Stroke

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Associations of Early Systolic Blood Pressure Control and Outcome After Thrombolysis-Eligible Acute Ischemic Stroke: Results From the ENCHANTED Study

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BACKGROUND AND PURPOSE: In thrombolysis-eligible patients with acute ischemic stroke, there is uncertainty over the most appropriate systolic blood pressure (SBP) lowering profile that provides an optimal balance of potential benefit (functional recovery) and harm (intracranial hemorrhage). We aimed to determine relationships of SBP parameters and outcomes in thrombolyzed acute ischemic stroke patients.

METHODS: Post hoc analyzes of the ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study), a partial-factorial trial of thrombolysis-eligible and treated acute ischemic stroke patients with high SBP (150–180 mm Hg) assigned to low-dose (0.6 mg/kg) or standard-dose (0.9 mg/kg) alteplase and intensive (target SBP, 130–140 mm Hg) or guideline-recommended (target SBP <180 mm Hg) treatment. All patients were followed up for functional status and serious adverse events to 90 days. Logistic regression models were used to analyze 3 SBP summary measures postrandomization: attained (mean), variability (SD) in 1–24 hours, and magnitude of reduction in 1 hour. The primary outcome was a favorable shift on the modified Rankin Scale. The key safety outcome was any intracranial hemorrhage.

RESULTS: Among 4511 included participants (mean age 67 years, 38% female, 65% Asian) lower attained SBP and smaller SBP variability were associated with favorable shift on the modified Rankin Scale (per 10 mm Hg increase: odds ratio, 0.76 [95% CI, 0.71–0.82]; $P<0.001$ and 0.86 [95% CI, 0.76–0.98]; $P=0.025$) respectively, but not for magnitude of SBP reduction (0.98, [0.93–1.04]; $P=0.564$). Odds of intracranial hemorrhage was associated with higher attained SBP and greater SBP variability (1.18 [1.06–1.31]; $P=0.002$ and 1.34 [1.11–1.62]; $P=0.002$) but not with magnitude of SBP reduction (1.05 [0.98–1.14]; $P=0.184$).

CONCLUSIONS: Attaining early and consistent low levels in SBP <140 mm Hg, even as low as 110 to 120 mm Hg, over 24 hours is associated with better outcomes in thrombolyzed acute ischemic stroke patients.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01422616.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: blood pressure ■ hypertension ■ intracranial hemorrhage ■ ischemic stroke

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Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
BP	blood pressure
ENCHANTED	Enhanced Control of Hypertension and Thrombolysis Stroke Study
ICH	intracranial hemorrhage
IST-3	International Stroke Trial
mRS	modified Rankin Scale
OR	odds ratio
PROBE	Prospective, Randomized, Open-Label, Blinded-End Point
r-tPA	recombinant tissue-type plasminogen activator
SBP	systolic blood pressure
TIMS-China	Thrombolysis Implementation and Monitor of acute ischemic stroke in China

Intravenous thrombolysis treatment with r-tPA (recombinant tissue-type plasminogen activator/alteplase) is a proven effective medical therapy in acute ischemic stroke (AIS). Although co-morbid elevated blood pressure (BP) is common after AIS,[1] often to extreme levels, and is associated with poor outcomes,[2] there is controversy over the benefits of peri-thrombolysis BP control, where guidelines consistently recommend an systolic BP (SBP) <185 mm Hg[3,4] in thrombolyzed AIS patients. However, the recently completed BP arm of the quasi-factorial ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) suggests an even lower target may further improve outcomes in this patient group. In thrombolysis-eligible and treated AIS patients with elevated SBP (150–180 mm Hg), intensive BP control (target SBP, 130–140 mm Hg within 1 hour) was not shown to improve clinical recovery as compared with standard (SBP<180 mm Hg) BP lowering over 72 hours,[5–9] but the treatment did lead to significant reductions in the key safety outcome of intracranial hemorrhage (ICH) and in particular large intracerebral hemorrhage.[8]

Among the various measures used to define SBP control,[10–14] studies have shown that higher mean,[15–17] greater variability,[18–20] and smaller reductions[19,20] in post-thrombolysis SBP are associated with higher odds of ICH[15,17–20] and worse functional outcome from AIS.[17–20] However, such observational analyzes may be complicated by residual confounding and incomplete assessment of interactions between variables, the optimal level of SBP control for functional recovery and risk of ICH without worsening cerebral ischemia is unknown. Therefore, we undertook post hoc analyzes of the completed ENCHANTED data set of both the combined alteplase-dose[6,7,9] and BP arms[5,8] to determine associations of summary measures—attained (mean) and variability (SD) during 1 to 24 hours, and magnitude of reduction in 1 hour of early SBP control, and key clinical outcomes. The aim was to determine the strength and direction of associations, explore any effect modification by patient characteristics, and identify a SBP lowering profile that provided an optimal balance of potential benefit (functional independence) and harm (ICH and serious adverse events).

METHODS

Data Availability

Individual de-identified participant data used in these analyses can be shared by formal request with protocol and statistical analysis plan from any qualified investigator to the Research Office of The George Institute for Global Health, Australia. A tailored data set specific to the research question will be shared for 6 months, and the data can be only accessed by qualified statisticians for the proposed analysis.

