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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Abstract

Background Systolic blood pressure (SBP) >185mmHg is a contraindication to thrombolytic 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 alteplase-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 in modified Rankin scale scores, analysed using unadjusted ordinal logistic regression. The key secondary safety outcome was any intracranial haemorrhage. Other safety outcomes included symptomatic intracerebral haemorrhage (sICH) according to standard definitions on centrally adjudicated brain images. There were 917 participants also in the alteplase dose-comparison arm. Analyses were by intention-to-treat. This trial is registered with ClinicalTrials.gov, NCT01422616.

Findings Between March 3, 2012 and April 30, 2018, we randomised 2227 and analysed 2196 alteplase-eligible AIS patients in the intention-to-treat population, with 1466 (67·2%) administered a standard-dose among 2182 actually given iv alteplase. Of these 2196 patients (835 [38·0%] female, 1618 [73·7%] Asian ethnicity, mean age 66·7 [standard deviation 12·2] years), their median baseline National Institutes of Health Stroke Scale score was 7 (interquartile range 4·0–12·0) at a median time from onset to randomisation of 3·3 (interquartile range 2·6–4·1) hours. 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 (standard deviation 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 interval [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 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. Overall, these results indicate that intensive BP lowering is safe but they may not support a major shift towards this treatment being applied in those receiving thrombolysis for mild-to-moderate severity of AIS. The observed reduction in intracranial haemorrhage, including major types of ICH, did not lead to improved clinical outcome. Further research is required to define the underlying mechanisms of benefit and harm of early intensive BP lowering in this patient group.

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Introduction

Timely administration of intravenous (iv) thrombolytic 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 harm from intracranial haemorrhage when iv alteplase (recombinant tissue plasminogen activator) 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) 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, controversy persists in respect of peri-thrombolysis blood pressure (BP) control, where guidelines consistently contraindicate the use of alteplase in patients with 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 the best outcome in the nadir SBP 141–150mmHg. An ongoing concern, however, has been that rapid BP reduction 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 is 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 benefit and risk 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 comply with 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 control (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 in the intensive group to enhance the SBP difference between groups; (ii) increased the time of randomisation to the BP arm from within 4·5 to 6 hours of stroke onset

188 to avoid trial–related procedures delaying the achievement of 1 hour door-to-needle-time
189 quality performance in the administration of iv alteplase as part of routine practice; (iii)
190 increased the time to achieve the target SBP from 60 minutes from the commencement of
191 alteplase to 60 minutes from randomisation; (iv) changed the key secondary outcome from
192 whether intensive BP lowering reduced sICH to reduction in any intracranial haemorrhage to
193 increase study power; and (v) reduced the sample size from 3300 to 2304 participants.
194 Furthermore, a final protocol amendment in February 2017: (i) changed the primary outcome
195 from a conventional binary assessment of poor clinical outcome (modified Rankin scale
196 [mRS] scores of 3–6) to an ordinal shift analysis of the full range of category scores (0–6) of
197 the mRS at 90 days to increase study power; which resulted in (ii) a further reduction in
198 sample size to 2100 participants consequent upon this change in the primary outcome. Until
199 the conclusion of the alteplase dose arm in August 2015, participants could additionally be
200 randomised to low–dose (0·6mg/kg, maximum of 60mg; 15% as bolus, 85% as infusion over
201 1 hour) or standard-dose (0·9mg/kg, maximum of 90mg; 10% as bolus, 90% as infusion over
202 1 hour) iv alteplase. Subsequently, the attending clinician investigator could choose the dose
203 of iv alteplase to use according to his/her interpretation of the evidence.

