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Blood Pressure Reduction in Acute Ischemic Stroke According to Time to Treatment: A Subgroup Analysis of the CATIS Trial

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Conflicts of interest

None.

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Abstract

Objective—The optimal time to initiate antihypertensive therapy among patients with acute ischemic stroke remains uncertain. We tested the effects of blood pressure (BP) reduction among patients with acute ischemic stroke according to time from onset to initiation of antihypertensive treatment.

Methods—We randomly assigned 4,071 acute ischemic stroke patients with elevated systolic BP to receive antihypertensive treatment or to discontinue all antihypertensive medications during hospitalization. The primary outcome was a combination of death and major disability and secondary outcomes included the modified Rankin score, recurrent stroke, vascular disease events, and all-cause mortality.

Results—At 24 hours after randomization, the differences in systolic BP reductions were 8.7, 9.5, and 9.6 mm Hg between the antihypertensive treatment and control groups among patients receiving treatment within <12, 12–23, and 24–48 hours after stroke onset, respectively ($p<0.001$ in all subgroups). At day 14 or hospital discharge, the primary and secondary outcomes were not significantly different between the treatment and control groups in all subgroups. At the 3-month follow-up, death or major disability (odds ratio 0.73; 95% CI 0.55–0.96; p=0.03), recurrent stroke (odds ratio 0.25; 95% CI 0.08–0.74; p=0.01), and vascular events (odds ratio 0.41; 95% CI 0.18–0.95; p=0.04) were significantly reduced in the antihypertensive treatment group only among participants who received treatment between 24–48 hours.

Conclusions—BP reduction might reduce 3-month death and major disability and recurrent stroke among patients with acute ischemic stroke who receive antihypertensive treatment between 24–48 hours after stroke onset.

Keywords

acute ischemic stroke; antihypertensive treatment; major disability; mortality; recurrent stroke; vascular events

Introduction

Elevated blood pressure (BP) is common in the acute phase of ischemic stroke, occurring in about 75% of all patients [1,2]. However, several large clinical trials have reported that BP reduction with antihypertensive medications does not reduce death or major disability in acute ischemic stroke patients with elevated BP levels [3–5]. In the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS), mean systolic BP was reduced from 166.7 to 144.7 mmHg (12.7%) within 24 hours and to 137.3 mmHg at day 7 after randomization among

patients with acute ischemic stroke [4]. Nevertheless, BP reduction with antihypertensive medications, compared with the absence of hypertensive medication, did not reduce death and major disability at 14 days or 3 months [4].

Elevated BP in patients with acute ischemic stroke often reflects uncontrolled or undiagnosed hypertension. However, an early hypertensive response to physical and psychological stresses from brain ischemia is an important contributing factor for elevated BP in acute ischemic stroke patients. This initial hypertensive response is self-limiting, most marked in the first few hours following the onset of cerebral ischemia, and resolving over several days [6,7]. Therefore, the timing for initiation of antihypertensive treatment could be important in determining clinical outcomes.

CATIS was a multicenter randomized controlled trial designed to test whether moderate lowering of BP within the first 48 hours after the onset of an acute ischemic stroke would reduce death and major disability [4]. It provides a unique opportunity to test the effects of BP reduction on death, major disability, recurrent stroke, and vascular events among patients with acute ischemic stroke according to the pre-specified subgroups of time from onset to antihypertensive treatment within <12, 12–23, and 24–48 hours.

Methods

Trial participants

CATIS was a multicenter, single-blind, blinded end-points randomized clinical trial conducted in 26 hospitals across China. The details of trial design, methods, and main results were published elsewhere [4]. In brief, we recruited 4,071 patients ≥22 years who had ischemic stroke, confirmed by computed tomography or magnetic resonance imaging of the brain within 48 hours of symptom onset and who had an elevated systolic BP between 140 to <220 mm Hg. Patients with a systolic BP ≥220 mm Hg or diastolic BP ≥120 mm Hg, severe heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis, or resistant hypertension; those in a deep coma; and those treated with intravenous thrombolytic therapy were excluded.

CATIS was approved by the institutional review boards at Tulane University in the United States and Soochow University in China, as well as ethical committees at the 26 participating hospitals. Written consent was obtained from all study participants or their immediate family members. A data and safety monitoring board met at least annually to review the accumulating data for safety and to monitor the trial for either superiority or inferiority of BP reduction on the clinical outcomes.

