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Rationale, design, and progress of the ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED) trial: An international multicenter 2 × 2 quasi-factorial randomized controlled trial of low- vs. standard-dose rt-PA and early intensive vs. guideline-recommended blood pressure lowering in patients with acute ischaemic stroke eligible for thrombolysis treatment.

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Abstract

RATIONALE: Controversy exists over the optimal dose of intravenous (i.v.) recombinant tissue plasminogen activator (rt-PA) and degree of blood pressure (BP) control in acute ischaemic stroke (AIS). Asian studies suggest low-dose (0·6 mg/kg) is more efficacious than standard-dose (0·9 mg/kg) i.v. rt-PA, and guidelines recommend reducing systolic BP to <185 mmHg before and <180 mmHg after use of i.v. rt-PA, despite observational studies indicating better outcomes at much lower (<140 mmHg) systolic BP levels in this patient group.

AIMS: The study aims to assess in thrombolysis-eligible AIS patients whether: (i) low-dose (0·6 mg/kg body weight; maximum 60 mg) i.v. rt-PA has non-inferior efficacy and lower risk of symptomatic intracerebral haemorrhage (sICH) compared to standard-dose (0·9 mg/kg body weight; maximum 90 mg) i.v. rt-PA; and (ii) early intensive BP lowering (systolic target 130-140 mmHg) has superior efficacy and lower risk of any ICH compared to guideline-recommended BP control (systolic target < 180 mmHg).

DESIGN: The ENhanced Control of Hypertension And Thrombolysis strokE stuDy (ENCHANTED) trial is an independent,2 × 2 quasi-factorial, active-comparison, prospective, randomized, open blinded endpoint (PROBE), clinical trial that is evaluating Arm [A] 'rt-PA dose' and/or Arm [B] 'BP control', using central Internet randomization and data collection in patients fulfilling local criteria for

thrombolysis and clinician uncertainty over the study treatments. The treatment arms will be analyzed separately.

STUDY OUTCOMES: The primary study outcome in both trial Arms is death or disability according to the modified Rankin scale (mRS, scores 2-6) assessed at 90 days. Secondary outcomes include sICH, any ICH, a shift ('improvement') in function across mRS scores, separately on death and disability, early neurological deterioration, recurrent major vascular events, health-related quality of life, length of hospital stay, need for permanent residential care, and health care costs.

RESULTS: Following launch of the trial in February 2012, the study has recruited more than 2500 patients across a global network of approximately 100 sites in 15 countries. The required sample sizes are 3300 for Arm [A] and 2300 for Arm [B], which will provide >90% power to detect non-inferiority of low-dose i.v. rt-PA and superiority of intensive BP lowering on the primary clinical outcome, respectively.

CONCLUSIONS: Low-dose i.v. rt-PA and early intensive BP lowering could provide more affordable and safer use of thrombolysis treatment for patients with AIS worldwide.