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

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Summary

Background Systolic blood pressure of more than 185 mm Hg is a contraindication to thrombolytic treatment with intravenous alteplase in patients with acute ischaemic stroke, but the target systolic blood pressure for optimal outcome is uncertain. We assessed intensive blood pressure lowering compared with guideline-recommended blood pressure lowering in patients treated with alteplase for acute ischaemic stroke.

Methods We did an international, partial-factorial, open-label, blinded-endpoint trial of thrombolysis-eligible patients (age ≥18 years) with acute ischaemic stroke and systolic blood pressure 150 mm Hg or more, who were screened at 110 sites in 15 countries. Eligible patients were randomly assigned (1:1, by means of a central, web-based program) within 6 h of stroke onset to receive intensive (target systolic blood pressure 130–140 mm Hg within 1 h) or guideline (target systolic blood pressure <180 mm Hg) blood pressure lowering treatment over 72 h. The primary outcome was functional status at 90 days measured by shift in modified Rankin scale scores, analysed with unadjusted ordinal logistic regression. The key safety outcome was any intracranial haemorrhage. Primary and safety outcome assessments were done in a blinded manner. Analyses were done on intention-to-treat basis. This trial is registered with ClinicalTrials.gov, number NCT01422616.

Findings Between March 3, 2012, and April 30, 2018, 2227 patients were randomly allocated to treatment groups. After exclusion of 31 patients because of missing consent or mistaken or duplicate randomisation, 2196 alteplase-eligible patients with acute ischaemic stroke were included: 1081 in the intensive group and 1115 in the guideline group, with 1466 (67·4%) administered a standard dose among the 2175 actually given intravenous alteplase. Median time from stroke onset to randomisation was 3·3 h (IQR 2·6–4·1). Mean systolic blood pressure over 24 h was 144·3 mm Hg (SD 10·2) in the intensive group and 149·8 mm Hg (12·0) in the guideline group (p<0·0001). Primary outcome data were available for 1072 patients in the intensive group and 1108 in the guideline group. Functional status (mRS score distribution) at 90 days did not differ between groups (unadjusted odds ratio [OR] 1·01, 95% CI 0·87–1·17, p=0·8702). Fewer patients in the intensive group (160 [14·8%] of 1081) than in the guideline group (209 [18·7%] of 1115) had any intracranial haemorrhage (OR 0·75, 0·60–0·94, p=0·0137). The number of patients with any serious adverse event did not differ significantly between the intensive group (210 [19·4%] of 1081) and the guideline group (245 [22·0%] of 1115; OR 0·86, 0·70–1·05, p=0·1412). There was no evidence of an interaction of intensive blood pressure lowering with dose (low *vs* standard) of alteplase with regard to the primary outcome.

Interpretation Although intensive blood pressure lowering is safe, the observed reduction in intracranial haemorrhage did not lead to improved clinical outcome compared with guideline treatment. These results might not support a major shift towards this treatment being applied in those receiving alteplase for mild-to-moderate acute ischaemic stroke. Further research is required to define the underlying mechanisms of benefit and harm resulting from early intensive blood pressure lowering in this patient group.

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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 lowering treatment on the risk of clinical outcome. We identified no randomised trials or meta-analyses. Randomised trials of blood pressure lowering treatment in patients with acute ischaemic stroke without thrombolysis treatment suggest a benefit from very early treatment with glyceryl trinitrate patch within 6 h of the onset of symptoms, but no benefit at times thereafter for this or any type of blood pressure lowering treatment.

Added value of this study

ENCHANTED is the only randomised controlled trial of intensive versus guideline-recommended blood pressure lowering treatment during and for up to 72 h after intravenous thrombolysis for acute ischaemic stroke. The primary outcome of functional status (measured on the modified Rankin scale) at 90 days did not differ significantly between groups. The key safety outcome of any intracranial haemorrhage was significantly less frequent after intensive than after guideline-recommended blood pressure lowering treatment, and consistent reductions in adjudicated symptomatic intracerebral haemorrhage across a range of definitions were observed, albeit without statistical significance.

Implications of all the available evidence

Overall, these results will reassure clinicians that intensive blood pressure control is not associated with an increased risk of death or disability from adverse effects on the cerebral ischaemic penumbra in patients with acute ischaemic stroke receiving intravenous thrombolytic treatment. Such treatment could potentially reduce the risk of major intracranial haemorrhage, but further research is required to define the underlying mechanisms of benefit and harm resulting from early intensive blood pressure lowering in cases of hyperacute acute ischaemic stroke. Moreover, further trials with a greater difference in blood pressure between treatment groups are required to provide more definitive evidence to support the treatment in patients with more severe acute ischaemic stroke requiring thrombolysis or endovascular reperfusion therapy.

Introduction

Timely administration of intravenous thrombolytic treatment is the mainstay of hyperacute reperfusion treatment in patients with acute ischaemic stroke, even with the advent of mechanical thrombectomy for those with proximal large vessel occlusion.[1] The evidence strongly suggests that administration of intravenous alteplase (recombinant tissue plasminogen activator) within 4·5 h of acute ischaemic stroke onset results in a net benefit over harm from intracranial haemorrhage.[2,3] Ongoing research seeks to improve the efficacy and safety of mechanical and pharmacological reperfusion therapies in eligible patients with acute ischaemic stroke.

The alteplase dose-assessment arm of the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) was unable to clearly show non-inferiority of low-dose intravenous alteplase compared with the standard dose with respect to death and dependency at 90 days, despite significant reductions in early (7-day) mortality and symptomatic intracerebral haemorrhage.[4] However, controversy persists regarding control of peri-thrombolysis blood pressure, for which guidelines consistently contraindicate the use of alteplase in patients with systolic blood pressure of more than 185 mm Hg.[5] Two large registries[6,7] have reported a positive association between increasing systolic blood pressure and increased risk of symptomatic intracerebral haemorrhage, even below this threshold: frequency of symptomatic intracerebral haemorrhage was four times higher in patients with systolic blood pressure of more than 170 mm Hg than it was in those with systolic blood pressure of 141–150 mm Hg.[7] A U-shaped association for death and dependency is also evident, with the best outcomes associated with systolic blood pressure of 141–150 mm Hg. An ongoing concern, however, has been that rapid blood pressure reduction in the absence of reperfusion might worsen cerebral ischaemia due to hypoperfusion in failing collateral circulation into the ischaemic penumbra.[8]

The second, blood pressure control-assessment arm of the ENCHANTED trial was driven by uncertainty over whether any potential benefits related to a reduced risk of thrombolysis-related intracranial haemorrhage could be offset by worsened cerebral ischaemia associated with intensive blood pressure lowering. Herein, we report the results of the blood pressure control arm of the ENCHANTED trial, which tested the hypotheses that, following use of intravenous alteplase, a strategy of intensive blood pressure lowering (target systolic blood pressure 130–140 mm Hg) is superior to guideline-recommended blood pressure lowering (target systolic blood pressure <180 mm Hg) for improving functional recovery and reducing the risk of intracranial haemorrhage in patients with acute ischaemic stroke.

