Original Investigation

Effects of Immediate Blood Pressure Reduction on Death and Major Disability in Patients With Acute Ischemic Stroke
The CATIS Randomized Clinical Trial

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IMPORTANCE Although the benefit of reducing blood pressure for primary and secondary prevention of stroke has been established, the effect of antihypertensive treatment in patients with acute ischemic stroke is uncertain.

OBJECTIVE To evaluate whether immediate blood pressure reduction in patients with acute ischemic stroke would reduce death and major disability at 14 days or hospital discharge.

DESIGN, SETTING, AND PARTICIPANTS The China Antihypertensive Trial in Acute Ischemic Stroke, a single-blind, blinded end-points randomized clinical trial, conducted among 4071 patients with nonthrombolysed ischemic stroke within 48 hours of onset and elevated systolic blood pressure. Patients were recruited from 26 hospitals across China between August 2009 and May 2013.

INTERVENTIONS Patients (n = 2038) were randomly assigned to receive antihypertensive treatment (aimed at lowering systolic blood pressure by 10% to 25% within the first 24 hours after randomization, achieving blood pressure less than 140/90 mm Hg within 7 days, and maintaining this level during hospitalization) or to discontinue all antihypertensive medications (control) during hospitalization (n = 2033).

MAIN OUTCOMES AND MEASURES Primary outcome was a combination of death and major disability (modified Rankin Scale score ≥3) at 14 days or hospital discharge.

RESULTS Mean systolic blood pressure was reduced from 166.7 mm Hg to 144.7 mm Hg (−12.7%) within 24 hours in the antihypertensive treatment group and from 165.6 mm Hg to 152.9 mm Hg (−7.2%) in the control group within 24 hours after randomization (difference, −5.5% [95% CI, −4.9 to −6.1%]; absolute difference, −9.1 mm Hg [95% CI, −10.2 to −8.1]; $P < .001$). Mean systolic blood pressure was 137.3 mm Hg in the antihypertensive treatment group and 146.5 mm Hg in the control group at day 7 after randomization (difference, −9.3 mm Hg [95% CI, −10.1 to −8.4]; $P < .001$). The primary outcome did not differ between treatment groups (683 events [antihypertensive treatment] vs 681 events [control]; odds ratio, 1.00 [95% CI, 0.88 to 1.14]; $P = .98$) at 14 days or hospital discharge. The secondary composite outcome of death and major disability at 3-month posttreatment follow-up did not differ between treatment groups (500 events [antihypertensive treatment] vs 502 events [control]; odds ratio, 0.99 [95% CI, 0.86 to 1.15]; $P = .93$).

CONCLUSION AND RELEVANCE Among patients with acute ischemic stroke, blood pressure reduction with antihypertensive medications, compared with the absence of hypertensive medication, did not reduce the likelihood of death and major disability at 14 days or hospital discharge.

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Editorial page 469

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Stroke is the second leading cause of death and the leading cause of serious, long-term disability worldwide.[1] Clinical trials have documented that lowering blood pressure reduces the risk of stroke in hypertensive[2,3] and normotensive patients with a history of stroke or transient ischemic attack.[4-6] Although the benefit of lowering blood pressure for primary and secondary prevention of stroke has been established, the effect of immediate antihypertensive treatment in patients with acute ischemic stroke and elevated blood pressure is uncertain.[7,8] Elevated blood pressure is common during acute ischemic stroke. In the US National Hospital Ambulatory Medical Care Survey, 76.5% of patients with acute ischemic stroke had systolic blood pressures of 140 mm Hg or greater on arrival at the emergency department.[9] Observational studies have reported that a decrease in blood pressure within the first 48 hours after symptom onset was associated with poorer, better, or no difference in adverse clinical outcomes among patients with acute ischemic stroke.[10-12] There are no published clinical trials with sufficient statistical power to address the question of whether lowering blood pressure reduces adverse clinical outcomes among patients with acute ischemic stroke.

The China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) was a multicenter randomized controlled trial designed to test whether moderate lowering of blood pressure within the first 48 hours after the onset of an acute ischemic stroke would reduce death and major disability at 14 days or hospital discharge. In addition, we also evaluated the effects of antihypertensive treatment during the acute phase of ischemic stroke on 3-month mortality, major disability, and vascular events, as assessed at a posttreatment follow-up visit.

Methods

Trial Design and Participants

CATIS was a multicenter, single-blind, blinded end-points randomized clinical trial conducted in 26 hospitals across China. Details of the trial design and methods are summarized in the eMethods in Supplement. In brief, we recruited 4071 patients 22 years or older 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 blood pressure between 140 mm Hg and less than 220 mm Hg. Individuals with a systolic blood pressure of 220 mm Hg or greater or diastolic blood pressure of 120 mm Hg or greater were excluded because current clinical guidelines recommend antihypertensive treatment in such patients.[7,13] In addition, patients with severe heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis, or resistant hypertension, and those in a deep coma, were excluded. Patients treated with intravenous thrombolytic therapy (ie, intravenous recombinant tissue plasminogen activator [rtPA]) at baseline were excluded because of different requirements for blood pressure reduction.[7]

This study 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.

