

# Hypertension

## ORIGINAL ARTICLE

# Antihypertensive Treatments After Acute Ischemic Stroke: to Continue or Not?

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**BACKGROUND:** How to manage existing antihypertensive treatment is a common clinical dilemma after acute ischemic stroke; whether such treatment should be continued immediately or delayed remains unclear.

**METHODS:** We performed prespecified subgroup analyses of the CATIS (China Antihypertensive Trial in Acute Ischemic Stroke) and CATIS-2 (China Antihypertensive Trial in Acute Ischemic Stroke II). The CATIS randomly assigned 4071 patients with acute ischemic stroke to receive immediate or discontinued antihypertensive treatment during hospitalization. The CATIS-2 randomized 4810 patients to early (within 24–48 hours) or delayed antihypertensive treatment (reinitiated on day 8). The primary outcome was a combination of death or major disability (modified Rankin Scale score  $\geq 3$ ).

**RESULTS:** A total of 1997 participants (49.1%) in CATIS and 2540 participants (52.9%) in CATIS-2 were taking antihypertensive medications at the time of stroke onset. Among those with existing antihypertensive use, immediate continuous versus no antihypertensive treatment in CATIS was not associated with decreased or increased odds of the primary outcome at 14 days or hospital discharge (odds ratio, 1.07 [95% CI, 0.89–1.29]). In CATIS-2, early versus delayed antihypertensive treatment did not demonstrate a significant association with the primary outcome at 90 days (odds ratio, 1.15 [95% CI, 0.89–1.48]). In addition, in participants without prior antihypertensive medication use, the study outcomes did not differ between the 2 comparison groups in either trial ( $P_{\text{interaction}} > 0.05$ ).

**CONCLUSIONS:** Early continuation of antihypertensive treatment did not decrease or increase the odds of adverse clinical outcomes compared with no treatment or delayed treatment among patients with prestroke antihypertensive treatment.

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**Key Words:** antihypertensive agents ■ blood pressure ■ death ■ hemorrhagic stroke ■ ischemic stroke

**M**ore than three-quarters of patients with ischemic stroke have elevated blood pressure (BP) during the acute phase.<sup>1,2</sup> Existing clinical trials have indicated that BP levels can be successfully and safely reduced after the onset of acute ischemic stroke, but there is no evidence that such early intervention confers significant benefits.<sup>3–8</sup> Up to 50% of patients are already taking antihypertensive medications before the onset of

ischemic stroke. A major unresolved issue in acute ischemic stroke care is how to manage prestroke antihypertensive treatment.<sup>9–11</sup>

Although the benefit of antihypertensive medications for primary prevention and secondary prevention of stroke has been established, it remains unclear whether such treatment should be continued immediately after the onset of a stroke or delayed until a plateau.

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## NOVELTY AND RELEVANCE

### What Is New?

This study comprehensively evaluated early antihypertensive strategies in patients with ischemic stroke with or without prestroke antihypertensive medication use.

### What Is Relevant?

Early continuation of antihypertensive treatment did not decrease or increase the odds of adverse clinical outcomes compared with no treatment or delayed treatment, regardless of existing antihypertensive treatment.

### Clinical/Pathophysiological Implications?

No immediate blood pressure intervention or delaying treatment to 8 days after stroke did not increase the risk of adverse clinical outcomes in patients with and without a history of antihypertensive medication use. Preexisting antihypertensive therapy could be withheld in the first few days after stroke onset.

## Nonstandard Abbreviations and Acronyms

<b>BP</b>	blood pressure
<b>CATIS</b>	China Antihypertensive Trial in Acute Ischemic Stroke
<b>CATIS-2</b>	China Antihypertensive Trial in Acute Ischemic Stroke II
<b>COSSACS</b>	Continue or Stop Post-Stroke Antihypertensives Collaborative Study
<b>ENOS</b>	Efficacy of Nitric Oxide in Stroke
<b>INTERACT4</b>	Fourth Intensive Ambulance Delivered Blood Pressure Reduction in Hyper-Acute Stroke Trial
<b>mRS</b>	modified Rankin Scale
<b>OR</b>	odds ratio

