Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international randomised, open-label, blinded-endpoint phase 3 trial

Craig S. Anderson PhD[1,2,3] *; Yining Huang MD[4] *; Richard I. Lindley MD[5]; Xiaoying Chen BMgt[1]; Hisatomi Arima PhD[1,6]; Guofang Chen MD[7]; Qiang Li MBiostat[1]; Laurent Billot MRes[1]; Candice Delcourt PhD[1,8], Philip M. Bath FMedSci[9]; Joseph P. Broderick MD[10]; Andrew M. Demchuk MD[11]; Geoffrey A. Donnan MD[12]; Alice C. Durham MSc[13]; Pablo M. Lavados MD[14,15]; Tsong-Hai Lee PhD[16]; Christopher Levi MD[17,18,19]; Sheila O. Martins PhD[20]; Veronica V. Olavarria MD[14]; Jeyaraj D. Pandian DM[21]; Mark W. Parsons PhD[22]; Octavio M. Pontes-Neto PhD[23]; Stefano Ricci MD[24]; Shoichiro Sato PhD[25]; Vijay K. Sharma MD[26]; Federico Silva MD[27]; Lili Song PhD[3]; Nguyen H. Thang MD[28]; Ji-Guang Wang PhD[29]; Xia Wang PhD[1]; Mark Woodward PhD[1,30,31]; John Chalmers[1] ** PhD; Thompson G. Robinson[12,32] ** MD; for the ENCHANTED Investigators and Coordinators

*Co-First Authors, **Co-Senior Authors

[1]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia

[2]Neurology Department, Royal Prince Alfred Hospital, Sydney Health Partners, Sydney, NSW, Australia

[3]The George Institute China at Peking University Health Sciences Center, Beijing, China

[4]Department of Neurology, Peking University First Hospital, Beijing, China

[5]Westmead Clinical School, University of Sydney, NSW, Australia

[6]Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan.

[7]Department of Neurology, Xuzhou Central Hospital, Xuzhou, China

[8]Neurology Department, Prince Royal Alfred Hospital, University of Sydney, Sydney, NSW, Australia

[9]Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK

[10]Department of Neurology and Rehabilitation Medicine, University of Cincinnati Neuroscience Institute, University of Cincinnati, Cincinnati, USA

[11]Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Canada

[12]The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Victoria, Australia

[13]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

[14]Departamento de Neurologia y Psiquiateria, Clinica Alemana de Santiago, Facultad de Medicina, Clinica Alemana Universidad del Desarrollo, Santiago, Chile

[15]Departamento de Ciencias Neurológicas, Facultad de Medicina, Universidad de Chile, Santiago, Chile

[16]Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taoyuan, Taiwan

[17]University of Newcastle, School of Medicine and Public Health, University Drive, Callaghan, NSW, Australia

[18]Hunter Medical Research Institute, New Lambton Heights, NSW 2305, Australia

[19]The Sydney Partnership for Health, Education, Research and Enterprise, Ingham Institute for Applied Medical Research, Liverpool, NSW, Australia

[20]Stroke Division of Neurology Service, Hospital de Clinicas de Porto Alegre, University of Rio Grande do Sul, Porto Alegre, Brazil

[21]Department of Neurology, Christian Medical College, Ludhiana, Punjab, India 141008

[22]Neurology Department, Royal Melbourne Hospital, University of Melbourne, Melbrourne, Victoria, Australia

[23]University of Sao Paulo, Ribeirao Preto Medical School, Department of Neurosciences and Behavioral Sciences, Ribeirao Preto, Brazil

[24]Uo Neurologia, USL Umbria 1, Sedi di Citta di Castello e Branca, Italy

[25]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

[26]Yong Loo Lin School of Medicine, National University of Singapore and Division of Neurology, National University Hospital, Singapore

[27]Neurovascular Sciences Group, Neurosciences Department, Bucaramanga, Colombia

[28]Department of Cerebrovascular Disease, The People 115 Hospital, Ho Chi Min, Vietnam

[29]Shanghai Institute for Hypertension, Rui Jin Hospital and Shanghai Jiaotong University School of Medicine, Shanghai, China

[30]Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA

[31]The George Institute for Global Health, University of Oxford, Oxford, UK

[32]NIHR Leicester Biomedical Research Centre, The Glenfield Hospital, Leicester, UK

Corresponding Author
Professor Craig S Anderson
The George Institute for Global Health
PO Box M201, Missenden Road, NSW 2050, AUSTRALIA
T: +61-2-9993-4500; F: +61-2-9993-4502; E: canderson@georgeinstitute.org.au

Short title: ENCHANTED BP intensity arm

Tables: 2

Figures: 4

Supplementary Tables: 15

Supplementary Figure: 2

List of tables and figures:

Table 1: Baseline characteristics of patients with acute ischaemic stroke who received intravenous alteplase according to randomised treatment group

Table 2: Key primary and secondary outcomes at Day 90

Figure 1: Trial profile

Figure 2: Systolic and diastolic blood pressure trends from randomisation to Day 7

Figure 3: Modified Rankin scale score at 90 days by treatment arm

Figure 4: Primary outcome by pre-specified subgroups

Word Count: Abstract 462, Body 4591

Research in context, word count: 224

Keywords: acute ischaemic stroke, thrombolysis, intracerebral haemorrhage, blood pressure lowering, hypertension

Abstract

Background High systolic blood pressure (SBP, >185mmHg) is a contraindication for thrombolysis treatment with intravenous (iv) alteplase in acute ischaemic stroke (AIS), but the target level for optimal outcome is uncertain. We assessed the efficacy and safety of intensive BP lowering in thrombolysis-treated AIS.

Methods In an international partial-factorial, open-label, blinded-endpoint trial, we randomly assigned thrombolysis-eligible AIS patients within 6 hours of onset to intensive (target SBP 130-140mmHg within 1 hour) versus guideline-recommended (SBP <180mmHg) BP lowering over 72 hours. The primary outcome was functional status at 90 days, measured by shift ('improvement') in modified Rankin scale scores, analysed using unadjusted ordinal logistic regression. The key secondary safety outcome was any intracranial haemorrhage. Other safety outcomes included major symptomatic intracerebral haemorrhage (sICH) according to standard definitions based on central adjudication of brain images. 917 participants were also in the alteplase dose-comparison arm. Analyses were by intention-to-treat. This trial is registered with ClinicalTrials.gov, NCT01422616.

Findings We randomised 2227 and analysed 2196 iv alteplase-treated AIS patients (38% female, 73·7% Asian ethnicity) of mean age 66·7 years (standard deviation 12·2), with median baseline National Institutes of Health Stroke Scale score of 7 (interquartile range 4·0–12·0) at a median time from onset to randomisation was 3·3 hours (interquartile range 2·6-4·1) between March 3, 2012 and April 30, 2018. There were 1081 assigned to intensive and 1115 to guideline BP lowering; groups being well balanced at baseline. Average SBP over 24 hours was 144mmHg (standard deviation 10) and 150mmHg (12) in the intensive and guideline groups, respectively (p<0·0001). Functional status at 90 days did not differ between groups (odds ratio [OR] 1·01, 95% confidence intervals [CI] 0·87–1·17; p=0·8702). Significantly fewer patients had any intracranial haemorrhage after intensive compared to

guideline BP management (14·8% *vs.* 18·7%, OR 0·75, 95%CI 0·60–0·94; p=0·0137). Clinician-reported intracranial haemorrhage as a serious adverse event (5·5% vs. 9·0%, OR 0·59, 95%CI 0·42-0·82; p=0·0017) and major parenchymal ICH-related haematoma on central brain imaging review (13·2% vs. 16·1%, OR 0·79, 95%CI 0·62-1·00; p=0·0542) were also lower in the intensive group. The frequency of adjudicated sICH across several definitions was low and not significantly different between groups. There was no evidence of an interaction of intensive BP lowering with randomised dose of alteplase with regard to the primary outcome.

Interpretation Intensive compared to guideline-based BP lowering did not improve functional outcome at 90 days in alteplase-treated AIS patients of mild-to-moderate severity. A significant reduction in any intracranial haemorrhage, but not sICH, was observed. These results provide reassurance that intensive BP control is not associated with adverse effects on the cerebral ischaemic penumbra, and of potential benefits from a lower risk of thrombolysis-associated intracranial haemorrhage in AIS. Further trials with a greater separation of SBP between treatment groups are required to provide more definite evidence.