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

210 The trial protocol was approved by appropriate regulatory and ethical authorities at
211 participating centres. Written consent was obtained from each participant, or his/her approved
212 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 were used, outlined in appendices to the trial protocol. 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 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 with use of NIHSS and Glasgow coma scale (GCS) scores, was assessed at baseline, and at 24 and 72 hours. Brain imaging

(CT and/or MRI) was conducted at baseline, and at 24 hours, and additionally if clinically indicated; local investigator identification of early cerebral ischaemia/infarction, and hyperdense artery sign were recorded; and 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 in measures of functioning according to the full range of scores on the mRS;[11] a global 7-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; primary cause of death; duration of initial hospitalisation in days; and health-related quality of life (HRQoL), as assessed on the ©EuroQoL group EQ-5D-3L™, according to an overall health utility score at 90 days.[12]

The key secondary 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 (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 was associated with significant neurological deterioration and/or death. The key measure of sICH was from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), defined as 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 (SITS-MOST).[6] Other criteria for sICH that were used in other studies are outlined in the 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 14% relative reduction in the poor outcome in the intensive BP lowering group,[7] taking account of a 5% drop-out and potential negative interaction between low-dose alteplase and

intensive BP lowering. However, as the ordinal shift approach provides efficiency gains, a re-estimation of the sample size based on an ordinal mRS analysis indicated that the estimated treatment effect could be detected with a sample size of 2100.[10] 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 for logistic regression. A priori,[10] the primary analysis for superiority of intensive versus guideline BP lowering were unadjusted, but we also performed pre-specified 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 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 (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. The corresponding author had full access to the study data and took overall 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 following approval of a protocol and signed data access agreement 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, S2 and S3). 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%) 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%) were on prior antihypertensive treatment, 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%) patients received iv alteplase, and at a standard dose of 0·9 mg/kg body in 1466 (67·2%), including 469 (32·0%) who participated in the alteplase-dose arm and 997 (68·0%) based upon a cut-off dose >0.75mg/kg actually given (supplementary table S3). The median time

from the initiation of treatment with iv alteplase to commencement of any iv BP lowering treatment was 20 mins (IQR 0 to 85) and 30 mins (IQR 0 to 157) in the intensive and guideline groups, respectively (p=0·0925).. There were 2140 (97·4%) participants received BP lowering treatment according to the assigned protocol (appendix table S4). 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 S5). 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 S6). SBP levels were 146mmHg and 153mmHg (mean Δ -6·4mmHg, 95% confidence interval [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 S7). Overall average SBP levels within 24 hours were significantly lower in the intensive group (144 vs. 150mmHg, p<0·0001; appendix tables S6 and S7). SBP remained lower in the intensive compared to the guideline group for the subsequent 6 days (figure 2, appendix tables S5, S6 and S7). There were no significant differences in other clinical management over the 7 day post-randomisation period (appendix table S5).

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 S4). The proportional odds assumptions was tested and was not significant (p=0·6036). 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 S8 and figure S1 [A] and [B]).

No significant differences were seen in the odds of death or 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) 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 group versus 9·7% in the guideline group (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 the primary cause of death, duration of the initial hospitalisation, and HRQoL as an overall health utility score (appendix tables S9 and S10). Post-hoc analysis showed no heterogeneity in the treatment effect on the primary outcome according to quartiles of baseline NIHSS scores (appendix table S11 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). The absolute difference was 3·9% (95%CI 0·8% to 7·1%; p=0·0141) and the number need to treat to benefit is 25. 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; table 2). 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 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 S12).

There was no significant difference in the overall frequency of SAEs between intensive and guideline BP-lowering groups (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 S13). 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) as an SAE, which were predominantly driven by non-fatal events (appendix table S13).

A post-hoc analysis was made of BP management 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 at 1 hour 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 significantly lower at 148mmHg and 153mmHg (mean Δ -5·1mmHg, 95%CI -3·2 to -6·7) after August 2015 (appendix, table S14). Similarly, the mean 1 hour SBP difference (mmHg) significantly 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 S15). 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 in the first 24 hours post-randomisation, the 602 patients who did were significantly more often female, non-Asian, with higher initial SBP and neurological impairment, and greater history of hypertension, prior stroke, coronary artery disease and atrial fibrillation, and evidence of proximal clot

occlusion on the initial CT scan, and less small vessel disease on final diagnosis (appendix, table S15). All efficacy and safety outcomes were significantly worse for the treated than non-treated patients allocated to the guideline-based BP management group in adjusted analyses (appendix, table S16).

