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 to avoid trial–related procedures delaying

the achievement of 1 hour door-to-needle-time quality performance in the administration of iv alteplase as part of routine practice; (iii) increased the time to achieve the target SBP from 60 minutes from the commencement of alteplase to 60 minutes from randomisation; (iv) changed the key secondary outcome from whether intensive BP lowering reduced sICH to reduction in any intracranial haemorrhage to increase study power; and (v) reduced the sample size from 3300 to 2304 participants. Furthermore, a final protocol amendment in February 2017: (i) changed the primary outcome from a conventional binary assessment of poor clinical outcome (modified Rankin scale [mRS] 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; which resulted in (ii) 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 in August 2015, participants could additionally be randomised to low–dose (0·6mg/kg, maximum of 60mg; 15% as bolus, 85% as infusion over 1 hour) or standard-dose (0·9mg/kg, maximum of 90mg; 10% as bolus, 90% as infusion over 1 hour) iv alteplase. Subsequently, the attending clinician investigator could choose the dose of iv alteplase to use according to his/her interpretation of the evidence.

Key exclusion criteria were that a patient: was unlikely to benefit from thrombolysis (e.g. advanced dementia); had a very high likelihood of death within 24 hours; had significant co-morbidity that would interfere with the outcome assessments or follow-up (known significant pre-stroke disability, estimated scores 2–5 on the mRS); had a specific contraindication to alteplase or any of the BP lowering agents to be used; and 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 his/her approved surrogate for patients who were too unwell to comprehend the information.

Randomisation and masking

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

Procedures

The trial sought to assess a management strategy of BP lowering to achieve and maintain intensive (130–140mmHg) and guideline (<180mmHg) SBP targets. Therefore, local treatment protocols based on available iv (bolus and infusion), oral and topical medications 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 the risk of intracranial haemorrhage in severely hypertensive patients and/or the benefit of BP reduction. However, others have reported that such protocol violations are associated with significantly more frequent sICH.[20]

Strengths and limitations

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

First, the trial involved an AIS population of predominantly mild-to-moderate severity, with a median NIHSS of 7, as compared to previous trial and registry data of AIS patients with median NIHSS scores of 12 and 13, respectively.[2,3] However, with increasing use of iv thrombolysis, the NIHSS is more reflective of the usual treated AIS population, including that in clinical trials. For example, the median NIHSS in a recent comparison of tenecteplase with alteplase was 4.[21] Even so, our results are potentially influenced by selection bias, whereby clinicians excluded cases of severe stroke with risks of intensive BP lowering treatment that were perceived to be high, and for the effects of iv alteplase are modest in mild AIS. Secondly, there may be concerns about the generalisability of the trial results to all populations, as nearly three-quarters were Asian. Whilst acknowledging reduced statistical power in subgroup analysis, there was importantly no heterogeneity of the treatment effect by ethnicity, and where the high prevalence of intracranial atherosclerosis and related intracranial stenosis, and cerebral small vessel disease, in an Asian population may have increased the risks of hypoperfusion related to intensive BP control.[22] In addition, the higher prevalence of hypertension and associated small vessel disease in Asians may have increased the risk of sICH.[23] Finally, the achieved SBP difference being smaller than anticipated 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

552 treatment in patients with more severe AIS requiring thrombolysis and/or endovascular
553 reperfusion therapy.
554

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

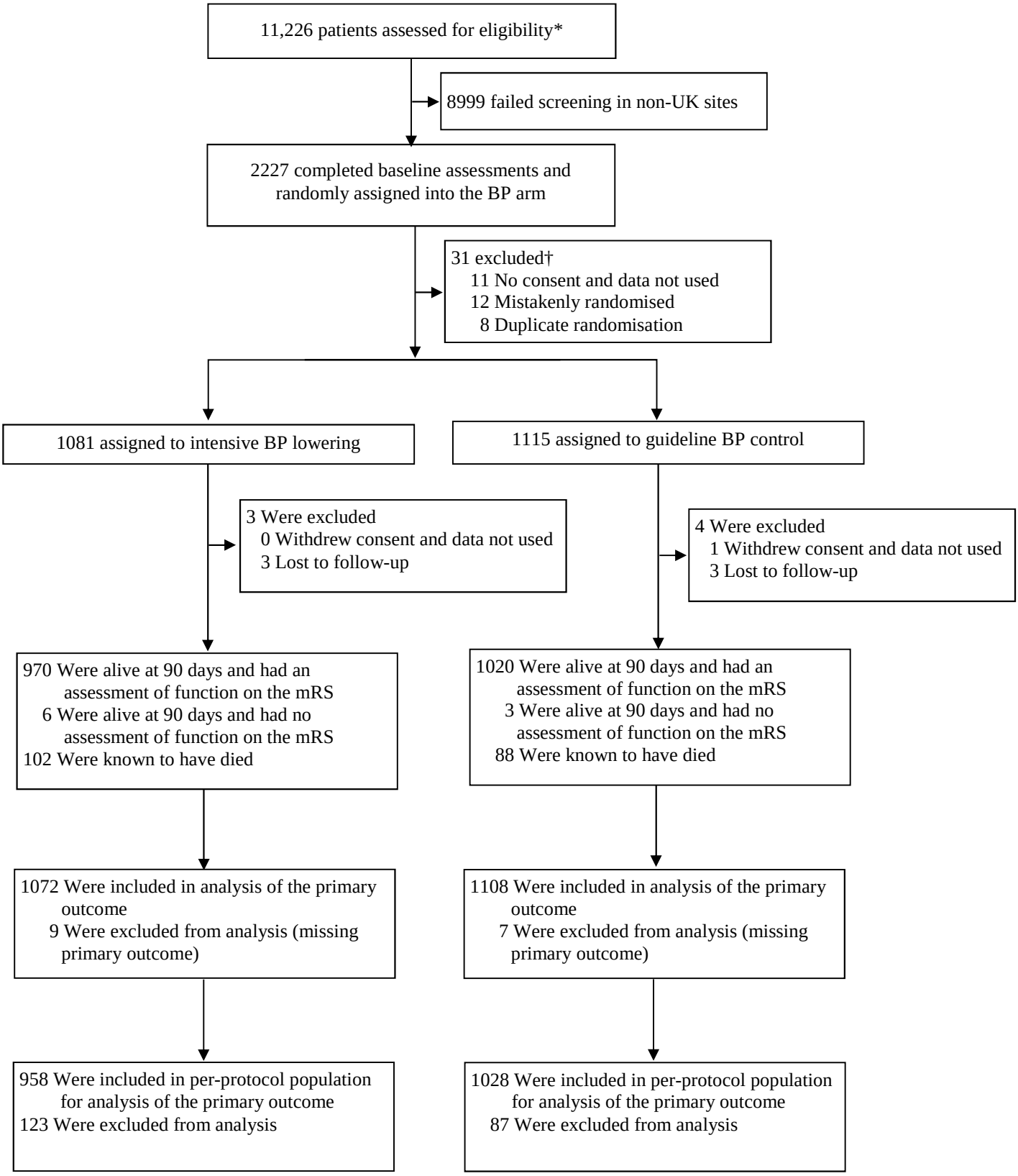
Footnote: The figure shows the raw distribution of scores on the modified Rankin scale (mRS) at 90 days. Scores on the mRS range from 0 to 6, with 0 indicating no symptoms, 1 symptoms without clinical significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability,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

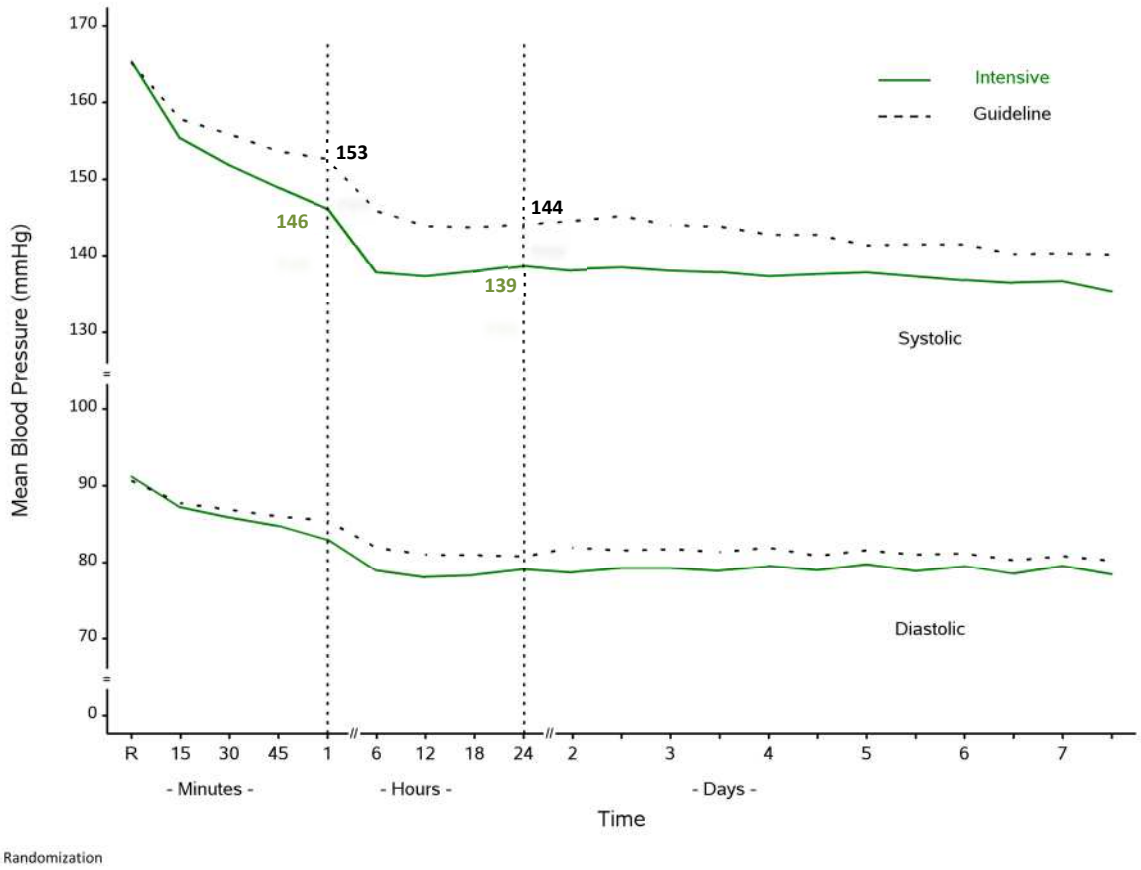
standard-dose (0·9mg/kg; 10% as bolus, 90% as infusion over 1 hour). The marginal effect for factorial design (n=917 participants), for intensive *vs* guideline BP lowering, odds ratio 0·92 (95%CI 0·73-1·16; p=0·4901).