Funding Main funding from the National Health and Medical Research Council of Australia and the UK Stroke Association.

Introduction

Timely administration of intravenous (iv) thrombolysis treatment is the mainstay of hyperacute reperfusion treatment in patients with acute ischaemic stroke (AIS), even with the advent of mechanical thrombectomy for those with large proximal vessel occlusion.[1] The evidence is strong for a net benefit over harms from serious intracranial haemorrhage when iv alteplase is administered within 4·5 hours of AIS onset.[2,3] Ongoing research seeks to improve the efficacy and safety of mechanical and pharmacological reperfusion therapies in eligible AIS patients.

The dose arm of the ENhanced Control of Hypertension ANd Thrombolysis strokE StuDy (ENCHANTED) has previously reported that, compared to standard-dose, low-dose iv alteplase was not shown to be non-inferior with respect to death and dependency at 90 days, despite a significant reduction in early (7 day) mortality and symptomatic intracerebral haemorrhage (sICH).[4] However, there is ongoing controversy in respect of peri-thrombolysis blood pressure (BP) control, where guidelines consistently contraindicate the use of alteplase in patients with high levels (systolic BP [SBP] >185mmHg).[5] Two large registries have reported a positive association of increasing SBP and higher risks of sICH, even below this threshold;[6,7] sICH being four times higher in patients with a SBP >170mmHg compared to those with levels of 141–150mmHg.[7] A U-shaped association for death and dependency is also evident, with best outcome in the nadir SBP 141–150mmHg. An ongoing concern, however, has been that rapid BP reductions in the absence of reperfusion may worsen cerebral ischaemia from hypoperfusion in failing collateral circulation into the ischaemic penumbra.[8]

Therefore, the second arm of the ENCHANTED trial was driven by uncertainty over whether any potential benefits for improving outcome in relation to a reduced risk of thrombolysis-related intracranial haemorrhage are offset by the harm of intensive BP lowering worsening cerebral ischaemia. Herein, we report the results of the BP-control arm of the ENCHANTED

trial, which tested the hypotheses that following use of iv alteplase, a strategy of intensive (SBP 130–140mmHg) is superior to guideline-recommended (SBP <180mmHg) BP lowering for improving functional recovery and reducing the risk of intracranial haemorrhage in AIS patients.

Methods

Study design and participants

ENCHANTED was an international, multi-centre, prospective, randomised, open-label, blinded-endpoint (PROBE) trial which used a 2x2 partial-factorial design to assess the effectiveness of low-dose versus standard-dose alteplase, previously published;[5] and intensive versus guideline-recommended BP control, this publication. Details of the study design and rationale have been published,[9] and the protocol is available online. The statistical analysis plan was submitted for publication prior to study unblinding.[10]

Adult AIS patients aged ≥18 years and SBP ≥150mmHg were eligible if they fulfilled standard criteria for thrombolysis with iv alteplase, and the treating clinician had uncertainty over the benefits and risks of the intensity of BP control during and for up to 72 hours (or hospital discharge [or death] if this occurred earlier) after thrombolytic treatment. Although there was no specified upper SBP level, patients were required to guidelines for the use of thrombolysis, which included having a SBP ≤185mmHg prior to administration of iv alteplase. Participants were randomly assigned to a strategy of intensive BP lowering (target SBP 130–140mmHg within 60 minutes of randomisation) or guideline-recommended BP lowering (target SBP <180mmHg) after commencement of iv alteplase. A protocol amendment in November 2013: (i) reduced the SBP target from 140–150mmHg to 130–140mmHg to enhance the SBP difference between intensive and guideline groups; (ii) increased the time of randomisation to the BP arm from within 4.5 to 6 hours of stroke onset

to prevent quality performance related delays in administration of iv alteplase as part of routine practice in regard to trial-related procedures; (iii) increased the time to achieve the target SBP from 60 minutes of commencement of alteplase to 60 minutes following randomisation; (iv) changed the key secondary outcome from whether intensive BP lowering reduced sICH to reduction in any intracranial haemorrhage to increase study power; and (v) reduced sample size from 3300 to 2304 participants. Furthermore, a final protocol amendment in February 2017: (i) changed the primary outcome from a conventional binary assessment of poor clinical outcome (modified Rankin scale [mRS] score of 3–6) to an ordinal shift analysis of the full range of category scores (0–6) of the mRS at 90 days to increase study power; and (ii) a further reduction in sample size to 2100 participants consequent upon the change in primary outcome. Until the conclusion of the alteplase dose arm in August 2015, participants could additionally be randomised to low-dose (0.6mg/kg; 15% as bolus, 85% as infusion over 1 hour) or standard-dose (0.9mg/kg; 10% as bolus, 90% as infusion over 1 hour) iv alteplase. Subsquently, the attending clinician investigator could chose the dose of iv alteplase to use according to his/her interpretation of the evidence.

Key exclusion criteria were: the patients was unlikely to benefit from thrombolysis (e.g. advanced dementia); very high likelihood of death within 24 hours; other significant medical co-morbidity that was likely to interfere with the outcome assessments or follow-up (known significant pre-stroke disability, estimated scores 2–5 on the mRS); specific contraindication to alteplase or any of the BP agents to be used; and participation in another clinical trial involving evaluation of a pharmacological agent (see appendix for full inclusion and exclusion criteria).

The trial protocol was approved by appropriate regulatory and ethical authorities at participating centres. Written consent was obtained from each participant, or their approved surrogate for patients who were too unwell to comprehend the information.

Randomisation and masking

After confirmation of patient eligibility, randomisation was undertaken centrally via a password-protected web-based program at The George Institute for Global Health, Sydney, Australia. A minimisation algorithm was used to achieve approximate balance in randomisation according to three key prognostic factors: (i) site of recruitment, (ii) time from the onset of symptoms (<3 vs. ≥3 hours) and (iii) severity of neurological impairment according to the National Institutes of Health Stroke Scale (NIHSS) score (<10 vs. ≥10 points). Final follow-up was undertaken at 90 days, in person or by telephone, by trained and certified staff who were unaware of the randomised treatment assignment.

Procedures

The trial sought to assess a management strategy of BP lowering to achieve and maintain intensive (130–140mmHg) and guideline (<180mmHg) SBP targets. Therefore, local treatment protocols based on available iv (bolus and infusion), oral and topical medications, provided as appendices to the trial protocol, were used. All patients were to be managed in an acute stroke unit, or alternative environment with appropriate staffing and monitoring, and receive active care and best practice management according to local guidelines. The use of endovascular thrombectomy, which increased in clinical practice during the course of the trial, was permitted.

Non-invasive BP monitoring was undertaken using an automated device applied to the non-hemiparetic arm (or right arm in situations of coma or tetraparesis) with the patient resting supine for ≥3 minutes according to a standard protocol. Following thrombolysis, BP measurements were recorded every 15 minutes for 1 hour, hourly from 1 to 6 hours, and 6-hourly from 6 to 24 hours. Thereafter, BP was recorded twice daily for 1 week (or hospital discharge or death, if earlier). Neurological status, including NIHSS and Glasgow coma scale (GCS) scores, was assessed at baseline, and at 24 and 72 hours, and 7 days. Brain imaging

(CT and/or MRI) was conducted at baseline, and at 24 hours, and additionally if clinically indicated; analyses were undertaken centrally for diagnoses of categories of intracranial haemorrhage by expert assessors who were blind to clinical details and treatment allocation (appendix).

A detailed list of the assessment schedule is contained in the study protocol (available online). In brief, screening logs with details of key reasons for excluding potentially eligible patients were maintained at all sites except in the UK, where this activity is not required by the health authority. Socio-demographic and clinical details were obtained at randomisation. Follow-up data were collected at 24 and 72 hours, 7 days (or at hospital discharge if earlier), and 28 and 90 days. Remote and on-site quality control monitoring and data verification were undertaken throughout the study (appendix).

