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Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke

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ABSTRACT

BACKGROUND

Thrombolytic therapy for acute ischemic stroke with a lower-than-standard dose of intravenous alteplase may improve recovery along with a reduced risk of intracerebral hemorrhage.

METHODS

Using a 2-by-2 quasi-factorial open-label design, we randomly assigned 3310 patients who were eligible for thrombolytic therapy (median age, 67 years; 63% Asian) to low-dose intravenous alteplase (0.6 mg per kilogram of body weight) or the standard dose (0.9 mg per kilogram); patients underwent randomization within 4.5 hours after the onset of stroke. The primary objective was to determine whether the low dose would be noninferior to the standard dose with respect to the primary outcome of death or disability at 90 days, which was defined by scores of 2 to 6 on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]). Secondary objectives were to determine whether the low dose would be superior to the standard dose with respect to centrally adjudicated symptomatic intracerebral hemorrhage and whether the low dose would be noninferior in an ordinal analysis of modified Rankin scale scores (testing for an improvement in the distribution of scores). The trial included 935 patients who were also randomly assigned to intensive or guideline-recommended blood-pressure control.

RESULTS

The primary outcome occurred in 855 of 1607 participants (53.2%) in the low-dose group and in 817 of 1599 participants (51.1%) in the standard-dose group (odds ratio, 1.09; 95% confidence interval [CI], 0.95 to 1.25; the upper boundary exceeded the noninferiority margin of 1.14; P=0.51 for noninferiority). Low-dose alteplase was noninferior in the ordinal analysis of modified Rankin scale scores (unadjusted common odds ratio, 1.00; 95% CI, 0.89 to 1.13; P=0.04 for noninferiority). Major symptomatic intracerebral hemorrhage occurred in 1.0% of the participants in the low-dose group and in 2.1% of the participants in the standard-dose group (P=0.01); fatal events occurred within 7 days in 0.5% and 1.5%, respectively (P=0.01). Mortality at 90 days did not differ significantly between the two groups (8.5% and 10.3%, respectively; P=0.07).

CONCLUSIONS

This trial involving predominantly Asian patients with acute ischemic stroke did not show the noninferiority of low-dose alteplase to standard-dose alteplase with respect to death and disability at 90 days. There were significantly fewer symptomatic intracerebral hemorrhages with low-dose alteplase. (Funded by the National Health and Medical Research Council of Australia and others; ENCHANTED ClinicalTrials.gov number, NCT01422616.)

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Thrombolytic therapy with intravenous alteplase (recombinant tissue-type plasminogen activator) at a dose of 0.9 mg per kilogram of body weight is an effective treatment for acute ischemic stroke, despite increasing the risk of intracerebral hemorrhage.[1-3] However, the Japanese drug safety authority has approved the use of alteplase at a dose of 0.6 mg per kilogram after an uncontrolled, open-label study showed that this dose resulted in equivalent clinical outcomes and a lower risk of intracerebral hemorrhage than that reported in published studies in which the 0.9-mg-per-kilogram dose was used.[4] Other registry studies in Asia[5-11] have shown inconsistent results, but a high risk of symptomatic intracerebral hemorrhage was observed among Asian patients treated with 0.9 mg of alteplase per kilogram in the United States.[12] Differing perceived risks of intracerebral hemorrhage and treatment affordability have led to variations in the doses of intravenous alteplase used to treat patients with acute ischemic stroke in Asia.[8-11]

The Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) was designed to compare low-dose with standard-dose intravenous alteplase in patients with acute ischemic stroke. Using a quasi-factorial design, we are also assessing the effects of early intensive lowering of blood pressure as compared with guideline-recommended management in patients with elevated blood pressure; this part of the trial is scheduled to be completed in 2018. We report the results of the alteplase part of the trial, which was completed in December 2015.

Methods

Trial Design and Oversight

In an international, multicenter, prospective, randomized, open-label trial with blinded outcome evaluation, two doses of intravenous alteplase were compared in patients with an acute ischemic stroke who were eligible for thrombolytic therapy; administration of the drug was commenced within 4.5 hours after the onset of the stroke. Patients with elevated systolic blood pressure (range, 150 to 220 mm Hg) could also be randomly assigned to early and intensive lowering of blood pressure (target systolic blood pressure <140 mm Hg within 1 hour) or conventional guideline-directed management of blood pressure (target systolic blood pressure <180 mm Hg) with the use of locally available intravenous agents.

