Effects of intensive blood pressure lowering on cerebral ischaemia in thrombolysed patients: insights from the ENCHANTED trial

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eClinicalMedicine 2023;57: 101849

Published Online 15 February 2023
https://doi.org/10.1016/j.eclinm.2023.101849

Summary

Background **Intensive blood pressure lowering may adversely affect evolving cerebral ischaemia. We aimed to determine whether intensive blood pressure lowering altered the size of cerebral infarction in the 2196 patients who participated in the Enhanced Control of Hypertension and Thrombolysis Stroke Study, an international randomised controlled trial of intensive (systolic target 130–140 mm Hg within 1 h; maintained for 72 h) or guideline-recommended (systolic target <180 mm Hg) blood pressure management in patients with hypertension (systolic blood pressure >150 mm Hg) after thrombolysis treatment for acute ischaemic stroke between March 3, 2012 and April 30, 2018.**

Methods **All available brain imaging were analysed centrally by expert readers. Log-linear regression was used to determine the effects of intensive blood pressure lowering on the size of cerebral infarction, with adjustment for potential confounders. The primary analysis pertained to follow-up computerised tomography (CT) scans done**

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between 24 and 36 h. Sensitivity analysis were undertaken in patients with only a follow-up magnetic resonance imaging (MRI) and either MRI or CT at 24–36 h, and in patients with any brain imaging done at any time during follow-up. This trial is registered with ClinicalTrials.gov, number NCT01422616.

Findings There were 1477 (67.3%) patients (mean age 67.7 [12.1] y; male 60%, Asian 65%) with available follow-up brain imaging for analysis, including 635 patients with a CT done at 24–36 h. Mean achieved systolic blood pressures over 1–24 h were 141 mm Hg and 149 mm Hg in the intensive group and guideline group, respectively. There was no effect of intensive blood pressure lowering on the median size (ml) of cerebral infarction on follow-up CT at 24–36 h (0.3 [IQR 0.0–16.6] in the intensive group and 0.9 [0.0–12.5] in the guideline group; log Δmean −0.17, 95% CI −0.78 to 0.43). The results were consistent in sensitivity and subgroup analyses.

Interpretation Intensive blood pressure lowering treatment to a systolic target <140 mm Hg within several hours after the onset of symptoms may not increase the size of cerebral infarction in patients who receive thrombolysis treatment for acute ischaemic stroke of mild to moderate neurological severity.

Funding National Health and Medical Research Council of Australia; UK Stroke Association; UK Dementia Research Institute; Ministry of Health and the National Council for Scientific and Technological Development of Brazil; Ministry for Health, Welfare, and Family Affairs of South Korea; Takeda.

Keywords: Blood pressure; Acute ischaemic stroke; Clinical trial; Brain imaging; Cerebral infarction; Thrombolysis

Research in context

Evidence before this study

We searched PubMed and Embase, from inception to 3 June 2022, for studies which have assessed the association of blood pressure lowering and infarct size in patients with acute ischaemic stroke, using the keywords "ischaemic stroke", "blood pressure" and "infarct size/volume" without any language restriction. Few randomised controlled trials with small sample sizes report that early use of oral antihypertensive treatment does not change the size of cerebral infarction in patients with acute ischaemic stroke. While observational studies show conflicting results for a reduction in blood pressure being associated with larger size of infarction, uncertainty persists over whether different levels of blood pressure control influence cerebral infarction after thrombolysis treatment for acute ischaemic stroke.

Added value of this study

This imaging analysis pertains to data derived from the international ENCHANTED study, the only randomised controlled trial that has compared a management strategy of intensive blood pressure lowering towards a systolic target of <140 mm Hg within 1 h with the longstanding guideline-recommended level (systolic target <180 mm Hg) of control, during and for up to 72 h after, the use of intravenous thrombolysis treatment for eligible patients with acute ischaemic stroke. The primary analysis for the size of cerebral infarction, measured centrally using MiStar software on CT scans performed at 24–36 h post-randomisation, did not differ significantly between groups, after adjustment for various confounding variables. The neutral result was consistent in sensitivity analysis using all available follow-up brain imaging, and in analysis across 10 pre-specified subgroups of patients.

Implications of all the available evidence

These results provide evidence to reassure clinicians that intensive BP initiated within 6 h from the onset of symptoms to a systolic target of less than 140 mm Hg within 1 h may not significantly change the size of cerebral infarction in patients who receive intravenous thrombolysis after acute ischaemic stroke with predominantly mild to moderate levels of neurological severity. Further clinical trials are necessary to better define the safety and efficacy of this treatment in relation to the level of control of blood pressure and in certain high-risk patients, such as those who receive endovascular treatment for acute ischaemic stroke from large vessel occlusion.

Introduction

The role of intensive blood pressure lowering in patients with acute ischaemic stroke remains a controversial topic.[1] In the only randomised controlled trial specifically designed to address this issue specifically in patients eligible to receive thrombolysis treatment, the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED),[2] there was no benefit on functional recovery from the ancillary use of intensive (systolic blood pressure target lower than 140 mm Hg within 1 h) versus

standard (guideline-recommended systolic blood pressure lower than 180 mm Hg) management. However, the trial showed that all forms of intracranial haemorrhage were significantly less frequent in the intensive blood pressure lowering group. Why this effect did not translate into improvement of clinical outcome may have re-enforced established concerns that such treatment compromises the ischaemic penumbra from the complex interplay between reperfusion injury and collateral blood flow.