Intervention

In the CATIS trial, the antihypertensive treatment aimed at lowering systolic BP by 10%–25% within the first 24 hours after randomization, achieving a BP <140/90 mmHg within 7 days, and maintaining this level of BP control during the remainder of a patient's hospitalization. Several antihypertensive agents, including intravenous angiotensin-converting enzyme inhibitors (first-line), were used individually or in combination to achieve the targeted BP reduction according to a pre-specified stepwise treatment algorithm

(Supplementary Figure 1). After randomization, patients in the treatment group immediately started study antihypertensive medications according to the protocol while patients in the control group discontinued all antihypertensive medications. At their hospital discharge, patients in both groups were prescribed antihypertensive medications according to clinical guidelines.

Randomization was conducted centrally and was stratified by participating hospitals and use of antihypertensive medications. The randomization schedules were generated using SAS PROC PLAN and concealed until an eligible participant was ready for enrollment. Although treating study physicians and nurses were not blinded to group assignment, the patients and research staff who collected study outcome data were masked to treatment allocation.

Measurements

Patients' demographic characteristics and medical history were collected at the time of enrollment. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating a more severe neurologic deficit) by trained neurologists at baseline, 14 days or hospital discharge, and at a 3-month posttreatment follow-up visit [8]. Computed tomography or magnetic resonance imaging of the brain was performed according to standard techniques to confirm the diagnosis of ischemic stroke in all trial participants. Three BP measurements were obtained at baseline by trained nurses according to a common protocol adapted from procedures recommended by the American Heart Association and the average was used for analysis [9]. BP was measured with the participant in a supine position using a standard mercury sphygmomanometer and one of four cuff sizes (pediatric, regular adult, large adult, or thigh) based on participant arm circumference. After randomization, three BP measurements were obtained every two hours for the first 24 hours, every four hours during the second and third days, and three times a day thereafter until hospital discharge or death.

The primary outcome was a combination of death and major disability, defined as a score of three to five on the modified Rankin Scale. Scores on the modified Rankin Scale range from zero to six, with a score of zero indicating no symptoms; a score of five indicating severe disability; and a score of six indicating death [10]. Secondary outcomes included an ordered seven-level categorical score of the modified Rankin Scale for neurologic functional status, vascular disease events (e.g., vascular deaths, nonfatal stroke, nonfatal myocardial infarction, hospitalized and treated angina, hospitalized and treated congestive heart failure, and hospitalized and treated peripheral arterial disease), recurrent fatal and nonfatal stroke, and all-cause mortality.

Study outcomes were assessed at 14 days or at hospital discharge if earlier than 14 days and at three months in person by trained neurologists and research nurses unaware of treatment assignment. Data on medical history, deaths, vascular events, BP, NIHSS score, and modified Rankin Scale score were obtained. Death certificates were obtained for deceased participants, and hospital data were abstracted for all vascular events. A trial-wide outcomes assessment committee, blinded to treatment assignment, reviewed and adjudicated vascular events based on criteria established in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [11].

Statistical analysis

Data were analyzed according to participants' randomized treatment assignments, regardless of their subsequent medication status (intention-to-treat). Participants were divided into three pre-specified subgroups according to time from stroke onset to the initiation of antihypertensive treatment (<12, 12–23 and 24–48 hours). Within each subgroup, the proportions of participants with the primary and secondary outcomes at 14 days or discharge and at 3-month posttreatment follow-up were compared between the antihypertensive treatment and control groups using a χ^2 test at a 2-sided α level of 5%, without correction for multiple comparisons, because subgroup analysis was used to generate study hypotheses, rather than test a hypothesis. Logistic regression analysis was used to estimate unadjusted odds ratios (ORs) and 95% CIs associated with antihypertensive treatment compared with no antihypertensive treatment. In addition, the median and interquartile range of modified Rankin Scale scores were calculated, and the difference was compared using the Wilcoxon rank-sum test [12]. Ordinal logistic regression was used to estimate the effect of BP reduction on the full range of the modified Rankin scale [13]. We assessed the heterogeneity of the treatment effect on the primary and secondary outcomes according to subgroups by time from onset of stroke to randomization by adding an interaction term in logistic regression models. Data analyses were performed using SAS version 9.4 (SAS Institute Inc) and Stata version 12 (StataCorp).