Continuing existing antihypertensive drugs could help reduce vascular damage, hemorrhagic transformation, and early stroke recurrence, and prevent rebound fluctuations of BP or heart rate caused by the cessation of therapy.<sup>12,13</sup> On the other hand, BP-lowering treatment could lead to the insufficient blood supply to the salvageable ischemic penumbra and may further cause cerebral hypoperfusion.<sup>12,14</sup>

The COSSACS (Continue or Stop Post-Stroke Antihypertensives Collaborative Study) and the ENOS trial (Efficacy of Nitric Oxide in Stroke) have consistently reported that continuing versus temporarily stopping prestroke antihypertensive drugs after acute stroke did not improve functional outcome but even worsened several clinical outcomes.<sup>9–11</sup> These 2 trials were conducted in patients with both acute ischemic and hemorrhagic stroke; the findings may not apply to those with ischemic stroke alone. Therefore, the optimal time to start or restart antihypertensive therapy in the acute period for patients with ischemic stroke with or without prior use of antihypertensive medications remains uncertain.

The CATIS (China Antihypertensive Trial in Acute Ischemic Stroke) was designed to test the efficacy of immediate versus discontinued antihypertensive treatment after the onset of an acute ischemic stroke.<sup>3</sup> The CATIS-2 (China Antihypertensive Trial in Acute Ischemic Stroke II) aimed to compare the effect of early antihypertensive treatment started within 24 to 48 hours of ischemic stroke onset versus delaying treatment until day 8 on reducing dependency or death.<sup>4</sup> Here, we report the prespecified subgroup analyses of CATIS and CATIS-2 to test the efficacy of immediately continuous BP reduction versus no treatment or delayed treatment and to comprehensively explore the effective timing of restarting previous antihypertensive treatments, according to prior antihypertensive medication use.

## METHODS

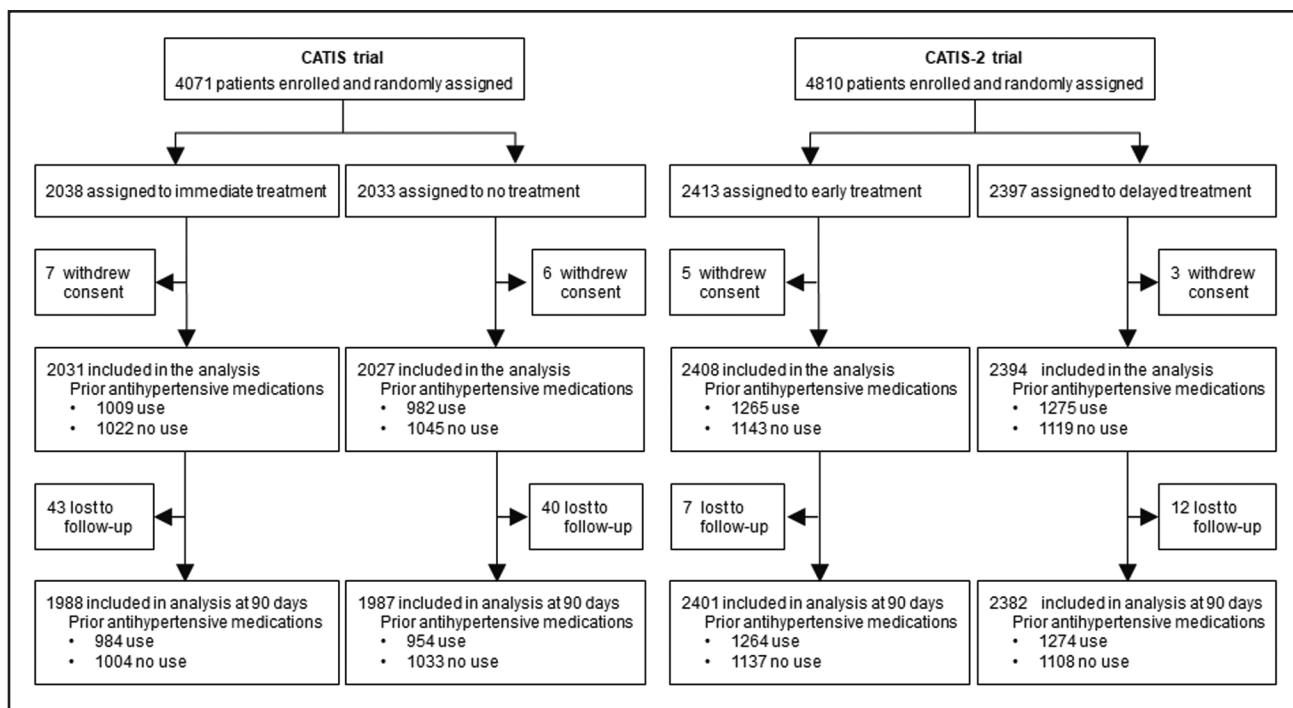
### Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### CATIS