Study Design Population

Details of the study design and main results of the BP and alteplase dose arms of the ENCHANTED trial have been detailed elsewhere.[5–9] In brief, ENCHANTED was an international, 2×2 partial-factorial, multi-center, PROBE (Prospective, Randomized, Open-Label, Blinded-End Point) trial. All ENCHANTED adult (age ≥18 years) participants had a clinical diagnosis of AIS confirmed by brain imaging and fulfilled local criteria for thrombolysis treatment. The alteplase-dose evaluation arm[7] was conducted from March 1, 2012 to August 31, 2015, and included a total of 3310 participants randomly assigned to receive low-dose (0.6 mg/kg; 15% as bolus and 85% as infusion over 1 hour) or standard-dose (0.9 mg/kg; 10% as bolus and 90% as infusion over 1 hour) intravenous alteplase. The BP arm[8] was conducted from March 3, 2012 to April 30, 2018, and included a total 2227 participants with elevated SBP (150–180 mm Hg) where the attending clinician had uncertainty over the benefits and risks of the intensity of BP control, immediately and for 72 hours (or hospital discharge or death if this occurred earlier) after thrombolytic treatment. Although there was no specified upper SBP level, international guidelines recommend patients have SBP ≤185 mm Hg before administration of intravenous alteplase.[3] Participants were randomly assigned to a strategy of intensive BP lowering (target SBP, 130–140 mm Hg within 60 minutes of randomization) or guideline-recommended BP lowering (target SBP <180 mm Hg) after the commencement of intravenous alteplase. The study protocol was approved by the appropriate ethics committee at each participating center, and written informed consent was obtained from each patient or an appropriate surrogate. The study is registered with Clinicaltrials.gov (number: NCT01422616).

Procedures

The management strategy of BP lowering treatment was according to local protocols based upon available intravenous (bolus and infusion), oral, and topical medications.[8] All patients were to be managed in an acute stroke unit, or an alternative environment with appropriate staffing and monitoring, and

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receive active care and best practice management according to local guidelines. The use of endovascular thrombectomy was allowed but was uncommon during the course of the trial.

Noninvasive BP monitoring was undertaken using an automated device applied to the nonhemiparetic 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, and 6 hourly from 1 to 24 hours. Thereafter, BP was recorded twice daily for 1 week (or until hospital discharge or death, if earlier). Neurological status, according to the National Institutes of Health Stroke Scale and Glasgow Coma Scale, was assessed at baseline, 24 and 72 hours, and 7 days. Brain imaging (computerized tomography and/or magnetic resonance imaging) was conducted at baseline, and 24 hours, and additionally if clinically indicated, analyzes were undertaken centrally for diagnoses of categories of ICH by expert assessors who were blind to clinical details and treatment allocation. Socio-demographic and clinical details were obtained at randomization, while follow-up data were collected at 24 and 72 hours, 7 days (or at hospital discharge if earlier), and 28 and 90 days.

For each participant, summary measures of SBP control were attained SBP: the mean of 5 time-points of SBP measures between 1 and 24 hours; variability of SBP: the SD of the same measures between 1 and 24 hours; and magnitude of early reduction of SBP: the difference between randomization SBP and the lowest attained SBP within the first hour. For sensitivity analysis, the latter measure was further defined as magnitude of later reduction of SBP: the difference between SBP at randomization and the lowest attained level within the first 24 hours. Linear interpolation (PROC TRANSREG in SAS) were used to estimate missing SBP measurements at defined time-points, and regression functions with 3-knot splines were fitted to allow enough change points to capture the projected turn of SBP trajectory without undue overestimation.[21]

Outcomes

For these analyzes, the primary outcome was functional status as defined by the distribution of scores on the modified Rankin Scale (mRS). Secondary outcomes were any ICH reported by investigators with or without central adjudication of relevant brain imaging within 7 days after randomization; mRS scores 0 to 1; mRS scores 0 to 2; and death within 90 days. Safety outcomes were death or neurological deterioration, defined as an increase from baseline of ≥4 points on the National Institutes of Health Stroke Scale or a decrease from baseline of ≥2 points on the Glasgow Coma Scale, within 7 days; and any fatal or nonfatal serious adverse event according to standard definition.

Data Analysis

The relationships of early SBP control parameters and death or disability were first explored using the locally estimated scatterplot smoothing procedure. When this suggested a potential nonlinear relationship (quadratic or cubic), either a squared (X^2) or cubed (X^3) term was added to the regression model, respectively. Next, interaction effects (attained×magnitude, variability×magnitude, attained×variability, and magnitude×attained×variability) were assessed; if there was no significant interaction, a reduced model was run without an interaction term. For all the analyses involving the primary outcome of functional status (ordinal shift in the distribution of scores on the mRS), we first checked that the proportional odds assumption, and if it was violated, we used secondary outcome of mRS score of 0 to 1.

