

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

Yining Huang¹, Vijay K. Sharma^{2*}, Thompson Robinson³, Richard I. Lindley⁴, Xiaoying Chen⁴, Jong Sung Kim⁵, Pablo Lavados^{6,7}, Verónica Olavarría⁶, Hisatomi Arima⁴, Sully Fuentes⁴, Huy Thang Nguyen⁸, Tsong-Hai Lee⁹, Mark W. Parsons¹⁰, Christopher Levi¹⁰, Andrew M. Demchuk¹¹, Philip M. W. Bath¹², Joseph P. Broderick¹³, Geoffrey A. Donnan¹⁴, Sheila Martins¹⁵, Octavio M. Pontes-Neto¹⁶, Federico Silva¹⁷, Jeyaraj Pandian¹⁸, Stefano Ricci¹⁹, Christian Stapf²⁰, Mark Woodward,⁴ Jiguang Wang²¹, John Chalmers⁴, and Craig S. Anderson⁴ for the ENCHANTED investigators

Correspondence: Vijay K. Sharma*, Division of Neurology, Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

E-mail: drvijay@singnet.com.sg

¹Department of Neurology, Peking University First Hospital, Beijing, China

²Division of Neurology, Department of Medicine, National University Hospital and YLL School of Medicine, National University of Singapore, Singapore

³Department of Cardiovascular Sciences and NIHR Biomedical Research Unit, University of Leicester University, Leicester, UK

⁴The George Institute for Global Health, Royal Prince Alfred Hospital and University of Sydney, Sydney, Australia

⁵Asan Medical Center, University of Ulsan, Seoul, South Korea

⁶Clinica Alemana de Santiago, Universidad del Desarrollo, Santiago, Chile

⁷Universidad de Chile, Santiago, Chile

⁸Stroke Unit, People's 115 Hospital, Ho Chi Minh City, Vietnam

⁹Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan

¹⁰John Hunter Hospital, Hunter Medical Research Institute, University of Newcastle, Newcastle, Australia

¹¹Calgary Stroke Program, Department of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada

¹²Stroke trials Unit, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK

¹³Departments of Neurology and Rehabilitation Medicine and Radiology, University of Cincinnati Neuroscience Institute, University of Cincinnati Academic Health Center, Cincinnati, OH, USA

¹⁴The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia

¹⁵Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Rio Grande do Sul, Brazil

¹⁶Stroke Service – Neurology Division, Department of Neuroscience and Behavior, Ribeirão Preto School of Medicine, University of Sao Paulo, Ribeirão Preto, SP, Brazil

¹⁷Fundación Cardiovascular, Bucaramanga, Colombia

¹⁸Department of Neurology, Christian Medical College, Ludhiana, India

¹⁹Direttore, UO Neurologia, USL Umbria 1, Sedi di Città di Castello e Branca, Italy

²⁰Department of Neurology, APHP – Hôpital Lariboisière and DHU NeuroVasc Paris – Sorbonne, Univ Paris Diderot – Sorbonne Paris Cité, Paris, France

²¹The Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Rationale Controversy exists over the optimal dose of intravenous (iv) 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) iv rt-PA, and guidelines recommend reducing systolic BP to <185 mmHg before and <180 mmHg after use of iv 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) iv 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) iv 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,

Received: 3 December 2014; Accepted: 8 March 2015; Online publication: 2 April 2015

Conflict of interest: C Anderson reports receiving fees for Advisory Panels of The Medicines Company and Pfizer, and speaking at seminars for Takeda China, Covidien and Bayer. J Broderick has received research monies to Department of Neurology from Genentech for PRISMS Trial; travel to Australian Stroke Unit Heads conference in 2013 paid for by Boehringer Ingelheim; study medication from Genentech and study catheters supplied during Protocol Versions 1–3 by Concentric Inc, EKOS Corp, and Cordis Neurovascular for the third Interventional Management of Stroke (IMS III) trial.

Trial Registration: The study is registered at ClinicalTrials.gov (NCT01422616), ISRCTN Register (ISRCTN82387104) and Australian New Zealand Clinical Trial Registry (ACTRN12611000236998).

Funding: The study is funded by the National Health and Medical Research Council (NHMRC) of Australia (Project Grant 1020462), the Stroke Association of United Kingdom (Reference TSA 2012/01), and the National Council for Scientific and Technological Development of Brazil (CNPq grant number 467322/2014-7).

DOI: 10.1111/j.12486

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 iv rt-PA and superiority of intensive BP lowering on the primary clinical outcome, respectively.

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

Key words: acute ischaemic stroke, Alteplase, dose, hypertension, rt-PA, thrombolysis

Introduction and rationale

Intravenous (iv) recombinant tissue plasminogen activator (rt-PA) (or Alteplase) remains the only approved drug for achieving early recanalization of an occluded intracranial artery in the setting of acute ischaemic stroke (AIS), and the earlier the treatment is given the bigger the proportional benefit (1,2). Use of iv rt-PA in AIS was licensed on the basis of the pivotal National Institute of Neurological Disorders and Stroke (NINDS) trial (3), where an iv dose of 0.9 mg/kg body weight (10% as bolus, 90% as a one-hour infusion; maximum dose 90 mg), chosen on the basis of small dose-escalation studies (4–6), was shown to improve outcomes when given to carefully selected patients within three-hours of symptom onset. On the basis of a meta-analysis of the initial clinical trials of iv rt-PA (7) and the later positive third European Cooperative Acute Stroke Study (ECASS III) (8), most guidelines now recommend an extension of the time criteria to 4.5 h in those AIS patients without severe neurological deficit or clear major risks (9). The totality of the current evidence among nearly 7,000 patients randomized trials of thrombolysis is now strong for iv rt-PA providing an overall net benefit despite a 2–7% risk of major symptomatic intracerebral haemorrhage (sICH) (1,2). Despite the early risk of fatal ICH (2–3%), patients who receive iv rt-PA within a few hours after the onset of AIS have an overall ≥ 30% relative increased chance of having little or no residual disability (1,2). A consideration of the entire spectrum of clinically important outcomes relevant to the use of rt-PA within three-hours of onset of AIS indicates a number needed to benefit of 3 compared to a number need to harm of 30 (10).