Outcomes

The pre-specified primary outcome at 90 days was a shift ('improvement') in measures of daily function according to the full range of scores on the mRS;[11] a global seven-level assessment of disability, where scores of 0 or 1 indicate a favourable outcome without/with symptoms but no disability, 2 to 5 increasing levels of disability (and dependency), and 6 death. Other secondary efficacy outcomes were assessed by the conventional dichotomous analysis of the mRS at 90 days; 2 to 6 (disability or death) or 3 to 6 (major disability or death) versus the remaining scores. In addition, the following outcomes were assessed: cause-specific mortality within 90 days; death or neurological deterioration (≥4 points decline in NIHSS) within 24 and 72 hours; duration of initial hospitalisation in days; and health-related quality of life (HRQoL), as assessed on the EuroQoL as an overall health utility score (EQ-5D-3L) at 90 days.[12]

The key secondary safety outcome was any intracranial haemorrhage reported by investigators with or without central adjudication of relevant brain imaging within 7 days

after randomisation. This outcome included intracerebral haemorrhage (ICH), subarachnoid haemorrhage, and other forms of haemorrhage within the cranium identified on an adjudicated scan; any intracranial haemorrhage reported by an investigator with a description of the results of brain imaging without central verification; and any coding according to Medical Dictionary for Regulatory Activities (MedDRA) definitions of intracranial haemorrhage reported as a serious adverse event (SAE). Another safety outcome was the topography of ICH identified on centrally adjudicated brain images in relation to a patient's symptoms: that is sICH, where ICH leads to significant neurological deterioration and/or death, as defined by several criteria used in other studies (appendix). Other pre-specified safety outcomes included all-cause and cause-specific SAEs, overall and by vital status, until trial completion, coded according to MedDRA definitions.

Statistical analysis

Power calculations were based on the estimated treatment effects on a conventional binary assessment of 'poor outcome' (mRS scores 3 to 6). Assuming poor outcomes of 43% and 50% in the intensive and guideline BP lowering groups, respectively, a sample size of 2304 (1152 per group) was estimated to provide >90% power (using a two-sided α=0.05) to detect a 13% relative reduction in the poor outcome in the intensive BP lowering group,[7] with 5% drop-out, and assuming a potential interaction between low-dose alteplase and intensive BP lowering. However, as the ordinal shift approach provides efficiency gains by decreasing the required sample size, re-estimation of the sample size based on ordinal mRS analysis indicated that the estimated treatment effect could be detected with a sample size of 2100. This sample size was also estimated to provide >40% reduction in any intracranial haemorrhage associated with a 15mmHg difference in SBP between randomised groups on the basis of SITS-ISTR data.[7]

Statistical analyses were conducted on an intention-to-treat (ITT) basis. Shift analyses were undertaken using ordinal logistic regression, and dichotomous analyses used logistic regression. A priori,[10] the primary analyses for superiority of intensive versus guideline BP lowering were unadjusted, but we also performed sensitivity analyses of the treatment effects on all outcomes adjusted for the minimisation and key prognostic covariates (age, sex, ethnicity, pre-morbid function [mRS scores 0 or 1], pre-morbid use of antithrombotic agents [aspirin, other antiplatelet agent or warfarin], and history of stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomised alteplase dose), as well as a per-protocol analysis. Consistency of treatment effect across 10 pre-specified subgroups was assessed through tests for interaction, obtained from adding interaction terms to statistical models with main effects only. An independent data and safety monitoring committee monitored the trial progress and safety with the use of formal stopping rules, and undertook two interim analyses. All tests were two-sided and the nominal level of α was 5%. No adjustment was made for multiplicity. SAS software, version 9·3 (SAS Institute, Cary, NC) was used for analyses.

Role of the funding source

The sponsors had no role in the study design, data collection, data analysis, data interpretation or writing of the report. All authors had full access to the study data. The corresponding author had final responsibility for the decision to submit the paper for publication.

Data availability

Individual de-identified participant data used in these analyses will be shared by request from any qualified investigator via the Research Office of The George Institute for Global Health, Australia.

Results

Baseline characteristics

From March 3, 2012 to April 30, 2018, a total of 2227 AIS patients who were screened from 110 sites in 15 countries underwent randomisation (figure 1, appendix tables S1 and S2). However, 31 patients were excluded due to missing consent or mistaken/duplicate randomisation, leaving 2196 included in the ITT analysis: 1081 randomly assigned to intensive BP lowering and 1115 to guideline BP lowering. There were 925 (42%) participants who were also enrolled in the alteplase-dose arm of the trial; 456 randomly receiving low-dose alteplase and 469 standard-dose alteplase. Treatment groups were well balanced in respect of baseline demographic and clinical characteristics (table 1). The mean age was 66·9 years (standard deviation [SD] 12·2) and 835 (38·0%) participants were female (table 1). Most patients were recruited in Asia (73·7%; 65·0% in China), and their median NIHSS score before treatment was 7 (range 0 to 42, interquartile range [IQR] 4 to 12). 1012 participants (46·2%) reported receiving prior treatment for hypertension on hospital admission, and mean SBP before treatment was 165mmHg (SD 9). The median time from onset to randomisation was 3·3 hours (IQR 2·6 to 4·1). Only 32 (1·5%) of patients received endovascular thrombectomy treatment.

BP and other management over the first 7 days

Adherence to assigned treatment was high and did not differ between groups: 2182 (99·4%) received alteplase, and 2140 participants (97·4%) received BP lowering treatment according to the assigned protocol (appendix, table S3). Significantly higher rates of both any BP lowering (858 [80·1%] *vs.* 602 [54·3%]; p<0·0001), and specifically in the use of iv drugs (671 [62·7%] *vs.* 391 [35·3%]; p<0·001) were administered in the intensive group during the first 24 hours post-randomisation (appendix table S4). The intensive group also received more BP lowering therapy over the subsequent 7 days in hospital (72·6% *vs.* 63·2%; p<0·0001; appendix, table S5). SBP levels were 146mmHg and 153mmHg (mean Δ -6·4mmHg, 95%

confidence intervals [CI] -5·0 to -7·9) at 1 hour, and 139mmHg and 144mmHg (mean Δ -5·3mmHg, 95%CI -3·9 to -6·7) at 24 hours, between the intensive and guideline groups, respectively (figure 2, appendix table S6). Overall average SBP levels within 24 hours were significantly lower in the intensive group (144 vs. 150mmHg, p<0·0001; appendix, tables S5 and S6). SBP remained lower in the intensive compared to the guideline group for the subsequent 6 days (figure 2, appendix tables S4, S5 and S6). There were no significant differences in other clinical management over the 7 day post-randomisation period (appendix table S4).

Efficacy outcomes

The primary outcome of mRS at 90 days was assessed in 2180 participants (99·3%), most of the time by telephone; 6 (0·3%) were lost to follow-up and 1 withdrew from the 90-day follow-up assessment (figure 1, appendix table S3). There was no significant difference in the 90-day mRS distribution (shift) with an unadjusted odds ratio (OR) of 1·01 (95%CI 0·87–1·17, p=0·8702; table 2 and figure 3). These results were consistent in an analysis after adjustment for the minimisation and key prognostic variables. There was no heterogeneity of the treatment effect on the primary outcome across pre-specified subgroups (figure 4). In particular, there was no significant interaction between alteplase dose and intensity of BP lowering in the 917 patients recruited into both randomisation arms (p=0·2481; figure 4, appendix table S7 and figure S1 [A] and [B]).

No significant differences were seen in the odds of death and disability at 90 days, whether defined by a mRS of 2 to 6 (OR 0·94, 95%CI 0·79–1·11, p=0·4660; table 2) or 3 to 6 (OR 1·00, 95%CI 0·84–1·20, p=0·9968; table 2). The unadjusted and adjusted per-protocol analyses were also consistent in showing no significant differences in the treatment effect for overall functional outcome on the mRS between intensity of BP lowering (table 2). Death or significant neurological deterioration within 24 hours was 10·2% in the intensive BP-

lowering arm versus 9·7% in the guideline arm (OR 1·06, 95%CI 0·80–1·40, p=0·7013), and mortality at 90 days was 9·4% versus 7·9% (OR 1·22, 95%CI 0·90–1·64, p=0·1989; table 2). No significant differences were evident in any of the other secondary clinical outcomes, including primary cause of death, duration of the initial hospitalisation, and HRQoL as an overall health utility score (appendix tables S8 and S9). Post-hoc analysis showed no heterogeneity in the treatment effect on the primary outcome according to quartiles of baseline NIHSS scores (appendix table S10 and figure S2).

