───────────────────────────┐              ┌───────────────────────────┐
    │ 418 Were assigned to receive │           │ 403 Were assigned to receive │
    │ alteplase and were included in │         │ placebo and were included in │
    │ the intention-to-treat population │      │ the intention-to-treat population │
    └───────────────────────────┘              └───────────────────────────┘
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43 Were excluded from the per-protocol analyses
  12 Did not receive treatment
  4 Had uncontrolled hypertension
  10 Did not meet age criterion
  10 Did not meet CT criteria
  1 Received treatment outside 3–4.5-hr window
  6 Had other reason

48 Were excluded from the per-protocol analyses
  13 Did not receive treatment
  13 Had uncontrolled hypertension
  6 Did not meet age criterion
  7 Did not meet CT criteria
  7 Received treatment outside 3–4.5-hr window
  2 Had other reason

375 Received alteplase and were included in the per-protocol population

355 Received placebo and were included in the per-protocol population

Figure 1. Numbers of Patients Who Were Enrolled, Randomly Assigned to a Study Group, and Included in the Per-Protocol Population.

The intention-to-treat population was defined as all patients who were enrolled and randomly assigned to a study group. The per-protocol population was defined as all randomly assigned patients who received alteplase or placebo and who were not excluded because of major protocol violations, which included, most notably, noncompliance with the current European Summary of Product Characteristics for alteplase (excluding time window of treatment). Of the randomly assigned patients, 771 were evaluated by means of CT and 50 by means of MRI at baseline. Among the 418 patients assigned to treatment with alteplase, 13 were lost to follow-up, and among the 403 patients assigned to receive placebo, 10 were lost to follow-up; the worst possible outcome for the primary end point was imputed for these patients. Among those excluded from per-protocol analyses, reasons for exclusion listed as "other" included a history of both stroke and diabetes, treatment with an oral anticoagulant within 24 hours, broken medication code, treatment with a prohibited medication, no ischemic stroke, and either no informed consent or withdrawal of consent.

distribution of group assignments at any time. The size of the blocks was withheld from the investigators to make sure that they were unaware of the treatment assignments. Alteplase and matched placebo were reconstituted from a lyophilized powder in sterile water for injection. Of the total dose, 10% was administered as a bolus, and the remainder was given by continuous intravenous infusion over a period of 60 minutes. With the exception of the extended time window, alteplase was to be used in accordance with current European labeling.

STUDY MANAGEMENT

The steering committee designed and oversaw the trial. An independent data and safety monitoring board regularly monitored the safety of the trial. The data and safety monitoring board did not have access to functional outcome data but received a group assignment of A or B for death and C or D for monitoring of symptomatic intracranial hemorrhage to ensure unbiased review of each of the two main safety outcomes. The chair of the data and safety monitoring board, who contributed to the design of the trial but had no

Table 1. Major Inclusion and Exclusion Criteria.
Main inclusion criteria
Acute ischemic stroke
Age, 18 to 80 years
Onset of stroke symptoms 3 to 4.5 hours before initiation of study-drug administration
Stroke symptoms present for at least 30 minutes with no significant improvement before treatment
Main exclusion criteria
Intracranial hemorrhage
Time of symptom onset unknown
Symptoms rapidly improving or only minor before start of infusion
Severe stroke as assessed clinically (e.g., NIHSS score >25) or by appropriate imaging techniques*
Seizure at the onset of stroke
Stroke or serious head trauma within the previous 3 months
Combination of previous stroke and diabetes mellitus
Administration of heparin within the 48 hours preceding the onset of stroke, with an activated partial-thromboplastin time at presentation exceeding the upper limit of the normal range
Platelet count of less than 100,000 per cubic millimeter
Systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or aggressive treatment (intravenous medication) necessary to reduce blood pressure to these limits
Blood glucose less than 50 mg per deciliter or greater than 400 mg per deciliter
Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal
Oral anticoagulant treatment
Major surgery or severe trauma within the previous 3 months
Other major disorders associated with an increased risk of bleeding

* A severe stroke as assessed by imaging was defined as a stroke involving more than one third of the middle cerebral-artery territory. NIHSS denotes National Institutes of Health Stroke Scale in which total scores range from 0 to 42, with higher values reflecting more severe cerebral infarcts.

role in the conduct of the study, was invited to be part of the writing committee after completion of the trial. Monitoring and data management were undertaken by the sponsor of the trial. Statistical analyses were performed simultaneously by an independent external statistician and the statistician of the sponsor. The steering committee had complete access to the trial data after the database had been locked and assumed complete responsibility for the final statistical analysis and interpretation of the results. All study committees are listed in the Appendix. All the authors vouch for the accuracy and completeness of the data and analyses.

CONCOMITANT THERAPIES

Treatment with intravenous heparin, oral anticoagulants, aspirin, or volume expanders such as hetastarch or dextrans during the first 24 hours after administration of the study drug had been completed was prohibited. However, the use of subcutaneous heparin (≤10,000 IU), or of equivalent doses of low-molecular-weight heparin, was permitted for prophylaxis against deep-vein thrombosis.

CLINICAL ASSESSMENT

Patients were assessed by an examiner who was unaware of the treatment assignment. Assessments were made at the time of enrollment, at 1, 2, and 24 hours after administration of the study drug was begun, and on days 7, 30, and 90 after administration of the drug. In addition, the patients' clinical condition (e.g., blood pressure, oxygenation, and heart rate) was closely monitored for the first 24 hours. Initial assessments included a physical examination, CT or MRI, and the quantification of any neurologic deficit with the use of the National Institutes of Health Stroke Scale (NIHSS), a 15-item scale that measures the level of neurologic impairment. Total scores on the NIHSS range from 0 to 42, with higher values

reflecting more severe cerebral infarcts (<5, mild impairment; ≥25, very severe neurologic impairment).[13] Examiners were trained and certified in the use of the NIHSS examination. Patients were assessed with the NIHSS on days 1, 7, 30, and 90. The modified Rankin scale,[14] a measure of disability, was used to assess patients on days 30 and 90. Scores on the modified Rankin scale range from 0 (no symptoms at all) to 6 (death); a score of 5 indicates severe disability (the patient is bedridden and incontinent and requires constant nursing care and attention). Investigators were instructed in the use of the modified Rankin scale by watching video clips from a training DVD.[15] During the follow-up period, two other commonly used functional scales were also applied[16]: the Barthel Index[17] and the Glasgow Outcome Scale.[18] The Barthel Index, which assesses the ability to perform activities of daily living, on a scale that ranges from 0 (complete dependence on help with activities of daily living) to 100 (independence), was scored on days 30 and 90. We assigned a score of 0 to patients who died. The Glasgow Outcome Scale, a 5-point scale on which 1 indicates independence, 3 severe disability, and 5 death, was scored on day 90.

ASSESSMENT OF HEMORRHAGES AND ADJUDICATION OF SYMPTOMATIC INTRACRANIAL HEMORRHAGE

CT or MRI was performed before treatment and 22 to 36 hours after treatment. Additional CT studies were performed at the discretion of the investigators. Members of the safety outcome adjudication committee, who were unaware of the treatment assignments, reviewed all CT or MRI scans, classified the findings according to the ECASS morphologic definitions,[2] and logged the results in a database. On the basis of these findings, the chairs of the safety outcome adjudication committee and the steering committee, who remained unaware of the treatment assignments, together adjudicated whether each death or score change indicating neurologic deterioration was likely to have been due to intracranial hemorrhage, other brain injury or disease, or neither of these causes.

OUTCOME MEASURES

The primary efficacy end point was disability at day 90 (3-month visit), as assessed by means of the modified Rankin scale, dichotomized as a favorable outcome (a score of 0 or 1) or an unfa-

vorable outcome (a score of 2 to 6). The secondary efficacy end point was a global outcome measure that combined the outcomes at day 90 of a score of 0 or 1 on the modified Rankin scale, a score of 95 or higher on the Barthel Index, a score of 0 or 1 on the NIHSS, and a score of 1 on the Glasgow Outcome Scale.[1] Further functional end points were based on predefined cutoff points for the NIHSS score (a score of 0 or 1, or more than an 8-point improvement in the score), the score on the modified Rankin scale (dichotomized as 0 to 2 or 3 to 6), and the Barthel Index (≥95 points), assessed on day 90 and also on day 30. Because of recent interest in the scientific community in a stratified analysis of the outcome distribution of the modified Rankin scale at day 90, this type of evaluation was undertaken according to the methods described previously.[19]

Safety end points included overall mortality at day 90, any intracranial hemorrhage, symptomatic intracranial hemorrhage, symptomatic edema (defined as brain edema with mass effect as the predominant cause of clinical deterioration), and other serious adverse events. In the ECASS III protocol, symptomatic intracranial hemorrhage was defined as any apparently extravascular blood in the brain or within the cranium that was associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration. To allow comparison with published data, a post hoc analysis of rates of symptomatic intracranial hemorrhage was also performed according to definitions used in other trials.[1,3,12,20]

STATISTICAL ANALYSIS

Efficacy end points were assessed in the intention-to-treat population, which included all randomly assigned patients, whether or not they were treated. In the case of missing data on outcome among patients known to be alive, the worst possible outcome score was assigned. For the primary end point, between-group differences were calculated with the use of the chi-square test of proportions (with a two-sided alpha level of 5%). Ninety-five percent confidence intervals were calculated for odds ratios and for relative risk. In keeping with the study protocol, all predefined analyses were performed without adjustment for confounding factors. A post hoc adjusted analysis (logistic re-

gression) of the primary end point was undertaken in the intention-to-treat population. This analysis was performed by including all baseline variables in the model and retaining those that were significant at P<0.10. For the secondary end point — the probability of a favorable outcome with alteplase as compared with placebo — a

global odds-ratio test based on a linear logistic-regression model (a method that uses generalized estimation equations to perform a Wald-type test)[21,22] was used. For the per-protocol population (Fig. 1), the same statistical tests were applied. The post hoc stratified analysis of scores on the modified Rankin scale was adjusted for the two most strongly prognostic baseline variables: the NIHSS score and the time to the start of treatment.[19]

The calculation of the sample size was based on the analysis of pooled data from the cohorts that received thrombolysis or placebo between 3 and 4.5 hours after the onset of symptoms[5] (with data from the first ECASS trial[3] excluded because of the higher dose of alteplase used in that trial). On the basis of these data, we calculated that 400 patients per group were required in order to have 90% power to detect an odds ratio of 1.4 for the primary end point.

RESULTS

STUDY PATIENTS

Between July 29, 2003, and November 13, 2007, a total of 821 patients from 130 sites in 19 European countries were randomly assigned to a study group: 418 patients were assigned to receive alteplase and 403 patients were assigned to receive placebo (Fig. 1). Grouped according to 0.5-hour intervals, 10.0% of the patients were treated between 3 and 3.5 hours, 46.8% between 3.5 and 4 hours, and 39.2% between 4 and 4.5 hours (Table 2). (The values do not add up to 100% because data on the exact time of treatment initiation were not available for 12 patients in the alteplase group and 15 patients in the placebo group; in addition, treatment was initiated after 4.5 hours in 1 patient in the alteplase group and 5 patients in the placebo group.) Baseline demographic and clinical characteristics of the two groups were similar (Table 2), except that there were significant differences between the groups (before adjustment for multiple comparisons) with respect to the initial severity of the stroke and the presence or absence of a history of stroke.

EFFICACY

For the primary end point, 219 of the 418 patients in the alteplase group (52.4%) had a favorable outcome (defined as a score of 0 or 1 on the modified Rankin scale), as compared with 182 of

Table 2. Demographic and Baseline Characteristics of the Patients.

Characteristic	Study Group		P Value*
	Alteplase (N=418)	Placebo (N=403)	
Age (yr)	64.9±12.2	65.6±11.0	0.36
Male sex (%)	63.2	57.3	0.10
Weight (kg)	78.5±15	78.0±16	0.62
NIHSS score†			0.03
Mean	10.7±5.6	11.6±5.9	
Median	9	10	
Systolic pressure (mm Hg)	152.6±19.2	153.3±22.1	0.63
Diastolic pressure (mm Hg)	84.4±13.5	83.9±13.6	0.58
Diabetes (%)	14.8	16.6	0.47
Previous use of aspirin or antiplatelet drugs (%)	31.1	32.5	0.65
Hypertension (%)	62.4	62.8	0.88
Atrial flutter or fibrillation (%)	12.7	13.6	0.67
History of stroke (%)	7.7	14.1	0.003
Smoking status (%)‡			0.93
Never smoked	48.6	46.2	
Ex-smoker	20.6	24.6	
Current smoker	30.6	28.8	
Time to treatment initiation			
Median	3 hr 59 min	3 hr 58 min	0.49
By 0.5-hr period§			0.44
≥3.0 to ≤3.5 hr (%)	9.6	10.4	
>3.5 to ≤4.0 hr (%)	45.7	47.9	
>4.0 to ≤4.5 hr (%)	41.6	36.7	

* Any difference between groups occurred despite randomization and was therefore due to chance. Post hoc P values are merely illustrative and have not been adjusted for multiple comparisons, for which P=0.004 would be considered to indicate statistical significance.
† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher values reflecting more severe neurologic impairment (<5, mild impairment; ≥25, very severe impairment).
‡ Data for smoking status were not available for one patient in the alteplase group and two patients in the placebo group.
§ Percentages do not add up to 100 because no exact time of treatment initiation was available for 12 patients in the alteplase group and 15 patients in the placebo group; in addition, treatment was initiated after 4.5 hours in 1 patient in the alteplase group and in 5 patients in the placebo group.