Details of the design and statistical analysis plan of the trial have been published previously.[13,14] An international steering committee, whose members designed the trial with an advisory committee, was responsible for the conduct and reporting of the trial. The George Institute for Global Health coordinated the trial, managed the database, and performed the analyses. The study drug used (alteplase) was that available for routine use at clinical centers; there was no commercial input into any aspect of the trial. The first author wrote the first and subsequent drafts of the manuscript. All the authors commented on drafts of the manuscript, approved the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of this report to the trial protocol (available with the full text of this article at NEJM.org).

The trial protocol was approved by all appropriate regulatory authorities and ethics committees at the participating centers. All participants, or an approved surrogate for those who were too unwell to comprehend the information, provided written informed consent. Details of the monitoring procedures are provided in the Supplementary Appendix (available at NEJM.org).

Patients and Procedures

Patients were recruited at 111 clinical centers in 13 countries. Patients were eligible if they were 18 years of age or older, had an acute ischemic stroke, and met guideline-recommended criteria for treatment with intravenous alteplase. For details of the inclusion and exclusion criteria, see the Supplementary Appendix.

After confirmation of patient eligibility, randomization was performed centrally with the use of a minimization algorithm according to center, time from stroke onset (<3 vs. ≥3 hours), and severity of neurologic impairment (score of <10 vs. ≥10 on the National Institutes of Health Stroke Scale [NIHSS]; range, 0 to 42, with higher scores indicating greater severity of stroke). Participants were randomly assigned to receive either a standard dose of intravenous alteplase (0.9 mg per kilogram of estimated, or measured, body weight; 10% as a bolus and 90% as an infusion over a period of 60 minutes; maximum dose, 90 mg) or a low dose (0.6 mg per kilogram, 15% as a bolus and 85% as an infusion over a period of 60 minutes; maximum dose, 60 mg), to be commenced within 4.5 hours after symptom onset. Concomitant therapy followed national practice guidelines,

including the use of endovascular thrombectomy devices, where approved.

Demographic and clinical data were obtained at the time of randomization. Follow-up data were obtained at 24 and 72 hours (including repeat NIHSS scores and measured body weight) and at 7 days (or hospital discharge, if sooner), 28 days, and 90 days, unless death occurred earlier. The 28-day and 90-day evaluations were conducted in person or by telephone, by trained and certified staff who remained unaware of the randomized treatment assignments. Brain imaging was performed at trial entry and at 24 hours, and additionally if clinically indicated, and was analyzed centrally for any hemorrhage by expert assessors who were unaware of the treatment assignments (see the Supplementary Appendix).

OUTCOMES

The prespecified primary outcome was the combined end point of death or disability at 90 days, which was defined by scores of 2 to 6 on the modified Rankin scale,[15] a global seven-level measure of functioning in which scores of 0 or 1 indicate a good outcome with no or minimal neurologic symptoms, scores of 2 to 5 indicate a poor outcome with increasing degree of disability, and 6 indicates death. The key secondary outcome, which was also designated as a safety outcome, was intracerebral hemorrhage, defined according to criteria from a number of other studies (see the Supplementary Appendix); the main definition of intracerebral hemorrhage that we used was the definition in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)[16]: a large local or remote parenchymal pattern (>30% of the infarcted area affected by hemorrhage, with mass effect or extension outside the infarct) and neurologic deterioration from baseline (increase of ≥4 points in the NIHSS score) or death within 36 hours. This definition was finalized and described in the statistical analysis plan of our trial after publication of the original protocol.

Other secondary efficacy outcomes were the distribution of modified Rankin scale scores at 90 days,[17] major disability (modified Rankin scale score >2) at 90 days, deaths at 7 days and 90 days, neurologic deterioration (increase of ≥4 points in the NIHSS score) during the 72 hours after randomization, death and neurologic deterioration (increase of ≥4 points in the NIHSS score) during the 72 hours after randomization, health-related quality of life on the EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D; summary health utility scores range from −0.109 to 1, with higher scores indicating better health)[18] at 90 days (for details on scoring, see the Supplementary Appendix), length of initial hospital stay, recurrent acute myocardial infarction and recurrent ischemic stroke, admission to a long-term residential care facility at 90 days, and use of health services (for economic analyses that have not yet been conducted). Prespecified safety outcomes were all serious adverse events reported until trial completion. Tertiary outcomes included all-cause mortality, place of death, trends in modified Rankin scale scores during follow-up, length of stay in the intensive care unit (ICU), rate of thrombectomy, and individual items of the EQ-5D.

