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

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RobotReviewer report

Risk of bias table

trial	design	n	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
stroke trombolisi a 9 ore.pdf	RCT	310	+	+	+	+

Characteristics of studies

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Population	1. 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. 2. 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. 3. 11 Me thods 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.
Intervention	1. 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. 2. A total of 113 patients were randomly assigned to the alteplase group and 112 to the placebo group.

	3. 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.
Outcomes	1. 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 [score at baseline) and in the analyses of the dichotomous secondary efficacy outcomes and the dichotomous safety outcomes. 2. 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. 3. 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 ,â•50% and ,â•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).

Bias	Judgement	Support for judgement
Random sequence generation	low	1. A total of 113 patients were randomly assigned to the alteplase group and 112 to the placebo group. 2. 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 S1in the Supplementary Appendix). 3. A research version of RAPID software was provided free of charge to the trial sites by iSchemaView.
Allocation concealment	low	1. patients were assigned to the alteplase group and 112 patients to the placebo group (Fig. 2. We thank Werner Hacke and Peter Ringleb (Heidelberg, Germany) for advice as external advisory board members; Simon McBride, Christopher Stanbridge, and Karen Harrap (Commonwealth Scientific and Industrial Research Organization) for creation of the electronic case record and Web randomization software ; Matus Straka and Roland Bammer for assistance with implementation of RAPID software; and Elise Cowley, Rachael McCoy, and Michele Sallaberger (Neuroscience Trials Australia) for trial management. 3. Neither company was involved in the design, conduct, or reporting of the trial.
Blinding of participants and personnel	low	1. 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. 2. patients were assigned to the alteplase group and 112 patients to the placebo group (Fig. 3. Boehringer Ingelheim provided the alteplase and matching placebo used in this trial.
Blinding of	low	1. 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.

outcome assessment

2. 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.
3. Neither company was involved in the design, conduct, or reporting of the trial.

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