Discussion

Our trial was driven by uncertainty over whether any benefit of intensive BP lowering in 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 BP management (<180mmHg) after iv alteplase therapy, was not associated with a significant difference in the primary outcome of functional recovery, as assessed by shift 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. However, intensive BP control was associated with a significant reduction in intracranial haemorrhage, and there was consistent reduction in major ICH across different measures.

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 level of equipoise. Although we recruited to our target sample size and achieved a high level of follow-up over 90 days, the SBP difference on average 6 mmHg between randomised groups was much smaller than the 15 mmHg envisaged and reduced as the trial progressed. In part this reflected a shift in clinician behaviour towards targeting lower SBP levels 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 (rt-

PA) trial in AIS.[16] It also relates to complexities in the titration of SBP to the target according to study protocol for patients in the intensive group, as this may have been considered too low for some clinicians and/or reflected difficulties of aggressive BP lowering in AIS.

It is well recognised that SBP is an important prognostic factor after acute stroke, with a SBP 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] However, BP elevations are higher in patients who are less likely to reperfuse, have bigger strokes, and thus more likely to get BP 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, 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, cardio-emboli or lacunar AIS, and in post-hoc analysis of stroke severity based on quartiles of increasing NIHSS score. Since CT or MR angiography was not

mandated in this pragmatic study, artery status was not determined in most patients and large vessel occlusion was only confirmed in 97 patients in the intensive group on CT/MR angiography. . 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 higher 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 are 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, alteplase-associated ICH in a hypertensive population with evidence of 'brain vessel fragility' compared with large space-occupying, alteplase-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 in any PH, in adjudicated brain images. Finally, it is important to note that the ENCHANTED trial excluded patients with SBP >185 mmHg in keeping with the licensed indication for the use of iv alteplase, and no comment can be made with respect to

485 the risk of intracranial haemorrhage in severely hypertensive patients and/or the benefit of BP
486 reduction. However, others have reported that such protocol violations are associated with
487 significantly more frequent sICH.[20]

488 ***Strengths and limitations***

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

496 First, the trial involved an AIS population of predominantly mild-to-moderate severity, with a
497 median NIHSS of 7, as compared to previous trial and registry data of AIS patients with
498 median NIHSS scores of 12 and 13, respectively.[2,3] However, with increasing use of iv
499 thrombolysis, the NIHSS is more reflective of the usual treated AIS population, including that
500 in clinical trials. For example, the median NIHSS in a recent comparison of tenecteplase with
501 alteplase was 4.[21] Even so, our results are potentially influenced by selection bias, whereby
502 clinicians excluded cases of severe stroke with risks of intensive BP lowering treatment that
503 were perceived to be high, and for the effects of iv alteplase are modest in mild AIS.
504 Secondly, there may be concerns about the generalisability of the trial results to all
505 populations, as nearly three-quarters were Asian. Whilst acknowledging reduced statistical
506 power in subgroup analysis, there was importantly no heterogeneity of the treatment effect by
507 ethnicity, and where the high prevalence of intracranial atherosclerosis and related intracranial
508 stenosis, and cerebral small vessel disease, in an Asian population may have increased the
509 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 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-randomisation 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 results of the main Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2), albeit in ICH patients.[24] Although most participants in the intensive group of our trial had BP lowering treatment initiated soon after administration of iv alteplase, when the risk of reperfusion-related ICH is greatest, there is uncertainty over the most appropriate timing, approach and agent(s) for BP lowering, pre- and post-thrombolysis.

