

## **Comparative effects of intensive- versus standard-BP lowering treatment in patients with severe ischemic stroke in the ENCHANTED trial**

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**Key words:** thrombolysis, large vessel occlusion, hypertension, recanalization, ischemic stroke, trial

## **ABSTRACT**

**Objective:** Limited data exist on the optimum level of systolic blood pressure (BP) in thrombolized patients with acute ischemic stroke (AIS). We aimed to determine the effects of intensive BP lowering, specifically in patients with severe AIS who participated in the international, Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED).

**Methods:** Pre-specified subgroup analyzes of the BP arm of ENCHANTED, a multicenter, partial-factorial, open, blinded outcome assessed trial, in which 2227 thrombolysis-eligible and treated AIS patients with elevated systolic BP (>150 mmHg) were randomized to intensive (target 130-140 mmHg) or guideline-recommended (<180 mmHg) BP management. Severe stroke was defined by computed tomography or magnetic resonance angiogram confirmation of large-vessel occlusion, receipt of endovascular therapy, final diagnosis of large artery atheromatous disease, or high (>10) baseline neurological scores on the National Institutes of Health Stroke Scale (NIHSS). The primary efficacy outcome was death or any disability (modified Rankin scale [mRS] scores 2-6). The key safety outcome was intracranial hemorrhage (ICH). Treatment effects estimated in logistic regression models are reported as odds ratios with 95% confidence intervals (CIs).

**Results:** There were 1,311 patients (mean age 67 years; 37% female; median baseline NIHSS of 11 [range 6.0-15.0]) with severe AIS. Overall, there was no significant difference in the primary outcome of death or disability. However, intensive BP lowering significantly increased mortality (odds ratio 1.52, 95% CI 1.09-2.13; P=0.014) compared to guideline BP lowering, despite significantly lowering clinician-reported ICH (odds ratio 0.63, 95% CI 0.43-0.92; P=0.016).

**Conclusion:** Intensive BP lowering is associated with increased mortality in patients with severe AIS despite lowering the risk of ICH. Further randomized trials are required to provide reliable evidence over the optimum systolic BP target in the most serious type of AIS.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT01422616

## INTRODUCTION

Guidelines have understandably extrapolated the conventionally-recommended conservative level of blood pressure (BP) control (<180 AND <105 mmHg) in patients with acute ischemic stroke (AIS) eligible for reperfusion therapy with intravenous thrombolysis to those patients with large vessel occlusion, the most serious type of AIS [1]. However, as there is limited direct randomized evidence, wide ranging opinions exist as to the most appropriate level of systolic BP control before, during and after, endovascular thrombectomy for large vessel occlusion AIS [2]. The situation appears complex, with poor functional outcome associated with high pre-endovascular thrombectomy systolic BP (>140mmHg) [3], low intra-procedural systolic BP (<140 mmHg) with general anaesthesia [4], and high systolic BP immediately post endovascular thrombectomy (>160mmHg) [5]. Moreover, post-hoc analyses of the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial suggest J- or U-shaped correlations of baseline systolic BP and adverse outcome [3]. All these data suggest that ‘moderate’ levels of systolic BP control could provide the optimal outcome from endovascular thrombectomy, but there are ongoing concerns that BP lowering treatment may increase the risk of harms in large vessel occlusion AIS [6], particularly where the AIS lesion is large [7].

Recently, the BP arm of the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) showed no overall benefit of intensive BP reduction (systolic BP target 130-140 mmHg) compared with guideline BP control (<180 mmHg) in thrombolysis-eligible AIS patients [8, 9], despite a significant reduction in intracranial hemorrhage (ICH). However, only a modest 5 mmHg systolic BP separation was achieved between the randomized groups, most AIS patients had mild-moderate neurological severity (median NIHSS score 7), and few had endovascular thrombectomy which was being introduced into routine clinical practice during the course of the trial. Although there was no significant heterogeneity of the treatment effect

by neurological severity and across other pre-specified subgroups, we wished to undertake more detailed investigation of the effects of intensive versus guideline systolic BP lowering in patients with severe AIS.