Safety outcomes

Assessment of the key secondary (safety) outcome of any intracranial haemorrhage was derived from adjudicated brain scans in 323 (87·5%) and other reports in 164 (51·0%) (appendix). This outcome was significantly lower in the intensive than guideline BP management group (160 [14·8%] *vs.* 209 [18·7%], OR 0·75, 95%CI 0·60–0·94; p=0·0137; table 2). MedDRA coding of clinician-reported intracranial haemorrhage as an SAE was also significantly lower in the intensive BP group (59 [5·5%] *vs.* 100 [9·0%] in the guideline group, OR 0·59, 95%CI 0·42–0·82; p=0·0017). The intensive BP lowering group also had lower frequencies of adjudicated sICH across a broad range of definitions (table 2), although these differences were not significant. Similarly, adjudicated large parenchymal ICH was non-significantly lower in the intensive BP group (56 [5·2%] *vs.* 80 [7·2%], OR 0·71, 95%CI 0·50–1·01; p=0·0535; table 2, and appendix table S11).

There was no significant difference in the overall frequency of SAE between intensive and guideline BP-lowering arms (24·1% *vs.* 27·7%), nor in the number of patients with any SAE (19·4% *vs.* 21·9%, OR 0·86, 95%CI 0·70–1·06, p=0·1554; appendix table S12). However, intensive BP lowering was associated with significantly lower reported intracranial haemorrhage (6·1% *vs.* 9·3%, p=0.0050) and ICH (5·5% *vs.* 9·0%, p=0.0017), which were predominantly driven by non-fatal events (appendix table S12).

BP management was assessed over the course of the study, and SBP difference between the randomised groups tended to decline over time. Prior to completion of the alteplase-dose arm of the trial in August 2015, mean SBP levels over 24 hours were 145mmHg and 153mmHg (mean Δ -8·2mmHg, 95% CI -6·0 to -10·4) between the intensive and guideline groups, respectively; the corresponding figures were 148mmHg and 153mmHg (mean Δ -5·1mmHg, 95%CI -3·2 to -6·7) after August 2015 (appendix, table S13). Similarly, the mean 24 hour SBP difference (mmHg) reduced from -9·9 (95%CI -2·9 to -16·9) to -4·2 (95%CI 2.3 to -10·7) between the first and last years of the study (appendix, table S13). Clinical characteristics of patients in the guideline group were reclassified according to the use of intravenous BP lowering treatment. Compared to those who did not receive any BP lowering treatment, the 602 patients who did were significantly more often female, non-Asian, with higher initial SBP, and greater history of hypertension, prior stroke, coronary artery disease and atrial fibrillation (appendix, table S14). All efficacy and safety outcomes were significantly better for the treated than non-treated patients allocated to the guideline-based BP management group (appendix, table S15).

Discussion

Our trial was driven by uncertainty over whether any benefit of intensive BP lowering improving outcome in AIS, due largely from a reduced risk of thrombolysis-related ICH, may be offset by the harm of promoting cerebral ischaemia. The main finding was that in thrombolysis-treated patients with predominantly mild-to-moderate severity AIS, a strategy of intensive BP lowering (target SBP 130-140mmHg within 1 hour) compared to current guideline-recommended (<180mmHg) BP management after iv alteplase therapy, was not associated with a significant difference in the primary outcome of functional recovery, as assessed by shift (‘improvement’) in the distribution of mRS scores at 90 days. This result was consistent in sensitivity and per-protocol analyses, and across key pre-specified

subgroups. Yet, intensive BP control was also associated with a significant reduction in intracranial haemorrhage, and across measures of sICH although not significantly so. So why was a reduction in intracranial haemorrhage not converted into an overall improvement in patient outcomes?

The ENCHANTED trial adds important new information on the role of early intensive BP lowering in the context of thrombolysed AIS patients, but it also highlights some of the challenges in conducting an open trial in a critical illness with temporal change in the degree of equipoise. Although we recruited to our target sample size and achieved a high level of follow-up over 90 days, the SBP differences between randomized groups were much smaller than planned. In part this reflected a shift in clinician behavior towards targeting lower SBP levels than is recommended in guidelines derived from the protocol of the National Institutes of Neurological Diseases and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) trial in AIS.[16] It also reflects complexities in the titration of SBP according to study protocol for patients in the intensive group.

It is well recognized that SBP is an important prognostic factor after acute stroke, with a systolic target of 140-150mmHg being associated with best outcome in several observational studies.[13,14] To date, randomised evaluations of BP lowering treatment in AIS with a broad time window from the onset of symptoms and modest SBP reductions have been neutral.[15] However, post-hoc analysis of the pivotal NINDS rt-PA trial reported that the use of BP lowering therapy after randomisation in hypertensive patients in the rt-PA group was associated with less favourable outcome.[16] Conversely, post-hoc analysis from the more recent Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), specifically in patients with large vessel occlusion, demonstrated a U-shaped relationship between baseline SBP and outcome; with a SBP nadir of 120mmHg being associated with best outcome.[17]

The concern of many clinicians is that rapid BP reductions in the absence of mechanical and/or pharmacological reperfusion may worsen cerebral ischaemia from potential hypoperfusion with compromised autoregulation and collateral flow.[8] It is conceivable that in our trial, any benefit from intensive BP reduction on outcome from reduction in intracranial haemorrhage was off-set by hypoperfusion of the ischaemic penumbra. Yet, we observed no significant heterogeneity of the treatment effect in subgroups where large vessel occlusion might be anticipated. This includes AIS subtypes classified on the basis of clinician-diagnosis of large vessel disease or cardio-emboli, and in post-hoc analysis of stroke severity based on quartiles of increasing NIHSS score. Nonetheless, large vessel occlusion was only confirmed in 97 patients in the intensive arm in this pragmatic study, where CT or MR angiography was not mandated. Thus, further studies of intensive BP lowering in the context of mechanical and pharmacological reperfusion therapy in proven large vessel occlusion are required.

As previously outlined, a benefit of intensive BP control investigated in ENCHANTED was on the rate of intracranial haemorrhage. From the SITS-International Stroke Thrombolysis Register of 11080 patients, Ahmed and colleagues reported a linear association between SBP and sICH up to 24 hours after thrombolysis.[7] Similarly, Berge and colleagues in a post-hoc analysis of the third International Stroke Trial (IST-3) reported an association between each 10mmHg rise in baseline SBP and risk of sICH, with large SBP declines over 24 hours significantly associated with reducing sICH risk.[18] As the only randomised trial of intensive BP reduction in thrombolysis-treated AIS patients, ENCHANTED suggests there may be benefits in lowering the risk of intracranial haemorrhage, despite no significant decrease in adjudicated sICH being seen. This may reflect variable benefit of intensive BP reduction on petechial, reperfusion-associated ICH in a hypertensive population with evidence of 'brain vessel fragility' compared with large space-occupying, thrombolysis-associated parenchymal ICH, as previously suggested by Butcher and colleagues.[19] However, as ENCHANTED

recruited mainly mild-moderate severity AIS patients, the study was under-powered to assess the effects of treatment on sICH, where the frequencies of death and/or major neurological deterioration were low. Even so, there was consistency in lower rates of sICH across all classifications in the intensive versus guideline groups, and there were non-significant reductions in both petechial (HI 1 and 2) and space-occupying (PH 1 and 2), and borderline significant reduction any PH, in adjudicated brain images. Finally, it is important to note that the ENCHANTED trial excluded patients with a SBP >185 mmHg in keeping with the licensed indication for use of i.v. alteplase, and no comment can be made with respect to the risk of intracranial haemorrhage in severely hypertensive patients, and/or the benefits of BP reduction. However, others have reported that such protocol violations are associated with significantly more frequent sICH.[20]

Strengths and limitations

Key strengths of this randomised controlled trial of intensive versus guideline BP control during and for up to 72 hours following iv thrombolysis for AIS were its large size and international recruitment, which enhance the generalisability of the results and impact on clinical practice worldwide. In addition, robust methodologies were used to ensure blinding of the key efficacy measure, through central co-ordination of mRS follow-up by staff unaware of treatment allocation, and of the safety outcomes, with central blinded adjudication of intracranial haemorrhage. Nonetheless, there were a several potential limitations.