The application of endovascular thrombectomy for ischaemic stroke due to large-vessel occlusion, which has accelerated in use since ENCHANTED was completed, has drawn further attention on the role of controlling blood pressure as a means of reducing reperfusion injury and enhancing functional recovery. The 2021 Blood Pressure Target in Acute Stroke to Reduce hemorrhaGe After Endovascular Therapy (BP-TARGET) trial[3] showed that more intensive systolic blood pressure control (mean achieved in 24 h, 128 mm Hg) versus standard systolic blood pressure control (mean achieved in 24 h, 138 mm Hg) was safe but without showing any improvement in clinical outcomes in 324 patients after successful endovascular thrombectomy for acute ischaemic stroke from large-vessel occlusion of the anterior circulation. More recently, however, the Enhanced Control of Hypertension and Thrombectomy Stroke Study (ENCHANTED2/MT)[4] showed that intensive control of systolic blood pressure to lower than 120 mm Hg resulted in worse functional recovery in 816 patients who received endovascular thrombectomy for acute ischaemic stroke from any intracranial large-vessel occlusion. Herein, we present further analyses of the ENCHANTED 'blood pressure control' arm of the effects of intensive blood pressure lowering on the size of cerebral infarction identified on brain imaging obtained during the follow-up of participants as part of their routine standard of care.

Methods

Study design

This work is pre-specified secondary analysis of the 'blood pressure control' arm of ENCHANTED, a partial-factorial, international, open-label, blinded-endpoint trial conducted at 110 hospitals in 15 countries between March 2012 and April 2018. The design and main results are outlined elsewhere.[2,5] In brief, a total of 2196 patients with acute ischaemic stroke who fulfilled standard criteria for thrombolysis treatment with intravenous alteplase, and had an elevated systolic blood pressure (>150 mm Hg) were randomly assigned to intensive (systolic target 130–140 mm Hg within 1 h; maintained for 72 h) or guideline-recommended (systolic target <180 mm Hg) blood pressure management. The study protocol was approved by the ethics committee at each participating hospital, and written informed consent was obtained from all participants or their approved surrogate.

Procedures

Baseline demographic and clinical characteristics were collected upon hospital presentation and randomisation. Neurological severity was measured on the National Institutes of Health Stroke Scale (NIHSS; range 0–42, with higher scores indicating greater severity)[6] at baseline, and 24 and 72 h. The functional outcome of participants was assessed on the modified Rankin scale (range 0 [no symptoms] to 6 [death]), administered through telephone or in-person interview by trained researchers blind to treatment allocation, at 7 (or at hospital discharge, if earlier), 28 and 90 days. All computerised tomography (CT) and magnetic resonance imaging (MRI) on participants, undertaken at baseline (i.e. confirmation of diagnosis) and on follow-up at 24–36 h (routine assessment of infarct size and reperfusion injury), and at other time points as clinically indicated (i.e. neurological deterioration), were uploaded to a secure purpose-built web-based system for central analysis at The George Institute for Global Health. Training and instruction of clinician assessors in the interpretation of abnormalities on brain imaging included the structured interpretation of acute (presence/absence of acute ischaemic lesion, its size, swelling, any haemorrhagic transformation, arterial thrombus or angiography findings) and pre-stroke (old infarcts, leukoaraiosis, brain volume loss) imaging findings derived from the University of Edinburgh, and previously used in third International Stroke Trial (IST-3).[7] The brain imaging assessor group included a radiologist (GBZ) and three experienced neurologists (CC, LYZ, and SO), who undertook online training on the software and data forms, which included the rating of 21 CT scans from participants of the ENCHANTED alteplase-dose arm study.[8,9] Full details of their performance are provided in the Appendix (p 4).

The primary outcome was the size of post-thrombolysis cerebral infarction measured on follow-up brain imaging. The primary analysis was on CT scans undertaken at 24–36 h post-randomisation, as undertaken according to usual standard of care. Three sets of sensitivity analysis were conducted on other approaches to assessing the brain imaging: follow-up MRI alone at 24–36 h, combined measures from either a CT or MRI at 24–36 h, and measures from all follow-up brain imaging. In each analysis set, for patients with multiple scans at different time points, the earliest follow-up scan was selected for analysis. Secondary outcomes were intracranial haemorrhage and large parenchymal haematoma (PH2), defined according to the Heidelberg bleeding classification system,[10] and the type and volume of intracranial haemorrhage, location of cerebral infarction, and functional recovery according to scores on the modified Rankin scale at 90 days.

Brain imaging in Digital Imaging and Communications in Medicine (DICOM) format, identified only with a patient's unique study number, were used to measure the size of cerebral infarction (ml) by computer-assisted multi-slice morphometric and voxel threshold techniques using software MiStar version 3.2 (Apollo Medical Imaging Inc, Melbourne, VIC, Australia).[11] This software was automatically applied to each brain imaging (CT or MRI) slice to calculate the size of identifiable cerebral infarction (Hounsfield units for CT with hypodensity, imaging sequence for diffusion weighted imaging of MRI), which was then summed manually to calculate total size. Reliability of this method has been validated elsewhere.[12,13]

All follow-up scans were reviewed by at least one assessor; a second assessor confirmed any and parenchymal haemorrhage. If there was any disagreement, a third assessor was required to finalise the diagnosis and classification. Other brain imaging abnormalities, such as cerebral atrophy and old infarcts, were also collected. All assessors were blinded to treatment group, outcomes, and time of scan. Finally, 10% of all scans were double reviewed to assess inter-rater quality[14] (Appendix p 4).

