Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits
The PRISMS Randomized Clinical Trial

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IMPORTANCE More than half of patients with acute ischemic stroke have minor neurologic deficits (National Institutes of Health Stroke Scale [NIHSS] score of 0-5) at presentation. Although prior major trials of alteplase included patients with low NIHSS scores, few without clearly disabling deficits were enrolled.

OBJECTIVE To evaluate the efficacy and safety of alteplase in patients with NIHSS scores of 0 to 5 whose deficits are not clearly disabling.

DESIGN, SETTING, AND PARTICIPANTS The PRISMS trial was designed as a 948-patient, phase 3b, double-blind, double-placebo, multicenter randomized clinical trial of alteplase compared with aspirin for emergent stroke at 75 stroke hospital networks in the United States. Patients with acute ischemic stroke whose deficits were scored as 0 to 5 on the NIHSS and judged not clearly disabling and in whom study treatment could be initiated within 3 hours of onset were eligible and enrolled from May 30, 2014, to December 20, 2016, with final follow-up on March 22, 2017.

INTERVENTIONS Participants were randomized to receive intravenous alteplase at the standard dose (0.9 mg/kg) with oral placebo (n = 156) or oral aspirin, 325 mg, with intravenous placebo (n = 157).

MAIN OUTCOMES AND MEASURES The primary outcome was the difference in favorable functional outcome, defined as a modified Rankin Scale score of 0 or 1 at 90 days via Cochran-Mantel-Haenszel test stratified by pretreatment NIHSS score, age, and time from onset to treatment. Because of early termination of the trial, prior to unblinding or interim analyses, the plan was revised to examine the risk difference of the primary outcome by a linear model adjusted for the same factors. The primary safety end point was symptomatic intracranial hemorrhage (sICH) within 36 hours of intravenous study treatment.

RESULTS Among 313 patients enrolled at 53 stroke networks (mean age, 62 [SD, 13] years; 144 [46%] women; median NIHSS score, 2 [interquartile range {IQR}, 1-3]; median time to treatment, 2.7 hours [IQR, 2.1-2.9]), 281 (89.8%) completed the trial. At 90 days, 122 patients (78.2%) in the alteplase group vs 128 (81.5%) in the aspirin group achieved a favorable outcome (adjusted risk difference, −1.1%; 95% CI, −9.4% to 7.3%). Five alteplase-treated patients (3.2%) vs 0 aspirin-treated patients had sICH (risk difference, 3.3%; 95% CI, 0.8%-7.4%).

CONCLUSIONS AND RELEVANCE Among patients with minor nondisabling acute ischemic stroke, treatment with alteplase vs aspirin did not increase the likelihood of favorable functional outcome at 90 days. However, the very early study termination precludes any definitive conclusions, and additional research may be warranted.

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ild stroke is the most commonly cited reason for nonuse of intravenous alteplase among patients with ischemic stroke who present to the hospital within the guideline-based eligible treatment window of 4.5 hours. Yet prospective data suggest that 30% of such patients have functional disability at 90 days after stroke. Reasons for the development of disability might include underappreciated deficits, stroke progression, or medical comorbidities leading to additional medical events, including recurrent stroke. Vessel reperfusion may avert disability because of the first 2 of these reasons. Clinical use of alteplase for ischemic stroke with low National Institutes of Health Stroke Scale (NIHSS) scores has increased in recent years, presumably based on concern for this substantial post-stroke disability.

Although alteplase is the standard of care for patients with ischemic stroke and disabling deficits regardless of severity judged by NIHSS scores, the optimal management of patients with not clearly disabling deficits is unclear. Most major trials of alteplase (NINDS Parts 1 and 2; ECASS 1, 2, and 3; Atlantis Parts A and B; and EPITHET) explicitly excluded varying subsets of patients with the mildest deficits (see eTable 1 in Supplement 1 for exclusion criteria). The IST 3 trial permitted enrollment of patients with minor deficits, but only when the local enrolling physician had personal equipoise regarding benefit and without collecting data to distinguish which enrolled patients had disabling vs nondisabling deficits at presentation. In the absence of definitive evidence, current US clinical guidelines indicate uncertainty regarding use of alteplase in patients with low NIHSS scores and nondisabling deficits (strength of recommendation class IIb [weak]; quality of evidence level C-LD [limited data]).