First, the trial involved an AIS population of predominantly mild-to-moderate severity, with a median NIHSS of 7·0, as compared to previous trial and registry data of AIS patients with median NIHSS scores of 12·0 and 13·0, respectively.[2,3] However, with increasing use of iv thrombolysis, the NIHSS is more reflective of the usual treated AIS population, including that in clinical trials. For example, the median NIHSS in a recent comparison of tenecteplase with alteplase was 4·0.[21] Secondly, there may be concerns about the generalisability of the trial

results to all populations, as nearly three-quarters were Asian. Importantly, though, there was no heterogeneity of the treatment effect by ethnicity, and where the high prevalence of intracranial atherosclerosis and related intracranial stenosis, and cerebral small vessel disease, in an Asian population may have increased the risks of hypoperfusion related to intensive BP control.[22] In addition, the higher prevalence of hypertension and associated small vessel disease in Asians may have increased the risk of sICH.[23] Finally, the achieved SBP difference being smaller than anticipated which likely resulted in the trial being under-powered. In part this may be attributed to a natural fall in SBP following re-canalisation/reperfusion in both groups, but it is also likely that this reflected the impact of there being a high proportion (54·5%) of participants in the guideline group who received some form of BP lowering therapy, and 35·5% receiving any iv therapy; and these patients had better outcomes compared to those who did not receive treatment. The use of post-randomization iv BP lowering agent may reflect increased familiarity with local BP-lowering protocols in stroke units following the publication and international guideline adoption of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2), albeit in ICH patients.[24]

Summary

A strategy of intensive compared to guideline BP lowering during and for up to 72 hours after iv thrombolysis in mild-to-moderate severity, predominantly Asian, AIS patients did not improve functional outcome at 90 days. However, there were significantly lower rates of intracranial haemorrhage, though this was non-significant for sICH. Overall, these results do not support a major shift towards more intensive BP lowering in those receiving thrombolysis for mild-to-moderate severity of AIS. The observed reduction in ICH did not lead to improved clinical outcome, and further research will be required to understand the underlying mechanisms of benefits and harms of early intensive BP lowering.

Research in Context

Evidence before this study

We searched Medline (from Jan 1, 1946) and Embase (from Jan 1, 1966) on Aug 20, 2018, with relevant text words and medical subject headings in any language that included "ischaemic stroke", "thrombolysis" and "blood pressure lowering". Studies were eligible for inclusion if they assessed the effect of blood pressure (BP) lowering treatment on the risk of clinical outcome. We identified no randomised trials or meta-analyses.

Added value of this study

ENCHANTED is the only randomised controlled trial of intensive versus guideline BP lowering during and for up to 72 hours following intravenous thrombolysis for acute ischaemic stroke. The primary outcome of functional status at 90 days did not differ significantly between groups. The key secondary safety outcome of any intracerebral haemorrhage was significantly lower following intensive BP treatment, although a consistent reduction in adjudicated symptomatic intracerebral haemorrhage across a range of definitions was not statistically significant.

Implications of all the available evidence

Overall, these results will reassure clinicians that intensive BP control is not associated with increased risk of death or dependency from adverse effects on the cerebral ischaemic penumbra in acute ischaemic stroke. There may be the potential for such treatment to reduce the risk of symptomatic intracerebral haemorrhage, but trials with a greater separation of BP between treatment groups may be required to provide more definite evidence.

Contributors

CSA, JC, RIL, TGR and YH conceived the trial. CSA was the chief investigator. CSA, RIL, XC, JC, TGR, ACD were responsible for the day-to-day running of the trial. RIL led the adjudication of neuroimaging and serious adverse events. QL did the statistical analysis with supervision from LB. TGR, CSA, JC and YH wrote the first draft of the manuscript; all authors revised this draft. All authors read and approved the final version.

Acknowledgements

The study is supported by grants from the National Health and Medical Research Council (NHMRC) of Australia (Project Grant numbers 1020462 and 1101113), the Stroke Association of the United Kingdom (TSA 2012/01 and 2015/01), the Ministry of Health and the National Council for Scientific and Technological Development of Brazil (CNPQ: 467322/2014-7, 402388/2013-5), the Ministry for Health, Welfare and Family Affairs of the Republic of Korea (HI14C1985) (for the alteplase-dose arm), and a research grant from Takeda to support the conduct of the study in China. The research team acknowledges the support of the National Institute for Health Research Clinical Research Network (NIHR CRN) for conduct of the trial in England, UK. CSA is a Senior Principal Research Fellow for the NHMRC; TGR and PMB are NIHR Senior Investigators. PMB is the Stroke Association Professor of Stroke Medicine.

We thank the investigators and research staff at the participating sites (appendix), and the members of the trial steering and data and safety monitoring committees (appendix). Above all, we thank the participants, and their families and friends.

Declaration of interests

CA has received grants from the National Health and Medical Research Council (NHMRC) of Australia and Takeda China, and honoraria for advisory board activities for Boehringer Ingelheim and Amgen, and speaker fees from Takeda; HY RIL ^{6}HA has received lecture fees from Baoyer, Daiichi-Sankya, Fukuda Denshi, Takeda and Jeijun, and personal fees from Kyowa-Kirin; PMB JPB has received grant support from the National Inssitute of Neurological Diseases and Stroke, and Genentech; AMD reports receiving speaker fees from Medtronic; PML has received research grants from Bayer, Boehringer Ingelheim, Conicyt, The George Institute and Clinica Alemana; CL reports; SOM reports speaker fees from Boehringer Ingelheim, Pfiser, Bayer, Medtronic; MWP reports ; OMPN reports speaker fees from Boehringer Ingelheim; SS is a consultant for Sanofi; VKS reports; FS reports; JGW reports MW reports personal fees for consultancy to Amgen; JC reports receiving grants from NHMRC and Idorsia; TGR reports grants from the UK Stroke Association; XC, GC, QL, LB, CD, GD, ACD, THL, VVO, JDP; SR; LS, NHT, and XW have no disclosures.

References

1. Goyal M, Menon B, van Zwam W, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; 387: 1723–31.
2. Emberson J, Lees K, 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.
3. Wardlaw J, 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.
4. Anderson C, Robinson T, Lindley R, et al. Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. *New Engl J Med* 2016; 374: 2313–23.
5. Intercollegiate Stroke Working Party. National Clinical Guidelines for Stroke. Royal College of Physicians, 5th Edition, 2016.
6. Wahlgren N, Ahmed N, Eriksson N, et al. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomised controlled trials: Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST). *Stroke* 2008; 39: 3316–22.
7. 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 Registry (SITS-ISTR). *Stroke* 2009; 40: 2442–9.

8. Aries M, Elting J, De Keyser J, et al. Cerebral autoregulation in stroke: a review of transcranial Doppler studies. *Stroke* 2010; 41: 2697–704.
9. Huang Y, Sharma V, Robinson T, et al. Rationale, design, and progress of the Enhanced control of hypertension and thrombolysis stroke study (ENCHANTED) trial: an international multicenter 2x2 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 ischemic stroke eligible for thrombolysis treatment. *Int J Stroke* 2015; 10: 778–8.
10. Anderson C, Woodward M, Arima H, et al. Statistical analysis plan for evaluating different intensities of blood pressure control in the Enhanced control of hypertension and thrombolysis stroke study (ENCHANTED). *Int J Stroke* 2018: in press
11. Quinn TJ, Dawson J, Walters MR, Lees KR. Reliability of the modified Rankin scale: a systematic review. *Stroke* 2009; 40: 3393–5.
12. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001; 33: 337–43.
13. Geeganage C, Bath P. Relationship between therapeutic changes in blood pressure and outcomes in acute stroke: a metaregression. *Hypertension* 2009; 54: 775–81.
14. Tikhonoff V, Zhang H, Richart T, Staessen J. Blood pressure as a prognostic factor after acute stroke. *Lancet Neurol* 2009; 8: 938–48.
15. Lee M, Ovbiagele B, Hong K-S, et al. Effect of blood pressure lowering in early ischemic stroke: meta-analysis. *Stroke* 2015; 46: 1863–89.
16. Brott T, Lu M, Kothari R, et al. Hypertension and its treatment in the NINDS rt-PA stroke trial. *Stroke* 1998; 29: 1504–9.