Intervention

CATIS was designed to evaluate whether an antihypertensive treatment intervention aimed at lowering systolic blood pressure by 10% to 25% within the first 24 hours after randomization, achieving a systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg within 7 days, and maintaining this level of blood pressure control during the remainder of a patient's hospitalization would reduce adverse clinical outcomes compared with a control group not receiving antihypertensive treatment. Randomization was conducted centrally and was stratified by participating hospitals and use of antihypertensive medications. The randomization schedules were generated using SAS PROC PLAN in SAS and concealed until an eligible participant was ready for enrollment. After the study participants had been randomly assigned to the antihypertensive treatment or control group, all home antihypertensive medications were discontinued.

Our trial was designed to test a blood pressure reduction strategy rather than the efficacy of specific antihypertensive drugs. As such, several antihypertensive agents, including intravenous angiotensin-converting enzyme inhibitors (enalapril, first-line), calcium channel blockers (second-line), and diuretics (third-line), could be used individually or in combination in the intervention group to achieve the targeted blood pressure reduction according to a prespecified treatment algorithm (eFigure 1 in Supplement). Patients in the control group discontinued home antihypertensive medications. After their hospital discharge, patients in both groups were prescribed antihypertensive medications according to clinical guidelines.[7,13] Although treating study physicians and nurses were not blinded to group assignment, trial participants as well as the investigators and research staff who collected study outcome data were masked to treatment allocation.

Measurements

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.[14] 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 blood pressure measurements were obtained at baseline by trained nurses according to a common protocol adapted from procedures recommended by the American Heart Association.[15] Blood pressure was measured with the participant in a supine position using a standard mercury

sphygmomanometer and 1 of 4 cuff sizes (pediatric, regular adult, large adult, or thigh) based on participant arm circumference. After randomization, 3 blood pressure measurements were obtained every 2 hours for the first 24 hours, every 4 hours during the second and third days, and 3 times a day thereafter until hospital discharge or death.

Outcome Assessment

The primary outcome was a combination of death within 14 days after randomization and major disability at 14 days or at hospital discharge if earlier than 14 days. The secondary outcome was a combination of all-cause mortality and major disability at the 3-month posttreatment follow-up. Major disability was defined as a score of 3 to 5 on the modified Rankin Scale at 14 days and 3 months after randomization. Scores on the modified Rankin Scale range from 0 to 6, with a score of 0 indicating no symptoms; a score of 5 indicating severe disability (ie, bedridden, incontinent, or requiring constant nursing care and attention); and a score of 6 indicating death.[16] Since development of the initial CATIS protocol, ordinal analysis of the modified Rankin Scale scores is now recommended for acute stroke trials.[17] Therefore, in the final statistical analysis plan, which was developed prior to initiation of data analysis, we included an ordered 7-level categorical score of the modified Rankin Scale as a secondary outcome for neurologic functional status. Other secondary outcomes included vascular disease events (eg, 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 assessed at the 3-month posttreatment follow-up visit.

Participants were followed up in person at month 3 by trained neurologists and research nurses unaware of treatment assignment. Data on medical history, deaths, vascular events, blood pressure, 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 ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial).[18]

Statistical Analysis

We estimated that with a sample of 4000 participants, the study would have 90% statistical power to detect an absolute risk reduction of 5% (or a relative risk reduction of 14%) in the primary outcome at a significance level of .05 for a 2-sided test.[19] The expected event rate for the primary outcome in the control group was estimated to be 35% based on our pilot data, which are more conservative than those reported from previous studies.[20] We further assumed that 8% of participants would be nonadherent or would be lost to follow-up.

Data were analyzed according to participants' randomized treatment assignments, regardless of their subsequent medication status (intention-to-treat). 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. Logistic regression analysis was used to estimate unadjusted odds ratios (ORs) and 95% CIs associated with antihypertensive treatment compared with no antihypertensive treatment. In a sensitivity analysis, ORs were adjusted for baseline age, sex, systolic blood pressure, NIHSS score, time from stroke onset to randomization, and history of antihypertensive medication use. Multiple imputation for missing data in the multivariable analyses was conducted using the Markov chain Monte Carlo method. 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.[21] Ordinal logistic regression was used to estimate the effect of blood pressure reduction on the full range of the modified Rankin scale.[22]

We assessed the heterogeneity of the treatment effect on the primary outcome in prespecified subgroups by age, sex, systolic blood pressure at baseline, NIHSS score at baseline, time from onset of stroke to randomization, history of hypertension, history of antihypertensive treatment, and subtypes of ischemic stroke by adding an interaction term in unadjusted logistic regression models. 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 blood pressure reduction on the clinical outcomes. Data analyses were performed using SAS version 9.4 (SAS Institute Inc) and Stata version 12 (StataCorp).

Results

Study Participants

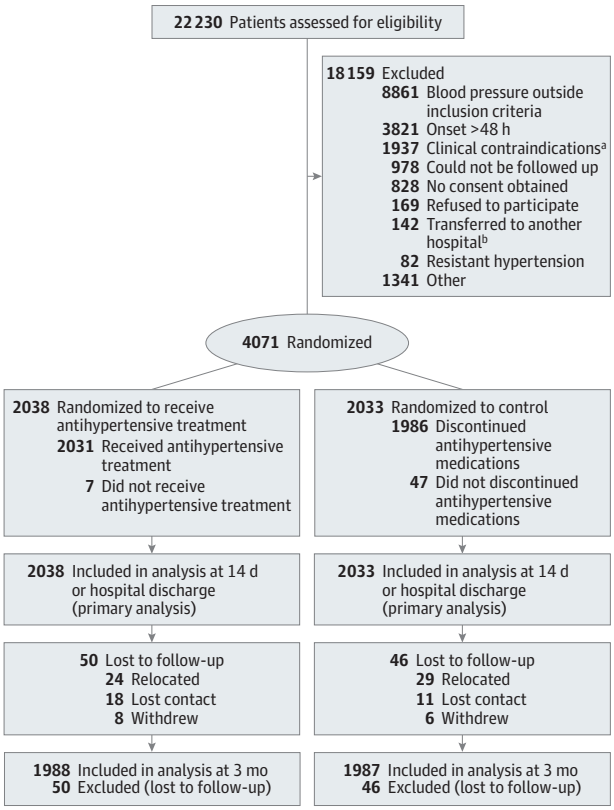
From August 2009 to May 2013, we screened 22 230 consecutive patients with acute ischemic stroke, and 4071 who were eligible and willing to participate were enrolled in CATIS (**Figure 1**).