The purpose of this study was to test the efficacy and safety of alteplase administered within 3 hours of onset of ischemic stroke symptoms among patients presenting with minor deficits (NIHSS score of 0-5) judged not clearly disabling at presentation.

Methods

Trial Design

The study was approved by institutional review boards for all study sites, and all enrolled patients provided written informed consent. The protocol, protocol amendment, and statistical analysis plan are provided in Supplement 2, Supplement 3, and Supplement 4, and detailed methods have been published. The Potential of rtPA for Ischemic Strokes With Mild Symptoms (PRISMS) trial was designed as a phase 3b, randomized, double-blind clinical trial testing the safety and efficacy of intravenous alteplase administered within 3 hours of symptom onset (time from witnessed onset or time from last known well time if unwitnessed). The time window of 3 hours was chosen to harmonize with the US Food and Drug Administration-labeled time window for use of alteplase in patients with disabling ischemic stroke.

Key Points

Question Does intravenous alteplase benefit patients with ischemic stroke presenting with minor neurologic deficits that are judged not clearly disabling?

Findings In this randomized clinical trial that included 313 of a planned 948 patients with acute ischemic stroke, there was no significant difference in the adjusted percentage with favorable functional outcome at 90 days for those treated with alteplase vs aspirin (78% vs 81%).

Meaning Although the study did not demonstrate a significant benefit of alteplase for patients with minor nondisabling acute ischemic stroke, the very early study termination precludes any definitive conclusions.

Patient Selection and Randomization

Inclusion criteria included clinical diagnosis of acute ischemic stroke, age 18 years or older, NIHSS score of 0 to 5, and deficits judged not to be clearly disabling at presentation. The study did not demonstrate a significant difference in the adjusted percentage with favorable functional outcome at 90 days for those treated with alteplase vs aspirin (78% vs 81%).

Study Intervention

Participants were randomized to receive either intravenous alteplase at standard dosing for ischemic stroke (0.9 mg/kg) with a placebo oral aspirin or oral aspirin, 325 mg, with placebo intravenous alteplase. The placebos were identical in appearance to active study drugs to maintain treatment blinding of
patients and investigators. Intravenous study treatment was to be administered within 3 hours of stroke onset. The same was encouraged for the oral study treatment; however, it could be administered up to 24 hours after symptom onset at institutions that required formal swallow evaluation. Clinical management after study treatment administration was to be in accordance with institutional protocols and clinical guidelines for care after alteplase administration. The study mandated follow-up neuroimaging (computed tomography or magnetic resonance imaging per institutional standard of care) within 22 to 36 hours after intravenous study treatment bolus.

**Study Outcomes**

The primary outcome end point was a modified Rankin Scale (mRS) score of 0 or 1 (total range, 0 [symptom free] to 6 [dead]), reflecting favorable functional outcome, evaluated at 90 days after enrollment and adjusted for age, time from symptom onset to treatment, and baseline NIHSS score.

Secondary outcome measures of efficacy, also assessed at 90 days, consisted of level of disability (assessed by the 6-level ordinal mRS score, collapsing levels 5 and 6) and global favorable recovery, which was defined as an mRS score of 0 or 1, NIHSS score of 0 or 1, Barthel Index of 95 or 100 (total range, 0 [totally dependent] to 100 [patient performs self-care and mobility without assistance]), and Glasgow Outcome Scale score of 1 (total range, 1 [good recovery] to 5 [death]).

Exploratory outcome measures of efficacy included ambulatory speed (10-Meter Walk Test), which assesses comfortable walking speed over 6 m; stroke-related quality of life (Stroke Impact Scale 16) score, which ranges from 0 to 100, with higher scores indicating better physical performance (strength, hand function, physical and instrumental activities of daily living, and mobility); and general health-related quality of life (EuroQoL Group EQ-5D) score, which ranges from 0 (death) to 1 (perfect health) at 90 days. Cognitive outcomes and a brief depression assessment were also assessed (results not presented in this article).