Table 3. Odds Ratios for Primary End Point and Secondary End Point, Including Components, in the Intention-to-Treat and Per-Protocol Populations at 90 Days.*

End Point	Intention-to-Treat Population				Per-Protocol Population			
	Alteplase Group (N=418) no. (%)	Placebo Group (N=403) no. (%)	Odds Ratio (95% CI)	P Value	Alteplase Group (N=375) no. (%)	Placebo Group (N=355) no. (%)	Odds Ratio (95% CI)	P Value
Primary end point								
mRS score of 0 or 1 — unadjusted analysis	219 (52.4)	182 (45.2)	1.34 (1.02–1.76)	0.04†	206 (54.9)	161 (45.4)	1.47 (1.10–1.97)	0.01†
mRS score of 0 or 1 — adjusted analysis‡	—	—	1.42 (1.02–1.98)	0.04§				
Secondary end point								
Global outcome¶	—	—	1.28 (1.00–1.65)	0.05	—	—	1.39 (1.07–1.80)	0.02
mRS score of 0 or 1‖	219 (52.4)	182 (45.2)	1.34 (1.02–1.76)	0.04†	206 (54.9)	161 (45.4)	1.47 (1.10–1.97)	0.01†
Barthel Index score ≥95**	265 (63.4)	236 (58.6)	1.23 (0.93–1.62)	0.16†	248 (66.1)	211 (59.4)	1.33 (0.99–1.80)	0.06†
NIHSS score of 0 or 1††	210 (50.2)	174 (43.2)	1.33 (1.01–1.75)	0.04†	197 (52.5)	155 (43.7)	1.43 (1.07–1.91)	0.02†
GOS score of 1‡‡	213 (51.0)	183 (45.4)	1.25 (0.95–1.64)	0.11†	200 (53.3)	165 (46.5)	1.32 (0.98–1.76)	0.06†

* GOS denotes Glasgow Outcome Scale, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, and NINDS National Institute of Neurological Disorders and Stroke.
† P value was obtained by the Pearson chi-square test of proportions.
‡ This analysis was adjusted for NIHSS score at presentation and the time to start of treatment.
§ P value was obtained by stepwise logistic regression.
¶ The global outcome analysis is a multidimensional calculation of a favorable outcome, defined by several individual outcome scales and entered into a statistical algorithm. This statistical approach is a global odds-ratio test based on a linear logistic-regression model (a method that uses generalized estimation equations to perform a Wald-type test). No percentages can be given owing to the underlying statistical method. The global odds ratio is the probability of a favorable outcome with alteplase as compared with placebo.
‖ Scores on the modified Rankin scale range from 0 (no symptoms at all) to 6 (death).
** The Barthel Index assesses the ability to perform activities of daily living on a scale that ranges from 0 (complete dependence on help with activities of daily living) to 100 (independence).
†† Scores on the NIHSS range from 0 to 42, with higher values reflecting more severe neurologic impairment (<5, mild impairment; ≥25, very severe impairment).
‡‡ The Glasgow Outcome Scale is a 5-point scale on which 1 indicates independence, 3 severe disability, and 5 death.
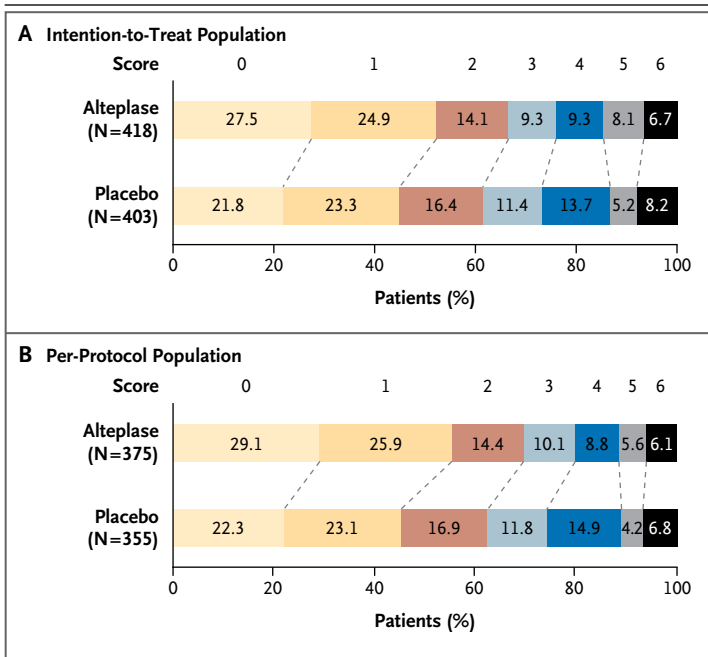
Figure 2. Distribution of Scores on the Modified Rankin Scale.

The distribution of scores is shown for the intention-to-treat population (Panel A) and the per-protocol population (Panel B) at the 3-month visit (90 days plus or minus 14 days). In both the intention-to-treat population and the per-protocol population, stratified analysis of the score distribution showed a significant difference between the study groups (P=0.02 for both comparisons by the Cochran–Mantel–Haenszel test, with adjustment for the baseline score on the National Institutes of Health Stroke Scale and for the interval between the onset of symptoms and the initiation of treatment). In the intention-to-treat population, the number of deaths recorded at the 3-month visit (59) was different from the overall number of deaths (66), since 7 deaths occurred after 90 days. The scores on the modified Rankin scale indicate the following: 0, no symptoms at all; 1, no significant disability despite symptoms (able to carry out all usual duties and activities); 2, slight disability (unable to carry out all previous activities but able to look after own affairs without assistance); 3, moderate disability (requiring some help but able to walk without assistance); 4, moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs without assistance); 5, severe disability (bedridden, incontinent, and requiring constant nursing care and attention); 6, death.

mained significantly associated with a favorable outcome (odds ratio, 1.42; 95% CI, 1.02 to 1.98; P=0.04) (Table 3 and Fig. S1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org).

Treatment with alteplase also resulted in a more favorable outcome than that with placebo for the secondary end point, as indicated by the global odds ratio. (Since the global odds-ratio test was based on a linear logistic-regression model, with generalized estimation equations used to perform a Wald-type test,[21,22] only probabilities, and not absolute numbers, for each treatment group can be provided.) The global odds ratio for a favorable outcome was 1.28 (95% CI, 1.00 to 1.65; P<0.05), indicating that the odds for a favorable outcome (the ability to return to an independent lifestyle) after stroke were 28% higher with alteplase than with placebo.

The overall distribution of scores on the modified Rankin scale is shown in Figure 2. The post hoc stratified analysis of scores on the modified Rankin scale at day 90 (performed with the use of the Cochran–Mantel–Haenszel test, with adjustment for the baseline NIHSS score and time to the start of treatment) also showed a favorable outcome with alteplase as compared with placebo (P=0.02).

The results of analyses of further functional end points are summarized in Table 4. In the intention-to-treat analysis, the odds ratios for a score of 0 or 1 on the modified Rankin scale, an NIHSS score of 0 or 1, and more than an 8-point improvement in the NIHSS score at day 30 showed a significant advantage of alteplase treatment, whereas there were no significant differences between the groups with respect to the other functional end points. Neurologic status up to day 30 did not differ significantly between the two groups.

SAFETY

A total of 66 patients died — 32 of the 418 patients in the alteplase group (7.7%) and 34 of the 403 in the placebo group (8.4%). Of these 66 patients, 25 died between days 1 and 7 (12 [2.9%] in the alteplase group and 13 [3.2%] in the placebo group), 18 between days 8 and 30 (10 [2.4%] and 8 [2.0%], respectively), and 16 between days 31 and 90 (6 [1.4%] and 10 [2.5%], respectively). Seven patients died after day 90 (four [1.0%] and three [0.7%], respectively).

the 403 patients in the placebo group (45.2%), representing an absolute improvement of 7.2 percentage points (odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; relative risk, 1.16; 95% CI, 1.01 to 1.34; P=0.04). In the post hoc intention-to-treat analysis, adjusted for confounding baseline variables (logistic regression), study-group assignment, baseline NIHSS score, smoking status, time from the onset of stroke to treatment, and presence or absence of prior hypertension were identified as significant at P<0.10. In the adjusted analysis, treatment with alteplase re-

There were more cases of intracranial hemorrhage in the alteplase group than in the placebo group (27.0% vs. 17.6%, P=0.001). The incidence of symptomatic intracranial hemorrhage with alteplase was less than 3 cases per 100 patients (10 of 418 patients [2.4%]), but that incidence was significantly higher than the incidence with placebo (1 of 403 [0.3%]; odds ratio, 9.85; 95% CI, 1.26 to 77.32; P=0.008). The incidence of symptomatic intracranial hemorrhage according to definitions used in other studies followed a similar pattern (Table 5 and Fig. S2 in the Supplementary Appendix). All symptomatic intracranial hemorrhages occurred within the first 22 to 36 hours after initiation of treatment.

The rate of symptomatic edema did not differ significantly between the study groups: 6.9% in the alteplase group and 7.2% in the placebo group (29 patients in each group; odds ratio, 0.96; 95% CI, 0.56 to 1.64; P=0.88) (Table 5). Other serious adverse events categorized according to organ system did not differ significantly between the two groups (Table 5).

DISCUSSION

In this randomized, placebo-controlled study, patients with acute ischemic stroke benefited from treatment with intravenous alteplase administered 3 to 4.5 hours after the onset of stroke symptoms. ECASS III is the second randomized trial (after the NINDS trial of 1995[1]) to show a significant treatment effect with intravenous alteplase in the unadjusted analysis of the primary end point. The treatment effect remained significant after adjustment for all prognostic baseline characteristics. The overall rate of symptomatic intracranial hemorrhage was increased with alteplase as compared with placebo, but mortality was not affected. Both of these findings are consistent with results from other randomized, controlled trials of thrombolysis in patients with acute ischemic stroke.[1,5,23] The results of the analysis of secondary end points and of the post hoc stratified analysis mirrored the primary efficacy results in favor of alteplase.

The initial severity of a stroke is a strong predictor of the functional and neurologic outcome and of the risk of death. Patients with severe stroke were excluded from this trial in order to meet the protocol requirements requested by the EMEA and to conform with the European label

Table 4. Odds Ratios for Further Functional End Points at Days 90 and 30 after Treatment in the Intention-to-Treat and Per-Protocol Populations.*

End Point	Day 90				Day 30			
	Intention-to-Treat Population		Per-Protocol Population		Intention-to-Treat Population		Per-Protocol Population	
	odds ratio (95% CI)	P value	odds ratio (95% CI)	P value	odds ratio (95% CI)	P value	odds ratio (95% CI)	P value
mRS score of 0 or 1†	1.34 (1.02–1.76)	0.04	1.47 (1.10–1.97)	0.001	1.42 (1.08–1.88)	0.01	1.46 (1.09–1.96)	0.01
mRS score of 0–2	1.30 (0.95–1.78)	0.11	1.41 (1.01–1.96)	0.04	1.23 (0.93–1.64)	0.15	1.32 (0.98–1.77)	0.07
Barthel Index score ≥95‡	1.23 (0.93–1.62)	0.15	1.33 (0.99–1.80)	0.06	1.28 (0.98–1.69)	0.08	1.35 (1.01–1.81)	0.04
NIHSS score of 0 or 1, or >8-point improvement from baseline§	—		—		1.35 (1.02–1.78)	0.03	1.46 (1.09–1.96)	0.01

* All analyses were prespecified, with the exception of those for a score on the National Institutes of Health Stroke Scale (NIHSS) of 0 or 1, or an improvement of more than 8 points, at day 90. A score of 0 or 1 on the modified Rankin scale (mRS) (the primary end point) and a score of 95 or higher on the Barthel Index at day 90 are components of the principal secondary end point; a score of 0 to 2 on the mRS has been used in other thrombolysis trials (e.g., SITS–MOST and ECASS II) as a primary or secondary end point. P values have not been adjusted for multiple testing.
† Scores on the modified Rankin scale range from 0 (no symptoms at all) to 6 (death).
‡ The Barthel Index assesses the ability to perform activities of daily living on a scale that ranges from 0 (complete dependence on help with activities of daily living) to 100 (independence).
§ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher values reflecting more severe neurologic impairment (<5, mild impairment; ≥25, very severe impairment). Because this analysis was not prespecified for day 90, no data for that time point were collected.