Of the 4071 participants, 2038 were randomly assigned to receive antihypertensive treatment and 2033 were assigned to control. The mean age was 62.0 years; 64.0% of participants were men, 49.1% were taking antihypertensive medication at admission, and 77.9% had strokes of thrombotic subtype. Baseline characteristics were balanced between the 2 groups (**Table 1**).

Blood Pressure Reduction

The mean systolic and diastolic blood pressure levels differed significantly between the 2 comparison groups from 4 hours to 14 days after randomization (**Figure 2**, **Table 2**). Within 24 hours, the mean systolic blood pressure was reduced by 21.8 mm Hg (12.7%) in the treatment group and 12.7 mm Hg (7.2%) in the control group (difference, −9.1 mm Hg [95% CI, −10.2 to −8.1]; $P < .001$). At day 7, the mean sys-

Figure 1. Study Flow



[a] Individuals with severe heart failure (New York Heart Association class III and IV), myocardial infarction, unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis, or in a deep coma.

[b] Eligible at screening visit but transferred to another hospital before randomization.

Table 1. Baseline Characteristics of the Trial Participants

Characteristics	Antihypertensive Treatment (n = 2038)	Control (n = 2033)
Age, mean (SD), y	62.1 (10.8)	61.8 (11.0)
Men, No. (%)	1317 (64.6)	1287 (63.3)
Time from onset to randomization, mean (SD), h	15.3 (12.9)	14.9 (13.0)
Blood pressure at entry, mean (SD), mm Hg		
Systolic	166.7 (17.3)	165.6 (16.5)
Diastolic	96.8 (10.8)	96.5 (11.4)
Body mass index, mean (SD)[a]	24.9 (3.2)	25.0 (3.1)
NIHSS score, median (IQR)[b]	4.0 (2.0-7.0)	4.0 (3.0-8.0)
History of hypertension, No. (%)	1610 (79.0)	1599 (78.7)
Current use of antihypertensive medications, No. (%)	1014 (49.8)	983 (48.4)
Hyperlipidemia, No. (%)	137 (6.7)	140 (6.9)
Diabetes mellitus, No. (%)	369 (18.1)	350 (17.2)
Coronary heart disease, No. (%)	216 (10.6)	228 (11.2)
Current cigarette smoking, No. (%)	725 (35.6)	760 (37.4)
Current alcohol drinking, No. (%)	614 (30.1)	639 (31.4)
Ischemic stroke subtype, No. (%)[c]		
Thrombotic	1575 (77.3)	1595 (78.5)
Embolic	99 (4.9)	103 (5.1)
Lacunar	417 (20.5)	385 (18.9)

Abbreviations: IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Scores range from 0 (normal neurologic status) to 42 (coma with quadriplegia).

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

tolic blood pressure was 137.3 mm Hg in the treatment group (with 65.7% achieving the target systolic blood pressure of <140 mm Hg) compared with 146.5 mm Hg in the control group (with 32.2% having a systolic blood pressure <140 mm Hg). At day 14, the mean systolic blood pressure was 135.2 mm Hg in the treatment group (with 72.0% achieving the target systolic blood pressure of <140 mm Hg) compared with 143.7 mm Hg in the control group (with 39.5% having a systolic blood pressure <140 mm Hg). The mean differences in systolic pressures between the 2 comparison groups were −9.3 mm Hg (95% CI, −10.1 to −8.4; $P < .001$) at day 7 after randomization and −8.6 mm Hg (95% CI, −9.7 to −7.4; $P < .001$) at day 14.

Other Treatments for Ischemic Stroke

Other treatments for ischemic stroke were prescribed by the study participants' physicians as part of their routine care according to Chinese stroke clinical guidelines and were balanced between the 2 groups (eTable 1 in Supplement). Patients in the control group discontinued home antihypertensive medications. For example, 33.4% of patients in the treatment group received heparin or low-molecular-weight heparin, compared with 34.1% in the control group ($P = .63$). In addition, 83.9% and 12.2% of patients in the treatment group received aspirin and clopidogrel, compared with 82.2% and 12.9% in the control group ($P = .15$ and .52). Furthermore, 2.6% of patients in the treatment group received intravenous fibrinolysis, compared with 2.3% in the control group ($P = .55$). Last, 2.3% of patients in the control group did not discontinue their home antihypertensive medications.

