ORIGINAL ARTICLE

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

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ABSTRACT

BACKGROUND

Under current guidelines, intravenous thrombolysis is used to treat acute stroke only if it can be ascertained that the time since the onset of symptoms was less than 4.5 hours. We sought to determine whether patients with stroke with an unknown time of onset and features suggesting recent cerebral infarction on magnetic resonance imaging (MRI) would benefit from thrombolysis with the use of intravenous alteplase.

METHODS

In a multicenter trial, we randomly assigned patients who had an unknown time of onset of stroke to receive either intravenous alteplase or placebo. All the patients had an ischemic lesion that was visible on MRI diffusion-weighted imaging but no parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR), which indicated that the stroke had occurred approximately within the previous 4.5 hours. We excluded patients for whom thrombectomy was planned. The primary end point was favorable outcome, as defined by a score of 0 or 1 on the modified Rankin scale of neurologic disability (which ranges from 0 [no symptoms] to 6 [death]) at 90 days. A secondary outcome was the likelihood that alteplase would lead to lower ordinal scores on the modified Rankin scale than would placebo (shift analysis).

RESULTS

The trial was stopped early owing to cessation of funding after the enrollment of 503 of an anticipated 800 patients. Of these patients, 254 were randomly assigned to receive alteplase and 249 to receive placebo. A favorable outcome at 90 days was reported in 131 of 246 patients (53.3%) in the alteplase group and in 102 of 244 patients (41.8%) in the placebo group (adjusted odds ratio, 1.61; 95% confidence interval [CI], 1.09 to 2.36; P=0.02). The median score on the modified Rankin scale at 90 days was 1 in the alteplase group and 2 in the placebo group (adjusted common odds ratio, 1.62; 95% CI, 1.17 to 2.23; P=0.003). There were 10 deaths (4.1%) in the alteplase group and 3 (1.2%) in the placebo group (odds ratio, 3.38; 95% CI, 0.92 to 12.52; P=0.07). The rate of symptomatic intracranial hemorrhage was 2.0% in the alteplase group and 0.4% in the placebo group (odds ratio, 4.95; 95% CI, 0.57 to 42.87; P=0.15).

CONCLUSIONS

In patients with acute stroke with an unknown time of onset, intravenous alteplase guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemia resulted in a significantly better functional outcome and numerically more intracranial hemorrhages than placebo at 90 days. (Funded by the European Union Seventh Framework Program; WAKE-UP ClinicalTrials.gov number, NCT01525290; and EudraCT number, 2011-005906-32.)

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*A complete list of investigators in the WAKE-UP trial is provided in the Supplementary Appendix, available at NEJM.org.

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Intravenous thrombolysis with alteplase, a recombinant tissue plasminogen activator, is the standard medical treatment for acute ischemic stroke within 4.5 hours after the onset of symptoms.[1-4] In 14 to 27% of strokes, the time of symptom onset is not known, frequently because stroke symptoms are recognized when the patient awakes from sleeping.[5,6] Such patients are generally excluded from treatment with intravenous alteplase, and only some of them are candidates for mechanical thrombectomy.

A substantial proportion of strokes that are evident after sleep probably occur in the last few hours before awakening, which would be within the approved time window for the use of intravenous thrombolysis.[7] Magnetic resonance imaging (MRI) in patients with stroke with a known time of symptom onset has identified the presence of a visible ischemic lesion on diffusion-weighted imaging, combined with the absence of a clearly visible hyperintense signal in the same region on fluid-attenuated inversion recovery (FLAIR), as predictive of symptom onset within 4.5 hours before imaging.[8-11] We conducted the Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial to determine whether treatment with alteplase would improve functional outcomes in patients with an unknown time of stroke onset and a mismatch between diffusion-weighted imaging and FLAIR findings on MRI.[12]

Methods

Trial Design

WAKE-UP was an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled clinical trial involving patients with an unknown time of onset of stroke. All the patients otherwise met the clinical criteria for intravenous thrombolysis. Patients could undergo randomization if in the judgment of the investigator MRI showed an acute ischemic lesion on diffusion-weighted imaging but no parenchymal hyperintensity with standard window settings on FLAIR (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The trial protocol (also available at NEJM.org) was approved by the national regulatory authority in each participating country. The trial was approved by the national or local ethics committee or institutional review board. Patients or their legal representatives provided written informed consent according to national and local regulations. There was an exception from explicit informed consent in emergency circumstances in some countries, as described previously.[13]

The trial, which was supported by the European Union Seventh Framework Program, was performed at 70 centers in eight European countries. Sites were selected if they were experienced stroke research centers, had a history of routine use of alteplase in standard stroke care, and could perform MRI for emergency stroke imaging. Investigators were certified by Web-based training on image interpretation and were certified in the use of the clinical examination scales for entry criteria and outcome assessment. A central image-reading committee reviewed all images acquired for patient enrollment, evaluated the decisions of local investigators regarding imaging inclusion and exclusion criteria, and provided feedback on disagreements on these matters to trial sites.