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

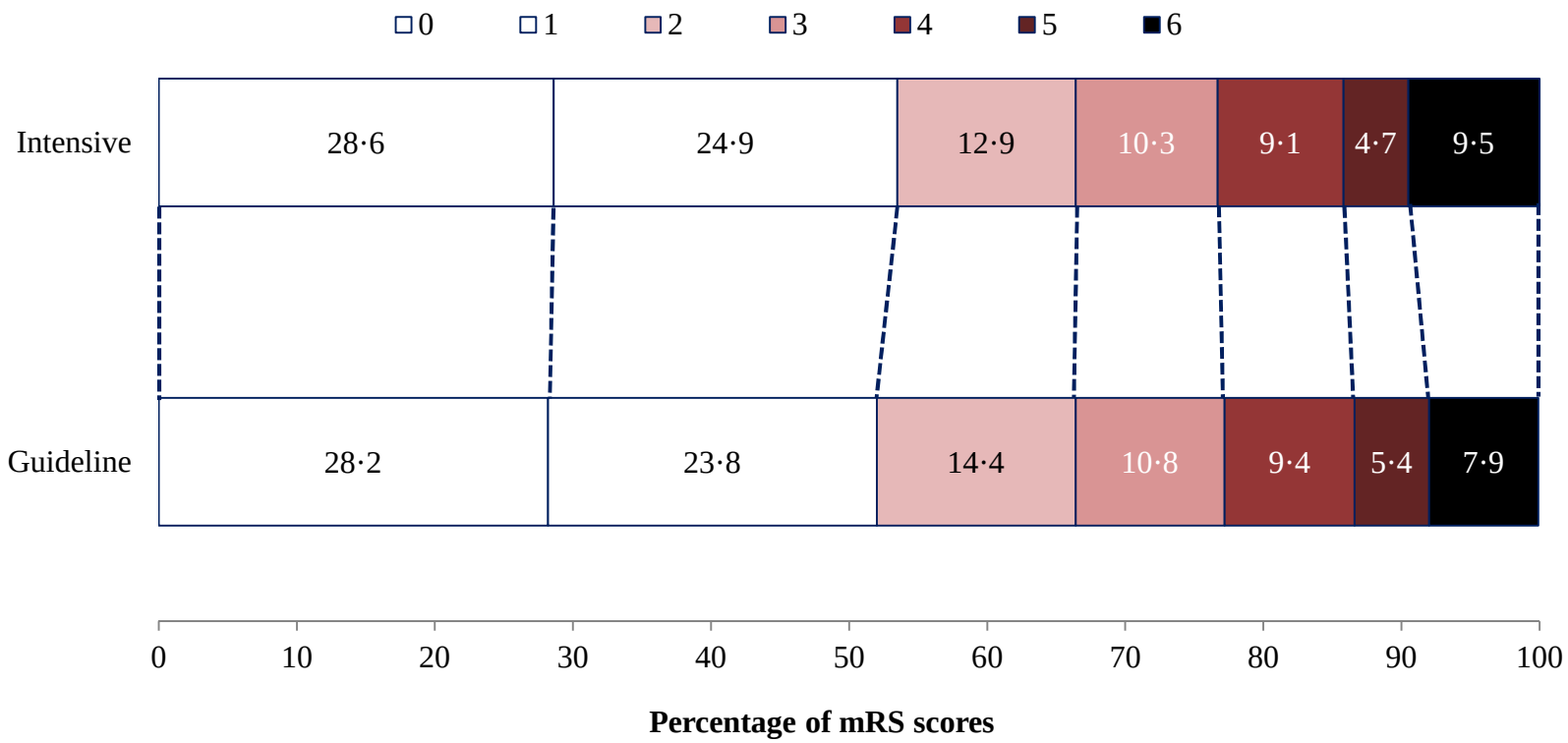
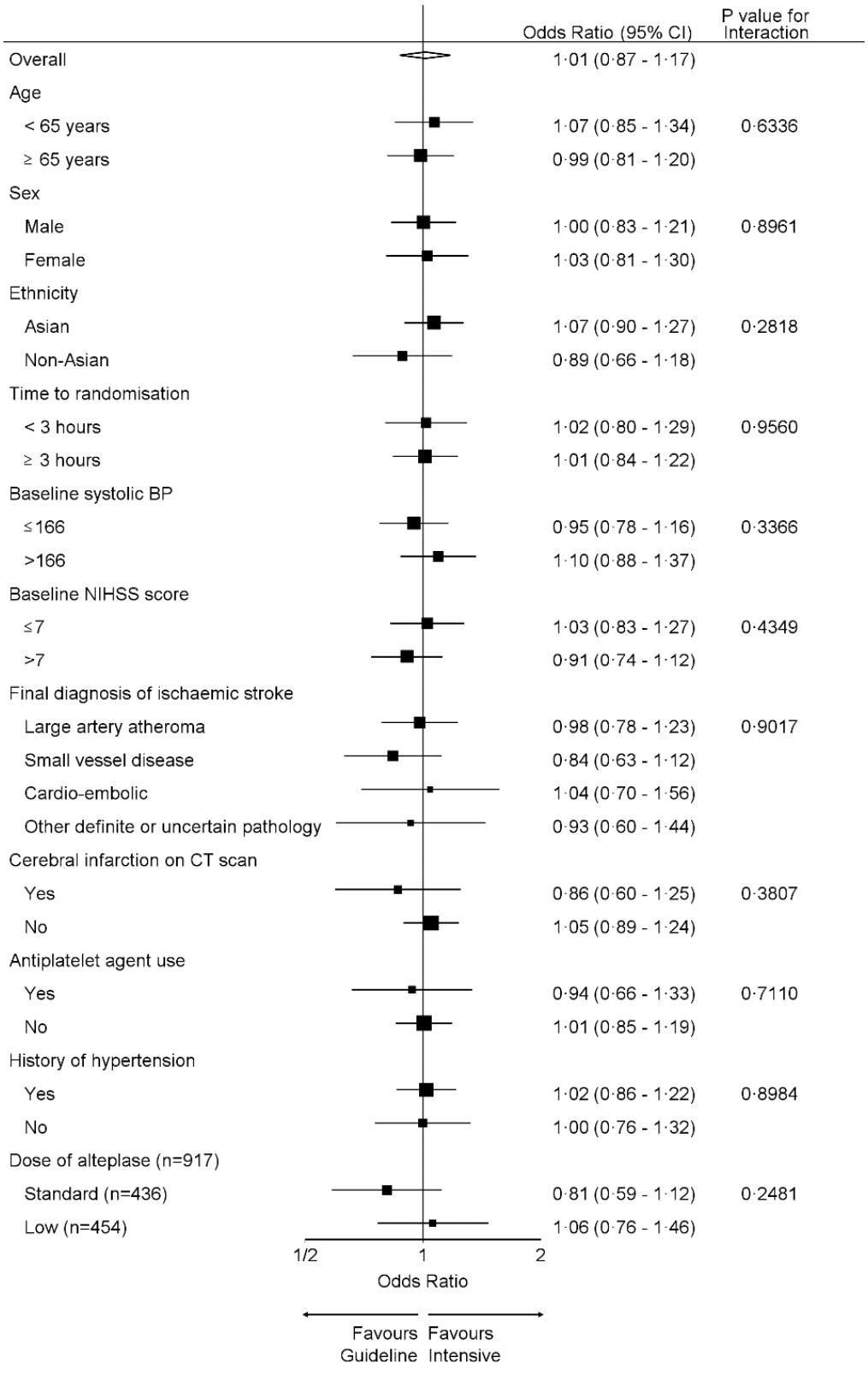


Figure 4: Primary outcome by pre-specified subgroups



Supplementary Appendix

This appendix formed part of the original submission and has been peer reviewed.
We post it as supplied by the authors.

Supplement to: Anderson CS, Huang Y, Lindley RI, et al. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international randomised, open-label, blinded-endpoint phase 3 trial. Lancet 2019 Published on line Feb XX http://

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Monitoring of the trial

1. Schedule for Monitoring of Sites

Regionally based research staff undertook quality control activities necessary for the conduct of the trial in accordance with the protocols, applicable guidelines and regulations. The first monitoring visit following initiation and activation of the site took place after a site had randomised three patients. The second monitoring visit took place after every 10–20 patients had been randomised. Subsequent monitoring visits took place after every 20–50 patients had been randomised after the previous visit, although the interval for monitoring visits was longer or shorter according to the rate of patient enrolment, quality issues, trial site compliance, or other trial site-specific issues. All sites were monitored at least every 12 months. Any significant deviation from the planned monitoring timelines was explained and documented in the monitoring visit report, and the monitoring plan was amended if appropriate.

The monitoring visit served to obtain 100% source data verification of the following data for all patients randomised: patient consent forms (patient consent forms were reviewed for compliance with ICH GCP); patient existence; diagnosis of ischaemic stroke; all outcome data; treatment allocation; and all serious adverse event (SAE) forms to source verification.

For 10 of randomly selected randomised patients, or patients identified by the International Coordinating Centre (ICC) or Regional Coordinating Centre (RCC), all data entered in the electronic case record form (eCRF) were verified against source data.

At the end of the study, 110 sites had received at least 1 interim monitoring visit and the median number of monitoring visits amongst these sites was 3; the mean number of monitoring visits was 4·4. A total of 483 monitoring visits were conducted: 84·6% of sites were visited 1 to 6 times, and 15·4% of sites were visited between 7 and 13 times.

Definitions of protocol violations and deviations

Protocol deviation / violations were defined as any unapproved changes, or departures from the study design or procedures of the study protocol that are under the investigator’s control and that had not been reviewed and approved by the ICC, ethics committee (EC)/institutional review board (IRB). Protocol deviation / violations were divided into 2 categories: 'major (reportable) violations' and 'minor (non-reportable) violations' which are also called 'Protocol Deviations'.

Major (reportable) Protocol Violations

Major protocol violations were any unapproved changes in the research study design and/or procedures that are within the investigator’s control and not in accordance with the approved study protocol that may have affected the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. All major violations were required to be reported to the relevant local ethics committee, regulatory authority and/or sponsor in keeping with relevant national guidance and/or conforming to national timelines for reporting. The ICC criteria for defining major violations included any of the following:

- the violation had harmed, or posed a significant or substantive risk of harm, to the research participant;
- The violation resulted in a change to the participant’s clinical or emotional condition or status;
- The violation had damaged the scientific completeness or soundness of the data collected for the study;

- The violation had evidence of wilful or knowing misconduct on the part of the investigator(s);
- The violation involved serious or continuing noncompliance with federal, state or local regulations.

Examples of major protocol violations included, but were not limited to:

1) enrolment of participants who did not meet the eligibility requirements;
2) failure to obtain informed consent prior to any study-specific tests/procedures;
3) failure to follow protocol procedures that specifically related to the primary safety or efficacy endpoints of the study.