STATISTICAL ANALYSIS

We designed the trial to assess the effects of two treatment variables — alteplase dose and intensity of blood-pressure control — on clinical outcomes, accounting for their potential interaction.[14] Differential patient recruitment resulted in the part of the trial dealing with alteplase dose being completed faster than the part dealing with intensity of blood-pressure control. For the primary analysis, we used an unadjusted logistic-regression model to test whether low-dose alteplase was noninferior to the standard dose. To satisfy the noninferiority hypothesis, the upper boundary of the 95% confidence interval for the odds ratio of the outcome with low-dose alteplase as compared with standard-dose alteplase had to fall below a margin of 1.14; this noninferiority margin was derived from a Cochrane meta-analyses of alteplase trials with effects on poor outcomes reported.[19,20] We estimated that a sample size of 3300 patients would provide at least 90% power to evaluate noninferiority, assuming 5% dropout and potential negative interaction between intensive blood-pressure control and low-dose alteplase, and would also provide at least 80% power to detect superiority of low-dose alteplase in achieving a 40% lower risk of symptomatic intracerebral hemorrhage than that with standard-dose alteplase, with 5% dropout. Consistency of treatment effect across 10 prespecified subgroups was assessed through tests for interaction.

A secondary efficacy analysis was a comparison of ordinal scores on the modified Rankin scale to test for the noninferiority of the low dose to the standard dose with the use of ordi-

Table 1. Characteristics of the Patients at Baseline and Their Treatment.*

Variable	Low-Dose Alteplase (N=1654)	Standard-Dose Alteplase (N=1643)
Age — yr		
Median	68	67
IQR	58–76	58–76
Female sex — no. (%)	634 (38.3)	614 (37.4)
Region of recruitment — no. (%)		
China	708 (42.8)	711 (43.3)
United Kingdom, continental Europe, or Australia	445 (26.9)	439 (26.7)
Asia, other than China	336 (20.3)	334 (20.3)
South America	165 (10.0)	159 (9.7)
Asian race — no./total no. (%)†	1043/1651 (63.2)	1036/1640 (63.2)
Medical history — no./total no. (%)‡		
Hypertension	1031/1648 (62.6)	1034/1640 (63.0)
Any stroke	287/1654 (17.4)	302/1643 (18.4)
Coronary artery disease	256/1648 (15.5)	223/1640 (13.6)
Atrial fibrillation	330/1645 (20.1)	306/1640 (18.7)
Diabetes mellitus	325/1648 (19.7)	321/1640 (19.6)
Hypercholesterolemia	297/1648 (18.0)	258/1640 (15.7)
Current cigarette use	377/1646 (22.9)	393/1638 (24.0)
Modified Rankin scale score of 0 before stroke§	1349/1647 (81.9)	1325/1639 (80.8)
Use of antihypertensive agent	755/1648 (45.8)	743/1640 (45.3)
Use of statin or other lipid-lowering agent	333/1646 (20.2)	282/1638 (17.2)
Use of aspirin or other antiplatelet agent	407/1647 (24.7)	345/1638 (21.1)
Warfarin anticoagulation	48/1647 (2.9)	34/1638 (2.1)
Blood pressure — mm Hg		
Systolic	149±20	150±20
Diastolic	84±13	85±13
NIHSS score — median (IQR)¶	8 (5–14)	8 (5–14)
Signs of cerebral ischemia on brain imaging — no./total no. (%)‖	388/1648 (23.5)	383/1640 (23.4)
Proximal vessel occlusion on CTA or MRA — no./total no. (%)‖	258/1622 (15.9)	248/1624 (15.3)
Final diagnosis at time of hospital discharge — no./total no. (%)**		
Nonstroke diagnosis	50/1625 (3.1)	47/1609 (2.9)
Large-artery occlusion due to clinically significant atheroma	622/1625 (38.3)	648/1609 (40.3)
Small-vessel or perforator lacunar disease	334/1625 (20.6)	339/1609 (21.1)
Cardioembolism	324/1625 (19.9)	317/1609 (19.7)
Dissection	14/1625 (0.9)	11/1609 (0.7)
Other or uncertain cause of stroke	281/1625 (17.3)	247/1609 (15.4)
Time from stroke onset to alteplase administration — min††		
Median	170	170
IQR	125–218	127–219
Estimated body weight before alteplase administration — kg	69.6±14.4	69.9±14.4

Table 1. (Continued.)