The trial was overseen by a steering committee and an independent data and safety monitoring board. The authors vouch for the accuracy and completeness of the data and adverse event reporting and for the fidelity of the trial to the protocol. There was no industry funding or involvement in any aspect of the trial.

Patients

Patients were eligible if they presented with clinical signs of acute stroke, were 18 to 80 years of age, and had been able to carry out usual activities in their daily life without support before the stroke. The patient either recognized stroke symptoms on awakening or could not report the timing of the onset of symptoms (e.g., as a result of aphasia or confusion). The time that had elapsed since the patient was last known to be well had to be more than 4.5 hours (with no upper limit) in order to exclude patients who otherwise would have fulfilled the standard eligibility criteria for the use of alteplase. Patients underwent MRI examination that included diffusion-weighted imaging, FLAIR, a sequence sensitive to hemorrhage, and time-of-flight magnetic resonance angiography of the circle of Willis. Patients underwent randomization if they had a mismatch between the presence of an abnormal signal on MRI diffusion-weighted imaging and no visible signal

change on FLAIR in the region of the acute stroke. Patients were excluded if MRI showed intracranial hemorrhage or lesions larger than one third of the territory of the middle cerebral artery. Also excluded from the trial were patients in whom thrombectomy was planned and those with severe stroke, which was defined as a score of more than 25 on the National Institute of Health Stroke Scale (NIHSS), which ranges from 0 to 42, with higher values indicating a greater neurologic deficit. Patients were also excluded if they had generally recognized contraindications to treatment with alteplase (except for the unknown time of symptom onset).[14]

RANDOMIZATION AND TREATMENT

Patients underwent randomization by means of a Web-based procedure with a permuted-block design according to trial center. Patients were assigned in a 1:1 ratio to receive 0.9 mg of alteplase per kilogram of body weight (with 10% administered as a bolus and the remainder by infusion during a 60-minute period) or matching placebo. Randomization was stratified according to age (≤60 or >60 years) and severity of symptoms as assessed on the NIHSS (score, ≤10 or >10). Concomitant treatment and procedures were performed according to the standard of care at each center in compliance with European or national guidelines for acute stroke.[14]

CLINICAL AND IMAGING ASSESSMENT

Clinical assessments were performed at baseline, at 22 to 36 hours after randomization, at 5 to 9 days (or at hospital discharge, if earlier), and at 90 days. Assessments included a recording of demographic characteristics, taking of a medical history, evaluation of laboratory values and scores on the NIHSS, an assessment of disability on the basis of the modified Rankin scale (which ranges from 0 [no symptoms] to 6 [death]), a review of concomitant medications, and an assessment of adverse events. Brain MRI was performed at baseline and 22 to 36 hours after randomization to detect intracranial hemorrhage and to assess infarct volume.

OUTCOME MEASURES

The primary efficacy end point was a favorable clinical outcome, which was defined as a score of 0 or 1 on the modified Rankin scale 90 days after randomization. Secondary efficacy end points were the ordinal score on the modified Rankin scale at 90 days; the proportion of patients with a treatment response at 90 days (defined as a score on the modified Rankin scale of 0 for patients with an NIHSS score of ≤7, a score of 0 or 1 for patients with an NIHSS score of 8 to 14, and a score of 0 to 2 for patients with an NIHSS score of >14); a global outcome score at 90 days, which was defined as a good outcome on four scales (a score of 0 or 1 on the modified Rankin scale and the NIHSS, a score of 95 to 100 on the Barthel Index [which assesses 10 categories of daily function and ranges from 0 to 100, with higher values indicating better independent function], and a score of 5 on the Glasgow Outcome Scale [which ranges from 1 to 5, with higher values indicating better neurologic recovery]); the 90-day score on the Beck Depression Inventory (which ranges from 0 to 63, with higher scores indicating more severe depressive symptoms); 90-day scores on two EuroQol–5 Dimensions (EQ-5D) scales (including a total score that ranges from 0 to 10, with higher values indicating greater problems across five dimensions of self-care and self-assessment of well-being, and a score on a visual analogue scale that ranges from 0 to 100, with higher scores indicating better health); and infarct volume on MRI 22 to 36 hours after randomization.