Methods

Study design and participants

ENCHANTED was an international, multicentre, prospective, randomised, open-label, blinded-endpoint trial with a 2×2 partial-factorial design, at 110 sites in 15 countries, to assess the effectiveness of low-dose versus standard-dose alteplase (previously published),[5]

and intensive versus guideline-recommended blood pressure control (described here). Details of the study design and rationale have been published elsewhere,[9] and the protocol is available in the appendix. The statistical analysis plan was submitted for publication before study unmasking.[10]

Adult patients (aged ≥18 years) with acute ischaemic stroke and systolic blood pressure 150 mm Hg or more were eligible if they fulfilled standard criteria for thrombolysis with intravenous alteplase, and if the treating clinician had uncertainty over the benefit and risk of the intensity of blood pressure control during and for up to 72 h (or hospital discharge or death, if this event occurred earlier) after thrombolytic treatment. Although there was no specified upper systolic blood pressure threshold, patients were required to comply with guidelines for the use of thrombolysis, which included having a systolic blood pressure of 185 mm Hg or lower before administration of intravenous alteplase. Participants were randomly assigned to a strategy of intensive blood pressure lowering (intensive group; target systolic blood pressure 130–140 mm Hg within 60 min of randomisation) or guideline-recommended blood pressure control (guideline group; target systolic blood pressure <180 mm Hg) after commencement of intravenous alteplase. On Nov 12, 2013, the protocol was amended as follows: systolic blood pressure target was reduced from 140–150 mm Hg to 130–140 mm Hg in the intensive group to enhance the systolic blood pressure difference between groups; time of randomisation to the blood pressure arm was increased from within 4·5 h to within 6 h of stroke onset to avoid trial-related procedures delaying the achievement of 1 h door-to-needle-time quality performance in the administration of intravenous alteplase as part of routine practice; time to achieve the target systolic blood pressure was increased from 60 min from the commencement of alteplase to 60 min from randomisation; to increase study power, the key secondary outcome was changed from whether intensive blood pressure lowering reduced symptomatic intracerebral haemorrhage to whether it reduced any intracranial haemorrhage; and sample size was reduced from 3300 to 2304 participants. Furthermore, a final protocol amendment on Feb 16, 2017, changed the primary outcome from a conventional binary assessment of poor clinical outcome (modified Rankin scale [mRS] scores 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 this change resulted in a further reduction in sample size to 2100 participants consequent upon this change in the primary outcome. Until the conclusion of the alteplase dose arm on Aug 17, 2015, participants could additionally be randomised to low-dose (0·6 mg/kg, maximum of 60 mg; 15% as bolus, 85% as infusion over 1 h) or standard-dose (0·9 mg/kg, maximum of 90 mg; 10% as bolus, 90% as infusion over 1 h) intravenous alteplase. Subsequently, the attending clinician investigator could choose the dose of intravenous alteplase to use according to their interpretation of the evidence.

Key exclusion criteria were that a patient was unlikely to benefit from thrombolysis (eg, had advanced dementia); had a very high likelihood of death within 24 h; had substantial comorbidity that would interfere with the outcome assessments or follow-up (known pre-stroke disability, with estimated scores 2–5 on the mRS); had a specific contraindication to alteplase or any of the blood pressure lowering drugs to be used; or was participating in another clinical trial 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 from their approved surrogate for patients who were too unwell to comprehend the information.

Randomisation and masking

After confirmation of patient eligibility, 1:1 randomisation was done 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: site of recruitment, time from the onset of symptoms (<3 h or ≥3 h), and severity of neurological impairment according to the National Institutes of Health Stroke Scale (NIHSS) score (<10 points or ≥10 points). Final follow-up was done at 90 days, in person or by telephone, by trained and certified staff who were unaware of the randomised treatment assignment. Central adjudication of safety outcomes was also done by assessors unaware of treatment allocation or clinical details.

Procedures

We sought to assess a management strategy of blood pressure lowering to achieve and maintain intensive (130–140 mm Hg) and guideline-recommended (<180 mm Hg) systolic blood pressure targets. Therefore, local treatment protocols based on available intravenous (bolus and infusion), oral, and topical medications were used (outlined in the appendix). All patients were to be managed in an acute stroke unit, or alternative environment with appropriate staffing and monitoring, and to 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 blood pressure monitoring was done 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 at least 3 min in accordance with a standard protocol. Following thrombolysis, blood pressure measurements were recorded every 15 min for 1 h, hourly from hours 1 to 6, and 6-hourly from hours 6 to 24. Thereafter, blood

