# Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke

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## ABSTRACT

### BACKGROUND

The time to initiate intravenous thrombolysis for acute ischemic stroke is generally limited to within 4.5 hours after the onset of symptoms. Some trials have suggested that the treatment window may be extended in patients who are shown to have ischemic but not yet infarcted brain tissue on imaging.

### METHODS

We conducted a multicenter, randomized, placebo-controlled trial involving patients with ischemic stroke who had hypoperfused but salvageable regions of brain detected on automated perfusion imaging. The patients were randomly assigned to receive intravenous alteplase or placebo between 4.5 and 9.0 hours after the onset of stroke or on awakening with stroke (if within 9 hours from the midpoint of sleep). The primary outcome was a score of 0 or 1 on the modified Rankin scale, on which scores range from 0 (no symptoms) to 6 (death), at 90 days. The risk ratio for the primary outcome was adjusted for age and clinical severity at baseline.

### RESULTS

After 225 of the planned 310 patients had been enrolled, the trial was terminated because of a loss of equipoise after the publication of positive results from a previous trial. A total of 113 patients were randomly assigned to the alteplase group and 112 to the placebo group. The primary outcome occurred in 40 patients (35.4%) in the alteplase group and in 33 patients (29.5%) in the placebo group (adjusted risk ratio, 1.44; 95% confidence interval [CI], 1.01 to 2.06; P=0.04). Symptomatic intracerebral hemorrhage occurred in 7 patients (6.2%) in the alteplase group and in 1 patient (0.9%) in the placebo group (adjusted risk ratio, 7.22; 95% CI, 0.97 to 53.5; P=0.05). A secondary ordinal analysis of the distribution of scores on the modified Rankin scale did not show a significant between-group difference in functional improvement at 90 days.

### CONCLUSIONS

Among the patients in this trial who had ischemic stroke and salvageable brain tissue, the use of alteplase between 4.5 and 9.0 hours after stroke onset or at the time the patient awoke with stroke symptoms resulted in a higher percentage of patients with no or minor neurologic deficits than the use of placebo. There were more cases of symptomatic cerebral hemorrhage in the alteplase group than in the placebo group. (Funded by the Australian National Health and Medical Research Council and others; EXTEND ClinicalTrials.gov numbers, NCT00887328 and NCT01580839.)

CURRENT GUIDELINES FOR ISCHEMIC stroke limit the time to initiate intravenous thrombolytic therapy to within 4.5 hours after the onset of stroke.[1,2] These guidelines are based mainly on a meta-analysis of trials that used noncontrast computed tomography (CT) for the selection of patients.[3] CT perfusion and perfusion-diffusion magnetic resonance imaging (MRI) can show potential viable brain tissue beyond 4.5 hours after the onset of stroke,[4] and reperfusion by means of thrombolysis has been shown to improve functional outcome in patients who have salvageable brain tissue beyond 4.5 hours.[5-8]

The selection of patients for reperfusion therapies on the basis of tissue viability rather than the time from the onset of stroke has also resulted in better outcomes than medical therapy in trials of thrombectomy.[9,10] The benefit of endovascular thrombectomy in patients with imaging evidence of salvageable brain tissue up to 24 hours after stroke onset has resulted in a disparity between the time windows used for thrombolytic therapy and thrombectomy.[1,2] We tested the hypothesis that intravenous thrombolysis with alteplase initiated between 4.5 and 9.0 hours after stroke onset or on awakening with stroke symptoms (for which the time of onset was not known) would provide a benefit in patients who had a small core volume of cerebral infarction that was disproportionate to a larger area of hypoperfusion.[11]

## METHODS

### TRIAL DESIGN

We conducted a phase 3, investigator-initiated, multicenter, randomized, placebo-controlled trial involving patients with acute ischemic stroke, in whom the assigned intervention was initiated between 4.5 and 9.0 hours after the onset of stroke or on awakening with stroke symptoms. The trial methods have been published previously,[11] and the protocol is available with the full text of this article at NEJM.org.