The primary safety end points were death and a composite outcome of death or dependence, which was defined as a score of 4 to 6 on the modified Rankin scale at 90 days. Secondary safety end points were symptomatic intracranial hemorrhage causing deterioration in neurologic symptoms[2,3,15-17] and the incidence of parenchymal hematoma type 2 (as defined by clots exceeding 30% of the infarct area) on MRI 22 to 36 hours after randomization.[15] The central image-reading board assessed the outcome on MRI at 22 to 36 hours in a blinded manner. Symptomatic intracranial hemorrhage was evaluated by a central safety-adjudication committee whose members were unaware of trial-group assignments.

STATISTICAL ANALYSIS

Primary and secondary efficacy outcomes were assessed in the intention-to-treat population, which included all the patients who had undergone randomization. The primary efficacy outcome was determined with the use of an unconditional logistic-regression model fitted to estimate

the odds ratio and 95% confidence interval.[18] The secondary efficacy outcome of the score on the modified Rankin scale was analyzed by fitting a proportional-odds logistic-regression model to calculate the common odds ratio as a measure of the likelihood that alteplase would lead to lower scores on the modified Rankin scale than would placebo (shift analysis). The global outcome score was analyzed with the use of a global estimate of the odds ratio (Wald-type test) from generalized estimation equations based on a linear logistic-regression model. Odds ratios and common odds ratios were adjusted for stratification factors of age and symptom severity at randomization. Analyses of secondary outcomes were not corrected for multiple comparisons, so the results cannot be used for hypothesis testing or inference. Post hoc Bonferroni-corrected results of secondary outcome analyses were calculated for reference with the P values of secondary outcomes. Missing data in the primary outcome analysis were imputed with the use of multiple imputation techniques (five imputed data sets),[18] with prediction based on trial group, baseline age, baseline NIHSS score, and NIHSS score measured on day 7. Analyses were performed with a two-sided alpha level of 0.05.

The same analyses were repeated in the per-protocol population after the exclusion of all the patients who had major protocol violations. Safety end points were assessed in the safety population with the use of an unconditional logistic-regression model to estimate the odds ratio and 95% confidence intervals associated with treatment effect, after adjustment for the stratification factors used at randomization. In the safety population, patients who received any amount of alteplase were assigned to the alteplase group; all other patients who received any amount of placebo were assigned to the placebo group. The sample-size calculation was based on pooled data from trials of thrombolysis for the treatment of stroke,[19] with an expected absolute between-group difference of 10 percentage points in the proportion of patients with the primary efficacy outcome. We calculated that 370 patients per group would be required to provide a power of 80% to show the expected treatment effect. Taking into account possible protocol violations and dropouts, we intended to enroll 800 patients (400 per trial group).

RESULTS

CHARACTERISTICS OF THE PATIENTS

The steering committee stopped enrollment on June 30, 2017, on the basis of the anticipated cessation of funding from the European Union. The decision to discontinue enrollment was made without an interim analysis of trial data.

From September 24, 2012, to June 30, 2017, a total of 1362 patients underwent screening at 61 centers in eight European countries. Of these patients, 859 were excluded, including 455 who had no mismatch between findings on MRI diffusion-weighted imaging and FLAIR and 15 for whom thrombectomy was planned (Fig. 1). A total of 503 patients underwent randomization, as compared with the anticipated enrollment of 800 patients.

Of the 503 enrolled patients, 254 were assigned to receive alteplase and 249 to receive placebo. Baseline demographic and clinical characteristics, including the interval from the time that the patients were last known to be well until the time of the initiation of treatment, were not significantly different between the groups, except for a higher rate of intracranial occlusion of the internal carotid artery in the alteplase group (Table 1). The median NIHSS score at the time of the baseline examination was 6 in the two groups. The most frequent reason for an unknown time of onset of stroke symptoms was that the patient had awakened from nighttime sleep with stroke symptoms (89% in the two groups). The median time between symptom recognition and administration of alteplase or placebo was 3.1 hours in the alteplase group and 3.2 hours in the placebo group; the median interval between the time that the patient was last known to be well and treatment initiation was 10.3 hours and 10.4 hours, respectively.

A total of 5 patients in the alteplase group and 4 patients in the placebo group did not receive the assigned drug. Of these patients, 1 from each group received open-label treatment with alteplase. Thus, 251 patients who received alteplase and 244 patients who received placebo were included in the safety population. A total of 13 patients in the intention-to-treat population (8 in the alteplase group and 5 in the placebo group) and 10 patients in the safety population (7 in the alteplase group and 3 in the placebo group) were lost to follow-up.