Table 5. Prespecified Safety End Points and Other Serious Adverse Events.*

Adverse Events	Alteplase Group (N=418)	Placebo Group (N=403)	Odds Ratio (95% CI)	P Value
	no. (%)			
Prespecified safety end points				
Any ICH	113 (27.0)	71 (17.6)	1.73 (1.24–2.42)	0.001
Symptomatic ICH				
According to ECASS III definition†	10 (2.4)	1 (0.2)	9.85 (1.26–77.32)	0.008
According to ECASS II definition‡	22 (5.3)	9 (2.2)	2.43 (1.11–5.35)	0.02
According to SITS–MOST definition§	8 (1.9)	1 (0.2)	7.84 (0.98–63.00)	0.02
According to NINDS definition¶	33 (7.9)	14 (3.5)	2.38 (1.25–4.52)	0.006
Fatal ICH	3 (0.7)	0	—	—
Symptomatic edema	29 (6.9)	29 (7.2)	0.96 (0.56–1.64)	0.89
Death	32 (7.7)	34 (8.4)	0.90 (0.54–1.49)	0.68
Other serious adverse events				
Total	105 (25.1)	99 (24.6)		
Infectious	16 (3.8)	23 (5.7)		
Neoplastic	4 (1.0)	3 (0.7)		
Blood and lymphatic	0	2 (0.5)		
Endocrine	0	1 (0.2)		
Metabolic and nutritional	2 (0.5)	0		
Psychiatric	3 (0.7)	4 (1.0)		
Neurologic	60 (14.4)	48 (11.9)		
Eye	1 (0.2)	0		
Cardiac	22 (5.3)	16 (4.0)		
Vascular	10 (2.4)	10 (2.5)		
Respiratory	14 (3.3)	24 (6.0)		
Gastrointestinal	5 (1.2)	8 (2.0)		
Hepatobiliary	3 (0.7)	3 (0.7)		
Skin	1 (0.2)	0		
Musculoskeletal	1 (0.2)	3 (0.7)		
Renal	4 (1.0)	2 (0.5)		
Reproductive system	1 (0.2)	0		
Congenital	0	1 (0.2)		
General	1 (0.2)	3 (0.7)		
Associated with injury	4 (1.0)	5 (1.2)		
Surgical	1 (0.2)	0		

* P values were obtained by Pearson chi-square test of proportions. ECASS denotes European Cooperative Acute Stroke Study, ICH intracranial hemorrhage, NIHSS National Institutes of Health Stroke Scale, NINDS National Institute of Neurological Disorders and Stroke, and SITS–MOST Safe Implementation of Thrombolysis in Stroke–Monitoring Study.

† The ECASS III definition of symptomatic intracranial hemorrhage was any hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death. In addition, the hemorrhage must have been identified as the predominant cause of the neurologic deterioration.

‡ The ECASS II definition was the same as that for ECASS III, except that establishment of a causal relationship between the hemorrhage and clinical deterioration or death was not a requirement.

§ The SITS–MOST definition was local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurologic deterioration, as indicated by a score on the NIHSS that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death.

¶ In the NINDS definition, a hemorrhage was considered symptomatic if it had not been seen on a previous CT scan but there was subsequently either a suspicion of hemorrhage or any decline in neurologic status. To detect intracranial hemorrhage, CT scans were required at 24 hours and 7 to 10 days after the onset of stroke and when clinical findings suggested hemorrhage.

of alteplase. It is likely that the milder initial severity of stroke overall among patients enrolled in this trial as compared with those in the NINDS trial[1] explains, for the most part, the improved outcomes in the placebo group in our study as compared with the outcomes in the placebo group in the NINDS trial. Outcomes in the placebo group in our study were similar to those observed in ECASS II.[3]

In this context, it is interesting to note that there has been a gradual decline in the overall initial severity of stroke and in mortality rates among patients enrolled in major randomized studies of acute ischemic stroke over the past two decades.[1-3] This observation may reflect the trend toward the use of thrombolytic agents in patients who have less severe acute ischemic stroke, as reflected in the results of SITS–MOST,[12] as well as the increased number of stroke units in Europe and the improved care provided in such units.

Some of the previous trials of treatment with alteplase for acute ischemic stroke included patients who received treatment within 0 to 6 hours after the onset of symptoms. However, these trials failed to show a significant advantage of alteplase therapy.[2,3,6,24] Potential explanations for the failure to show a significant difference in previous trials include the choice of end points, a time window of up to 6 hours, and a lack of statistical power. (In the ECASS II[3] and in the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS] trial,[6] the cohorts that were treated 3 to 4.5 hours after the onset of symptoms were much smaller, and these studies were therefore not powered to detect an effect size of 7 to 10%.)

Thrombolysis in patients with acute ischemic stroke is associated with an increased risk of symptomatic intracranial hemorrhage, which is the most feared complication. It is difficult, however, to compare the incidence of symptomatic intracranial hemorrhage across studies because of the varying definitions used. In our study, we modified the ECASS definition of symptomatic intracranial hemorrhage by specifying that the hemorrhage had to have been identified as the predominant cause of the neurologic deterioration. With the use of this definition, the difference in rates of symptomatic intracranial hemorrhage between the two study groups was significant (a difference of 2.14 percentage points), although the incidence of symptomatic intracranial hemorrhage among alteplase-treated patients was low.

To allow for comparison across trials, we also analyzed rates of symptomatic intracranial hemorrhage according to definitions used in other trials.[1-3,20] With these definitions, the rate of symptomatic intracranial hemorrhage in our trial was no higher than that reported in previous randomized trials or in SITS–MOST, despite the extended time window in our study.[12]

Although in our trial the incidence of symptomatic intracranial hemorrhage was higher in the alteplase group than in the placebo group, we did not observe a difference in mortality between the two groups. The overall mortality rate (approximately 8%) was lower than that in previous trials, probably also owing to the inclusion of patients with less severe strokes.

Early treatment remains essential. The effect size of thrombolysis is time-dependent. In the pooled analysis, treatment with alteplase is nearly twice as efficacious when administered within the first 1.5 hours after the onset of a stroke as it is when administered within 1.5 to 3 hours afterward (odds ratio for the global outcome, 2.81 for an interval of 0 to 90 minutes, 1.55 for 91 to 180 minutes, and 1.40 for 181 to 270 minutes).[5] In comparison, in ECASS III, the odds ratio was 1.34 for an interval of 181 to 270 minutes. For 1 patient to have a favorable outcome (a score of 0 or 1 on the modified Rankin scale), the number needed to treat is 14 with the extended time window. This effect size is clinically meaningful and thus extends the treatment window for patients who do not arrive at the hospital early. It does not mean, however, that patients who can be treated within 3 hours should have their treatment delayed. The "door-to-needle" time remains paramount and must be kept as short as possible to increase the chance of a positive outcome.

In this study, intravenous alteplase given 3 to 4.5 hours (median, 3 hours 59 minutes) after the onset of stroke symptoms was associated with a modest but significant improvement in the clinical outcome, without a higher rate of symptomatic intracranial hemorrhage than that reported previously among patients treated within 3 hours. Although our findings suggest that treatment with alteplase may be effective in patients who present 3 to 4.5 hours after the onset of stroke symptoms, patients should be treated with alteplase as early as possible to maximize the benefit. Having more time does not mean we should be allowed to take more time.

APPENDIX

The European Cooperative Acute Stroke Study (ECASS) investigators are as follows: Steering Committee — W. Hacke (chair), A. Dávalos, M. Kaste, R. von Kummer, V. Larrue, D. Toni, N. Wahlgren; Data and Safety Monitoring Board — K.R. Lees (chair), W.D. Heiss, E. Lesaffre, J.M. Orgogozo; Safety Outcome Adjudication Committee — R. von Kummer (chair), S. Bastianello, J.M. Wardlaw; Statisticians — J.-C. Peyrieux (STATMED, Lyon, France), C. Sauce (Boehringer Ingelheim); Trial Management Team at Boehringer Ingelheim — Z. Medeghri, R. Mazenc, C. Sauce, T. Machnig, E. Bluhmki; principal investigators (with the number of patients enrolled given in parentheses) — *Austria* (53): F. Aichner, C. Alf, U. Baumhackl, M. Brainin, C. Eggers, F. Gruber, G. Ladurner, K. Niederkorn, G. Noistering, J. Willeit; *Belgium* (22): G. Vanhooren (national coordinator), S. Blecic, B. Bruneel, J. Caekebeke, P. Laloux, P.J. Simons, V. Thijs; *Czech Republic* (18): M. Bar, H. Dvorakova, D. Vaclavik; *Denmark* (44): G. Boysen (national coordinator), G. Andersen, H.K. Iversen, B. Traberg-Kristensen; *Finland* (15): M. Kaste (national coordinator), R. Marttila, J. Sivenius; *France* (104): P. Trouillas (national coordinator), P. Amarenco, J. Bouillat, X. Ducrocq, M. Giroud, A. Jaillard, J.-M. Larrieu, V. Larrue, D. Leys, C. Magne, M.-H. Mahagne, D. Milhaud, D. Sablot, D. Saudeau; *Germany* (130): O. Busse (national coordinator), J. Berrouschot, J.H. Faiss, J. Glahn, M. Görtler, A. Grau, M. Grond, R. Haberl, G. Hamann, M. Hennerici, H. Koch, P. Krauseneck, J. Marx, S. Meves, U. Meyding-Lamadé, P. Ringleb, D. Schneider, A. Schwarz, J. Sobesky, P. Urban; *Greece* (2): K. Karageorgiou (national coordinator), A. Komnos; *Hungary* (9): A. Csányi, L. Csiba, A. Valikovics; *Italy* (147): D. Toni (national coordinator), G. Agnelli, G. Billo, P. Bovi, G. Comi, G. Gigli, D. Guidetti, D. Inzitari, N. Marcello, C. Marini, G. Orlandi, M. Pratesi, M. Rasura, A. Semplicini, C. Serrati, T. Tassinari; *the Netherlands* (5): P.J.A.M. Brouwers (national coordinator), J. Stam (national coordinator), H. Naess (national coordinator), B. Indredavik, R. Kloster; *Poland* (16): A. Czlonkowska (national coordinator), A. Kuczyńska-Zardzewialy, W. Nyka, G. Opala, S. Romanowicz; *Portugal* (13): L. Cunha (national coordinator), C. Correia, V. Cruz, T. Pinho e Melo; *Slovakia* (59): M. Brozman, M. Dvorak, R. Garay, G. Krastev, E. Kurca; *Spain* (111): J. Alvarez-Sabin (national coordinator), A. Chamorro, M. del Mar Freijo Guerrero, J.A.E. Herrero, A. Gil-Peralta, R. Leira, J.L. Martí-Vilalta, J. Masjuan Vallejo, M. Millán, C. Molina, E. Mostacero, T. Segura, J. Serena, J. Vivancos Mora; *Sweden* (14): E. Danielsson (national coordinator), B. Cederin, E. von Zweigberg, N.-G. Wahlgren, L. Welin; *Switzerland* (23): P. Lyrer (national coordinator), J. Bogousslavsky, H.-J. Hungerbühler, B. Weder; *United Kingdom* (22): G.A. Ford (national coordinator), D. Jenkinson, M.J. MacLeod, R.S. MacWalter, H.S. Markus, K.W. Muir, A.K. Sharma, M.R. Walters, E.A. Warburton.

REFERENCES

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333:1581-7.
2. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). JAMA 1995;274:1017-25.
3. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998;352:1245-51.
4. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA Stroke Study. Neurology 2000;55:1649-55.
5. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768-74.

6. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset — the ATLANTIS Study: a randomized controlled trial. JAMA 1999;282:2019-26.
7. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. Stroke 2000;31:811-6.
8. The European Stroke Organisation (ESO) Executive Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457-507.
9. National Institute for Health and Clinical Excellence (NICE). Alteplase for the treatment of acute ischaemic stroke. June 2007. (Accessed September 2, 2008, at http://www.nice.org.uk/TA122.)
10. Adams HP Jr, del Zoppo GJ, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke:

a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007;38:1655-711. [Errata, Stroke 2007;38(6):e38, 2007;38(9):e96.]
11. Albers GW, Olivot JM. Intravenous alteplase for ischaemic stroke. Lancet 2007; 369:249-50.
12. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-82. [Erratum, Lancet 2007;369:826.]
13. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989; 20:864-70.

14. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-7.

15. Quinn TJ, Lees KR, Hardemark HG, Dawson J, Walters MR. Initial experience of a digital training resource for modified Rankin scale assessment in clinical trials. Stroke 2007;38:2257-61.