Statistical analysis

The intention-to-treat approach was used for patients with available brain imaging. Due to skewed distribution of the size of cerebral infarction, log-linear regression models were used to determine the treatment effect of intensive blood pressure lowering on the size of cerebral infarction, with adjustment for pre-specified variables (age, sex, ethnicity, pre-morbid function [modified Rankin scale scores 0 or 1], pre-morbid use of antithrombotic agents [aspirin, other antiplatelet agent, or warfarin], history of stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomised dose of intravenous alteplase), and others covariates with a p value of <0.1 in univariate comparisons. To avoid infinity for log undetected size of cerebral infarction in building the models, the value 0.01 was used to replace size of 0. Logistic regression was used for the outcomes of intracranial haemorrhage and functional recovery (modified Rankin scale scores 2–6). The location of cerebral infarction, and the type and volume of intracranial haemorrhage, were compared between the two treatment groups, but only reported in univariate analysis due to the limited numbers of observations. Sensitivity analyses were in patients with MRI alone and a combination of measures on MRI/CT done at 24–36 h, and on any follow-up brain imaging. To understand if there was any modification of cerebral infarction and intracranial haemorrhage on the effect of intensive blood pressure lowering treatment on functional outcome, interaction terms were added to the adjusted models. Consistency of treatment effect across pre-specified subgroups was assessed through tests of interaction, by adding interaction terms to the statistical models for the main effects. Pre-specified subgroups included age (<65 vs ≥65 y), sex (male vs female), ethnicity (Asian vs non-Asian), time to randomisation (<3 vs ≥3 h), baseline systolic blood pressure (above vs below median), history of hypertension, neurological severity at baseline (above vs below median NIHSS scores), final pathological subtype, use of antiplatelet agent, and randomised dose of alteplase.

We also determined associations of the degree of '*attained control*' of blood pressure, defined as the mean of 5 time-points of systolic blood pressure measures reported between 1 and 24 h, and size of cerebral infarction in any follow-up scan (CT and MRI), with adjustment for pre-specified confounders that included age, sex, ethnicity, clinical severity (NIHSS scores), time to randomised blood pressure lowering, history of hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, previous stroke, pre-morbid disability, antithrombotic medication, trial arm, dose of intravenous alteplase, final pathological diagnosis of stroke, imaging modality (CT vs MRI), and time to second scan (<24 and ≥24 h). Two other parameters of systolic blood pressure control were also assessed in separate models: '*variability*', the standard deviation (SD) of the same measures between 1 and 24 h; and '*magnitude of early reduction*', the difference between the measures at randomisation and the lowest attained systolic blood pressure within 1 h. Because of a loss of observations due to missing data for some covariates, multiple imputation was conducted by chained equations with 30 imputations in the multivariable models. The associations of both continuous and categorical systolic blood pressure parameters and infarct size were explored in multivariable models, and checks were made for multivariable normality and multicollinearity.

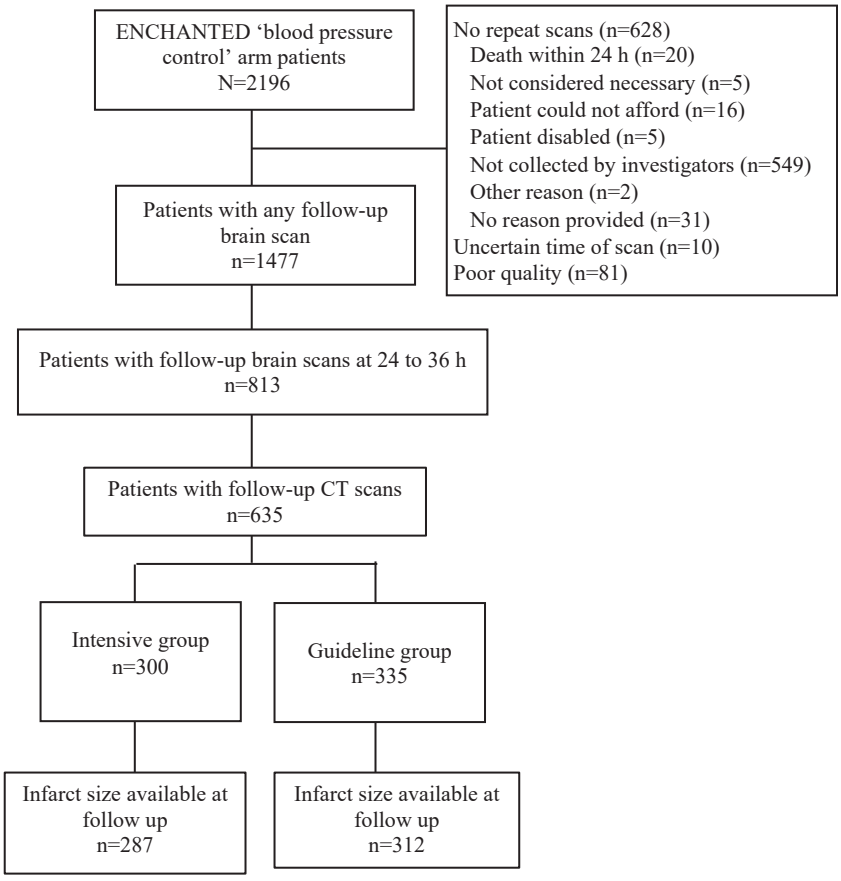
All tests are two-sided using a nominal level of α of 5%. SAS (version 9.2 or newer) was used in all analyses.

