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A placebo controlled trial of alteplase (rt-PA) in acute ischemic hemispheric stroke where thrombolysis is initiated between 3 and 4 hours after stroke onset. ECASS III

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Background: Both the scientific society and the European Health Authorities would like to know whether thrombolysis initiated between 3 and 4 hours after stroke onset is effective and safe as suggested by a pooled analysis of the ATLANTIS, ECASS and NINDS rt-PA trials. **Principal Investigator:** Werner Hacke, Department of Neurology, University of Heidelberg, Germany. **Purpose:** To evaluate efficacy and safety of rt-PA between 3 and 4 hours after stroke onset in European setting. **Design:** A multicenter, randomized, double blind, placebo controlled trial in 110 hospitals in 15 European countries. **Sample Size:** 800 patients with acute ischemic hemispheric stroke. **Study Population:** Male and female stroke patients, aged 18-80 years, without a severe stroke (NIHSS <25 on admission), evidence of ICH on admission CT, prior clinical stroke and concomitant diabetes, and without ordinary contraindications for thrombolysis can be enrolled if the patient or a legal representative/relative where applicable according to legal requirements of the country has signed an informed consent and there is no doubt of the patient's willingness to participate. **Interventions:** Patients will be randomized 1:1 to receive intravenous rt-PA (alteplase 0.9mg/kg bodyweight, maximally 90mg; 10% bolus plus one hour infusion) or placebo started between 3 and 4 hours from the onset of stroke. **Outcome Endpoints:** Primary efficacy endpoint is Modified Rankin Scale 0-1 at day 90 and secondary efficacy endpoint is Global Outcome (Modified Rankin Scale 0-1, Barthel Index 95-100, NIHSS 0-1, Glasgow Outcome Score 0-1) at day 90. Further efficacy parameters are ordinary disability and functional scales, infarct size on CT at various time points after stroke onset, Modified Rankin Scale at day 90 stratified by admission NIHSS and length of in-hospital stay. **Safety Endpoints:** Survival at day 90, stroke related neurological deaths, symptomatic cerebral hemorrhage, cerebral herniation and symptomatic brain edema, vital signs, adverse events, laboratory parameters. **Statistical Analysis:** ITT analysis, parallel group comparison, chi-square test on proportions (RRs), global OR statistics, logistic regression, ANOVA. Sample size allows detecting or disproving a difference of 10% in primary endpoint between the treatment groups with two-sided alpha level of 5% and power probability of about 90%. No interim analysis. **Trial Status:** Planned dates of the trial are from April, 2003 (first patient in) to October, 2005 (last patient out). **Conclusions:** The ECASS III trial will reveal whether it is possible to safely extend the time window for stroke thrombolysis by one hour, which could make the therapy available for a larger stroke population in Europe.