The CATIS was a multicenter, single-blinded, blinded endpoint randomized clinical trial conducted in 26 hospitals across China (<https://www.clinicaltrials.gov>; Unique identifier: NCT01840072). Details on the trial design, methods, and main results have been described previously (trial protocol in Supplemental 1).<sup>3</sup> In brief, 4071 patients aged ≥22 years who had an acute ischemic stroke confirmed by computed tomography or magnetic resonance imaging of the brain within 48 hours after symptom onset and who had systolic BP between 140 and 220 mmHg were recruited (Figure 1).

Participants were randomly assigned to receive immediate antihypertensive treatment or to the control group. Randomization was conducted centrally and was stratified by participating hospitals and use of antihypertensive medications. In the immediate antihypertensive treatment group, the goal was to reduce systolic BP by 10% to 25% within the first 24 hours after randomization, reach a systolic BP <140 mmHg and diastolic BP <90 mmHg within 7 days, and maintain this



**Figure 1. Flowchart of study population selection in CATIS (China Antihypertensive Trial in Acute Ischemic Stroke) and CATIS-2 (China Antihypertensive Trial in Acute Ischemic Stroke II).**

BP level during the remainder of a patient's hospitalization. In the control group, patients stopped taking all antihypertensive medications throughout the patient's hospitalization. At their hospital discharge, patients in both groups were prescribed antihypertensive medications according to clinical guidelines.

The primary outcome was a composite outcome of death and major disability (modified Rankin Scale [mRS] score, 3–6) at 14 days or hospital discharge.<sup>15</sup> The secondary outcome was a combination of death and major disability, death, recurrent stroke, and vascular events assessed at 90 days, as well as an ordered 7-level categorical score of the mRS for neurological functional status. The assessment of study outcomes was conducted by trained neurologists and research nurses who were unaware of the treatment assignment. A trial-wide outcomes assessment committee, blinded to treatment assignment, reviewed and adjudicated vascular events based on established criteria.

## CATIS-2

The CATIS-2 was a multicenter, open-label, blinded end-point randomized clinical trial conducted in 106 hospitals across China (<https://www.clinicaltrials.gov>; Unique identifier: NCT03479554). Details on the trial design, methods, and main results have been described previously (trial protocol in Supplemental 2).<sup>4,16</sup> In brief, we recruited 4810 patients aged ≥40 years with acute ischemic stroke, confirmed by computed tomography or magnetic resonance imaging of the brain, within 24 to 48 hours of symptom onset and who had an elevated systolic BP between 140 and 219 mmHg (Figure 1). Patients treated with intravenous thrombolytic treatment or endovascular thrombectomy at baseline were excluded in both CATIS and CATIS-2 because of different requirements for BP reduction within 24 hours.

Participants were randomly assigned to either the early treatment group or the delayed treatment group. The randomization schedule was concealed centrally and was stratified by participating hospitals with a random block size of 4, 6, and 8. All study participants discontinued home antihypertensive medications at the baseline examination if they were taking these drugs. Patients in the early treatment group received antihypertensive medications immediately after randomization aimed at lowering systolic BP by 10% to 20% within the first 24 hours, achieving a systolic BP <140 mmHg and diastolic BP <90 mmHg within 7 days, and maintaining this BP level during the 90-day follow-up. Patients in the delayed treatment group discontinued all antihypertensive medications after randomization and restarted antihypertensive therapy on day 8 aimed at achieving and maintaining a systolic BP <140 mmHg and a diastolic BP <90 mmHg during the 90-day follow-up. The CATIS and CATIS-2 were designed to test BP reduction strategies rather than the efficacy of specific antihypertensive drugs.