16. Kasner SE. Clinical interpretation and use of stroke scales. Lancet Neurol 2006; 5:603-12.

17. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J 1965;14:61-5.

18. Jennett B, Bond M. Assessment of outcome after severe brain injury: a practical scale. Lancet 1975;1:480-4.

19. Lees KR, Zivin JA, Ashwood T, et al. NXY-059 for acute ischemic stroke. N Engl J Med 2006;354:588-600.

20. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke 1997;28:2109-18.

21. Lefkopoulou M, Ryan L. Global tests for multiple binary outcomes. Biometrics 1993;49:975-88.

22. Tilley BC, Marler J, Geller NL, et al. Use of a global test for multiple outcomes in stroke trials with application to the National Institute of Neurological Disorders and Stroke t-PA Stroke Trial. Stroke 1996; 27:2136-42.

23. Lansberg MG, Albers GW, Wijman CA. Symptomatic intracerebral hemorrhage following thrombolytic therapy for acute ischemic stroke: a review of the risk factors. Cerebrovasc Dis 2007;24:1-10.

24. Savitz SI, Lew R, Bluhmki E, Hacke W, Fisher M. Shift analysis versus dichotomization of the modified Rankin scale outcome scores in the NINDS and ECASS-II trials. Stroke 2007;38:3205-12.

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The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial

*The IST-3 collaborative group**

Summary

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Background Thrombolysis is of net benefit in patients with acute ischaemic stroke, who are younger than 80 years of age and are treated within 4·5 h of onset. The third International Stroke Trial (IST-3) sought to determine whether a wider range of patients might benefit up to 6 h from stroke onset.

Methods In this international, multicentre, randomised, open-treatment trial, patients were allocated to 0·9 mg/kg intravenous recombinant tissue plasminogen activator (rt-PA) or to control. The primary analysis was of the proportion of patients alive and independent, as defined by an Oxford Handicap Score (OHS) of 0–2 at 6 months. The study is registered, ISRCTN25765518.

Findings 3035 patients were enrolled by 156 hospitals in 12 countries. All of these patients were included in the analyses (1515 in the rt-PA group *vs* 1520 in the control group), of whom 1617 (53%) were older than 80 years of age. At 6 months, 554 (37%) patients in the rt-PA group versus 534 (35%) in the control group were alive and independent (OHS 0–2; adjusted odds ratio [OR] 1·13, 95% CI 0·95–1·35, p=0·181; a non-significant absolute increase of 14/1000, 95% CI –20 to 48). An ordinal analysis showed a significant shift in OHS scores; common OR 1·27 (95% CI 1·10–1·47, p=0·001). Fatal or non-fatal symptomatic intracranial haemorrhage within 7 days occurred in 104 (7%) patients in the rt-PA group versus 16 (1%) in the control group (adjusted OR 6·94, 95% CI 4·07–11·8; absolute excess 58/1000, 95% CI 44–72). More deaths occurred within 7 days in the rt-PA group (163 [11%]) than in the control group (107 [7%], adjusted OR 1·60, 95% CI 1·22–2·08, p=0·001; absolute increase 37/1000, 95% CI 17–57), but between 7 days and 6 months there were fewer deaths in the rt-PA group than in the control group, so that by 6 months, similar numbers, in total, had died (408 [27%] in the rt-PA group *vs* 407 [27%] in the control group).

Interpretation For the types of patient recruited in IST-3, despite the early hazards, thrombolysis within 6 h improved functional outcome. Benefit did not seem to be diminished in elderly patients.

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Introduction

Each year, about 22 million people have a stroke worldwide,[1,2] of whom 4 million reside in high-income countries,[3,4] where thrombolytic therapy is affordable and feasible. The burden of ischaemic stroke among the elderly is large and increasing;[2,5] and we estimate that annually ischaemic stroke affects about a million people older than 80 years of age in high-income countries and about 3 million in low-income and middle-income countries.

Thrombolytic therapy with intravenous recombinant tissue plasminogen activator (rt-PA), when approved in Europe, was restricted to the treatment of patients younger than 80 years of age with acute ischaemic stroke who could be treated within 3 h. A Cochrane systematic review of the 11 completed trials of thrombolysis (including 3977 patients) with intravenous rt-PA for acute ischaemic stroke showed that treatment was associated with a significant increase in survival free of disability, despite an early 3% excess of fatal intracranial haemorrhage.[6] The review also suggested that treatment might be beneficial up to 6 h.[6] An individual patient data meta-analysis of a subset of intravenous rt-PA trials further showed that the earlier treatment was given, the greater the chance of a favourable outcome.[7] Older people have been under-represented in stroke trials in general,[8] and in stroke thrombolysis trials in particular (only 79 people aged older than 80 years had been included in trials of rt-PA).[6] As a result of the current European Union (EU) approval criteria, treatment is only applicable to a small proportion of patients with acute stroke.[9]

The Third International Stroke Trial (IST-3), therefore, had the following objectives: to establish the balance of benefits and harms of thrombolytic therapy with rt-PA in patients who did not exactly meet the licence criteria (especially elderly patients); determine whether a wider range of patients might benefit from this treatment; assess which categories of patients were most likely to benefit by investigating possible interactions between treatment effect and various factors (including age, stroke severity, and early brain imaging results); refine current estimates of the duration of the therapeutic time window; and to improve the external validity and precision of the existing estimates of the overall treatment effects (benefits and harms). The primary trial hypothesis was that 0·9 mg/kg rt-PA (maximum 90 mg) given to adult patients of all ages with acute ischaemic stroke, within 6 h of symptom onset, increased the proportion of people who were alive and independent at 6 months.

Methods
Study design and patients
IST-3 was a pragmatic[10] international, multicentre, randomised-controlled, open-treatment trial. The initial pilot phase was double-blinded and placebo-controlled. At the end of the pilot phase, since the main phase compared treatment with open control, several additional measures were introduced to minimise bias in the assessment of early and late outcomes.[11] We have published reports of the rationale for the trial,[12] the protocol,[13] an update on recruitment, amendments to the protocol and the baseline characteristics of the patients recruited,[11] and the statistical analysis plan.[14]

The eligibility criteria can be summarised in terms of the uncertainty principle.[15–17] Inclusion and exclusion criteria are listed in detail in the protocol.[13] Briefly, patients were eligible according to the following criteria: they had symptoms and signs of clinically definite acute stroke; the time of stroke onset was known; treatment could be started within 6 h of onset; and CT or MRI had reliably excluded both intracranial haemorrhage and structural brain lesions, which could mimic stroke (eg, cerebral tumour). Additionally, if the patient had a clear indication for intravenous thrombolysis with rt-PA, they were to be treated in accordance with local guidelines. Equally, if the patient had a clear contraindication to treatment they were not to be entered in the trial. Only if both the clinician and the patient (or a relevant proxy for the patient) felt that the treatment was promising but unproven, could the patient be included in the trial after appropriate informed consent from the patient or a valid proxy. The protocol was approved by the Multicentre Research Ethics Committees, Scotland (reference MREC/99/0/78), and by local ethical committees. This study is registered, ISRCTN25765518.

Procedures
Clinicians entered baseline data via a telephone voice-activated or a secure web-based randomisation system.

After the system had recorded and checked the data, patients were allocated either immediate thrombolysis with 0·9 mg/kg of intravenous rt-PA to a maximum of 90 mg (10% bolus with the remainder over 1 h) or control treatment. The system would not accept patients with blood pressure or glucose levels outside protocol-defined criteria (appendix pp 4–5) or other data inconsistencies. The system used a minimisation algorithm to achieve optimum balance for key prognostic factors (table 1), and from January, 2006, minimisation was additionally stratified by world region and then minimised on all the other key factors within regions.

To be eligible to join the trial, participating hospitals had to have an organised system of stroke care. Acute-care protocols were not specified by the trial, but had to include the components of effective stroke-unit care,[19] including, soon after admission, intravenous access, monitoring of physiological variables, correction of any abnormalities, and where clinically appropriate, intravenous-fluid therapy. All patients in the trial were to be treated within that organised system of stroke care, irrespective of treatment allocation. Patients allocated to the control group were to avoid treatment with rt-PA and received stroke care in the same clinical environment as those allocated to the rt-PA group. Both treatment groups had blood pressure monitored closely over the first 24 h. In the double-blinded phase, both groups were to avoid antiplatelet or anticoagulant therapy for 24 h. In the open phase, patients allocated to the control group were to start aspirin immediately. Blood pressure was managed in the same way in both treatment groups, according to local protocol. Additionally, all centres were asked for their pretrial experience of thrombolysis for treatment of stroke, and if the centre had, before joining the trial, a protocol for open-label use of rt-PA and had treated at least three people in the 12 months before joining the trial, the centre was classed as experienced.

All patients had a CT or MRI brain scan before randomisation and a follow-up scan at 24–48 h. A repeat brain scan was required if the patient deteriorated neurologically or intracranial haemorrhage was suspected for any reason. Although CT scanning was preferred, MRI was allowed. All scans were sent to the trial centre in Edinburgh for masked central rating of any signs of visible early ischaemia (presence and extent of hypo-attenuation, swelling, hyperattenuated artery), haemorrhage, and background brain changes (leukoaraiosis, atrophy, prior stroke lesions, non-stroke lesions) with validated rating methods.[20–25] Images were assessed with all original identifiers stripped from the record, and then viewed via a secure web-based image viewing system by an international panel of expert radiologists. All assessments were made masked to all patient details and treatment allocation.

The primary outcome specified in version 1·93 of the protocol and in the published statistical analysis plan[14] was the proportion of patients alive and independent as

See **Online** for appendix

For the **study protocol** see http://www.ist3.com

measured by the Oxford Handicap Score (OHS),[26] a commonly used variant of the modified Rankin score.[27] Patients with an OHS of 0, 1, or 2 were classed as independent. The statistical analysis plan specified an ordinal analysis of the OHS score at 6 months. Additional secondary outcomes were to be reported separately.

Events occurring within 7 days of stroke were recorded by the local trial clinician on the 7-day form: deaths subdivided by cause (swelling of the initial infarct, intracranial haemorrhage, other deaths from the initial stroke, recurrent ischaemic stroke, recurrent stroke of unknown type, any other cause); symptomatic intra-cranial haemorrhage; recurrent ischaemic stroke; recur-rent stroke of unknown type; neurological deterioration attributed to swelling of the initial ischaemic stroke; neurological deterioration not attributable to swelling of the initial ischaemic stroke or haemorrhage; and major extracranial haemorrhage (operational definitions of

	rt-PA (n=1515)	Control (n=1520)
Baseline variables collected before treatment allocation*		
Region†		
Northwest Europe (UK, Austria, Belgium, Switzerland)	792 (52%)	797 (52%)
Scandinavia (Norway, Sweden)	251 (17%)	250 (16%)
Australasia	89 (6%)	90 (6%)
Southern Europe (Italy, Portugal)	204 (13%)	204 (13%)
Eastern Europe (Poland)	174 (11%)	173 (11%)
Americas (Canada, Mexico)	5 (<1%)	6 (<1%)
Age (years)†		
18–50	59 (4%)	68 (4%)
51–60	98 (6%)	104 (7%)
61–70	188 (12%)	177 (12%)
71–80	353 (23%)	371 (24%)
81–90	706 (47%)	701 (46%)
>90	111 (7%)	99 (7%)
Sex†		
Female	782 (52%)	788 (52%)
NIHSS†		
0–5	304 (20%)	308 (20%)
6–10	422 (28%)	430 (28%)
11–15	306 (20%)	295 (19%)
16–20	270 (18%)	273 (18%)
>20	213 (14%)	214 (14%)
Delay in randomisation†‡		
0–3·0 h	431 (28%)	418 (28%)
3·0–4·5 h	577 (38%)	600 (39%)
4·5–6·0 h	507 (33%)	500 (33%)
>6·0 h	0 (0%)	2 (<1%)
Atrial fibrillation	473 (31%)	441 (29%)
Systolic blood pressure		
≤143 mm Hg	487 (32%)	492 (32%)
144–164 mm Hg	498 (33%)	518 (34%)
≥165 mm Hg	530 (35%)	510 (34%)
Diastolic blood pressure§		
≤74 mm Hg	462 (31%)	445 (29%)
75–89 mm Hg	541 (36%)	588 (39%)
≥90 mm Hg	500 (33%)	480 (32%)
Blood glucose¶		
≤5 mmol/L	254 (18%)	285 (21%)
6–7 mmol/L	664 (48%)	638 (46%)
≥8 mmol/L	455 (33%)	456 (33%)
		(Continues in next column)

	rt-PA (n=1515)	Control (n=1520)
(Continued from previous column)		
Treatment with antiplatelet drugs in previous 48 h†	775 (51%)	787 (52%)
Predicted probability of poor outcome at 6 months‖		
<40%	351 (23%)	378 (25%)
40–50%	169 (11%)	160 (11%)
50–75%	361 (24%)	357 (23%)
≥75%	634 (42%)	625 (41%)
Stroke clinical syndrome†**		
TACI	639 (42%)	666 (44%)
PACI	596 (39%)	551 (36%)
LACI	168 (11%)	164 (11%)
POCI	110 (7%)	136 (9%)
Other	2 (<1%)	3 (<1%)
Baseline variables collected from prerandomisation scan		
Expert reader's assessment of acute ischaemic change††	..	..
Scan completely normal	140 (9%)	129 (8%)
Scan not normal but no sign of acute ischaemic change	743 (49%)	781 (51%)
Signs of acute ischaemic change	624 (41%)	600 (40%)