**Data Collection and Monitoring**

Key clinical and radiological data were collected, including (1) baseline neuroimaging and NIHSS score; (2) 22- to 36-hour repeat neuroimaging and NIHSS score; (3) 5-day (or discharge if sooner) NIHSS score, stroke etiology, and discharge location; (4) 30-day mRS score by telephone follow-up; and (5) final 90-day mRS score, along with secondary and exploratory outcomes, assessed in person when possible. Ethnicity and race were self-reported (fixed categories) and were collected to consider the generalizability of the results. All adverse events, regardless of relationship to study treatment, were reported until 30 days after study treatment administration. After 30 days, only data on serious adverse events, nonserious adverse events of special interest (consisting of sICH events not otherwise reported, stroke recurrence, or suspected transmission of an infectious agent via a medicinal product), and adverse events resulting in withdrawal from the study were collected. Concomitant medication use was recorded at all visits.

Study monitors performed ongoing source data verification. An independent data monitoring committee, composed of 1 stroke neurologist, 1 emergency physician, 1 neuroradiologist, and 1 statistician, provided ongoing review of accumulating adverse events. The independent data monitoring committee was also charged with conducting the interim futility analysis, planned to take place after 50% of participants had completed follow-up. Two independent, blinded neuroradiologists at the central imaging core interpreted relevant imaging data.

Determination of presenting events as either ischemic cerebral events (stroke or transient ischemic attack) or neurovascular mimic was carried out by site investigators. For patients with neuroimaging evidence of new infarction, site investigators’ diagnoses of ischemic stroke were accepted without further review. For patients without neuroimaging evidence of new infarction, central review was performed by steering committee neurologists (P.K. and J.G.R.) prior to database lock and without unblinding, independently rendering diagnoses of ischemic cerebral event or neurovascular-mimicking condition. When assessments were discordant, discussions were held between the site investigator and central reviewer to ensure that all relevant data were considered in the final determination. The site principal investigators then made a final diagnostic determination.

**Statistical Analysis**

The trial was designed to detect a 9% absolute difference in the proportion of participants with favorable outcome with 80% power, using a 1-sided type I error rate of .025 to test the superiority hypothesis, under the assumption that 65% of participants randomized to receive aspirin would experience a favorable outcome, and allowing for 1 interim futility analysis. The sample size calculation was 1-sided to reflect the objective of establishing the superiority of alteplase over standard medical care. Accounting for these assumptions, the necessary sample size was calculated to be 856 participants. The sample size was adjusted to 948 participants to account for dilution of the treatment effect associated with nonadherence parameters (loss to follow-up, treatment crossovers, and neurovascular mimics [stroke and transient ischemic attack]). The planned 9% effect size was derived from a previously published post hoc analysis of the IST-3 trial subset of patients that met the PRISMS trial’s eligibility criteria (with the exception that qualifying deficits could not be ascertained as not clearly disabling). The steering committee expected that treatment effects of less than 9% were still likely to be clinically meaningful. It was anticipated that a higher rate of favorable outcome in participants randomized to aspirin and a lower rate
of nonadherence parameters would allow detection of a lower absolute treatment effect with the same 80% power.

The trial initially intended to test the primary end point via a Cochran-Mantel-Haenszel hypothesis test, stratified by age (<65 vs ≥65 years), time from symptom onset to treatment (0-2 vs >2 hours), and pretreatment NIHSS score (0-2 vs 3-5). Because the trial was terminated early by the sponsor for enrollment below target, it was recognized that the study would be underpowered to formally test the hypothesis. Therefore, the statistical analysis plan was finalized, prior to database lock and unblinding, to evaluate the size of an effect (and its associated uncertainty). The updated plan was to evaluate the hypothesis by examining the adjusted risk difference (point values and 95% CIs) in the rate of the primary outcome (mRS score of 0 or 1) using a linear model, which included treatment assignment, age, time from symptom onset to study treatment, and baseline NIHSS score as continuous covariates.