The primary outcome was a composite outcome of death and major disability at 90 days.<sup>15</sup> The secondary outcomes were ordinal mRS, death, recurrent stroke, and vascular events at the 90-day follow-up visit, as well as categorical and ordinal mRS at 14 days or hospital discharge. Trained research nurses and neurologists who were masked to treatment assignment conducted follow-up visits with participants at days 21 and 90. A study-wide end-point adjudication committee, whose members were blinded to participants' treatment assignments, reviewed and adjudicated all primary and secondary outcomes based on established criteria.

The CATIS and CATIS-2 were approved by the institutional review boards at Tulane University in the United States, Soochow University, and Beijing Tiantan Hospital, and all participating institutes in China. Written informed consent was provided by all participants or their representatives.

## Measurements

The demographic characteristics, medical histories, and ischemic stroke type were collected at the time of enrollment. Stroke severity was assessed using the National Institutes of Health Stroke Scale by trained neurologists.<sup>17</sup> Baseline BP measurements were obtained by trained nurses according to a common protocol adapted from procedures recommended by the American Heart Association.<sup>18</sup> History of hypertension was defined as a yes answer to the question, have you been told by the doctor that you have high BP? or to the question, are you currently taking a drug to lower BP? Antihypertensive medication use at baseline was defined by the latter question.

## Statistical Analysis

Data were analyzed using the intention-to-treat analysis (statistical analysis plan in *Supplement 3*). Participants were divided into 2 categories based on the use of prior antihypertensive medications. The data analysis was undertaken separately and independently in 2 categories. The proportions of the primary outcome and secondary outcomes in each trial between the 2 treatment groups were compared using a  $\chi^2$  test. The Kaplan-Meier cumulative incidence curves were used to estimate the cumulative incidence rates of death, recurrent stroke, and vascular events across the comparison groups. Logistic regression analyses were used to estimate odds ratios (ORs) and 95% CIs of the early treatment group compared with the control group. Ordinal logistic regression was used to estimate the effect of BP reduction intervention on the full range of the mRS score. Heterogeneity of the treatment effect on primary and secondary outcomes according to the use of prior antihypertensive medications was assessed by adding an interaction term in logistic regression models. Multiple imputation for missing data was conducted using the Markov chain Monte Carlo method with an arbitrary missing pattern, assuming a multivariate normal distribution for the data. Ten imputed data sets were generated, and the results from the 10 imputed data sets were combined for inference. Data analyses were performed using SAS, version 9.4 (SAS Institute, Inc, Cary, NC).

## RESULTS

### Study Participants

The CATIS recruited 4071 participants with acute ischemic stroke, with a mean age of 62.0 years. There were 1997 participants (49.1%) who were taking antihypertensive medications at baseline (1014 in the immediate antihypertensive treatment group and 983 in the no treatment group) and 2074 not taking antihypertensive medications (1024 in the immediate treatment group and 1050 in the no treatment group). Most baseline characteristics were balanced between the immediate treatment and control groups in participants with antihypertensive medication use and those without use (Table).

The CATIS-2 recruited 4810 participants with acute ischemic stroke, with a mean (SD) age of 63.7 years. There were 2540 participants (49.1%) who were taking antihypertensive medications at baseline (1265 in

the early antihypertensive treatment group and 1275 in the delayed treatment group), and 2262 not taking antihypertensive medications (1143 in the early treatment group and 1119 in the delayed treatment group). Baseline characteristics were well balanced between the early treatment group and the delayed treatment group in participants with antihypertensive medication use and those without use (Table).