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 4,071 eligible patients, 2,038 were randomly assigned to receive antihypertensive treatment and 2,033 were assigned to control. All participants were included in analysis at 14 days or hospital discharge and 3,975 (1,988 in intervention and 1,987 in control) participants were included in analysis at 3 months (Supplementary Figure 2).

There were 2,102 participants with stroke onset to treatment within <12 hours (1,018 in intervention and 1,084 in control), 739 were between 12–23 hours (405 in intervention and 334 in control), and 1,230 were between 24–48 hours (615 in intervention and 615 in control). Baseline characteristics were balanced between antihypertensive treatment and control comparison in each of the <12, 12–23 and 24–48 hour subgroups (Table 1).

Blood Pressure Reduction

At 24 hours after randomization, mean systolic BP was reduced by 22.0 (12.7%), 22.3 (12.9%), and 21.3 mmHg (12.5%) in the treatment group, and 13.3 (7.5%), 12.8 (7.4%), and 11.7 mmHg (6.6%) in the control group ($p<0.001$ for all group differences between treatment and control) for patients who received antihypertensive treatment within <12, 12–23, and 24–48 hours, respectively (Figure 1). Mean systolic BP was 137.7, 137.0, and 136.8 mmHg in the treatment group and 146.4, 146.2, and 146.9 mmHg in the control group at day 7 after randomization ($p<0.001$ for all group differences between treatment and control) for

patients who received antihypertensive treatment within <12, 12–23, and 24–48 hours, respectively. The corresponding systolic BP was 135.7, 135.2, and 134.2 mmHg in the treatment group and 143.2, 145.3, and 143.7 mmHg in the control group at day 14 or hospital discharge (p<0.001 for all group differences between treatment and control), respectively.

Clinical Outcomes at 14 Days or Hospital Discharge

At 14 days or hospital discharge, the composite outcome of death or major disability was not significantly different between the treatment and control groups according to subgroups by time from onset to initiation of antihypertensive treatment (Supplementary Table 1). Likewise, the median score from the modified Rankin Scale and death were not significantly different between the treatment and control groups.

Clinical Outcomes at 3 Months

At the 3-month visit, systolic BP was significantly lower in the treatment group than in the control group: −2.8 (−3.8 to −1.7), −2.1 (−4. to −0.2), and −3.7 (−5.0 to −2.4) mmHg among the <12, 12–23 and 24–48 hour subgroups, respectively (Table 2). The composite outcome of death or major disability was not significantly different between the treatment and control groups among patients who received antihypertensive treatment within <12 or 12–23 hours. However, antihypertensive treatment was associated with a 27% reduction in death or major disability (OR 0.73, 95% CI 0.55–0.96, p=0.03) among participants who received treatment between 24–48 hours (Table 3). Likewise, recurrent stroke, vascular events, and the composite outcome of vascular events and death were not significantly different between the treatment and control groups among patients who received antihypertensive treatment within <12 or 12–23 hours. Antihypertensive treatment was associated with a 75% reduction in recurrent stroke (OR 0.25, 95% CI 0.08 to 0.74, p=0.01) and a 59% reduction in vascular events (OR 0.41, 95% CI 0.18 to 0.95, p=0.04) among participants who received treatment between 24–48 hours.

After adjustment for age, sex, and NIHSS score, the effects of antihypertensive treatment on clinical outcomes were similar to those from unadjusted analyses (Supplementary Table 2). For example, the composite outcome of death and major disability, recurrent stroke, and vascular events at 3 months was not significantly different between the treatment and control groups among patients who received antihypertensive treatment <24 hours after stroke onset. On the other hand, recurrent stroke and vascular events at 3 months were significantly reduced and the composite outcome of death and major disability was borderline-significantly reduced among patients who initiated/resumed antihypertensive treatment between 24–48 hours.

Discussion

This pre-specified subgroup analysis of the CATIS trial indicated that initiation or resuming of antihypertensive medications between 24–48 hours after symptom onset might reduce 3-month death and major disability, recurrent stroke, and vascular events among patients with acute ischemic stroke. The difference in vascular events was mainly due to a difference in

recurrent strokes. On the other hand, initiation or resuming of antihypertensive medications within 24 hours of onset did not reduce or increase adverse clinical outcomes among patients with acute ischemic stroke. These findings suggest that antihypertensive treatment could be initiated or resumed among patients with acute ischemic stroke after 24 hours of stroke onset, which supports American Heart Association/American Stroke Association clinical guideline [14].