The design of the trial, the analysis and collection of the data, and the writing of the manuscript were performed by the members of the executive committee and by the investigators at the trial sites listed in the Supplementary Appendix, available at NEJM.org. All the authors vouch for the accuracy and completeness of the data, for the fidelity of the trial to the protocol, and for the reporting of adverse events. Boehringer Ingelheim provided the alteplase and matching placebo used in this trial. A research version of RAPID software was provided free of charge to the trial sites by iSchemaView. Neither company was involved in the design, conduct, or reporting of the trial. No confidentiality agreements were in place between the authors and either commercial entity.

After the results of the Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial were published in May 2018,[12] the data and safety monitoring board recommended the discontinuation of the trial because of loss of equipoise. Recruitment was suspended on June 6, 2018.

### PATIENTS

Patients were eligible for inclusion if they were at least 18 years of age; had excellent functional status before enrollment (defined by a score of <2 on the modified Rankin scale, on which scores range from 0 [no neurologic deficit] to 6 [death]); had a stroke with a clinical severity score at presentation of 4 to 26 on the National Institutes of Health Stroke Scale (NIHSS), on which scores range from 0 to 42, with higher scores indicating greater deficit; and had hypoperfused but salvageable regions of brain detected on automated perfusion imaging. Occlusion of a large cerebral vessel was not a prerequisite for inclusion. Imaging techniques included CT perfusion imaging or perfusion-diffusion MRI, and images were processed with the use of a research version of RAPID automated software (Stanford University and iSchemaView).

In estimating the volume of irreversibly injured ischemic-core tissue, we used a threshold for relative cerebral blood flow of less than 30% of that in normal brain regions[13] or we used diffusion-weighted MRI.[14] Critically hypoperfused brain was measured on perfusion MRI or CT perfusion imaging according to a delayed arrival of an injected tracer agent (time to maximum of the residue function exceeding 6 seconds).[15-17] Perfusion lesion–ischemic core mismatch was defined as a ratio greater than 1.2 between the volume of hypoperfusion and the volume of the ischemic core, an absolute difference in volume greater than 10 ml, and an ischemic-core volume of less than 70 ml.[5,18] Patients were not

eligible if the investigator was considering the use of endovascular thrombectomy at the time of enrollment.

The trial was approved by the institutional ethics committee at each participating site. Written informed consent was obtained from all the patients or their legal representatives before enrollment. Additional details of the inclusion and exclusion criteria are provided in the Supplementary Appendix.

### TRIAL INTERVENTIONS

The patients were randomly assigned, in a 1:1 ratio, to receive either alteplase (0.9 mg per kilogram of body weight [maximum, 90 mg], administered intravenously as a 10% bolus and 90% infusion over 1 hour) or matching placebo. Randomization was performed through a centralized website, with stratification according to geographic region (Australia, New Zealand, and Finland vs. Taiwan) and time of intervention (>4.5 to 6.0 hours after stroke onset, >6.0 to 9.0 hours after stroke onset, or on awakening with stroke symptoms). Guideline-based care for acute stroke was recommended for all patients.[1,2] From 2010 through February 2018, the guidelines did not include the use of endovascular thrombectomy in extended time windows.

### OUTCOMES

The primary outcome was a score of 0 or 1 on the modified Rankin scale at 90 days (indicating an excellent functional outcome with a return to all usual activities). The risk ratio for the primary outcome was adjusted for age and clinical severity of stroke (NIHSS score) at baseline. The secondary clinical outcomes were the score (0 to 6) on the modified Rankin scale at 90 days (with the distribution of scores in each trial group used in an ordinal analysis to assess functional improvement); a score of 0 to 2 on the modified Rankin scale at 90 days (indicating functional independence); and percentages of reperfusion of at least 50% and of at least 90% at 24 hours after the intervention (defined as ≥50% and ≥90% reductions, respectively, in the volume of the perfusion lesion in which there had been a delayed arrival of an injected tracer agent exceeding 6 seconds).[19] The prespecified tertiary outcomes were recanalization at 24 hours after stroke (defined as a score of 2 or 3 on the Arterial Occlusive Lesion scale [range, 0 to 3], indi-