For each outcome, the primary model included all 3 summary measures of SBP control as continuous variables, where associations are reported as odds ratios (OR) with 95% CI per 10 mm Hg SBP increase. The following baseline variables were included in multivariable analyzes: age, sex, ethnicity (Asian versus non-Asian), degree of neurological impairment (National Institutes of Health Stroke Scale score), premorbid function (mRS scores 0 versus 1), premorbid use of antithrombotic agents (aspirin, other antiplatelet agent, or warfarin) and antihypertensive agents, and history of hypertension, stroke, coronary artery disease, diabetes, atrial fibrillation, and randomized treatment (intensive BP control, guideline-recommended BP control, low-dose alteplase, and standard-dose alteplase). Next, the individual SBP summary measures were assessed as categorical variables for descriptive purposes, and reported as comparisons between each category and the reference category as OR with 95% CI. To determine any potential modifying effects, interaction terms with baseline covariates were added to the primary model. For any covariate that yielded a significant interaction effect, a subgroup analysis was conducted. Sensitivity analyzes using complete case data and BP control parameters from 2 to 7 days were also conducted.

Finally, a machine learning Stochastic Gradient boosting algorithm (with Gaussian distribution and applying 5000 trees)[22] was executed to estimate the relative influence of the 3 summary measures of SBP control and the covariables listed previously to assess their importance in explaining the variability of the outcomes of interest. The percentage relative influence was computed using an empirical-permutation procedure that evaluates the average decrease in accuracy across all the constructed trees (the largest the decrease, the more important the variable).

All analyzes were undertaken using SAS (version 9.2 or newer) and the GBM package in R. Statistical significance was set at 2-sided $P<0.05$ throughout.

Role of the Funding Source

The sponsors and funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all study data and share responsibility for the decision to submit the article for publication.

RESULTS

A total of 4511 ENCHANTED participants (mean age 67 years, female 37.9%, Asian ethnicity 65.4%) were included in these analyzes (Figure I in the Supplemental Material; Table 1). The median time from onset of symptoms to randomization (intensive versus guideline-recommended BP lowering treatment) was 2.9 hours (interquartile interval, 2.2–3.7). Other key baseline characteristics and details of study treatment, including alteplase dose and BP

Table 1. Baseline Characteristics, Early Systolic Blood Pressure Control, Other Treatments, and Outcomes

Variable	
Demographic	
Age, y	67 (12.7)
Female sex	1714/4511 (37.9)
Asian ethnicity	2948/4510 (65.4)
Clinical features	
SBP at randomization, mm Hg	154 (18.8)
DBP at randomization, mm Hg	86 (12.7)
Heart rate, bpm	79 (15.4)
NIHSS score	8 (5–13)
GCS	15 (14–15)
Medical history	
Hypertension	2916/4508 (64.7)
Stroke	816/4511 (18.1)
Acute coronary syndrome	637/4508 (14.1)
Diabetes	917/4508 (20.3)
Atrial fibrillation	804/4504 (17.9)
Estimated premorbid function (mRS)	
No symptoms (score 0)	3748/4505 (83.2)
Symptoms without any disability (score 1)	757/4505 (16.8)
Medication at time of admission	
Antihypertensive drug(s)	2060/4508 (45.7)
Antithrombotic drug(s)	1064/4505 (23.6)
Presumed stroke etiology	
Large artery disease due to significant atheroma	1796/4463 (40.2)
Small vessel disease	1056/4463 (17.9)
Cardioembolic	797/4463 (17.9)
Early SBP control	
Time from stroke onset to randomization, h	2.9 (2.2–3.7)
Attained SBP, mm Hg*	139 (15.3)
SBP variability, mm Hg†	12 (6.5)
Magnitude of SBP reduction in the first hour, mm Hg‡	16 (17)
Magnitude of SBP reduction in the 24 hours, mm Hg§	30 (18)
Randomized treatment	
Low-dose alteplase	1175/4511 (26.1)
Standard-dose alteplase	1151/4511 (25.5)
Standard-dose alteplase/standard BP management	240/4511 (5.3)
Standard-dose alteplase/early intensive BP management	221/4511 (4.9)
Low-dose alteplase/standard BP management	233/4511 (5.2)
Low-dose alteplase/early intensive BP management	222/4511 (4.9)
Standard BP management	638/4511 (14.1)
Early intensive BP management	631/4511 (14.0)
Outcomes	
mRS scores at 90 days	/4431
0	1146 (25.9)
1	1072 (24.2)
2	639 (14.4)
3	521 (11.8)
4	417 (9.4)
5	235 (5.3)
6	401 (9.1)
Any intracranial hemorrhage within 7 days	836/4511 (18.5)
Death or neurological deterioration‖ within 7 days	401/4511 (8.9)
Death within 90 days	557/4511 (12.4)
Any serious adverse event within 90 days	1095/4511 (24.3)

Data are numbers/denominator (%), mean (SD), or median (IQI). BP indicates blood pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; IQI, interquartile interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and SBP systolic blood pressure.

*Mean SBP in 1–24 h.

†SD of SBP in 1–24 h.

‡SBP at randomization minus minimum SBP within the first hour.

§SBP at randomization minus minimum SBP within the first 24 h.