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The first (CC), second (MO) and corresponding authors (CSA and LS), had full access to all the study data and had final responsibility for the decision to submit the paper for publication.

Results

Of the 2196 patients who participated in the ENCHANTED 'blood pressure control' arm, there were 1477 (67.3%) with available follow-up brain imaging (Fig. 1), which were undertaken at a median time of 26.7 h (IQR 23.4–29.3) from the onset of symptoms. The most common reason for missing brain imaging data in 719 patients was investigators failing to upload the images (n = 549, 25.0%). Five sites accounted for



BP denotes blood pressure, CT computed tomography

Fig. 1: **Patient flow for primary analysis.**

75.8% of the missing brain images (Appendix pp 5–7). There were 813 (55.0%) patients with brain imaging undertaken at 24–36 h, which included 635 and 193 with CT and MRI, respectively, including 15 patients who had both CT and MRI (Appendix pp 21–23). Comparisons between patients with and without brain imaging showed many significant differences in various characteristics of patients, but most of these were of minor clinically significant. The key differences were that patients with brain imaging were less often Asian, free of pre-stroke symptoms, and of intracranial atheroma being the likely cause of the stroke, and greater in having clinical severity, treatment with antihypertensives, statins for hypercholesterolaemia, and antiplatelet therapy, than those without brain imaging (Appendix pp 8–10).

For the primary analysis on follow-up CT scans at 24–36 h, these 635 patients (mean age 68.9 years [SD 11.9], female 41.3%) had a median NIHSS score of 7 (IQR 4–12). Table 1 shows that aside from less coronary and other heart disease, and slightly higher diastolic blood pressure in the intensive group, the characteristics of patients were well balanced between the treatment groups, in particular of no significant differences in any features of brain frailty (old vascular lesions, brain atrophy, and periventricular white matter changes) on brain imaging. The clear between-group differences were in relation to the various measures of systolic blood pressure control, with the mean achieved levels of systolic blood pressures over 1–24 h being 141 mm Hg and 149 mm Hg in the intensive group and guideline group, respectively (Appendix p 24). These findings were similar across the profile of patients in the other measures of brain imaging (Appendix pp 12–14).

Table 2 shows that the median size (ml) of cerebral infarction on CT done at 24–36 h were 0.3 (0.0–16.6) and 0.9 (0.0–12.5) in the intensive group and guideline group, respectively. The corresponding figures for MRI and CT/MRI at 24–36 h, and any follow-up brain imaging were 2.3 (0.6–25.7) and 2.9 (0.6–17.3), 0.7 (0.0–17.5) and 1.3 (0.0–12.8), and 1.0 (0.0–18.2) and 1.8 (0.0–16.1), respectively. Overall, there was no significant