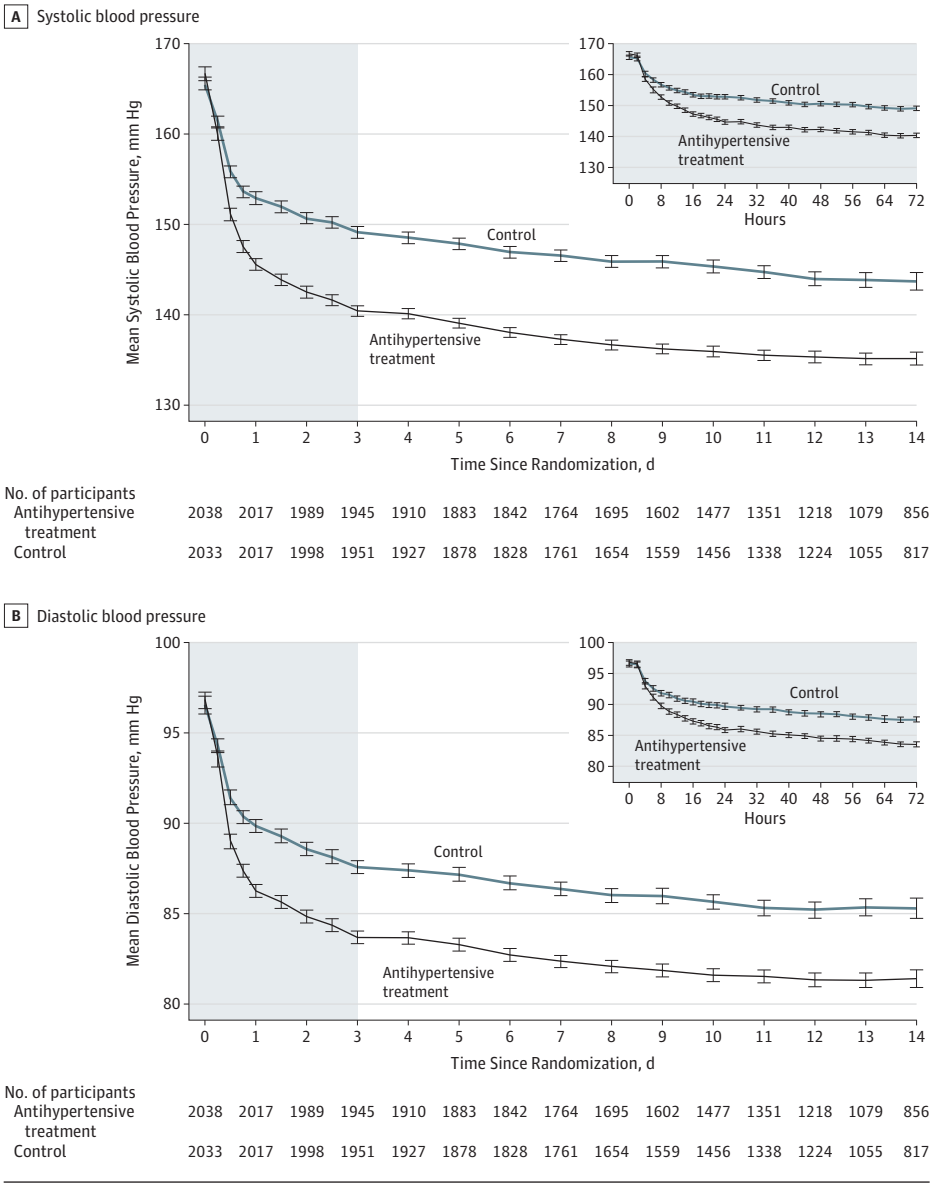
Clinical Outcomes at 14 Days or Hospital Discharge

At 14 days or hospital discharge, 683 of the trial participants (33.6%) in the antihypertensive treatment group, compared with 681 (33.6%) in the control group, had experienced death or a major disability (OR with antihypertensive treatment, 1.00 [95% CI, 0.88 to 1.14]; $P = .98$). The median score from the modified Rankin Scale was not significantly different between the 2 groups, and the odds of a higher modified Rankin Scale score were not associated with antihypertensive treatment (Table 2).

Clinical Outcomes at the 3-Month Posttreatment Follow-up Visit

At the 3-month visit, 84.5% of the participants in the antihypertensive treatment group and 75.4% in the control group reported the use of antihypertensive medications ($P < .001$)

Figure 2. Mean Systolic and Diastolic Blood Pressure Since Randomization, by Treatment Group



Three blood pressure measurements were obtained every 2 hours for the first 24 hours, every 4 hours during the second and third days, and 3 times a day afterward until discharge or death. Error bars indicate 95% confidence intervals. Tinted regions indicate range from 0 days (0 hours) to 3 days (72 hours).

(**Table 3**). Blood pressure was significantly lower in the antihypertensive treatment group than in the control group ($P < .001$). Among participants in the antihypertensive treatment group, 500 (25.2%) died or had a major disability, compared with 502 (25.3%) in the control group (OR with antihypertensive treatment, 0.99 [95% CI, 0.86 to 1.15]; $P = .93$). The median modified Rankin Scale score, death rate, and vascular disease events were similar between the 2 comparison groups, whereas recurrent stroke was slightly and nonsignificantly reduced in the antihypertensive treatment group (OR, 0.65 [95% CI, 0.40 to 1.04]; $P = .07$).

Subgroup Analysis

At 14 days or hospital discharge, the effects of antihypertensive treatment on the primary outcome were consistent across all prespecified subgroups (**Figure 3**). At the 3-month posttreatment follow-up visit, ORs for the primary outcome were not significantly different across the prespecified subgroups, except for time from stroke onset to treatment (**Figure 4**). Among patients who received antihypertensive treatment 24 hours or more after stroke onset, blood pressure lowering was associated with a significant reduction in the primary outcome (OR, 0.73 [95% CI, 0.55 to 0.97]; $P = .03$).