## **MATERIALS AND METHODS**

### *Study design*

These are post-hoc analyzes of ENCHANTED, an international, 2x2 partial-factorial, multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE) trial, as outlined elsewhere [8, 9]. In brief, the study included adult patients (age  $\geq 18$  years) with a clinical diagnosis of AIS confirmed by brain imaging who fulfilled standard criteria for thrombolysis treatment, including having a systolic BP  $\leq 185$  mmHg. The BP arm recruited 2227 participants with elevated systolic BP ( $\geq 150$  mmHg), where the treating clinician was uncertain of the balance of benefits and risks of different intensities of BP control over 72 hours (or hospital discharge [or death], if earlier) post-thrombolysis, between March 3, 2012 and April 30, 2018. Participants were randomly assigned to a strategy of intensive BP lowering (target systolic BP 130–140 mmHg  $< 60$  mins) or guideline-recommended BP lowering (target systolic BP  $< 180$  mmHg) within 6 hours of intravenous alteplase.

### *Definition of Severe Stroke*

For these analyzes, we pragmatically defined severe stroke as having at least one of the following characteristics: large vessel occlusion confirmed either on computed tomography or magnetic resonance angiogram (n=84) or use of endovascular thrombectomy (n=42), or clinician-reported final diagnosis of large artery atheromatous disease (due to significant intra- or extracranial atheroma) (n=952); and all patients with a high baseline score ( $> 10$ ) on the NIHSS (n=701).

### *Procedures*

Socio-demographic and clinical details were obtained at the time of randomization. BP lowering treatment was undertaken according to standardized protocols based upon the use of locally available intravenous (bolus and infusion), oral and/or topical antihypertensives. All patients were managed in an acute stroke unit, or alternative environment with appropriate staffing and monitoring, and received active care with best practice management according to guidelines. 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  $\geq 3$  minutes according to a standard protocol. BP measurements were recorded every 15 minutes for 1 hour, and 6-hourly from 1 to 24 hours, post-thrombolysis, and then twice daily for 7 days (or hospital discharge or death, if earlier). Neurological status, according to the NIHSS and Glasgow Coma Scale (GCS) scores, was assessed at baseline, and at 24 and 72 hours, and 7 days. Brain imaging (computed and/or magnetic resonance imaging) was conducted at baseline, and at 24 hours, and additionally if clinically indicated; analyzes were undertaken centrally for diagnoses of categories of ICH by trained readers blind to clinical details and treatment allocation. Clinical outcome data were collected at 24 and 72 hours, 7 days (or at hospital discharge if earlier), and 28 and 90 days.

### *Outcomes*

The primary efficacy outcome was death or any disability, defined as scores 2-6 on the modified Rankin scale (mRS). Secondary outcomes included death or major disability (mRS scores 3-6), all-cause specific mortality, and death or neurological deterioration ( $\geq 4$  points decline in NIHSS) within 24 and 72 hours. The key secondary safety outcome was any ICH reported by investigators with or without central adjudication of relevant brain imaging within 7 days post-randomization. Other safety outcomes included the topography of ICH identified on centrally adjudicated brain images in relation to a patient's symptoms: that is, symptomatic ICH,

whereby an ICH leads to significant neurological deterioration and/or death, as defined by several criteria used in other studies [8].

### *Statistical analysis*

Dichotomous logistic regression analyses were used to assess the treatment effect. Data were presented as odds ratios and 95% confidence intervals (CI). A priori [9], the primary analysis for the effect of intensive versus guideline-recommended BP lowering was unadjusted. Sensitivity analyses were performed on the subgroup of high baseline NIHSS (>10) and final diagnosis of large artery atheromatous disease to confirm the consistency of any association. All tests were two-sided and the significance level was set at 5%. SAS software version 9.3 was used for analyses.