Variable	Intensive group (n = 300)	Guideline group (n = 335)	Standardised difference	p value
Time from onset to randomisation, h	3.3 (2.5–4.0)	3.3 (2.6–4.0)	−0.06	0.46
Alteplase dosage, mg	0.9 (0.7–0.9)	0.9 (0.6–0.9)	0.04	0.59
Female	125/300 (42%)	137/335 (41%)	−0.02	0.84
Age, y	68.7 (12.3)	69.0 (11.5)	−0.03	0.74
Asian ethnicity	165/300 (55%)	176/335 (53%)	0.05	0.53
Systolic BP, mm Hg	165.7 (9.3)	166.4 (9.0)	−0.07	0.37
Diastolic BP, mm Hg	91.0 (11.5)	89.0 (11.7)	0.18	0.03
Heart rate, bpm	79.7 (15.0)	78.6 (14.5)	0.07	0.38
NIHSS score[a]	7 (4–12)	7 (4–12)	0.06	0.42
Severe (≥14)	64/300 (21%)	65/335 (19%)	0.05	0.55
GCS score[b]	15 (14–15)	15 (14–15)	−0.01	0.88
Hypertension	213/299 (71%)	245/335 (73%)	−0.04	0.59
Currently treated hypertension	161/299 (54%)	183/335 (55%)	−0.02	0.84
Coronary artery disease	33/299 (11%)	56/335 (17%)	−0.16	0.04
Other heart disease	9/299 (3%)	24/335 (7%)	−0.19	0.02
Atrial fibrillation	46/299 (15%)	61/334 (18%)	−0.08	0.33
Diabetes mellitus	61/299 (20.4)	83/335 (25%)	−0.10	0.19
Hypercholesterolaemia	49/299 (16%)	62/335 (19%)	−0.06	0.48
Current smoker	67/298 (23%)	78/334 (23%)	−0.02	0.80
Pre-stroke independent (mRS 0)	240/299 (80%)	275/335 (82%)	0.05	0.56
Anticoagulant use	6/299 (2%)	6/335 (2%)	0.06	0.84
Aspirin or other antiplatelet agent	61/299 (20%)	83/335 (25%)	−0.10	0.19
Statin/other lipid lowering treamtent	57/299 (19%)	77/335 (23%)	−0.10	0.23
Final diagnosis stroke[c]	295/298 (99%)	327/332 (99%)	0.04	0.58
Presumed pathology[c]			0.23	0.22
Extracranial atheroma	30/295 (10%)	32/327 (10%)		
Intracranial atheroma	60/295 (20%)	70/327 (21%)		
Small vessel disease	102/295 (35%)	90/327 (28%)		
Cardioembolic	45/295 (15%)	62/327 (19%)		
Dissection	2/295 (1%)	0/327 (0)		
Other/uncertain	56/295 (19%)	73/327 (22%)		
Systolic BP parameters, mm Hg				
Highest over 24 h	157.3 (15.9)	164.7 (14.6)	−0.49	0.0005
Lowest over 24 h	127.4 (12.2)	133.1 (15.4)	−0.41	<0.0001
Mean over 1–24 h	141 (10.6)	149 (12.7)	−0.63	<0.0001
Variability 1–24 h	12.2 (6.7)	13.0 (6.4)	−0.12	0.0230
Magnitude reduction in 1 h	24.2 (15.8)	17.5 (15.8)	0.42	<0.0001
NIHSS at 24 h	5 (2–10)	5 (2–10)	0.02	
Treatment				
Time from onset to alteplase treatment, h	3.0 (2.3–3.7)	3.0 (2.3–3.8)	−0.02	0.83
Endovascular thrombectomy	2/7 (29%)	5/11 (46%)	0.64[d]	0.64
Use of intravenous BP lowering treatment within 24 h	205/299 (69%)	132/333 (40%)	0.61	<0.0001
Brain imaging features				
Old vascular lesions	145/271 (54%)	165/304 (54%)	−0.18	0.85
Brain atrophy	193/297 (65%)	212/325 (65%)	−0.0184	0.95
Periventricular white matter changes	139/296 (47%)	158/325 (49%)	−0.02	0.68
Time from stroke onset to follow-up scan, h	28.7 (3%)	28.9 (3%)	−0.07	0.39

Data are n/N (%), mean (SD), or median (IQR). CT denotes computed tomography, GCS Glasgow coma scale, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale. [a]Scores range from 0 to 42, with higher scores indicating more severe neurological deficit. [b]Scores range from 15 (normal) to 3 (deep coma). [c]Diagnosis according to the clinician's interpretation of clinical features and results of investigations at the time of separation from hospital. [d]Fisher exact test and p value was reported instead of standardised differences.

Table 1: **Characteristics of patients with acute ischaemic stroke and CT scans at 24–36 h, by treatment group.**

Type of scan	Treatment group		Unadjusted			Adjusted[b]		
	Intensive	Guideline	n	Log Δmean (95% CI)[a]	p value	n	Log Δmean (95% CI)[a]	p value
CT at 24–36 h (n = 635)	0.3 (0.0–16.6)	0.9 (0.0–12.5)	599	−0.26 (−0.87–0.35)	0.40	591	−0.17 (−0.78–0.43)	0.58
MRI at 24–36 h (n = 193)	2.3 (0.6–25.7)	2.9 (0.6–17.3)	164	0.03 (−0.89–0.96)	0.94	162	−0.42 (−1.34–0.49)	0.36
CT/MRI at 24–36 h (n = 813)	0.7 (0.0–17.5)	1.3 (0.0–12.8)	752	−0.20 (−0.73–0.33)	0.46	742	−0.16 (−0.68–0.37)	0.56
Any scan (n = 1477)	1.0 (0.0–18.2)	1.8 (0.0–16.1)	1367	−0.26 (−0.64–0.13)	0.19	1347	−0.18 (−0.57–0.20)	0.36

Data are N for number of observations in the statistical analysis and median (IQR). BP denotes blood pressure, CI confidence interval, CT computed tomography, MRI magnetic resonance imaging. [a]Estimates of mean difference is reported for infarct size using a log-linear regression model. [b]Adjusted variables included pre-specified covariates (age, sex, ethnicity, pre-morbid function [modified Rankin scale 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) and further covariates that had a p value < 0.1 from the baseline characteristics (diastolic blood pressure, other heart disease for CT at 24–36 h, medical history of hypertension for MRI at 24–36 h, diastolic blood pressure and other heart disease for CT/MRI at 24–36 h, diastolic BP at admission for any follow-up scan); loss of observations arose from missing data for some covariates.

Table 2: **Intensive blood pressure lowering and infarct size (ml) in patients with acute ischaemic stroke by follow-up brain imaging.**

effect of intensive blood pressure lowering on cerebral infarction on CT (adjusted log mean difference –0.17, 95% CI –0.78 to 0.43; p = 0.58). The results were consistent across the sensitivity analyses and pre-specified subgroups (Fig. 2).