Summary

A strategy of intensive compared to guideline BP management 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. Overall, these results indicate that intensive BP lowering is safe in this patient group. Moreover, there were significantly lower rates of intracranial haemorrhage, and consistency in a reduced frequency major ICH. However, these results may not support a major shift in clinical practice towards more intensive BP lowering in those receiving thrombolysis for mild-to-moderate severity of AIS. As the observed reduction in ICH failed to improve clinical outcome, further research is required to understand the underlying mechanisms of benefit and harm of early intensive BP lowering in hyperacute AIS.

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 intracranial haemorrhage was significantly lower following intensive BP treatment, and there was a consistent reduction in adjudicated symptomatic intracerebral haemorrhage across a range of definitions albeit not being statistically significant.

Implications of all the available evidence

Overall, these results will reassure clinicians that intensive BP control is not associated with an increased risk of death or disability from adverse effects on the cerebral ischaemic penumbra in acute ischaemic stroke receiving intravenous thrombolytic treatment. There may be the potential for such treatment to reduce the risk of major intracranial haemorrhage, but further research is required to define the underlying mechanisms of benefit and harm of early intensive BP lowering in hyperacute AIS. Moreover, further trials with a greater separation of BP between treatment groups are required to provide more definitive evidence to support the

558 treatment in patients with more severe AIS requiring thrombolysis and/or endovascular
559 reperfusion therapy.
560

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. 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.

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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; RIL has 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, Nestle, 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, Medtronic; VVO has received research grants from Clínica Alemana de Santiago, The George Institute for Global Health, Boehringer Ingelheim, Lundbeck Chile, and Conicyt; MWP has received research grants from NHMRC; GAD has received advisory committee and speaker fees from Allergan, Amgen, Boehringer Ingelheim, Moleac and Servier. OMPN 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. HY, XC, GC, QL, LB, CD, ACD, THL, JDP; LS, VKS, FS, NHT, JGW, and XW have no disclosures.

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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).

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%)	ordinal OR 1·01 (0·87 to 1·17)	0·8702
1	267/1072 (24·9%)	264/1108 (23·8%)	ordinal aOR 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%)	OR 0·94 (0·79 to 1·11)	0·4660
	498/1072 (46·5%)	531/1106 (48·0%)	aOR 0·94 (0·78 to 1·14)	0·5508
Per Protocol analysis (mRS score ≥2)	451/958 (47·1%)	499/1028 (48·5%)	OR 0·94 (0·79 to 1·12)	0·5141
	451/958 (47·1%)	498/1026 (48·5%)	aOR 0·96 (0·79 to 1·16)	0·6595
Death or major disability (mRS score ≥3)	360/1072 (33·6%)	372/1108 (33·6%)	OR 1·00 (0·84 to 1·20)	0·9968
	360/1072 (33·6%)	371/1106 (33·5%)	aOR 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%)	OR 1·06 (0·80 to 1·40)	0·7013
In first 72 hours	146/1081 (13·5%)	139/1115 (12·5%)	OR 1·10 (0·85 to 1·41)	0·4687
Death at day 90	102/1081 (9·4%)	88/1115 (7·9%)	OR 1·22 (0·90 to 1·64)	0·1989
	102/1078 (9·5%)	88/1113 (7·9%)	aOR 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%)	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%)	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%)	OR 0·65 (0·33 to 1·28)	0·2143
Symptomatic ICH, NINDS criteria¶	70/1081 (6·5%)	84/1115 (7·5%)	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%)	OR 0·82 (0·55 to 1·23)	0·3431
Symptomatic ICH, ECASS3 criteria**	21/1081 (1·9%)	30/1115 (2·7%)	OR 0·72 (0·41 to 1·26)	0·2467
Symptomatic ICH, IST-3 criteria††	24/1081 (2·2%)	37/1115 (3·3%)	OR 0·66 (0·39 to 1·11)	0·1198
Large parenchymal ICH‡‡	143/1081 (13·2%)	180/1115 (16·1%)	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%)	OR 0·79 (0·62 to 1·00)	0·0542
Fatal ICH ≤7 days	5/1081 (0·5%)	14/1115 (1·3%)	OR 0·37 (0·13 to 1·02)	0·0541

aOR denoted adjusted odds ratio, 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; analyses of OR are unadjusted binary unless stated otherwise.