Low-dose (0.6 mg/kg body weight; maximum 60 mg) of iv rt-PA was first evaluated in 3 small double-blind randomized controlled trials of alteplase (which is similar to rt-PA) in

patients within six-hours of onset of AIS in Japan over 20 years ago (11,12). The results showed that 20 mega-international units (MIU) of alteplase (equal to 0.33 MIU/kg or 0.6 mg/kg of rt-PA) was superior to placebo and comparable to 30 MIU on both angiographic recanalization and clinical improvement. Importantly, massive ICH was more frequent in patients who received 30 MIU of alteplase. Low-dose rt-PA was subsequently approved for use in Japan because of concerns of higher risk of ICH in this population due to potential racial differences in coagulation-fibrinolysis factors (13), plasma concentrations of fibrinogen and plasminogen activator inhibitor (14), and genetic polymorphisms of coagulation factors (15). Interestingly, careful in-vitro studies indicate no further increase in the degree of clot lysis with rt-PA doses greater than 0.6 mg/kg (16). Moreover, use of a lower dose of rt-PA (0.5–0.75 mg/kg) for patients with acute myocardial infarction in Japan has resulted in rates of coronary artery patency comparable with the standard dose (1–1.25 mg/kg) used in other countries (13). The Japan Alteplase Clinical Trial (J-ACT) (17), undertaken with 0.6 mg/kg rt-PA in an open non-randomized evaluation of patients within three-hours of AIS, showed equivalent clinical outcomes but a reduced risk of sICH compared to the standard 0.9 mg/kg dose. J-ACT and comparable data from subsequent registries (18,19) led to regulatory approval of the 0.6 mg/kg dose as the standard treatment for AIS patients in Japan. However, this policy has led to confusion among clinicians in other parts of Asia as to the balance of benefits and risks of low- vs. standard-dose rt-PA. Thus, 0.6 mg/kg dose of rt-PA (which often requires use of only a single 50 mg vial of Actilyse® Boehringer Ingelheim or Alteplase® Genentech) has become an attractive 'low-cost' and possibly 'safer' option for elderly patients and for those who cannot afford the full dose. The high cost of rt-PA (~US\$2,000 per 2 × 50 mg vials for 0.9 mg/kg dose) is a major out-of-pocket expense for many people in fee-for-service health care systems of low-middle income countries (20). A recent systematic review of the published studies demonstrates wide variations in iv rt-PA dose regimes, therapeutic response, and risk of sICH across Asian patients (21). However, this study did not derive any conclusive differences in the therapeutic response or risk of sICH related to either rt-PA dose regimes in Asians, and acknowledged a lack of randomized evidence to support a widespread policy for low-dose iv rt-PA in patients with AIS. Additionally, the racial differences in coagulation factors and differential effects of low-dose rt-PA in some Asian studies could simply be due to the lower total dose given for a smaller body weight or a lower 'clot volume' due to the greater proportion of small vessel occlusive or 'lacunar' forms of AIS as compared to more large vessel and cardio-embolic strokes (high clot volume) in non-Asians. Accordingly, a Cochrane review emphasized no clear differences in indirect comparisons of different dosages of thrombolytic agents, which in the absence of head-to-head direct comparative studies, means there is uncertainty over the relative benefits and risks of low- vs. standard-dose rt-PA (22).

Another controversial issue in patients with AIS is the optimal management of co-occurring hypertension. Elevated systolic BP (>140 mmHg) is very common (>60%) early after the onset of AIS (23,24), with greater increases in BP evident in those patients

with pre-existing hypertension and larger strokes (25,26). While positive associations between increased systolic BP and poor outcome are generally documented, very low (<130 mmHg) systolic BP and large reductions in systolic BP are also associated with poor outcomes in AIS (24). Various explanations for elevated systolic BP in acute stroke include acute physiological stress, pain, unstable pre-existing hypertension or increased intracranial pressure. However, the observed U- or J-shaped relationship of BP and outcome (25,26) in patients with AIS may not be causally related. Patients with more severe strokes may have a more prominent autonomic response, and they may also develop lower BP levels as their condition worsens. Experimental models of focal cerebral ischaemia and reperfusion indicate that BP reduction reduces the size of cerebral ischaemia and improves reperfusion (27). Even so, any potential benefits of rapid lowering of BP in AIS must be balanced the risks of worsening ischaemia from potential hypoperfusion where autoregulation is failing within the ischaemic penumbra.

Although guidelines for BP control in AIS are consistent in contraindicating use of rt-PA in patients with uncontrolled BP (systolic > 185 and diastolic > 110 mmHg) (9), recent data suggest that lower BP levels are associated with better outcomes, particularly in those patients treated with iv rt-PA. In the original NINDS study (3), use of antihypertensive therapy was common in placebo as well as the active groups. Although BP treatment did not appear to influence outcomes, the small sample size ($n = 624$) and lack of randomized variation precluded firm conclusions to be drawn (28). Subsequent non-randomized studies indicate that 'inadequate control' of BP prior to, and after the use of rt-PA, is associated with a higher likelihood of sICH (29). The most compelling data are from the large Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) registry (30) of 6483 patients and the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) (31) of 11,080 patients with expanded measures including serial BP (baseline, 2 and 24 h), treatment and outcome data. In SITS-MOST, sICH occurred in 8.5% (95% confidence intervals [CI] 8–9%) patients and was associated with elevated baseline systolic BP (odds ratio [OR] 1.3, 95% CI 1.1–1.7 per 20 mmHg standard deviation) (30). Similarly, in SITS-ISTR, multivariable analyses showed that elevated systolic BP as a continuous variable was associated with a worse outcome ($P < 0.001$) and as a categorical variable had a linear association with sICH (31). A U-shaped association for death and dependency was evident, with best outcome in the nadir systolic BP 141–150 mmHg, with sICH being four times higher in patients with a systolic BP > 170 mmHg as compared to those with levels of 141–150 mmHg (31). All these data indicate that a $\geq 15\%$ reduction in a poor outcome after rt-PA. Thus, guidelines for the management of BP in AIS highlight the need for a definitive study, since their expert-derived recommendations (<185 mmHg systolic BP before rt-PA and <180 mmHg after rt-PA) provide only an indication of perceived harm from high BP (9). Neither the Scandinavian Candesartan Acute Stroke Trial (SCAST) (32) nor the recently completed Efficacy of Nitric Oxide in Stroke (ENOS) (33) trial

were specifically designed to address the role of very early (within a few hours), rapid and intensive BP lowering, in patients AIS who receive rt-PA. Importantly, the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT-2), which showed that rapid BP lowering (systolic target < 140 mmHg) is feasible, safe and improves functional outcome possibly by attenuating ICH expansion from reduced cerebral perfusion pressure, provides further rationale to test the efficacy of such a protocol in AIS patients treated with rt-PA (34).

Based on this background, we initiated the ENCHANTED trial to determine the impact of low-dose rt-PA and intensive BP lowering on death and disability defined by the modified Rankin scale (mRS) (35) at 90 days in AIS patients who are eligible to receive thrombolysis treatment. Herein, we outline the study protocol with several modifications, and progress to date.

Objectives

The ENCHANTED trial includes two parallel interventional Arms, the primary aims of which are to evaluate whether:

- compared with standard-dose, low-dose iv rt-PA is *non-inferior* for the clinical outcome of death or disability at 90 days (the corresponding null hypothesis is that low-dose is inferior to standard-dose rt-PA), and
- compared with standard guideline-recommended BP management, early intensive BP lowering is *superior* for the clinical outcome of death or disability at 90 days (the corresponding null hypothesis is that there is no difference in frequency of this outcome between randomized groups).