‖Neurological deterioration defined as an increase of ≥4 points on the NIHSS or a decline of ≥2 on the Glasgow Coma Scale within 24 h postrandomization.

lowering, are provided in Table 1. On average, the magnitude of SBP reduction in the first one and 24-hour postrandomization periods were 16 (17) and 30 (18) mm Hg, respectively; and attained level and variability of SBP were 139 (15.3) mm Hg and 12 (6.5) mm Hg, respectively, over 1 to 24 hours. There were 916 patients who participated in both randomized treatment arms (low-dose versus standard-dose alteplase and intensive versus guideline-recommended BP lowering treatment); 2326 and 1269 were randomized only to the alteplase dose and BP arms, respectively. SBP data were imputed for 1416 patients; 3095 patients had no imputation (42 without any SBP data, 149 died early, and 2904 with complete records).

As the locally estimated scatterplot smoothing plot suggested a potential U-shaped relationship between magnitude and death or disability (Figure II in the Supplemental Material), a squared (X^2) term was added to the regression model but was subsequently removed as it was not significant. All interaction terms were also not significant and thus also excluded from models. The proportional odds assumption was not rejected (P=0.250). Table 2 shows associations of the 3 SBP summary measures as continuous variables in a combined adjusted model. There were significant linear associations with functional status for attained level and variability of SBP: ORs were 0.84 (95% CI, 0.81–0.87; P<0.0001) and 0.88 (95% CI, 0.81–0.96; P=0.004) per 10 mm Hg increase, respectively. However, there was no association for magnitude (OR, 1.00 [95% CI, 0.97–1.04]; P=0.969). Similar significant/nonsignificant associations were observed for the SBP parameters and the other outcomes.

When the magnitude of SBP reduction was examined over 24 hours, significant linear associations were also seen for attained level and variability of SBP:

Table 2. Associations of Early Systolic Blood Pressure Levels and Outcomes

	OR* (95% CI)	*P* value	OR* (95% CI)	*P* value
	Attained		Attained	
Individual SBP summary measures	Mean SBP 1–24 hours		Mean SBP 1–24 hours	
Favorable shift on the mRS score at 90 days	0.84 (0.81–0.87)	<0.0001	0.85(0.82–0.89)	<0.0001
mRS score 0–1 at 90 days	0.81 (0.77–0.85)	<0.0001	0.83(0.78–0.87)	<0.0001
mRS score 0–2 at 90 days	0.83 (0.79–0.88)	<0.0001	0.85(0.81–0.90)	<0.0001
Any intracranial hemorrhage within 7 days	1.04 (0.98–1.10)	0.187	1.04(0.98–1.10)	0.242
Death or neurological deterioration† within 7 days	1.25 (1.16–1.33)	<0.0001	1.04(0.96–1.14)	0.335
Death within 90 days	1.07 (0.99–1.16)	0.092	1.23(1.14–1.32)	<0.0001
Any serious adverse event within 90 days	1.05 (1.00–1.11)	0.057	1.07(1.01–1.13)	0.021
	Variability		Variability	
	SD of SBP 1–24 hours		SD of SBP 1–24 hours	
Favorable shift on the mRS score at 90 days	0.88 (0.81–0.96)	0.004	0.84(0.76–0.93)	0.001
mRS score 0–1 at 90 days	0.91 (0.82–1.02)	0.103	0.87(0.77–0.99)	0.035
mRS score 0–2 at 90 days	0.85 (0.76–0.95)	0.004	0.81(0.71–0.92)	0.001
Any intracranial hemorrhage within 7 days	1.22 (1.08–1.37)	0.002	1.22(1.06–1.41)	0.007
Death or neurological deterioration† within 7 days	1.35 (1.18–1.54)	<0.0001	1.48(1.23–1.79)	<0.0001
Death within 90 days	1.32 (1.13–1.55)	0.001	1.32(1.12–1.55)	0.001
Any serious adverse event within 90 days	1.37 (1.23–1.54)	<0.0001	1.35(1.18–1.54)	<0.0001
	Magnitude		Magnitude	
	Baseline-minimum ≤1 h		Baseline-minimum ≤24 h	
Favorable shift on the mRS score at 90 days	1.00 (0.97–1.04)	0.969	1.03 (0.99–1.08)	0.117
mRS score 0–1 at 90 days	1.01 (0.96–1.05)	0.823	1.04 (0.98–1.09)	0.176
mRS score 0–2 at 90 days	0.99 (0.94–1.03)	0.542	1.04 (0.99–1.10)	0.124
Any intracranial hemorrhage within 7 days	1.01 (0.96–1.06)	0.685	1.00 (0.94–1.06)	0.936
Death or neurological deterioration† within 7 days	1.06 (1.00–1.12)	0.041	0.91 (0.84–0.99)	0.029
Death within 90 days	0.98 (0.91–1.05)	0.500	1.01 (0.95–1.09)	0.683
Any serious adverse event within 90 days	1.00 (0.95–1.04)	0.877	1.02 (0.96–1.07)	0.578

mRS indicates modified Rankin Scale (scores are 0=no symptoms, 1=symptoms without disability, 2=disability but independent function, 3=disability with some assistance, 4=disability with moderate assistance, 5=bedridden, full dependency, and 6=death); NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and SBP, systolic blood pressure.

