




Statistical analysis plan for evaluating different intensities of blood pressure control in the ENhanced Control of Hypertension And Thrombolysis strokeE study

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Abstract

Background: The ENhanced Control of Hypertension And Thrombolysis strokeE study (ENCHANTED) trial was initiated as a 2 × 2 partial-factorial active-comparison, prospective, randomized, open, blinded endpoint clinical trial to evaluate in thrombolysis-eligible acute ischemic stroke (AIS) patients whether: (1) Arm A – low-dose (0.6 mg/kg body weight) intravenous (iv) alteplase has noninferior efficacy and lower risk of symptomatic intracerebral hemorrhage (sICH) compared with standard-dose (0.9 mg/kg body weight) iv alteplase; and (2) Arm B – early intensive blood pressure (BP) lowering (systolic target 130–140 mmHg) has superior efficacy and lower risk of ICH compared with guideline-recommended BP control (systolic target <180 mmHg). Arm A was completed in 2016; Arm B is now concluding.

Objective: To outline in detail and make public the predetermined statistical analysis plan (SAP) for the ‘BP control’ arm of this study.

Methods: All data collected by participating researchers will be reviewed and formally assessed. Information pertaining to the baseline characteristics of patients, their process of care, and the delivery of treatments will be outlined, and for each item, statistically relevant descriptive elements will be described. For the trial outcomes, the most appropriate statistical comparisons to be made between groups are planned and described.

Results: A SAP was developed for the results of the BP control arm of this study that is transparent, available to the public, verifiable, and predetermined before completion of data collection.

Conclusions: We have developed a predetermined SAP for the ENCHANTED BP control arm to be followed to avoid analysis bias arising from prior knowledge of the study findings.

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Keywords

Hypertension, stroke, alteplase, thrombolysis, clinical trials, statistical analysis plan

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Thrombolytic therapy with intravenous (iv) alteplase (or recombinant tissue plasminogen activator (rtPA)) is the only proven medical treatment for acute ischemic stroke (AIS).¹ However, use is complicated by its narrow therapeutic time window (recommended < 4.5 h from the onset of symptoms); problems of access (e.g. delays in hospital presentation and high cost in low resource settings); limited efficacy, particularly in large clots occluding proximal segments of intracranial arteries; and the serious adverse effect of intracranial hemorrhage which can lead to early death. Further clinical trials are required to evaluate strategies to improve the access, efficacy and safety of iv alteplase in AIS patients.

The optimal level of blood pressure (BP) in thrombolysed AIS patients remains controversial. Elevated BP or 'hypertension' (i.e. systolic > 140 mmHg) is common (>60%) early after the onset of AIS,²⁻⁶ with the degree of increase being greater in patients with pre-existing hypertension and larger strokes,^{3,4} but levels tend to decline over the subsequent week. While generally positive associations between BP levels and poor outcomes are evident, very low (systolic < 130 mmHg) BP levels and large reductions in BP are also related to poor outcomes in AIS.⁴⁻⁶ Various explanations for elevated BP include acute physiological stress, pain, unstable pre-existing hypertension, or raised intracranial pressure, occurring in the context of a critical set of mechanisms operating in relation to the evolving cerebral ischemia/infarction to produce varying degrees of cerebral edema and hemorrhagic transformation from re-perfusion and collateral flow into the injured region of the brain. However, the observed U- or J-shaped relationship of BP and outcome⁶ may not be causally related; rather patients with more severe strokes (and who naturally have worse outcomes) may have a more prominent autonomic response resulting in higher BP at presentation, and the same type of patients may also develop lower BP levels as their condition worsens, sometimes as a pre-terminal event. To complicate matters further, hypertensive patients appear to have their cerebral autoregulation shifted to a higher level, whereas in all patients the critically vulnerable penumbral rim of the infarct core of AIS, cerebral autoregulation is likely to be disrupted so that cerebral perfusion pressure is directly related to systemic BP. Even so, experimental models of focal cerebral ischemia and reperfusion indicate that BP reduction reduces the size of cerebral ischemia and improves reperfusion.⁷