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See **Online** for appendix

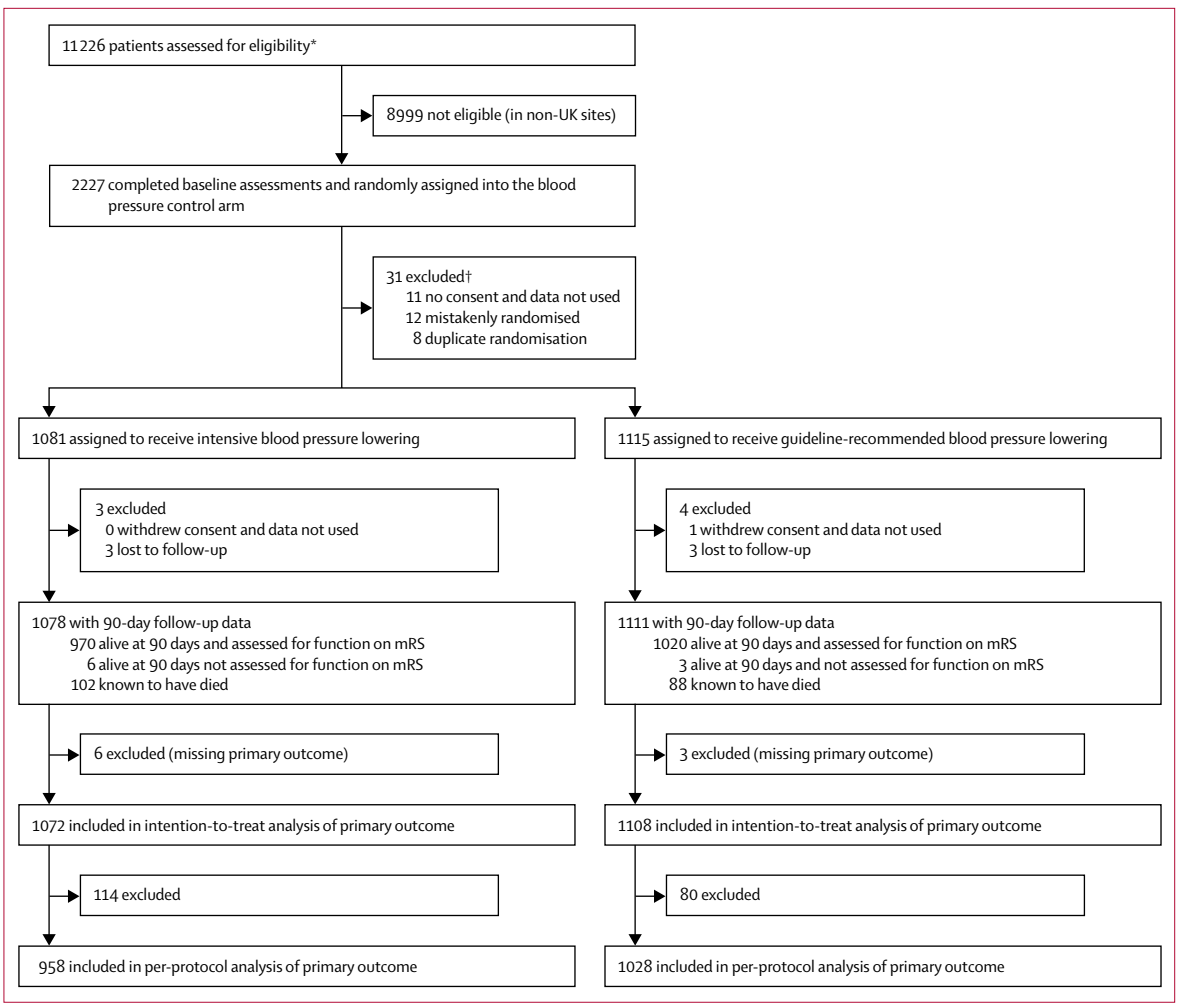

Figure 1: **Trial profile**
mRS=modified Rankin scale. *Screening logs not used at UK sites. †15 for intensive blood pressure lowering group, 8 for guideline-recommended blood pressure lowering group, and 8 for alteplase-dose arm (patients mistakenly randomised).

pressure was recorded twice daily for 1 week (or until hospital discharge or death, if earlier). Neurological status, measured on the NIHSS and Glasgow coma scale, was assessed at baseline, and 24 h and 72 h after start of alteplase treatment. Brain imaging (CT, MRI, or both) was done at baseline and at 24 h, and at additional timepoints if clinically indicated. Early cerebral ischaemia or infarction, and hyperdense artery sign, as identified by a local investigator, were recorded. Analyses were done centrally for diagnoses of categories of intracranial haemorrhage by expert assessors (appendix).

A detailed list of the assessment schedule is contained in the study protocol. 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). Sociodemographic and clinical details were obtained at randomisation. Follow-up data were collected at 24 h, 72 h, 7 days (or at hospital discharge if earlier), 28 days, and 90 days. Remote and on-site quality-control monitoring and data verification were done throughout the study (appendix).

Outcomes

The prespecified primary outcome, assessed at 90 days in the intention-to-treat population, was a shift in measures of functioning according to the full range of scores on the mRS,[11] a global, seven-level assessment of disability, in which scores of 0 or 1 indicate a favourable outcome without or with symptoms but no disability, scores of 2 to 5 indicate increasing levels of disability (and dependency), and a score of 6 indicates death. Other secondary efficacy outcomes were assessed by the conventional dichotomous analysis of mRS scores at 90 days: 2–6 (disability or death) versus less than 2, or 3–6 (major disability or death) versus less than 3. The following outcomes were also assessed: cause-specific mortality within 90 days; death or neurological deterioration (≥4 points decline in NIHSS) within 24 h and 72 h;

	Intensive blood pressure lowering group (n=1081)	Guideline-recommended blood pressure lowering group (n=1115)
Time from the onset of symptoms to randomisation, h	3·4 (2·5–4·1)	3·3 (2·6–4·1)
Sex		
Female	401/1081 (37·1%)	434/1115 (38·9%)
Male	680/1081 (62·9%)	681/1115 (61·1%)
Age, years	66·7 (12·4)	67·1 (12·0)
≥80	149/1081 (13·8%)	170/1115 (15·2%)
<80	932/1081 (86·2%)	945/1115 (84·8%)
Ethnicity		
Asian	795/1080 (73·6%)	823/1114 (73·9%)
Non-Asian	285/1080 (26·4%)	291/1114 (26·1%)
Clinical features		
Systolic blood pressure, mm Hg	165·4 (9·1)	165·2 (9·2)
Diastolic blood pressure, mm Hg	91·2 (11·6)	90·7 (11·3)
Heart rate, beats per minute	79·4 (14·6)	79·2 (15·0)
NIHSS score*	7 (4–12)	8 (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	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 premorbid 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%)

(Table 1 continues in next column)

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	Intensive blood pressure lowering group (n=1081)	Guideline-recommended blood pressure lowering group (n=1115)
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		
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 magnetic resonance angiogram showed 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 cause		
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 cause	118/1067 (11·1%)	138/1093 (12·6%)

Data are n (%), mean (SD), or median (IQR). NIHSS=National Institutes of Health Stroke Scale. GCS=Glasgow coma scale. mRS=modified Rankin scale. *Scores range from 0 to 42, with higher scores indicating more severe neurological deficit. †Scores 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 1: **Baseline characteristics**

primary cause of death; duration of initial hospitalisation in days; and health-related quality of life, as assessed on the EuroQoL group EQ-5D-3L,[12] according to an overall health utility score at 90 days.

The key safety outcome was any intracranial haemorrhage reported by investigators or after central adjudication of relevant brain imaging within 7 days after randomisation. This outcome included intracerebral haemorrhage, 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. Another safety outcome was the topography of intracerebral haemorrhage identified on centrally adjudicated brain images in association with a patient's symptoms (ie, symptomatic intracerebral haemorrhage, in which intracerebral haemorrhage was associated with substantial neurological deterioration or death). The key measure of symptomatic intracerebral haemorrhage was from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), defined as large or remote parenchymal intracerebral haemorrhage (type 2, defined as >30% of the infarcted area affected by haemorrhage with mass effect or extension outside the infarct) combined with neurological deterioration

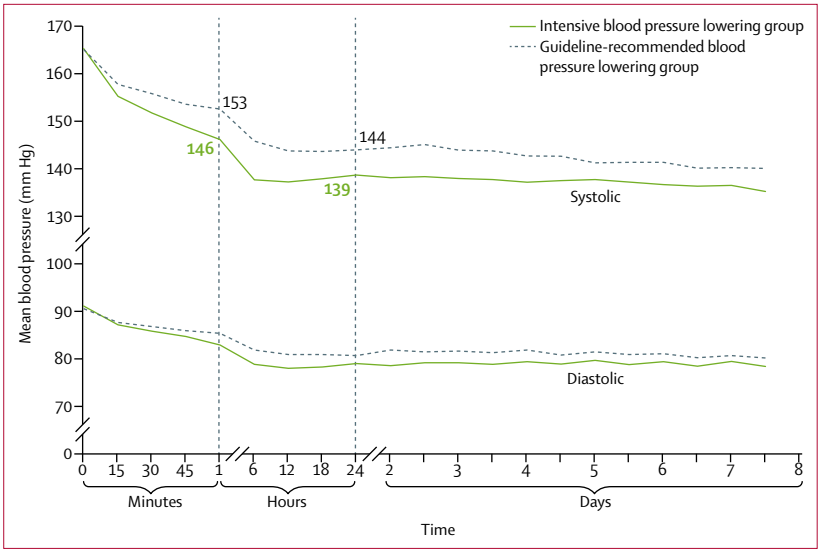

Figure 2: **Mean systolic and diastolic blood pressure from randomisation to day 7**
Blood pressure values are shown for intensive and guideline-recommended blood pressure lowering groups based on recordings at 15-min intervals for the first hour after randomisation (time 0), hourly from hours 1 to 6, 6-hourly until 24 h, and twice daily until day 7. Mean between-group difference in systolic blood pressure over 24 h was 5·5 mm Hg (95% CI 4·5–6·4).

