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

Written by **Maria Vinall**

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

nurses more accurately predict 90-day outcome among patients with acute ICH compared with two commonly used validated scales

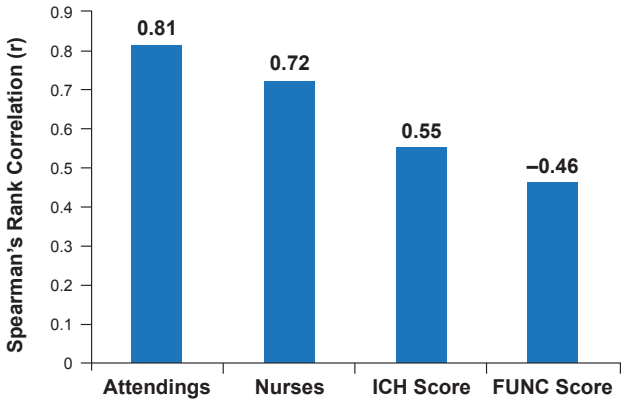
Determining accurate prognoses for ICH patients is crucial as it drives early decisions regarding life-sustaining therapy, informs patient and family counseling, and influences ICH research including study design and patient enrollment [Holloway RG et al. *Neurology* 2013]. Although multiple ICH clinical scales have been developed, none have had their accuracy tested against the early judgment of physicians and nurses. The objective of the PICH study was to compare the accuracy of the ICH Score [Hemphill JC et al. *Stroke* 2001; *Neurology* 2009] and FUNC score [Rost NS et al. *Stroke* 2008] with subjective clinical judgment for predicting functional outcome at 3 months among patients with acute ICH. Eligible patients included adults participating in the larger Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study at five centers. Clinician participants comprised of one physician and one nurse caring for each patient. Clinicians were asked to predict the 3-month mRS score for each patient—within 24 hours of each patient admission—and to indicate whether they would recommend comfort care only to the patient's family. ICH and FUNC scores were calculated for each patient upon admission; a blinded 3-month actual mRS was also obtained via ERICH follow-up.

Scores on the ICH scale range from 0 to 6, based on the sum of the scores of 5 components: the Glasgow Coma Scale (GCS) score (counting as 0, 1, or 2 points), ICH volume ≥30 mL, the presence of intraventricular hemorrhage, whether the hemorrhage is of infratentorial origin and, age < or ≥80 years. A score of 6 indicates a high probability for a poor outcome. Among various other outcomes, the ICH score has been validated to predict the probability of achieving functional independence at 90 days. The FUNC score was specifically designed to predict functional independence at 90 days. Scores range from 0 to 11, with a score of 11 indicating the highest probability for favorable outcome. The FUNC score is based on five factors: ICH volume (counting as 0, 2, or 4 points), age (<70, 70 to 79, and ≥80 years; counting as 0, 1, or 2 points), ICH location (lobar, deep, or other; counting as 2, 1, or 0 points), GCS score (counting as 0 or 2 points), and the presence of pre-ICH cognitive impairment.

Of the 405 patients from the ERICH study who were eligible to participate in PICH, 100 were enrolled. Participants were a mean age of 66.8 years; 64% had a GCS score of 13 to 15; the ICH was deep in 53% of patients, lobar in 36%, and infratentorial in 11%. The ICH volume was <30 cc in 70% of patients, between 30 and 60 cc in 16%, and >60 cc in 13%. Among the clinicians, 70% of the physicians were neurologists with 75% of the predictions being made by attending physicians and 25% by trainees. Among the nurses, 71% had a neuroscience specialty.

Although all correlations for the clinician predictions and clinical scales with 3-month mRS were significant ($p<0.02$ for all), the subjective predictions made by both attending physicians and nurses had a higher Spearman's rank correlation with the actual 3-month mRS than either clinical scale (Figure 1).

Figure 1. Correlation of Subjective Predictions and Clinical Scales With Actual 3-Month mRS Score



ICH=intracerebral hemorrhage; all p values <0.05 for comparisons between clinician correlations and ICH/FUNC scores correlations with 3-month mRS. FUNC score correlation is negative since lower score predict poor outcome.

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When the 18 patients for whom only comfort care was likely recommended were removed from the analysis, the Spearman's rank correlation for the subjective predictions remained higher than those for either clinical score ($p<0.05$). The results were similar when data for only survivors were analyzed.

The study is limited by several factors: the clinician participants making predictions were not formally trained in the mRS, early predictions were difficult to obtain and led to 218 potential patients being excluded, and, finally, the cohort contained many patients with low GCS and ICH volume.

Stroke Severity Adjusted Triage Can Benefit Patients

Written by Brian Hoyle

Evan Allen, MD, MBA, Florida Hospital Neuroscience Institute, Orlando, Florida, USA, described the benefits of a state-wide severe stroke adjusted triage (SAST) system that bypasses a geographically-closer primary stroke center