Although intracranial haemorrhage was less frequent in the intensive blood pressure group compared to the guideline group (13% vs 16%) in patients with follow-up CT at 24–36 h, this was not significant (adjusted OR 0.74, 95% CI 0.46–1.19; p = 0.21) (Appendix p 15). Similarly, there were no significant differences in PH, or death or disability (mRS scores 2–6) at 90 days, between two groups (Appendix p 15). Moreover, there was no significant difference in the location of infarction, and type and volume of intracranial haemorrhage, between the treatment groups (Appendix pp 16–17). However, there was a significant interaction between the size of cerebral infarction and intracranial haemorrhage (p < 0.0001) (Appendix p 18).

Of 1463 patients with complete data on the various parameters of early blood pressure control, the mean attained systolic blood pressure was 144 (SD 12.5) mm Hg, with a variability of 12 (SD 6.3) mm Hg in the first 24 h post-randomisation (Appendix p 19). There was a significant association between the degree of attained mean systolic blood pressure over 24 h and size of infarction in patients with any follow-up brain imaging (log mean difference 0.20, 95% CI 0.03–0.38; p = 0.02, Appendix p 20) after adjustment for pre-specified variables. This indicates that for every 10 mm Hg increase in attained systolic blood pressure there was a 22% (95% CI 3%–46%) increase in the size of infarction. A J-shape association was found between categories of attained systolic blood pressure and size of infarction, after adjustment (model 1), with the smallest infarct being for systolic blood pressure between 110 mm Hg and 120 mm Hg (Appendix pp 25, 26). There were no significant associations between variability and magnitude of systolic blood pressure and infarction, either in complete case analysis or after multiple imputation (Appendix pp 25, 26).

Discussion

In this pre-planned secondary analysis of the brain images collected on participants of the ENCHANTED trial, we show no clear effect of early intensive blood pressure lowering to a systolic target of <140 mm Hg, as compared to the management of systolic blood pressure <180 mm Hg, on the size of cerebral infarction in patients who had received intravenous thrombolysis for acute ischaemic stroke. The results were consistent in sensitivity analysis with different approaches to using all available brain imaging data, and in pre-specified subgroups of patients. As there was a significant positive association between the levels of attained systolic blood pressure and size of cerebral infarction, from as low as 120 mm Hg, the treatment target level of systolic blood pressure for achieving optimal functional recovery may be much lower than is recommended in guidelines.

Several small clinical trials have suggested that the use of oral antihypertensive agents does not modify the size of cerebral infarction,[15,16] but there are limited data in relation to the effects on functional outcome, and until recently and especially so, in high-risk patients such as those with large-vessel occlusion. Observational studies indicate that a higher baseline blood pressure is associated with larger cerebral infarction, which indicates either a reactive response to ischaemia or greater collateral blood flow.[17,18] Conversely, the presence of larger cerebral infarction is associated with a decrease in blood pressure immediately before and after reperfusion treatment where there is incomplete recanalisation.[19–21] Some studies suggest that a moderate reduction in systolic blood pressure, or individualised antihypertensive therapy according to baseline blood pressure, has no impact on the size of cerebral infarction or volume of hypoperfusion, regardless of whether or not recanalisation is achieved[22,23]; this may indicate that collateral flow is an important moderating factor.[24] Our randomised results, therefore, provide some reassurance that a moderate degree of reduction in systolic blood pressure is safe in a broad range of patients who