Data are number (%). Percentages exclude missing values from denominators. rt-PA=recombinant tissue plasminogen activator. NIHSS=National Institutes of Health Stroke Scale. TACI=total anterior circulation infarct. PACI=partial anterior circulation infarct. LACI=lacunar infarct. POCI=posterior circulation infarct. *Data for these variables were gathered via the web-based or telephone randomisation system and had to be entered, complete, and have passed range and consistency checks before the system would issue a treatment allocation. †Variables were used in the minimisation algorithm. ‡Two patients in the control group were randomly assigned at more than 6 h (protocol violation). One of these was recorded as having severe swelling on the randomisation scan, because the stroke had in fact occurred about 24 h earlier. §Diastolic blood pressure missing for 12 patients in the rt-PA group and seven in the control group. ¶For the first 282 patients, glucose levels were not recorded. After patient 282, glucose levels were measured at randomisation. One further patient had a missing value. ‖Risk predicted by novel model designed by Konig and colleagues.[18] This model predicts outcome (death or Bartel Index <95) at 3 months. If we assume that those who die between 3 months and 6 months were dependent at 3 months, and those who do not die between 3 months and 6 months do not change their dependency status, then the risk estimates are likely to be quite accurate for death or dependency at 6 months. **Stroke clinical syndrome derived from baseline clinical features assigned by an algorithm (algorithm available on request). For the randomisation algorithm TACI, PACI, and POCI were combined as non-lacunar so the process ensured balance in the number of lacunar syndromes in each treatment group. ††Expert panel's masked assessment of prerandomisation scan. This assessment was done by members of the expert panel after randomisation and masked to treatment allocation and all clinical details. Prerandomisation scans were unavailable for eight patients in the rt-PA group and ten in the control group.

Table 1: Baseline characteristics

each of these events are provided in the published protocol[13] and statistical analysis plan[14]). Other fatal and non-fatal non-cerebral events were also recorded and coded. Data on potential reports of any of these events were extracted from the trial database and presented to the adjudication committee who were masked to treatment allocation.

Randomisation and masking

To avoid predictable alternation of treatment allocation, and thus potential loss of allocation concealment, patients were allocated with a probability of 0·80 to the treatment group that would minimise the difference between the groups on the key prognostic factors. Additional details of the procedures used in the double-blinded phase of the study are reported elsewhere.[11] The randomisation system informed local clinicians of the patients' unique trial identification number, and the weight-adjusted dose of drug or placebo in the double-blinded phase, or of the weight-adjusted drug dose among those allocated thrombolysis in the open phase, to be given as a 10% bolus with the remainder by an infusion over 1 h.

With the exception of the 276 patients treated in the double-blinded phase of the trial, treatment was given openly and neither the patient nor the treating clinicians were masked. Hospital staff completed an early outcome form at 7 days, death, or hospital discharge, whichever occured first, recording details of events occurring in hospital within 7 days, details of background treatments given and functional status. 6 months after randomisation, general practitioners (or hospital coordinators) were contacted by the IST-3 trial office staff to check that the patient was alive and inform them that they might be approached for follow-up. If appropriate, the IST-3 trial office masked staff then mailed a postal questionnaire to patients to assess outcome. Non-responders were contacted by telephone, and follow-up data was obtained by telephone interview. In Italy and Austria, all follow-ups were done as telephone interviews by a clinician, who was masked to treatment allocation and was highly experienced in outcome assessment. In Portugal, patients were followed up in clinic by clinicians not involved in the patients' initial treatment, again, masked to treatment allocation as far as possible. To assess the durability of any treatment benefit beyond 6 months, patients recruited in the UK (and in other countries where appropriate funding had been obtained) were also followed up at 18 months. All follow-up done by patient contact for these analyses ceased on March 31, 2012, but recording of deaths from national registries of deaths continues in UK, Norway, and Sweden.

Statistical analysis

At the outset of the trial in 2000, we estimated that, among the type of patients likely to be recruited at the time, to detect both an absolute difference of 10% in the proportion of patients alive and independent at 6 months after treatment and to have sufficient power to permit reliable analyses of the prespecified subgroups, a sample of 6000 patients would be needed. A trial of that size could detect a clinically worthwhile net benefit of as little as 3% absolute difference in the primary outcome (80% power, $\alpha=0\cdot05$). However, it was clear by 2007 that obtaining a sample of 6000 was no longer feasible, and the Steering Committee agreed a revised recruitment target.[11] The sample size, re-estimated in 2007 on the basis of event rates in both treatment groups combined, was 3100. This sample size gave 80% power to detect an absolute difference of 4·7% in the primary outcome.[11]

We monitored the quality and integrity of the accumulating clinical data according to a protocol agreed with the study sponsors, which involved central statistical monitoring according to the principles described by Buyse and colleagues,[28] supplemented by onsite monitoring and detailed source data verification in a random sample of 10% of records in centres that had recruited more than 30 patients, or when patterns in the data at a centre seemed anomalous. All IST-3 monitoring procedures were compliant with requirements of all study sponsors, the national ethics committees and regulatory agencies in the 12 participating countries, and they met all appropriate regulatory and Good Clinical Practice requirements. All baseline data, 7-day, and 6-month outcome data were subject to verification checks built into the randomisation and data management system. We monitored all baseline and postrandomisation imaging, which provided additional cross-checks on recruited patients and centre performance. An expert radiologist checked all scans, masked to clinical details and treatment allocation, immediately on receipt at the trial office, for evidence of adverse events and protocol deviations. The independent data monitoring committee met at least annually to review the unmasked data on major outcome events in the trial, on the background stroke-unit care received by trial patients (to ensure it was equal in both treatment groups), relevant external data (including updates of the Cochrane systematic review and reports from large-scale registries of rt-PA use) in strict confidence throughout the course of the trial. The committee judged these data never met the protocol-specified criteria to recommend modification of the protocol or halt recruitment to the study.

The statistical analysis plan was published[14] before unmasking of the authors to the data. All randomly assigned patients were included in the analysis. Masked analysis of the patients' baseline characteristics showed clear differences in key prognostic factors (age, stroke severity, degree of ischaemic change on baseline CT or MRI) in patients randomly assigned at different times after stroke onset, which might complicate the estimation of the effect of treatment overall and in subgroups.[11] Therefore, the primary analysis of the effect of treatment on the primary outcome was adjusted by logistic regression

for linear effects for the following covariates: age; National Institutes of Health stroke scale (NIHSS) score; time from onset of stroke symptoms to randomisation; and presence (*vs* absence) of ischaemic change on the prerandomisation brain scan according to expert assessment. An unadjusted analysis is also presented.

The trial did not meet its original target of 6000 patients, and so was no longer adequately powered to detect a 3% absolute difference in the primary outcome (with 80% power and α=0·05). The statistical-analysis-plan writing committee, which did not have access to the accumulating data, was therefore expanded to include an independent statistician (Gordon Murray, University of Edinburgh, Edinburgh, UK) to advise on the correct approach. The writing group was persuaded by the recent empirical evidence that the ordinal method was both statistically more efficient (effectively reducing the sample size required in stroke trials[29]) and robust against substantial deviations from the proportional assumption.[30] We therefore specified in the statistical analysis plan an ordinal logistic regression analysis, as a secondary outcome, in which the OHS as a dependent variable had 5 levels: levels 4, 5, and 6 were combined into a single level and levels 0, 1, 2, 3 were retained as distinct.

In this model the treatment odds ratios between one level and the next were assumed to be constant, so a single parameter summarises the shift in outcome

distribution between treatment and control groups. For patients known to be alive at 6 months, but with an unknown OHS, we used the level of function recorded on the 7-day form (ie, measured at 7 days or before discharge from hospital) to impute 6-month functional status.[14] We chose this simple form of imputation because it effectively classified 6-month outcomes in patients for whom both 7-day and 6-month data were known (data not shown). Analyses were done with SAS (version 9.2).

Role of the funding source
The sponsors of the study had no role in design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Between May, 2000, and July, 2011, 3035 patients were enrolled in 156 centres in 12 countries. Baseline characteristics were well balanced between treatment groups (figure 1, table 1). 1617 (53%) patients were older than 80 years of age. Vital status at 6 months was known for 99% (3011 of 3035) of patients. Overall, 2581 (95%) of 2714 patients with data (data for some relevant variables were not collected in the initial phase) did not meet the prevailing EU-licence-approval criteria. Additional baseline characteristics are shown in appendix pp 2–3.

Of those assigned to the rt-PA group, 26 (2%) did not receive any rt-PA treatment, and of those assigned to the control group, seven (<1%) received at least some rt-PA. Among patients allocated to the rt-PA group, the mean time from randomisation to injection of the bolus was 18 min, the mean time from onset to treatment was 4·2 h (SD 1·2), median 4·2 h (IQR 3·2–5·2). Appendix pp 2–3 documents deviations from the protocol and the background treatments that were given during the first 7 days. Most patients were cared for in a stroke unit, and there was no evidence of a major imbalance in the use of background treatments or place of care (admissions ward, or stroke unit) over the first 7 days; an analysis of blood pressure in patients measured after randomisation showed no significant difference at each timepoint over the first 24 h in either systolic or diastolic blood pressures between the two treatment groups. However, the proportion of those who had spent at least 1 day in a high-dependency area was somewhat higher among patients assigned to the rt-PA group than in the control group (328 [24%] *vs* 237 [17%]), though in both groups, the median stay in such an area was just 1 day. 76 (49%) centres were classed as experienced in treating stroke with thrombolysis, and 1143 patients were recruited by these centres.

Patients recruited within 1–2 h of onset were significantly more likely to have a more severe neurological deficit did than those recruited at later timepoints after onset (test for linear trend p<0·0001). Similarly, patients
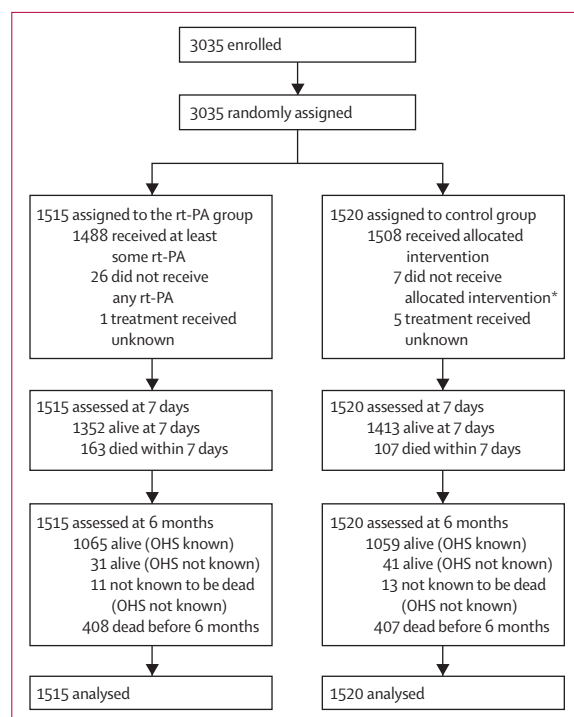

Figure 1: Trial profile
rt-PA=recombinant tissue plasminogen activator. OHS=Oxford Handicap Score. *Of the patients allocated to control, seven actually received some rt-PA. Appendix pp 4–5 gives more detail of treatment actually received and background care.