17. Mulder M, Ergezen S, Lingsma H, et al. Baseline blood pressure effect on the benefit and safety of intra-arterial treatment in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands). *Stroke* 2017; 48: 1869–76.
18. Berge E, Cohen G, Lindley R, et al. Effects of blood pressure and blood pressure-lowering treatment during the first 24 hours among patients in the Third International Stroke Trial of thrombolytic treatment for acute ischemic stroke. *Stroke* 2015; 46: 3362–9.
19. Butcher K, Christensen S, Parsons M, et al. Postthrombolysis blood pressure elevation is associated with hemorrhagic transformation. *Stroke* 2010; 41: 72–7.
20. Waltimo T, Haapaniemi E, Surakka I, et al. Post-thrombolytic blood pressure and symptomatic intracerebral hemorrhage. *Eur J Neurol* 2016; 23: 1757–62.
21. Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol* 2017; 16: 781–8.
22. Liao X, Wang Y, Pan Y, et al. Standard-dose intravenous tissue-type plasminogen activator for stroke is better than low doses. *Stroke* 2014; 45: 2354–8.
23. The IST3 Collaborative Group. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third international stroke trial (IST-3). *Lancet Neurol* 2015; 14: 485–96.
24. Anderson C, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *New Engl J Med* 2013; 368: 2355–65.

Table 1: Baseline characteristics of patients with acute ischaemic stroke who received intravenous alteplase according to randomised treatment group

	Intensive BP lowering group (N=1081)	Guideline BP control group (N=1115)
Time from the onset of symptoms to randomisation, h	3·4 (2·5–4·1)	3·3 (2·6–4·1)
Demography		
Sex, female	401/1081 (37·1%)	434/1115 (38·9%)
Age, years	66·7 (12·4)	67·1 (12·0)
≥80	149/1081 (13·8%)	170/1115 (15·2%)
Asian ethnicity	795/1080 (73·6%)	823/1114 (73·9%)
Clinical features		
Systolic BP, mmHg	165 (9)	165 (9)
Diastolic BP, mmHg	91 (12)	91 (11)
Heart rate, beats per minute	79 (15)	79 (15)
NIHSS score*	7·0 (4–12)	8·0 (4–12)
GCS score†	15 (14–15)	15 (14–15)
Medical History		
Hypertension	773/1078 (71·7%)	795/1114 (71·4%)
Currently treated hypertension	493/1078 (45·7%)	519/1114 (46·6%)
Previous stroke (ischaemic, haemorrhagic or uncertain)	205/1081 (19·0%)	209/1115 (18·7%)
Coronary artery disease	154/1078 (14·3%)	155/1114 (13·9%)
Other heart disease (valvular or other)	42/1078 (3·9%)	52/1114 (4·7%)
Atrial fibrillation confirmed on electrocardiogram	140/1078 (13·0%)	172/1112 (15·5%)
Diabetes mellitus	230/1078 (21·3%)	266/1114 (23·9%)
Hypercholesterolaemia	120/1078 (11·1%)	129/1114 (11·6%)
Current smoker	218/1077 (20·2%)	226/1113 (20·3%)
Estimated pre-morbid function (mRS)		
No symptoms (score 0)	924/1078 (85·7%)	953/1113 (85·6%)
Symptoms without any disability (score 1)	154/1078 (14·3%)	160/1113 (14·4%)
Medication at time of admission		
Warfarin anticoagulation	14/1078 (1·3%)	15/1114 (1·3%)
Aspirin or other antiplatelet agent	174/1078 (16·1%)	212/1114 (19·0%)
Statin or other lipid lowering agent	154/1078 (14·3%)	184/1114 (16·5%)
Brain imaging features		

	Intensive BP lowering group (N=1081)	Guideline BP control group (N=1115)
CT scan used	1056/1078 (98·0%)	1096/1114 (98·4%)
MRI scan used	81/1078 (7·5%)	78/1114 (7·0%)
Visible early ischaemic changes	160/1078 (14·8%)	175/1114 (15·7%)
Visible cerebral infarction	176/1078 (16·3%)	167/1114 (15·0%)
CT or MR angiogram shows a proximal vessel occlusion	97/1076 (9·0%)	91/1113 (8·2%)
Final diagnosis‡		
Non-stroke mimic	16/1074 (1·5%)	17/1093 (1·6%)
Presumed stroke aetiology		
Large artery disease due to significant intracranial atheroma	387/1067 (36·3%)	416/1093 (38·1%)
Large artery disease due to significant extracranial atheroma	70/1067 (6·6%)	79/1093 (7·2%)
Small vessel disease	333/1067 (31·2%)	290/1093 (26·5%)
Cardioembolic	139/1067 (13·0%)	150/1093 (13·7%)
Dissection	4/1067 (0·4%)	3/1093 (0·3%)
Other or uncertain aetiology	118/1067 (11·1%)	138/1093 (12·6%)

Data are n (%), mean (SD), or median (IQR). P values are based on Chi-square, T test, or Wilcoxon signed-rank test

BP denotes blood pressure, CT computerised tomography, GCS Glasgow coma scale, MRI magnetic resonance imaging, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale.

*Scores on the National Institutes of Health stroke scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurological deficit.

†Scores on the Glasgow coma scale (GCS) range from 15 (normal) to 3 (deep coma).

‡Diagnosis according to the clinician's interpretation of clinical features and results of investigations at the time of separation from hospital.

Table 2: Key primary and secondary efficacy and safety outcomes at day 90

Outcome	Intensive group (N=1081)	Guideline group (N=1115)	Treatment effect (95%CI)	p value
Efficacy outcomes				
Primary outcome, day 90				
Improvement in mRS, according to categories*				
0	307/1072 (28·6%)	312/1108 (28·2%)	Unadjusted ordinal OR 1·01 (0·87 to 1·17)	0·8702
1	267/1072 (24·9%)	264/1108 (23·8%)	Adjusted ordinal OR 1·03 (0·88 to 1·20)	0·7171
2	138/1072 (12·9%)	160/1108 (14·4%)		
3	110/1072 (10·3%)	120/1108 (10·8%)		
4	98/1072 (9·1%)	104/1108 (9·4%)		
5	50/1072 (4·7%)	60/1108 (5·4%)		
6 (death)	102/1072 (9·5%)	88/1108 (7·9%)		
Other efficacy outcomes				
Death or disability (mRS score ≥2)	498/1072 (46·5%)	532/1108 (48·0%)	Unadjusted binary OR 0·94 (0·79 to 1·11)	0·4660
	498/1072 (46·5%)	531/1106 (48·0%)	Adjusted binary OR 0·94 (0·78 to 1·14)	0·5508
Per Protocol analysis (mRS score ≥2)	451/958 (47·1%)	499/1028 (48·5%)	Unadjusted binary OR 0·94 (0·79 to 1·12)	0·5141
	451/958 (47·1%)	498/1026 (48·5%)	Adjusted binary OR 0·96 (0·79 to 1·16)	0·6595
Death or major disability (mRS score ≥3)	360/1072 (33·6%)	372/1108 (33·6%)	Unadjusted binary OR 1·00 (0·84 to 1·20)	0·9968
	360/1072 (33·6%)	371/1106 (33·5%)	Adjusted binary OR 1·01 (0·83 to 1·24)	0·9090
Death or neurological deterioration†				
In first 24 hours	100/1081 (10·2%)	108/1115 (9·7%)	Unadjusted binary OR 1·06 (0·80 to 1·40)	0·7013
In first 72 hours	146/1081 (13·5%)	139/1115 (12·5%)	Unadjusted binary OR 1·10 (0·85 to 1·41)	0·4687
Death at day 90	102/1081 (9·4%)	88/1115 (7·9%)	Unadjusted binary OR 1·22 (0·90 to 1·64)	0·1989
	102/1078 (9·5%)	88/1113 (7·9%)	Adjusted binary OR 1·18 (0·86 to 1·64)	0·3077
Safety Outcomes				
Key safety outcome				
Any intracranial haemorrhage‡	160/1081 (14·8%)	209/1115 (18·7%)	Unadjusted binary OR 0·75 (0·60 to 0·94)	0·0137
Other safety outcomes				
Any intracranial haemorrhage reported as a serious adverse event	59/1081 (5·5%)	100/1115 (9·0%)	Unadjusted binary OR 0·59 (0·42 to 0·82)	0·0017
Major ICH based on central adjudication of brain imaging				
Symptomatic ICH, SITS-MOST criteria§	14/1081 (1·3%)	22/1115 (2·0%)	Unadjusted binary OR 0·65 (0·33 to 1·28)	0·2143
Symptomatic ICH, NINDS criteria¶	70/1081 (6·5%)	84/1115 (7·5%)	Unadjusted binary OR 0·85 (0·61 to 1·18)	0·3321