Sensitivity Analysis

After adjustment for baseline age, sex, systolic blood pressure, NIHSS score, time from stroke onset to randomization, and history of antihypertensive medication use, the OR with antihypertensive treatment was 1.09 (95% CI, 0.92 to 1.28; $P = .33$) for death or major disability at 14 days or hospital discharge and 1.05 (95% CI, 0.89 to 1.25; $P = .55$) for

Table 2. Blood Pressure Reduction and Primary and Secondary Outcomes at 14 Days or Hospital Discharge

Variable	Antihypertensive Treatment (n = 2038)	Control (n = 2033)	Blood Pressure Difference or OR (95% CI)	*P* Value
Blood pressure reduction				
Blood pressure at 24 h after randomization, mean (SD), mm Hg				
Systolic	144.7 (15.0)	152.9 (15.9)	−8.1 (−9.1 to −7.2)	<.001
Diastolic	85.9 (8.9)	89.6 (9.6)	−3.8 (−4.3 to −3.2)	<.001
Absolute blood pressure changes from baseline to 24 h after randomization, mean (SD), mm Hg				
Systolic	−21.8 (15.9)	−12.7 (17.3)	−9.1 (−10.2 to −8.1)	<.001
Diastolic	−11.0 (10.5)	−6.9 (11.0)	−4.1 (−4.7 to −3.4)	<.001
Proportional blood pressure changes from baseline to 24 h after randomization, mean (SD), %				
Systolic	−12.7 (8.7)	−7.2 (9.8)	−5.5 (−4.9 to −6.1)	<.001
Diastolic	−10.7 (10.1)	−6.4 (11.1)	−4.3 (−3.6 to −4.9)	<.001
Blood pressure at day 7 after randomization, mean (SD), mm Hg				
Systolic	137.3 (11.8)	146.5 (13.6)	−9.3 (−10.1 to −8.4)	<.001
Diastolic	82.4 (7.2)	86.4 (8.1)	−4.0 (−4.5 to −3.5)	<.001
Blood pressure at day 14 after randomization, mean (SD), mm Hg				
Systolic	135.2 (10.4)	143.7 (14.0)	−8.6 (−9.7 to −7.4)	<.001
Diastolic	81.4 (7.4)	85.3 (8.3)	−3.9 (−4.6 to −3.1)	<.001
Primary outcome				
Death or major disability, No. (%)[a]	683 (33.6)	681 (33.6)	1.00 (0.88 to 1.14)	.98
Secondary outcomes				
Score on modified Rankin scale[b], median (IQR)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)		.70
Participants, No. (%)				
0 (no symptoms)	204 (10.0)	154 (7.6)	0.98 (0.88 to 1.09)[c]	.70
1 (no significant disability despite symptoms)	653 (32.2)	701 (34.6)		
2 (slight disability)	491 (24.2)	491 (24.2)		
3 (moderate disability)	292 (14.4)	297 (14.7)		
4 (moderately severe disability)	258 (12.7)	285 (14.1)		
5 (severe disability)	108 (5.3)	77 (3.8)		
6 (dead)	25 (1.2)	25 (1.2)		
Death, No. (%)	25 (1.2)	25 (1.2)	1.00 (0.57 to 1.74)	.99
Duration of initial hospitalization, median (IQR), d	13.0 (9.0 to 14.0)	13.0 (9.0 to 14.0)		.28

Abbreviations: IQR, interquartile range; OR, odds ratio.

[a] Modified Rankin Scale score of 3 or greater.

[b] 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.

[c] Odds of a 1-unit higher modified Rankin score.

death or major disability at the 3-month posttreatment follow-up visit.

Discussion

In this randomized clinical trial, mean systolic blood pressure was reduced by 12.7% within the first 24 hours after randomization and was less than 140 mm Hg by day 5 and afterward in patients with acute ischemic stroke who received antihypertensive treatment within 48 hours of symptom onset. In addition, blood pressure remained significantly lower at 3 months' follow-up in the antihypertensive treatment group compared with the control group. However, the primary outcome of death or major disability was not different at 14 days or hospital discharge and at 3-month posttreatment follow-up after randomization between the antihypertensive treatment group and the control group, in whom antihypertensive medications had been discontinued during their hospitalization. Median modified Rankin Scale scores were not significantly different between the 2 comparison groups at 14 days or discharge and at 3-month posttreatment follow-up. Furthermore, rates of vascular events, recurrent stroke, and all-cause mortality were not significantly different between the 2 comparison groups at the 3-month posttreatment follow-up visit. These findings suggest that unless a patient's systolic blood pressure is 220 mm Hg or more or diastolic pressure is 120 mm Hg or more, the decision to lower blood pressure with antihypertensive treatment in patients with acute ischemic

