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**Publishing Title:** Impact of Treatment Delay, Age and Stroke Severity on the Effects of Intravenous Thrombolysis With Alteplase in Acute Ischemic Stroke: An Individual-patient-data Meta-analysis

**Author Block:** Jonathan R Emberson*, Univ of Oxford, Oxford, United Kingdom; Kennedy R Lees*, Univ of Glasgow, Glasgow, United Kingdom; Patrick Lyden*, Dept of Neurology, Los Angeles, CA; Lisa Blackwell, Univ of Oxford, Oxford, United Kingdom; Gregory W Albers, Stanford Univ, Stanford, CA; Erich Bluemki, Boehringer Ingelheim, Ingelheim, Germany; Thomas G Brott, Mayo Clinic, Jacksonville, FL; Geoffrey Cohen, Univ of Edinburgh, Edinburgh, United Kingdom; Stephen Davis, Univ of Melbourne, Melbourne, Australia; Geoffrey Donnan, The Florey Inst of Neuroscience and Mental Health, Melbourne, Australia; James Grotta, The Univ of Texas Health Science Ctr at Houston, Houston, TX; George Howard, Univ of Alabama, Birmingham, AL; Markku Kaste, Helsinki Univresity Central Hosp, Helsinki, Finland; Masatoshi Koga, Natl Cerebral and Cardiovascular Ctr, Suita, Japan; Ruediger Von Kummer, Technische Univ, Dresden, Germany; Maarten Lansberg, Stanford Univ, Stanford, CA; Richard Lindley, Univ of Sydney, Sydney, Australia; Gordon Murray, Univ of Edinburgh, Edinburgh, United Kingdom; Jean Marc Olivot, Stanford Stroke Ctr, Stanford, CA; Mark Parsons, Univ of Newcastle, Newcastle, Australia; Barbara Tilley, Univ of Texas Health Science Ctr Sch of Public Health, Houston, TX; Danilo Toni, Sapienza Univ, Rome, Italy; Kazunori Toyoda, Natl Cerebral and Cardiovascular Ctr, Suita, Japan; Nils Wahlgren, Karolinska Inst, Clinical Neuroscience, Stockholm, Sweden; Joanna Wardlaw, William Whiteley, Univ of Edinburgh, Edinburgh, United Kingdom; Gregory J del Zoppo, Univ of Washington, Seattle, WA; Colin Baigent +, Univ of Oxford, Oxford, United Kingdom; Peter Sandercock #, Univ of Edinburgh, Edinburgh, United Kingdom; Werner Hacke #, Univ of Heidelberg, Heidelberg, Germany; for the Stroke Thrombolysis Trialists' Collaboration; *, # Equal contribution; + Corresponding author

**Abstract Body:**

Background: Intravenous recombinant tissue plasminogen activator (rt-PA) is effective in the treatment of acute ischemic stroke but there remains debate regarding its use at different times since stroke onset, as well as its use in older patients and patients who have had the least or most severe strokes.

Methods: Pre-specified independent individual-patient-data meta-analysis of 6756 patients from 9 randomized trials involving rt-PA versus placebo/open control. The primary outcome was no significant disability at 3-6 months (modified Rankin Score [mRS] 0-1). Secondary outcomes included symptomatic intracranial haemorrhage (sICH) and 90-day mortality.

Results: rt-PA significantly increased the odds of achieving mRS 0-1, including among patients treated within 3-4.5 hours, with earlier treatment associated with greater proportional benefits (delay ≤3 hours: 259 [33%] among rt-PA allocated patients vs 176 [23%] among control allocated patients, OR 1.75 [95% CI 1.35-2.27]; delay 3-4.5 hours: 485 [35%] vs 432 [30%], 1.26 [1.05-1.51]; delay >4.5 hours: 401 [33%] vs 357 [31%], 1.15 [0.95-1.40]). For mRS 0-1, the
95% confidence interval around the time at which there was no benefit had a lower limit of 5.0 hours. Proportional treatment benefits were similar irrespective of age or stroke severity. Despite an early 6-fold increase in sICH, much of which was fatal, there was no significant excess of mortality after 90 days (608 [17.9%] vs 556 [16.5%]; HR 1.11 [0.99-1.25]).

Conclusions: Irrespective of age or stroke severity, and despite the early risk from intracerebral hemorrhage, rt-PA significantly improves the odds of surviving with no significant disability when delivered within 4.5 hours of stroke onset.

Author Disclosure Block:

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