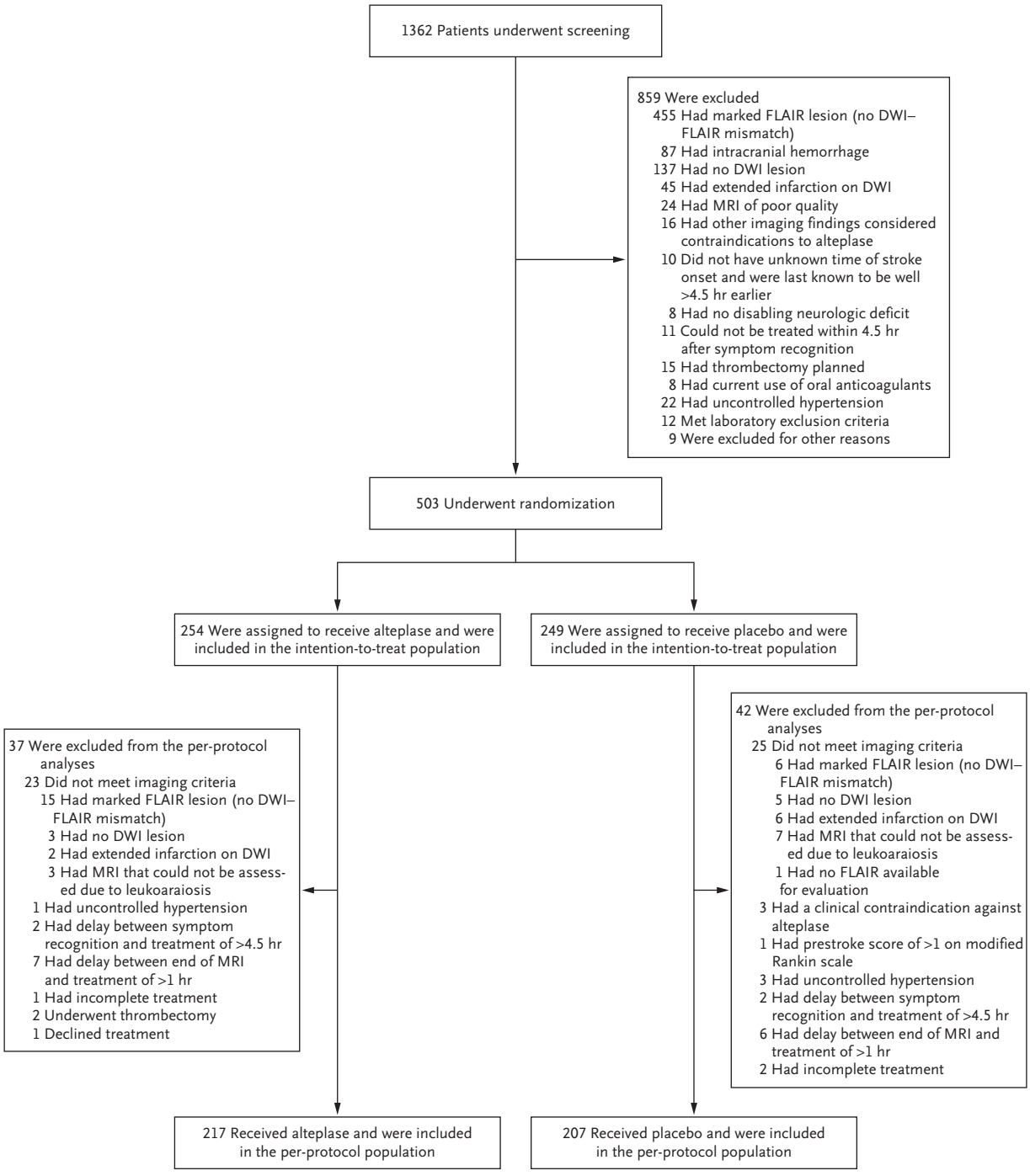

Figure 1. Enrollment and Outcomes.