cating partial or complete opening of the artery, respectively, with the presence of distal blood flow)[20] in the patients who had occlusion of a cerebral vessel detected on CT or MR angiography at baseline; and major neurologic improvement (defined as a reduction in the NIHSS score of ≥8 points or a score of 0 or 1 within 24 hours, 72 hours, and 90 days after the intervention). Safety outcomes were death within 90 days after the intervention and symptomatic intracranial hemorrhage, which was adjudicated in a blinded manner by a central panel of stroke neurologists and neuroradiologists as parenchymal hematoma type 2 (confluent blood clot occupying >30% of the infarct with substantial mass effect) within 36 hours after intervention, accompanied by an increase of at least 4 points in the NIHSS score from baseline.[21]

### STATISTICAL ANALYSIS

We originally estimated that a sample size of 400 patients would provide the trial 80% power to detect a between-group difference of 15 percentage points in the primary outcome (36% in the alteplase group and 21% in placebo group) at a two-sided significance level of $P=0.05$, with allowance for 90 patients to be lost to follow-up or have data that could not be evaluated.[11] The effect size was based on the results of our previous trial (Echoplanar Imaging Thrombolytic Evaluation Trial [EPITHET]) that compared alteplase with placebo administered 3 to 6 hours after the onset of stroke in patients who had a mismatch in perfusion-weighted MRI and diffusion-weighted MRI.[5] After a blinded review of the observed number of patients who had data that could not be evaluated and the number who were lost to follow-up, the sample size was revised to 310 patients (see the final protocol). A prespecified adaptive sample-size reestimation was also performed in a blinded manner with the use of data from the first 200 patients.[22] This analysis confirmed a final intended sample size of 310 patients.[23]

The statistical analysis plan, available in the protocol, was finalized before the database was locked.[23] Statistical analyses were performed with the use of Stata software, version 13 (StataCorp). We used covariate-adjusted modified Poisson regression with robust error estimation[24] to compare the trial groups in the prespecified primary outcome analysis (adjusted for age and NIHSS

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score at baseline) and in the analyses of the dichotomous secondary efficacy outcomes and the dichotomous safety outcomes.[23] For consistency with the original protocol, we also analyzed the results using logistic-regression modeling and report them in the Supplementary Appendix. The proportional-odds assumption was valid according to the Brant test and the approximate likelihood-ratio test. Therefore, an ordinal logistic-regression model with adjustment for age and NIHSS score at baseline was used to compare the trial groups across the full range of scores on the modified Rankin scale (data were combined for scores of 5 and 6), with the effect estimate for an improvement of at least 1 point in the score presented as a common odds ratio with a 95% confidence interval. The primary analysis for all clinical outcomes was prespecified to be adjusted for baseline prognostic factors of age and NIHSS score; we report both covariate-adjusted and unadjusted results. Treatment effects for secondary outcomes are presented as adjusted risk ratios with 95% confidence intervals.

Because the analyses of the secondary or tertiary outcomes did not include adjustment for multiple comparisons, the results are reported as point estimates with unadjusted 95% confidence intervals. The handling of missing data and sensitivity analyses are described in the statistical analysis plan (see the protocol).

Preplanned subgroup analyses explored the effects of age (<75 vs. ≥75 years and <80 vs. ≥80 years), severity of stroke at baseline (NIHSS score <10 or ≥10), time to intervention (>4.5 to 6.0 hours, >6.0 to 9.0 hours, or on awakening with stroke), geographic region (Australia, New Zealand, and Finland vs. Taiwan), and presence of any large-vessel occlusion. Large-vessel occlusion was defined as occlusion of the internal carotid or middle cerebral artery (M1 or proximal [retrievable] M2 segments or both) and was independently graded on MR or CT angiography in a blinded manner by two assessors who then reached a consensus.