Variable	Low-Dose Alteplase (N=1654)	Standard-Dose Alteplase (N=1643)
Any alteplase given to patients — no. (%)	1628 (98.4)	1617 (98.4)
Bolus dose — mg	6.2±1.2	6.3±2.1
Infusion dose — mg	35.5±7.3	56.0±11.3
Concurrent inclusion in part of trial dealing with blood-pressure control — no. (%)	460 (27.8)	475 (28.9)
Assigned to intensive blood-pressure lowering	224 (13.5)	232 (14.1)
Assigned to standard blood-pressure lowering	236 (14.3)	243 (14.8)

* Plus–minus values are means ±SD. There were no significant differences between trial groups in the characteristics listed, except in the administered dose of alteplase as a bolus (P=0.05) and as an infusion (P<0.001). CTA denotes computed tomographic angiography, IQR interquartile range, and MRA magnetic resonance angiography.
† Race was self-reported.
‡ Medical history was based on self-report, with the exception of the presence of atrial fibrillation, which was based on findings on electrocardiography performed at the time of presentation.
§ The modified Rankin scale evaluates global disability; scores range from 0 (no symptoms) to 6 (death).
¶ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits. Scores ranged from 0 to 40 in the low-dose group and from 0 to 42 in the standard-dose group.
‖ This finding was reported by clinician investigators.
** Diagnoses were determined by clinician investigators.
†† Times ranged from 28 to 1673 minutes (0.47 to 27.88 hours) in the low-dose group and from 11 to 1678 minutes (0.18 to 27.97 hours) in the standard-dose group.

nal logistic regression, after the assumption of proportionality of the odds was confirmed in a likelihood-ratio test.[17] A new assumption-free approach[21] was used to confirm the conclusion. We also performed secondary analyses of the primary outcome with adjustment for minimization and key prognostic covariates[14], as well as secondary analyses in the per-protocol population according to criteria outlined in the Supplementary Appendix. Multiple imputation was to be used if more than 10% of observations were missing. An independent data and safety monitoring board monitored the trial progress and safety with the use of formal stopping boundaries. For ease of interpretation, all reported P values for noninferiority are multiplied by 2 so that an alpha of 0.05 can be used in analyses. The other P values (those for superiority) are two-sided. All P values were prespecified not to be adjusted. SAS software, version 9.3 (SAS Institute), was used for analyses.

RESULTS

PATIENTS

From March 2012 through August 2015, a total of 3310 of the 69,325 patients who were screened underwent randomization (Fig. S1 and Table S1 in the Supplementary Appendix); 1654 patients were assigned to low-dose alteplase and 1643 to standard-dose alteplase. There were no significant differences between the low-dose group and the standard-dose group in baseline demographic and clinical characteristics (Table 1, and Table S2 in the Supplementary Appendix), nor in the number of patients assigned to each of the blood-pressure-lowering groups. The median age of the patients was 67 years (14% were ≥80 years of age), and 38% were women. Approximately two thirds of the patients were Asian, and 43% were recruited from China. The median NIHSS score before treatment was 8 (range, 0 to 42; interquartile range, 5 to 14), and the median time from stroke onset to randomization was 2.7 hours (interquartile range, 2.0 to 3.5).

INTERVENTIONS

In both groups, the mean time from the onset of stroke to administration of alteplase was 170 minutes; the mean dose of alteplase administered as an infusion was 35.5 mg in the low-dose group and 56.0 mg in the standard-dose group (P<0.001) (Table 1). The distribution of dosing and the protocol violations are outlined in Figure

S2 and Tables S3 and S4 in the Supplementary Appendix. Postrandomization management, including endovascular thrombectomy and rates of recanalization, was similar in the two groups during the first 7 days (Table S5 in the Supplementary Appendix). Outcome at 90 days was assessed by telephone in 84.6% of the patients in the low-dose group and in 83.6% of the patients in the standard-dose group; the rest of the patients were assessed by in-person examination. The sources of information for the modified Rankin scale scores were balanced between the groups (Table S6 in the Supplementary Appendix).

BLOOD-PRESSURE CONTROL

In the part of the trial dealing with blood-pressure control that included 935 patients with elevated systolic blood pressure (range, 150 to 220 mm Hg), 224 patients in the low-dose group (13.5%) and 232 in the standard-dose group (14.1%) were assigned to rapid blood-pressure reduction. In both alteplase dose groups, the mean systolic blood pressure levels were significantly lower, by 7 to 9 mm Hg, with intensive blood-pressure control than with standard blood-pressure management at 1 hour and 6 hours after randomization (Table S7 in the Supplementary Appendix).