	rt-PA (n=1515)	Control (n=1520)	Adjusted analysis*		Unadjusted analysis†		
			Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Absolute difference per 1000 (95% CI)‡
Died within 7 days	163 (11%)	107 (7%)	1·60 (1·22 to 2·08)	0·001	1·59 (1·23 to 2·07)	0·0004	37 (17 to 57)
Died between 7 days and 6 months	245 (16%)	300 (20%)	0·73 (0·59 to 0·89)	0·002	0·78 (0·65 to 0·95)	0·011	−36 (−63 to −8)
Status at 6 months							
Vital status unknown, disability imputed	11	13	..	..	..	..	..
Alive at 6 months, disability imputed	31	41	..	..	..	..	..
Known 6 month vital and disability status	1473	1466	..	..	..	..	..
Number included in analysis (status known or imputed)	1515	1520	..	..	..	..	..
OHS at 6 months§							
0	138 (9%)	116 (8%)	..	..	..	..	..
1	225 (15%)	204 (13%)	..	..	..	..	..
2	191 (13%)	214 (14%)	..	..	..	..	..
3	235 (16%)	193 (13%)	..	..	..	..	..
4	115 (8%)	140 (9%)	..	..	..	..	..
5	203 (13%)	246 (16%)	..	..	..	..	..
Died before 6 months	408 (27%)	407 (27%)	0·96 (0·80 to 1·15)	0·672	1·01 (0·86 to1·19)	0·924	2 (−30 to 33)
Alive and favourable outcome (0+1)	363 (24%)	320 (21%)	1·26 (1·04 to 1·53)	0·018	1·18 (0·99 to 1·41)	0·055	29 (−1 to 59)
Alive and independent (0+1+2)¶	554 (37%)	534 (35%)	1·13 (0·95 to 1·35)	0·181	1·06 (0·92 to1·24)	0·409	14 (−20 to 48)

Data are number (%) unless otherwise stated. rt-PA=recombinant tissue plasminogen activator. OHS=Oxford Handicap Scale. *Odds ratios and p values were calculated by logistic regression after adjusting for age (linear), National Institutes of Health Stroke Scale (linear), time (linear), and presence or absence of visible acute ischaemic change on baseline scan as judged by the expert reader. †p value calculated from test of difference between percentages for rt-PA and control, using normal approximation. ‡Absolute difference calculated as rt-PA – control, so a positive number indicates this outcome was more frequent in the treatment group. §OHS: 0, no symptoms at all; 1, symptoms, but these do not interfere with everyday life; 2, symptoms that have caused some changes in lifestyle but patients are still able to look after themselves; 3, symptoms that have significantly changed lifestyle and patients need some help looking after themselves; 4, severe symptoms requiring help from other people but not so bad as to need attention day and night; 5, severe handicap needing constant attention day and night. ¶Primary outcomes.

Table 2: Deaths by 6 months and functional outcome at 6 months

recruited at earlier time points were significantly older than those recruited later (test for linear trend p<0·0001). The proportion of patients with a definitely visible ischaemic lesion (*vs* only possible or no early ischaemic change) on baseline imaging rose with time (test for linear trend p=0·0045).

At 6 months, 554 (37%) in the rt-PA group versus 534 (35%) in the control group were alive and independent in activities of daily living (OHS 0–2; table 2). A secondary ordinal analysis provided evidence of a favourable shift in the distribution of OHS scores at 6 months with treatment (p<0·001; figure 2). More patients died within 7 days in the rt-PA group than in the control group, but between 7 days and 6 months there were correspondingly fewer deaths in the rt-PA group.

Symptomatic intracranial haemorrhage and fatal or non-fatal deterioration due to swelling of the infarct within 7 days occurred in more patients in the rt-PA group than in the control group (table 3). rt-PA was associated with a significant increase in extracranial haemorrhages (table 3).

To assess the effect of treatment on the primary outcome, the statistical analysis plan predefined a small subset of key prognostic subgroups (figure 3). The
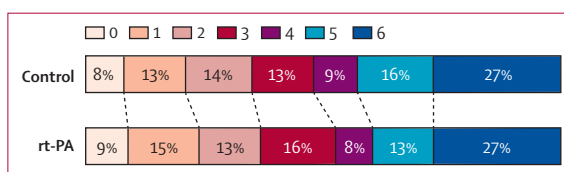
Figure 2: **Outcome at 6 months: Oxford Handicap Scale (OHS) by treatment group**

For the ordinal analysis, which was adjusted for age, National Institutes of Health Stroke Scale (NIHSS), delay (all linear), and and presence or absence of visible acute ischaemic change on baseline scan as judged by the expert reader, the statistical analysis plan prespecified that OHS levels 4, 5, and 6 were grouped and 0, 1, 2, 3 remained discrete. In that analysis, the common odds ratio was 1·27 (95% CI 1·10–1·47; p=0·001). An ordinal analysis with OHS levels 0, 1, 2, 3, 4, 5, and 6 all discrete, adjusted in the same way, gave an odds ratio of 1·17 (95% CI 1·03–1·33; p=0·016). rt-PA=recombinant tissue plasminogen activator.

subgroup analyses are of the adjusted effects and take account of the fact that, for a specific prognostic factor, the distribution of other factors might differ between subcategories. For example, in older patients the time to randomisation was shorter. The subgroup analyses for a specific factor provide estimated effects within sub-categories that adjust for such imbalances. Overall, little variation occurred in the adjusted effects of treatment in different subgroups. However, a significant difference

	rt-PA (n=1515)	Control (n=1520*)	Adjusted analysis†		Absolute difference per 1000 (95% CI)‡
			Odds ratio (95% CI)	p value	
Cerebral events					
Symptomatic swelling of original infarct§					
Non-fatal	21 (1%)	17 (1%)	1·23 (0·64 to 2·35)	0·539	3 (–5 to 11)
Fatal	47 (3%)	25 (2%)	1·89 (1·14 to 3·14)	0·013	15 (4 to 25)
Total	68 (4%)	42 (3%)	1·66 (1·11 to 2·49)	0·014	17 (4 to 31)
Symptomatic intracranial haemorrhage¶					
Non-fatal	49 (3%)	9 (1%)	5·56 (2·72 to 11·4)	<0·0001	26 (17 to 36)
Fatal	55 (4%)	7 (<1%)	8·12 (3·68 to 17·9)	<0·0001	32 (22 to 42)
Total	104 (7%)	16 (1%)	6·94 (4·07 to 11·8)	<0·0001	58 (44 to 72)
Neurological deterioration not due to swelling or haemorrhage					
Non-fatal	107 (7%)	79 (5%)	1·37 (1·02 to 1·86)	0·038	19 (2 to 36)
Fatal	38 (3%)	49 (3%)	0·74 (0·48 to 1·14)	0·167	–7 (–19 to 5)
Total	145 (10%)	128 (8%)	1·14 (0·88 to 1·46)	0·320	11 (–9 to 32)
Recurrent ischaemic stroke					
Non-fatal	18 (1%)	15 (1%)	1·21 (0·61 to 2·42)	0·583	2 (–5 to 9)
Fatal	3 (0%)	5 (<1%)	0·61 (0·14 to 2·57)	0·499	–1 (–5 to 2)
Total	21 (1%)	20 (1%)	1·06 (0·57 to 1·97)	0·846	1 (–8 to 9)
Recurrent stroke of unknown type					
Non-fatal	1 (<1%)	2 (<1%)	0·50 (0·05 to 5·56)	0·574	–1 (–3 to 2)
Fatal	2 (<1%)	1 (<1%)	1·98 (0·18 to 22·3)	0·581	1 (–2 to 3)
Total	3 (<1%)	3 (<1%)	0·98 (0·20 to 4·89)	0·981	0 (–3 to 3)
Non-cerebral events‖					
Myocardial infarction					
Non-fatal	18 (1%)	19 (1%)	0·89 (0·46 to 1·71)	0·717	–1 (–8 to 7)
Fatal	5 (<1%)	4 (<1%)	1·25 (0·33 to 4·68)	0·738	1 (–3 to 5)
Total	23 (2%)	23 (2%)	0·95 (0·53 to 1·71)	0·859	0 (–9 to 9)
Extracranial bleed					
Non-fatal	14 (1%)	1 (<1%)	14·5 (1·90 to 110)	0·010	9 (4 to 14)
Fatal	2 (<1%)	2 (<1%)	0·99 (0·14 to 7·13)	0·995	0 (–3 to 3)
Total	16 (1%)	3 (<1%)	5·46 (1·59 to 18·8)	0·007	9 (3 to 14)
Allergic reaction					
Non-fatal	12 (1%)	0 (0%)	..	..	8 (3 to 12)
Fatal	0 (0%)	0 (0%)	..	..	0 (0 to 0)
Total	12 (1%)	0 (0%)	..	..	8 (3 to 12)
Total deaths from cerebral causes within 7 days	145 (10%)	87 (6%)	1·76 (1·32 to 2·34)	0·0001	38 (20 to 57)
Total deaths from non-cerebral causes within 7 days**	18 (1%)	20 (1%)	0·89 (0·47 to 1·69)	0·717	–1 (–9 to 7)
Total deaths within 7 days	163 (11%)	107 (7%)	1·60 (1·22 to 2·08)	0·001	37 (17 to 57)

Data are number (%) unless otherwise stated. rt-PA=recombinant tissue plasminogen activator. *One patient in the control group was missing a 7-day form but did return a 6-month form, so was known to be alive at 7 days. This case has been omitted from the analysis. †Odds ratio and p value calculated from logistic regression after adjusting for age (linear), National Institutes of Health Stroke Scale (linear), time (linear), and presence or absence of visible acute ischaemic change on baseline scan. When no events occurred in one treatment group the logistic model was not applied. ‡Absolute difference was calculated as rt-PA–control, so a positive number indicates this outcome was more frequent in the treatment group. §Symptomatic swelling of the original infarct was defined as significant neurological deterioration accompanied by evidence of significant brain swelling as determined by the independent masked expert assessment of the scan defined as: shift of the midline away from the side of the ventricle or effacement of the basal cisterns or uncal herniation on a postrandomisation scan (or autopsy if not rescanned before death). The presence of some degree of haemorrhagic transformation was permitted, provided it was not identified by the expert CT reader to be a major contributor to the mass effect. ¶Symptomatic intracranial haemorrhage was defined as significant neurological deterioration accompanied by clear evidence of significant intracranial haemorrhage on the postrandomisation scan (or autopsy if not rescanned and death occurs after 7 days). Significant haemorrhage was present on any postrandomisation scan if the expert reader both noted the presence of significant haemorrhagic transformation of the infarct or parenchymal haematoma and indicated that haemorrhage was a major component of the lesion (or was remote from the lesion and likely to have contributed significantly to the burden of brain damage). This event included clinical events described as a recurrent stroke within 7 days, in which the recurrent stroke was confirmed to be caused by an intracranial haemorrhage. ‖Non-fatal cerebral events are exclusive. However, non-fatal non-cerebral events are not exclusive. A given patient could have one or more non-fatal non-cerebral events and a non-fatal cerebral event. **The deaths in the fatal rows are exclusive (a patient can only contribute to one of the fatal rows). Total deaths from non-cerebral causes include deaths not attributed to myocardial infarction, extracranial bleed, or allergic reaction.