A sensitivity analysis confined to patients with final diagnoses of acute cerebral ischemia was also planned. Additional exploratory analyses of the primary outcome were pre-specified to test the consistency of the findings: (1) unadjusted risk difference; (2) logistic regression, adjusting for pretreatment NIHSS score, age, and time to treatment; (3) risk difference adjusted for additional potential covariate imbalances using a propensity score; and (4) repeated-measures model (in which mRS score outcomes at day 30 and day 90 were modeled jointly by a logistic regression).

Missing primary outcome data (90-day mRS scores) were prespecified for imputation with the 30-day mRS score result, when available, and otherwise imputed via hot-deck method, which randomly selected the outcome value from a pool of patients with observed mRS scores matched by treatment group, age, pretreatment NIHSS score, and time of symptom onset.

The secondary outcome of ordinal analysis was achieved by fitting a proportional odds model with mRS score at day 90 as the dependent variable and treatment group, pretreatment NIHSS score, age, and time from symptom onset to treatment as the continuous predictors. Quadratic terms for the continuous covariates would be added to the model, if the Wald P value for the quadratic term was less than 0.1. The proportional odds assumption was tested by the score test.

The secondary outcome of global favorable recovery was derived from a generalized linear model with logit-link function, computed with generalized estimating equations. This global statistic simultaneously evaluated the effect in all 4 outcome measures (mRS score of 0 or 1, NIHSS score of 0 or 1, Barthel Index of 95 or 100, and Glasgow Outcome Scale score of 1).

Analyses for heterogeneity of treatment effect for the primary outcome were prespecified for subgroups of age, baseline NIHSS score, and time from symptom onset to treatment. Odds ratios (ORs) were estimated using multivariable logistic regressions. P values were estimated by adding the interaction of each subgroup and treatment variable to the logistic regression model. A possible interaction was prespecified as P < .10.

A post hoc analysis evaluated the likelihood of alteplase benefit, given study findings, for clinical interpretation and future trial planning purposes. Using an uninformative prior on the treatment-specific unadjusted outcome proportions, the posterior distribution of the risk difference was constructed via simulation to calculate the probability of alteplase benefit. This uninformative prior β[1, 1] reflects a uniform distribution on the interval [0, 1]; this prior was used to construct the posterior distribution of the risk difference via simulation to calculate the probability of alteplase benefit. The analysis was not adjusted for differences in age, time to treatment, or baseline NIHSS score, as with the primary outcome. The trial steering committee clinicians were surveyed in December 2015 (prior to study termination and without unblinding) to propose effect sizes that would change clinical practice toward treatment in the context of various associated sICH risk rates of alteplase. They suggested that an alteplase effect size as low as 6% might still change clinical practice toward treatment in the context of a 3% increased sICH risk. Therefore, the post hoc analysis considered the likelihood of (1) any benefit of alteplase and (2) an absolute benefit of alteplase of more than 6%.

For statistical analyses, SAS version 9.2 or higher (SAS Institute Inc) was executed on the SunOS version 5.10 (SUN 64) platform. The post hoc Bayesian analysis was executed using WinBUGS14.

Early Study Termination
Study enrollment was terminated on December 20, 2016, by the sponsor, prior to database lock and without unblinding, because of patient recruitment below target. This was a financial decision based on the fact that the trial could not be completed within the allotted funds in the specified time frame. The interim futility analysis was not completed for consideration of this decision because less than 50% of patients had completed follow-up. Neither the sponsor, the independent data monitoring committee, nor the steering committee evaluated study data as part of the decision to terminate the trial. The academic members of the steering committee recommended against termination but accepted this financial decision by the sponsor. The sponsor assured that the accrued data would be fully analyzed and disseminated to maximize the contributions of the enrolled patients and thereby maintain ethical responsibilities. The independent data monitoring committee had 2 reviews of aggregate data and recruitment rates but did not participate in the decision to terminate enrollment; the committee was informed of the decision after it was made. After enrollment was halted, all enrolled patients were to complete protocol-specified procedures through 90-day follow-up. As a result of the early termination of the study, the plan for analysis of the primary outcome was revised as detailed above.