(≥4 points on the NIHSS) or leading to death within 24–36 h.[6] Other criteria for symptomatic intracerebral haemorrhage that were used in other studies are outlined in the appendix. Other prespecified safety outcomes included all-cause and cause-specific serious adverse events (overall and by vital status) until trial completion, coded according to MedDRA definitions. Outcomes were assessed in both intention-to-treat and per-protocol populations. We also did post-hoc analyses on the between-group systolic blood pressure differences over the study period, a comparison of the characteristics of patients assigned to the guideline-recommended blood pressure management group according to receipt of any intravenous blood pressure lowering, and the effects of treatment on the NIHSS as a continuous measure.

Statistical analysis

Power calculations were based on the estimated treatment effects on a conventional binary assessment of poor outcome (mRS scores 3–6). Assuming poor outcomes of 43% in the intensive blood pressure lowering group and 50% in the guideline-recommended blood pressure lowering group, a sample size of 2304 (1152 per group) was estimated to provide more than 90% power (using a two-sided α=0·05) to detect a 14% relative reduction in poor outcome in the intensive group,[7] taking account of a 5% drop-out and potential negative interaction between low-dose alteplase and intensive blood pressure lowering. However, as the ordinal shift approach provides efficiency gains, a re-estimation of the sample size based on an ordinal analysis of mRS scores indicated that the estimated treatment effect could be detected with a sample size of 2100.[10] This sample size was also estimated to provide more than a 40% reduction in any intracranial haemorrhage associated with a 15 mm Hg difference in systolic blood pressure between randomised groups on the basis of Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) data.[7]

Statistical analyses were done on an intention-to-treat basis. We did shift analyses using ordinal logistic regression for the primary efficacy outcome, and dichotomous logistic regression analyses for all other outcomes. Treatment effects were presented as odds ratios (ORs) with 95% CIs. A priori,[10] the primary analysis for superiority of intensive versus guideline-recommended blood pressure lowering was unadjusted, but we also did prespecified sensitivity analyses of the treatment effects on all outcomes adjusted for minimisation and key prognostic covariates (age; sex; ethnicity; premorbid function [mRS scores 0 or 1]; premorbid use of antithrombotic agents [aspirin, other antiplatelet agent, or warfarin]; 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 ten prespecified 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 progress of the trial every 6 months. All tests were two-sided and the nominal level of α was 5%. No adjustment was made for multiplicity. SAS software version 9.3 was used for analyses.

This trial is registered with ClinicalTrials.gov, number NCT01422616, and is now closed at all participating sites.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all data in the study and had overall responsibility for the decision to submit for publication.

Results

From March 3, 2012, to April 30, 2018, 2227 patients with acute ischaemic stroke were randomly allocated (figure 1, appendix). 31 patients were excluded because of missing consent, or mistaken or duplicate randomisation, leaving 2196 included in the intention-to-treat analysis: 1081 (49·2%) in the intensive group and 1115 (50·8%) in the guideline group. 925 (42·1%) participants were also enrolled in the alteplase dose arm of the trial (456 [20·8%] receiving low-dose alteplase and 469 [21·4%] standard-dose alteplase). Treatment groups were well balanced with respect to baseline demographic and clinical characteristics (table 1). The overall mean age was 66·9 years (SD 12·2) and 835 (38·0%) participants were female. 1618 (73·7%) patients were recruited in Asia (1428 [65·0%] in China). Median NIHSS score before

treatment was 7 (range 0–42, IQR 4–12). 1012 (46·2% of 2192 participants with available data) were receiving antihypertensive treatment at the time of enrolment, and mean systolic blood pressure before treatment was 165·3 mm Hg (SD 9·2). The median time from stroke onset to randomisation was 3·3 h (IQR 2·6–4·1). Only 42 (1·9%) patients received endovascular thrombectomy treatment.

Adherence to assigned treatment was high and did not differ between groups: 2175 (99·0%) patients received any intravenous alteplase, of whom 1466 (67·4%) received a standard dose (0·9 mg/kg body mass), including 469 (32·0%) who participated in the alteplase dose arm, and 997 (68·0%) who did not participate in the alteplase dose arm but whose actual administered dose was more than the 0·75 mg/kg cutoff dose (appendix). The median time from the initiation of treatment with intravenous alteplase to commencement of any intravenous blood pressure lowering treatment was 20 min (IQR 0–85) in the intensive group and 30 min (0–153) in the guideline group (p=0·0925). 2140 (97·4%) of the 2196 participants received blood pressure lowering treatment in accordance with the assigned protocol (appendix). In the intensive group, the proportions of patients administered any blood pressure lowering treatment (858 [80·1%] of 1071 *vs* 602 [54·3%] of 1108 with available data; p<0·0001) and administered intravenous blood pressure lowering drugs (671 [62·7%] of 1071 *vs* 391 [35·3%] of 1108; p<0·0001) during the first 24 h post-randomisation were significantly higher than those in the guideline group (appendix). Additionally, a greater proportion of patients in the intensive (772 [72·6%] of 1063) than in the guideline group (689 [63·2%] of 1091) received blood pressure lowering therapy over days 2–7 in hospital (p<0·0001; appendix). Mean systolic blood pressure levels were 146·2 mm Hg in the intensive group and 152·7 mm Hg in the guideline group (mean difference –6·4 mm Hg, 95% CI –7·9 to –5·0) at 1 h, and 138·8 mm Hg in the intensive group and 144·1 mm Hg in the guideline group (mean difference –5·3 mm Hg, –6·7 to –3·9) at 24 h; figure 2, appendix). Overall mean systolic blood pressure levels within 24 h were significantly lower in the intensive than in the guideline group (144·3 mm Hg [SD 10·2] *vs* 149·8 mm Hg [12·0], p<0·0001; appendix). Systolic blood pressure remained lower in the intensive than in the guideline group for the subsequent 6 days (figure 2, appendix). There were no significant differences in other clinical management over the 7-day post-randomisation period (appendix).