PRIMARY OUTCOME

Scores on the modified Rankin scale for assessment of the primary outcome could not be obtained, owing to withdrawal of consent or loss to follow-up, in 47 of the patients assigned to low-dose alteplase and 44 assigned to standard-dose alteplase (Fig. S1 in the Supplementary Appendix). In the modified intention-to-treat analysis, the primary outcome (scores of 2 to 6 on the modified Rankin scale) occurred in 855 of 1607 patients (53.2%) in the low-dose group and in 817 of 1599 patients (51.1%) in the standard-dose group (odds ratio, 1.09; 95% confidence interval [CI], 0.95 to 1.25; the upper boundary of the 95% confidence interval exceeded the prespecified boundary for noninferiority of 1.14; one-sided P=0.51 for noninferiority) (Table 2, and Fig. S3 in the Supplementary Appendix). In an adjusted analysis of the intention-to-treat population, the rate was 53.3% in the low-dose group and 50.9% in the standard-dose group (odds ratio, 1.13; 95% CI, 0.97 to 1.31; P=0.88 for noninferiority); in an adjusted analysis in the per-protocol population, the rates were 53.5% and 51.3%, respectively (odds ratio, 1.13; 95% CI, 0.96 to 1.32; one-sided P=0.89 for noninferiority). There was no heterogeneity of effect between patients who began alteplase treatment less than 3 hours after stroke onset and those who began treatment 3 or more hours after stroke onset (Fig. S5 in the Supplementary Appendix), and there was no significant interaction between intensity of blood-pressure lowering and alteplase dose (P=0.29).

SECONDARY OUTCOMES

In an unadjusted ordinal analysis of the distribution of modified Rankin scale scores in the two groups, the odds ratio with low-dose alteplase as compared with standard-dose alteplase was 1.00 (95% CI, 0.89 to 1.13; P=0.04 for noninferiority) (Table 2). The assumption-free, adjusted, and per-protocol alternative approaches were consistent in showing no significant difference in the treatment effect for overall functional outcome on the modified Rankin scale between doses of alteplase (Fig. 1, and Figs. S3, S4, and S6 and Tables S8, S9, and S10 in the Supplementary Appendix).

Major symptomatic intracerebral hemorrhage according to SITS-MOST criteria occurred in 17 of 1654 patients (1.0%) in the low-dose group and in 35 of 1643 patients (2.1%) in the standard-dose group (odds ratio, 0.48; 95% CI, 0.27 to 0.86; P=0.01) (Table 2). There was no significant interaction between intensive blood-pressure lowering and alteplase dose group with respect to the risk of major symptomatic intracerebral hemorrhage (P=0.71). Symptomatic intracerebral hemorrhage according to other criteria also occurred significantly less frequently in the low-dose group than in the standard-dose group (Table 2, and Fig. S7 in the Supplementary Appendix); for example, the rate of fatal events within 7 days was 0.5% in the low-dose group and 1.5% in the standard-dose group (odds ratio, 0.37; 95% CI, 0.17 to 0.80; P=0.01). There was no heterogeneity in the effect of alteplase dose on the risk of symptomatic intracerebral hemorrhage between Asians and non-Asians (Fig. S8 in the Supplementary Appendix).

Mortality at 7 days was 3.6% in the low-dose group versus 5.3% in the standard-dose group (odds ratio, 0.67; 95% CI, 0.48 to 0.94; P=0.02), and mortality at 90 days was 8.5% versus 10.3%