The secondary objectives are to determine whether:

- compared to standard-dose, low-dose iv rt-PA reduces the risk of sICH (the corresponding null hypothesis is that there is no difference in the frequency of sICH between groups of differing doses of iv rt-PA), and
- compared to guideline-recommended BP management, early intensive BP lowering after iv rt-PA reduces the risk of any ICH (the corresponding null hypothesis is that there is no difference in the rate of any ICH between groups of differing intensities of BP lowering). *This outcome of any ICH was changed from sICH in the protocol in November 2013 in line with a reduction in sample size for Arm [B] 'BP intensity' from 3,300 to 2,300 patients. We undertook this change because recruitment into Arm [B] was slower than projected and it was not feasible for the study to achieve the original planned sample size to determine superiority of intensive BP lowering on the secondary 'safety' outcome of sICH. A lower sample size of 2300 was more realistic to determine safety for the alternative but still clinically relevant outcome of any ICH. The effects of early intensive BP lowering on sICH will be explored in analyses.*
- Other secondary outcomes are to define the effects on a shift ('improvement') in measures of disability according to full range of scores on the mRS (35); excellent and good functional outcomes; separately on death and disability; early neurological deterioration; recurrent acute myocardial infarction and AIS; health-related quality of life (HRQoL); length of hospital stay; need for permanent residential care; and health care costs.

Methods

Trial design

ENCHANTED is an independent, investigator-initiated and conducted, international, multicenter, 2 × 2 quasi-factorial, prospective, open-label, assessor-blinded end-point (PROBE), randomized controlled trial that involves a package of 2 linked comparative treatment Arms ('rt-PA dose' and 'BP control'). The trial is being conducted in accordance with local and international regulatory and ethical requirements. All participating hospitals receive approval from required regulatory authorities, ethics committee (EC) or institutional review board (IRB), prior to initiation of the trial.

Trial population

Each hospital site is required to keep a log of all patients presenting with a diagnosis of AIS and who were considered for the study but subsequently excluded. The screening log records each patient's initials and date of admission together with a brief description of the main reason as to why a patient was not randomized. The log is used by the research staff to monitor recruitment and identify specific barriers to randomization of eligible patients. It is also a requirement for reporting the results of clinical trials.

Study personnel consider all patients presenting with AIS for enrollment. Table 1 reports the ENCHANTED inclusion and exclusion criteria. To be eligible, patients must fulfill local criteria for use of iv rt-PA, and the attending clinician is required to sequentially consider their level of clinical uncertainty over the balance of potential benefits and risks pertaining to Arm [A] the appropriate dose of rt-PA and Arm [B] the level of BP control, in

each particular patient. Patients will not be eligible if one or more of the following are noted: being unlikely to benefit from rt-PA (e.g. advanced dementia), deemed to have a very high likelihood of death within the next 24 h, or have another medical illness that is likely to interfere with either the outcome assessments or follow-up. Investigators are able to undertake all investigations according to their usual standard of care in their management of patients with AIS, including urgent referral for cerebral angiography for consideration of endovascular clot retrieval in selected sites. Thus, ENCHANTED is a pragmatic trial designed to evaluate the effectiveness of interventions in real-life routine best practice conditions.

Before participation, written consent is obtained from each participant or their approved surrogate for patients who are too unwell to comprehend the information. Study investigators may withdraw a patient from the trial at any time without prejudice and explanation. Alternatively, the study participants/legally acceptable representative can opt to withdraw at any stage, although efforts should still be undertaken to obtain outcome data at 90 days.

Baseline assessment before randomization

All patients receive the following assessments prior to randomization: clinical evaluation of stroke severity using the National Institutes of Health stroke scale (NIHSS) (36) and pre-ictus functional independence (mRS 0–2); non-contrast brain CT-scan (or MRI) with or without angiography (or perfusion) according to standard practice, to confirm the diagnosis of AIS and exclude ICH or a relevant structural abnormality; baseline characteristics (age, gender), risk factors (hypertension, diabetes mellitus, hyper-

Table 1 Inclusion/exclusion criteria for the ENCHANTED trial

Patient specific inclusion criteria: All patients are eligible if they fulfill general eligibility criteria for thrombolytic treatment with rt-PA as well as specific criteria:

1. are ≥ 18 years of age;
2. have a clinical diagnosis of acute ischaemic stroke confirmed by brain imaging;
3. are able to receive rt-PA treatment within 4.5 h of symptom onset;
4. have a systolic blood pressure (BP) ≤ 185 mmHg (the guideline recommended level for use of rt-PA; patients with higher BP can still be included provided the BP is reduced to the entry level prior to commencement of rt-PA);
5. and fulfill other specific criteria for each arm
 - a. *Specific criteria for Arm [A] of low-dose vs. standard-dose rt-PA*
 - i. No definite indication nor contraindication for either dose of rt-PA.
 - b. *Specific criteria for Arm [B] of intensive vs. guideline recommended BP lowering*
 - i. Patient will (or has) received i.v. rt-PA treatment, either a randomized dose within the trial or a physician decided dose as part of a standard care;
 - ii. Sustained elevated systolic BP level, defined as 2 readings ≥ 150 mmHg 2 minutes apart;
 - iii. Able to commence intensive BP lowering treatment within six-hours of stroke onset. *This criteria was changed from 4.5 h of stroke onset in November 2013 to allow clinicians to fast-track use of rt-PA treatment in patients who were not participating in Arm [A] rt-PA dose, and allow a slightly longer time period in which to randomize patients into Arm [B] BP lowering, either intensive (target <140 mmHg systolic) or usual care.*
 - iv. No definite indication or contraindication to immediate 'intensive' systolic BP lowering (to a target of 130–140 mmHg). *The intensive BP lowering target was changed from 140–150 mmHg to 130–140 mmHg in the protocol in November 2013 to ensure that BP control is actually 'intensive' as compared to control group.*

Patient specific exclusion criteria: Patients will not be eligible if one or more of the following are noted:

1. unlikely to benefit from the therapy due to pre-existing disability (e.g. advanced dementia) or very high likelihood of death within 24 h;
2. has another medical illness that interferes with outcome assessments
3. is unlikely to adhere to follow-up procedures
4. not consenting to participate in ENCHANTED
5. previously enrolled in ENCHANTED

cholesterolaemia, coronary artery disease, atrial fibrillation) and prior use of antihypertensive medications; and a detailed clinical examination including vital signs (pulse, BP) and assessment of the neurological deficit (NIHSS).