The intention-to-treat population included all the patients who were randomly assigned to a trial group. The per-protocol population included all the patients who had undergone randomization, who had received alteplase or placebo, and who had not been excluded because of a major protocol violation. DWI denotes diffusion-weighted imaging, FLAIR fluid-attenuated inversion recovery, and MRI magnetic resonance imaging.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Variable	Alteplase Group (N=254)	Placebo Group (N=249)
Mean age ±SD — yr	65.3±11.2	65.2±11.9
Male sex — no. (%)	165 (65.0)	160 (64.3)
Reason for unknown time of symptom onset — no. (%)		
Nighttime sleep	227 (89.4)	222 (89.2)
Daytime sleep	12 (4.7)	11 (4.4)
Aphasia, confusion, or other	15 (5.9)	16 (6.4)
Median interval between last time the patient was known to be well and symptom recognition (IQR) — hr	7.2 (4.7–8.7)	7.0 (5.0–9.0)
Medical history — no. (%)		
Arterial hypertension	135 (53.1)	131 (52.6)
Diabetes mellitus	43 (16.9)	39 (15.7)
Hypercholesterolemia	93 (36.6)	85 (34.1)
Atrial fibrillation	30 (11.8)	29 (11.6)
History of ischemic stroke	37 (14.6)	31 (12.4)
Median NIHSS score (IQR)†	6 (4–9)	6 (4–9)
Vessel occlusion on time-of-flight MRA — no./total no. (%)		
Any	84/249 (33.7)	84/246 (34.1)
Intracranial internal carotid artery	24/249 (9.6)	11/246 (4.5)
Middle cerebral artery main stem	35/249 (14.1)	37/246 (15.0)
Middle cerebral artery branch	32/249 (12.9)	36/246 (14.6)
Other‡	12/249 (4.8)	12/246 (4.9)
Median lesion volume on diffusion-weighted imaging (IQR) — ml	2.0 (0.8–7.9)	2.5 (0.7–8.8)
Median time from symptom recognition to MRI (IQR) — hr	2.6 (1.9–3.3)	2.6 (2.1–3.3)
Median time between end of MRI and treatment initiation (IQR) — min	25 (16–35)	26 (18–37)
Median time from symptom recognition to treatment initiation (IQR) — hr	3.1 (2.5–3.8)	3.2 (2.6–3.9)
Interval between last time that the patient was last known to be well and treatment initiation (IQR) — hr	10.3 (8.1–12.0)	10.4 (8.1–12.1)

* There was no significant difference between the two groups, except for a higher rate of intracranial occlusion of the internal carotid artery in the alteplase group (P=0.03 without adjustment for multiple testing). IQR denotes interquartile range, MRA magnetic resonance angiography, MRI magnetic resonance imaging, and SD standard deviation.
† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating a greater deficit.
‡ Other types include occlusion of the anterior or posterior cerebral artery and the vertebral or basilar artery.

EFFICACY OUTCOMES

Treatment with alteplase was associated with a favorable outcome (a score of 0 or 1 on the modified Rankin scale) at 90 days in 131 of 246 patients (53.3%) in the alteplase group and in 102 of 244 patients (41.8%) in the placebo group (adjusted odds ratio, 1.61; 95% confidence interval [CI], 1.09 to 2.36; P=0.02) (Table 2). Because of the absence of correction for multiple testing, the P values for secondary outcomes cannot be used for hypothesis testing or inference. For reference, post hoc Bonferroni adjustment for multiple comparisons of secondary outcomes required a significance level of P<0.007. The median score on the modified Rankin scale at 90 days was 1 (interquartile range, 1 to 3) in the alteplase group and 2 (interquartile range, 1 to 3) in the placebo group (common odds ratio, 1.62; 95% CI, 1.17 to

Table 2. Primary and Secondary Efficacy Outcomes (Intention-to-Treat Population).*

Outcome	Alteplase Group (N=254)	Placebo Group (N=249)	Effect Variable	Adjusted Value (95% CI)†	P Value
Primary efficacy end point					
Favorable outcome at 90 days — no./total no. (%)‡	131/246 (53.3)	102/244 (41.8)	Odds ratio	1.61 (1.09 to 2.36)	0.02
Secondary efficacy end points					
Median score on modified Rankin scale at 90 days (IQR)§	1 (1 to 3)	2 (1 to 3)	Common odds ratio	1.62 (1.17 to 2.23)	0.003¶
Correlation between treatment response at 90 days and deficit level at baseline — no./total no. (%)‖	72/246 (29.3)	44/244 (18.0)	Odds ratio	1.88 (1.22 to 2.89)	0.004¶
Global Outcome Score at 90 days**			Odds ratio	1.47 (1.07 to 2.04)	0.02¶
Median score on Beck Depression Inventory at 90 days (IQR)††	6.0 (2.0 to 11.0)	7.0 (2.0 to 14.0)	Mean difference ($\log_e$)	–0.04 (–0.22 to 0.15)	0.69¶
Total score on EQ-5D at 90 days‡‡	1.9±2.1	2.4±2.4	Mean difference	–0.52 (–0.88 to –0.16)	0.004¶
Score on visual analog scale on EQ-5D at 90 days§§	72.6±19.7	64.9±23.8	Mean difference	7.64 (3.75 to 11.51)	<0.001¶
Median infarct volume at 22–36 hr (IQR) — ml ¶¶	3.0 (0.8 to 17.7)	3.3 (1.1 to 16.6)	Mean difference ($\log_e$)	–0.16 (–0.47 to 0.15)	0.32¶