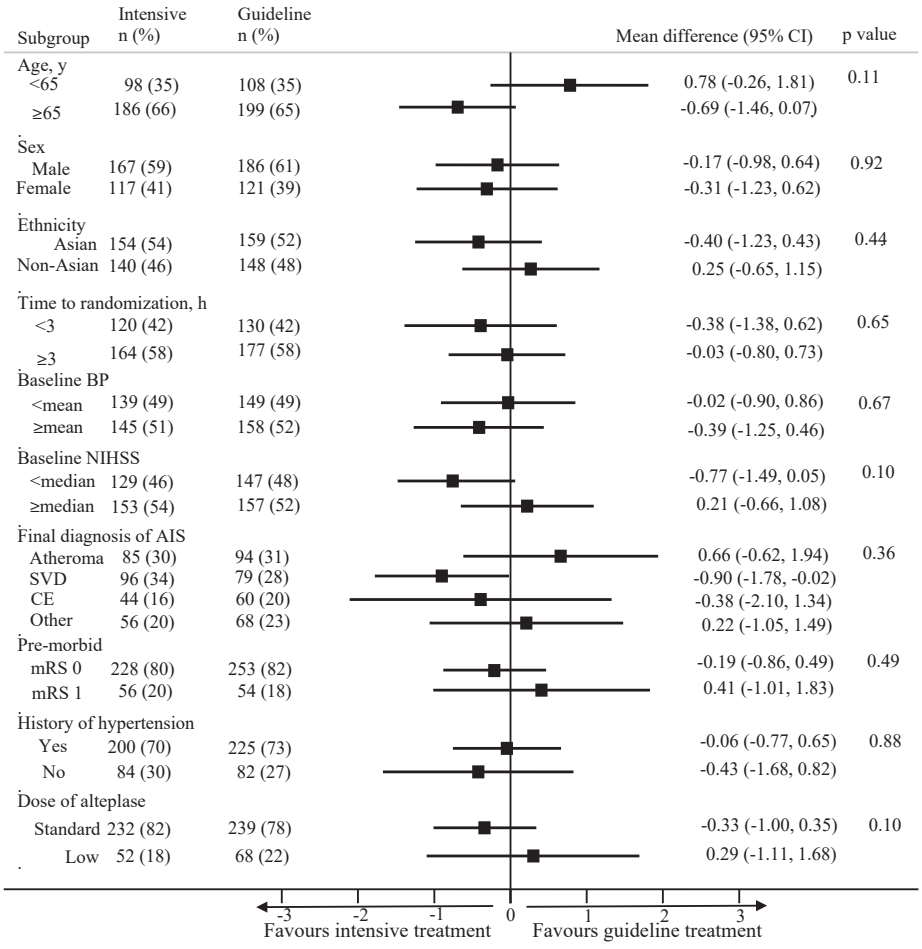


***Fig. 2:* Subgroup of intensive blood pressure lowering and infarct size* on CT scans**. AIS denotes acute ischaemic stroke, BP blood pressure, CE cardioembolism, CI confidence interval, mRS modified Rankin scale, NIHSS National Institute of Health Stroke Scale, SVD small vessel disease. *Estimates of mean difference are reported for infarct size using log-linear regression model adjusted 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, diastolic blood pressure and other heart disease.

are treated with intravenous thrombolysis for acute ischaemic stroke according to proven indications.

However, our results have not established the optimal systolic blood pressure target in thrombolysed patients. An observational study suggests a U-shaped relation of mean systolic blood pressure over 24 h and the size of cerebral infarction, with a level of between 181 and 200 mm Hg being associated to the smallest volume,[21] which is contrary to our analysis in which the pooled analysis indicates a benefit at a systolic level as low as 110–120 mm Hg. Potential explanations for these discrepancies are indication bias whereby investigators have applied a conservative strategy of blood pressure control in patients with large infarction, and in that the largest contribution of data was from patients with tiny infarcts. Clearly, the role of target-based blood pressure lowering according to various clinical factors, such as during and after reperfusion therapy and according to the location of vessel occlusion, deserves further investigation.[25] The BP-TARGET trial[3] result of a systolic target of 100–129 mmHg being safe after successful endovascular thrombectomy has been called into question following the early stopping of the ENCHANTED2/MT trial due to clearly identified harms.[4] More intensive blood pressure lowering is likely to have an adverse effect on blood flow within the cerebral microcirculation. The results of brain imaging from ENCHANTED2/MT and pooling of data between these and other trials are eagerly awaited.

We hypothesised that an interaction between intensive blood pressure lowering, and the size of cerebral infarction and risk of intracranial haemorrhage, might explain the neutral result of ENCHANTED on functional outcome.[26] The inability for our analysis to show a

clear reduction in intracranial haemorrhage, as was shown in the main results,[2] might be due to reduced power from reduced sample size and selection bias in a subgroup. The size of cerebral infarction is a stronger predictor of functional outcome than the volume of haemorrhage,[27] especially when it petechial and clinically for asymptomatic.[28] Accordingly, the finding of no significant interaction between the size of cerebral infarction, intracranial haemorrhage and blood pressure lowering groups, suggests that any potential benefit of blood pressure lowering may be offset by reductions in the risk of intracerebral haemorrhage being limited to irreversible cerebral infarction.

Key strengths of our study include the large amount of brain imaging data that were acquired from participants of an international multicentre randomised controlled trial specifically designed to evaluate different intensities of blood pressure control as part of the routine management of patients eligible for treatment with intravenous thrombolysis. Our analyses were prespecified, the imaging readers had a background in neurology and received formal training, and the quality control assessments were undertaken with a formal assessment of inter-rater reliability. Even so, our study has several limitations that must be considered when interpreting the findings. Clearly, the dataset is compromised by inevitable selection bias due to the inclusion criteria used in a pragmatic randomised trial where patients with sustained systolic blood pressure of 150–185 mm Hg were included but various logistical challenges precluded near complete collection of brain images according to consistent brain scanning procedures. The brain imaging were conducted according to routine local practice rather than a standardised protocol specifying time, imaging modality, and technical requirements. Even though our sensitivity analyses of patients with follow-up brain scans at different times were consistent with the primary analysis restricted to those with CT done at 24–36 h, the potential for bias, measurement error and counfounding. As most patients eligible for thrombolysis treatment have a mild to moderate level of neurological impairment, they have a correspondingly low volume of cerebral ischaemia/infarction and subsequent likelihood of a good outcome with low risk of complications, including intracranial haemorrhage. Although the expert imaging assessors were blind to clinical information, their work was challenging when it was undertaken primarily on CT images and explains the low degrees of cerebral infarction that was identified. Finally, as only a modest difference in systolic blood pressure between randomised groups was achieved in ENCHANTED, and only one third of all participants were included in the primary brain imaging analysis, the neutral result of this study might be due to it being underpowered. Such effects have now been brought into the spotlight with the results of ENCHANTED2/MT. Further research examining the complex relationships of blood pressure, collateral blood flow, cerebral ischaemia, and intracranial haemorrhage, evaluated using advanced imaging (MRI, multimodal CT, etc) are clearly warranted.