Outcome	Intensive group (N=1081)	Guideline group (N=1115)	Treatment effect (95%CI)	p value
Symptomatic ICH, ECASS2 criteria‖	46/1081 (4·3%)	57/1115 (5·1%)	Unadjusted binary OR 0·82 (0·55 to 1·23)	0·3431
Symptomatic ICH, ECASS3 criteria**	21/1081 (1·9%)	30/1115 (2·7%)	Unadjusted binary OR 0·72 (0·41 to 1·26)	0·2467
Symptomatic ICH, IST-3 criteria††	24/1081 (2·2%)	37/1115 (3·3%)	Unadjusted binary OR 0·66 (0·39 to 1·11)	0·1198
Large parenchymal ICH‡‡	143/1081 (13·2%)	180/1115 (16·1%)	Unadjusted binary OR 0·79 (0·62 to 1·00)	0·0542
Any ICH on brain imaging ≤7 days	143/1081 (13·2%)	180/1115 (16·1%)	Unadjusted binary OR 0·79 (0·62 to 1·00)	0·0542
Fatal ICH ≤7 days	5/1081 (0·5%)	14/1115 (1·3%)	Unadjusted binary OR 0·37 (0·13 to 1·02)	0·0541

ECASS denotes European Cooperative Acute Stroke Study; ICH, intracerebral haemorrhage; International Stroke Trial; mRS modified Rankin scale, NINDS National Institutes of Neurological Diseases and Stroke; OR odds ratio, SITS-MOST Safe Implementation of Thrombolysis in Stroke-Monitoring Study

*The mRS evaluates global disability; scores range from 0=no symptoms to 6=death; the primary outcome was an assessment of scores across all seven levels of the mRS determined using a 'shift' analysis of the ordinal data; the OR was unadjusted

†Neurological deterioration defined by an increase from baseline to 24 hours of ≥4 on the National Institutes of Health Stroke Scale (NIHSS) or a decline of ≥2 on the Glasgow coma scale

‡Key safety secondary outcome was any reported intracranial haemorrhage noted on a local brain imaging report within 7 days after randomization, any haemorrhage noted on a centrally adjudicated scan, and any intracranial haemorrhage reported by a clinician as a serious adverse event. Intracranial haemorrhage includes ICH, subarachnoid haemorrhage, and subdural and extradural haemorrhage

§large or remote parenchymal ICH (type 2, defined as >30% of the infarcted area affected by haemorrhage with mass effect or extension outside the infarct) combined with neurological deterioration (≥4 points on the NIHSS) or leading to death within 24 to 36 hours

¶any ICH associated with neurological deterioration (≥1 point change in NIHSS score) from baseline or death within 24 to 36 hours

‖any ICH with neurological deterioration (≥4 points on the NIHSS) from baseline or death within 24 to 36 hours

**any ICH with neurological deterioration (≥4 points increase on the NIHSS) from baseline or death within 36 hours

††either significant ICH (local or distant from the cerebral infarct) or significant haemorrhagic transformation of a cerebral infarct on brain imaging with clinically significant deterioration or death within the first 7 days of treatment

‡‡any type 2 parenchymal 'haematoma' of ICH

Figure Legends

Figure 1: Trial profile

Figure 2: Trends in systolic and diastolic blood pressure from randomisation to day 7

Footnote: Trends are presented for intensive (solid line) and guideline (dashed line) blood pressure lowering groups based on recordings at 15 minute intervals for the first hour after randomisation, hourly from 1 to 6 hours, 6-hourly until 24 hours, and then twice daily until day 7. Mean (95% confidence interval) difference in systolic blood pressure over 24 hours was 5·5 (4·5-6·4) mmHg.

Figure 3: Modified Rankin score (mRS) outcome at 90 days by treatment group

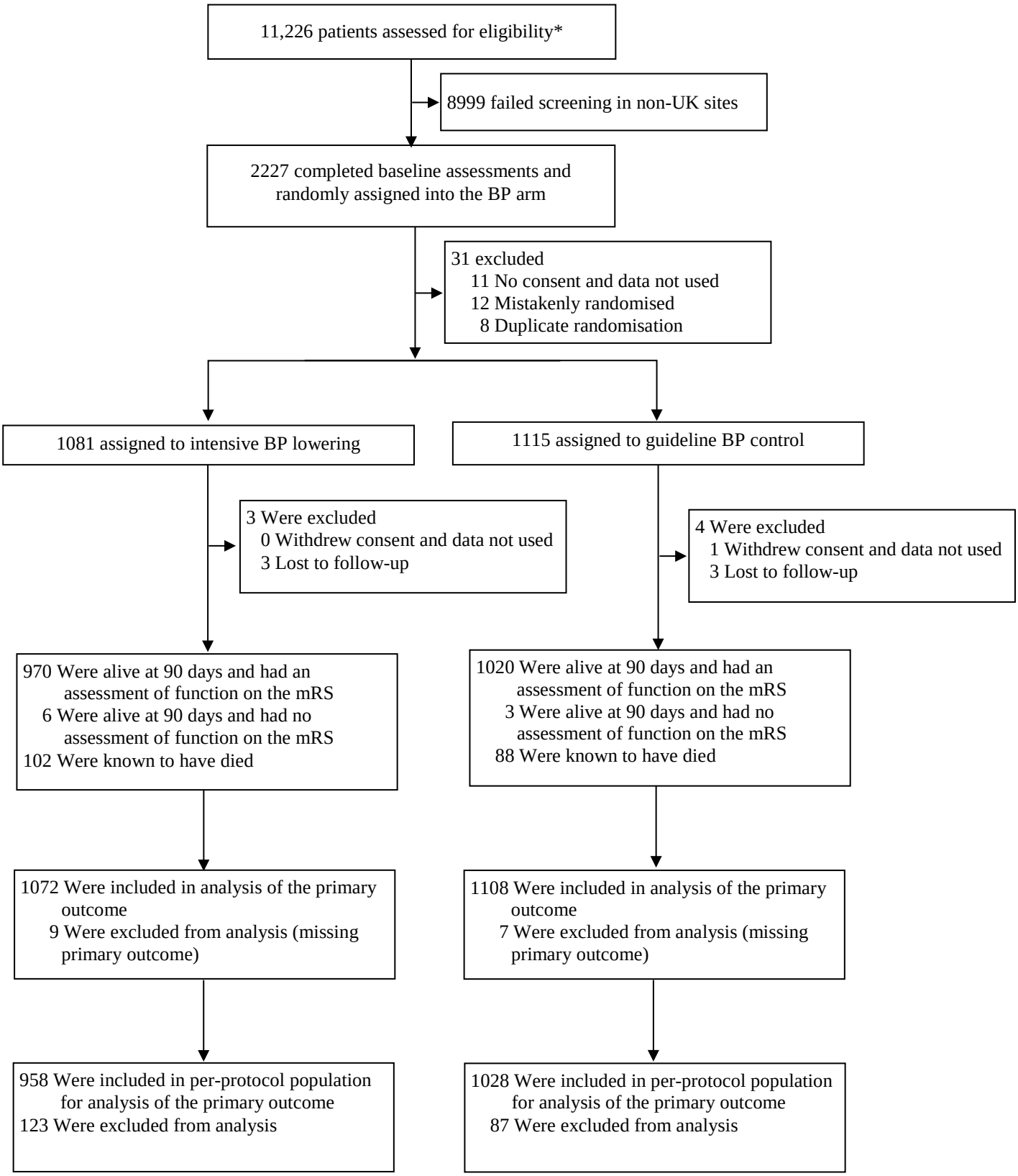
Footnote: The figure shows the raw distribution of scores on the modified Rankin scale (mRS) at 90 days. Scores on the mRS range from 0 to 6, with 0 indicating no symptoms, 1 symptoms without clinical significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