*OR per 10 mm Hg increase in SBP summary measure, adjusted for age, sex, Asian vs non-Asian, degree of neurological impairment (NIHSS score), premorbid function (mRS scores 0 or 1), premorbid use of antithrombotic agents (aspirin, other antiplatelet agent, or warfarin) and antihypertensive agents, and history of hypertension, stroke, coronary artery disease, diabetes, and atrial fibrillation, and randomized treatment (intensive BP control, guideline-recommended BP control, low-dose alteplase and standard-dose alteplase).

†Neurological deterioration defined as an increase of ≥4 points on the NIHSS or a decline of ≥2 on the Glasgow Coma Scale within 24 h postrandomization.

OR were 0.85 (95% CI, 0.82–0.89; *P*<0.0001) and 0.84 (95% CI, 0.76–0.93; *P*=0.028) per 10 mm Hg increase, respectively. Attained SBP was significantly associated with mRS scores 0 to 1 (0.81 [0.77–0.85]; *P*<0.0001); death or neurological deterioration within 7 days (1.25 [1.16–1.33]; *P*<0.0001), but not for any ICH, death, and any serious adverse event (Table 2). There were significant linear associations between SBP variability and all the other outcomes: adjusted OR per 10 mm Hg SBP increase for mRS scores 0 to 2 (0.85 [0.76–0.95]; *P*=0.004); any ICH (1.22 [1.08–1.37]; *P*=0.002); death or neurological deterioration within 7 days (1.35 [1.18–1.54]; *P*<0.01); death (1.32 [1.130–1.55]; *P*=0.001); and serious adverse event (1.37 [1.23–1.54]; *P*<0.0001).

Assessment of the SBP summary measures as categories produced some variation in the shape and significance of associations with outcomes (Figure; Table I in the Supplemental Material). The general pattern was for lower categories of attained SBP to be associated with greater odds of favorable outcomes. However, a significant linear trend existed for functional status, whereby attained SBP levels of 110 to 120 mm Hg were associated with the lowest odds of the favorable outcome. For variability, there were significantly positive linear trends across categories with unfavorable outcomes, except for ICH. No significant associations were apparent with the increasing magnitude of SBP reduction.

The associations of SBP summary measures and functional outcomes were consistent in sensitivity