Table 3: **Fatal and non-fatal cerebral and non-cerebral events within 7 days of randomisation**
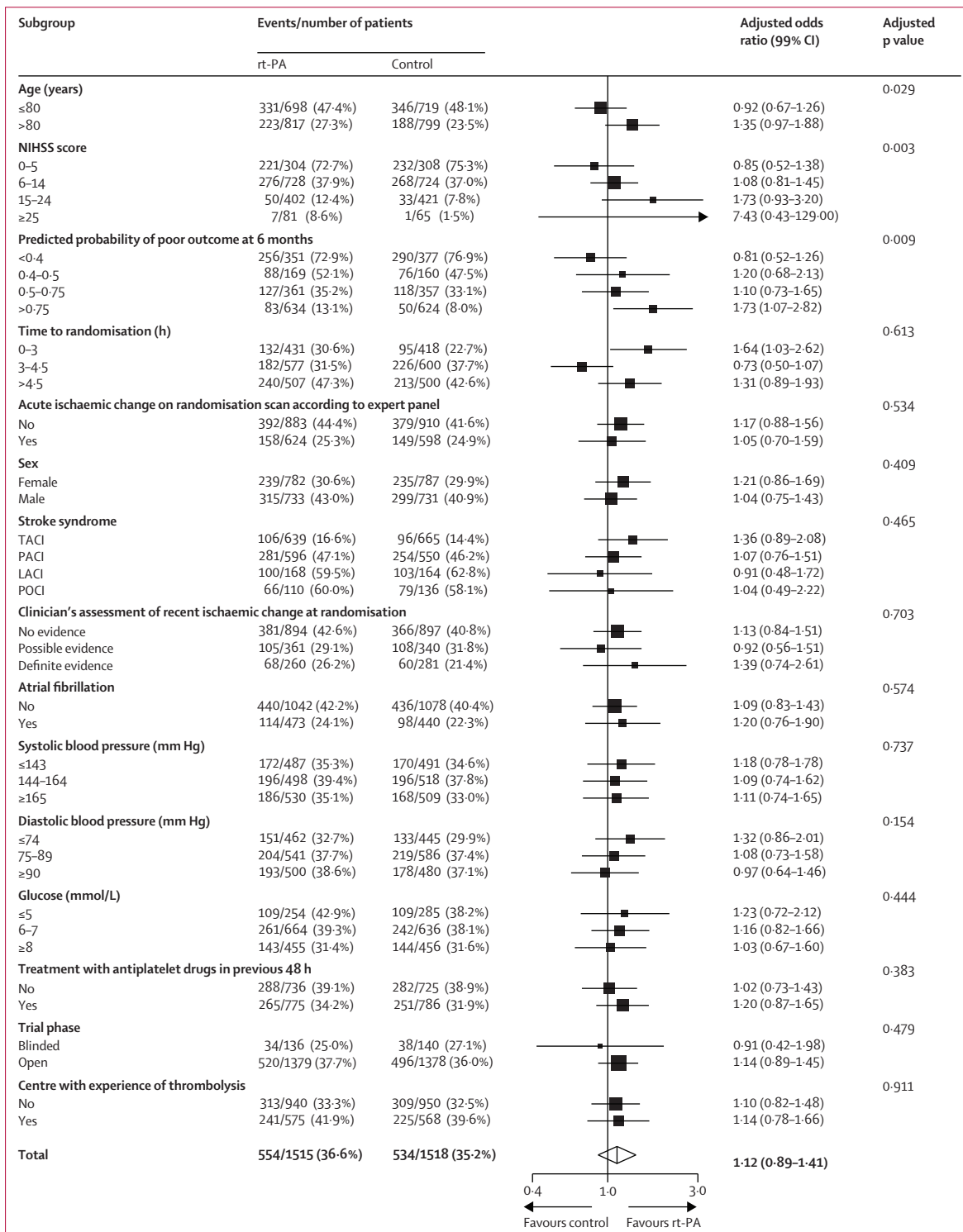
Subgroup	Events/number of patients			Adjusted odds ratio (99% CI)	Adjusted p value
	rt-PA	Control			
Age (years)					0·029
≤80	331/698 (47·4%)	346/719 (48·1%)		0·92 (0·67–1·26)	
>80	223/817 (27·3%)	188/799 (23·5%)		1·35 (0·97–1·88)	
NIHSS score					0·003
0–5	221/304 (72·7%)	232/308 (75·3%)		0·85 (0·52–1·38)	
6–14	276/728 (37·9%)	268/724 (37·0%)		1·08 (0·81–1·45)	
15–24	50/402 (12·4%)	33/421 (7·8%)		1·73 (0·93–3·20)	
≥25	7/81 (8·6%)	1/65 (1·5%)		7·43 (0·43–129·00)	
Predicted probability of poor outcome at 6 months					0·009
<0·4	256/351 (72·9%)	290/377 (76·9%)		0·81 (0·52–1·26)	
0·4–0·5	88/169 (52·1%)	76/160 (47·5%)		1·20 (0·68–2·13)	
0·5–0·75	127/361 (35·2%)	118/357 (33·1%)		1·10 (0·73–1·65)	
>0·75	83/634 (13·1%)	50/624 (8·0%)		1·73 (1·07–2·82)	
Time to randomisation (h)					0·613
0–3	132/431 (30·6%)	95/418 (22·7%)		1·64 (1·03–2·62)	
3–4·5	182/577 (31·5%)	226/600 (37·7%)		0·73 (0·50–1·07)	
>4·5	240/507 (47·3%)	213/500 (42·6%)		1·31 (0·89–1·93)	
Acute ischaemic change on randomisation scan according to expert panel					0·534
No	392/883 (44·4%)	379/910 (41·6%)		1·17 (0·88–1·56)	
Yes	158/624 (25·3%)	149/598 (24·9%)		1·05 (0·70–1·59)	
Sex					0·409
Female	239/782 (30·6%)	235/787 (29·9%)		1·21 (0·86–1·69)	
Male	315/733 (43·0%)	299/731 (40·9%)		1·04 (0·75–1·43)	
Stroke syndrome					0·465
TACI	106/639 (16·6%)	96/665 (14·4%)		1·36 (0·89–2·08)	
PACI	281/596 (47·1%)	254/550 (46·2%)		1·07 (0·76–1·51)	
LACI	100/168 (59·5%)	103/164 (62·8%)		0·91 (0·48–1·72)	
POCI	66/110 (60·0%)	79/136 (58·1%)		1·04 (0·49–2·22)	
Clinician's assessment of recent ischaemic change at randomisation					0·703
No evidence	381/894 (42·6%)	366/897 (40·8%)		1·13 (0·84–1·51)	
Possible evidence	105/361 (29·1%)	108/340 (31·8%)		0·92 (0·56–1·51)	
Definite evidence	68/260 (26·2%)	60/281 (21·4%)		1·39 (0·74–2·61)	
Atrial fibrillation					0·574
No	440/1042 (42·2%)	436/1078 (40·4%)		1·09 (0·83–1·43)	
Yes	114/473 (24·1%)	98/440 (22·3%)		1·20 (0·76–1·90)	
Systolic blood pressure (mm Hg)					0·737
≤143	172/487 (35·3%)	170/491 (34·6%)		1·18 (0·78–1·78)	
144–164	196/498 (39·4%)	196/518 (37·8%)		1·09 (0·74–1·62)	
≥165	186/530 (35·1%)	168/509 (33·0%)		1·11 (0·74–1·65)	
Diastolic blood pressure (mm Hg)					0·154
≤74	151/462 (32·7%)	133/445 (29·9%)		1·32 (0·86–2·01)	
75–89	204/541 (37·7%)	219/586 (37·4%)		1·08 (0·73–1·58)	
≥90	193/500 (38·6%)	178/480 (37·1%)		0·97 (0·64–1·46)	
Glucose (mmol/L)					0·444
≤5	109/254 (42·9%)	109/285 (38·2%)		1·23 (0·72–2·12)	
6–7	261/664 (39·3%)	242/636 (38·1%)		1·16 (0·82–1·66)	
≥8	143/455 (31·4%)	144/456 (31·6%)		1·03 (0·67–1·60)	
Treatment with antiplatelet drugs in previous 48 h					0·383
No	288/736 (39·1%)	282/725 (38·9%)		1·02 (0·73–1·43)	
Yes	265/775 (34·2%)	251/786 (31·9%)		1·20 (0·87–1·65)	
Trial phase					0·479
Blinded	34/136 (25·0%)	38/140 (27·1%)		0·91 (0·42–1·98)	
Open	520/1379 (37·7%)	496/1378 (36·0%)		1·14 (0·89–1·45)	
Centre with experience of thrombolysis					0·911
No	313/940 (33·3%)	309/950 (32·5%)		1·10 (0·82–1·48)	
Yes	241/575 (41·9%)	225/568 (39·6%)		1·14 (0·78–1·66)	
Total	**554/1515 (36·6%)**	**534/1518 (35·2%)**		**1·12 (0·89–1·41)**	

0·4　　1·0　　3·0

Favours control ← → Favours rt-PA

Figure 3: **Adjusted effect of treatment on the primary outcome (alive and independent, Oxford Handicap Score 0, 1, or 2) in subgroups**
The key predefined subgroups were age 80 years or younger, age older than 80 years, time from stroke onset to randomisation (0–3·0 h, 3·0–4·5 h, 4·5–6·0 h), initial stroke severity as measured by National Institutes of Health stroke score, and the appearance of the baseline brain scan on expert read for each subgroup (whether ischaemic change is visible or not). The treatment odds ratio in each subgroup has been adjusted for the linear effects of the other key variables (age, NIHSS, and delay) but not for the presence or absence visible ischaemic change. It is for this reason that the adjusted odds ratio in the "Total" row at the bottom of the table does not exactly agree with the odds ratio in table 2. The choice of cut-points to define certain subgroups is slightly different to those given in table 1.[14] On the graph, for each subgroup, the horizontal line represents the 99% CI, the diamond is centred on the overall estimate and it represents the 95% CI. The graph was generated with R (version 2.11.1). rt-PA=recombinant tissue plasminogen activator. NIHSS=National Institutes of Health Stroke Scale. TACI=total anterior circulation infarct. PACI=partial anterior circulation infarct. LACI=lacunar infarct. POCI=posterior circulation infarct.

did occur in the adjusted effect of treatment between patients older than 80 years and in patients 80 years or younger (p=0·027), suggesting greater benefit in those older than 80 years of age; contrary to expectations.[14] Treatment appeared at least as effective in this age group as in younger patients. Significant trends towards larger effects of treatment in more severe strokes were also seen (as assessed by the NIHSS and by the predicted probability of a poor outcome[18]). Benefit was greatest in patients treated within 3 h, but there was insufficient power to examine decay of benefit with time. An analysis of the treatment effect in each of three equal-sized cohorts of patients (ie, those recruited in 2000–06, 2007–08, 2009–11) did not provide any evidence of period effects (data not shown). We also undertook a sensitivity analysis restricted to the 2939 (96%) patients with known 6-month vital and disability status (appendix pp 4–5), and the results were not qualitatively different from those in table 2.

Discussion

Although the increase in the number of patients treated with rt-PA who were alive and independent at 6 months was smaller than originally anticipated and was not significant, the secondary analysis provides supportive evidence of benefit. The ordinal analysis provided evidence that on average, patients treated with intravenous thrombolysis up to 6 h after stroke survived with less disability. At 6 months, vital status was known for most patients and there was no evidence of any difference in the number of deaths, despite the excess of deaths within 7 days of stroke (mainly due to intracranial haemorrhage). Since mortality at 6 months was equal in the two groups, and in view of the evidence that the lower the patients' degree of disability at 6 months, the greater their subsequent survival,[31] long-term follow-up beyond 6 months is important. Follow-up for survival, therefore, continues in the UK, Norway, and Sweden to assess whether an overall survival advantage from rt-PA after 6 months emerges.

Since we sought to recruit older patients and patients who did not strictly meet prevailing licence criteria for thrombolytic therapy with rt-PA, we anticipated a higher risk of adverse events, chiefly symptomatic intracranial haemorrhage. The patient information leaflet stated that rt-PA treatment might be associated with an increased risk of fatal intracranial haemorrhage of 4%, which indeed was the rate reported in the trial. Furthermore, applying a similar definition of symptomatic intracerebral haemorrhage as in the Cochrane systematic review, the frequency of this disorder within 7 days in IST-3 patients treated with rt-PA (6·8%) was comparable with the 7·3% reported in the Safe Implementation of Thrombolysis in Stroke (SITS) registry of 6483 patients treated within licence in routine clinical practice.[32] We also expected a higher risk of death in the control group, and a smaller proportion alive and independent than in

previous trials. Reassuringly, despite the different event rates in the control group, for most of the outcomes, there was no clear evidence that the effects of treatment were qualitatively different in IST-3 to those seen in earlier randomised trials, with two exceptions. We identified significant trends towards larger effects of treatment in patients with more severe strokes. We also anticipated a reduction in fatal and non-fatal neurological deterioration due to swelling of the initial infarct,[6] so the clear 17 per 1000 excess was unexpected, and inconsistent with data from previous trials.[6]

As proposed by Kent and colleagues,[33] we reported the effect of treatment on the primary outcome in several prespecified subgroups and included the effects subdivided by the result of a prognostic score. Benefit with treatment was greatest within 3 h, but the analyses did not have sufficient power to define the shape of the relation between benefit and time beyond 3 h. The effect of treatment in patients older than 80 years of age was at least as large as in patients younger than 80 years of age. A formal test for trend showed a significant difference for greater benefit of rt-PA in patients with increasingly severe strokes. However, in view of the overall non-significant benefit for the primary outcome, the significant interactions across subgroups in these analyses should be interpreted with caution. As specified in the statistical analysis plan, we planned additional secondary analyses to explore these apparent effects on the primary outcome (and on other outcomes, such as symptomatic intracranial haemorrhage) and to decide if these effects were due to chance.

Lyden[34] has identified limitations in these data, chiefly that IST-3 recruited only half the number of patients originally intended and so was underpowered for the primary outcome (and more so for the subgroup analyses). The many changes in the regulatory environment over the course of the trial delayed the approval of the trial in many centres and precluded the participation of several countries and hence was a significant factor in our failing to achieve our original target.[11] Nonetheless, the trial was the largest-ever trial of thrombolysis therapy for stroke[34] (over three times larger than any previous trial) and included more patients treated within 3 h of stroke (n=849) than were included in the National Institute of Neurological Disorders and Stroke (NINDS) trial (n=624), the only previous trial examining specifically treatment within 3 h (panel). The fact that most of the IST-3 patients treated within 3 h were older than 80 years of age (n=726), yet achieved similar benefit to younger patients in NINDS trial, adds to the NINDS trial.