Randomization

After confirmation of eligibility, patients are randomized via a central Internet-based system at The George Institute for Global Health in Sydney, Australia. This is done by connecting the study site to the server at the International Coordinating Centre (ICC) for registration and randomization of the patient. The randomization sequence uses a minimization algorithm to ensure balance in key prognostic factors, according to site of recruitment, time from the onset of symptoms (<3 vs. ≥3 h) and NIHSS score (<10 vs. ≥10 points). Once Arm A is completed, the randomization system will be programmed to allow randomization only of patients into Arm B.

The study was initially designed with a fixed time point for the randomization of patients into one or both Arms of the study. However, recruitment was slow for Arm [B] 'BP control' due to various factors including low frequency of 'hypertensive patients', investigator concerns that the extra time required to obtain consent was impacting on 'door-to-needle' (DTN) time quality performance, and requirement for greater monitoring of patients associated with administering more intensive BP lowering treatment. This led us to change the protocol in November 2013 by uncoupling the time of randomization for the Arms of the study. This allows investigators the option of randomizing patients into Arm [B] either (a) at the time of randomization into Arm [A], or (b) at a later time point within six-hours after the onset of AIS. This 6 hour time window from the onset of symptoms to the commencement of intensive BP lowering as an inclusion criterion for patient who have not been included in Arm [A] 'rt-PA dose', allows investigators to give rt-PA as part of usual care and then randomize patients into Arm [B] 'BP control'. Given that most patients receive rt-PA at two- to three-hours after stroke onset, this change has meant that intensive BP lowering can commence within about three- to four-hours after administering the bolus dose of rt-PA.

Interventions

Site investigators have the choice of randomizing patients into one or both treatment Arms of the study: Arm [A] comprises standard-dose (0.9 mg/kg; 10% bolus and 90% infusion over 60 min; maximum 90 mg) or low-dose (0.6 mg/kg; 15% bolus and 85% infusion over 60 min; maximum 60 mg) iv rt-PA; and Arm [B] comprises intensive BP lowering (target systolic BP 130–140 mmHg within 60-minutes of randomization, and to maintain this level for at least 72 h, or hospital discharge [or death] if this occurs earlier) or guideline-recommended BP lowering (target SBP < 180 mmHg) after commencement of iv rt-PA.

The protocol originally stated that the intensive group in Arm [B] should have a systolic BP target of 140–150 mmHg within 30 min of randomization. However, it was noted that the systolic BP differences between randomized groups was less than projected (10–14 mmHg). This was because some investigators were overly cautious in their approach to treatment in the intensive group or conversely too aggressive toward the standard care group. Thus, the

protocol was changed to the systolic BP target of 130–140 mmHg within 60 min in November 2013.

The site investigator has the choice of continuing or stopping their patients' antihypertensive medication prior to randomization and they are free to use locally available and approved antihypertensive agents according to a pre-specified treatment protocol. They are to titrate BP by repeat iv bolus or infusion of medication, with a systolic BP of 130 mmHg being the safety threshold for cessation of therapy. Patients are switched to oral BP lowering agents when stable. The study schema is shown in Fig. 1.

For Arm [A] 'rt-PA dose', it should be noted that the bolus dose has been set to be similar between treatment groups, so that the only difference between groups is in the total dose of rt-PA.

Background care

All patients will be managed in a facility with an adequate nurse : patient ratio and capacity for repeated neurological examination and non-invasive BP and heart rate monitoring (consistent recordings using automatic devices, every 15 min for one-hour, then 6 hourly for 20 h, then twice daily for one-week). All BP measurements are from the non-paretic arm (or right arm in situations of coma or tetraparesis), with the patient resting supine for ≥3 min. All patients are to receive active care and best practice management according to guidelines, and where neurointervention with intra-arterial thrombolysis and/or endovascular mechanical clot retrieval is allowed according to local practice.

An acute stroke unit is defined as an area that: is a geographically specific area where patients with acute stroke are managed; has staff organized as part of a coordinated multidisciplinary team; has staff who have special knowledge and skills in the management of acute stroke; provides ongoing education about stroke management for staff, patients and caregivers; and has written protocols for assessment and management of common problems related to stroke.

During the study treatment and follow-up period, the usual management of patients will be followed according to published guidelines for AIS. It is anticipated that background care may include significant use of treatments including drugs and endovascular intervention. Use of other therapies will be documented and compared between countries and should be balanced between randomized groups.

Data collection and follow-up

All patients are followed daily for one-week, and then at 28 and 90 days, unless death occurs earlier. Patients who are unable to complete the protocol are still followed up and analyzed according to the 'intention-to-treat' principle. Key demographic and clinical data are collected at the time of randomization. Follow-up data is collected at 24 and 72 h, and at 7 (or hospital discharge if sooner), 28 and 90 days. The 90-day evaluation is conducted in-person or by telephone, by trained staff who are blind to the treatment allocation. Brain imaging (CT and/or MRI) is conducted according to standardized techniques at baseline, and at 24 ± 3 h, and additionally if clinically indicated. The scans are collected in DICOM format, de-identified, and analyzed at the ICC. Table 2

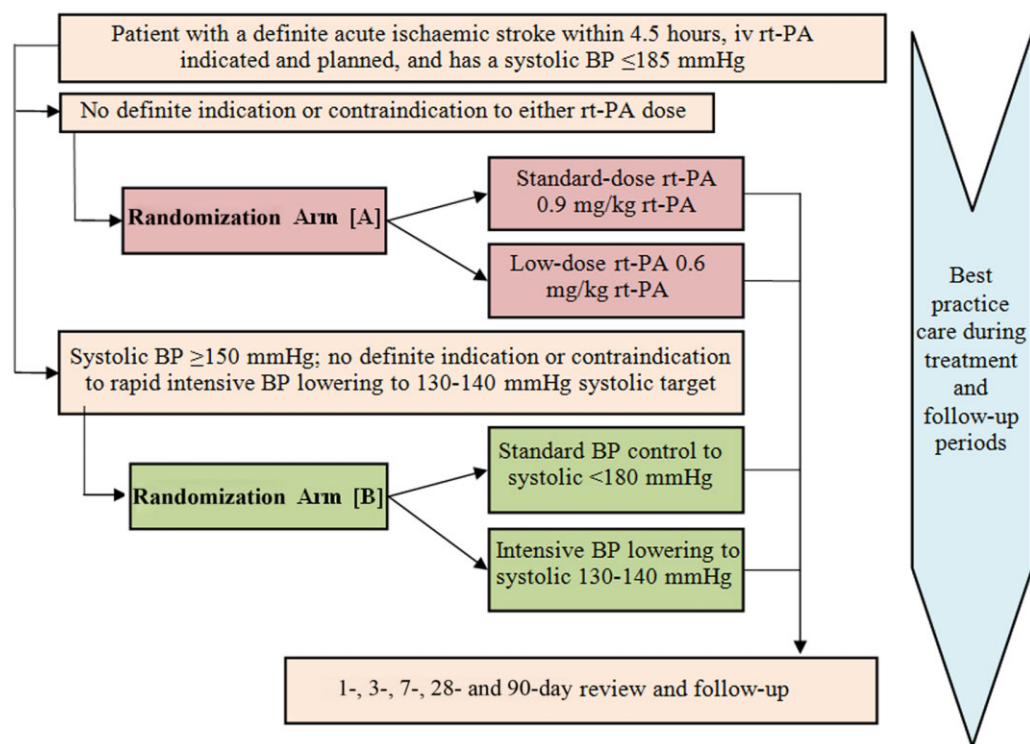


Fig. 1 Study schema.