The primary outcome of mRS at 90 days was assessed in 2180 (99·3%) participants (1072 in the intensive group and 1108 in the guideline group), mostly by telephone (figure 1, appendix). The proportional odds assumption was tested and was not significant (p=0·6036). There was no significant difference (shift) in the 90-day mRS score distribution (table 2, figure 3). These results were consistent after adjustment for minimisation and key prognostic variables (table 2). No heterogeneity of treatment effect on primary outcome was found across prespecified subgroups (figure 4). In particular, alteplase

	Intensive blood pressure lowering group	Guideline-recommended blood pressure lowering group	Treatment effect	p value
Improvement in mRS according to category* at day 90	..	..	1·01 (0·87–1·17)†, 0·97 (0·83–1·13)†‡	0·8702†, 0·7171†‡
0	307/1072 (28·6%)	312/1108 (28·2%)	..	..
1	267/1072 (24·9%)	264/1108 (23·8%)	..	..
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	102/1072 (9·5%)	88/1108 (7·9%)	..	..
Death or disability (mRS score 2–6) within 90 days				
Intention-to-treat analysis				
Unadjusted	498/1072 (46·5%)	532/1108 (48·0%)	0·94 (0·79–1·11)	0·4660
Adjusted	498/1072 (46·5%)	531/1106 (48·0%)	0·94 (0·78–1·14)‡	0·5508
Per-protocol analysis				
Unadjusted	451/958 (47·1%)	499/1028 (48·5%)	0·94 (0·79–1·12)	0·5141
Adjusted	451/958 (47·1%)	498/1026 (48·5%)	0·96 (0·79–1·16)‡	0·6595
Death or major disability (mRS score 3–6) within 90 days				
Unadjusted	360/1072 (33·6%)	372/1108 (33·6%)	1·00 (0·84–1·20)	0·9968
Adjusted	360/1072 (33·6%)	371/1106 (33·5%)	1·01 (0·83–1·24)‡	0·9090
Death or neurological deterioration§				
In first 24 h	110/1081 (10·2%)	108/1115 (9·7%)	1·06 (0·80–1·40)	0·7013
In first 72 h	146/1081 (13·5%)	139/1115 (12·5%)	1·10 (0·85–1·41)	0·4687
Death within 90 days				
Unadjusted	102/1081 (9·4%)	88/1115 (7·9%)	1·22 (0·90–1·64)	0·1989
Adjusted	102/1078 (9·5%)	88/1113 (7·9%)	1·18 (0·86–1·64)‡	0·3077

Frequency data are n/N (%). Treatment effect is presented as odds ratio (95% CI) of intensive versus guideline-recommended blood pressure lowering, analysed by unadjusted binary logistic regression unless stated otherwise. mRS=modified Rankin scale. *The primary outcome was an assessment of scores across all seven levels of the mRS (ranging from 0 [no symptoms] to 6 [death]), done using a shift analysis of the ordinal data. †Calculated with ordinal logistic regression. ‡Adjusted for 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]; history of stroke, coronary artery disease, diabetes, and atrial fibrillation; and randomised alteplase dose). §Defined by an increase between baseline and 24 h of ≥4 on the National Institutes of Health Stroke Scale or a decline of ≥2 on the Glasgow coma scale.

Table 2: **Efficacy outcomes**

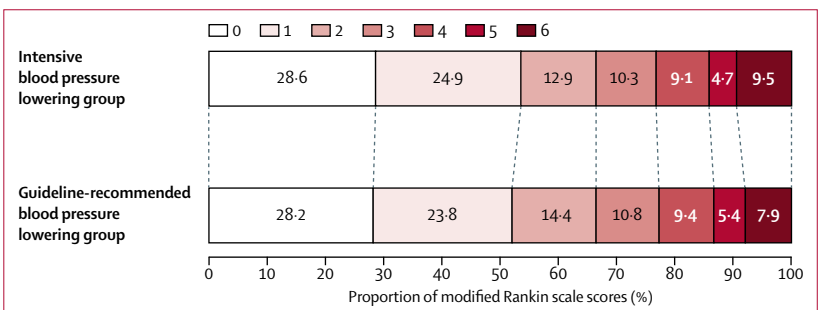

Figure 3: **Distribution of modified Rankin scale scores at 90 days by treatment group**
Raw distribution of scores is shown. Scores range from 0 to 6: 0=no symptoms, 1=symptoms without clinically significant disability, 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability, and 6=death.

