

# Thrombolytic Therapy

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Thrombolytic therapy, which can restore neurologic functions if given early enough, has received approval by every major regulatory authority in the world and has revealed benefit in several post-marketing studies including the Pan-European SITSMOST registry for use within 3 hours of stroke onset (1). However, the short time window is seen by many as the major obstacle for this treatment becoming generally used in acute stroke. Currently, in Denmark, only 4% of all stroke admissions are treated with iv-tPA. In contrast, in the metropolitan areas up to one third of acute stroke evaluations are considered candidates for thrombolytic therapy thanks to logistic adjustments. Research into extending the time window since the original FDA approval in 1996 included several studies using tPA at longer time windows between 3 and 6 hours. Although, each of these studies came out negative, a pooled meta-analysis suggested that a benefit would hold up to 4.5 hours after stroke onset – the rationale for the ECASS III study (2).

The results of the European Cooperative Acute Stroke Study III (ECASS III), reported in the New

England Journal on September 25th 2008, teach us many lessons, some medical and some political, and clearly provide sufficient evidence that iv-tPA is safe and effective for patients with acute stroke in this extended 4.5 hour time window (3). The design of ECASS III closely resembled that of the original National Institute of Neurological Disorders and Stroke (NINDS) trial of tPA for acute stroke, with the important exception that ECASS III enrolled patients who presented between 3 and 4.5 hours after the onset of symptoms, instead of 3 hours after stroke onset. Moreover, patients with severe strokes (patients with scores of 25 or higher on the National Institutes of Health Stroke Scale [NIHSS], in which scores range from 0 to 42, with higher values reflecting more severe cerebral infarcts), as well as those with a past history of stroke and diabetes were excluded from enrolment. As a result in ECASS III patients in general had less severe strokes and fewer patients were diabetic making the outcomes of the placebo group in ECASS III somewhat better than those in the placebo group in the NINDS trial.

ECASS III enrolled a total of 821 patients and randomly assigned 418 to the tPA group and 403 to the placebo group. The median time for the administration of tPA was 3 hours 59 minutes. More patients had a favorable outcome with tPA than with placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; P = 0.04). In the global analysis, the

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outcome was also improved with tPA as compared with placebo (odds ratio, 1.28; 95% CI, 1.00 to 1.65;  $P < 0.05$ ). The incidence of intracranial hemorrhage was higher with tPA than with placebo (for any intracranial hemorrhage, 27.0% vs. 17.6%;  $P = 0.001$ ; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%;  $P = 0.008$ ) but mortality did not differ significantly between the groups (7.7% and 8.4%, respectively;  $P = 0.68$ ). There was no significant difference in the rate of other serious adverse events. ECASS III did not specifically exclude enrolment of patients that were taking primary or secondary prevention with antiplatelet agents (although they did not report the numbers) and allowed small doses of subcutaneous heparin be used during the 24 hours after thrombolytic therapy. However, further studies are urgently needed to study the effect of combining antithrombotic agents with thrombolysis for acute stroke, in order to prevent not only venous clots but also reocclusion of the target vessel.

The ECASS III results should not be misunderstood as a *carte blanche* but rather that more patients can now be candidates. In other words, established door to needle times need to remain untouched or if anything further diminished. Since the inclusion and exclusion criteria of ECASS III were rather broad, patients who present with acute stroke will likely qualify for treatment. When data are collected properly, the evidence consistently suggests that roughly one third of all patients with stroke present to a treatment facility within the appropriate time window and satisfy the

criteria for acute thrombolytic therapy. The frequently (and above) quoted statistic that only 4% of all patients with stroke receive rt-PA must therefore be viewed as a condemnation of our health care system and neurology in particular. Stroke patients are coming in large numbers, while we are hardly responding at all.

The real lesson of ECASS III is not that we can wait longer before treating but that we advance the patient access to acute stroke care and develop a contingency plan for patients with acute stroke. This includes an understanding of the vascular pathology at play, the appreciation of ischemic tissue at risk and appropriate facilities that allow targeted treatments. It is time to wave good-bye to the all too convenient concept of one size must fit all (or nobody) in acute stroke therapy.

## Referencer

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3. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with Alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-1329