Table 3. Secondary Outcomes at 3-Month Posttreatment Follow-up Visit

Variables	Antihypertensive Treatment (n = 1988)	Control (n = 1987)	Blood Pressure Difference or OR (95% CI)	*P* Value
Blood pressure at 3 mo after randomization, mean (SD) mm Hg				
Systolic	139.3 (11.7)	142.2 (2.5)	−2.9 (−3.7 to −2.2)	<.001
Diastolic	86.0 (7.9)	87.4 (8.0)	−1.4 (−1.9 to −0.9)	<.001
Use of antihypertensive medication, No. (%)	1667 (84.5)	1487 (75.4)	1.78 (1.52 to 2.09)	<.001
Death or major disability, No. (%)[a]	500 (25.2)	502 (25.3)	0.99 (0.86 to 1.15)	.93
Score on modified Rankin scale, median (IQR)	1.0 (1.0 to 3.0)	1.0 (1.0 to 3.0)		.52
Participants, No. (%)				
0 (no symptoms at all)	377 (19.0)	341 (17.2)	0.96 (0.86 to 1.08)[c]	.52
1 (no significant disability despite symptoms)	666 (33.5)	690 (34.7)		
2 (slight disability)	445 (22.4)	454 (22.8)		
3 (moderate disability)	253 (12.7)	265 (13.3)		
4 (moderately severe disability)	136 (6.8)	130 (6.5)		
5 (severe disability)	43 (2.2)	53 (2.7)		
6 (dead)	68 (3.4)	54 (2.7)		
Death, No. (%)	68 (3.4)	54 (2.7)	1.27 (0.88 to 1.82)	.20
Recurrent stroke, No. (%)	28 (1.4)	43 (2.2)	0.65 (0.40 to 1.04)	.07
Vascular events, No. (%)[b]	48 (2.4)	59 (3.0)	0.81 (0.55 to 1.19)	.28
Death or vascular events, No. (%)	92 (4.6)	94 (4.7)	0.98 (0.73 to 1.31)	.88

Abbreviations: IQR, interquartile range; OR, odds ratio.

[a] Modified Rankin score of 3 or greater.

[b] 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.

[c] Odds of a 1-unit higher modified Rankin score.

stroke does not improve or worsen outcome and therefore should be based on individual clinical judgment.

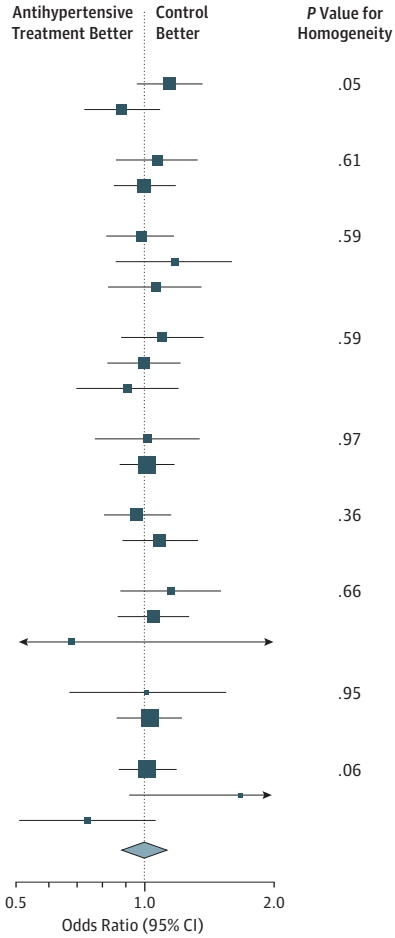
There are limited data from clinical trials on the effect of antihypertensive treatment in patients with acute ischemic stroke. A meta-analysis of clinical trials assessing the calcium channel blocker nimodipine showed no neuroprotective effect in patients with acute ischemic stroke.[23] Two of these trials reported that nimodipine therapy within 48 hours of stroke onset was associated with worse clinical outcomes in patients with acute ischemic stroke.[24,25] Recently, a few preliminary randomized trials of blood pressure reduction in acute ischemic stroke have been published.[26-29] A phase 2 pilot trial of therapy with the angiotensin receptor blocker candesartan cilexetil was stopped early because of significantly lower mortality and fewer vascular events at 12 months in the treatment group, although blood pressure was similar between the 2 study groups.[26] However, a larger phase 3 trial (SCAST [Scandinavian Candesartan Acute Stroke Trial]) of candesartan therapy enrolling 2029 patients with acute stroke (ischemic or hemorrhagic) showed that the composite vascular end point did not differ between the treatment groups at 6 months, despite a significant difference in blood pressure.[29] Furthermore, poorer functional outcomes were reported in the candesartan group. Two other preliminary trials enrolling patients with acute ischemic or hemorrhagic stroke also indicated that antihypertensive treatment failed to reduce adverse clinical events.[27,28]

Several aspects of our study are novel. This is, to our knowledge, the first randomized trial with sufficient statistical power to test the effect of immediate blood pressure reduction on adverse clinical outcomes in patients with acute ischemic stroke. Previous large trials have been conducted in patients with acute intracerebral hemorrhage[30] or in patients with either acute ischemic or hemorrhagic stroke.[29] In addition, this trial compares active antihypertensive treatment with the temporary discontinuation of antihypertensive medications in control participants during hospitalization. Furthermore, this study tests an antihypertensive treatment strategy using a single drug or a combination of multiple drug classes to achieve target blood pressure levels during hospitalization. On the other hand, SCAST was designed to examine the effect of the angiotensin receptor blocker candesartan compared with placebo on clinical outcomes in patients with acute stroke.[29] The difference in systolic blood pressure between candesartan and placebo was 0.4 mm Hg within 24 hours and 4.9 mm Hg by day 7.[29] The current trial achieved significantly greater blood pressure reduction between the treatment and control groups. However, the findings from this trial indicate that antihypertensive treatment did not reduce or increase death or major disability in patients with acute ischemic stroke.

