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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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.
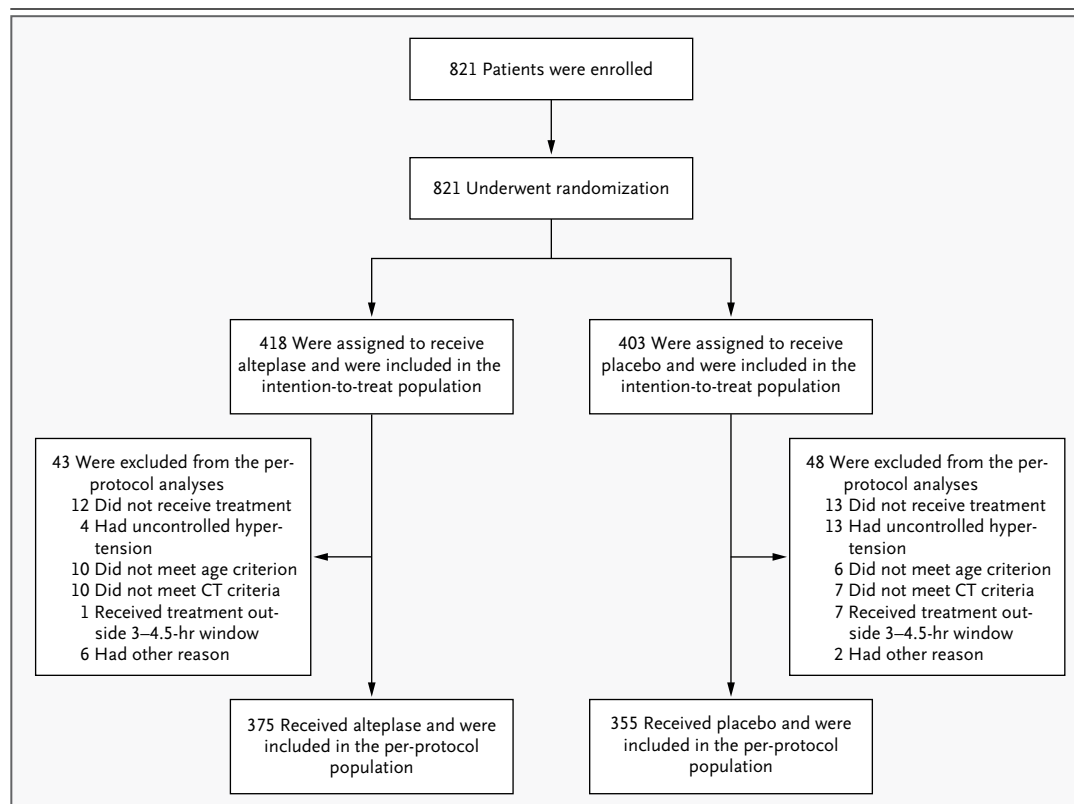
METHODS

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

                        821 Underwent randomization


    418 Were assigned to receive          403 Were assigned to receive
    alteplase and were included in the    placebo and were included in the
    intention-to-treat population         intention-to-treat population


43 Were excluded from the per-            48 Were excluded from the per-
    protocol analyses                        protocol analyses
12 Did not receive treatment             13 Did not receive treatment
 4 Had uncontrolled hyper-               13 Had uncontrolled hyper-
    tension                                  tension
10 Did not meet age criterion             6 Did not meet age criterion
10 Did not meet CT criteria               7 Did not meet CT criteria
 1 Received treatment out-                7 Received treatment out-
    side 3–4.5-hr window                      side 3–4.5-hr window
 6 Had other reason                       2 Had other reason


    375 Received alteplase and were       355 Received placebo and were
    included in the per-protocol          included in the per-protocol
    population                            population
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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 ($\leq$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

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	

Table 2. Demographic and Baseline Characteristics of the Patients.

* 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)	Placebo Group (N=403)	Odds Ratio (95% CI)	P Value	Alteplase Group (N=375)	Placebo Group (N=355)	Odds Ratio (95% CI)	P Value
	no. (%)				no. (%)			
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.
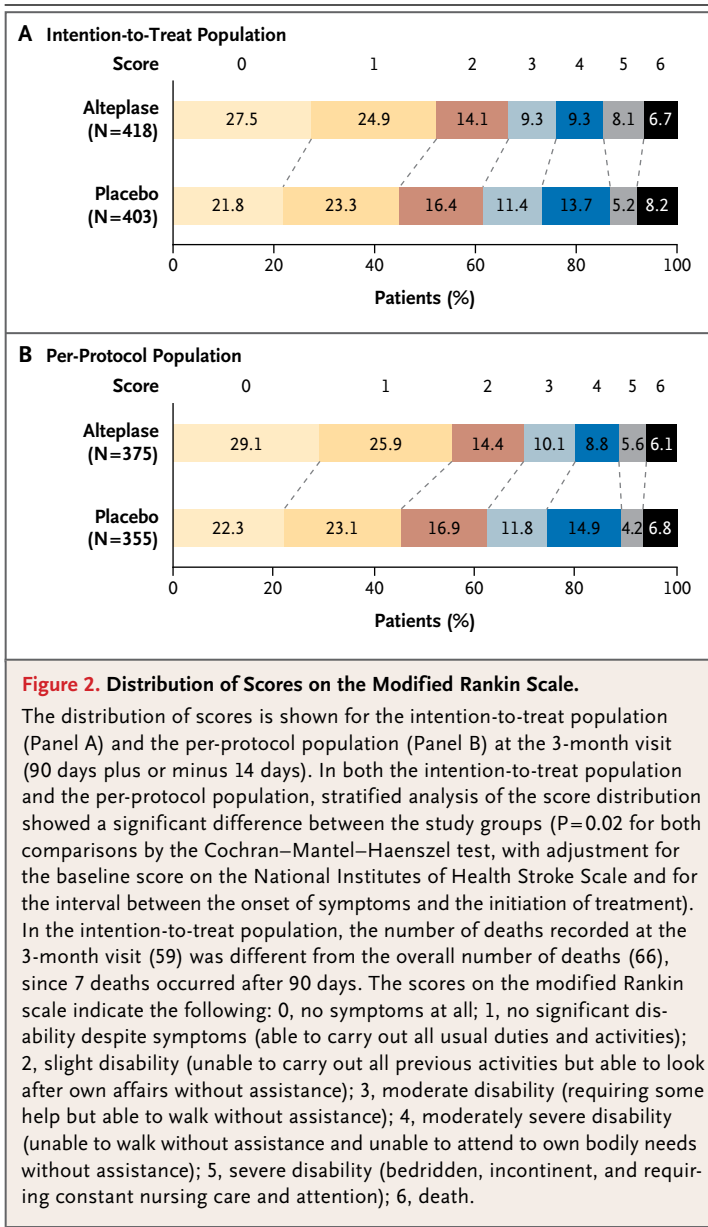§ P value was obtained by stepwise logistic regression.
¶ The global outcome analysis is a multidimensional calculation of a favorable outcome, defined by several individual outcome scales and entered into a statistical algorithm. This statistical approach is a global odds-ratio test based on a linear 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.

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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	Favorable Outcome with Alteplase as Compared with Placebo							
	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); *Norway* (14): 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.

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