Table 2 Schedule of evaluations

Evaluation	Prior to randomization	Day				
		1 and 2	3*	7*	28 [†]	90 [†]
Eligibility	X					
Brain imaging (CT ± angiogram or MRI)	X	X				
BP	X	X‡ For time points see the footer	X	X		
	BP × 2		12 hourly	12 hourly		
Heart rate	X					
Consent	X					
Clinical history, prior medications	X					
Body weight (kg)	X			X		
Physical exam GCS/NIHSS	X	X	X			
Functional assessment with mRS				X	X	X
HRQoL assessment with EQ5D					X	X
Routine blood tests	X	X				
BP lowering treatment		X	X	X	X	X
Standard stroke care		X	X	X		
Hospitalized or not				X	X	X
Contact details for follow-up		X		X		

*On this day or the day of discharge if prior to days 3 or 7.

[†]Information is collected at a face-to-face consultation or through a telephone interview.

‡Every 15 min for one-hour after initiation of rt-PA; every 15 min for one-hour after initiation of BP lowering; hourly from one-hour to six-hours after initiation of rt-PA; 6 hourly from six-hours to 24 h after initiation of rt-PA; at any point where intravenous bolus drugs are administered, BP and HR should be recorded 5 and 15 min later.

CT, denotes computerized tomography; EQ5D, 5-dimensions health questionnaire; GCS, Glasgow coma scale; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institutes of Health stroke scale; rt-PA, recombinant tissue plasminogen activator.

illustrates the schedule and nature of data collection during the study period. Data entry is completed via a password protected website held by the ICC.

Study outcomes

The primary outcome for both Arms of the ENCHANTED trial is the combined endpoint of death and disability as defined by the dichotomized '0–1' ('excellent outcome') vs. '2–6' ('dead or dependent') on the mRS at 90 days. The secondary outcome for Arm [A] is sICH defined by all major criteria: (a) sICH based on NINDS criteria of brain imaging confirmed ICH with any neurological deterioration (≥ 1 point change in NIHSS score) from baseline or death within 36 h; and (b) sICH defined by SITS-MOST criteria (30) as large local or remote parenchymal ICH (type 2) combined with a neurological deterioration (≥ 4 points on the NIHSS) from baseline or death within 36 h. Other outcomes are ICH of any type on brain imaging ≤ 7 days of treatment; death or disability by the shift analysis of mRS scores (37,38); death; disability; neurological deterioration (≥ 4 -points decline in NIHSS) during 72-h; HRQoL by the EuroQoL (39); admission to residential care; and health service use for calculation of resources and costs.

Data management

The study database includes web-based data entry onto electronic Case Report Forms (CRF) developed by The George Institute for Global Health. Each participating hospital site enters data using an electronic signature (unique username and password). All changes that are made have an electronic audit trail with electronic signature and date. Both the ICC and Regional Coordinating Centre (RCC) staff have access to online reports on overall study status, CRF completion status, and serious adverse events (SAE) reports, to assist with monitoring the data quality.

Quality assurance

The aim of the non-inferiority trial Arm [A] is to demonstrate that any difference in outcomes between the two doses of rt-PA is small enough to allow a conclusion that the effect of low-dose rt-PA is not inferior to standard-dose rt-PA. We have assumed that effective recanalization of an occluded cerebral artery in AIS is more dependent on the time from the onset of symptoms to injection of the bolus dose of rt-PA rather than the total dose (and duration) of the subsequent infusion of rt-PA. Thus, the study has been designed with a similar loading dose but differing infusion dose of rt-PA according to body weight between the low-dose and standard-dose treatment arms.

We recognized that the success of a non-inferiority trial is dependent on addressing certain parameters with the potential for bias toward the null, that is where the observed treatment difference decreases from the true difference between treatments. This could arise if there is imprecise or poorly implemented entry criteria, poor adherence to the protocol (including dosing errors or delays in the use of rt-PA), use of concomitant treatments and background care with effects that may overlap with rt-PA, and poor measurement of outcomes. While each of these issues may on their own have only small (or no) influence on the variability of the outcome (variance), collectively they can reduce the observed difference between randomized groups, potentially

leading to a false conclusion over non-inferiority. Thus, central monitoring includes regular checks of the accumulating data to ensure sites adhere to the 'gold standard' short DTN time (i.e. average 60 min) (9) and the initial estimates of body weight for dosing of rt-PA are checked against measured body weight in patients after they are admitted to stroke units. Independent experienced neurologists review and adjudicate all brain imaging related to all deaths and assess any ICH in all follow-up scans. All CT or MRI images are uploaded onto a secure web-based database which uses MIStar version 3.2.63 (Apollo Medical Imaging Technology, Melbourne, Vic., Australia), to allow blinded assessment.

Central and regionally based, research staff undertake remote monitoring and on-site data verification. The initial on-site monitoring visit takes place after the first few patients are randomized at a site, and thereafter sites are monitored at least every 12 months according to recruitment and data quality. Monitoring serves to confirm that investigators are adhering to the protocol and Good Clinical Practice (GCP) Guidelines, and the accuracy of the data. To ensure adherence to appropriate randomized dose of rt-PA, sites are required to register the Actilyse vial number(s) within 24 h of randomization and store the packages for checking at monitoring visits. Site monitoring by research staff aims to confirm: (i) demographic and consent details of randomized patients; (ii) details of all SAEs against source documents; (iii) collection/correction of outstanding/missing data; and (iv) checking of selected variables against source medical documents in a 10% random selection of patients.

Data safety monitoring committee (DSMB)

The external DSMB employs the Haybittle-Peto rule as a guide for proof beyond reasonable doubt in the monitoring of both efficacy and safety information in the trial. The DSMB regularly monitors SAEs (deaths, ICH and neurological deterioration), for which any excess would trigger discussions over stopping for harm.