Table 2. Primary and Secondary Outcomes at 3 Months.*

Outcome	Low-Dose Alteplase (N=1654)	Standard-Dose Alteplase (N=1643)	Odds Ratio with Low-Dose Alteplase (95% CI)	P Value†	P Value for Noninferiority‡
Primary outcome: death or disability — no./total no. (%)§	855/1607 (53.2)	817/1599 (51.1)	1.09 (0.95 to 1.25)		0.51
Secondary outcomes					
Symptomatic intracerebral hemorrhage — no. (%)					
By SITS-MOST criteria¶	17 (1.0)	35 (2.1)	0.48 (0.27 to 0.86)	0.01	
By NINDS criteria‖	98 (5.9)	131 (8.0)	0.73 (0.55 to 0.95)	0.02	
Score on the modified Rankin scale — no./total no. (%)			1.00 (0.89 to 1.13)**		0.04
0: No symptoms at all	403/1607 (25.1)	397/1599 (24.8)			
1: No substantive disability despite symptoms	349/1607 (21.7)	385/1599 (24.1)			
2: Slight disability	250/1607 (15.6)	225/1599 (14.1)			
3: Moderate disability requiring some help	211/1607 (13.1)	181/1599 (11.3)			
4: Moderate–severe disability requiring assistance with daily living	165/1607 (10.3)	154/1599 (9.6)			
5: Severe disability, bed-bound and incontinent	89/1607 (5.5)	87/1599 (5.4)			
6: Death	140/1607 (8.7)	170/1599 (10.6)			
Death or major disability — no./total no. (%)††	605/1607 (37.6)	592/1599 (37.0)	1.03 (0.89 to 1.19)	0.73	
Death within 90 days — no. (%)	140 (8.5)	170 (10.3)	0.80 (0.63 to 1.01)	0.07	
Overall health utility score on the EQ-5D‡‡	0.64±0.40	0.64±0.41	0.00 (–0.03 to 0.03)§§	0.86	
Admission to residential care — no./total no. (%)	36/1513 (2.4)	43/1476 (2.9)	0.81 (0.52 to 1.27)	0.36	
Median duration of hospitalization (IQR) — days	10 (5 to 17)	10 (5 to 18)	–0.47 (–1.93 to 1.00)§§	0.53	
Death or neurologic deterioration in 72 hr — no. (%)¶¶	177 (10.7)	192 (11.7)	0.91 (0.73 to 1.12)	0.37	
Serious adverse event — no. (%)‖‖	415 (25.1)	448 (27.3)	0.89 (0.76 to 1.04)	0.16	

* Plus–minus values are means ±SD. CI denotes confidence interval.
† The P values are for the comparison of the low-dose group with the standard-dose group.
‡ The noninferiority margin was 1.14 (i.e., an upper boundary of the 95% confidence interval for the odds ratio with low-dose alteplase as compared with standard-dose alteplase of less than 1.14).
§ Disability was defined by a score of 2 to 5 on the modified Rankin scale, with higher scores indicating a greater degree of disability. Death was defined by a modified Rankin scale score of 6.
¶ The main definition of symptomatic intracerebral hemorrhage used in the study was the definition from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): a large local or remote parenchymal intracerebral hemorrhage (>30% of the infarcted area affected by hemorrhage with mass effect or extension outside the infarct) in combination with neurologic deterioration from baseline (increase of ≥4 in in the NIHSS score) or death within 36 hours.
‖ Symptomatic intracerebral hemorrhage was also assessed according to National Institute of Neurological Diseases and Stroke (NINDS) trial criteria: any intracerebral hemorrhage with neurologic deterioration (increase of ≥1 in the NIHSS score) from baseline or death within 36 hours.
** The common odds ratio was estimated from an ordinal logistic-regression model and indicates the odds of a decrease of 1 in the modified Rankin scale score, with a common odds ratio greater than 1 favoring standard-dose alteplase.
†† Major disability was defined by a score of 3 to 5 on the modified Rankin scale.
‡‡ The EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) covers five domains of health-related quality of life: mobility, self-care, usual activities, pain–discomfort, and anxiety–depression. Scores from these levels are combined to provide an overall health utility score ranging from –0.109 to 1, with higher scores indicating better health. Data were available for 1594 patients in the low-dose group and 1591 patients in the standard-dose group.
§§ Shown in the estimated difference with 95% confidence interval.
¶¶ Neurologic deterioration was defined as an increase from baseline of at least 4 in the NIHSS score.
‖‖ Serious adverse events were defined by standard criteria and included those that resulted in death, were life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in persistent or substantive disability or incapacity, or resulted in a medical or surgical intervention to prevent permanent impairment to body structure or function. Details on serious adverse events are provided in Table S12 in the Supplementary Appendix.

