TIMING OF ALTEPLASE FOR ACUTE STROKE

Intravenous alteplase (recombinant tissue plasminogen activator) is restricted for use within 3 h from stroke onset by marketing authorizations. Some patients are treated beyond this approved time frame, however, even though short-term survival is reduced by late treatment. A study reported in the *Lancet* aimed to establish the useful time window for treatment with alteplase. "We considered that a pooled analysis of the existing data would best inform on the timing of treatment," explains lead investigator Kennedy Lees.

Eight major trials, which included a total of 3,670 patients randomly assigned to receive alteplase or placebo, were analyzed to determine the relationship between time from stroke onset to start of treatment (OTT) and favorable 3-month outcome, defined either by modified Rankin score 0–1 alone, or by a composite measure consisting of three neurological function scores (modified Rankin score, Barthel Index, and NIH Stroke Scale).

The association between OTT and favorable outcome was significant for both the modified Rankin score and composite end point. Odds of a favorable outcome increased as OTT decreased, and no benefit was seen after around 270 min. Assessment at 3 months found an association between OTT and mortality, and a significant increase in deaths at OTT beyond 4.5 h. The rates of severe parenchymal hemorrhage were independent of OTT, which indicates that factors other than timing of treatment might cause death.

Results from this analysis are important as they show for the first time that treatment beyond 4.5 h may be harmful. Lees emphasizes that "we should not be treating patients after 4.5 h unless we can identify patients who are less likely to be harmed and more likely to benefit from late initiation of treatment. We need to strive to shorten delays to treatment in all patients."

Helene Myrvang

Original article Lees, K. R. *et al.* Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trails. *Lancet* **375**, 1695–1703 (2010)