†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: Mean systolic and diastolic blood pressure levels 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 scale (mRS) outcome at 90 days by treatment group

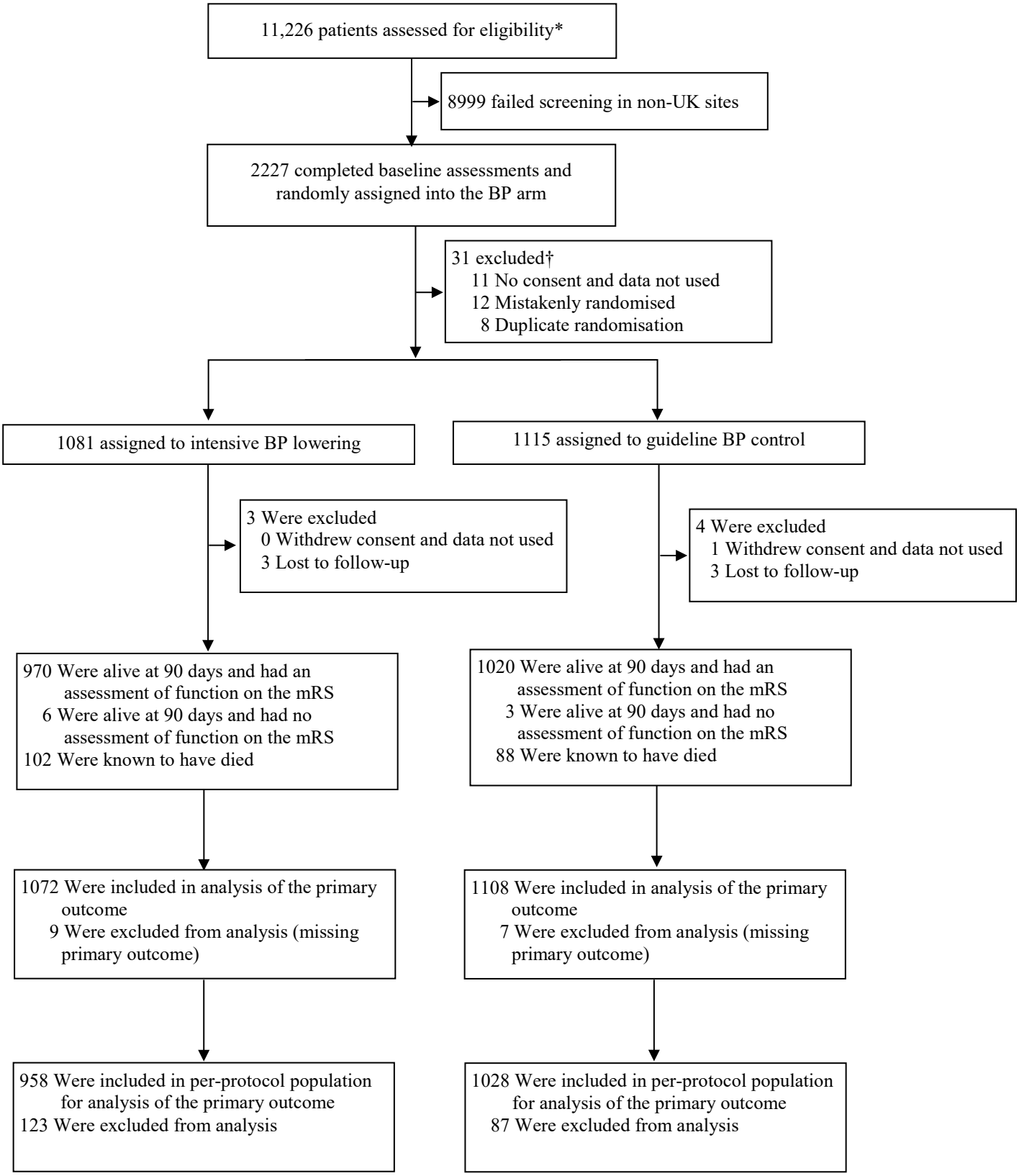
Footnote: The figure shows the raw distribution of scores on the modified Rankin scale (mRS) at 90 days. Scores on the mRS range from 0 to 6, with 0 indicating no symptoms, 1 symptoms without clinical significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability,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