Minor (non-reportable) Protocol Violations (also called Protocol Deviations)

Minor protocol violations were any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the the approved study protocol that do not have a major impact on either the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Minor protocol violations were not necessarily reportable to the IRB/EC. ICC criteria for minor violations included all of the following:

- the violation did not harm or pose a significant risk of substantive harm to the research participant, and;
- the violation did not result in a change to the participant's clinical or emotional condition or status, and;
- the violation did not damage the completeness, accuracy and reliability of the data collected for the study, and;
- the violation did not result from wilful or knowing misconduct on the part of the investigator(s), and;
- the violation did not involve serious or continuing noncompliance with federal, state or local regulations.

Examples of minor protocol violations included, but are not limited to:

1) routine safety laboratory work for a participant without new clinical concerns and a history of previously normal laboratory values were inadvertently omitted at a study visit or performed outside of the protocol-defined window;
2) the patient was unable to complete the self-administered quality of life questionnaire when they were capable to doing so;
3) follow up visits / assessments were performed outside of protocol defined time points or time windows.

Details of the assessment of intracranial haemorrhage

There were 368 subjects with any intracranial haemorrhage, among whom 313 had their CT scans reviewed centrally for adjudication.

The definition of any intracranial haemorrhage was: any type of haemorrhage noted on brain imaging ≤7 days after randomisation and a positive response of haemorrhage was noted on any of the following sources: report as a serious adverse event (SAE); MedDRA coding of a SAE; any ICH on an adjudicated CT scan. Cross-checks of these three sources and of the hospital management form were routinely undertaken during the course of the study.

There were 55 subjects who did not have their CT scan adjudicated (ie no adjudicated scan):

1. 20 had a report of an intracranial haemorrhage on their case record form (CRF)
2. 4 had a report of an intracranial haemorrhage on the SAE form
3. 10 reported intracranial haemorrhage on the SAE form, and also had a MedDRA coding of an intracranial haemorrhage (clinical-reported intracranial haemorrhage).
4. 21 had a report of an intracranial haemorrhage on the SAE form and also had a MedDRA code of an intracranial haemorrhage (clinical-reported intracranial haemorrhage), and had a report of intracranial haemorrhage on a CRF.

The coding of intracerebral haemorrhage (ICH) on brain imaging used the following criteria of haemorrhagic infarction (HI) and parenchymal haemorrhage (PH):

HI 1 (small petechiae along infarct margins)

HI 2 (confluent petechiae within infarcted area without space-occupying effect)

PH 1 (blood clot[s] in <30% of infarcted area with slight space-occupying effect)

PH 2 (blood clot[s] in >30% of infarcted area with substantial space-occupying effect)

In addition, independent assessors were asked to adjudicate if the haemorrhage was considered to be the predominant cause of neurological worsening, and if there was evidence of midline shift. These assessments enabled the following definitions of symptomatic intracerebral haemorrhage (sICH) to be adjudicated:

- 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);[1]
- any ICH associated with neurological deterioration (≥1 point change in NIHSS score) from baseline or death within 24 to 36 hours (NINDS);[2]
- any ICH with neurological deterioration (≥4 points on the NIHSS) from baseline or death within 24 to 36 hours (ECASS2);[3]
- any ICH with neurological deterioration (≥4 points increase on the NIHSS) from baseline or death within 36 hours (ECASS3);[4]
- either significant ICH (local or distant from the infarct) or significant haemorrhagic transformation of an infarct on brain imaging with clinically significant deterioration or death within the first 7 days of treatment (IST3);[5] and
- fatal ICH, any type 2 parenchymal ICH and death within 7 days.

References

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2. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333:1581-1587.
3. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). *Lancet* 1998; 352: 1245-1251.
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5. The IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomized controlled trial. *Lancet* 2012; 379:2352-2363.

Table S1: Reasons for excluding patients based on screening logs at non-UK sites (N=8999)*

Reason	n (%)
Age <18 years	393 (4·4)
Unable to receive treatment	568 (6·3)
Unable to achieve systolic blood pressure ≤185 mmHg	70 (0·8)
Definite contraindication for intravenous alteplase	2124 (23·6)
Clinician decision not to use intravenous alteplase	732 (8·1)
Patient considered unlikely to benefit from thrombolysis	181 (2·0)
Patient considered at very high likelihood of death within next 24 hours of stroke onset	175 (1·9)
Other medical illness that interferes with outcome assessments	242 (2·7)
Participation in another clinical trial	42 (0·5)
High likelihood that patient will not be able to be followed up	101 (1·1)
Patient and/or legal surrogate refused	1359 (15·1)
Patient or family unable to pay for alteplase	100 (1·1)
Other reasons	2156 (24·0)
Thrombolysis arm only - clinician decided against use of low-dose alteplase	14 (0·2)
BP lowering arm only - systolic BP <150 mmHg	607 (6·8)
BP lowering arm only - definite indication for intensive BP lowering therapy	17 (0·2)
BP lowering arm only - clinician decided against intensive BP lowering	118 (1·3)

*Data pertain to screening logs submitted from all hospital sites outside of the UK and outline the reasons for patients failing to meet the study inclusion criteria. Screening logs were not used in the UK, where 72,213 patients with acute ischaemic stroke were identified in the prospectively collected minimum data collection on all hospitalised patients with acute stroke collected as part of the Sentinel Stroke National Audit Program (SSNAP) during the study period. Of these, 62,825 were considered eligible but were not given intravenous alteplase, while 9388 received alteplase outside of the trial.

Table S2: Randomised patients included in the intention-to-treat population, by country

Country	**Total**
Australia	13
Brazil	175
Chile	54
China	1428
Colombia	6
Hong Kong	2
India	35
Italy	30
South Korea	0*
Singapore	16
Spain	4
Taiwan	16
Thailand	2
United Kingdom	259
Vietnam	156
Total	*2196*

*South Korea did not participate in the BP-control arm of the study; several patients were mistakenly randomised after completion of the alteplase dose-arm and were deleted from the database

Table S3: Randomised patients, by treatment arms in the trial

S3 [A] Study population according to randomised dose of intravenous alteplase

	BP control arm			
	Intensive group	Guideline group	Not randomised	Total
Alteplase-dose arm	N (%)	N (%)	N (%)	N (%)
Standard-dose	232 (5·1)	243 (5·3)	1168 (25·5)	1643 (35·9)
Low-dose	224 (4·9)	236 (5·2)	1194 (26·1)	1654 (36·2)
Not randomised	639 (14·0)	632 (13·9)	0 (0·0)	1271 (27·9)
Total	1092 (23·9)	1118 (24·5)	2362 (51·7)	*4572 (100)*

S3 [B] Study population according to actual administered dose of intravenous alteplase*

	BP control arm			
	Intensive group	Guideline group	Not randomised	Total
Alteplase-dose	N (%)	N (%)	N (%)	N (%)
Standard-dose	737 (16·2)	729 (16·0)	1167 (25·6)	2633 (57·8)
Low-dose	374 (8·2)	347 (7·6)	1194 (26·2)	1915 (42·0)
Missing	4	5	0	9
Total	1092 (23·9)	1118 (24·5)	2362 (51·7)	*4572 (100)*

*After completion of the alteplase-dose arm of the study, participants allocated to an alteplase-dose arm were based on cut-off dose of 0.75ml/kg that was actually given

BP denotes blood pressure

Table S4: Compliance with trial treatment protocol and method of 90 day outcome assessment

Outcome	Intensive BP lowering (N=1115) n\N (%)	Standard BP control (N=1081) n\N (%)
Randomisation violations		
Acute stroke syndrome not ischaemic stroke	1/1115 (0·1)	0/1081 (0·0)
Dependent pre-stroke	1/1115 (0·1)	1/1081 (0·1)
Significant comorbid condition	1/1115 (0·1)	1/1081 (0·1)
Systolic BP >185 mmHg	14/1115 (1·3)	16/1081 (1·5)
Systolic BP <150 mmHg	3/1115 (0·3)	1/1081 (0·1)
Other	2/1115 (0·2)	2/1081 (0·2)
Treatment compliance		
Alteplase not given	7/1115 (0·6)	7/1081 (0·6)
BP lowering treatment protocol not followed	9/1115 (0·8)	47/1081 (4·3)
Unblinded outcome assessment	25/1115 (2·2)	26/1081 (2·4)
Method of 90 day outcome assessment		
In-person assessment	178/1021 (17·4)	161/971 (16·6)
Telephone assessment	825/1021 (80·8)	800/971 (82·4)
Assessor predicted treatment allocation	10/978 (1·0)	10/978 (1·0)

BP denotes blood pressure

Table S5: Use of alteplase, and BP lowering treatment and other management, from randomisation to Day 7

	Intensive group (N=1081)	Guideline group (N=1115)	p value
Alteplase treatment			
Any given	1070/1081 (99·0)	1105/1115 (99·1)	0·7714
Bolus dose, mg	6·1 (2·4)	6·0 (1·3)	0·2493
Infusion over 60 mins dose, mg	49·1 (13·5)	48·8 (13·6)	0·5087
Patients outside therapeutic range	25/1080 (2·3)	28/1115 (2·5)	0·7644
Time from randomisation to treatment, mins	-2·9 (-38·6–7·5)	-3·4 (-37·7–7·0)	0·8120
Time from stroke onset to treatment, mins	181 (140–225)	185 (140–225)	0·5753
BP Management			
Any blood pressure medication taken in first 24 hours	858/1071 (80·1)	602/1108 (54·3)	<0·0001
Time from alteplase to treatment, mins	20 (0–85)	30 (0–153)	0·0925
Time from randomisation to treatment, mins	11·3 (-2·3–43·1)	18·3 (-19·6–128·1)	0·0706
Time from stroke onset to treatment, mins	220 (161–275)	240 (180–331)	0·0004
Method of iv medication administration			
Bolus	307/1068 (28·7)	166/1108 (15·0)	<0·0001
Infusion	497/1069 (46·5)	301/1108 (27·2)	<0·0001
Number of different iv medications taken			
1	498/1071 (46·5)	324/1108 (29·2)	<0·0001
2	153/1071 (14·3)	88/1108 (7·9)	
≥3	46/1071 (4·3)	21/1108 (1·9)	
Systolic BP at 24 hours, mmHg	139 (15)	144 (18)	<0·0001
Average systolic BP within 24 hours, mmHg	144 (10)	150 (12)	<0·0001
Any iv BP lowering treatment in first 24 hours	671/1071 (62·7)	391/1108 (35·3)	<0·0001
Any iv BP lowering treatment in days 2–7	396/1063 (37·3)	257/1091 (23·6)	<0·0001
Other management			