Our study findings might have important clinical significance. Clinical trials showed a neutral effect of immediate BP reduction within 24 hours after symptom onset on death or dependency among patients with acute ischemic stroke [15]. However, the optimal time to initiate antihypertensive treatment among acute ischemic stroke patients with elevated BP levels has not been established. Experts have recommended not starting antihypertensive drugs within the first 24 hours [14] or within the first seven days of acute ischemic stroke [16].

Our study indicated that BP reduction starting between 24–48 hours after onset might be beneficial among patients with acute ischemic stroke, but there are also other possible explanations for our findings. For example, there was a significant difference in use of antihypertensive medication and BP levels between intervention and control groups at 3 months, especially among those receiving treatment between 24–48 hours, which might have partially contributed to the reduced clinical outcomes associated with antihypertensive treatment in this subgroup. Further, approximately 40% of patients in both groups received an osmotic diuretic (mannitol and/or glycerol) which was not recommended as standard treatment in clinical guidelines. It is also possible that our finding in the 24–48 hour subgroup was due to the play of chance, since this is a subgroup analysis with low statistical power and multiple comparisons problem [17]. Therefore, our study findings cannot provide a definite answer to guide clinical patient care. However, our analysis generates an important clinical hypothesis which should be tested in large clinical trials.

The findings from this subgroup analysis are also different from those from other trials. Several randomized trials have reported that immediate antihypertensive treatment did not reduce or increase adverse clinical outcomes in patients with acute stroke [3–5,18,19], but the Controlling Hypertension and Hypotension Immediately Post-Stroke showed a borderline significant reduction in mortality between antihypertensive and placebo treatment among 179 patients with acute stroke who were treated on average 20 hours following onset [18]. In the Scandinavian Candesartan Acute Stroke Trial (SCAST), the angiotensin-receptor blocker candesartan was associated with a reduced composite vascular endpoint for the subgroup of patients treated very early (<6 hours), although the interaction by subgroups was not significant (p=0·08) [3]. The Efficacy of Nitric Oxide in Stroke (ENOS) Trial subgroup analysis suggested that transdermal glyceryl trinitrate was associated with improved functional outcomes and fewer deaths when administered within 6 hours of stroke onset [5,20].

Elevated BP in patients with acute ischemic stroke usually falls spontaneously over the next few hours or days after onset [6,21]. The potential causes of this transient increase in BP include disturbed cerebral autoregulation, damage or compression of brain regions that

regulate BP, neuroendocrine disturbance, and nonspecific mechanisms such as headache, urine retention, infection, and psychological stress [6,21]. Therefore, an optimal strategy for management of BP might be to avoid antihypertensive treatment during the first 24 hours after stroke onset, when collateral circulation compromise is still a substantial concern in most patients [7,14]. However, approximately 65%–80% of acute stroke patients with elevated BP have a history of hypertension and over 50% have used antihypertensive medications prior to stroke onset [1,2]. Therefore, it may be important to initiate or resume antihypertensive treatment beginning in the 24- to 48-hour period to help prevent secondary injury [7,15]. In addition, hypertension is the most important prevalent risk factor for stroke, and BP reduction is the most effective intervention to prevent recurrent stroke and cardiovascular mortality among patients with a history of stroke [22,23]. Early antihypertensive treatment will help patients to transition to long-term antihypertensive therapy for secondary prevention [7,14]. This subgroup analysis provides data to support a 24-hour delay in antihypertensive treatment among patients with acute ischemic stroke.