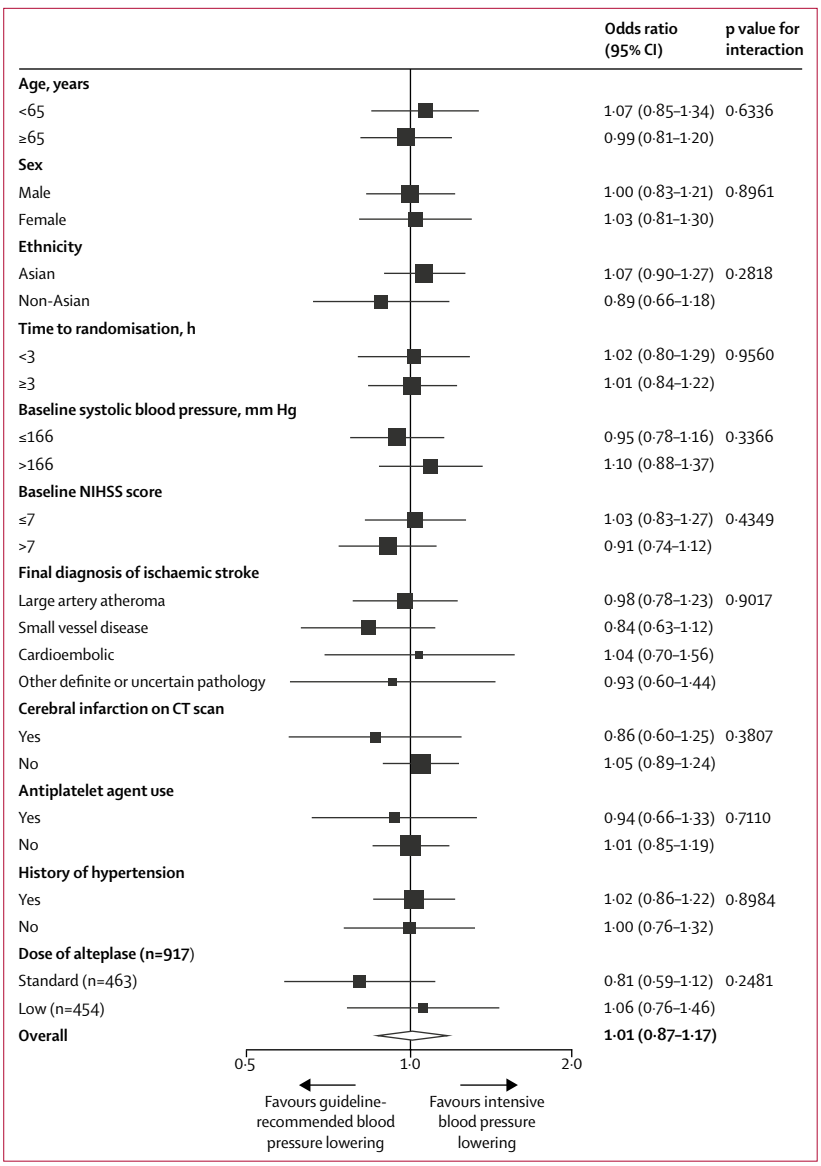

Figure 4: **Primary outcome by prespecified subgroups**
The primary efficacy outcome was shift in the modified Rankin scale score distribution (range 0 [no symptoms] to 6 [death]) at 90 days. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events), and horizontal lines represent 95% CIs. Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. For systolic blood pressure and NIHSS score, subgroups were dichotomised by median value. Dose of alteplase is divided into low (0·6 mg/kg; 15% as bolus, 85% as infusion over 1 h) or standard (0·9 mg/kg; 10% as bolus, 90% as infusion over 1 h). The marginal effect for factorial design (n=917 participants) for intensive versus guideline blood pressure lowering was odds ratio 0·92 (95% CI 0·73–1·16, p=0·4901). NIHSS=National Institutes of Health Stroke Scale.

dose and intensity of blood pressure lowering showed no significant interaction in the 917 patients recruited into both randomisation arms (p=0·2481; figure 4, appendix).

No significant differences were seen in the odds of death or disability at 90 days, whether defined by an mRS score of 2–6 or 3–6 (table 2). The unadjusted and adjusted per-protocol analyses were also consistent in showing no significant differences between the groups in treatment effect for overall functional outcome on mRS (table 2). Death or substantial neurological deterioration within 24 h and death within 90 days occurred in similar proportions of patients in the intensive and the guideline groups (table 2). No significant differences were evident in any of the other secondary clinical outcomes, including the primary cause of death, duration of initial hospitalisation, and health-related quality of life as an overall health utility score (appendix). Post-hoc analysis showed no heterogeneity in the treatment effect on the primary outcome according to quartiles of baseline NIHSS scores (appendix).

Assessment of the key safety outcome, any intracranial haemorrhage, was derived from adjudicated brain scans in 323 (87·5%) patients and other reports in 164 (51·0%) patients (appendix). This outcome was significantly less frequent in the intensive group than in the guideline group (table 3). The absolute difference was 3·9% (95% CI 0·8–7·1; p=0·0141) and the number need to treat to benefit was 25. MedDRA-coded clinician-reported intracranial haemorrhage as a serious adverse event was also significantly less frequent in the intensive group than in the guideline group (table 3). Furthermore, the intensive group had lower frequencies of adjudicated symptomatic intracerebral haemorrhage across a broad range of definitions than did the guideline group (table 3), and adjudicated large parenchymal intracerebral haemorrhage was less frequent in the intensive group (56 [5·2%]) than in the guideline group (80 [7·2%]; OR 0·71, 0·50–1·01, p=0·0535; appendix), although these differences were not significant.

The overall number of serious adverse events was similar in the intensive group (277) and the guideline group (334), and the number of patients with any serious adverse event did not differ significantly between the groups (210 [19·4%] of 1081 *vs* 245 [22·0%] of 1115; OR 0·86, 0·70–1·05, p=0·1412; appendix). However, compared with the guideline-recommended strategy, intensive blood pressure lowering was associated with significantly lower frequencies of intracranial haemorrhage (66 [6·1%] *vs* 105 [9·4%]; OR 0·63, 0·45–0·86, p=0·0040) and intracerebral haemorrhage (59 [5·5%] *vs* 100 [9·0%]; OR 0·59, 0·42–0·82, p=0·0017) reported as serious adverse events, and these events were predominantly non-fatal (appendix). The overall frequency of serious adverse events that the clinician attributed to intensive blood pressure lowering was less than 2·0% (appendix).

A post-hoc analysis of blood pressure management over the course of the study showed that systolic blood pressure difference between the two groups tended to decline over time. Mean systolic blood pressure levels at 1 h were 145 mm Hg in the intensive and 153 mm Hg in the guideline group (mean difference –8·2 mm Hg, 95% CI –10·4 to –6·0) before the end of the alteplase dose arm of the trial (Aug 17, 2015), and 148 mm Hg in the intensive and 153 mm Hg in the guideline group after the end of the alteplase dose arm, with a significantly decreased mean

difference (–5·1 mm Hg, –6·7 to –3·2, p=0·0352; appendix). Similarly, the mean 1 h systolic blood pressure difference significantly decreased from –9·9 mm Hg (–16·9 to –2·9) to –4·2 mm Hg (–10·7 to 2·3) between the first and last years of the study (appendix).

Post hoc, the clinical characteristics of patients in the guideline group were reclassified according to use of intravenous blood pressure lowering treatment. Compared with patients who did not receive any blood pressure lowering treatment in the first 24 h post-randomisation, among the 602 patients who did receive such treatment were significantly higher proportions of non-Asian patients, patients with a history of hypertension, coronary artery disease, and atrial fibrillation, and patients with evidence of proximal clot occlusion on the initial CT scan; higher initial systolic blood pressure and neurological impairment; and fewer patients with small vessel disease on final diagnosis (appendix). All efficacy and safety outcomes were significantly worse for treated than for non-treated patients allocated to the guideline group in adjusted analyses (appendix).

	Intensive blood pressure lowering group	Guideline-recommended blood pressure lowering group	Treatment effect	p value
Any intracranial haemorrhage*	160/1081 (14·8%)	209/1115 (18·7%)	0·75 (0·60–0·94)	0·0137
Any intracranial haemorrhage reported as a serious adverse event	59/1081 (5·5%)	100/1115 (9·0%)	0·59 (0·42–0·82)	0·0017
Major intracerebral haemorrhage based on central adjudication of brain imaging				
Symptomatic intracerebral haemorrhage, SITS-MOST criteria†	14/1081 (1·3%)	22/1115 (2·0%)	0·65 (0·33–1·28)	0·2143
Symptomatic intracerebral haemorrhage, NINDS criteria‡	70/1081 (6·5%)	84/1115 (7·5%)	0·85 (0·61–1·18)	0·3321
Symptomatic intracerebral haemorrhage, ECASS2 criteria§	46/1081 (4·3%)	57/1115 (5·1%)	0·82 (0·55–1·23)	0·3431
Symptomatic intracerebral haemorrhage, ECASS3 criteria¶	21/1081 (1·9%)	30/1115 (2·7%)	0·72 (0·41–1·26)	0·2467
Symptomatic intracerebral haemorrhage, IST-3 criteria	24/1081 (2·2%)	37/1115 (3·3%)	0·66 (0·39–1·11)	0·1198
Large parenchymal intracerebral haemorrhage‖	56/1081 (5·2%)	80/1115 (7·2%)	0·71 (0·50–1·01)	0·0535
Any intracerebral haemorrhage on brain imaging within 7 days	143/1081 (13·2%)	180/1115 (16·1%)	0·79 (0·62–1·00)	0·0542
Fatal intracerebral haemorrhage within 7 days	5/1081 (0·5%)	14/1115 (1·3%)	0·37 (0·13–1·02)	0·0541