	Intensive group (N=1081)	Guideline group (N=1115)	p value
Cerebral angiogram undertaken	55/1078 (5·1)	53/1114 (4·8)	0·7095
Occluded cerebral vessel identified	32/54 (59·3)	29/53 (54·7)	0·6351
Endovascular clot retrieval used	25/55 (45·5)	17/53 (32·1)	0·1539
Intubation and ventilation	52/1063 (4·9)	44/1091 (4·0)	0·3342
Fever occurrence	183/1063 (17·2)	190/1091 (17·4)	0·9025
Fever treated	161/990 (16·3)	166/997 (16·6)	0·8159
Nasogastric feeding given	172/1063 (16·2)	185/1091 (17·0)	0·6281
Patient mobilised by therapist	414/1063 (38·9)	435/1091 (39·9)	0·6604
Compression stockings used	88/1063 (8·3)	81/1091 (7·4)	0·4611
Subcutaneous heparin used	228/1081 (21·1)	225/1115 (20·2)	0·5974
Any antithrombotic agent (antiplatelet or heparin) used in first 24 hours	135/1078 (12·5)	152/1112 (13·7)	0·4269
Iv traditional Chinese medicine administered	470/1063 (44·2)	483/1091 (44·3)	0·9788
Iv steroids administered	25/1063 (2·4)	17/1091 (1·6)	0·1829
Iv mannitol administered	117/1071 (10·9)	129/1108 (11·6)	0·5964
Hemicraniectomy performed	9/1063 (0·8)	13/1091 (1·2)	0·4260
Any neurosurgery performed	19/1081 (1·8)	28/1115 (2·5)	0·2225
Any stroke unit admission	475/1063 (44·7)	481/1091 (44·1)	0·7804
Any intensive care unit admission	211/1063 (20·8)	219/1090 (20·1)	0·6878
Any rehabilitation given	494/1063 (46·5)	538/1091 (49·3)	0·1871
Decision to withdrawal active care	32/1063 (3·0)	24/1091 (2·2)	0·2373

Data are n (%), mean (standard deviation), or median (interquartile interval)

BP denotes blood pressure, iv intravenous

Table S6: Blood pressure lowering treatment

	Intensive group (N=1081)	Guideline group (N=1115)	p value
BP lowering in the first 24 hours after randomisation			
Minimum (SD) systolic BP within 24 hours, mmHg	125 (12)	131 (159)	<0·0001
Maximum (SD) systolic BP within 24 hours, mmHg	164 (16)	168 (16)	<0·0001
Intravenous agent used			
labetalol	127/1071 (11·9)	58/1108 (5·2)	<0·0001
metoprolol	6/1071 (0·6)	5/1108 (0·5)	0·7198
atenolol	1/1071 (0·1)	2/1108 (0·2)	0·5834
nicardipine	77/1071 (7·2)	48/1108 (4·3)	0·0041
clevidipine	1/1071 (0·1)	1/1108 (0·1)	0·9808
nimodipine	191/1071 (17·8)	95/1108 (8·6)	<0·0001
nifedipine	23/1071 (2·1)	10/1108 (0·9)	0·0174
urapidil	6/1071 (0·6)	5/1108 (0·5)	0·7198
sodium nitroprusside	145/1071 (13·5)	70/1108 (6·3)	<0·0001
nitroglycerin	106/1071 (9·9)	31/1108 (2·8)	<0·0001
isosorbide dinitrate	11/1071 (1·0)	5/1108 (0·5)	0·1155
frusemide	58/1071 (5·4)	49/1108 (4·4)	0·2835
prazosin	2/1071 (0·2)	2/1108 (0·2)	0·9729
hydralazine	16/1071 (1·5)	10/1108 (0·9)	0·2037
clonidine	11/1071 (1·0)	3/1108 (0·3)	0·0272
enalapril	6/1071 (0·6)	3/1108 (0·3)	0·2922
Other medication(s)	50/1071 (4·7)	44/1108 (4·0)	0·4231
Topical nitrates used	60/1070 (5·6)	26/1108 (2·3)	<0·0001

	Intensive group (N=1081)	Guideline group (N=1115)	p value
Oral agents used			
angiotensin converting enzyme inhibitor / angiotensin II receptor antagonist	238/1071 (22·2)	129/1108 (11·6)	<0·0001
diuretic	65/1071 (6·1)	53/1108 (4·8)	0·1849
beta blocker	70/1071 (6·5)	88/1108 (7·9)	0·2057
calcium channel blocker	268/1071 (25·0)	154/1108 (13·9)	<0·0001
oral sympathetic antagonist	5/1071 (0·5)	10/1108 (0·9)	0·2188
Other medication(s)	51/1071 (4·8)	64/1108 (5·8)	0·2898
BP lowering treatment in Days 2-7			
Any BP medication taken	772/1063 (72·6)	689/1091 (63·2)	<0·0001
Any iv BP lowering treatment	439/1063 (41·3)	321/1091 (29·4)	<0·0001
Number of different iv medications taken			
1	273/1063 (25·7)	217/1091 (19·9)	<0·0001
2	106/1063 (10·0)	70/1091 (6·4)	
≥3	42/1063 (4·0)	23/1091 (2·1)	
BP lowering treatment at Day 90			
Any BP lowering treatment at Day 90	719/968 (74·3)	709/1018 (69·7)	0·0246

Data are n (%) and mean (SD)
BP denotes blood pressure, SD standard deviation

Table S7: Systolic and diastolic blood pressures, and differences, by time-points up to 7 days

[A] Systolic

Time point	Intensive Group (N=1081)			Guideline group (N=1115)			BP difference			
	n	Mean	SD	n	Mean	SD	Mean	SE of mean	Lower 95CI	Upper 95CI
Randomisation	1081	165·3	9·2	1115	165·2	9·2	0·2	0·4	-0·6	0·9
15min	1054	155·3	16·7	1092	157·8	16·9	-2·5	0·7	-3·9	-1·1
30min	1056	151·8	16·8	1083	155·9	17·1	-4·0	0·7	-5·5	-2·6
45min	1046	148·9	16·2	1079	153·6	17·1	-4·7	0·7	-6·1	-3·3
1hr	*1060*	*146·2*	*16·8*	*1090*	*152·7*	*17·0*	*-6·4*	*0·7*	*-7·9*	*-5·0*
6hr	1064	137·8	14·8	1095	145·9	17·7	-8·1	0·7	-9·5	-6·8
12hr	1061	137·3	15·1	1090	143·8	17·3	-6·5	0·7	-7·9	-5·2
18hr	1056	138·0	15·0	1083	143·7	17·3	-5·8	0·7	-7·1	-4·4
24hr	*1045*	*138·8*	*15·0*	*1075*	*144·1*	*17·8*	*-5·3*	*0·7*	*-6·7*	*-3·9*
Day 2 am	1052	138·2	15·0	1082	144·5	17·8	-6·3	0·7	-7·7	-4·9
Day 2 pm	1034	138·4	15·3	1063	145·2	18·4	-6·8	0·7	-8·2	-5·3
Day 3 am	1008	138·0	16·3	1048	144·0	18·0	-6·0	0·8	-7·5	-4·5
Day 3 pm	965	137·8	15·1	997	143·8	18·6	-6·0	0·8	-7·5	-4·5
Day 4 am	950	137·3	16·1	972	142·8	17·5	-5·5	0·8	-7·0	-4·0
Day 4 pm	922	137·6	15·7	935	142·7	18·7	-5·2	0·8	-6·7	-3·6
Day 5 am	906	137·8	15·2	922	141·4	18·3	-3·6	0·8	-5·1	-2·0
Day 5 pm	865	137·3	15·7	883	141·5	17·9	-4·2	0·8	-5·8	-2·6
Day 6 am	858	136·8	16·0	873	141·5	17·7	-4·7	0·8	-6·3	-3·1
Day 6 pm	828	136·4	15·8	847	140·2	18·1	-3·8	0·8	-5·4	-2·2
Day 7 am	825	136·6	15·5	838	140·3	18·0	-3·7	0·8	-5·3	-2·1
Day 7 pm	792	135·3	14·7	807	140·2	17·6	-4·8	0·8	-6·4	-3·3

BP denotes blood pressure, CI denotes confidence interval, SD standard deviation, SE standard error

[B] Diastolic

Time point	Intensive Group (N=1081)			Guideline Group (N=1115)			BP difference			
	n	Mean	SD	n	Mean	SD	Mean	SE of mean	Lower 95CI	Upper 95CI
Randomisation	1081	91·2	11·6	1115	90·7	11·3	0·5	0·5	-0·4	1·5
15min	1054	87·2	12·8	1092	87·8	13·5	-0·5	0·6	-1·6	0·6
30min	1056	85·9	12·5	1083	86·9	13·2	-1·0	0·6	-2·1	0·1
45min	1046	84·8	12·6	1080	86·0	12·9	-1·2	0·6	-2·3	-0·1
1hr	*1060*	*83·0*	*12·6*	*1090*	*85·5*	*12·9*	*-2·4*	*0·5*	*-3·5*	*-1·4*
6hr	1064	78·9	12·3	1095	81·9	12·7	-3·0	0·5	-4·0	-1·9
12hr	1061	78·1	12·3	1090	81·0	13·1	-2·9	0·5	-4·0	-1·9
18hr	1056	78·4	11·9	1083	81·0	12·5	-2·6	0·5	-3·7	-1·6
24hr	*1045*	*79·1*	*11·4*	*1075*	*80·8*	*12·7*	*-1·7*	*0·5*	*-2·7*	*-0·6*
Day 2 am	1052	78·7	12·0	1082	82·0	12·6	-3·3	0·5	-4·3	-2·2
Day 2 pm	1034	79·3	12·0	1063	81·6	12·9	-2·3	0·5	-3·4	-1·3
Day 3 am	1008	79·3	12·1	1048	81·8	13·1	-2·5	0·6	-3·6	-1·4
Day 3 pm	965	78·9	12·0	997	81·4	12·4	-2·4	0·6	-3·5	-1·4
Day 4 am	950	79·5	11·9	972	82·0	12·6	-2·4	0·6	-3·5	-1·3
Day 4 pm	922	79·0	11·4	935	80·9	12·2	-1·9	0·5	-3·0	-0·8
Day 5 am	906	79·8	11·7	923	81·6	12·3	-1·8	0·6	-2·9	-0·7
Day 5 pm	865	78·9	11·2	883	81·0	11·8	-2·1	0·5	-3·2	-1·1
Day 6 am	858	79·5	11·6	873	81·2	11·9	-1·7	0·6	-2·8	-0·5
Day 6 pm	828	78·6	11·0	847	80·3	11·3	-1·8	0·5	-2·8	-0·7
Day 7 am	825	79·6	11·1	837	80·8	11·3	-1·2	0·6	-2·3	-0·2
Day 7 pm	792	78·5	10·5	806	80·3	11·5	-1·8	0·6	-2·9	-0·7

CI denotes confidence interval, SBP systolic blood pressure, SD standard deviation, SE standard error

Table S8: Subgroup analyses of the primary outcome, scores on the modified Rankin scale