In conclusion, this subgroup analysis of the CATIS trial indicates that initiation or resuming of antihypertensive treatment between 24–48 hours after acute ischemic stroke onset is safe and might reduce 3-month death and major disability and recurrent stroke compared to initiation of antihypertensive treatment after hospital discharge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BP	blood pressure
CATIS	China Antihypertensive Trial in Acute Ischemic Stroke
CI	confidence interval

IQR	interquartile range
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
SD	standard deviation

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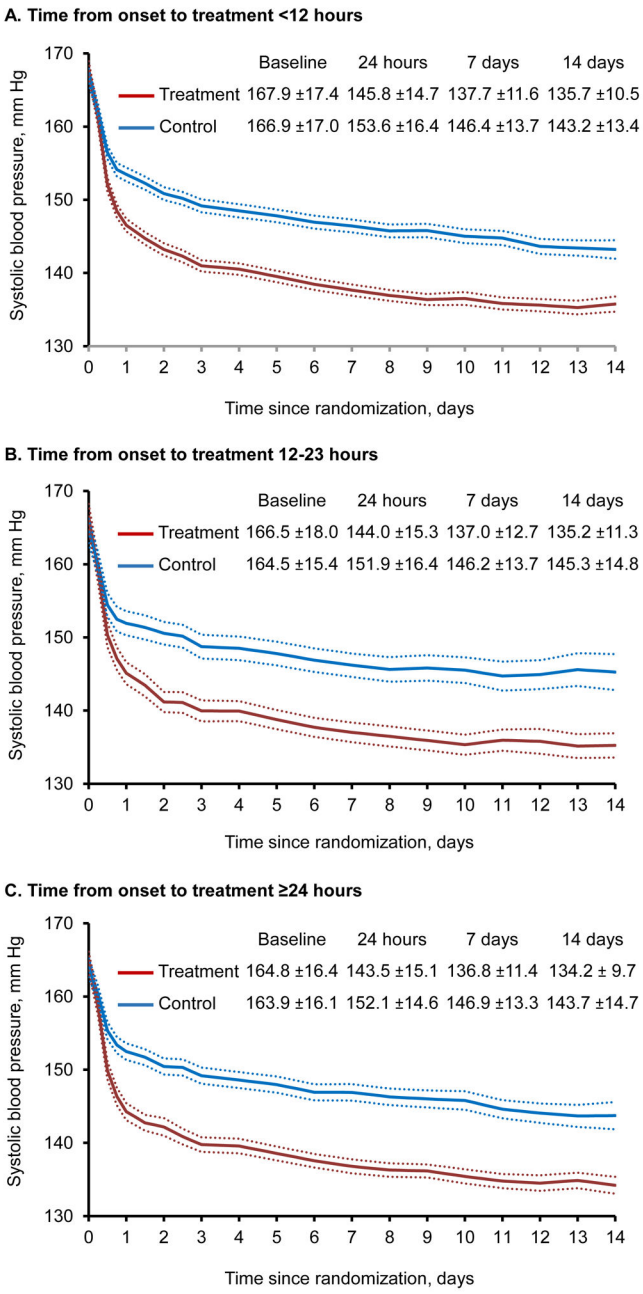

Figure 1.

Mean and 95% confidence interval of systolic BP since randomization by treatment group. Upper panel: subgroup initiated antihypertension treatment <12 hours; middle panel: 12–23 hours; and lower panel: 24–48 hours.

Table 1

Baseline Characteristics of Trial Participants According to Time from Onset to Treatment