The absence of masking is most relevant for the assessment of the events within 7 days. However, every possible precaution was taken to ensure masking of the expert panel assessing the scans, and the adjudication committee, who also assessed clinical data on all potential cerebral events. The proportional effect of

treatment on fatal and non-fatal events within 7 days was very similar, which perhaps suggest that masking of the assessors was successful. The self-assessment at 6 months by patients or their carer by postal question-naire or masked telephone interview was unmasked and so could be subject to reporting bias.[34] However, self-reported outcome by patients is necessarily subjective and affected by many things besides knowledge of treatment allocation. The subgroup analysis subdivided by trial phase provides some reassurance in that no significant difference was seen in the effect of treatment on the primary outcome in the double-blind phase and the open phase (figure 3). The measurement of outcome with OHS at 6 months is different from previous trials that measured the modified Rankin score at 3 months. When we planned IST-3 in 1998, the modified Rankin score and OHS were judged to be equivalent. Both are derivatives of the original Rankin scale, developed by members of our group. While the proportion of patients recorded as dependent might be slightly different with each scale, the choice of outcome scale would not bias the assessment of treatment effect between treatment and control groups.

The outcome was recorded at 6 months and 18 months, to assess the effects on survival free of disability after a few months and also in the long term (the longer the benefit persists, the greater the cost-effectiveness). The longer time to follow-up allowed any differential effect of rt-PA on early and late death to become clearer. Outcome (other than survival) was not recorded at 3 months, although the proportional effects on death and disability seen at 6 months in IST-3 are comparable with those seen at 3 months in previous trials.

Lyden also comments that the sampling approach to monitoring in IST-3 was less intense than in many commercial studies, and is a potential concern, but also states: "many clinical trialists believe that source verification of some clinical trial data assures safety, accuracy, and validity of the trial data. Authorities do not agree on the minimum quantity of verified data to assure validity (100%, half, 10% sample)...but there is no evidence to suggest any problems with the [IST-3] data set due to limited monitoring."[34]

When the results of IST-3 are incorporated into an updated systematic review,[35] the estimates of relative treatment effect are broadly compatible with the previous rt-PA trials for each of the main outcomes: alive and independent; death at final follow-up; and fatal intracranial haemorrhage.

Our trial was underpowered to reliably detect important subgroup effects, and so a collaborative individual patient data meta-analysis (the Stroke Thrombolysis Trialists Collaboration [STTC]) has been established, which will include data from all the completed intravenous rt-PA trials and will update the previous pooled analysis.[7] The meta-analysis will explore which baseline factors, other than time, might modify the effects of treatment on major

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Panel: Research in context

Systematic review

To update the published systematic review of randomised-controlled trials of recombinant tissue plasminogen activator (rt-PA) in patients with acute ischaemic stroke and incorporate the third International Stroke Trial (IST-3) results,[6] we searched for additional randomised trials of intravenous rt-PA versus control within 6 h of onset of acute ischaemic stroke up to March 30, 2012, in the Cochrane Stroke Trials Registry (November, 2011), Internet Stroke Trials Centre (March, 2011), Medline and Embase (search strategy available on request), and references lists in review articles and conference abstracts. The primary analysis was for all patients treated up to 6 h after stroke. Data were available for 7012 patients in 12 trials. We tested for heterogeneity between the estimates of effect for key outcomes from two strata: all trials before IST-3 and IST-3. The tests for heterogeneity in the proportional effects of treatment across these two strata were not significant for symptomatic intracranial haemorrhage (χ^2 2·13, p=0·1), deaths within 7 days (χ^2 1·44, p=0·2), deaths by the end of follow-up (χ^2 1·0, p=0·3) and, the proportion alive and independent (modified Rankin score 0–2: χ^2 3·08, p=0·08). Similarly, no heterogeneity occurred across the two strata for patients of all ages treated within 3 h (χ^2 0·25, p=0·6). The review established that the effects of treatment reported in IST-3—in this wider range of patients (generally outside the current approvals)—were consistent with those seen in previous trials.

Interpretation

By providing estimates on the benefits and harms of treating patients with acute ischaemic stroke outside the current approvals, IST-3 enables clinicians to consider thrombolytic treatment for a wider range of patients, especially those older than 80 years of age. The data reinforce the need for further efforts to increase the proportion of all ischaemic strokes treated within 3 h. The additional data from IST-3 give greater confidence that mortality is not increased by treatment. The implications for ongoing research are that the data strengthen the rationale for the ongoing trials of thrombolysis in patients presenting more than 4·5 h after onset of stroke, and suggest that the imposition of upper age limits on future trials in acute stroke will become harder to justify.

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outcomes (such as death, functional outcome, and intracerebral haemorrhage), and so provide better guidance for clinicians and patients to apply this treatment as effectively as possible in routine practice.

For the types of patient recruited in IST-3 (about three quarters of whom were randomised after 3 h, and half of all patients were older than 80 years of age), by 6 months there was evidence that rt-PA improved functional outcome. The data add weight to the policy of treating patients as soon as possible, and also justify extending treatment to patients older than 80 years of age. The data do not support any restriction of treatment on the basis of stroke severity or the presence of early ischaemic change on the baseline brain scan. The data support the need for randomised trials of thrombolysis in selected patients more than 4·5 h after stroke.

to the study. GV, AC, AK, EB, KBS, VM, AP, GJH, KM, MB, SR, GG, SJP, AA, MC, and PL acted as National Coordinators. PS drafted the Article and all authors commented on drafts and approved the final version.

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Conflicts of interest
EB has received honoraria for lectures at meetings arranged by Boehringer Ingelheim, and reimbursement for costs for attending these meetings. AC has received lecture fees and conference travel costs from Boehringer Ingelheim. GB has received honoraria and speaker fees from Boehringer Ingelheim, Sanofi Synthlabo Aventis, Hoffman La Roche, and Novo Nordisk. AK has received lecture fees and conference travel costs from Boehringer Ingelheim. RIL has received payment in his role as conference scientific committee member and for occasional lectures from Boehringer Ingelheim; has attended national stroke meetings organised and funded by Boehringer Ingelheim; and is not a member of any industry advisory boards. PS has received lecture fees (paid to the Division of Clinical Neurosciences, University of Edinburgh) and travel expenses from Boehringer Ingelheim for occasional lectures given at international conferences; and was a member of the Independent Data and Safety Monitoring Board (DSMB) of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial funded by Boehringer Ingelheim and received attendance fees and travel expenses for attending DSMB meetings (paid to the Division of Clinical Neurosciences, University of Edinburgh). KBS has received an honorarium for a lecture from Boehringer Ingelheim and had costs for participating in scientific meetings reimbursed; is a member of the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) and the Cardiovascular Working Party. The views expressed in this article are the personal views of KBS and should not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties. VM has received an unrestricted educational grant for a meeting on thrombolysis in stroke at which IST-3 was discussed. JMW received reimbursement for reading CT scans for European Cooperative Acute Stroke Study III (ECASS III) from Boehringer Ingelheim in the form of funding to her department, the Division of Clinical Neurosciences, University of Edinburgh; is the contact reviewer for the Cochrane systematic reviews of thrombolytic treatment for acute stroke; has attended meetings held by Boehringer Ingelheim as an unpaid independent external adviser during the licensing of rt-PA, but was refunded her travel expenses and the time away from work; has attended and spoken at national and international stroke meetings organised and funded by Boehringer Ingelheim for which she received honoraria and travel expenses; and is director of the Brain Research Imaging Centre for Scotland, which is located within the Department of Clinical Neurosciences at the University of Edinburgh, Edinburgh, Scotland and houses a research MRI scanner, which was funded by the UK Research Councils Joint Research Equipment Initiative, supplemented by grants and donations from various other sources including Novartis, Schering, General Electric, and Boehringer Ingelheim. These commercial sources contributed to the purchase of the scanner, but not the running costs or any individual studies. All other members of the writing committee declare that they have no conflicts of interest.

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References
1   Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol* 2007; **6:** 182–87.
2   Rothwell PM, Coull AJ, Giles MF, et al, and the Oxford Vascular Study. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004; **363:** 1925–33.
3   Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009; **8:** 355–69.
4   Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; **367:** 1747–57.
5   Islam MS, Anderson CS, Hankey GJ, et al. Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: the Perth Community Stroke Study. *Stroke* 2008; **39:** 776–82.
6   Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2009; **4:** CD000213.
7   Lees KR, Bluhmki E, von Kummer R, et al, and the ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010; **375:** 1695–703.
8   Sanossian N, Ovbiagele B. Prevention and management of stroke in very elderly patients. *Lancet Neurol* 2009; **8:** 1031–41.
9   Bembenek J, Kobayashi A, Sandercock P, Czlonkowska A. How many patients might receive thrombolytic therapy in the light of the ECASS-3 and IST-3 data? *Int J Stroke* 2010; **5:** 430–31.
10 Ware JH, Hamel MB. Pragmatic trials—guides to better patient care? *N Engl J Med* 2011; **364:** 1685–87.
11 Sandercock P, Lindley R, Wardlaw J, et al, and the IST-3 collaborative group. Update on the third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke and baseline features of the 3035 patients recruited. *Trials* 2011; **12:** 252.
12 Whiteley W, Lindley R, Wardlaw J, Sandercock P, and the IST-3 Collaborative Group. Third international stroke trial. *Int J Stroke* 2006; **1:** 172–76.
13 Sandercock P, Lindley R, Wardlaw J, et al. Third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke. *Trials* 2008; **9:** 37.
14 Sandercock P, Lindley R, Wardlaw J, Whiteley W, Murray G, and the ST-3 collaborative group. Statistical analysis plan for the third International Stroke Trial (IST-3); part of a 'thread' of reports of the trial. *Int J Stroke* 2012; **7:** 186–87.
15 Warlow C, D'Hooghe M, Joos F, et al. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet* 1991; **337:** 1235–43.
16 Peto R, Baigent C. Trials: the next 50 years. Large scale randomised evidence of moderate benefits. *BMJ* 1998; **317:** 1170–71.
17 Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *Lancet* 2001; **357:** 373–80.
18 König IR, Ziegler A, Bluhmki E, et al, and the Virtual International Stroke Trials Archive (VISTA) Investigators. Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. *Stroke* 2008; **39:** 1821–26.
19 Langhorne P, Pollock A, and the Stroke Unit Trialists' Collaboration. What are the components of effective stroke unit care? *Age Ageing* 2002; **31:** 365–71.
20 Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet* 2000; **355:** 1670–74.
21 Wardlaw JM, Sellar RJ. A simple practical classification of cerebral infarcts on CT and its interobserver reliability. *AJNR Am J Neuroradiol* 1994; **15:** 1933–39.
22 Wardlaw JM, Farrall AJ, Perry D, et al, and the Acute Cerebral CT Evaluation of Stroke Study (ACCESS) Study Group. Factors influencing the detection of early CT signs of cerebral ischemia: an internet-based, international multiobserver study. *Stroke* 2007; **38:** 1250–56.
23 van Swieten JC, Hijdra A, Koudstaal PJ, van Gijn J. Grading white matter lesions on CT and MRI: a simple scale. *J Neurol Neurosurg Psychiatry* 1990; **53:** 1080–83.
24 Cordonnier C, Potter GM, Jackson CA, et al. Improving inter-rater agreement about brain microbleeds. Development of the Brain Observer MicroBleed Scales (BOMBS). *Stroke* 2009; **49:** 94–99.
25 Farrell C, Chappell F, Armitage PA, et al. Development and initial testing of normal reference MR images for the brain at ages 65–70 and 75–80 years. *Eur Radiol* 2009; **19:** 177–83.
26 Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project—1981–86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 1990; **53:** 16–22.
27 van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; **19:** 604–07.
28 Buyse M, George SL, Evans S, et al. The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. *Stat Med* 1999; **18:** 3435–51.
29 Bath PM, Gray LJ, Collier T, Pocock S, Carpenter J, and the Optimising Analysis of Stroke Trials (OAST) Collaboration. Can we improve the statistical analysis of stroke trials? Statistical reanalysis of functional outcomes in stroke trials. *Stroke* 2007; **38:** 1911–15.
30 McHugh GS, Butcher I, Steyerberg EW, et al. A simulation study evaluating approaches to the analysis of ordinal outcome data in randomized controlled trials in traumatic brain injury: results from the IMPACT Project. *Clin Trials* 2010; **7:** 44–57.
31 Slot KB, Berge E, Dorman P, Lewis S, Dennis M, Sandercock P, and the Oxfordshire Community Stroke Project, the International Stroke Trial (UK), and the Lothian Stroke Register. Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies. *BMJ* 2008; **336:** 376–79.
32 Wahlgren N, Ahmed N, Dávalos A, et al, and the SITS-MOST investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007; **369:** 275–82.
33 Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. *Trials* 2010; **11:** 85.
34 Lyden PD. In Anticipation of International Stroke Trial-3 (IST-3). *Stroke* 2012; published online May 3. DOI:10.1161/STROKEAHA.112.656876.
35 Wardlaw J M, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet* 2012; published online May 23. DOI:10.1016/S0140-6736(12)60738-7.