## RESULTS

### PATIENTS

From August 2010 through June 2018, a total of 225 patients were enrolled at 16 centers in Australia, 1 center in New Zealand, 10 centers in Taiwan, and 1 center in Finland. A total of 113 patients were assigned to the alteplase group and 112 patients to the placebo group (Fig. S1 in the Supplementary Appendix). The mean (±SD) ages were 73.7±12.7 years in the alteplase group and 71.0±12.7 years in the placebo group. The median NIHSS score at the initial clinical assessment was 12.0 (interquartile range, 8.0 to 17.0) in the alteplase group and 10.0 (interquartile range, 6.0 to 16.5) in the placebo group. Of the entire trial population, 25% of the patients received the assigned intervention in the later time window (>6.0 to 9.0 hours after stroke onset) and 10% in the earlier time window (>4.5 to 6.0 hours after stroke onset); the remainder (65%) awoke with stroke symptoms with an unknown time of onset (Table 1, and Table S1 in the Supplementary Appendix).

### EFFICACY

The primary outcome of a modified Rankin scale score of 0 or 1 was attained by 35.4% of the patients in the alteplase group and by 29.5% of those in the placebo group (adjusted risk ratio, 1.44; 95% confidence interval [CI], 1.01 to 2.06; P=0.04) (Table 2 and Fig. 1). The unadjusted risk ratio did not show a significant difference between the trial groups.

With respect to the secondary outcomes, an ordinal analysis of the distribution of scores on the modified Rankin scale in each trial group did not show a significant between-group difference in functional improvement at 90 days, as indicated by the lower boundary of the 95% confidence interval that crossed 1.00 (common odds ratio, 1.55; 95% CI, 0.96 to 2.49). A modified Rankin scale score of 0 to 2 (indicating functional independence) was attained by 49.6% of patients in the alteplase group and by 42.9% of those in the placebo group (adjusted risk ratio, 1.36; 95% CI, 1.06 to 1.76). Treatment with alteplase resulted in a percentage of reperfusion of at least 50% at 24 hours in 71.7% of the patients in the alteplase group and in 52.3% of those in the placebo group (adjusted risk ratio, 1.35; 95% CI, 1.09 to 1.67) and of at least 90% in 50.0% of the patients in the alteplase group and in 28.4% among those in the placebo group (adjusted risk ratio, 1.73; 95% CI, 1.22 to 2.46); however, inferences should not be made from these results because there was no plan for correction for multiple comparisons (Fig. S2 in the Supplementary Appendix).

**Table 1. Characteristics of the Patients at Baseline.\***

| Characteristic | Alteplase (N=113) | Placebo (N=112) |
|---|---|---|
| Age — yr | 73.7±11.7 | 71.0±12.7 |
| Male sex — no. (%) | 59 (52.2) | 66 (58.9) |
| Median NIHSS score (IQR)† | 12.0 (8.0–17.0) | 10.0 (6.0–16.5) |
| Clinical history of atrial fibrillation — no. (%) | 46 (40.7) | 36 (32.1) |
| Geographic region — no. (%) | | |
|     Australia, New Zealand, and Finland | 90 (79.6) | 88 (78.6) |
|     Taiwan | 23 (20.4) | 24 (21.4) |
| Time from stroke onset to randomization — no. (%) | | |
|     >4.5 to 6.0 hr | 12 (10.6) | 11 (9.8) |
|     >6.0 to 9.0 hr | 28 (24.8) | 28 (25.0) |
|     Awoke with stroke symptoms‡ | 73 (64.6) | 73 (65.2) |
| Median time from stroke onset to hospital arrival (IQR) — min | 308 (227–362) | 293 (230–357) |
| Median time from stroke onset to initiation of intravenous therapy (IQR) — min | 432 (374–488) | 450 (374–500) |
| Median time from hospital arrival to initiation of intravenous therapy (IQR) — min | 124 (81–179) | 127 (87–171) |
| Imaging result | | |
|     Large-vessel occlusion — no.(%)§ | 78 (69.0) | 81 (72.3) |
|     Median volume of irreversibly injured ischemic-core tissue at initial imaging (IQR) — ml¶ | 4.6 (0–23.2) | 2.4 (0–19.5) |
|     Median perfusion-lesion volume at initial imaging (IQR) — ml‖ | 74.3 (40.1–134.0) | 78 (47.7–111.8) |

\* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal) to 42 (death), with higher scores indicating greater deficit.
‡ Among patients who awoke with stroke symptoms, the onset of stroke was estimated as the midpoint of sleep (i.e., the time between going to sleep and waking up with symptoms); these patients underwent randomization if they were within 9 hours of the estimated time of onset.
§ Large-vessel occlusion is defined as occlusion of the internal carotid artery, first division of the middle cerebral artery (M1), and proximal portion of the second division of the middle cerebral artery (M2).
¶ The volume of irreversibly injured ischemic-core tissue was calculated with the use of a threshold for relative cerebral blood flow of less than 30% of that in normal brain tissue or with the use of diffusion-weighted MRI.
‖ To define the critically hypoperfused tissue, perfusion-lesion volume was calculated as the volume of tissue in which there had been delayed arrival of an injected tracer agent exceeding 6 seconds.

With respect to the tertiary outcomes, recanalization at 24 hours after stroke occurred in 67.3% of the patients in the alteplase group and in 39.4% of those in the placebo group (adjusted risk ratio, 1.68; 95% CI, 1.29 to 2.19), and early major neurologic improvement at 24 hours occurred in 23.9% of the patients in the alteplase group and in 9.8% of those in the placebo group (adjusted risk ratio, 2.76; 95% CI, 1.45 to 5.26). There were no significant interactions observed between trial group and any subgroup, including subgroups defined according to large-vessel occlusion status and time to intervention. (See also Figs. S3 and S4 in the Supplementary Appendix.)

## SAFETY

The percentage of patients who died within 90 days after the intervention did not differ significantly between the alteplase group and the placebo group (13 of 113 patients [11.5%] vs. 10 of 112 patients [8.9%]; adjusted risk ratio, 1.17; 95% CI, 0.57 to 2.40; P=0.67). Death within 7 days occurred in 9 of 225 patients (4.0%) in the trial population — 5 in the alteplase group (2 of whom had symptomatic hemorrhage) and 4 in the placebo group.

Symptomatic intracranial hemorrhage occurred in 7 of 113 patients (6.2%) in the alteplase group and in 1 of 112 patients (0.9%) in the placebo