* EQ-5D denotes EuroQol–5 Dimensions.
† Odds ratios, common odds ratios, and differences are for the alteplase group, as compared with the placebo group. Odds ratios and common odds ratios were adjusted for stratification factors (i.e., age and symptom severity) at randomization but were not adjusted for multiple comparisons.
‡ A favorable outcome was defined as a score of 0 or 1 on the modified Rankin scale of neurologic disability (which ranges from 0 [no symptoms] to 6 [death]) at 90 days. A total of 8 patients in the alteplase group and 5 in the placebo group were lost to follow-up.
§ The between-group comparison of median scores on the modified Rankin scale was analyzed by means of a logistic-regression model.
¶ P values and confidence intervals for secondary outcomes have not been adjusted for multiple comparisons and cannot be used for hypothesis testing or inference. The values are shown for reference to a post hoc calculation of a P value adjusted for seven secondary outcome comparisons. Post hoc adjustment for multiple comparisons of secondary outcomes by means of the Bonferroni method required a significance level of P<0.007.
‖ A correlation between the treatment response at 90 days and the deficit level at baseline was defined as a score of 0 on the modified Rankin scale among patients with mild deficits at study entry (NIHSS score, ≤7), a score of 0 or 1 among patients with moderate deficits (NIHSS score, 8 to 14), and a score of 0 to 2 among patients with severe deficits (NIHSS score, >14).
** The Global Outcome Score is a multidimensional calculation of a favorable outcome that combines the estimation of treatment effect on four different scales into a single odds ratio, so there is no corresponding global numerator. The four measures are a score or 0 or 1 on the modified Rankin scale and on the NIHSS, a score of 95 to 100 on the Barthel Index (which assesses 10 categories of daily function and ranges from 0 to 100, with higher values indicating better independent function), and a score of 5 on the Glasgow Outcome Scale (which ranges from 1 to 5, with higher values indicating better neurologic recovery).
†† Scores on the Beck Depression Inventory range from 0 to 63, with higher scores indicating more severe depressive symptoms.
‡‡ Total scores on the EQ-5D scale range from 0 to 10, with higher values indicating more problems across the five dimensions of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.
§§ Scores on the EQ-5D visual analog scale range from 0 (indicating the worst imaginable health state) to 100 (indicating the best imaginable health state).
¶¶ The infarct volume was measured on diffusion-weighted imaging 22 to 36 hours after randomization. The final infarct volume was missing for 27 patients in the alteplase group and 15 in the placebo group.

2.23; unadjusted P=0.003) (Fig. 2). The proportion of patients who had a treatment response at 90 days that was defined in relation to the severity of stroke at baseline was higher in the alteplase group than in the placebo group (72 of 246 patients [29.3%] and 44 of 244 patients [18.0%], respectively). Measures of quality of life at 90 days (including the scores on two EQ-5D scales) numerically favored treatment with alteplase, but the infarct volume at 22 to 36 hours after randomization was similar in the two groups (3 ml in the alteplase group and 3.3 ml in the placebo group), and the global outcome scores were numerically similar (Table 2). The effect of alteplase on the global outcome score was not significant after correction for multiple testing.

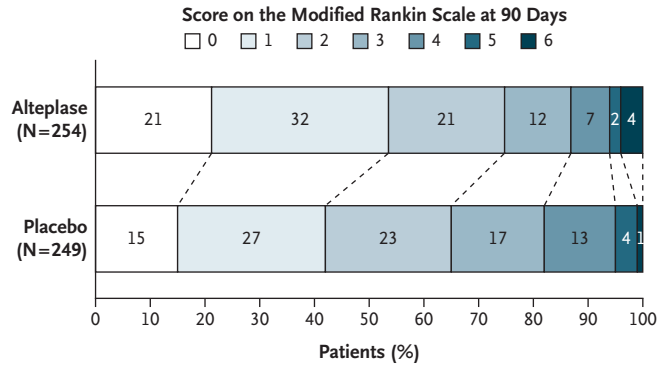

Figure 2. Distribution of Scores on the Modified Rankin Scale at 90 Days (Intention-to-Treat Population).

Shown are the differences in the scores on the modified Rankin scale among patients in the alteplase group and the placebo group at 90 days. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Numbers indicate rounded proportions. There was a significant difference favoring the alteplase group over the placebo group in the overall distribution of scores (adjusted common odds ratio, 1.62; 95% confidence interval, 1.17 to 2.23; P=0.003).

In the per-protocol population, treatment with alteplase was associated with an adjusted odds ratio of the primary efficacy outcome of 1.54 (95% CI, 1.02 to 2.32; P=0.04) (Table S1 in the Supplementary Appendix).