	<12 hours			12–23 hours			≥24 hours		
	Treatment (n=1,018)	**Control (n=1,084)**	**P value**	**Treatment (n=405)**	**Control (n=334)**	**P value**	**Treatment (n=615)**	**Control (n=615)**	**P value**
Male, n (%)	678 (66.6)	696 (64.2)	0.25	251 (62.0)	211 (63.2)	0.74	388 (63.1)	380 (61.8)	0.64
Age, mean (SD), years	62.9 (10.8)	62.2 (11.2)	0.18	60.8 (10.6)	61.8 (10.2)	0.21	61.6 (10.8)	61.2 (11.1)	0.55
Time from onset to randomization, mean (SD), hours	5.1 (2.8)	5.1 (2.8)	0.83	16.5 (3.9)	16.1 (3.8)	0.11	31.5 (9.4)	31.6 (9.4)	0.81
Blood pressure at entry, mean (SD), mmHg									
Systolic	167.9 (17.4)	166.9 (17.0)	0.20	166.5 (18.0)	164.5 (15.4)	0.12	164.8 (16.4)	163.9 (16.1)	0.33
Diastolic	96.9 (11.1)	96.8 (11.6)	0.79	96.9 (10.6)	96.6 (10.9)	0.66	96.5 (10.6)	96.1 (11.3)	0.47
Body mass index, mean (SD), kg/m^2	24.9 (3.3)	25.0 (3.2)	0.81	24.8 (2.8)	25.2 (3.3)	0.09	25.0 (3.2)	24.9 (2.9)	0.75
History of hypertension, n (%)	785 (77.1)	851 (78.5)	0.44	313 (77.3)	251 (75.1)	0.50	512 (83.3)	497 (80.8)	0.27
Use of antihypertensive medications, n (%)	489 (48.0)	501 (46.2)	0.40	199 (49.1)	162 (48.5)	0.86	326 (53.0)	320 (52.0)	0.73
Hyperlipidemia, n (%)	64 (6.3)	77 (7.1)	0.45	30 (7.4)	27 (8.1)	0.73	43 (7.0)	36 (5.9)	0.42
Diabetes, n (%)	180 (17.7)	185 (17.1)	0.71	76 (18.8)	64 (19.2)	0.89	113 (18.4)	101 (16.4)	0.37
History of coronary heart disease, n, (%)	113 (11.1)	122 (11.3)	0.91	42 (10.4)	40 (12.0)	0.49	61 (9.9)	66 (10.7)	0.64
Current cigarette smoking, n, (%)	387 (38.0)	406 (37.5)	0.79	136 (33.6)	136 (40.7)	0.05	202 (32.8)	218 (35.4)	0.34
Current alcohol drinking, n (%)	300 (29.5)	340 (31.4)	0.35	125 (30.9)	116 (34.7)	0.27	189 (30.7)	183 (29.8)	0.71
NIHSS score at baseline *, median (IQR)	5.0 (3.0–8.0)	5.0 (3.0–9.0)	0.35	4.0 (3.0–7.0)	4.0 (3.0–7.0)	0.73	4.0 (2.0–6.0)	4.0 (2.0–7.0)	0.08
Ischemic stroke subtype†, n (%)									
Thrombotic	770 (75.6)	838 (77.3)	0.37	328 (81.0)	260 (77.8)	0.29	477 (77.6)	497 (80.8)	0.16

	<12 hours			12–23 hours			≥24 hours		
	Treatment (n=1,018)	**Control (n=1,084)**	**P value**	**Treatment (n=405)**	**Control (n=334)**	**P value**	**Treatment (n=615)**	**Control (n=615)**	**P value**
Embolic	61 (6.0)	71 (6.5)	0.60	15 (3.7)	13 (3.9)	0.89	23 (3.7)	19 (3.1)	0.53
Lacunar	213 (20.9)	202 (18.6)	0.19	71 (17.5)	66 (19.8)	0.44	133 (21.6)	117 (19.0)	0.26

SD = standard deviation, IQR = interquartile range. Difference in means between the antihypertensive treatment and control groups was tested using a Student's t test, percentages using a χ^2 test, and medians using the Wilcoxon rank-sum test.

*Scores range from 0 (normal neurologic status) to 42 (coma with quadriplegia).

†Twelve patients with both thrombotic and embolic, 93 with thrombotic and lacunar, 6 with embolic and lacunar, and 1 with all 3 subtypes.

Table 2

Blood Pressure, Use of Antihypertensive Medication, and Clinical Outcomes at 3-Month Post-treatment Follow-up Visit According to Time from Onset to Treatment