Guidelines for BP control in AIS are consistent in contraindicating the use of iv alteplase in patients with 'uncontrolled' BP according to the definitions used in the pivotal National Institutes of Neurological Diseases

and Stroke (NINDS) rtPA stroke study⁸: that is, with systolic BP >185 mmHg prior to administration of the bolus of iv alteplase, and to maintain systolic BP <180 mmHg during the infusion of alteplase and for 24 h afterwards.⁹ However, there is now a considerable body of evidence to suggest that lower BP levels may improve outcomes, particularly by reducing the risk of sICH following the use of iv alteplase. In the original NINDS study,⁸ use of antihypertensive therapy was common in both the placebo and active groups, so although this treatment did not appear to influence outcomes, the small sample size ($n = 624$) and lack of randomized comparison precluded firm conclusions to be drawn over the role of BP control on outcomes.¹⁰ Subsequent non-randomized studies have indicated that 'inadequate control' of BP (or pre-treatment BP alteplase protocol violations) prior to, and after, the use of alteplase is associated with a higher likelihood of sICH.¹¹⁻¹⁷ The most compelling data are from the large prospective registry studies: the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)¹⁴ that included 6483 patients from 285, mainly European, centers between 2002 and 2006; and the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR)¹⁵ which included expanded measures of serial BP (baseline, and 2 and 24 h), treatment and outcome data in 11,080 patients registered between 2002 and 2006. In SITS-MOST, elevated baseline systolic BP (odds ratio [OR] 1.3, 95% confidence interval [CI] 1.1-1.7 per 20 mmHg standard deviation) was associated with sICH, which occurred in 8.5% (95% CI 8-9%) according to the use of a strict definition. In SITS-ISTR, multivariable analyses showed that: elevated systolic BP levels (i) as a continuous variable was associated with a worse outcome ($P < 0.001$); and (ii) as a categorical variable had a linear association with sICH, and a U-shaped association for death and dependency, such that the best outcome occurred in the nadir 141-150 mmHg; and sICH was four times higher in patients with a post-alteplase systolic BP >170 mmHg compared with those with levels of 141-150 mmHg. Furthermore, withholding antihypertensive therapy for several days in patients with prior hypertension was associated with worse outcomes, whereas initiation of antihypertensive therapy in newly recognized cases of moderate hypertension was associated with a favourable outcome. The increased risk of sICH associated with hypertension may persist for at least several hours after administration of iv alteplase.^{16,17} More recent data have emerged in relation to the use of endovascular clot retrieval; the optimal level of systolic BP control appears to be in the range 130-140 mmHg.¹⁸

In the absence of randomized data, a clear consensus on the optimal BP control before, during and after alteplase in alteplase-treated AIS patients is lacking. As the largest randomized evaluation of alteplase in AIS, the ENhanced Control of Hypertension And Thrombolysis stroke stuDY (ENCHANTED) was designed as a comparative-effectiveness trial to resolve uncertainty over the most efficacious dose of alteplase as well as the most appropriate level of control of elevated BP in the context of AIS.¹⁹ The dose-arm of ENCHANTED ($n=3310$) concluded in 2016, finding that low-dose alteplase was not statistically non-inferior to a standard-dose alteplase on the conventional binary outcome of death or any disability, defined by scores 2 to 6 on the standard outcome measure of the modified Rankin scale (mRS) at 90 days after stroke onset.¹⁹ However, low-dose alteplase was clearly non-inferior for overall functional recovery, according to an ordinal 'shift' analysis of the full range of scores on the mRS, and substantially reduced the risk of sICH, the most feared complication of this treatment.¹⁹

As low-dose alteplase and early intensive BP lowering both have the potential to make thrombolytic treatment more efficacious, safer and affordable in patients with AIS around the world, it was important that ENCHANTED had pragmatic features to allow its efficient conduct in the context of routine clinical practice, and for the results to be widely generalizable. The study protocol for ENCHANTED has been outlined elsewhere.^{19,20} In brief, the study was designed as a partial-factorial randomized controlled trial involving two linked comparative treatment arms – 'alteplase dose' and 'BP control' – with overlapping eligibility criteria. As well as providing flexibility over patient recruitment into one or both treatment arms according to clinician uncertainty and available resources, the study design allowed for the two treatment arms to be evaluated separately to provide a reliable estimate of a clinically worthwhile beneficial effect of a treatment strategy that would influence clinical practice.

Herein we describe the statistical analysis plan (SAP) for the ENCHANTED 'BP control' arm. This SAP was completed prior to completion of the data collection, and is what investigators will adhere to in analyzing the results of the study pertaining to the intensity of BP control in the context of using alteplase for AIS. The SAP was approved and signed off by the study Steering Committee in August 2018. Participant recruitment to the alteplase dose arm was completed in April 2018, and final patient follow-up occurred in August 2018. The statistical analyses specified in the SAP occurred in October 2018, and the main results announced at the AHA/ASA International Stroke Conference in Hawaii in February 2019.

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