## **RESULTS**

There were 1,311 patients (mean age  $67\pm 12$  years; 37% female; median baseline NIHSS of 11 [range 6.0-15.0]) with severe AIS included in these analyzes (Figure I in the Supplementary Files). Computed tomography or magnetic resonance angiographic imaging was performed in 84 patients (6.4%), with large vessel occlusion identified in 56 (4.3%) and endovascular thrombectomy performed in 42 (3.2%) patients. In our severe stroke group there were no significant differences in the baseline characteristics or management over 7 days between the guideline and intensive BP lowering groups (Table 1 and Table I in Supplementary Files). There were 938 (72%) patients with a history of hypertension, and 576 (44%) were on prior antihypertensive therapy. In keeping with the randomized allocation, patients in the intensive BP lowering group were more likely to have received BP lowering therapy, in particular intravenous agents within 24 hours and all types of therapy from 24 hours to Day 7 (Table I in Supplementary Files); with significant between-group systolic BP differences post-randomization (Figure 1).

Overall, there was no significant difference in the primary outcome of death or disability (mRS scores 2-6), between the guideline and intensive BP lowering in patients with severe AIS (Table 2 and Figure 2). However, there was a significant reduction in clinician-reported ICH with intensive BP lowering (odds ratio 0.63, 95% CI 0.43-0.92; P=0.016), but this was not significant for the key safety outcome of any ICH (P=0.065). There were no significant treatment differences in symptomatic ICH across a range of definitions but there was a significant increase in deaths (odds ratio 1.52, 95% CI 1.09-2.13; P=0.014) in the intensive BP lowering group, compared to guideline BP lowering (Table 2).

Sensitivity analyses demonstrated a significant association between high baseline NIHSS (>10) and death within 90 days (odds ratio 1.57, 95% CI 1.08-2.28; P=0.018) and death or neurological deterioration in 7 days (odds ratio 1.57, 95% CI 1.07-2.31; P=0.021) (Table I in Supplementary Files).

## **DISCUSSION**

In these post-hoc secondary analyzes of the ENCHANTED study, we have shown that in the subgroup of severe AIS patients, there were diverging effects of increased death and reduced ICH from intensive BP lowering, but without any influence on the overall odds of good functional outcome.

A widely accepted hypothesis is that any potential benefits of intensive BP lowering in reducing the risk of re-perfusion ICH are offset by worsening functional outcome from exacerbating the ischemic penumbra [10, 11]. However, previous meta-analyses have not clearly shown that early BP lowering treatment adversely affects the likelihood of death, dependency, stroke recurrence, and other vascular outcomes [7]. Overall, the BP arm of ENCHANTED showed that BP lowering treatment is safe, and appears to reduce the likelihood of ICH. However, as there was no influence on functional outcome, it is possible that these benefits on ICH risk were

independent of the ischemic lesion, although the systolic BP differences over time between randomized groups were small.

Our finding of increased mortality from intensive BP lowering has physiological rationale from a cerebral hemodynamic perspective: moderate-severe AIS is associated with greater cerebral blood flow velocity asymmetries between unaffected and affected hemispheres, worsened cerebral autoregulation ipsilateral to the infarct, and bilateral neurovascular coupling impairment [12]. It is accepted that in ambulatory subjects with mild and moderate hypertension, the brain is able to quickly adapt the cerebral vasculature to protect against hypoperfusion when antihypertensive therapy is commenced [13]. However, in those with chronic hypertension, akin to over 70% of patients within this study, the autoregulatory curve is presumed to have shifted to right, although individual variability exists as to the magnitude of such a shift, or indeed its timing [14]. Unfortunately, this shift may potentiate an increased likelihood of harm as the lower limit of autoregulation and acute hypoperfusion in the presence of large vessel occlusion may explain why intensive BP lowering has adverse outcome. However, in hypertensives without acute cerebrovascular disease, as included in the randomized trial of intensive versus standard BP control (SPRINT) trial, the intensive (<120mmHg) BP target was associated with lower incidence of stroke and overall lower all-cause mortality. Our study does not support patients with acute (or acute on chronic) hypertension and AIS being treated with a similar intensive strategy [15].