	<12 hours				12–23 hours				≥24 hours				P value for homogeneity
	Treatment (n=995)	Control (n=1,055)	Blood pressure difference or OR (95% CI)	P value	Treatment (n=393)	Control (n=329)	Blood pressure difference or OR (95% CI)	P value	Treatment (n=600)	Control (n=603)	Blood pressure difference or OR (95% CI)	P value	
Blood pressure at 3 months after randomization, mm Hg													
Systolic	139.7 (11.7)	142.5 (12.8)	−2.8 (−3.8 to −1.7)	<0.001	139.6 (12.1)	141.7 (13.2)	−2.1 (−4. to −0.2)	0.03	138.4 (11.4)	142.0 (11.5)	−3.7 (−5.0 to −2.4)	<0.001	
Diastolic	86.2 (8.3)	87.7 (8.1)	−1.5 (−2.2 to −0.8)	<0.001	86.1 (7.6)	86.9 (8.4)	−0.7 (−1.9 to 0.4)	0.22	85.5 (7.5)	87.2 (7.5)	−1.7 (−2.5 to −0.8)	<0.001	
Use of antihypertensive medication, n (%)	833 (83.7)	771 (73.1)	1.89 (1.53 to 2.35)	<0.001	335 (85.2)	263 (79.9)	1.45 (0.98 to 2.14)	0.06	499 (83.2)	453 (75.1)	1.64 (1.23 to 2.17)	<0.001	
Death or major disability [*], n (%)	298 (30.0)	295 (28.0)	1.10 (0.91 to 1.33)	0.32	93 (23.7)	66 (20.1)	1.24 (0.87 to 1.76)	0.25	109 (18.2)	141 (23.4)	0.73 (0.55 to 0.96)	0.03	0.03
Score on modified Rankin scale [†], median (IQR)	1.0 (1.0–3.0)	2.0 (1.0–3.0)		0.80	1.0 (1.0–2.0)	1.0 (1.0–2.0)		0.89	1.0 (1.0–2.0)	1.0 (1.0–2.0)		0.18	0.49
Participants, n (%)													
0 (no symptoms)	182 (18.3)	180 (17.1)	0.98 (0.84 to 1.14) [‡]	0.80	77 (19.6)	52 (15.8)	0.98 (0.76 to 1.28) [‡]	0.89	118 (19.7)	109 (18.1)	1.15 (0.94 to 1.14) [‡]	0.18	0.49
1 (no significant disability despite symptoms)	316 (31.8)	340 (32.2)			131 (33.3)	131 (39.8)			219 (36.5)	219 (36.3)			
2 (slight disability)	199 (20.0)	240 (22.8)			92 (23.40)	80 (24.3)			154 (25.7)	134 (22.2)			
3 (moderate disability)	135 (13.6)	155 (14.7)			57 (14.5)	31 (9.4)			61 (10.2)	79 (13.1)			
4 (moderately severe disability)	84 (8.4)	73 (6.9)			22 (5.6)	20 (6.1)			30 (5.0)	37 (6.1)			
5 (severe disability)	32 (3.2)	32 (3.0)			3 (0.8)	8 (2.4)			8 (1.3)	13 (2.2)			
6 (dead)	47 (4.7)	35 (3.3)			11 (2.8)	7 (2.1)			10 (1.7)	12 (2.0)			
Death, n (%)	47 (4.7)	35 (3.3)	1.45 (0.93 to 2.26)	0.11	11 (2.8)	7 (2.1)	1.33 (0.51 to 3.46)	0.57	10 (1.7)	12 (2.0)	0.84 (0.36 to 1.95)	0.68	0.53
Recurrent stroke, n (%)	17 (1.7)	22 (2.1)	0.82 (0.43 to 1.55)	0.53	7 (1.8)	5 (1.5)	1.18 (0.37 to 3.74)	0.78	4 (0.7)	16 (2.7)	0.25 (0.08 to 0.74)	0.01	0.11
Vascular events [††], n (%)	29 (3.0)	32 (3.1)	0.96 (0.58 to 1.60)	0.88	11 (2.8)	8 (2.5)	1.16 (0.46 to 2.91)	0.76	8 (1.3)	19 (3.2)	0.41 (0.18 to 0.95)	0.04	0.18
Death or vascular events, n (%)	62 (6.2)	56 (5.3)	1.19 (0.82 to 1.72)	0.37	17 (4.3)	12 (3.7)	1.19 (0.56 to 2.54)	0.64	13 (2.2)	26 (4.3)	0.49 (0.25 to 0.97)	0.04	0.07

Difference in mean blood pressure between the antihypertensive treatment and control groups was tested using a Student's t test, the percentages of composite death or major disability, all-cause mortality, recurrent stroke, vascular events, and use of antihypertensive medication using a χ^2 test, the medians of Rankin score using the Wilcoxon rank-sum test, and odds ratios of ordinal Rankin scores using ordinal logistic regression.

[*]Modified Rankin Score of 3 or greater.

† Scores on the modified Rankin Scale, for which a score of 0 indicates no symptoms, a score of 5 indicates severe disability, and a score of 6 indicates death.

‡ Odds of a 1-unit higher modified Rankin score.

†† Includes vascular deaths, nonfatal stroke, nonfatal myocardial infarction, hospitalized and treated angina, hospitalized and treated congestive heart failure, and hospitalized and treated peripheral arterial disease.