### The CATIS: BP Decrease

The mean systolic and diastolic BP levels were different between the immediate antihypertensive treatment group and the control group at 24 hours after randomization (Figure 2; *Figure S1*). Within 24 hours after randomization, mean (SD) systolic BP was decreased by 20.7 (16.2) mm Hg (12.0%) in the immediate treatment group and by 12.0 (17.4) mm Hg (6.8%) in the control group for patients with prior antihypertensive medication use (*Table S1*). The mean (SD) systolic BP was decreased by 23.0 (15.6) mm Hg (13.4%) in the immediate treatment group and 13.4 (17.2) mm Hg (7.6%) in the control group for patients without medication use. The mean systolic and diastolic BP levels were also significantly lower in the immediate treatment group than in the control group at 7 and 14 days after randomization. At the 90-day posttreatment follow-up visit, mean systolic and diastolic BPs were still significantly lower in the immediate treatment group than in the control group; the systolic BP differences were  $-3.2$  (95% CI,  $-4.3$  to  $-2.1$ ) mm Hg for patients with prior antihypertensive medication use and  $-2.7$  (95% CI,  $-3.8$  to  $-1.6$ ) mm Hg for patients without medication use (both  $P > 0.05$ ; *Table S1*).

### The CATIS: Immediate Versus No Treatment

At 14 days or hospital discharge, among participants who have already taken antihypertensive medications, immediately continuous antihypertensive treatment compared with no treatment was not associated with decreased risk of the primary outcome of death or major disability (OR, 1.07 [95% CI, 0.89–1.29]). Similarly, the primary outcome was not significantly different between the immediate treatment group and control group in patients without prior antihypertensive medication use (OR, 0.95 [95% CI, 0.79–1.13];  $P_{\text{interaction}} = 0.36$ ; Figure 3).

In addition, immediate antihypertensive treatment was not associated with the mRS scores at 14 days or hospital discharge both in patients with and without prior antihypertensive medication use ( $P_{\text{interaction}} = 0.25$ ). The ORs associated with the immediate treatment group were 1.05 (95% CI, 0.89–1.22) and 0.92 (95% CI, 0.79–1.07) for a higher mRS score among participants with and without a medication use history, respectively (*Figure S2*). The Kaplan-Meier curves showed that there was no significant difference in death and vascular events between

**Table.** Baseline Characteristics of Study Participants According to Use of Antihypertensive Medications

	CATIS						CATIS-2					
	Use of antihypertensive medications			No use of antihypertensive medications			Use of antihypertensive medications			No use of antihypertensive medications		
	Immediate treatment	No treatment	P value	Immediate treatment	No treatment	P value	Early treatment	Delayed treatment	P value	Early treatment	Delayed treatment	P value
No. of patients	1014	983		1024	1050		1265	1275		1143	1119	
Male sex	615 (60.7)	577 (58.7)	0.37	702 (68.6)	710 (67.6)	0.65	765 (60.5)	781 (61.3)	0.69	794 (69.5)	782 (69.9)	0.83
Age, y	62.5 (10.6)	62.3 (10.8)	0.54	61.6 (11.1)	61.5 (11.3)	0.77	64.6 (9.9)	64.3 (9.8)	0.34	63.2 (10.5)	62.6 (10.8)	0.18
Time from onset to randomization, h	16.0 (13.4)	15.7 (13.4)	0.63	14.6 (12.3)	14.2 (12.5)	0.37	36.2 (9.5)	35.8 (10.0)	0.25	36.2 (8.8)	36.6 (10.7)	0.34
NIHSS score*	4 (2–7)	4 (2–8)	0.85	4 (2–7)	5 (3–8)	0.04	3 (2–5)	3 (2–5)	0.97	3 (2–5)	3 (2–5)	0.53
Smoking	320 (31.6)	301 (30.6)	0.65	405 (39.6)	459 (43.7)	0.05	379 (30.0)	370 (29.0)	0.60	450 (39.4)	445 (39.8)	0.83
Alcohol drinking	263 (25.9)	262 (26.7)	0.72	351 (34.3)	377 (35.9)	0.44	231 (18.3)	244 (19.1)	0.57	314 (27.5)	284 (25.4)	0.26
BP at entry, mm Hg												
Systolic	166.6 (17.2)	165.8 (16.8)	0.31	166.7 (0.54)	165.4 (16.3)	0.07	162.7 (15.1)	162.7 (15.1)	0.90	163.1 (14.6)	162.9 (14.7)	0.84
Diastolic	97.0 (10.3)	96.5 (11.7)	0.30	96.6 (11.3)	96.6 (11.1)	0.97	91.2 (9.6)	91.1 (10.0)	0.84	92.5 (10.1) American	92.5 (10.0)	0.95
Medical history												
Hyperlipidemia	88 (8.7)	86 (8.8)	0.96	49 (4.8)	54 (5.1)	0.71	49 (3.9)	44 (3.5)	0.57	33 (2.9)	23 (2.1)	0.20
Diabetes	220 (21.7)	220 (22.4)	0.71	149 (14.6)	130 (12.4)	0.15	382 (30.2)	352 (27.6)	0.15	223 (19.5)	209 (18.7)	0.61
CHD	137 (13.5)	129 (13.1)	0.80	79 (7.7)	99 (9.4)	0.16	126 (10.0)	122 (9.6)	0.74	74 (6.5)	59 (5.3)	0.22
Previous stroke							426 (33.7)	411 (32.2)	0.44	191 (16.7)	208 (18.6)	0.24
Cause of stroke			0.46			0.17			0.32			0.43
LAA	792 (78.1)	777 (79.0)		783 (76.5)	818 (77.9)		648 (51.2)	616 (48.3)		564 (49.3)	538 (48.1)	
SAO	195 (19.2)	185 (18.8)		222 (21.7)	200 (19.1)		539 (42.6)	571 (44.8)		487 (42.6)	474 (42.4)	
CE/others	58 (5.7)	46 (4.7)		41 (4.0)	57 (5.4)		78 (6.2)	88 (6.9)		92 (8.1)	107 (9.6)	