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Total (N=2196) n\N (%)	OR	95%CI	p interaction
Age						
<65 years				1·07	0·85–1·34	0·6336
0	157/452 (34·7)	157/476 (33·0)	314/928 (33·8)			
1	125/452 (27·7)	127/476 (26·7)	252/928 (27·2)			
2	57/452 (12·6)	73/476 (15·3)	130/928 (14·0)			
3	48/452 (10·6)	50/476 (10·5)	98/928 (10·6)			
4	26/452 (5·8)	36/476 (7·6)	62/928 (6·7)			
5	16/452 (3·5)	9/476 (1·9)	25/928 (2·7)			
6	23/452 (5·1)	24/476 (5·0)	47/928 (5·1)			
≥65 years				0·99	0·81–1·20	
0	150/620 (24·2)	155/632 (24·5)	305/1252 (24·4)			
1	142/620 (22·9)	137/632 (21·7)	279/1252 (22·3)			
2	81/620 (13·1)	87/632 (13·8)	168/1252 (13·4)			
3	62/620 (10·0)	70/632 (11·1)	132/1252 (10·5)			
4	72/620 (11·6)	68/632 (10·8)	140/1252 (11·2)			
5	34/620 (5·5)	51/632 (8·1)	85/1252 (6·8)			
6	79/620 (12·7)	64/632 (10·1)	143/1252 (11·4)			
Sex						
Male				1·00	0·83–1·21	0·8961
0	200/674 (29·7)	197/676 (29·1)	397/1350 (29·4)			
1	174/674 (25·8)	159/676 (23·5)	333/1350 (24·7)			
2	79/674 (11·7)	106/676 (15·7)	185/1350 (13·7)			
3	67/674 (9·9)	75/676 (11·1)	142/1350 (10·5)			

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Total (N=2196) n\N (%)	OR	95%CI	p interaction
4	55/674 (8·2)	58/676 (8·6)	113/1350 (8·4)			
5	36/674 (5·3)	27/676 (4·0)	63/1350 (4·7)			
6	63/674 (9·3)	54/676 (8·0)	117/1350 (8·7)			
Female				1·03	0·81–1·30	
0	107/398 (26·9)	115/432 (26·6)	222/830 (26·7)			
1	93/398 (23·4)	105/432 (24·3)	198/830 (23·9)			
2	59/398 (14·8)	54/432 (12·5)	113/830 (13·6)			
3	43/398 (10·8)	45/432 (10·4)	88/830 (10·6)			
4	43/398 (10·8)	46/432 (10·6)	89/830 (10·7)			
5	14/398 (3·5)	33/432 (7·6)	47/830 (5·7)			
6	39/398 (9·8)	34/432 (7·9)	73/830 (8·8)			
Ethnicity						
Asian				1·07	0·90–1·27	0·2818
0	260/791 (32·9)	253/820 (30·9)	513/1611 (31·8)			
1	185/791 (23·4)	191/820 (23·3)	376/1611 (23·3)			
2	98/791 (12·4)	112/820 (13·7)	210/1611 (13·0)			
3	73/791 (9·2)	84/820 (10·2)	157/1611 (9·7)			
4	79/791 (10·0)	78/820 (9·5)	157/1611 (9·7)			
5	33/791 (4·2)	42/820 (5·1)	75/1611 (4·7)			
6	63/791 (8·0)	60/820 (7·3)	123/1611 (7·6)			
Non-Asian				0·89	0·66–1·18	
0	47/281 (16·7)	59/287 (20·6)	106/568 (18·7)			
1	82/281 (29·2)	72/287 (25·1)	154/568 (27·1)			
2	40/281 (14·2)	48/287 (16·7)	88/568 (15·5)			

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Total (N=2196) n\N (%)	OR	95%CI	p interaction
3	37/281 (13·2)	36/287 (12·5)	73/568 (12·9)			
4	19/281 (6·8)	26/287 (9·1)	45/568 (7·9)			
5	17/281 (6·0)	18/287 (6·3)	35/568 (6·2)			
6	39/281 (13·9)	28/287 (9·8)	67/568 (11·8)			
Time to randomisation						
< 3 hours				1·02	0·80–1·29	0·9560
0	126/411 (30·7)	131/436 (30·0)	257/847 (30·3)			
1	96/411 (23·4)	103/436 (23·6)	199/847 (23·5)			
2	49/411 (11·9)	55/436 (12·6)	104/847 (12·3)			
3	43/411 (10·5)	43/436 (9·9)	86/847 (10·2)			
4	38/411 (9·2)	42/436 (9·6)	80/847 (9·4)			
5	28/411 (6·8)	24/436 (5·5)	52/847 (6·1)			
6	31/411 (7·5)	38/436 (8·7)	69/847 (8·1)			
≥3 hours				1·01	0·84–1·22	
0	181/661 (27·4)	181/672 (26·9)	362/1333 (27·2)			
1	171/661 (25·9)	161/672 (24·0)	332/1333 (24·9)			
2	89/661 (13·5)	105/672 (15·6)	194/1333 (14·6)			
3	67/661 (10·1)	77/672 (11·5)	144/1333 (10·8)			
4	60/661 (9·1)	62/672 (9·2)	122/1333 (9·2)			
5	22/661 (3·3)	36/672 (5·4)	58/1333 (4·4)			
6	71/661 (10·7)	50/672 (7·4)	121/1333 (9·1)			
Baseline systolic BP						
≤166 mmHg				0·95	0·78–1·16	0·3366

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Total (N=2196) n\N (%)	OR	95%CI	p interaction
0	163/584 (27·9)	188/615 (30·6)	351/1199 (29·3)			
1	153/584 (26·2)	145/615 (23·6)	298/1199 (24·9)			
2	85/584 (14·6)	87/615 (14·1)	172/1199 (14·3)			
3	56/584 (9·6)	64/615 (10·4)	120/1199 (10·0)			
4	52/584 (8·9)	55/615 (8·9)	107/1199 (8·9)			
5	28/584 (4·8)	36/615 (5·9)	64/1199 (5·3)			
6	47/584 (8·0)	40/615 (6·5)	87/1199 (7·3)			
>166 mmHg				1·10	0·88–1·37	
0	144/488 (29·5)	124/493 (25·2)	268/981 (27·3)			
1	114/488 (23·4)	119/493 (24·1)	233/981 (23·8)			
2	53/488 (10·9)	73/493 (14·8)	126/981 (12·8)			
3	54/488 (11·1)	56/493 (11·4)	110/981 (11·2)			
4	46/488 (9·4)	49/493 (9·9)	95/981 (9·7)			
5	22/488 (4·5)	24/493 (4·9)	46/981 (4·7)			
6	55/488 (11·3)	48/493 (9·7)	103/981 (10·5)			
Baseline NIHSS score						
≤7				1·03	0·83–1·27	0·4349
0	220/553 (39·8)	225/552 (40·8)	445/1105 (40·3)			
1	178/553 (32·2)	159/552 (28·8)	337/1105 (30·5)			
2	66/553 (11·9)	75/552 (13·6)	141/1105 (12·8)			
3	41/553 (7·4)	35/552 (6·3)	76/1105 (6·9)			
4	23/553 (4·2)	31/552 (5·6)	54/1105 (4·9)			
5	11/553 (2·0)	11/552 (2·0)	22/1105 (2·0)			
6	14/553 (2·5)	16/552 (2·9)	30/1105 (2·7)			

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Total (N=2196) n\N (%)	OR	95%CI	p interaction
>7				0·91	0·74–1·12	
0	87/519 (16·8)	87/556 (15·6)	174/1075 (16·2)			
1	89/519 (17·1)	105/556 (18·9)	194/1075 (18·0)			
2	72/519 (13·9)	85/556 (15·3)	157/1075 (14·6)			
3	69/519 (13·3)	85/556 (15·3)	154/1075 (14·3)			
4	75/519 (14·5)	73/556 (13·1)	148/1075 (13·8)			
5	39/519 (7·5)	49/556 (8·8)	88/1075 (8·2)			
6	88/519 (17·0)	72/556 (12·9)	160/1075 (14·9)			
Subtype of ischaemic stroke						
Large artery disease				0·98	0·78–1·23	0·9017
0	121/455 (26·6)	123/494 (24·9)	244/949 (25·7)			
1	97/455 (21·3)	116/494 (23·5)	213/949 (22·4)			
2	65/455 (14·3)	73/494 (14·8)	138/949 (14·5)			
3	47/455 (10·3)	58/494 (11·7)	105/949 (11·1)			
4	57/455 (12·5)	60/494 (12·1)	117/949 (12·3)			
5	29/455 (6·4)	25/494 (5·1)	54/949 (5·7)			
6	39/455 (8·6)	39/494 (7·9)	78/949 (8·2)			
Small vessel disease				0·84	0·63–1·12	
0	124/333 (37·2)	122/289 (42·2)	246/622 (39·5)			
1	102/333 (30·6)	81/289 (28·0)	183/622 (29·4)			
2	43/333 (12·9)	38/289 (13·1)	81/622 (13·0)			
3	34/333 (10·2)	28/289 (9·7)	62/622 (10·0)			
4	19/333 (5·7)	10/289 (3·5)	29/622 (4·7)			
5	4/333 (1·2)	7/289 (2·4)	11/622 (1·8)			

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Total (N=2196) n\N (%)	OR	95%CI	p interaction
6	7/333 (2·1)	3/289 (1·0)	10/622 (1·6)			
Cardioembolic				1·04	0·70–1·56	
0	27/139 (19·4)	24/149 (16·1)	51/288 (17·7)			
1	29/139 (20·9)	29/149 (19·5)	58/288 (20·1)			
2	15/139 (10·8)	18/149 (12·1)	33/288 (11·5)			
3	17/139 (12·2)	17/149 (11·4)	34/288 (11·8)			
4	12/139 (8·6)	22/149 (14·8)	34/288 (11·8)			
5	7/139 (5·0)	20/149 (13·4)	27/288 (9·4)			
6	32/139 (23·0)	19/149 (12·8)	51/288 (17·7)			
Other definite/uncertain pathology				0·93	0·60–1·44	
0	24/115 (20·9)	29/136 (21·3)	53/251 (21·1)			
1	34/115 (29·6)	32/136 (23·5)	66/251 (26·3)			
2	13/115 (11·3)	30/136 (22·1)	43/251 (17·1)			
3	12/115 (10·4)	17/136 (12·5)	29/251 (11·6)			
4	9/115 (7·8)	10/136 (7·4)	19/251 (7·6)			
5	10/115 (8·7)	8/136 (5·9)	18/251 (7·2)			
6	13/115 (11·3)	10/136 (7·4)	23/251 (9·2)			
Cerebral infarction on CT scan						
Yes				0·86	0·60–1·25	0·3807
0	33/181 (18·2)	29/168 (17·3)	62/349 (17·8)			
1	39/181 (21·5)	42/168 (25·0)	81/349 (23·2)			
2	27/181 (14·9)	33/168 (19·6)	60/349 (17·2)			
3	28/181 (15·5)	21/168 (12·5)	49/349 (14·0)			
4	19/181 (10·5)	15/168 (8·9)	34/349 (9·7)			