In summary, our follow-up brain imaging analysis of the ENCHANTED 'blood pressure control' arm to define the effects of treatment on the footprint of cerebral infarction might provide some reassurance that a management strategy to lower systolic blood pressure, initiated within 6 h after the onset of symptoms, to a target near 140 mm Hg within 1 h, may be safe on the basis of finding no apparent between-group difference in the size of cerebral infarction on follow-up scans, even though there were only small blood pressure differences between groups. However, we have not adequately explained why a highly significant reduction in intracranial haemorrhage from intensive blood pressure lowering did not translate into improved functional outcome. Moreover, we have been unable to provide recommendations over the optimal levels of blood pressure control in specific patient groups with acute ischaemic stroke. Further analysis of ENCHANTED2/MT,[4] and results of similar trials in patient who have received endovascular therapy and that of the ongoing Intensive Ambulance-delivered Blood Pressure Reduction in Hyper-Acute Stroke Trial (INTERACT4)[29] due in 2024, are expected to provide further insights into the effects of early intensive blood pressure lowering in different patient groups and clinical settings.

Contributors

CC read images, interpreted the data, and wrote the first draft of the report with input from MO. MO did the statistical analyses with input from CC. CSA obtained funding. CSA and LS planned and supervised this sub-analysis of the ENCHANTED trial, interpreted data, and wrote the report. CSA, LS, CC, and MO accessed and verified the raw data. SO, LYZ, and GBZ read images, and LL managed the reading process. JMW and GM provided training in acute stroke brain imaging, and the interpretation, standardising scores, and cross-checking 10% of data for the patients in both dose arm and BP arm. SO, LYZ, GBZ, CD, GM, LL, LB, QL, XC, MP, JPB, AMD, PMB, GAD, CL, JC, RIL, SM, OMP, PMV, VO, PL, TGR, JMW, GL, and XW provided comments on the report.

Data sharing statement

De-identified participant data used in these analyses can be shared by formal request to the corresponding author, Craig Anderson, canderson@georgeinstitute.org.au.

Declaration of interests

GM received a research grant from the UK Stroke Association, and consulting fee and honoraria from Canon Medical. JB has received consulting fees from Roche, and honoraria on the Executive Committee for TIMELESS Trial from Genentech. AMD received grants from Medtronic and Circle CVI, and has received consulting fees and honoraria from HLS Therapeutics, Hoffmann LaRoche Servier, Astra Zeneca, and Boehringer Ingelheim. He is also a member on Data Safety and Monitoring Boards (DSMB) for Philips and Lumosa, and has a role on the Canadian Stroke Consortium and Canadian Partnership for Stroke Recovery. PB has received research grants from the UK Stroke Association, British Heart Foundation, NIHR HTA, and NUH Charity, and honoraria for advisory board activities from DiaMedica, Phagenesis, and Roche. He is also the Chair and Co-Chair of DSMBs for ESPS-2 and AVERT-Dose, respectively, and has stock from DiaMedica. AMD has

stock from Circle CVI. RIL has received grants from the National Health and Medical Research Council (NHMRC). JC reports receiving a Program Grant the NHMRC from of Australia and is the Chair of the Steering Committee for ENCHANTED. SM has received grants from Ministry of Health PROADI SUS Hospital Moinhos de Vento, including RESILIENT Direct TNK, RESILIENT Extend IV, TRIDENT, and PROMOTE trials. She also received honoraria from Boehringer Ingelheim, Medtronic, Penumbra, Novartis, Novo Nordisk, Pfizer, Bayer, Servier, and Daiichi Sankyo, has participated on a DSMB for Johnson and Johnson's Executive Board for the Librexia clinical trial, and is the President of World Stroke Organisation and Brazilian Stroke Network. PMV has received a research grant from ANID Fondecyt Regular, Chile, and is member of the Scientific Advisors Committee to the Chilean Ministry of Sciences and Technology, for the COVID-19 vaccine national strategy. VVO has received a research grant from ANID Fondecyt Regular 1,181,333 Chile and a research grant from Boehringer Ingelheim. PL has received a research grant from ANID Fondecyt Regular, Chile, and honoraria from Boehringer Ingelheim, and has a role on a DSMB for Boehringer Ingelheim and the Chilean Ministry of Health, and is the President of the Chilean Stroke Association. CSA and LS received research grants from the NHMRC, MRC, Takeda China, and Penumbra. The other authors declare no competing interests.

Acknowledgments

Some of these analyses were presented at the European Stroke Organisation Conference in Lyon, France, 4 to 6 May 2022. The ENCHANTED study was supported by grants from the National Health and Medical Research Council (NHMRC) of Australia (project grant numbers 1020462 and 1101113); the UK Stroke Association (TSA 2012/01 and 2015/01); the Ministry of Health and the National Council for Scientific and Technological Development of Brazil (CNPQ 467322/2014–7 and 402388/2013–5); the Ministry for Health, Welfare, and Family Affairs of South Korea (HI14C1985; for the alteplase-dose arm); and a research grant from Takeda for conduct of the study in China. JMW is part-funded by the UK Dementia Research Institute, which is funded by the Medical Research Council (MRC), Alzheimer's Society and Alzheimer's Research. TR and PMB are National Institute of Health and Care Research (NIHR) Senior Investigators.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101849.

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