Sample size

Arm [A] 'rt-PA dose' primary clinical outcome. The Cochrane review of thrombolysis in AIS notes the rate of death or disability (mRS score of 2–6) in patients treated with standard-dose iv rt-PA as 50%, and non-randomized studies suggest that low-dose rt-PA provides a similar clinical outcome (i.e. risk ratio 1.0) (2,39). For comparison between low- and standard-dose rt-PA, a non-inferiority margin has been proposed that is based on the Cochrane review where the overall risk ratio of standard-dose rt-PA vs. control with respect to death or disability was 0.76 (95%CI 0.66–0.87). Taking a conservative approach, the 40th percentile point around the risk reduction estimate (0.77) rather than the observed risk ratio is taken as the more robust reference to describe the effects of standard-dose rt-PA (this translates into a margin of excess risk of placebo vs. standard-dose rt-PA of 1.29). A non-inferiority margin of 1.14 has been set to provide assurance that low-dose rt-PA retains at least half the efficacy of standard-dose rt-PA, provided the upper limit of 95% CI of low- vs. standard-dose rt-PA is less than this non-inferiority margin (Fig. 2). The sample size takes account of the potential for a negative interaction between intensive BP lowering and low-dose

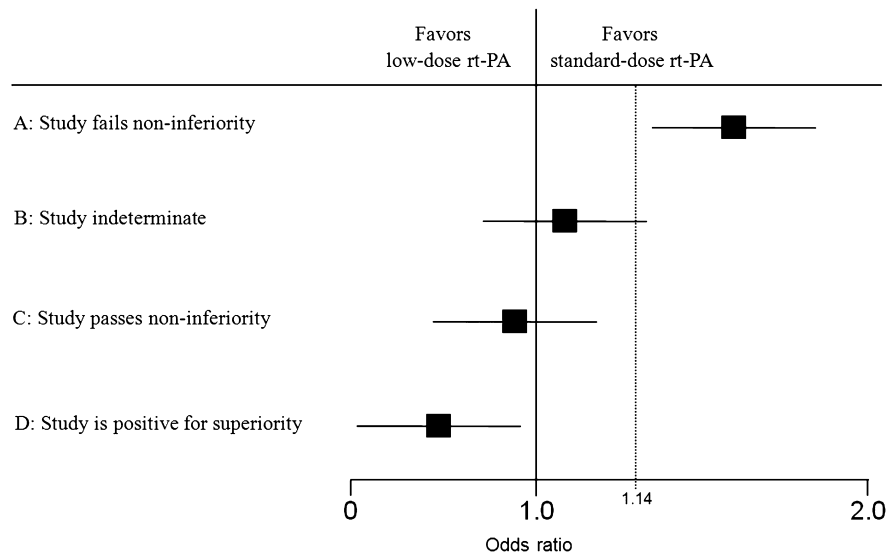


Fig. 2 Illustration and interpretation of non-inferiority boundary for low-dose compared to standard-dose recombinant tissue plasminogen activator (rt-PA). A, low-dose rt-PA is inferior to standard-dose rt-PA; B, indeterminate comparison of efficacy between doses of rt-PA; C, low-dose rt-PA has the same benefit as standard-dose rt-PA; D, low-dose rt-PA is superior to standard-dose rt-PA.

rt-PA. Resulting calculations produced a sample size of 3300 (1650 per group) to provide at least 90% power (1-sided $\alpha = 0.025$) to achieve the non-inferiority setting, assuming 5% drop-out. Once non-inferiority has been confirmed, it is then possible to evaluate if low-dose rt-PA is superior to standard-dose rt-PA.

Arm [B] 'BP control' primary clinical outcome. Using results from the SITS-ISTR registry (31) and assuming a potential interaction between low-dose rt-PA and intensive BP lowering, a sample size of 2300 (1150 per group) will provide > 90% power (2-sided $\alpha = 0.05$) to detect a 14% relative reduction in the primary outcome in the intensive BP lowering group, assuming 5% drop-out.

Secondary outcome of sICH in Arm [A] 'rt-PA dose'. Based on past results (2,31,40) and assuming a potential interaction between low-dose rt-PA and intensive BP lowering, a sample size of 3300 (1650 patients per group) will provide > 80% power (2-sided $\alpha = 0.05$) to detect > 40% relative reduction in sICH for the low-dose rt-PA group, assuming 5% drop-out.

Secondary outcome of any ICH in Arm [B] BP control. Similarly, the study will provide > 90% power (2-sided $\alpha = 0.05$) to detect reductions in any ICH from intensive BP lowering, assuming 5% drop out.

Statistical analyses

ENCHANTED will follow the intention-to-treat principle for analyses. However, sensitivity per-protocol analysis may also be conducted for non-inferiority analysis. Baseline characteristics will be summarized by treatment groups. The primary end-point of death and disability will be analyzed by a chi-square test, as will the categorical secondary outcomes. In Arm [A], low-dose rt-PA will be considered non-inferior to standard-dose rt-PA with regard to the primary endpoint if the upper limit of the 95% CI for risk ratio is < 1.14 . Continuous endpoints will be summarized by means or medians, with the treatment effects tested by Wilcoxon test that assumes skewed data. If these data are not accept-

ably skewed, mixed models will be used to describe the health utility score over time. The primary analysis will be unadjusted. Descriptive statistics will be provided for safety data. SAE and treatment discontinuation due to them will be tabulated using standard terminology. Heterogeneity of treatment on the primary endpoint will be assessed in pre-defined subgroups: age (< 65 vs. ≥ 65 years); gender; time-to-treatment (< 3 vs. ≥ 3 h); systolic BP (above vs below mean); ethnicity (Asia vs. non-Asia); visible cerebral infarction; presumed subtype of AIS (cardio-embolic, lacunar, atherothrombotic, and other); NIHSS at baseline (above vs below median); and evidence of proximal cerebral artery clot occlusion on angiography (yes vs. no). Analyses will be specified a priori in a full statistical analysis plan.

Study organization

The management of ENCHANTED includes a Steering Committee who have overall responsibility for the execution of study design, protocol, data collection and analysis plan, as well as publications. They have the right to appoint new members and co-opt others to add to the integrity of the conduct of the study and analyses. An Operational Committee based at the ICC is in charge of the central coordination of the study. There are RCCs, DSMB, an Imaging Adjudication Committee, and an Advisory Committee of international experts. Approximately 100 sites are responsible for recruiting patients and collecting data in Asia, Australia, South America and the United Kingdom. Hospitals are administratively tied through a structure designed to enhance effective communication and collaboration as well as monitor and maintain operations through adherence to a common protocol.