The effects of antihypertensive treatment on the composite outcome of death and major disability at 14 days or discharge and at 3-month posttreatment follow-up were consistent across subgroups defined by age, sex, systolic blood pressure at admission, NIHSS score, time from onset of stroke to randomization, history of hypertension, current use of antihypertensive medications, and subtypes of ischemic stroke. The time from stroke onset to antihypertensive treatment was 15 hours on average, with a wide range. The study findings should be applicable to various subgroups of patients with acute ischemic stroke.

Figure 3. Effect of Antihypertensive Treatment on Death or Major Disability at 14 Days or Hospital Discharge

Subgroup	Antihypertensive Treatment Total, No.	Antihypertensive Treatment Events, No. (%)	Control Total, No.	Control Events, No. (%)	Odds Ratio (95% CI)	P Value for Homogeneity
Age, y						
<65	1198	352 (29.4)	1203	325 (27.0)	1.12 (0.94-1.34)	.05
≥65	833	331 (39.7)	824	356 (43.2)	0.87 (0.71-1.05)	
Sex						
Women	715	267 (37.3)	743	269 (36.2)	1.05 (0.85-1.30)	.61
Men	1316	416 (31.6)	1284	412 (32.1)	0.98 (0.83-1.15)	
Time to randomization, h						
<12	1015	376 (37.0)	1082	412 (38.1)	0.96 (0.80-1.14)	.59
12-23	401	132 (32.9)	331	99 (29.9)	1.15 (0.84-1.57)	
≥24	609	172 (28.2)	609	167 (27.4)	1.04 (0.81-1.34)	
Baseline SBP, mm Hg						
<160	715	225 (31.5)	765	228 (29.8)	1.08 (0.87-1.35)	.59
160-179	838	288 (34.4)	851	297 (34.9)	0.98 (0.80-1.19)	
≥180	478	170 (35.6)	411	156 (38.0)	0.90 (0.69-1.19)	
History of hypertension						
No	428	150 (35.0)	430	151 (35.1)	1.00 (0.75-1.32)	.97
Yes	1603	533 (33.3)	1597	530 (33.2)	1.00 (0.87-1.16)	
Use of antihypertension medications						
No	1022	354 (33.8)	1045	366 (35.0)	0.95 (0.79-1.13)	.36
Yes	1009	338 (33.5)	982	315 (32.1)	1.07 (0.88-1.29)	
Baseline NIHSS score						
0-4	1065	134 (12.6)	1009	113 (11.2)	1.14 (0.87-1.49)	.66
5-15	871	460 (52.8)	923	479 (51.9)	1.04 (0.86-1.25)	
≥16	95	89 (93.7)	93	89 (95.7)	0.67 (0.18-2.44)	
Baseline Rankin score						
<3	914	47 (5.1)	900	46 (5.1)	1.01 (0.66-1.53)	.95
≥3	1117	636 (56.9)	1125	635 (56.4)	1.02 (0.86-1.21)	
Stroke subtype						
Thrombolic	1513	539 (35.6)	1540	544 (35.3)	1.01 (0.87-1.18)	.06
Embolic	93	60 (64.5)	92	48 (52.2)	1.67 (0.92-3.01)	
Lacunar	366	66 (18.0)	338	78 (23.1)	0.73 (0.51-1.06)	
Overall	2031	683 (33.6)	2027	681 (33.6)	1.00 (0.88-1.14)	



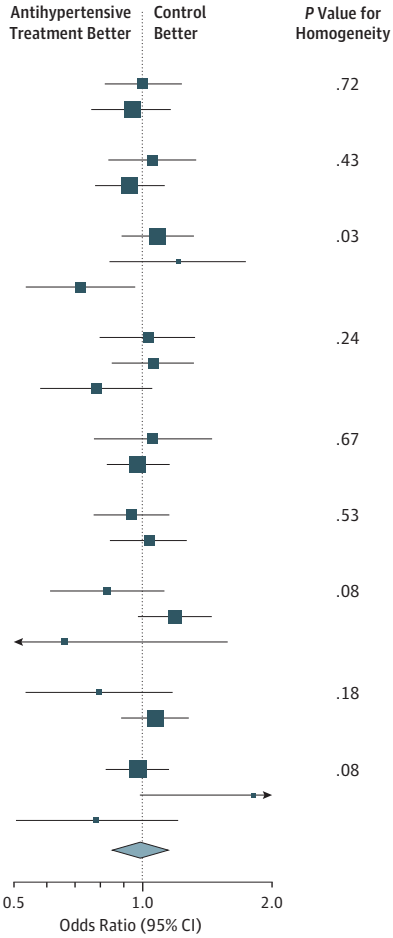
Major disability was defined as a score of 3 to 6 on the modified Rankin Scale (score of 0 indicates no symptoms, score of 5 indicates severe disability, and score of 6 indicates death). Each percentage is based on the number of participants in that subgroup. Data markers indicate point estimates (with the area of the square proportional to the number of events); error bars indicate 95% CIs. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal neurologic status) to 42 (coma with quadriplegia).

Our study had more than 90% statistical power to detect a 5% absolute risk reduction (or 14% relative risk reduction) in the composite outcome of death and major disability, which was recommended as a clinically meaningful risk reduction in acute stroke trials.[19] In addition, mean systolic blood pressure was reduced by 12.7% within the first 24 hours and systolic pressure less than 140 mm Hg was achieved by day 5 in the antihypertensive treatment group. Sufficient statistical power and well-separated blood pressure levels during the trial minimize the probability of false-negative findings in our study.