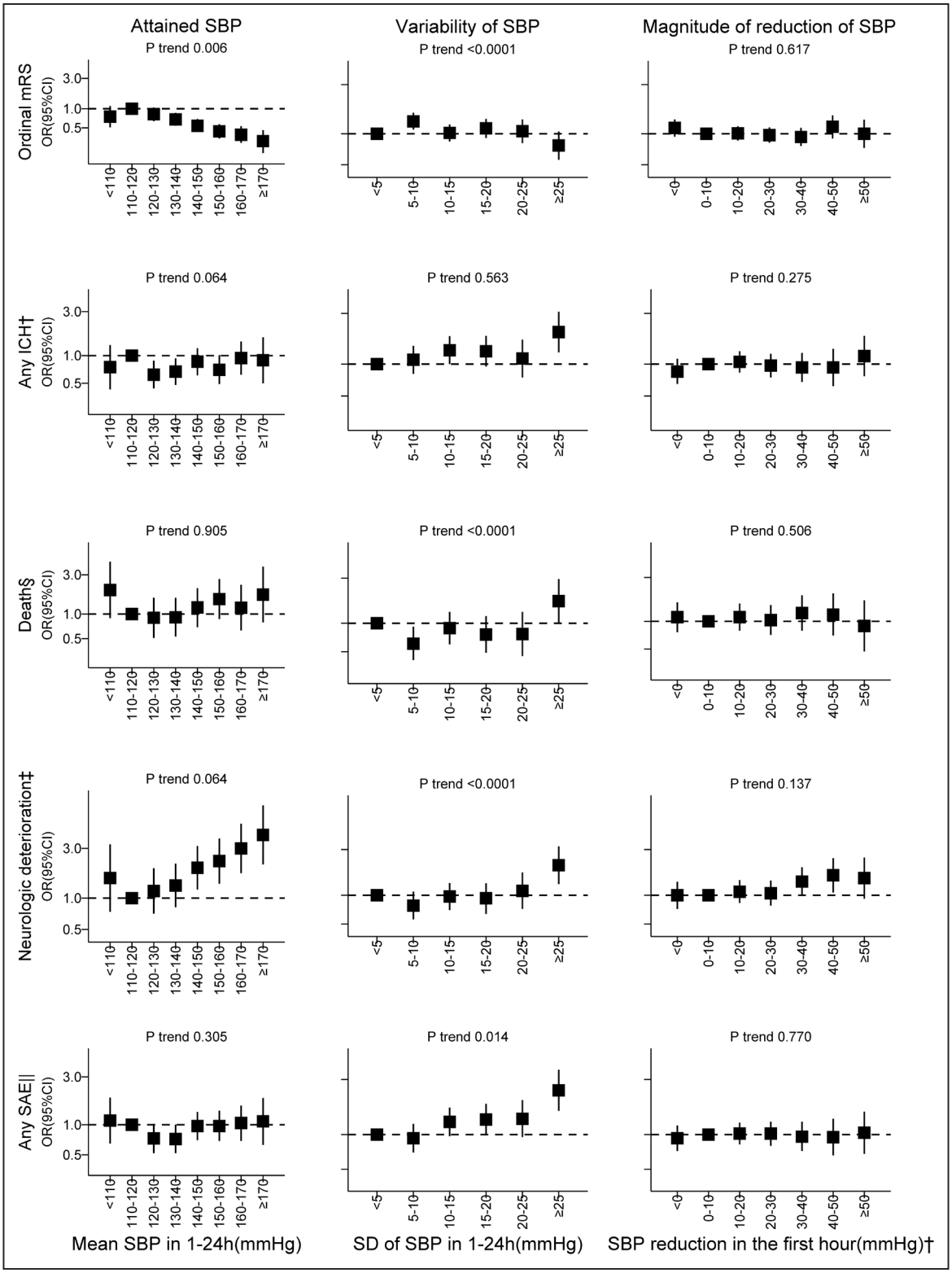

Figure. Associations of categorical systolic blood pressure (SBP) summary measures and outcomes.
*Any intracranial hemorrhage (ICH) within 7 d. †Death or neurological deterioration defined as an increase of ≥4 points on the National Institutes of Health Stroke Scale (NIHSS) or a decline of ≥2 on the Glasgow Coma Scale within 7 d postrandomization. ‡Any serious adverse event (SAE) within 90 d. Odds ratio (OR) and 95% CI are comparisons between each category and the reference, adjusted for age (<65 vs ≥65), sex, ethnicity (Asian vs non-Asian), degree of neurological impairment (NIHSS score <8 vs ≥8), premorbid function (modified Rankin Scale [mRS] scores 0 vs 1), premorbid use of antithrombotic agents (aspirin, other antiplatelet agent, or warfarin) and antihypertensive agents, and history of hypertension, stroke, coronary artery disease, diabetes mellitus, and atrial fibrillation, and randomized treatment (intensive blood pressure control, guideline-recommended blood pressure control, low-dose alteplase, and standard-dose alteplase).

analyzes using complete case data (Table II in the Supplemental Material) and BP control parameters from 2 to 7 days (Table III in the Supplemental Material). There were significant interactions between history of hypertension (P=0.007 for interaction) and SBP summary measures with functional status (Table IV in the Supplemental Material). For patients with a history of hypertension, every 10 mm Hg increase in attained and variability of SBP were associated with ≈25% increased odds of unfavorable functional status. The association of the variability of SBP reduction and functional status was attenuated and not significant in patients with history of hypertension (Table V in the Supplemental Material).

Table VI in the Supplemental Material shows that the three SBP summary measures had equal importance on associations with outcomes: relative influence of attained, variability, and magnitude on ordinal analysis of the mRS (12.74, 14.66, and 13.66, respectively) and any ICH (16.39, 18.97, and 19.26, respectively).

DISCUSSION

In these post hoc secondary analyzes of SBP data from 4511 thrombolyzed AIS participants of the ENCHANTED trial, we have shown continuous associations between SBP levels over 24 hours and clinical outcomes. Specifically, for every 10 mm Hg of SBP reduction down to as low as 110 to 120 mm Hg early after symptom onset, there was a ≈20% reduction in the odds of unfavorable functional status, and separately, greater SBP variability over 24 hours was similarly related to poor functional outcome and ICH.

There have been several lines of investigation over optimal SBP in thrombolyzed AIS patients,[15–17] with higher mean levels, greater variability, and a more modest reduction in SBP being associated with unfavorable outcomes. However, these studies may not have fully accounted for confounders and interactions between variables. Our analyzes, therefore, extend such data in providing new observation on the prognostic significance of early SBP control in AIS. Using continuous data, our finding of higher attained SBP and unfavorable outcomes in AIS supports results of the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register,[17] where U-shaped relations of functional outcome and death centered around a nadir SBP of 141 to 150 mm Hg for optimal favorable outcome was evident. Our analyzes showed more skewed, J-shaped relationships for adverse outcomes, with a nadir as low as 110 to 120 mm Hg, which is much lower than the guideline recommendation of SBP <180 mm Hg. Although an excess in mortality for hospitalized AIS patients has been shown for SBP levels of <100 mm Hg and SBP <120 mm Hg on admission and discharge, respectively,[23] we did not find any clear safety concerns from SBP lowering to these levels in our analyzes, and provides some reassurance over genuine concerns of harm from such treatment promoting cerebral ischemia in the vulnerable penumbral region in AIS. The rationale is that high systemic BP is required to maintain penumbral blood flow from altered cerebral autoregulation in AIS,[24,25] and that elevated BP is reactive and naturally declines in most cases over several days.[26] Yet, data are accumulating showing not significant hypoperfusion from intensive BP lowering in those with altered cerebral perfusion thresholds and impaired cerebral autoregulation.[27]

Our analyzes also provide support for a prior meta-analysis[28] showing a link between greater SBP variability and poor functional outcome being extended to include a broad range of adverse outcomes including ICH. It is plausible that large fluctuations in SBP may stress the endothelium of cerebral vessels of the ischemic brain and trigger hemorrhage. Furthermore, we provide further support for previous analyzes showing that a lower SBP is associated with a reduced risk of death and disability, such as in the third IST-3 (International Stroke Trial) where a modest decline in SBP (10-20 mm Hg) from use of any BP treatment within 24 hours of symptom onset was associated with reduced risk of unfavorable outcome, irrespective of the type of agents used.[19] Conversely, the TIMS-China (Thrombolysis Implementation and Monitor of acute ischemic stroke in China) study showed that a substantial decrease (>25 mm Hg), compared with a moderate decrease (12–24 mm Hg), in SBP over 24 hours was significantly associated with a better outcome[20]; although either a large increase (>25 mm Hg) or no change in SBP was also significantly associated with ICH as compared with a small decrease (1–9 mm Hg) in SBP.