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Total (N=2196) n\N (%)	OR	95%CI	p interaction
5	12/181 (6·6)	11/168 (6·5)	23/349 (6·6)			
6	23/181 (12·7)	17/168 (10·1)	40/349 (11·5)			
No				1·05	0·89–1·24	
0	274/891 (30·8)	283/939 (30·1)	557/1830 (30·4)			
1	228/891 (25·6)	221/939 (23·5)	449/1830 (24·5)			
2	111/891 (12·5)	127/939 (13·5)	238/1830 (13·0)			
3	82/891 (9·2)	99/939 (10·5)	181/1830 (9·9)			
4	79/891 (8·9)	89/939 (9·5)	168/1830 (9·2)			
5	38/891 (4·3)	49/939 (5·2)	87/1830 (4·8)			
6	79/891 (8·9)	71/939 (7·6)	150/1830 (8·2)			
Antiplatelet agent use						
Yes				0·94	0·66–1·33	0·7110
0	37/174 (21·3)	38/212 (17·9)	75/386 (19·4)			
1	41/174 (23·6)	54/212 (25·5)	95/386 (24·6)			
2	21/174 (12·1)	35/212 (16·5)	56/386 (14·5)			
3	20/174 (11·5)	27/212 (12·7)	47/386 (12·2)			
4	17/174 (9·8)	24/212 (11·3)	41/386 (10·6)			
5	11/174 (6·3)	16/212 (7·5)	27/386 (7·0)			
6	27/174 (15·5)	18/212 (8·5)	45/386 (11·7)			
No				1·01	0·85–1·19	
0	270/898 (30·1)	274/895 (30·6)	544/1793 (30·3)			
1	226/898 (25·2)	209/895 (23·4)	435/1793 (24·3)			
2	117/898 (13·0)	125/895 (14·0)	242/1793 (13·5)			
3	90/898 (10·0)	93/895 (10·4)	183/1793 (10·2)			

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Total (N=2196) n\N (%)	OR	95%CI	p interaction
4	81/898 (9·0)	80/895 (8·9)	161/1793 (9·0)			
5	39/898 (4·3)	44/895 (4·9)	83/1793 (4·6)			
6	75/898 (8·4)	70/895 (7·8)	145/1793 (8·1)			
History of hypertension						
Yes				1·02	0·86–1·22	0·8984
0	212/768 (27·6)	219/792 (27·7)	431/1560 (27·6)			
1	189/768 (24·6)	181/792 (22·9)	370/1560 (23·7)			
2	99/768 (12·9)	109/792 (13·8)	208/1560 (13·3)			
3	78/768 (10·2)	85/792 (10·7)	163/1560 (10·4)			
4	71/768 (9·2)	78/792 (9·8)	149/1560 (9·6)			
5	38/768 (4·9)	45/792 (5·7)	83/1560 (5·3)			
6	81/768 (10·5)	75/792 (9·5)	156/1560 (10·0)			
No				1·00	0·76–1·32	
0	95/304 (31·3)	93/315 (29·5)	188/619 (30·4)			
1	78/304 (25·7)	82/315 (26·0)	160/619 (25·8)			
2	39/304 (12·8)	51/315 (16·2)	90/619 (14·5)			
3	32/304 (10·5)	35/315 (11·1)	67/619 (10·8)			
4	27/304 (8·9)	26/315 (8·3)	53/619 (8·6)			
5	12/304 (3·9)	15/315 (4·8)	27/619 (4·4)			
6	21/304 (6·9)	13/315 (4·1)	34/619 (5·5)			
Dose of intravenous alteplase						
Standard-dose				0·81	0·59–1·12	0·2481
0	63/224 (28·1)	69/239 (28·9)	132/463 (28·5)			

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Total (N=2196) n\N (%)	OR	95%CI	p interaction
1	43/224 (19·2)	54/239 (22·6)	97/463 (21·0)			
2	26/224 (11·6)	40/239 (16·7)	66/463 (14·3)			
3	26/224 (11·6)	18/239 (7·5)	44/463 (9·5)			
4	27/224 (12·1)	26/239 (10·9)	53/463 (11·4)			
5	11/224 (4·9)	17/239 (7·1)	28/463 (6·0)			
6	28/224 (12·5)	15/239 (6·3)	43/463 (9·3)			
Low-dose				1·06	0·76–1·46	
0	64/221 (29·0)	66/233 (28·3)	130/454 (28·6)			
1	45/221 (20·4)	44/233 (18·9)	89/454 (19·6)			
2	32/221 (14·5)	33/233 (14·2)	65/454 (14·3)			
3	25/221 (11·3)	29/233 (12·4)	54/454 (11·9)			
4	21/221 (9·5)	28/233 (12·0)	49/454 (10·8)			
5	13/221 (5·9)	10/233 (4·3)	23/454 (5·1)			
6	21/221 (9·5)	23/233 (9·9)	44/454 (9·7)			

BP denotes blood pressure, CT computerised tomography, NIHSS National Institutes of Health Stroke Scale, OR odds ratio

Table S9: Primary causes of death

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	OR	95% CI	p value
Day 90					
Direct effects of primary event	47/1081 (4·3)	35/1115 (3·1)	1·40	0·90–2·19	0·1369
Acute intracerebral haemorrhage	15/1081 (1·4)	19/1115 (1·7)	0·81	0·41–1·61	0·5489
Recurrent stroke					
Intracerebral haemorrhage	-	-	-	-	-
Ischaemic stroke	4/1081 (0·4)	2/1115 (0·2)	2·07	0·38–11·31	0·4024
Undifferentiated stroke	0/1081 (0·0)	1/1115 (0·1)	-	-	0.9999
Acute myocardial infarction/coronary event	2/1081 (0·2)	5/1115 (0·4)	0·41	0·08–2·13	0·2892
Other vascular	7/1081 (0·6)	3/1115 (0·3)	2·42	0·62–9·37	0·2020
Non-vascular	27/1081 (2·5)	23/1115 (2·1)	1·22	0·69–2·13	0·4752
Day 7					
Direct effects of primary event	30/1081 (2·8)	30/1115 (2·7)	1·03	0·62–1·72	0·9032
Acute intracerebral haemorrhage	7/1081 (0·6)	15/1115 (1·3)	0·48	0·19–1·18	0·1083
Recurrent stroke					
Intracerebral haemorrhage	-	-	-	-	-
Ischaemic stroke	1/1081 (0·1)	2/1115 (0·2)	0·52	0·05–5·69	0·5885
Undifferentiated stroke	-	-	-	-	-
Acute myocardial infarction/coronary event	2/1081 (0·2)	3/1115 (0·4)	0·69	0·11–4·12	0·6813
Other vascular	1/1081 (0·1)	0/1115 (0·0)	-	-	-
Non-vascular	3/1081 (0·3)	1/1115 (0·1)	3·10	0·32–29·85	0·3275

Table S10: Other secondary outcomes

Outcome	Intensive group (N=1081)	Guideline group (N=1115)	Effect estimate†	95% CI	p value
EQ-5D score, overall health utility					
N, mean (SD)*	1068 0·68 (0·41)	1104 0·68 (0·40)	0·01	-0·03–0·04	0·7415
Median (iqr)	0·85 (0·52–1·00)	0·85 (0·52–1·00)			
Living at home, n/N (%)	927/979 (94·7)	977/1027 (95·1)	0·91	0·61–1·36	0·6518
Living in residential care, n/N (%)	11/979 (1·1)	10/1027 (1·0)	1·16	0·49–2·73	0·7418
Duration of initial hospitalisation					
N, mean (SD)*	1024 14·7 (17·2)	1067 15·3 (18·3)	-0·60	-2·12–0·93	0·4431
Median	10 (6–15)	10 (6–15)			

EQ-5D denotes EuroQoL quality of life questionnaire, iqr interquartile range, SD standard deviation
*Mean difference for EQ-5D utility score and duration of hospitalisation.
†Hazard ratio for hospital discharge at day 90, and odds ratio for living at home and living in residential care

Table S11: Improvement in functional outcome (defined by shift in mRS scores) by baseline severity of neurological impairment (defined by scores on the NIHSS)

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	OR	95%CI		P interaction
0 to 5			1·10	0·85	1·43	0·5874
0	172/373 (46·1)	177/385 (46·0)				
1	112/373 (30·0)	99/385 (25·7)				
2	45/373 (12·1)	50/385 (13·0)				
3	21/373 (5·6)	27/385 (7·0)				
4	10/373 (2·7)	17/385 (4·4)				
5	8/373 (2·1)	5/385 (1·3)				
6	5/373 (1·3)	10/385 (2·6)				
6 to 10			1·03	0·80	1·34	
0	89/356 (25·0)	88/368 (23·9)				
1	105/356 (29·5)	112/368 (30·4)				
2	51/356 (14·3)	60/368 (16·3)				
3	51/356 (14·3)	36/368 (9·8)				
4	34/356 (9·6)	40/368 (10·9)				
5	11/356 (3·1)	13/368 (3·5)				
6	15/356 (4·2)	19/368 (5·2)				
11 to 15			0·85	0·60	1·20	
0	33/184 (17·9)	34/200 (17·0)				
1	31/184 (16·8)	33/200 (16·5)				
2	23/184 (12·5)	32/200 (16·0)				
3	25/184 (13·6)	37/200 (18·5)				

	Intensive group (N=1081)	Guideline group (N=1115)			
4	25/184 (13·6)	29/200 (14·5)			
5	13/184 (7·1)	13/200 (6·5)			
6	34/184 (18·5)	22/200 (11·0)			
≥16			0·88	0·59	1·29
0	13/159 (8·2)	13/155 (8·4)			
1	19/159 (11·9)	20/155 (12·9)			
2	19/159 (11·9)	18/155 (11·6)			
3	13/159 (8·2)	20/155 (12·9)			
4	29/159 (18·2)	18/155 (11·6)			
5	18/159 (11·3)	29/155 (18·7)			
6	48/159 (30.2)	37/155 (23·9)			

mRS denotes modified Rankin scale, NIHSS National Institutes of Health Stroke Scale

Table S12: Classification of type of intracerebral haemorrhage, by treatment group

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	OR	95%CI		p value
HI1 (small petechiae along infarct margins)	39 (3·6)	47 (4·2)	0·85	0·55	1·31	0·4636
HI2 (confluent petechiae within infarcted area without space-occupying effect)	39 (3·6)	42 (3·8)	0·96	0·61	1·49	0·8433
PH1 (blood clot(s) in <30% of infarcted area with slight space-occupying effect)	33 (3·1)	43 (3·9)	0·79	0·49	1·25	0·3040
PH2 (blood clot(s) in >30% of infarcted area with substantial space-occupying effect)	25 (2·3)	40 (3·6)	0·64	0·38	1·06	0·0804
Any PH	56 (5·2)	80 (7·2·)	0·71	0·50	1·01	0·0535