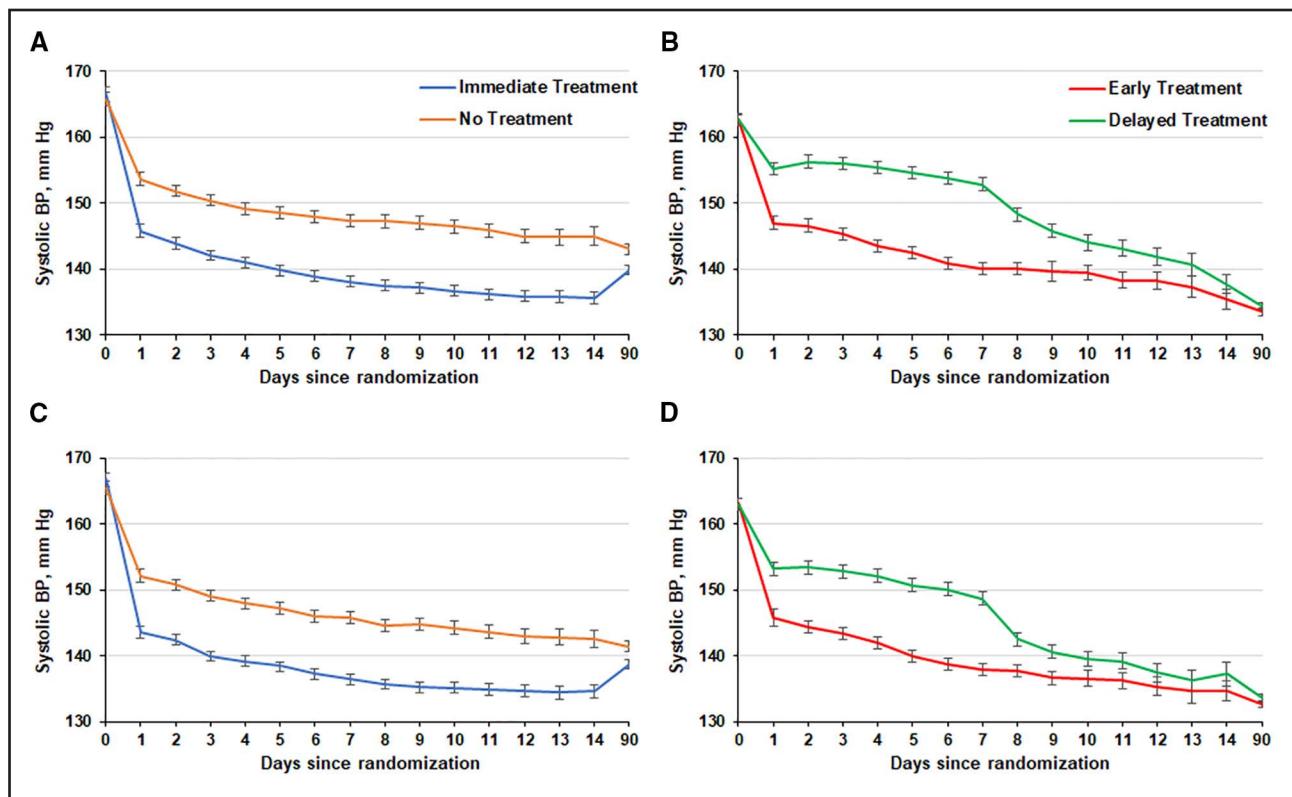
BP indicates blood pressure; CATIS, China Antihypertensive Trial in Acute Ischemic Stroke; CATIS-2, China Antihypertensive Trial in Acute Ischemic Stroke II; CE, cardioembolism; CHD, coronary heart disease; LAA, large-artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; NIHSS, National Institutes of Health Stroke Scale; and SAO, small-artery occlusion lacunar.