Strengths of our study include the large and international data set, where the high component of vascular comorbidity was highlighted with some two-thirds of AIS patients having a history of hypertension and nearly half taking antihypertensive medication. The pragmatic design and practice-mirroring frequency of BP measurements with analyzes that sort to provide a comprehensive assessment of SBP change in the context of multiple confounders provides some reassurance over the generalizability of the findings to real-world clinical practice. Weaknesses include the important point that we have used the ENCHANTED trial as a cohort study, and many of the observed BP changes were NOT as a result of a randomized comparison. Therefore, despite our efforts to determine the independent significance, ranking, and shape of associations of key early SBP control summary measures, we cannot presume causality in such observational analyzes, and such multiple post hoc testing raises the potential for chance associations. The BP Arm of ENCHANTED did not show any treatment effect on the standard primary functional outcome, possibly due to only modest SBP differences being attained between randomized groups in a patient group with predominantly

mild-moderate neurological impairment. We conducted regression imputation, so the variability of the imputed data might be underestimated. Uncertainty persists over the balance of benefits and risks of intensive BP lowering in patient subgroups, in particular for those eligible for modern endovascular thrombectomy for treatment of large vessel occlusive AIS, and in patients with carotid stenosis.

In summary, we have shown that early rapid and sustained SBP reduction to levels below140 mm Hg over 24 hours are associated with more favorable outcomes after thrombolysis for AIS.

ARTICLE INFORMATION

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Supplemental Material

Tables I–VI
Figures I and II

REFERENCES

1. Qureshi AI, Ezzeddine MA, Nasar A, Suri MF, Kirmani JF, Hussein HM, Divani AA, Reddi AS. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med*. 2007;25:32–38. doi: 10.1016/j.ajem.2006.07.008
2. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA; IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke*. 2002;33:1315–1320. doi: 10.1161/01.str.0000014509.11540.66
3. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al; American Heart Association Stroke Council. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e110. doi: 10.1161/STR.0000000000000158
4. Royal college of physicians intercollegiate stroke working party. *National clinical guideline for stroke*, 5th edition. Royal college of physicians 2016.