Figure 4: Primary outcome by pre-specified subgroups

Footnote: The primary efficacy outcome was shift in the modified Rankin scale distribution Range 0 [no symptoms] to 6 [death]) at 90 days. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurological deficits. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events), and horizontal lines represent 95% confidence intervals. For systolic blood pressure and NIHSS score, values are equal to or above the median of distribution versus below the distribution. CT denotes computed

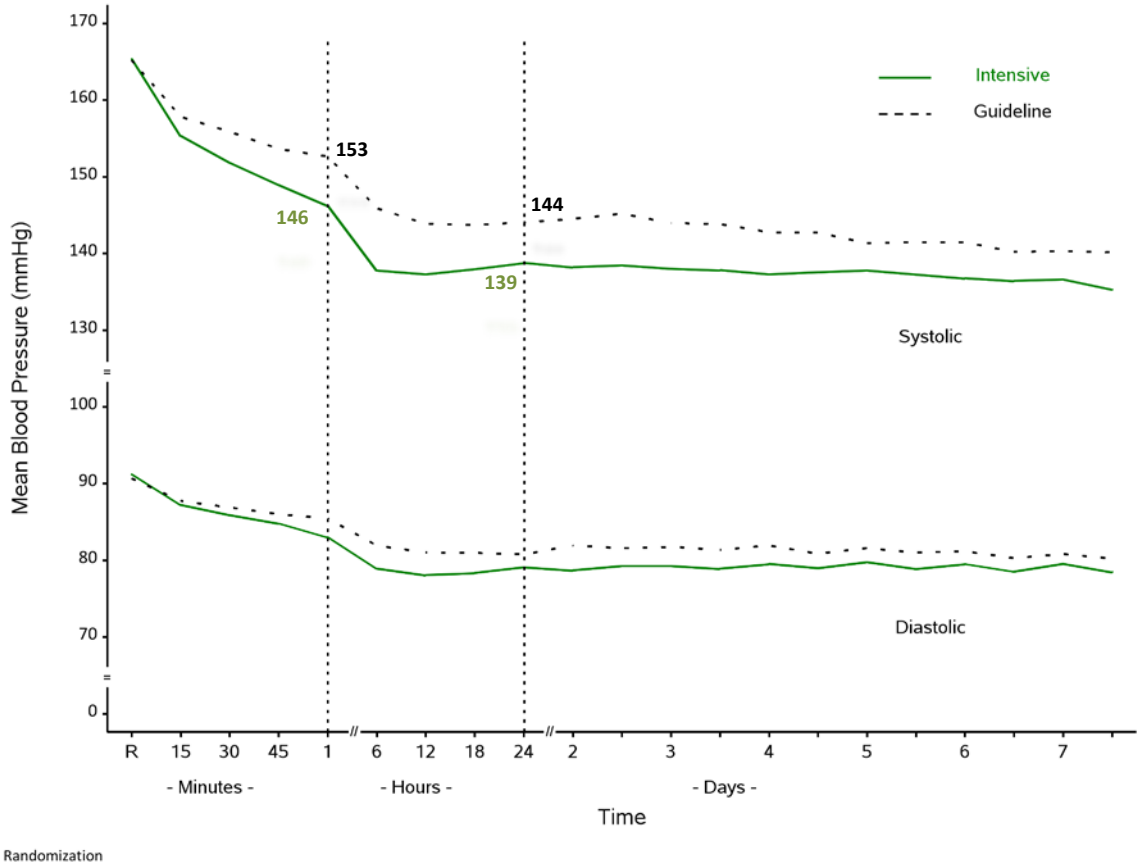
tomography. Dose of alteplase refers to low-dose (0·6mg/kg; 15% as bolus, 85% as infusion over 1 hour) or standard-dose (0·9mg/kg; 10% as bolus, 90% as infusion over 1 hour).

Figure 1: Trial profile



*Screening logs not used at UK sites

Figure 2: Trends in systolic and diastolic blood pressure from randomisation to day 7



R: Randomization

Figure 3: Modified Rankin score (mRS) outcome at 90 days by treatment group

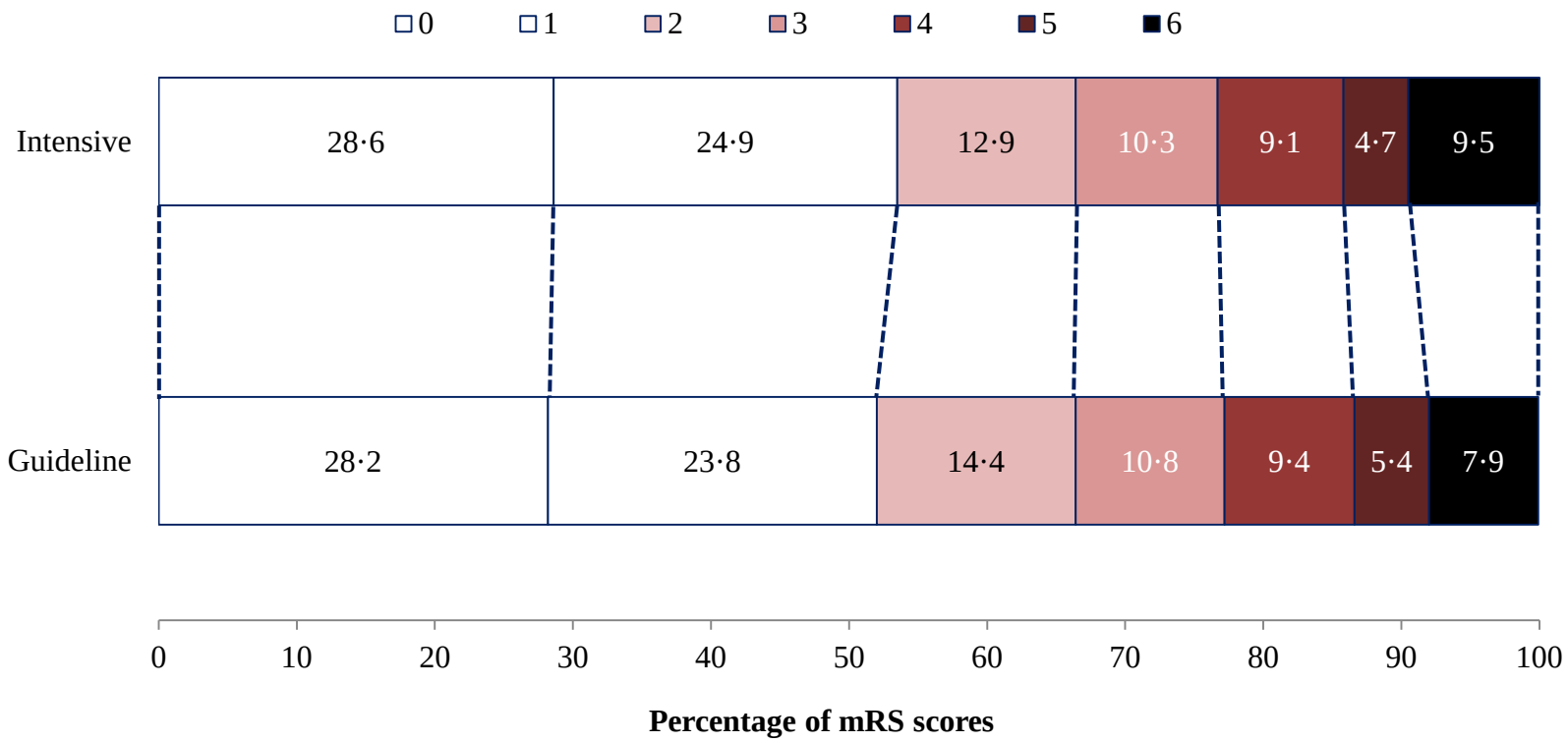


Figure 4: Primary outcome by pre-specified subgroups