SAFETY OUTCOMES

In the safety population at 90 days, death or an inability to live independently (score on the modified Rankin scale, 4 to 6) occurred in 33 of 244 patients (13.5%) in the alteplase group and 44 of 241 patients (18.3%) in the placebo group (adjusted odds ratio, 0.68; 95% CI, 0.39 to 1.18; P=0.17) (Table 3). Death was reported in 10 patients (4.1%) in the alteplase group and in 3 patients (1.2%) in the placebo group (adjusted odds ratio, 3.38; 95% CI, 0.92 to 12.52; P=0.07). In the alteplase group, 4 deaths were attributed to symptomatic intracranial hemorrhage and 1 to recurrent ischemic stroke 12 days after treatment. The other 5 deaths were attributed to noncerebral causes unrelated to the initial stroke or treatment. In one of the patients who died from symptomatic intracranial hemorrhage, the central image-reading board determined that the initial lesion volume exceeded one third of the territory of the middle cerebral artery, which constituted a violation of the protocol for inclusion in the trial. A second patient who died had uncontrolled hypertension within the first hours after treatment. The other 2 patients who died from symptomatic intracranial hemorrhage had been treated according to the protocol.

Parenchymal hemorrhage type 2 occurred more frequently in the alteplase group (4.0%) than in the placebo group (0.4%; adjusted odds ratio, 10.46; 95% CI, 1.32 to 82.77; P=0.03). No significant difference between groups was observed for various definitions of symptomatic intracranial hemorrhage, although the frequency of such events was higher in the alteplase group (Table 3). The rate of symptomatic intracranial hemorrhage according to the definition of the Safe Implementation of Thrombolysis in Stroke Monitoring Study[16] was 2.0% in the alteplase group versus 0.4% in the placebo group (P=0.15). Recurrent symptomatic ischemic stroke and space-occupying brain infarction were more frequent with alteplase than with placebo (6.8% vs. 3.3% for recurrent symptomatic stroke and 2.4% vs. 0.8% for brain infarction).

In the alteplase group, 56 patients (22.3%) had at least one serious adverse event, as compared with 52 patients (21.3%) in the placebo group (P=0.83). Serious adverse events in the category of nervous system disorders, which included symptomatic intracranial hemorrhage and recurrent stroke, were more frequent with alteplase than with placebo (13.5% vs. 8.6%). A detailed list of serious adverse events is provided in Table S4 in the Supplementary Appendix.

ANALYSIS OF PRESPECIFIED SUBGROUPS

Early discontinuation of the trial did not provide adequate statistical power to analyze differences in subgroups. No evidence of heterogeneity of treatment effect was detected in the two prespecified subgroups of age and severity of stroke as assessed on the NIHSS (Fig. S2 in the Supplementary Appendix).

DISCUSSION

In this trial involving patients with an unknown time of onset of stroke who presented with MRI findings of an ischemic lesion on diffusion-weighted imaging but no clearly visible signal change in the corresponding region on FLAIR,

Table 3. Safety Outcomes.

Outcome	Alteplase Group (N=251)	Placebo Group (N=244)	Adjusted Odds Ratio (95% CI)*	P Value
	no. (%)			
Primary†				
Death or dependency at 90 days	33 (13.5)	44 (18.3)	0.68 (0.39–1.18)	0.17
Death at 90 days	10 (4.1)	3 (1.2)	3.38 (0.92–12.52)	0.07
Secondary				
Symptomatic intracranial hemorrhage				
As defined in SITS-MOST‡	5 (2.0)	1 (0.4)	4.95 (0.57–42.87)	0.15
As defined in ECASS II§	7 (2.8)	3 (1.2)	2.40 (0.60–9.53)	0.21
As defined in ECASS III¶	6 (2.4)	1 (0.4)	6.04 (0.72–50.87)	0.10
As defined in NINDS‖	20 (8.0)	12 (4.9)	1.78 (0.84–3.71)	0.13
Parenchymal hemorrhage type 2**	10 (4.0)	1 (0.4)	10.46 (1.32–82.77)	0.03
Other††				
Space-occupying brain infarction or edema with clinical deterioration	6 (2.4)	2 (0.8)		
Recurrent ischemic stroke				
Asymptomatic‡‡	58 (23.1)	55 (22.5)		
Symptomatic	17 (6.8)	8 (3.3)		
Major extracranial bleeding	3 (1.2)	0		
Severe anaphylactic reaction	0	1 (0.4)		

* Odds ratios were adjusted for the stratification factors (i.e., age and symptom severity) at randomization.
† The primary safety outcome was analyzed in 244 patients in the alteplase group and in 241 in the placebo group because of loss to follow-up.
‡ The definition of symptomatic intracranial hemorrhage according to the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS–MOST) 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.
§ The definition according to the European Cooperative Acute Stroke Study (ECASS) II 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.
¶ The definition according to ECASS III was the same as that in ECASS II, plus the hemorrhage must have been identified as the predominant cause of the neurologic deterioration.
‖ The definition according to the National Institute of Neurological Disorders and Stroke (NINDS) was any new hemorrhage associated with any neurologic deterioration.
** Parenchymal hemorrhage type 2 was defined as an intracerebral hemorrhage that involved more than 30% of the infarcted area with a substantial space-occupying effect or that was remote from the original infarcted area.
†† Other safety outcomes were determined by the safety adjudication committee on the basis of the evaluation of clinical and imaging information. Odds ratios and P values were not calculated for these comparisons.
‡‡ Asymptomatic recurrent stroke was defined as any new lesion on follow-up MRI that was not considered to be a growth of the original stroke lesion.