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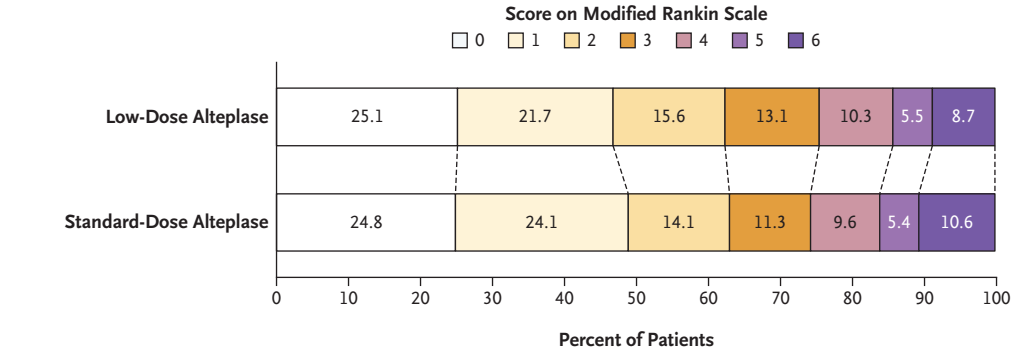

Figure 1. Functional Outcomes at 90 Days, According to Score on the Modified Rankin Scale.

Shown is the raw distribution of scores on the modified Rankin scale at 90 days in the group that received a low dose of alteplase (0.6 mg per kilogram of body weight) and the group that received the standard dose of alteplase (0.9 mg per kilogram). Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 symptoms without clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

(odds ratio, 0.80; 95% CI, 0.63 to 1.01; P=0.07) (Fig. S9 and Table S11 in the Supplementary Appendix). No significant between-group differences were evident in other secondary outcomes (Table 2). Other outcomes, including length of stay in the ICU, recurrent vascular events, and individual components of the EQ-5D, are not reported here.

SUBGROUP ANALYSES

There was no significant heterogeneity of treatment effect on the primary outcome across prespecified subgroups (Fig. 2). The interaction between alteplase dose and aspirin or other antiplatelet therapy was not significant (P=0.05); however, this interaction was significant (P=0.02) in a post hoc unadjusted ordinal analysis of modified Rankin scale scores (Fig. S10 in the Supplementary Appendix). Post hoc analyses showed consistency in the effect of alteplase dose on death at 90 days across subgroups and no clear relation with baseline NIHSS score (Fig. S11 and S12 in the Supplementary Appendix).

SAFETY

There was no significant difference between the low-dose group and the standard-dose group in the overall reported rate of serious adverse events, which occurred in 25.1% and 27.3% of the patients, respectively (P=0.16). However, significantly fewer patients in the low-dose alteplase group than in the standard-dose alteplase group had (unadjudicated) fatal cerebral hemorrhage events (1.3% vs. 2.5%, P=0.02). All serious adverse events are listed in Table S12 in the Supplementary Appendix.

DISCUSSION

In patients with acute ischemic stroke who met guideline-recommended criteria for thrombolytic reperfusion treatment, a dose of 0.6 mg of alteplase per kilogram was not shown to be noninferior to a dose of 0.9 mg of alteplase per kilogram with respect to the primary outcome of death or disability at 90 days. Our trial was driven by concern about high risks of intracerebral hemorrhage with alteplase, particularly among Asians, because preliminary studies have had differing results with respect to the effectiveness and risks of this treatment.[8,11] Using several definitions of symptomatic intracerebral hemorrhage,[22] we observed fewer clinically important cases in the group assigned to low-dose alteplase than in the group assigned to standard-dose alteplase, and the difference in risk was consistent in Asians and non-Asians.

The distribution of modified Rankin scale scores in the two groups at 90 days indicates that the lower rate of death with low-dose alteplase than with standard-dose alteplase was accompanied by more patients surviving with mild to moderately severe grades of residual disability. There was no heterogeneity of treatment effect on the primary outcome in prespecified subgroups, but these analyses had low statistical