CI denotes confidence interval, HI haemorrhagic infarction, OR odds ratio, PH parenchymal haemorrhage

Table S13: Serious adverse events (SAEs) during follow-up

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Odds ratio	95 CI	p value
All SAEs					
Number of events (including deaths)	277/1148 (24·1)	333/1204 (27·7)			
Number of fatal events	115/1148 (10·0)	91/1204 (7·6)			
Number of non-fatal events	162/1148 (14·1)	242/1204 (20·1)			
Number of subjects with any SAE	210/1081 (19·4)	244/1115 (21·9)	0·86	0·70–1·06	0·1554
SAE by category					
Intracranial haemorrhage	66/1081 (6·1)	104/1115 (9·3)	0·63	0·46–0·87	0·0050
Associated with major neurological deterioration	30/1081 (2·8)	43/1115 (3·9)	0·71	0·44–1·14	0·1594
Associated with minor neurological deterioration	15/1081 (1·4)	22/1115 (2·0)	0·70	0·36–1·35	0·2890
Subarachnoid haemorrhage	3/1081 (0·3)	3/1115 (0·3)	1·03	0·21–5·12	0·9697
Intracerebral haemorrhage	59/1081 (5·5)	100/1115 (9·0)	0·59	0·42–0·82	0·0017
Extracranial haemorrhage	7/1081 (0·6)	9/1115 (0·8)	0·80	0·30–2·16	0·6608
Ischaemic stroke	64/1081 (5·9)	67/1115 (6·0)	0·98	0·69–1·40	0·9302
Undifferentiated stroke	8/1081 (0·7)	11/1115 (1·0)	0·75	0·30–1·87	0·5343
Acute coronary stroke	17/1081 (1·6)	10/1115 (0·9)	1·77	0·80–3·87	0·1562
Other vascular	27/1081 (2·5)	23/1115 (2·1)	1·22	0·69–2·13	0·4952
Pneumonia	40/1081 (3·7)	34/1115 (3·0)	1·22	0·77–1·95	0·3987
Sepsis	8/1081 (0·7)	21/1115 (1·9)	0·39	0·17–0·88	0·0236
Fracture	2/1081 (0·2)	1/1115 (0·1)	2·06	0·19–22·81	0·5541
Other non-vascular	18/1081 (1·7)	26/1115 (2·3)	0·71	0·39–1·30	0·2672
Angioedema	0/1081 (0·0)	1/1115 (0·1)			
Other SAE	4/1081 (0·5)	7/1115 (0·6)	0·59	0·17–2·01	0·3978

By Subgroup: Fatal

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Odds ratio	95 CI	p value
Number of subjects with fatal SAE	102/1081 (9·4)	87/1115 (7·8)	1·23	0·91–1·66	0·1731
By category					
Intracranial haemorrhage	25/1081 (2·3)	23/1115 (2·1)	1·12	0·63–1·99	0·6890
Associated with major neurological deterioration	19/1081 (1·8)	20/1115 (1·8)	0·98	0·52–1·85	0·9490
Associated with minor neurological deterioration	4/1081 (0·4)	2/1115 (0·2)	2·07	0·38–11·31	0·4024
Subarachnoid haemorrhage	1/1081 (0·1)	0/1115 (0·0)			
Intracerebral haemorrhage	21/1081 (1·9)	22/1115 (2·0)	0·98	0·54–1·80	0·9589
Extracranial haemorrhage	0/1081 (0·0)	1/1115 (0·1)			
Ischaemic stroke	39/1081 (3·6)	34/1115 (3·0)	1·19	0·75–1·90	0·4660
Undifferentiated stroke	1/1081 (0·1)	0/1115 (0·0)			
Acute coronary stroke	11/1081 (1·0)	7/1115 (0·6)	1·63	0·63–4·21	0·3158
Other vascular	9/1081 (0·8)	2/1115 (0·2)	4·67	1·01–21·67	0·0489
Pneumonia	21/1081 (1·9)	16/1115 (1·4)	1·36	0·71–2·62	0·3572
Sepsis	4/1081 (0·4)	6/1115 (0·5)	0·69	0·19–2·44	0·5609
Other non-vascular	2/1081 (0·2)	2/1115 (0·2)	1·03	0·15–7·34	0·9753
By Subgroup: non-fatal					
Number of subjects with non-fatal SAE	126/1081 (11·7)	174/1115 (15·6)	0·71	0·56–0·91	0·0072
By category					
Intracranial haemorrhage	42/1081 (3·9)	82/1115 (7·4)	0·51	0·35–0·75	0·0005
Associated with major neurological deterioration	12/1081 (1·1)	24/1115 (2·2)	0·51	0·25–1·03	0·0589
Associated with minor neurological deterioration	11/1081 (1·0)	20/1115 (1·8)	0·56	0·27–1·18	0·1282
Subarachnoid haemorrhage	2/1081 (0·2)	3/1115 (0·3)	0·69	0·11–4·12	0·6813
Intracerebral haemorrhage	39/1081 (3·6)	79/1115 (7·1)	0·49	0·33–0·73	0·0004
Extracranial haemorrhage	7/1081 (0·6)	8/1115 (0·7)	0·90	0·33–2·50	0·8424

Outcome	Intensive group (N=1081) n\N (%)	Guideline group (N=1115) n\N (%)	Odds ratio	95 CI	p value
Ischaemic stroke	25/1081 (2·3)	33/1115 (3·0)	0·78	0·46–1·31	0·3457
Undifferentiated stroke	7/1081 (0·6)	11/1115 (1·0)	0·65	0·25–1·69	0·3819
Acute coronary stroke	6/1081 (0·6)	3/1115 (0·3)	2·07	0·52–8·29	0·3048
Other vascular	18/1081 (1·7)	21/1115 (1·9)	0·88	0·47–1·66	0·6988
Pneumonia	25/1081 (2·3)	22/1115 (2·0)	1·18	0·66–2·10	0·5829
Sepsis	4/1081 (0·4)	16/1115 (1·4)	0·26	0·09–0·77	0·0148
Fracture	2/1081 (0·2)	1/1115 (0·1)	2·06	0·19–22·81	0·5541
Other non-vascular	16/1081 (1·5)	24/1115 (2·2)	0·68	0·36–1·29	0·2415
Angioedema	0/1081 (0·0)	1/1115 (0·1)			
Other SAE	4/1081 (0·4)	7/1115 (0·6)	0·59	0·17–2·01	0·3978

Table S14: Blood pressure levels at 1 hour over the course of the trial, by treatment group

[A] Systolic blood pressure before and after the end of the alteplase-dose arm in August 2015

	Intensive group (N=1081)			Guideline group (N=1115)			BP difference			p value
Recruitment period	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**Mean**	**Lower 95%CI**	**Upper 95%CI**	**for interaction**
before August 2015	472	144·5	17·4	491	152·7	17·5	-8·2	-10·4	-6·0	0·0352
after August 2015	588	147·6	16·3	599	152·6	16·6	-5·1	-6·9	-3·2	

BP denotes, blood pressure, CI confidence interval, SD standard deviation

[B] Systolic blood pressure at yearly intervals throughout trial, by treatment group

	Intensive group (N=1081)			Guideline group (N=1115)			BP difference			p value
Recruitment year	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**Mean**	**Lower 95%CI**	**Upper 95%CI**	**for trend**
2012	44	147·6	14·8	45	157·6	18·6	-9·9	-16·9	-2·9	0·0414
2013	104	145·9	18·1	109	153·5	16·2	-7·7	-12·3	-3·1	
2014	200	144·0	18·6	207	153·0	17·9	-9·0	-12·6	-5·5	
2015	163	144·1	14·9	170	150·9	17·5	-6·8	-10·3	-3·3	
2016	197	147·1	15·8	203	150·7	17·1	-3·6	-6·8	-0·4	
2017	292	147·5	16·9	306	153·4	15·9	-5·9	-8·6	-3·3	
2018	60	150·1	16·8	50	154·3	17·6	-4·2	-10·7	2·3	

BP denotes blood pressure, CI confidence interval, SD standard deviation.

Table S15: Baseline characteristics in the guideline group, by use of any blood pressure lowering treatment in the first 24 hours

Variable	Treated (N=602)	Not treated (N=506)	p value
Time from stroke onset to randomisation (hrs), mean (SD)	3·39 (1·05)	3·33 (1·05)	0·3276
Female, n (%)	248/602 (41·2)	183/506 (36·2)	0·0871
Age (years), mean (SD)	67·9 (12·2)	66·1 (11·7)	0·0131
≥80, n (%)	107/602 (17·8)	63/506 (12·5)	0·0143
Asian ethnicity	417/ 602 (69·3)	400/506 (79·1)	0·0002
Systolic BP (mmHg), mean (SD)	167 (9)	163 (9)	<0·0001
Diastolic BP (mmHg), mean (SD)	92 (11)	90 (11)	0·0041
Heart rate (beats per minute), mean (SD)	81 (16)	77 (13)	<0·0001
NIHSS score*			
NIHSS, median (iqr)	8 (5-13)	7 (4-11)	0·0001
≥14, n (%)	134/602 (22·3)	81/506 (16·0)	0·0088
GCS score†			
GCS score, median (Q1 Q3)	15 (14-15)	15 (14-15)	0·0014
Severe (3-8), n (%)	23/602 (3·8)	17/506 (3·4)	0·6820
Hypertension, n (%)	455/602 (75·6)	336/506 (66·4)	0·0008
Currently treated hypertension, n (%)	311 602 (51·7)	205/506 (40·5)	0·0002
Previous stroke, n (%)	122/602 (20·3)	87/506 (17·2)	0·1929
Coronary artery disease, n (%)	102/602 (16·9)	52/506 (10·3)	0·0014
Other heart disease (valvular or other), n (%)	33/602 (5·5)	19/506 (3·8)	0·1758
Atrial fibrillation confirmed on ECG, n (%)	113/600 (18·8)	57/506 (11·3)	0·0005
Diabetes Mellitus, n (%)	152 602 (25·2)	111/506 (21·9)	0·1968
Hypercholesterolaemia, n (%)	81/602 (13·5)	48/506 (9·5)	0·0402
Current smoker, n (%)	114/601 (19·0)	111/506 (21·9)	0·2215
Pre-stroke function (mRS)			

Variable	Treated (N=602)	Not treated (N=506)	p value
No symptoms, n (%)	504/601 (83·9)	443/506 (87.5)	0·0820
No significant disability, n (%)	97/601 (16·1)	63/506 (12.5)	0·0820
Medication at time of admission			
Warfarin anticoagulation, n(%)	12/602 (2·0)	3 506 (0·6)	0·0445
Aspirin or other anti-platelet agent, n(%)	135/602 (22·4)	76/506 (15·0)	0·0018
Statin or other lipid lowering agent, n(%)	117/602 (19·4)	66/506 (13·0)	0·0043
Brain imaging features			
CT scan used, n (%)	592/602 (98·3)	498/506 (98·4)	0·9163
MRI scan used, n (%)	38/602 (6·3)	40/506 (7·9)	0·3019
Visible early ischaemic changes, n (%)	96/602 (15·9)	79/506 (15·6)	0·8792
Visible cerebral infarction, n (%)	88/602 (14·6)	79/506 (15·6)	0·6448
Visible cerebral infarction with mass effect, n (%)	7/602 (1·2)	7/506 (1·4)	0·7433
CT or MR angiogram show proximal occlusion, n (%)	62/601 (10·3)	29/506 (5·7)	0·0057
Final diagnosis at time of hospital separation‡			
Non-stroke, n (%)	9/589 (1·5)	8/502 (1·6)	0·9305
Presumed stroke pathology, n (%)			
Large artery disease	273/589 (46·3)	221/502 (44·0)	0·4418
Small vessel disease	117/589 (19·9)	172/502 (34·3)	<0·0001
Cardio-emboli	100/589 (17·0)	50/502 (10·0)	0·0008
Other or uncertain aetiology	90/589 (15·3)	51/502 (10·2)	0·0224

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

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

*Scores on the National Institutes of Health stroke scale (NIHSS).