Nonetheless, intensively lowering BP was associated with less ICH. Previously, very limited small retrospective analyses have examined clinical outcome in those receiving BP lowering pre-thrombolysis. This showed no relationship to higher rates of ICH or poor outcome [10]. Our results suggest that as ICH occurrence was lower in the intensively managed group; ICH occurrence alone does not explain the increased risk of death in the intensively lowered group at day 90.

ENCHANTED was first randomized clinical trial to examine the effects of intensive BP lowering in thrombolysed patients, and herein we have attempted to explore the effects of such treatment in those with severe AIS. Prior data from subgroup analyzes of the angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST) trial demonstrated no association with composite vascular endpoint or functional outcome in those receiving blood pressuring lowering and thrombolysis for AIS [16]. The large sample of a broad range of AIS patients who had systematic outcome assessments are strengths of the ENCHANTED trial. However, a clear limitation is the inability to systematically confirm the presence of large vessel occlusion angiographically, although there is clear correlation between NIHSS scores and large vessel occlusion on arteriogram. An additional consideration is the generalizability of the findings with reference to 90-day outcome, particularly if the hypothesis of BP lowering in the presence of impaired autoregulation associated with severe AIS is to be considered [14]. Concerns over generalizability may also be raised by the majority of the cohort being Asian but it could be argued that this ethnic group may be at high risk of risks of hypoperfusion and worsening ischemia from their a high prevalence of intracranial atheromatous disease and cerebral small vessel disease. In addition, without data on carotid status, we are unable to infer whether this contributed to potential risks of hypoperfusion and subsequent mortality [11]. Lastly, we did not assess whether recanalization occurred, or the extent to which BP varied, within the first 24 hours post-AIS, which is relevant to systolic BP variability and outcomes [17].

In summary, our study has shown that in patients suffering severe AIS, intensive BP lowering treatment showed benefits of reduced ICH and increased odds of death, without this translating into any over change in functional recovery. Given the increasing use of endovascular thrombectomy in severe AIS, there is urgent need to establish the most appropriate level of BP control that provides the optimal balance of potential benefits and harms.

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**Itemised list of tables and figures:**

**Table 1.** Baseline characteristics

**Table 2:** Efficacy and safety outcomes at 90 days

**Figure 1.** Mean systolic and diastolic blood pressure from randomization to Day 7

**Figure 2.** Distribution of modified Rankin scale scores at 90 days, by BP treatment strategy

**Table 1. Baseline characteristics in patients with severe acute ischemic stroke**

	BP lowering group		P value
	Guideline (n=669)	Intensive (n=642)	
Time from onset to randomization, hr	3.3 (2.6 - 4.0)	3.3 (2.5 - 4.1)	0.961
Age, yr	67.4 (11.8)	67.1 (12.4)	0.852
Female	255 (38.1)	225 (35.0)	0.249
Asian	549 (82.1)	507 (79.0)	0.158
Systolic BP, mmHg	165 (9)	165 (9)	0.972
Diastolic BP, mmHg	91 (11)	91 (12)	0.824
Heart rate, b.p.m.	79 (15)	79 (15)	0.832
Alteplase dose, mg	0.8 (0.1)	0.8 (0.1)	0.702
Glasgow coma score	14(13 - 15)	14 (12 - 15)	0.381
NIHSS	11 (6 - 15)	11 (6 - 15)	0.647
History of hypertension	478 (71.4)	460 (71.8)	0.900
Antihypertensive agent(s) use	286 (42.8)	290 (45.2)	0.364
History of stroke	137 (20.5)	138 (21.5)	0.651
History of coronary artery disease	105 (15.7)	116 (18.1)	0.246
History of other heart disease	35 (5.2)	28 (4.4)	0.465
History of diabetes mellitus	156 (23.3)	139 (21.7)	0.479
History of hypercholesterolemia	62 (9.3)	63 (9.8)	0.730
Cigarette smoker	145 (21.7)	128 (20.0)	0.456
Premorbid function			
mRS score 0	577 (86.2)	545 (85.0)	0.527
mRS score 1	92 (13.8)	96 (15.0)	
Antiplatelet use	108 (16.1)	91 (14.2)	0.326
Anticoagulant use	10 (1.5)	9 (1.4)	0.891
Glucose lowering therapy	91 (13.6)	77 (12.0)	0.390
Lipid lowering therapy	81 (12.1)	80 (12.5)	0.837

Values are n (%), mean (SD) or median (iqr)

BP denotes blood pressure, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale.