**Table 2. Efficacy and Safety Outcomes.***

| Outcome | Alteplase (N=113) | Placebo (N=112) | Adjusted Effect Size (95% CI)† | P Value | Unadjusted Effect Size (95% CI)† | P Value |
|---|---|---|---|---|---|---|
| | *no./total no. (%)* | | | | | |
| **Primary outcome** | | | | | | |
| Score of 0 to 1 on the modified Rankin scale at 90 days‡ | 40/113 (35.4) | 33/112 (29.5) | 1.44 (1.01–2.06) | 0.04 | 1.2 (0.82–1.76) | 0.35 |
| **Secondary outcomes** | | | | | | |
| Score on the modified Rankin scale at 90 days | | | | | | |
| 0 | 14/113 (12.4) | 12/112 (10.7) | | | | |
| 1 | 26/113 (23.0) | 21/112 (18.8) | | | | |
| 2 | 16/113 (14.2) | 15/112 (13.4) | | | | |
| 3 | 15/113 (13.3) | 16/112 (14.3) | | | | |
| 4 | 15/113 (13.3) | 24/112 (21.4) | | | | |
| 5 | 14/113 (12.4) | 14/112 (12.5) | | | | |
| 6 | 13/113 (11.5) | 10/112 (8.9) | | | | |
| Functional improvement§ | | | 1.55 (0.96–2.49) | | 1.18 (0.74–1.87) | |
| Functional independence¶ | 56/113 (49.6) | 48/112 (42.9) | 1.36 (1.06–1.76) | | 1.16 (0.87–1.54) | |
| Percentage of reperfusion at 24 hr | | | | | | |
| ≥90% | 53/106 (50.0) | 31/109 (28.4) | 1.73 (1.22–2.46) | | 1.76 (1.23–2.51) | |
| ≥50% | 76/106 (71.7) | 57/109 (52.3) | 1.35 (1.09–1.67) | | 1.37 (1.10–1.70) | |
| **Tertiary outcomes** | | | | | | |
| Recanalization at 24 hr | 72/107 (67.3) | 43/109 (39.4%) | 1.68 (1.29–2.19) | | 1.71 (1.30–2.23) | |
| Major neurologic improvement‖ | | | | | | |
| At 24 hr | 27/113 (23.9) | 11/112 (9.8) | 2.76 (1.45–5.26) | | 2.43 (1.27–4.67) | |
| At 72 hr | 32/112 (28.6) | 22/112 (19.6) | 1.56 (0.97–2.52) | | 1.45 (0.90–2.34) | |
| At 90 days | 59/101 (58.4) | 49/99 (49.5) | 1.17 (0.91–1.52) | | 1.18 (0.91–1.53) | |
| **Safety outcomes** | | | | | | |
| Death within 90 days after intervention | 13/113 (11.5) | 10/112 (8.9) | 1.17 (0.57–2.40) | 0.67 | 1.29 (0.59–2.82) | 0.53 |
| Symptomatic intracranial hemorrhage within 36 hr after intervention | 7/113 (6.2) | 1/112 (0.9) | 7.22 (0.97–53.54) | 0.053 | 6.94 (0.86–55.73) | 0.07 |

\* Adjusted analyses of the scores on the modified Rankin scale, death, symptomatic intracerebral hemorrhage, and major neurologic improvement included age and baseline NIHSS score as covariates. Adjusted analyses of reperfusion and recanalization included site of arterial occlusion as a covariate.

† Effect sizes were assessed as risk ratios, except for functional improvement. The 95% confidence intervals for the secondary and tertiary outcomes were not adjusted for multiple comparisons.

‡ Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no neurologic deficit, 1 no clinically significant disability (return to all usual activities), 2 slight disability (able to handle own affairs without assistance but unable to carry out all previous activities), 3 moderate disability requiring some help (e.g., with shopping, cleaning, and finances but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requiring constant nursing care and attention), and 6 death.

§ Functional improvement was defined as an improvement of at least 1 point on the modified Rankin scale at 90 days and was assessed as a common odds ratio in an ordinal logistic-regression analysis (with data combined for scores of 5 and 6).

¶ Functional independence was defined as a score of 0 to 2 on the modified Rankin scale at 90 days.

‖ Major neurologic improvement was classified as a reduction in NIHSS score of at least 8 points or a score of 0 or 1 at 24 hours, 72 hours, or 90 days.
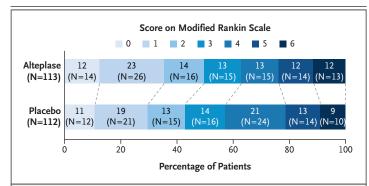
group (adjusted risk ratio, 7.22; 95% CI, 0.97 to 53.54; P=0.053). One patient in the alteplase group had hemorrhagic transformation of the infarction before the infusion at the site of subsequent bleeding. Details regarding adverse events, including causes of death and serious adverse events, are provided in Tables S3 and S4, respectively, in the Supplementary Appendix.

## DISCUSSION

Among the patients who had acute ischemic stroke and a favorable perfusion-imaging profile detected by automated perfusion imaging, the use of alteplase therapy between 4.5 and 9.0 hours after the onset of stroke or at the time the patient awoke with stroke symptoms resulted in a higher percentage of patients with a score of 0 or 1 on the modified Rankin scale (indicating no or minimal deficits, respectively) than the use of placebo, with an unadjusted absolute between-group difference of 6 percentage points. In an ordinal analysis of the distribution of scores on the modified Rankin scale at 90 days, the lower boundary of the 95% confidence interval of the common odds ratio for functional improvement crossed 1.00 and therefore was unlikely to show a significant difference between the trial groups. Findings for the other outcomes, including recanalization, reperfusion, and early neurologic improvement, were supportive of the observed benefit of alteplase with respect to the primary outcome, but the analyses were not adjusted for multiple comparisons.