†Scores on the Glasgow coma scale (GCS).

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

Table S16: Efficacy and safety outcomes in the guideline group, by use of intravenous blood pressure lowering treatment

Outcome	Treated n\N (%)	Non-treated n\N (%)	OR	95%CI		p value[a]
Death or disability (mRS score 2+3+4+5+6)						
Adjusted	330 599 (55·1)	198/503 (39·4)	1·61	1·23	2·11	0·0005
Per Protocol - adjusted	308/550 (56·0)	187/473 (39·5)	1·63	1·24	2·15	0·0005
Death or major disability (mRS score 3+4+5+6)						
Adjusted	242 599 (40·4)	127/503 (25·2)	1·70	1·28	2·27	0·0003
Symptomatic intracerebral haemorrhage						
SITS-MOST criteria	19/602 (3·2)	3/506 (0·6)	5·46	1·61	18·57	0·0065
NINDS criteria	60/602 (10·0)	24/506 (4·7)	2·22	1·36	3·63	0·0014
ECASS2 criteria	46/602 (7·6)	11/506 (2·2)	3·72	1·91	7·27	0·0001
ECASS3 criteria	27/602 (4·5)	3/506 (0·6)	7·87	2·37	26·11	0·0007
IST-3 criteria	31/602 (5·1)	6/506 (1·2)	4·52	1·87	10·93	0·0008
Clinician-reported	73/602 (12·1)	27/506 (5·3)	2·45	1·55	3·87	0·0001
Fatal (≤7days)	13/602 (2·2)	1/506 (0·2)	11·15	1·45	85·50	0·0204
Any intracranial haemorrhage	139/602 (23·1)	70/506 (13·8)	1·87	1·36	2·56	0·0001
Death at Day 90 - adjusted	65/601 (10·8)	22/506 (4·3)	1·96	1·15	3·33	0·0128
mRS categories (adjusted)						
0	131/599 (21·9)	181/503 (36·0)	0·59	0·47	0.73	<0·0001
1	138/599 (23·0)	124/503 (24·7)				
2	88/599 (14·7)	71/503 (14·1)				
3	73/599 (12·2)	46/503 (9·1)				
4	65/599 (10·9)	39/503 (7·8)				
5	39/599 (6·5)	20/503 (4·0)				
6 (death at 90 days)	65/599 (10·9)	22/503 (4·4)				
Any intracranial haemorrhage - adjusted	138/601 (23·0)	70/506 (13·8)	1·56	1·12	2·18	0·0093

ECASS denotes European Cooperative Acute Stroke Study; 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

Figure Legends

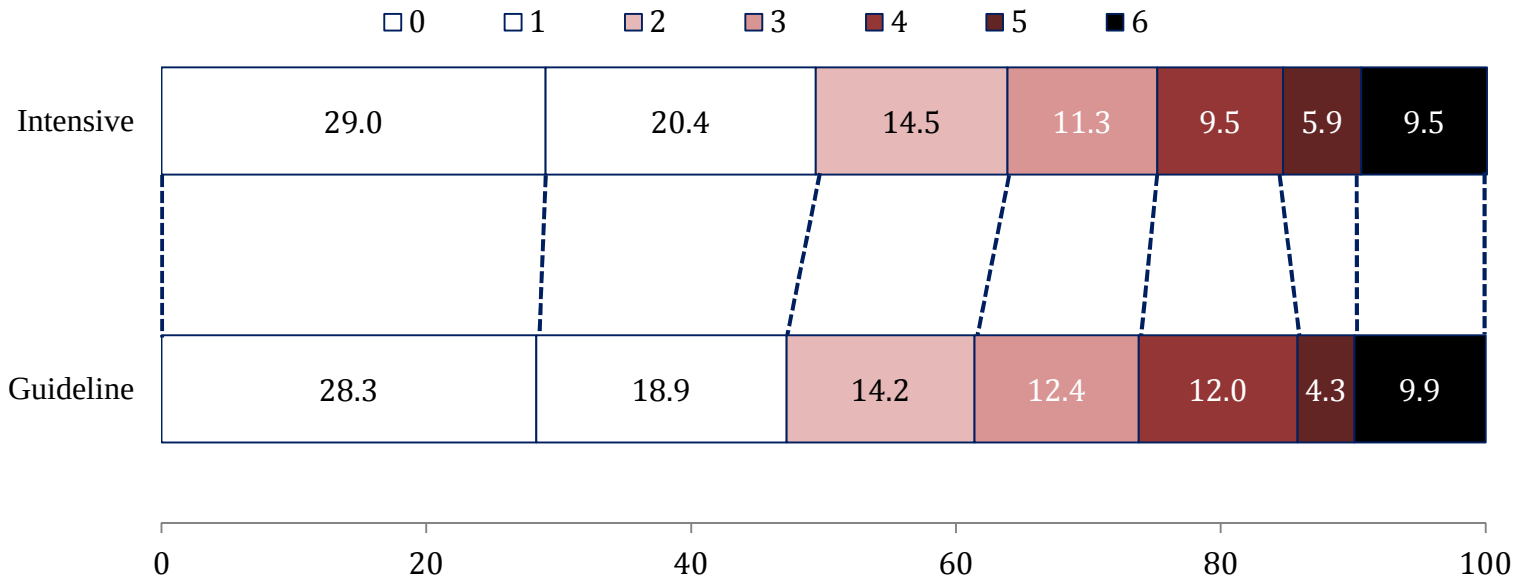
Figure S1: Modified Rankin scale (mRS) outcome at 90 days by treatment group for patients treated with [A] low-dose alteplase, and [B] standard-dose alteplase

Footnote: The figure shows the raw distribution of scores on the modified Rankin scale (mRS) at 90 days by low-dose and standard-dose trial arms. 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 S2: National Institutes of Health Stroke Scale score by quartiles for primary outcome

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, and have been split into quartiles. Black squares represent point estimates and horizontal lines represent 95% confidence intervals.

Figure S1 [A] low-dose alteplase arm (n=454)



Supplementary Figure 2[B] standard-dose alteplase (n=463)

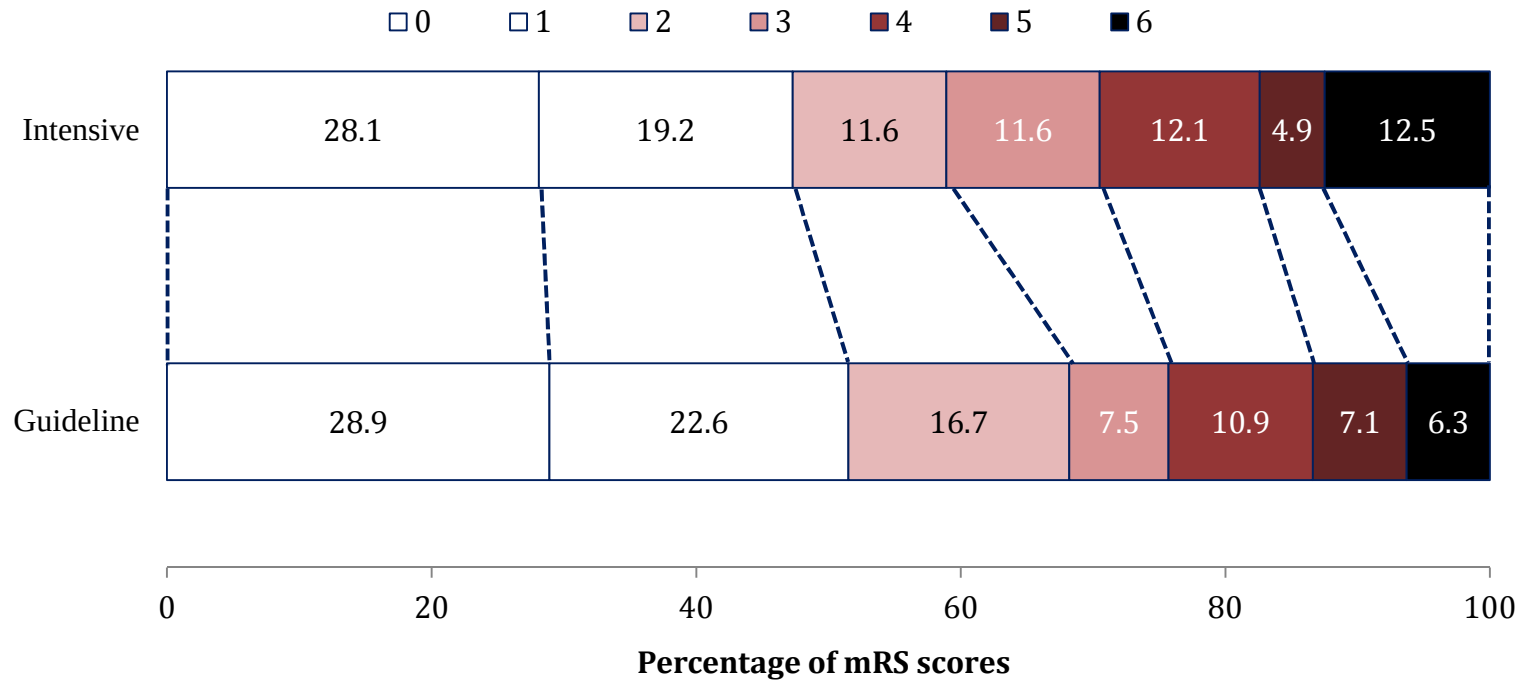


Figure S2: Primary outcome by quartiles of NIHSS score