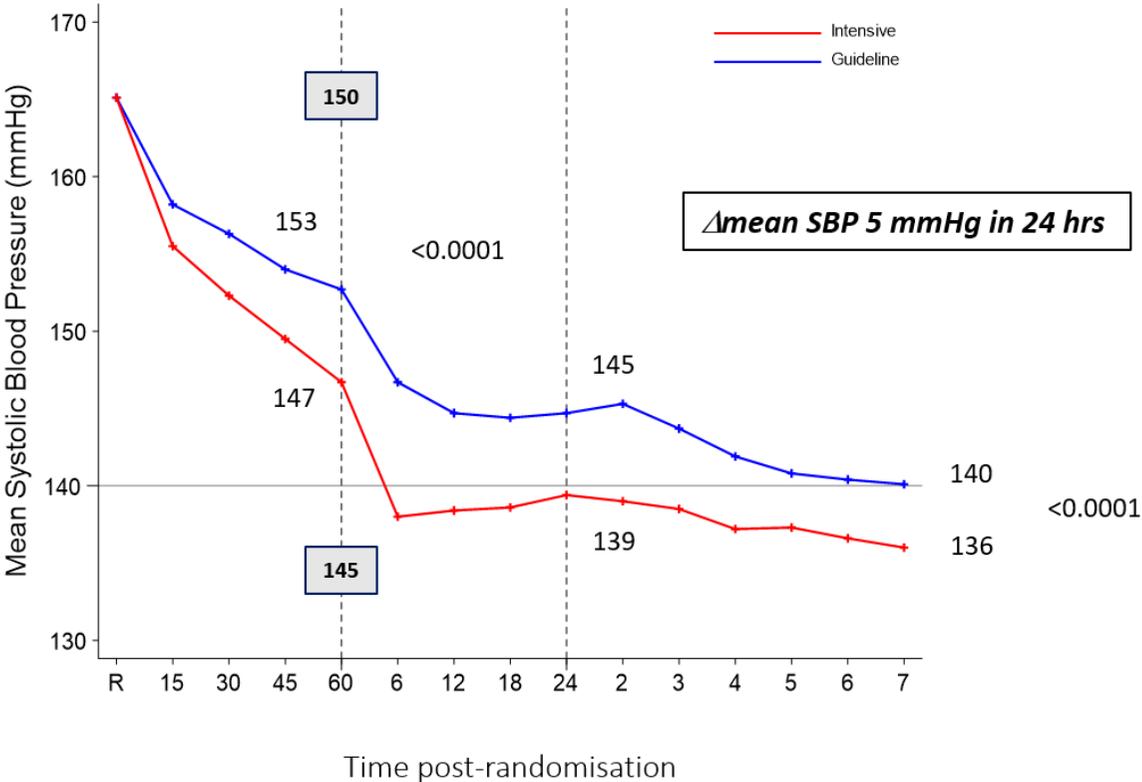
**Table 2. Efficacy and safety outcomes at 90 days in patients with severe acute ischemic stroke**