Frequency data are n/N (%). Treatment effect is presented as odds ratio (95% CI) of intensive versus guideline-recommended blood pressure lowering, analysed by unadjusted binary logistic regression. Intracranial haemorrhage includes intracerebral haemorrhage, subarachnoid haemorrhage, and subdural and extradural haemorrhage. SITS-MOST=Safe Implementation of Thrombolysis in Stroke-Monitoring Study. NINDS=National Institutes of Neurological Diseases and Stroke. ECASS=European Cooperative Acute Stroke Study. IST=International Stroke Trial. NIHSS=National Institutes of Health Stroke Scale. *Any reported intracranial haemorrhage noted on a local brain imaging report within 7 days after randomisation, any haemorrhage noted on a centrally adjudicated scan, and any intracranial haemorrhage reported by a clinician as a serious adverse event. †Large or remote parenchymal intracerebral haemorrhage (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 24–36 h. ‡Any intracerebral haemorrhage associated with neurological deterioration (≥1 point change in NIHSS score) from baseline, or death within 24–36 h. §Any intracerebral haemorrhage with neurological deterioration (≥4 points on the NIHSS) from baseline, or death within 24–36 h. ¶Any intracerebral haemorrhage with neurological deterioration (≥4 points increase on the NIHSS) from baseline, or death within 36 h. Either significant intracerebral haemorrhage (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 intracerebral haemorrhage.

Table 3: **Safety outcomes at day 90**

Discussion

Our trial was driven by uncertainty over whether any benefit of intensive blood pressure lowering in terms of improving outcome in patients with acute ischaemic stroke, gained largely from a reduced risk of thrombolysis-related intracerebral haemorrhage, could be offset by the harm of promoting cerebral ischaemia. The main finding was that, in thrombolysis-treated patients with acute ischaemic stroke of predominantly mild-to-moderate severity, a strategy of intensive blood pressure lowering (target systolic blood pressure 130–140 mm Hg within 1 h) compared with current guideline-recommended blood pressure management (target <180 mm Hg) after intravenous alteplase therapy was not associated with a significant difference in functional recovery, as assessed by a shift in the distribution of mRS scores at 90 days. This result was consistent in sensitivity and per-protocol analyses, and across key prespecified subgroups. However, intensive blood pressure lowering was associated with a significant reduction in the incidence of intracranial haemorrhage, as well as slight (non-significant) reductions in major intracerebral haemorrhage, consistent across different measures.

The ENCHANTED trial adds important new information on the role of early intensive blood pressure lowering in the context of thrombolysed patients with acute ischaemic stroke, but it also highlights some of the challenges of doing an open trial in a critical illness with temporal change in the level of equipoise. Although we recruited to our target sample size and achieved a high rate of follow-up over 90 days, the average systolic blood pressure difference of 6 mm Hg between randomised groups was much smaller than the 15 mm Hg envisaged, and decreased as the trial progressed. In part, this finding reflected a shift in clinician behaviour towards targeting lower systolic blood pressure in the guideline group than is recommended in guidelines derived from the protocol of the National Institutes of Neurological Diseases and Stroke (NINDS) recombinant tissue plasminogen activator trial in acute ischaemic stroke.[13] It also relates to complexities in the titration of systolic blood pressure to the target according to the study protocol for patients in the intensive group: this target might have been considered too low for some clinicians, or reflected difficulties of aggressive blood pressure lowering in acute ischaemic stroke.

Systolic blood pressure is an important prognostic factor after acute stroke, with a systolic blood pressure target of 140–150 mm Hg being associated with best outcome in several observational studies.[14,15] To date, randomised evaluations of blood pressure lowering treatment in acute ischaemic stroke with a broad time window from the onset of symptoms and modest systolic blood pressure reductions have been neutral.[16] By

contrast, post-hoc analysis of the pivotal NINDS trial showed that the use of blood pressure lowering therapy after randomisation in hypertensive patients in the recombinant tissue plasminogen activator group was associated with less favourable outcome compared with that of patients who did not receive any such treatment.[13] However, blood pressure elevations are higher in patients who are less likely to reperfuse, have bigger strokes, and are thus more likely to get blood pressure lowering treatment. 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, showed a U-shaped relationship between baseline systolic blood pressure and outcome, with a systolic blood pressure nadir of 120 mm Hg being associated with best outcome.[17]

Many clinicians are concerned that rapid blood pressure reductions in the absence of mechanical or pharmacological reperfusion might worsen cerebral ischaemia from potential hypoperfusion with compromised autoregulation and collateral flow.[8] In our trial, any benefit from intensive blood pressure reduction on outcome due to reduction in intracranial haemorrhage might have been offset by hypoperfusion of the ischaemic penumbra. However, we observed no significant heterogeneity of treatment effect in subgroups where large vessel occlusion might be anticipated, including acute ischaemic stroke subtypes classified on the basis of clinician-diagnosis of large vessel disease, cardioemboli, or lacunar acute ischaemic stroke, and in post-hoc analysis of stroke severity based on quartiles of increasing NIHSS score. Since CT or magnetic resonance angiography was not mandated in this pragmatic study, artery status was not assessed in most patients and large vessel occlusion was only confirmed in 97 patients in the intensive group on CT or magnetic resonance angiography. Thus, further studies of intensive blood pressure lowering in the context of mechanical and pharmacological reperfusion therapy in cases of proven large vessel occlusion are required.