The approach to imaging classification in this trial was different from that in the WAKE-UP trial,[12] which used MRI to identify patients with stroke with an unknown time of onset that was likely to be within 4.5 hours. In our trial, for the 65% of the patients had stroke symptoms on awakening, the onset of stroke was estimated as the midpoint of sleep (i.e., the time between going to sleep and waking up with symptoms); these patients underwent randomization if they were within 9 hours of the estimated time of onset. In contrast, the onset of stroke was measured from the time the patient was last known to be well in the DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergo-



**Figure 1. Scores on the Modified Rankin Scale at 90 Days.**

Shown is the distribution of the scores on the modified Rankin scale at 90 days for all patients (intention-to-treat analysis). Scores range from 0 to 6, with 0 indicating no neurologic deficit, 1 no clinically significant disability (return to all usual activities), 2 slight disability (able to handle own affairs without assistance but unable to carry out all previous activities), 3 moderate disability requiring some help (e.g., with shopping, cleaning, and finances but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requiring constant nursing care and attention), and 6 death. The primary outcome of a score of 0 or 1 on the modified Rankin scale occurred in a higher percentage of patients in the alteplase group than in the placebo group. A secondary ordinal analysis of the distribution of scores on the modified Rankin scale at 90 days did not show a significant between-group difference in functional improvement (common odds ratio, 1.55; 95% confidence interval, 0.96 to 2.49). Percentages may not total 100 because of rounding.

ing Neurointervention with Trevo) and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trials of thrombectomy guided by imaging selection in the extended time window.[9,10] With this definition, our trial would have included patients who were within approximately 12 hours from the onset of stroke.

The positive results of the WAKE-UP trial drove the decision to terminate the current EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits) trial; however, the patient population and imaging selection differed in the two trials. The clinical severity of stroke was milder in the WAKE-UP trial, with a median NIHSS score of 6, and the MRI-based selection model aimed to identify patients with stroke onset within the standard 4.5-hour thrombolysis window.[12]

In the current trial, the percentage of patients who had symptomatic intracerebral hemorrhage was higher in the alteplase group (6% of patients) than in the placebo group (1% of patients). This finding is similar to that observed

in the EPITHET trial of alteplase therapy initiated between 3 and 6 hours after stroke (7% of patients)[5] and in the DAWN[9] and DEFUSE 3[10] trials of late-window thrombectomy (6% of patients in both studies).[12]

Limitations of our trial include the premature termination of recruitment at 73% of the planned sample size. We were also unable to show a significant difference in the secondary outcome of functional improvement, as gauged by the 95% confidence interval in an ordinal analysis. In contrast to the adjusted analyses emphasized in the results of the trial, the findings from the unadjusted analyses of primary and secondary outcomes did not differ significantly between trial groups. However, imbalances in the baseline covariates of age and clinical severity of stroke occurred in favor of the placebo group. Our "door-to-needle time" of approximately 2 hours was longer than recommended in the guidelines.[1,2] The majority of patients in the trial had large-vessel occlusion. Since the initiation of the trial, endovascular thrombectomy has been introduced for certain patients, who would have been eligible for our trial.[1,2]

In conclusion, the use of alteplase therapy in patients who had a favorable perfusion-imaging profile between 4.5 and 9 hours after stroke onset or on awakening with stroke symptoms resulted in no or minor neurologic deficits more often than the use of placebo. Because of the limited power of our conclusions as a result of premature termination of the trial and the lack of a significant between-group difference in the secondary outcome of functional improvement, further trials of thrombolysis in this time window are required.

## APPENDIX

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