the functional outcome at 90 days was more favorable among the patients who received intravenous thrombolysis with alteplase than among those who received placebo. This MRI mismatch pattern was chosen because it suggests that the stroke occurred within approximately the previous 4.5 hours, the accepted interval for treatment with thrombolysis. In this selected group of patients with stroke, those in the alteplase group had a rate of freedom from neurologic deficit or major disability that was 11.5 percentage points higher than that in the placebo group at 90 days. Intravenous alteplase was associated with numerically better scores on the modified Rankin scale and with a shift toward better outcomes in all categories on the scale than was placebo.

Since we enrolled patients with an unknown time of symptom onset, they would have been excluded from most previous trials of thrombolysis involving patients with stroke. A pooled analysis of previous trials of intravenous thrombolysis showed a time-dependent effect of drug administration on outcome, with a significant benefit for alteplase within 4.5 hours after symptom onset.[1] In our trial, patients were selected on the basis of mismatch between findings on MRI diffusion-weighted imaging and FLAIR.[11,12] Interobserver agreement for this combination of findings was 73 to 78% in two previous studies.[11,20] The presence of intracranial-artery occlusion or penumbral pattern before thrombolysis was not a prerequisite for randomization in the trial, and we did not assess recanalization or reperfusion as a biologic marker of treatment effectiveness.

Approximately two thirds of the patients who were screened in our trial did not undergo randomization, mainly because they did not have the mismatch pattern of recent stroke on MRI required for enrollment. The exclusion of patients who planned to undergo thrombectomy limits the generalization of our findings. It is possible that some patients with severe stroke from large-vessel occlusion in the anterior circulation were not enrolled in our trial and were treated with thrombectomy outside the trial. We have no systematic information on the availability of endovascular thrombectomy in the centers that participated in the trial, and the inception of these services changed during the conduct of the trial as a result of studies that showed a benefit for thrombectomy in patients with stroke with large-vessel occlusion on the basis of various imaging characteristics. The results of two clinical trials, DAWN (DWI [Diffusion-Weighted Imaging] or CTP [Computed Tomographic Perfusion] Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo)[21] and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke),[22] showed a benefit for mechanical thrombectomy in patients with stroke with an unknown time of symptom onset, severe stroke, and large-vessel occlusion and became available after enrollment in our trial was stopped. In our trial, approximately 20% of the patients had an occlusion of a large intracranial artery and would have qualified for treatment with thrombectomy in DAWN and DEFUSE 3.

Our trial provides evidence of benefit from reperfusion treatment with alteplase in patients with minor or moderate stroke who would not usually be eligible for endovascular treatment. The treatment effect of alteplase among patients with mild or moderate stroke of the type included in our trial is consistent with a pooled analysis of thrombolysis trials, which did not show a significant difference in the efficacy of alteplase treatment depending on stroke severity.[23]

There were numerically more deaths and significantly more patients with type 2 parenchymal hemorrhage in the alteplase group than in the placebo group. This finding was similar to that in a pooled analysis of stroke thrombolysis trials that showed a trend toward an increased rate of death associated with alteplase treatment.[19,21] The incidence of symptomatic intracranial hemorrhage was higher in the alteplase group in our trial regardless of the definition used to denote this complication, which was consistent with the findings of previous trials of thrombolysis for the treatment of stroke.[21] The trial was stopped early because of a discontinuation of funding and enrolled fewer patients than planned. This factor limits the interpretation of the safety results because the observed trend toward a higher rate of death in the alteplase group may have become significant with a larger sample size.

The analysis in prespecified subgroups did not reveal heterogeneity in treatment effect according to the score (≤10 or >10) on the NIHSS. However, the small number of patients with an NIHSS score of more than 10 limits the validity

of the subgroup analysis. Despite the clinical benefit of alteplase, the infarct volume on MRI at 22 to 36 hours after randomization was not significantly different between the two trial groups. This finding is similar to the results of DEFUSE 3,[23] in which the clinical benefit of thrombectomy was not reflected by a smaller infarct volume at 24 hours.

In conclusion, among patients with acute stroke and an unknown time of symptom onset who had MRI findings of an ischemic lesion on diffusion-weighted imaging but no parenchymal hyperintensity in the corresponding region on FLAIR, intravenous thrombolysis with alteplase resulted in a better functional outcome than treatment with placebo.

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APPENDIX

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