Results
Study Population
From May 1, 2014, to December 20, 2016, 313 patients were enrolled, with a mean age of 62 years (SD, 13 years), 144 (46%)
women, a median NIHSS score of 2 (interquartile range, 1-3), and a median time from symptom onset to start of study treatment of 2.7 hours (interquartile range, 2.1-2.9). Of the 313 enrolled patients, 281 (89.8%) completed the trial’s primary outcome assessment and data for the remainder were imputed as prespecified. Study randomization, enrollment, and follow-up are shown in Figure 1 and patient characteristics in Table 1. Study groups were generally well balanced, with the most common medical risk factors being hypertension (80.1%) and hyperlipidemia (72.3%), and atrial fibrillation in only 12.8%. The most prevalent neurologic deficits at enrollment were sensory (46%), facial palsy (39%), and dysarthria (28%), as shown in the context of associated deficits in eFigure 1 in Supplement 1.

Features of the presenting event are shown in Table 2. Final diagnosis was acute cerebral ischemia in 87.0% of patients and neurovascular mimic in 13.0%. Among patients with acute cerebral ischemia, the most common stroke mechanisms were small vessel disease (36.6%) and undetermined mechanism (31.5%), with cardioembolism (13.6%) and large artery atherosclerosis (11.0%) less frequent.

Primary Outcome
In the primary analysis, 122 patients (78.2%) randomized to alteplase had favorable outcomes at 90 days compared with 128 patients (81.5%) randomized to aspirin (adjusted absolute risk difference, −1.1%; 95% CI, −9.4% to 7.3%). The full distribution of levels of disability on the mRS score at 90 days are shown in Figure 2 and eTable 2 in Supplement 1, and distributions without missing data imputation are shown in eFigure 2 in Supplement 1.

Secondary Outcomes
Secondary outcomes, including the ordinal analysis of mRS scores (OR, 0.81; 95% CI, 0.5-1.2) and global favorable recovery (OR, 0.86; 95% CI, 0.5-1.4), did not significantly favor either group (Table 3).

Adverse Events
Adverse event results are shown in Table 4. The primary adverse event, sICH within 36 hours, occurred in 5 patients, all treated with alteplase (3.2% vs O2; absolute risk difference, 3.3%; 95% CI, 0.8%-7.4%) (eFigure 3 in Supplement 1). Four sICH...
events were parenchymal hematoma type 2 (hematomas exceeding 30% of the infarction area with significant space-occupying effect) and 1 was a remote parenchymal hematoma type 1 (small petechial hemorrhage outside of the infarction bed). Symptomatic ICH volumes in each of the 5 patients were 0.4, 10, 18, 29, and 70 cm³; mRS scores at 90 days were 1, 2, 2, 3, and 4; and none of the patients with sICH died. Serious adverse events occurred in 40 patients (26.0%) treated with alteplase compared with 20 (13.1%) treated with aspirin; all adverse events are summarized in eTable 3 in Supplement 1.

One patient who was treated with alteplase died at 90 days of volvulus, adjudicated as related to a history of bowel obstruction and resection and unrelated to study treatment.

### Exploratory Outcomes and Analyses

All prespecified exploratory outcomes and sensitivity analyses for the primary outcome showed no statistically significant differences between groups (Table 3). Changes in NIHSS scores over time are shown in eFigure 4 in Supplement 1. Heterogeneity of treatment effect was not observed for
subgroups based on age ($P = .92$ for interaction), baseline NIHSS score ($P = .10$ for interaction), or time from symptom onset to treatment ($P = .70$ for interaction) (eFigure 5 in Supplement 1).

**Post Hoc Analysis**

In a post hoc Bayesian analysis, when the primary efficacy end point results of the current study were added to an uninformed prior, the posterior probability that alteplase therapy would improve favorable outcomes (mRS score of 0 or 1 at 90 days) to any degree was 23%, and the probability that alteplase therapy would improve favorable outcomes by more than an absolute 6% was 1.9%. The 95% credible interval of the unadjusted risk difference was −12.2% to 5.5%.