Current status of the trial and funding

The ENCHANTED trial is currently recruiting patients in approximately 100 centers within 15 countries and overall has randomized more than 2624 patients as of February 2015. Figure 3 and Table 3 show that the great majority of participants are into Arm [A] rt-PA dose as compared to Arm [B] BP control. Table 4 demonstrates that there are comparable baseline

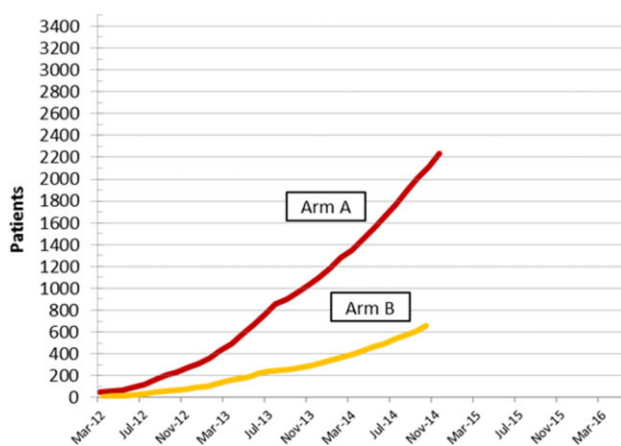
Table 3 Recruitment into the ENCHANTED trial by randomization and treatment Arms, as of September 2014

	Arm [B] 'BP control'			Total
	Standard	Intensive	Not randomized	
Arm [A] 'rt-PA dose'	N (%)	N (%)	N (%)	N (%)
Standard dose rt-PA	133 (6.6)	135 (6.7)	708 (35.4)	976 (48.8)
Low-dose rt-PA	149 (7.4)	133 (6.6)	700 (35.0)	982 (49.1)
Not randomized	23 (1.1)	20 (1)	0	43 (2.1)
Total	305 (15.2)	288 (14.4)	1408 (70.4)	2001 (100)

Table 4 Baseline characteristics of patients by treatment arms, as of September 2014

	Arm [A] 'rt-PA dose' (N = 1958)	Arm [B] 'blood pressure control' (N = 593)
Age, mean (SD), year	66 (13)	66 (12)
Male, n (%)	1209 (62)	368 (62)
China recruitment, n (%)	809 (41)	407 (69)
Systolic BP, mean (SD) mmHg	149 (20)	165 (9)
Diastolic BP, mean (SD) mmHg	85 (13)	92 (12)
NIHSS, mean (SD)	10 (6)	10 (6)
Body weight, mean (SD), kg	70 (15)	70 (13)
Time from onset to hospital arrival, median (iqr), hours	1.3 (0.8–2.0)	1.3 (0.7–2.0)
Time from hospital arrival to rt-PA, median (iqr), hours	1.3 (0.8–1.9)	1.7 (1.1–2.25)
CT or MRI angiography shows cerebral artery occlusion, n (%)	321 (16)	50 (8)
One-hour, post-randomization, systolic BP difference between treatment groups, mmHg	0	8

NIHSS denotes National Institutes of Health stroke scale; BP, blood pressure; CT, computerized tomography; MRI, magnetic resonance imaging.

**Fig. 3** Recruitment into treatment Arms of ENCHANTED trial.

demographic and clinical characteristics between Arms of the study. The DSMB have recommended continuation of the trial.

The study is funded by grants from the National Health and Medical Research Council (NHMRC) of Australia, the Stroke Association of the United Kingdom, and the National Council for Scientific and Technological Development of Brazil. The authors are solely responsible for the design and conduct of this trial, all trial analyses, and drafting and editing of the manuscript, and its final contents.

Conclusion

Thrombolytic treatment with iv rt-PA is an established treatment for AIS (1,2,39), with the FDA approved standard-dose of

0.9 mg/kg being proposed after small dose finding studies: escalating doses of rt-PA were administered to patients within 90 min from AIS onset in Part I (4), and between 91 and 180 minutes from onset in Part II (5). No sICH was noted in the 58 patients who received ≤ 0.85 mg/kg iv rt-PA in Part I vs. 3/26 patients who had received a dose of ≥ 0.95 mg/kg. Higher doses of iv rt-PA were significantly related to the risk of sICH, but there was no clear correlation between early neurological improvement and rt-PA dose. Based on these findings, an arbitrary intermediate dose between 0.85 and 0.95 mg/kg was selected for the NINDS efficacy trial (3). However, Japanese authorities subsequently approved a lower dose of 0.6 mg/kg based on concerns of hazard leading to comparable efficacy studies in that population. The better efficacy and safety of this lower dose has been suggested in many studies across Asia as well as part of 'bridging' thrombolysis in endovascular treatment trials of AIS in the United States (41).

One of the major drawbacks to the use of iv rt-PA is the major adverse effect of sICH, with an apparent higher risk in particular patient subgroups, including Asians (42) and those who are hypertensive at presentation (30,31). Other drawbacks to iv rt-PA are limited access, service organizational issues, and relatively high cost. As most strokes occur in developing countries, only low cost treatments that are widely applicable will have significant public health impact. Since low-dose rt-PA and early intensive BP lowering both fulfill these requirements, ENCHANTED could have a major impact in reducing the burden of stroke by providing evidence for a cheaper, safer and effective treatment for AIS, used either alone or in combination. Given the applicability to millions of people with AIS worldwide each year, the results of the

ENCHANTED trial could have a major impact on the current clinical practice.

Acknowledgements

Steering Committee: John Chalmers (Chair), Craig Anderson (Principal Investigator), Hisatomi Arima, Yining Huang, Jong Sung Kim, Pablo Lavados, Tsong-Hai Lee, Richard I Lindley, Christopher Levi, Sheila Martins, Jeyaraj D Pandian, Mark Parsons, Octavio M Pontes-Neto, Vijay K Sharma, Nguyen Huy Thang, Christian Stapf, Thompson Robinson, Jiguang Wang.

Advisory Committee: Philip Bath, Joseph Broderick, Andrew Demchuk, Geoffery Donnan.

Data Safety Monitoring Board: R John Simes, Graeme Hankey, Peter Sandercock, Marie-Germaine Boussier, KS Lawrence Wong.

Statisticians: Laurent Billot, Mark Woodward, Qiang Li.

International Coordinating Center: Xiaoying Chen, Joyce Lim, Elizabeth Knight, Sharon Tucker, Leibo Liu, Sully Fuentes, Elizaveta Ivanova, Cheryl Carcel, Elizabeth Odgers, Elizabeth Sanders, Emma Thembani, Ruchita Vaghasiya, Kerry Jenson, Xia Wang.

Regional Coordinating Centers: South America – Veronica Olavarria, Francisca Gonzalez, Bernardita Portales, Alejandra Malavera, Magda Carla Ouriques Martins; China – Ying Guo, Ziwei Xu, Zhen Xi, Ting Zhang, Yan Zhao, Nan Li, Ruolan Jia, Wei Li; South Korea – Yunjeong In, Su Jin Kim, Jung Eun Ahn; Taiwan – Chiny-Yi Wang, Shan-Jin Ryu; United Kingdom – Tracy Kumar, Alice Durham, Hardeep Aujla; Vietnam – Hong Ha Uyen.

