Survival Benefit of rt-PA Not Affected by Age When Delivered Up to 4.5 Hours Post Event

Written by **Maria Vinall**

Intravenous recombinant tissue plasminogen activator (rt-PA) is effective in the treatment of acute ischemic stroke; however, there has been some doubt regarding the timing of its use, its use in older patients, as well as its use in patients with different levels of stroke severity. Jonathan R. Emberson, MSc, PhD, University of Oxford, United Kingdom, presented data indicating that regardless of patient age, rt-PA improves the odds of surviving with no significant disability when delivered within 4.5 hours of stroke onset, with earlier treatment leading to proportionally bigger benefit.

The goal of this independent meta-analysis was to examine the extent to which treatment delay, age, and stroke severity modify the effect of rt-PA on stroke outcomes. The effects of rt-PA on the risk of symptomatic intracranial hemorrhage (sICH) and mortality was also assessed. The primary efficacy outcome was the odds of achieving an mRS score of 0/1 at 3 to 6 months post stroke. Safety endpoints included 90-day mortality, sICH defined by parenchymal hemorrhage of type 2 (PH2) within 7 days, or Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) definition of PH2 type hemorrhage within 36 hours, and fatal ICH within 7 days. The full analysis plan has been previously published [Stroke Thrombolysis Trialists' Collaborative Group. *Int J Stroke* 2013].

The analysis included data from 6756 participants from nine trials (Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke trials A/B; European Cooperative Acute Stroke Studies I/II/III; Echoplanar Imaging Thrombolytic Evaluation Trial; National Institute of Neurological Disorders and Stroke trials A/B; and the Third International Stroke Trial [IST-3]) in which subjects were randomized to rt-PA (n=3391) or control (n=3365). Approximately 44% of the subjects were from IST-3. Although these patients were older than those in the other trials (77 vs 66 years), mean treatment delay was similar (4.2 vs 3.9 hours), and average stroke severity was the same NIHSS score of 12).

The odds of achieving an mRS 0/1 were significantly improved with rt-PA, with the benefits being more significant with earlier treatment. There was a significant 75% improvement in the odds of a patient achieving mRS 0/1 when treatment was delivered within 3 hours (95% CI, 1.35 to 2.27) and a significant 26% improvement when delivered between 3 and 4.5 hours post event (95% CI, 1.05 to 1.51). There was a 15% nonsignificant improvement when treatment was delivered >4.5 hours post stroke. There was no evidence that age or stroke severity altered the proportional benefits of rt-PA and clear evidence of benefit in a subgroup of patients aged >80 years (OR, 1.56; 95% CI, 1.17 to 2.08).

The average incidence of ICH was low in the control group but increased among patients receiving rt-PA. This was particularly true for fatal ICH within 7 days in the rt-PA group. By 90 days, the rate of excess death from any cause was not significantly different (Table 1). The 11% relative difference in excess death at 90 days was primarily driven by the increased risk of fatal ICH by Day 7 in the rt-PA group.

Table 1. Safety Outcomes

	rt-PA	Control	RR (95% CI)
Number randomized	3391	3365	
sICH			
PH2 at 7 days	231 (6.8%)	44 (1.3%)	5.55 (4.01-7.70)
SITS-MOST at 36 hours	124 (3.7%)	19 (0.6%)	6.67 (4.11-10.8)
Fatal ICH (within 7 days)	91 (2.7%)	13 (0.4%)	7.14 (3.98-12.8)
Death within 90 days	608 (17.9%)	556 (16.5%)	1.11 (0.99-1.25)

ICH=intracranial hemorrhage; PH2=parenchymal hemorrhage of type 2; rt-PA=recombinant tissue plasminogen activator; SITS-MOST=Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

Although the proportional increase in the early risk of fatal ICH was similar irrespective of treatment delay, age, or stroke severity, and was present even among those patients who were treated within 3 hours, the absolute risk increased with stroke severity. Dr. Emberson suggested that since the rates of death from all causes between Days 8 and 90 did not differ significantly, and since there was no excess in 90-day mortality among those treated earlier, that early treatment with rt-PA may contribute to a late benefit in mortality among patients who survive the first week following their stroke.

Early Clinician Prediction Outperforms Clinical Scales in Predicting Functional Outcome for Patients With Acute ICH

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David Y. Hwang, MD, Yale School of Medicine, New Haven, Connecticut, USA, presented the results of the Prediction in Intracerebral Hemorrhage study [PICH]. PICH was a prospective observational cohort study which showed that early clinical judgment by attending physicians and