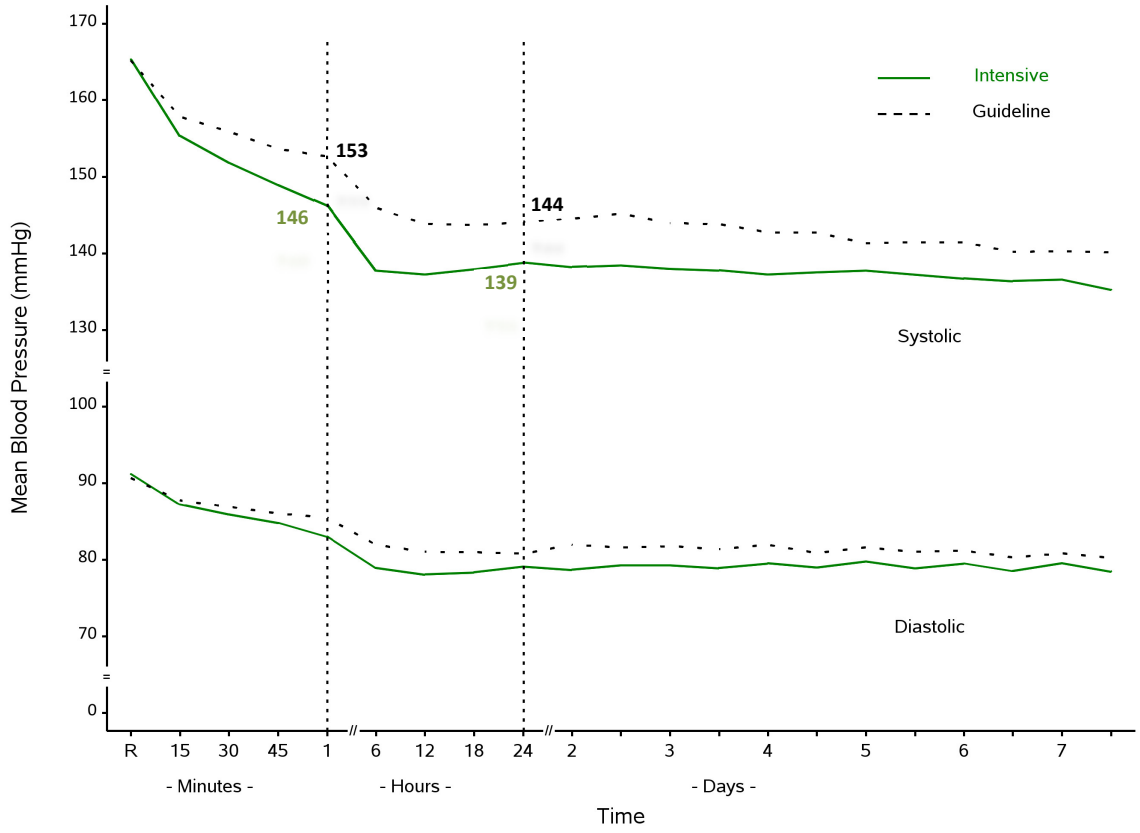
over 1 hour) or standard-dose (0·9mg/kg; 10% as bolus, 90% as infusion over 1 hour). The marginal effect for factorial design (n=917 participants), for intensive *vs* guideline BP lowering, odds ratio 0·92 (95%CI 0·73-1·16; p=0·4901).

Figure 1: Trial profile



BP denotes blood pressure
*Screening logs not used at UK sites
†15 to intensive BP group, 8 to guideline BP group and 8 to alteplase-dose arm.