Our study must be interpreted in light of several limitations. The trial excluded patients with acute ischemic stroke and blood pressure of 220/120 mm Hg or greater, so the study findings cannot be applied to such patients. However, less than 0.1% of patients with acute stroke in US emergency departments[9] and less than 0.5% of the 22 230 patients assessed for eligibility in our study had an admission blood pressure of 220/120 mm Hg or greater. In addition, patients treated with intravenous thrombolytic therapy (ie, intravenous rtPA) at baseline were excluded from this trial. Although intravenous rtPA is the standard treatment for acute ischemic stroke, the proportion of patients who received the therapy is low.[31-33] For example, of 1 154 247 patients with acute ischemic stroke in a US national registry, only 66 692 (5.8%) were treated with intravenous rtPA.[33] Only 2.4% of patients with acute ischemic stroke were treated with intravenous thrombolytic therapy (1.6% with intravenous rtPA) in the China National Stroke Registry.[34] Therefore, our findings most likely are applicable for the majority of patients, who currently do not receive intravenous thrombolytic therapy. Patients included in this trial had a lower median NIHSS score of 4 (interquartile range, 2-8), compared with 7 (interquartile range, 2-10) in Chinese

Figure 4. Effect of Antihypertensive Treatment on Death or Major Disability at 3 Months

Subgroup	Antihypertensive Treatment Total, No.	Antihypertensive Treatment Events, No. (%)	Control Total, No.	Control Events, No. (%)	Odds Ratio (95% CI)	P Value for Homogeneity
Age, y						
<65	1172	224 (19.1)	1182	223 (18.9)	1.02 (0.83-1.25)	.72
≥65	816	276 (33.8)	805	279 (34.7)	0.96 (0.78-1.18)	
Sex						
Women	701	196 (28.0)	726	193 (26.6)	1.07 (0.85-1.35)	.43
Men	1287	304 (23.6)	1261	309 (24.5)	0.95 (0.79-1.14)	
Time to randomization, h						
<12	993	298 (30.0)	1054	295 (28.0)	1.10 (0.91-1.34)	.03
12-23	392	92 (23.5)	328	66 (20.1)	1.22 (0.85-1.74)	
≥24	597	108 (18.1)	600	139 (23.2)	0.73 (0.55-0.97)	
Baseline SBP, mm Hg						
<160	702	155 (22.1)	754	162 (21.5)	1.04 (0.81-1.33)	.24
160-179	820	223 (27.2)	830	215 (25.9)	1.07 (0.86-1.33)	
≥180	466	122 (26.2)	403	125 (31.0)	0.79 (0.59-1.06)	
History of hypertension						
No	420	107 (25.5)	425	104 (24.5)	1.06 (0.77-1.44)	.67
Yes	1568	393 (25.1)	1562	398 (25.5)	0.98 (0.83-1.15)	
Use of antihypertension medications						
No	1004	256 (25.5)	1033	273 (26.4)	0.95 (0.78-1.16)	.53
Yes	984	244 (24.8)	954	229 (24.0)	1.04 (0.85-1.28)	
Baseline NIHSS score						
0-4	1050	89 (8.5)	993	100 (10.1)	0.83 (0.61-1.12)	.08
5-15	848	335 (39.5)	901	320 (35.5)	1.19 (0.98-1.44)	
≥16	90	76 (84.4)	92	82 (89.1)	0.66 (0.28-1.58)	
Baseline Rankin score						
<3	900	50 (5.6)	883	61 (6.9)	0.79 (0.54-1.17)	.18
≥3	1088	450 (41.4)	1103	441 (40.0)	1.06 (0.89-1.26)	
Stroke subtype						
Thrombolic	1482	392 (26.5)	1513	408 (27.0)	0.97 (0.83-1.15)	.08
Embolic	89	47 (52.8)	88	34 (38.6)	1.78 (0.98-3.23)	
Lacunar	362	48 (13.3)	329	54 (16.4)	0.78 (0.51-1.19)	
Total	1988	500 (25.2)	1987	502 (25.3)	0.99 (0.86-1.15)	



Major disability was defined as a score of 3 to 6 on the modified Rankin Scale (score of 0 indicates no symptoms, score of 5 indicates severe disability, and score of 6 indicates death). Each percentage is based on the number of participants in that subgroup. Data markers indicate point estimates (with the area of the square proportional to the number of events); error bars indicate 95% CIs. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal neurologic status) to 42 (coma with quadriplegia).

national registry data.[35] We did not detect a significant interaction between NIHSS score and blood pressure reduction in this trial. Another limitation of this trial is the lack of repeated neurologic function tests and brain imaging studies within the first 24 hours of blood pressure lowering. These measures might provide early indicators to identify patient subgroups that might be more benefited or harmed by blood pressure reduction.[30] In addition, this trial was conducted exclusively in Chinese patients. The management of acute stroke may not be representative of Western populations; eg, there was a high use of heparin among the study patients. However, previous studies have demonstrated that the association between blood pressure and stroke is consistent between Chinese and Western populations.[4,30]

Conclusions

Among patients with acute ischemic stroke, blood pressure reduction with antihypertensive medications, compared with the absence of hypertensive medication, did not reduce the likelihood of death and major disability at 14 days or hospital discharge.

ARTICLE INFORMATION

Author Contributions: Drs He and Y. Zhang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs He and Y. Zhang contributed equally to this work.

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