Outcome	BP lowering group		Odds ratio (95% CI)	P value
	Guideline (n/N, %)	Intensive (n/N, %)		
Death or disability at 90 days (mRS scores 2-6)	378/667 (56.7)	368/638 (57.7)	1.04 (0.84-1.3)	0.713
Death or major disability at 90 days (mRS scores 3-6)	283/667 (42.4)	283/638 (44.4)	1.08 (0.87-1.35)	0.482
Death within 90 days	67/669 (10.0)	93/642 (14.5)	1.52 (1.09-2.13)	0.014
Death or neurological deterioration in 24 hours	78/ 669 (11.7)	86/642 (13.4)	1.17 (0.84-1.63)	0.342
Death or neurological deterioration in 7 days	106/669 (15.8)	124/642 (19.3)	1.27 (0.96-1.69)	0.099
Symptomatic intracerebral hemorrhage				
SITS-MOST criteria	16/669 (2.4)	11/642 (1.7)	0.71 (0.33-1.55)	0.390
NINDS criteria	67/669 (10.0)	61/642 (9.5)	0.94 (0.65-1.36)	0.754
ECASS2 criteria	43/669 (6.4)	41/642 (6.4)	0.99 (0.64-1.55)	0.976
ECASS3 criteria	20/669 (3.0)	18/642 (2.8)	0.94 (0.49-1.79)	0.841
IST-3 criteria	25/669 (3.7)	21/642 (3.3)	0.87 (0.48-1.57)	0.647
Clinician-reported	75/669 (11.2)	47/642 (7.3)	0.63 (0.43-0.92)	0.016
Fatal ( $\leq$ 7 days)	10/669 (1.5)	4/642 (0.6)	0.41 (0.13-1.32)	0.137
Any adjudicated intracerebral hemorrhage	142/669 (21.2)	118/642 (18.4)	0.84 (0.64-1.1)	0.197
Any intracranial hemorrhage	164/669 (24.5)	130/642 (20.2)	0.78 (0.6-1.01)	0.065

BP denotes blood pressure, CI confidence interval, ECASS European Co-operative Acute Stroke Study, IST International Stroke Trial, mRS modified Rankin Scale, NINDS National Institute of Neurological Disorders and Stroke, SITS-MOST Safe Implementation of Thrombolysis in Stroke Monitoring Study.

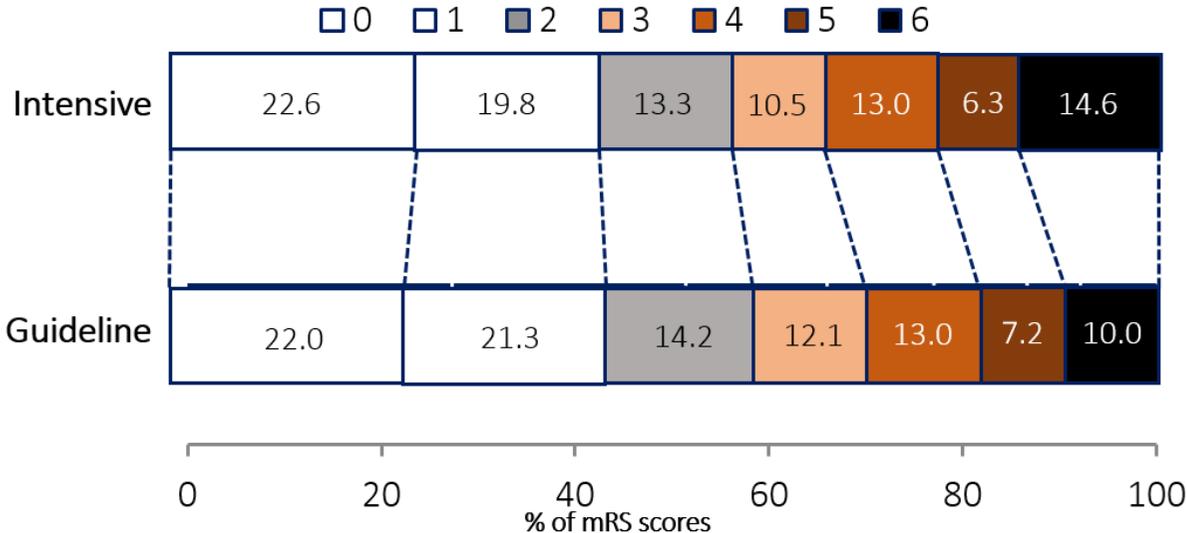
**Figures**

**Figure 1. Mean systolic and diastolic blood pressure from randomization to Day 7 in 1,311 patients with severe acute ischemic stroke**



Footnote: SBP denotes systolic blood pressure

**Figure 2. Distribution of modified Rankin scale scores at 90 days, by BP treatment strategy in 1,311 patients with severe acute ischemic stroke**



Footnote: BP denotes blood pressure