**Discussion**

Among patients with minor, nondisabling acute ischemic stroke, treatment with alteplase compared with aspirin did not increase the likelihood of favorable functional outcome at 90 days. Treatment benefit with alteplase was also not demonstrated for secondary and exploratory end points at 90 days. The study results raise the hypothesis that even a 6% treatment effect might be unlikely. However, the very early study termination precludes any definitive conclusions.

The trial tested alteplase in a unique ischemic stroke subpopulation. The operational definition of not clearly disabling deficits at presentation was intended to capture patients for whom treatment evidence was lacking and community equipoise for treatment benefit was present. Single-center clinical data without this type of explicit operationalization has suggested that 30% of these types of patients would have disability (mRS score of 2–6) at 90 days,2,3 higher than the observed 19% rate. Better outcomes may have been observed in the current study because of the formal definition of the population and other trial entry criteria selecting for healthier patients. The functional outcomes of patients enrolled in the trial may have been improved by earlier administration of aspirin (75%) within 3.1 hours of onset compared with general practice recommendations (within 24–48 hours).8 Additionally, prior observational cohorts not undergoing thrombolysis may have included more severely affected patients, given recent trends toward increased use of alteplase for patients with minor stroke in clinical practice.4,5

An increase in sICH was associated with alteplase in this population (risk difference, 3.3%; 95% CI, 0.8%–7.4%) without an associated increase in mortality. In a nationwide US registry, among 5910 patients with NIHSS scores of 0 to 5 treated with alteplase in routine practice, a 1.8% (95% CI, 1.5%–2.2%) absolute risk of sICH was observed.17 The sICH risk associated with alteplase was anticipated to be even lower in the current trial, which consisted of patients who had both low NIHSS scores and deficits judged to not be clearly disabling. The point estimate for the absolute risk of sICH of 3.2% in the current trial was higher than this 1.8% rate but lower than the 5% to 6% risk of sICH associated with alteplase in patients with higher NIHSS scores; however, wide confidence intervals included both of these comparators.14,15 The sICH events in this trial had no associated mortality compared with the sICH events in the NINDS trials associated with 75% mortality.19

The findings from the current trial cannot be extrapolated to all patients with lower stroke severity based on an NIHSS score of 0 to 5. Those with disabling deficits, such as isolated leg weakness causing inability to walk and isolated aphasia preventing communication, were excluded from the current study.
Table 3. 90-Day Efficacy Results