Subgroup	Low-Dose Alteplase	Standard-Dose Alteplase	Odds Ratio (95% CI)	P Value for Interaction
	no. (%)			
Age				0.20
<65 yr	302 (43.9)	301 (44.3)	0.98 (0.79–1.22)	
≥65 yr	553 (60.2)	516 (56.1)	1.18 (0.98–1.42)	
Sex				0.53
Male	503 (50.9)	480 (48.0)	1.12 (0.94–1.34)	
Female	352 (57.0)	337 (56.4)	1.02 (0.82–1.29)	
Race				0.82
Asian	527 (51.5)	500 (49.0)	1.10 (0.93–1.31)	
Non-Asian	328 (56.4)	317 (54.7)	1.07 (0.85–1.35)	
Time from stroke onset to randomization				0.63
<3 hr	536 (54.5)	497 (51.8)	1.12 (0.93–1.34)	
≥3 hr	319 (51.1)	320 (50.1)	1.04 (0.84–1.30)	
Baseline systolic blood pressure				0.08
≤150 mm Hg	404 (50.6)	402 (51.6)	0.96 (0.79–1.17)	
>150 mm Hg	451 (55.7)	415 (50.6)	1.23 (1.01–1.49)	
Baseline NIHSS score				0.31
≤8	282 (34.9)	282 (34.6)	1.01 (0.83–1.24)	
>8	573 (71.8)	535 (68.3)	1.18 (0.95–1.46)	
Final diagnosis of ischemic stroke				0.88
Large-artery atheroma occlusion	356 (58.0)	362 (56.7)	1.05 (0.84–1.32)	
Small-vessel disease	114 (34.4)	110 (33.0)	1.07 (0.77–1.47)	
Cardioembolism	212 (67.5)	193 (61.7)	1.29 (0.93–1.79)	
Other definite or uncertain cause	138 (51.1)	117 (49.2)	1.08 (0.76–1.53)	
Cerebral infarction on CT				0.66
Yes	205 (58.9)	220 (58.0)	1.04 (0.77–1.39)	
No	649 (51.7)	597 (48.9)	1.12 (0.95–1.31)	
Use of antiplatelet agent				0.05
Yes	222 (56.3)	204 (60.7)	0.84 (0.62–1.12)	
No	632 (52.3)	612 (48.5)	1.16 (0.99–1.36)	
Evidence of atrial fibrillation				0.34
Yes	249 (66.9)	233 (68.3)	0.94 (0.69–1.28)	
No	603 (49.1)	584 (46.4)	1.11 (0.95–1.30)	

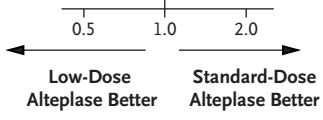

Figure 2. Effects of Low-Dose Alteplase as Compared with Standard-Dose Alteplase on the Primary Efficacy Outcome, According to Prespecified Subgroups.

The primary efficacy outcome was death or disability at 90 days, defined by scores of 2 to 6 on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]). Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events), and horizontal lines represent 95% confidence intervals. For systolic blood pressure and NIHSS score, values are equal to or above the median of distribution versus below the median of distribution. CT denotes computed tomography.

power. One fifth of our trial population were receiving antiplatelet therapy. Previous studies have shown an increased risk of intracerebral hemorrhage with standard-dose alteplase among patients receiving antiplatelet therapy.[23,24] In our prespecified analysis, there was no significant interaction between alteplase dose and antiplatelet treatment with respect to a poor outcome; however, the interaction was significant in a post hoc ordinal analysis of modified Rankin scale scores. The ongoing part of this trial is testing the effectiveness of intensive and early reduction of elevated systolic blood pressure on outcomes in patients with ischemic stroke. Analyses did not indicate any significant interaction between early intensive blood-pressure lowering and alteplase dose.

Efforts to minimize reporting biases in this

open-label trial included the measurement of body weight, blinded central adjudication of intracerebral hemorrhage, and blinded evaluation of clinical outcomes with the use of established criteria. Imprecision in estimates of the treatment effect may have arisen from interobserver variability in determining the scores on the modified Rankin scale,[15,25] which was administered principally by telephone. Analysis of the net change in functional outcome was based on equal weights assigned to each score (0 through 6) on the modified Rankin scale, but patient and provider assessments can vary across health transitions,[26] and functional recovery can continue beyond 90 days.[27] In our trial, selection bias was due to the inclusion of patients who had a predominantly mild severity of neurologic impairment and who were treated at a later time point after symptom onset than in other trials[1,3,4] and than in quality-assurance studies[12,16,28] of the use of alteplase in patients with acute ischemic stroke. The high percentage of Asian participants and concurrent intensive blood-pressure control in some patients may also raise concerns about generalizability, despite the finding that there were no significant interactions observed between Asians and non-Asians, nor with intensity of blood-pressure control.

In conclusion, in a group of predominantly Asian patients with acute ischemic stroke who were eligible for thrombolysis reperfusion therapy, a dose of alteplase of 0.6 mg per kilogram was not shown to be noninferior to the standard dose of 0.9 mg per kilogram with respect to the primary outcome of death and disability. Fewer patients treated with low-dose alteplase than with standard-dose alteplase (1% vs. 2%) had the secondary outcome of symptomatic intracerebral hemorrhage.

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APPENDIX

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