Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

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ABSTRACT

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

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.)
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 Neuro-
logical 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 throm-
bolysis treatment, as defined by each trial.2,3
A subsequent analysis of the NINDS study4
and the combined analysis5 of data from six ran-
domized trials,1-3,6,7 which investigated throm-
bolysis treatment for ischemic stroke in a total
of 2775 patients, showed a clear association be-
tween treatment efficacy and the interval between
the onset of symptoms and administration of the
thrombolytic agent. In the pooled analysis, a fa-
vorable 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 alte-
plase 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 symp-
tomatic intracranial hemorrhage or death.5 In-
ternational 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 coun-
tries, primarily because of delayed admission to
a stroke center.11
Thrombolysis with alteplase has been approved
in most countries. In Europe, the European Medici-
ies 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 con-
ﬁrmed that alteplase is as safe and effective in
routine clinical practice as it is in randomized
trials.12 The second request was that a random-
ized trial be conducted in which the therapeutic
time window was extended beyond 3 hours.
We describe the results of ECASS III, a ran-
domized, placebo-controlled, phase 3 trial de-
dsigned 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 hemor-
rhage or major ischemic infarction. In some cases,
magnetic resonance imaging (MRI) was per-
formed 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 admin-
istered up to 4.5 hours after the onset of symp-
toms,5 and a slow rate of patient recruitment.
The trial protocol and the amendments were ac-
cepted by the EMEA and were approved by the
institutional review boards of the participating
centers. All patients or legally authorized repres-
entatives 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 sys-
tem was used, with randomization at centers
performed in blocks of four to ensure a balanced
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
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.
reflecting more severe cerebral infarcts (<5, mild impairment; ≥25, very severe neurologic impairment). 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, 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. During the follow-up period, two other commonly used functional scales were also applied: the Barthel Index and the Glasgow Outcome Scale. The Barthel Index, which assesses the ability to perform activities of daily living, on a scale that ranges from 0 (total 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 MRJ 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 MRJ scans, classified the findings according to the ECASS morphologic definitions, 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 unfavorable 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. 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.

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.

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) 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.

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 (with data from the first ECASS trial 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.

### Table 2. Demographic and Baseline Characteristics of the Patients.

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

* 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 5 patients in the placebo group.

### 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 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.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Intention-to-Treat Population</th>
<th>Per-Protocol Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alteplase Group (N = 418)</td>
<td>Placebo Group (N = 403)</td>
</tr>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS score of 0 or 1 — unadjusted analysis</td>
<td>219 (52.4)</td>
<td>182 (45.2)</td>
</tr>
<tr>
<td>mRS score of 0 or 1 — adjusted analysis‡</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Secondary end point</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global outcome¶</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>mRS score of 0 or 1‖</td>
<td>219 (52.4)</td>
<td>182 (45.2)</td>
</tr>
<tr>
<td>Barthel Index score ≥95˝**</td>
<td>265 (63.4)</td>
<td>236 (58.6)</td>
</tr>
<tr>
<td>NIHSS score of 0 or 1††</td>
<td>210 (50.2)</td>
<td>174 (43.2)</td>
</tr>
<tr>
<td>GOS score of 1‡‡</td>
<td>213 (51.0)</td>
<td>183 (45.4)</td>
</tr>
</tbody>
</table>

* 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.
The distribution of scores is shown for the intention-to-treat population (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 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).

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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) 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.

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**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.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Day 90</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS score of 0 or 1†</td>
<td>1.34 (1.02–1.76)</td>
<td>1.30 (0.95–1.78)</td>
</tr>
<tr>
<td>mRS score of 0–2</td>
<td>1.30 (0.95–1.78)</td>
<td>1.23 (0.93–1.62)</td>
</tr>
<tr>
<td>Barthel Index score ≥95‡</td>
<td>1.23 (0.93–1.62)</td>
<td>1.33 (0.99–1.80)</td>
</tr>
<tr>
<td>NIHSS score of 0 or 1, or &gt;8-point improvement from baseline§</td>
<td>—</td>
<td>1.35 (1.02–1.78)</td>
</tr>
</tbody>
</table>

*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. The results of these analyses were prespecified. The NIHSS score of 0 or 1, or >8-point improvement from baseline was prespecified for day 90 only, and no data for that time point were collected.

†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).

‡Scores on the modified Rankin scale range from 0 (no symptoms at all) to 6 (death).

§Scores on the Barthel Index range from 0 (inability to perform activities of daily living) to 100 (independence).
**Table 5. Prespecified Safety End Points and Other Serious Adverse Events.**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Alteplase Group (N = 418)</th>
<th>Placebo Group (N = 403)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prespecified safety end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any ICH</td>
<td>113 (27.0)</td>
<td>71 (17.6)</td>
<td>1.73 (1.24–2.42)</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to ECASS III definition†</td>
<td>10 (2.4)</td>
<td>1 (0.2)</td>
<td>9.85 (1.26–77.32)</td>
<td>0.008</td>
</tr>
<tr>
<td>According to ECASS II definition‡</td>
<td>22 (5.3)</td>
<td>9 (2.2)</td>
<td>2.43 (1.11–5.35)</td>
<td>0.02</td>
</tr>
<tr>
<td>According to SITS–MOST definition§</td>
<td>8 (1.9)</td>
<td>1 (0.2)</td>
<td>7.84 (0.98–63.00)</td>
<td>0.02</td>
</tr>
<tr>
<td>According to NINDS definition¶</td>
<td>33 (7.9)</td>
<td>14 (3.5)</td>
<td>2.38 (1.25–4.52)</td>
<td>0.006</td>
</tr>
<tr>
<td>Fatal ICH</td>
<td>3 (0.7)</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Symptomatic edema</td>
<td>29 (6.9)</td>
<td>29 (7.2)</td>
<td>0.96 (0.56–1.64)</td>
<td>0.89</td>
</tr>
<tr>
<td>Death</td>
<td>32 (7.7)</td>
<td>34 (8.4)</td>
<td>0.90 (0.54–1.49)</td>
<td>0.68</td>
</tr>
<tr>
<td>Other serious adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>105 (25.1)</td>
<td>99 (24.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>16 (3.8)</td>
<td>23 (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>4 (1.0)</td>
<td>3 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic</td>
<td>0</td>
<td>2 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>0</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic and nutritional</td>
<td>2 (0.5)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>3 (0.7)</td>
<td>4 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>60 (14.4)</td>
<td>48 (11.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>1 (0.2)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>22 (5.3)</td>
<td>16 (4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>10 (2.4)</td>
<td>10 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>14 (3.3)</td>
<td>24 (6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5 (1.2)</td>
<td>8 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>3 (0.7)</td>
<td>3 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>1 (0.2)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1 (0.2)</td>
<td>3 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>4 (1.0)</td>
<td>2 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system</td>
<td>1 (0.2)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td>0</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>1 (0.2)</td>
<td>3 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated with injury</td>
<td>4 (1.0)</td>
<td>5 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>1 (0.2)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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 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.1,2,3,6,24 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 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


REFERENCES


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