References

- Emberson J, Lees KR, Lyden P *et al.* Effect of treatment delay, age and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014; **384**:1929–35.
- Wardlaw JM, Murray V, Berge E *et al.* Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet* 2012; **379**:2364–72.
- The national institute of disorders and stroke rt-PA stroke study group: tissue Plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; **333**:1581–7.
- Brott TG, Haley EC Jr, Levy DE *et al.* Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. *Stroke* 1992; **23**:632–40.
- Haley EC Jr, Levy DE, Brott TG *et al.* Urgent therapy for stroke. Part II. Pilot study of tissue plasminogen activator administered 91–180 minutes from onset. *Stroke* 1992; **23**:641–5.
- Haley EC Jr, Brott TG, Sheppard GL *et al.* Pilot randomized trial of tissue plasminogen activator in acute ischemic stroke: the TPA Bridging Study Group. *Stroke* 1993; **24**:1000–4.
- Hacke W, Donnan G, Fieschi C *et al.* Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004; **363**:768–74.
- Hacke W, Kaste M, Bluhmki E *et al.* Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; **359**:1317–29.
- Jauch EC, Saver JL, Adams HP *et al.* Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44**:870–947.
- Saver JL. Number needed to treat estimates incorporating effects over the entire range of clinical outcomes: novel derivation method and application to thrombolytic therapy for acute stroke. *Arch Neurol* 2004; **61**:1066–70.
- Mori E, Yoneda Y, Tabuchi M *et al.* Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. *Neurology* 1992; **42**:976–82.
- Yamaguchi T, Kikuchi H, Hayakawa H. Clinical efficacy and safety of intravenous tissue plasminogen activator in acute ischaemic stroke; in Yamaguchi T, Mori E, Minematsu K, Zoppo GD (eds): *Thrombolytic Therapy in Acute Ischaemic Stroke III*. Tokyo, Springer-Verlag, 1995:223–9.
- Ueshima S, Matsuo O. The differences in thrombolytic effects of administered recombinant t-PA between Japanese and Caucasians. *Thromb Haemost* 2002; **87**:544–6.
- Iso H, Folsom AR, Koike KA *et al.* Antigens of tissue plasminogen activator and plasminogen activator inhibitor 1: correlates in non-smoking Japanese and Caucasian men and women. *Thromb Haemost* 1993; **70**:475–80.
- Murata M. Genetic polymorphisms associated with thrombotic disorders in the Japanese population *Fibrinolysis Proteolysis* 2000; **14**:155–64.
- Shaw GJ, Meunier JM, Lindsell CJ, Pancioli AM, Holland CK. Making the right choice: optimizing rt-PA and eptifibatid lysis, an in vitro study. *Thromb Res* 2010; **126**:e305–11.
- Yamaguchi T, Mori E, Minematsu K *et al.* Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). *Stroke* 2006; **37**:1810–5.
- Toyoda K, Koga M, Naganuma M *et al.* Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. *Stroke* 2009; **40**:3591–5.
- Nakagawara J, Minematsu K, Okada Y *et al.* Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice: the Japan post-Marketing Alteplase Registration Study (J-MARS). *Stroke* 2010; **41**:1984–9.
- Pandian JD, Srikanth V, Read SJ, Thrift AG. Poverty and stroke in India: a time to act. *Stroke* 2007; **38**:3063–9.
- Sharma VK, Ng KW, Venketasubramanian N *et al.* Current status of intravenous thrombolysis for acute ischemic stroke in Asia. *Int J Stroke* 2011; **6**:523–30.
- Wardlaw JM, Koumellis P, Liu M. Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke. *Cochrane Database Syst Rev* 2013; (5):Art. No.: CD000514. doi: 10.1002/14651858.CD000514.pub3.
- Qureshi AI, Ezzeddine MA, Nasar A *et al.* Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med* 2007; **25**:32–8.
- Geeganage CM, Bath PM. Relationship between therapeutic changes in blood pressure and outcomes in acute stroke: a metaregression. *Hypertension* 2009; **54**:775–81.
- Qureshi AI. Acute hypertensive response in patients with stroke: pathophysiology and management. *Circulation* 2008; **118**:176–87.
- Tikhonoff V, Zhang H, Richart T, Staessen JA. Blood pressure as a prognostic factor after acute stroke. *Lancet Neurol* 2009; **8**:938–48.
- Elewa HF, Kozak A, Johnson MH, Ergul A, Fagan SC. Blood pressure lowering after experimental cerebral ischemia provides neurovascular protection. *J Hypertens* 2007; **25**:855–9.
- Brott T, Lu M, Kothari R *et al.* Hypertension and its treatment in the NINDS rt-PA Stroke Trial. *Stroke* 1998; **29**:1504–9.
- Tsivgoulis G, Frey JL, Flaster M *et al.* Pre-tissue plasminogen activator blood pressure levels and risk of symptomatic intracerebral hemorrhage. *Stroke* 2009; **40**:3631–4.
- Wahlgren N, Ahmed N, Eriksson N *et al.* Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: safe implementation of thrombolysis in stroke-monitoring study (SITS-MOST). *Stroke* 2008; **39**:3316–22.
- Ahmed N, Wahlgren N, Brainin M *et al.* Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe

- Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). *Stroke* 2009; **40**:2442–9.
- 32 Sandset EC, Bath PM, Boysen G *et al.* The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet* 2011; **377**:741–50.
- 33 The ENOS Trial Investigators. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet* 2015; **385**:617–28.
- 34 Anderson CS, Heeley E, Huang Y *et al.* Rapid blood pressure lowering in acute intracerebral hemorrhage. *New Engl J Med* 2013; **368**:2355–65.
- 35 Bamford JM, Sandercock PA, Warlow CP, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989; **20**:828.
- 36 Brott T, Adams HP Jr, Olinger CP *et al.* Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989; **20**:864–70.
- 37 Bath PMW, Lees KR, Schellinger PD *et al.* on behalf of the European Stroke Organisation Outcomes Working Group. Statistical analysis of the primary outcome in acute stroke trials. *Stroke* 2012; **43**:1171–8.
- 38 Howard G, Waller JL, Voeks JH *et al.* A simple, assumption-free, and clinically interpretable approach for analysis of modified Rankin outcomes. *Stroke* 2012; **43**:664–9.
- 39 Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001; **33**:337–43.
- 40 Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2014; (7):Art. No.: CD000213. doi: 10.1002/14651858.CD000213.pub3.
- 41 Georgiadis AL, Memon A, Shah QA *et al.* Comparison of partial (.6 mg/kg) versus full-dose (.9 mg/kg) intravenous recombinant tissue plasminogen activator followed by endovascular treatment for acute ischemic stroke: a meta-analysis. *J Neuroimaging* 2011; **21**:113–20.
- 42 Menon BK, Saver JL, Prabhakaran S *et al.* Rick score for intracranial haemorrhage in patients with acute ischemic stroke treated with intravenous tissue-type plasminogen activator. *Stroke* 2012; **43**:2293–9.