In the ENCHANTED trial, we also assessed the potential benefit of intensive blood pressure control in terms of the incidence of intracranial haemorrhage. From the SITS-ISTR of 11080 patients, Ahmed and colleagues[7] reported a linear association between systolic blood pressure and symptomatic intracerebral haemorrhage up to 24 h after thrombolysis. Similarly, in a post-hoc analysis of the third International Stroke Trial (IST-3), Berge and colleagues[18] reported an association between each 10 mm Hg higher baseline systolic blood pressure and risk of symptomatic intracerebral haemorrhage, with large systolic blood pressure declines over 24 h significantly associated with decreased risk of symptomatic intracerebral haemorrhage. As the only randomised trial of intensive blood pressure reduction in thrombolysis-treated acute ischaemic stroke patients, ENCHANTED suggests that there are benefits in lowering the risk of intracranial haemorrhage, despite no observed statistically significant decrease in adjudicated symptomatic intracerebral haemorrhage. This finding might reflect variable benefit of intensive blood pressure reduction on petechial, alteplase-associated, intracerebral haemorrhage in a hypertensive population with evidence of brain vessel fragility compared with large, space-occupying, alteplase-associated, parenchymal intracerebral haemorrhage, as previously suggested by Butcher and colleagues.[19] However, as ENCHANTED recruited mainly patients with acute ischaemic stroke of mild-to-moderate severity, the study was under-powered to assess the effects of treatment on symptomatic intracerebral haemorrhage, for which the frequencies of death and major neurological deterioration were low. Even so, the lower incidence of symptomatic intracerebral haemorrhage was consistent across all classifications in the intensive group versus the guideline group, and there were non-significant reductions in both petechial (haemorrhagic infarction 1 and 2) and space-occupying (parenchymal haemorrhage 1 and 2) intracerebral haemorrhage, and borderline significant reduction in any parenchymal haemorrhage, in adjudicated brain images. Finally, it is important to note that the ENCHANTED trial excluded patients with systolic blood pressure of more than 185 mm Hg, in keeping with the licensed indication for the use of intravenous alteplase, and thus no comment can be made with respect to the risk of intracranial haemorrhage or the benefit of blood pressure reduction in severely hypertensive patients. However, others have reported that such protocol violations are associated with significantly more frequent symptomatic intracerebral haemorrhage.[20]

The key strengths of this randomised controlled trial were its large size and international recruitment, which enhance the generalisability of the results and the possibility of influencing clinical practice worldwide. We used robust methodologies to ensure masking during assessment of the key efficacy measure (through central coordination of mRS follow-up by staff unaware of treatment allocation) and of the safety outcomes (with central adjudication of intracranial haemorrhage by assessors masked to clinical details and group allocation). Nonetheless, the study had several potential limitations.

First, the trial involved patients with acute ischaemic stroke of predominantly mild-to-moderate severity, with a median NIHSS score of 7, in contrast to previous trial and registry data of patients with acute ischaemic stroke with median NIHSS scores of 12 and 13, respectively.[2,3] However, with increasing use of intravenous thrombolysis, an NIHSS score of 7 is more reflective of the usual treated acute ischaemic stroke population, including those in clinical trials. For example, in a comparison of tenecteplase with alteplase, published in 2017, the median NIHSS was 4.[21] Even so, our results are potentially influenced by selection bias: clinicians might have excluded cases of severe stroke with high perceived risks from intensive blood pressure lowering treatment, but the effects of

intravenous alteplase are modest in mild acute ischaemic stroke. Second, there might be concerns about the generalisability of the trial results to all populations because nearly three-quarters of patients in the sample were Asian. We acknowledge reduced statistical power in the subgroup analyses; however, importantly, there was no heterogeneity of treatment effect by ethnicity, even though the high prevalence of intracranial atherosclerosis (and related intracranial stenosis) and of cerebral small vessel disease present in Asian populations might have increased the risks of hypoperfusion related to intensive blood pressure control.[22] In addition, the increased prevalence of hypertension and associated small vessel disease in Asian patients could have increased the risk of symptomatic intracerebral haemorrhage.[23] Finally, the smaller-than-anticipated systolic blood pressure difference between groups probably resulted in the trial being underpowered. In part, this reduced difference might be attributed to a natural fall in systolic blood pressure following recanalisation and reperfusion in both groups, but probably also reflected the effect of the high proportion (54·3%) of participants in the guideline group who received some form of blood pressure lowering therapy, and 35·3% who received any intravenous therapy in the first 24 h; and these patients had worse outcomes than those who did not receive treatment. The use of post-randomisation intravenous blood pressure lowering agents might reflect increased familiarity with local blood pressure lowering protocols in stroke units since the publication and international guideline adoption of the results of the main Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2), albeit in intracerebral haemorrhage patients.[24] Although most participants in the intensive group of our trial had blood pressure lowering treatment initiated soon after administration of intravenous alteplase, when the risk of reperfusion-related intracerebral haemorrhage is greatest, uncertainty remains over the most appropriate timing, approach, and agent(s) for blood pressure lowering, pre-thrombolysis and post-thrombolysis.

Intensive blood pressure lowering during and for up to 72 h after intravenous thrombolysis in predominantly Asian patients with acute ischaemic stroke of mild-to-moderate severity did not improve functional outcome at 90 days compared with that of patients who received guideline-recommended blood pressure management. Overall, the results indicate that intensive blood pressure lowering is safe in this patient group, with significantly decreased incidence of intracranial haemorrhage compared with that of the guideline group, and consistency in the reduced frequency of major intracerebral haemorrhage. However, these results might not support a major shift in clinical practice towards more intensive blood pressure lowering in those receiving thrombolysis for acute ischaemic stroke of mild-to-moderate severity. Because the observed reduction in intracerebral haemorrhage did not improve clinical outcome, further research is required to understand the underlying mechanisms of benefit and harm resulting from early intensive blood pressure lowering in patients with hyperacute acute ischaemic stroke.

Contributors

CSA, JC, RIL, TGR, and YH conceived the trial. CSA was the chief investigator. CSA, RIL, XC, JC, TGR, and ACD were responsible for the day-to-day running of the trial. RIL led the adjudication of neuroimaging. 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.

Declaration of interests

CSA has received grants from the National Health and Medical Research Council (NHMRC) of Australia and Takeda China, honoraria for advisory board activities for Boehringer Ingelheim and Amgen, and speaker fees from Takeda. RIL and MWP have received research grants from the NHMRC of Australia. HA has received lecture fees from Bayer, Daiichi-Sankyo, Fukuda Denshi, Takeda and Teijin, and personal fees for consultancy to Kyowa-Kirin. PMB has received honoraria for advisory board activities from DiaMedica, Moleac, Nestlé, Phagenesis and ReNeuron. JPB has received grants from the National Institute of Neurological Diseases and Stroke, and Genentech. AMD has received speaker fees from Medtronic. PML has received research grants from Bayer, Boehringer Ingelheim, Conicyt, The George Institute for Global Health, and Clínica Alemana. CL has received research grants from NHMRC and honoraria from Boehringer Ingelheim. SOM has received speaker fees from Boehringer Ingelheim, Pfizer, Bayer, and Medtronic. VVO has received research grants from Clínica Alemana de Santiago, The George Institute for Global Health, Boehringer Ingelheim, Lundbeck Chile, and Conicyt. GAD has received advisory committee and speaker fees from Allergan, Amgen, Boehringer Ingelheim, Moleac, and Servier. OMP-N has received speaker fees from Boehringer Ingelheim, Pfizer, and Medtronic. SR has received travel support from Bayer. SS has worked as a medical expert for Bayer, Japan, from the end of the study. MW has received personal fees for consultancy to Amgen. JC has received research grants from NHMRC and Idorsia. TGR and JMW have received research grants from the UK Stroke Association. YH, XC, GC, QL, LB, CD, ACD, T-HL, JDP, VKS, FS, LS, NHT, J-GW, and XW declare no competing interests.

Data sharing statement

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

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