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. (%) Intravenous Alteplase + Oral Placebo (n = 156)</th>
<th>Effect Estimate, Risk Difference or OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS score of 0 or 1, adjusted&lt;sup&gt;a&lt;/sup&gt;</td>
<td>122 (78.2)</td>
<td>−1.1 (−9.4 to 7.3)</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS score distribution at 90 d&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0: 70 (44.9) 1: 52 (33.3) 2: 18 (11.5) 3: 4 (2.6) 4: 8 (5.1) 5-6: 4 (2.6)</td>
<td>OR, 0.81 (0.5 to 1.2)</td>
</tr>
<tr>
<td><strong>Global favorable recovery&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td></td>
<td>OR, 0.86 (0.5 to 1.4)</td>
</tr>
<tr>
<td><strong>Exploratory Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS score of 0 or 1, unadjusted&lt;sup&gt;c&lt;/sup&gt;</td>
<td>122 (78.2)</td>
<td>−3.3 (−12.2 to 5.6)</td>
</tr>
<tr>
<td>NIHSS score of 0 or 1, adjusted&lt;sup&gt;d&lt;/sup&gt;</td>
<td>108 (85.7)</td>
<td>0.13 (0.65 to 2.6)</td>
</tr>
<tr>
<td>Barthel Index of 95 or 100, adjusted&lt;sup&gt;e&lt;/sup&gt;</td>
<td>107 (79.3)</td>
<td>0.04 (−0.1 to 0.1)</td>
</tr>
<tr>
<td>EuroQoL Group EQ-5D quality-of-life score,</td>
<td>85.1 (21.0)</td>
<td>−0.1 (−6.2 to 4.0)</td>
</tr>
<tr>
<td>Stroke Impact Scale 16 score, mean (SD)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>86.3 (21.4)</td>
<td></td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>5 (3.2)</td>
<td>6 (4.0)</td>
</tr>
<tr>
<td><strong>Exploratory Analyses for the Primary Outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute cerebral ischemia cases only (mimics</td>
<td>107/138 (77.5)</td>
<td>−1.4 (−10.5 to 7.7)</td>
</tr>
<tr>
<td>Propensity score-adjusted model&lt;sup&gt;g&lt;/sup&gt;</td>
<td>110/141 (78.0)</td>
<td>−2.3 (−11.1 to 6.6)</td>
</tr>
<tr>
<td>Logistic regression model&lt;sup&gt;h&lt;/sup&gt;</td>
<td>107/135 (80.7)</td>
<td>−2.4 (−11.2 to 6.4)</td>
</tr>
<tr>
<td>Repeated-measures model&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
<td>OR, 0.9 (0.5 to 1.7)</td>
</tr>
</tbody>
</table>
| * Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; OR, odds ratio.  
  * Positive values for risk differences and ORs greater than 1 favor alteplase.  
  * Adjusted risk difference values were calculated from a linear regression with treatment, age, time from symptom onset to treatment, and baseline NIHSS score. Quadratic terms for age and baseline NIHSS score were also added to the model if the Wald P value for the quadratic term was P < .10. Modified Rankin Scale scores range from 0 (symptom free) to 6 (dead).  
  * The proportional odds assumption was met (score test P = .50); therefore, the common OR was calculated by fitting a proportional odds model with mRS scores at day 90 as the dependent variable and treatment group, pretreatment NIHSS score, age, and time from symptom onset to treatment as the continuous predictors. Quadratic terms for the continuous covariates were added to the model if the Wald P value for the quadratic term was less than 0.1.  
  * The global favorable recovery statistic was derived from a generalized linear model with logit-link function computed using generalized estimating equations. This global statistic simultaneously evaluated the effect in all 4 outcome measures (mRS score of 0 or 1, NIHSS score of 0 or 1, Barthel Index of 95 or 100, and Glasgow Outcome Scale score of 1).  
  * Confidence interval was computed using the normal approximation method.  
  * The Barthel Index ranges from 0 (totally dependent) to 100 (patient performs self-care and mobility without assistance).  
  * The Stroke Impact Scale 16 score ranges from 0 (good recovery) to 5 (death).  
  * Ambulatory performance assesses comfortable walking speed for 6 meters.  
  * The EuroQoL Group EQ-5D score ranges from 0 (death) to 1 (perfect health).  
  * Propensity scores were derived from the logistic regression for treatment group with the following covariates: sex, race, ethnicity, smoking, history of hypertension, history of diabetes, history of atrial fibrillation, history of stroke, prior antiplatelet drug use, prior anticoagulant drug use, baseline glucose level, baseline systolic blood pressure, and baseline international normalized ratio.  
  * Adjusted OR was obtained from a logistic regression adjusted for pretreatment NIHSS score, age, and time from symptom onset to treatment as continuous covariates and quadratic terms for the continuous covariates if the Wald P value for the quadratic term was <0.1.  
  * Using all available mRS score responses at both day 30 and day 90. Odds ratios are adjusted for age, time from symptom onset to treatment, baseline NIHSS score, and quadratic terms for age (logistic) and age and baseline NIHSS score (repeated measures).  