5. Anderson CS, Woodward M, Arima H, Chen X, Lindley RI, Wang X, Chalmers J, Robinson TG. Statistical analysis plan for evaluating different intensities of blood pressure control in the ENhanced Control of Hypertension And Thrombolysis strokE stuDy. *Int J Stroke*. 2019;14:555–558. doi: 10.1177/1747493018806170
6. Huang Y, Sharma VK, Robinson T, Lindley RI, Chen X, Kim JS, Lavados P, Olavarría V, Arima H, Fuentes S, et al; ENCHANTED investigators. Rationale, design, and progress of the ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED) trial: An international multicenter 2×2 quasi-factorial randomized controlled trial of low- vs. standard-dose rt-PA and early intensive vs. guideline-recommended blood pressure lowering in patients with acute ischaemic stroke eligible for thrombolysis treatment. *Int J Stroke*. 2015;10:778–788. doi: 10.1111/ijs.12486
7. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee TH, Broderick JP, Chen X, Chen G, Sharma VK, et al; ENCHANTED Investigators and Coordinators. Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. *N Engl J Med*. 2016;374:2313–2323. doi: 10.1056/NEJMoa1515510
8. Anderson CS, Huang Y, Lindley RI, Chen X, Arima H, Chen G, Li Q, Billot L, Delcourt C, Bath PM, et al; ENCHANTED Investigators and Coordinators. 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;393:877–888. doi: 10.1016/S0140-6736(19)30038-8
9. Anderson CS, Woodward M, Arima H, Chen X, Lindley RI, Wang X, Chalmers J; ENCHANTED Investigators. Statistical analysis plan for evaluating low- vs. standard-dose alteplase in the ENhanced Control of Hypertension and Thrombolysis strokE stuDy (ENCHANTED). *Int J Stroke*. 2015;10:1313–1315. doi: 10.1111/ijs.12602
10. Manning L, Hirakawa Y, Arima H, Wang X, Chalmers J, Wang J, Lindley R, Heeley E, Delcourt C, Neal B, et al; INTERACT2 investigators. Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. *Lancet Neurol*. 2014;13:364–373. doi: 10.1016/S1474-4422(14)70018-3
11. Wang X, Arima H, Heeley E, Delcourt C, Huang Y, Wang J, Stapf C, Robinson T, Woodward M, Chalmers J, et al; INTERACT2 Investigators. Magnitude of blood pressure reduction and clinical outcomes in acute intracerebral hemorrhage: intensive blood pressure reduction in acute cerebral hemorrhage trial study. *Hypertension*. 2015;65:1026–1032. doi: 10.1161/HYPERTENSIONAHA.114.05044
12. Moullaali TJ, Wang X, Martin RH, Shipes VB, Qureshi AI, Anderson CS, Palesch YY. Statistical analysis plan for pooled individual patient data from two landmark randomized trials (INTERACT2 and ATACH-II) of intensive blood pressure lowering treatment in acute intracerebral hemorrhage. *Int J Stroke*. 2019;14:321–328. doi: 10.1177/1747493018813695
13. Arima H, Heeley E, Delcourt C, Hirakawa Y, Wang X, Woodward M, Robinson T, Stapf C, Parsons M, Lavados PM, et al; INTERACT2 Investigators; INTERACT2 Investigators. Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2. *Neurology*. 2015;84:464–471. doi: 10.1212/WNL.0000000000001205
14. Moullaali TJ, Wang X, Martin RH, Shipes VB, Robinson TG, Chalmers J, Suarez JI, Qureshi AI, Palesch YY, Anderson CS. Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. *Lancet Neurol*. 2019;18:857–864. doi: 10.1016/S1474-4422(19)30196-6
15. Butcher K, Christensen S, Parsons M, De Silva DA, Ebinger M, Levi C, Jeerakathil T, Campbell BC, Barber PA, Bladin C, et al; EPITHET Investigators. Postthrombolysis blood pressure elevation is associated with hemorrhagic transformation. *Stroke*. 2010;41:72–77. doi: 10.1161/STROKEAHA.109.563767
16. Waltimo T, Haapaniemi E, Surakka IL, Melkas S, Sairanen T, Sibolt G, Tatlisumak T, Strbian D. Post-thrombolytic blood pressure and symptomatic intracerebral hemorrhage. *Eur J Neurol*. 2016;23:1757–1762. doi: 10.1111/ene.13118
17. Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M, Lees KR, Toni D; SITS Investigators. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). *Stroke*. 2009;40:2442–2449. doi: 10.1161/STROKEAHA.109.548602
18. Endo K, Kario K, Koga M, Nakagawara J, Shiokawa Y, Yamagami H, Furui E, Kimura K, Hasegawa Y, Okada Y, et al. Impact of early blood pressure variability on stroke outcomes after thrombolysis: the SAMURAI rt-PA Registry. *Stroke*. 2013;44:816–818. doi: 10.1161/STROKEAHA.112.681007
19. Berge E, Cohen G, Lindley RI, Sandercock P, Wardlaw JM, Sandset EC, Whiteley W. Effects of blood pressure and blood pressure-lowering treatment during the first 24 hours among patients in the Third International Stroke Trial of Thrombolytic Treatment for Acute Ischemic Stroke. *Stroke*. 2015;46:3362–3369. doi: 10.1161/STROKEAHA.115.010319
20. Wu W, Huo X, Zhao X, Liao X, Wang C, Pan Y, Wang Y, Wang Y; TIMS-CHINA investigators. Relationship between blood pressure and outcomes in acute ischemic stroke patients administered lytic medication in the TIMS-China Study. *PLoS One*. 2016;11:e0144260. doi: 10.1371/journal.pone.0144260
21. Li C, Zhang Y, Xu T, Peng H, Wang D, Xu T, Sun Y, Bu X, Chen CS, Wang A, et al; CATIS investigators. Systolic blood pressure trajectories in the acute phase and clinical outcomes in 2-year follow-up among patients with ischemic stroke. *Am J Hypertens*. 2019;32:317–325. doi: 10.1093/ajh/hpy174
22. Friedman JH. Stochastic gradient boosting. *Comput Stat Data Anal*. 2002;38:367–378
23. Wohlfahrt P, Krajcoviechova A, Jozifova M, Mayer O, Vanek J, Filipovsky J, Cifkova R. Low blood pressure during the acute period of ischemic stroke is associated with decreased survival. *J Hypertens*. 2015;33:339–345. doi: 10.1097/HJH.0000000000000414
24. Olsen TS, Larsen B, Herning M, Skriver EB, Lassen NA. Blood flow and vascular reactivity in collaterally perfused brain tissue. Evidence of an ischemic penumbra in patients with acute stroke. *Stroke*. 1983;14:332–341. doi: 10.1161/01.str.14.3.332
25. Powers WJ. Acute hypertension after stroke: the scientific basis for treatment decisions. *Neurology*. 1993;43(3 pt 1):461–467. doi: 10.1212/wnl.43.3_part_1.461
26. Wallace JD, Levy LL. Blood pressure after stroke. *JAMA*. 1981;246:2177–2180.
27. Croall ID, Tozer DJ, Moynihan B, Khan U, O'Brien JT, Morris RG, Cambridge VC, Barrick TR, Blamire AM, Ford GA, et al; PRESERVE Study Team. Effect of standard vs intensive blood pressure control on cerebral blood flow in small vessel disease: the PRESERVE randomized clinical trial. *JAMA Neurol*. 2018;75:720–727. doi: 10.1001/jamaneurol.2017.5153
28. Manning LS, Rothwell PM, Potter JF, Robinson TG. Prognostic significance of short-term blood pressure variability in acute stroke: systematic review. *Stroke*. 2015;46:2482–2490. doi: 10.1161/STROKEAHA.115.010075