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



R: Randomization

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

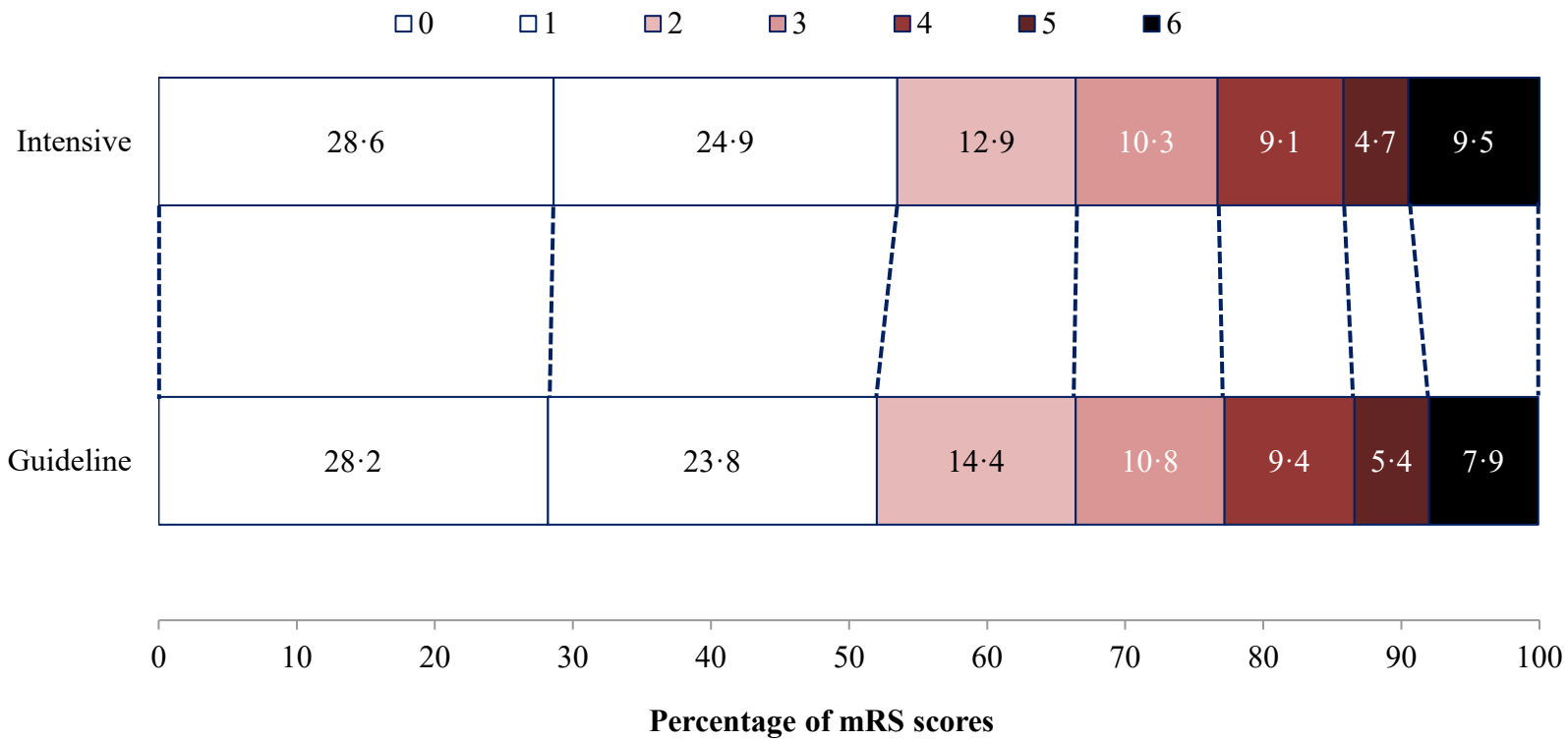


Figure 4: Primary outcome by pre-specified subgroups