Furthermore, clinical guidelines and scientific statements regarding alteplase recommend “no exclusion for patients with mild but nonetheless disabling stroke symptoms...”7,20 Additionally, patients with mild deficits who have large vessel occlusions (a minority in this population) may be more prone to stroke progression and thus may require further study.21-23
Limitations

This study has several limitations. First, the trial’s early termination leads to significant uncertainty of all observations. Second, within the bounds of formal trial entry criteria, some sites may have selectively recruited patients with even milder, rather than more severe, deficits despite efforts to minimize this selection bias. Third, the definition of “not clearly disabling” was subjective and required interpretation by individual clinicians. Although efforts were made to encourage consistency in assessment of eligible patients, this cannot be confirmed. Fourth, the loss to follow-up at day 90 was relatively high. However, mRS scores from day 30 (available for 78% of these patients) are known to permit robust imputation.24

Conclusions

Among patients with minor nondisabling acute ischemic stroke, treatment with alteplase compared with aspirin did not increase the likelihood of favorable functional outcome at 90 days. However, the very early study termination precludes any definitive conclusions, and additional research may be warranted.

ARTICLE INFORMATION

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Original Investigation Research

Author Contributions: Dr Khatri had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Khatri reports payment to her university department for research efforts from Genentech (lead PI of PRISMS), Neurosurgery (coinvestigator; CREATE grant), Lumosa (data and safety monitoring board and consultant), Cerenevox (investigator-initiated study, ENDO LOW PI) and the National Institutes of Health/National Institute of Neurological Disorders and Stroke. Dr Khatri also reports fees from Biogen (data and safety monitoring board) and Medpace/Novartis (coinvestigator). Dr Khatri was an unpaid consultant to Emopstö and received travel support from Neuravi (academic workshop). Dr Kleindorfer reports personal fees from Genentech Speakers Bureau. Dr Devlin reports research support from Genentech. Dr Sawyer reports personal fees from Medtronic. Dr Mejilla reports personal fees from Medtronic and grants from Genentech/Rochie. Drs Broderick, Chatterjee, and Jauch report fees from Genentech for membership on the steering committee of the PRISMS trial. Dr Levine reports personal fees and nonfinancial support from Genentech for membership on the steering committee of the PRISMS Trial and other grants from Genentech. Dr Romano reports personal fees from Genentech for membership on the steering committee of the PRISMS Trial and other grants from Genentech to the University of Miami to support his role as principal investigator of the Mild and Rapidly Improving Stroke Study. Dr Saver served as an unpaid steering committee member advising on the design and conduct of the PRISMS trial under a no-remuneration contract with Genentech. Dr Saver also served as an unpaid site investigator in the PRISMS trial, for which the University of California received payments on the basis of clinical trial contracts for the number of participants enrolled. Dr Saver reports receiving contracted hourly payments and travel reimbursement from Medtronic, Stryker, and Neuravi, and Boehringer Ingelheim (prevention only) for service on trial steering committee(s), making recommendations regarding best approaches to rigorous trial design and conduct. The University of California, Dr Saver’s institution, has patent rights in retrieval devices for stroke. Vascular research is a grant from Genentech to the University of Cincinnati for his role as the principal investigator of the PRISMS Imaging Core. Drs Purdon and Devenport are full-time employees of Genentech. Dr Yeatts reports personal fees from Genentech for membership on the steering committee of the PRISMS Trial and fees contracted to the institution from Card Inc for serving on a data monitoring committee. No other disclosures were reported.

Funding/Support: Genentech Inc funded the trial.

Role of the Funder/Sponsor: The initial protocol was proposed to Genentech Inc by the academic investigators for consideration. After requested modifications, Genentech Inc sponsored the study and participated in the writing, design, and conduct of the trial, including distribution of the study drug and oversight of study management. The sponsor did not have access to or manage the data.

A steering committee composed of academic investigators and sponsor representatives provided recommendations throughout the trial. The sponsor continued to support the decision to terminate the trial. The first draft of the manuscript and its revisions were drafted by the academic lead principal investigator (Dr Khatri). The sponsor, along with all coauthors, participated in data interpretation and critical review of the publication and reviewed the tables, listings, and graphs to ensure the accuracy of the data analysis and interpretation. The decision to submit for publication was made jointly by the steering committee and the sponsor. The sponsor did not have the right to veto the publication or the planned journal of submission.


Meeting Presentation: Results from this study were presented at the International Stroke Conference: January 25, 2018; Los Angeles, California.

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REFERENCES