\*Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits.

the immediate treatment group and the control group in subgroups (log-rank  $P>0.05$ ), while the immediate treatment group had lower rates of recurrent stroke among patients with prior antihypertensive medication use (log-rank  $P=0.01$ ; Figure 4; Figures S2 and S3). Antihypertensive treatment was associated with a decreased risk of recurrent stroke (OR, 0.42 [95% CI, 0.21–0.86]) only in patients with a medication use history, but there was no significant interaction between prior medication use and immediate treatment on the risk of recurrent stroke ( $P_{\text{interaction}}=0.09$ ). The secondary outcomes of 90-day mRS scores, death or major disability, death, and vascular events were all not significantly different between the immediate antihypertensive treatment group and control group as well (all  $P_{\text{interaction}}>0.05$ ; Figures 3 and 5).

## The CATIS-2: BP Decrease

The mean systolic and diastolic BP levels were different between the early treatment and delayed treatment groups at 24 hours and 7 days after randomization (Figure 2; Figure S1). The net systolic BP differences at 24 hours between the early treatment and delayed treatment groups were  $-8.1$  (95% CI,  $-9.4$  to  $-6.8$ ) mm Hg for patients with prior antihypertensive medication use and  $-7.5$  (95% CI,  $-9.2$  to  $-5.8$ ) mm Hg for those without medication use (both  $P<0.001$ ; Table S2). At 14 days, the net systolic BP differences between the early treatment and delayed treatment groups were  $-12.8$  (95% CI,  $-14.1$  to  $-11.5$ ) mm Hg for patients with antihypertensive medication use and  $-10.7$  (95% CI,  $-12.1$



**Figure 2. Mean systolic blood pressure (BP) since randomization by prior antihypertensive medication use.**

**A**, CATIS (China Antihypertensive Trial in Acute Ischemic Stroke): use of prior antihypertensive medications. **B**, CATIS-2 (China Antihypertensive Trial in Acute Ischemic Stroke II): use of prior antihypertensive medications. **C**, CATIS: no use of prior antihypertensive medications. **D**, CATIS-2: no use of prior antihypertensive medications. Error bars represent 95% CIs.

to  $-9.3$  mm Hg for those without (both  $P < 0.001$ ). After initiating antihypertensive medications on day 8 in the delayed treatment group, the mean systolic BP differences between the 2 treatment groups were  $-2.2$  mm Hg for patients with medication use ( $P = 0.04$ ) and  $-2.5$  mm Hg for those without medication use ( $P = 0.03$ ) at day 14 after randomization, and the differences further narrowed down at 90 days (Table S2).

### The CATIS-2: Early Versus Delayed Treatment

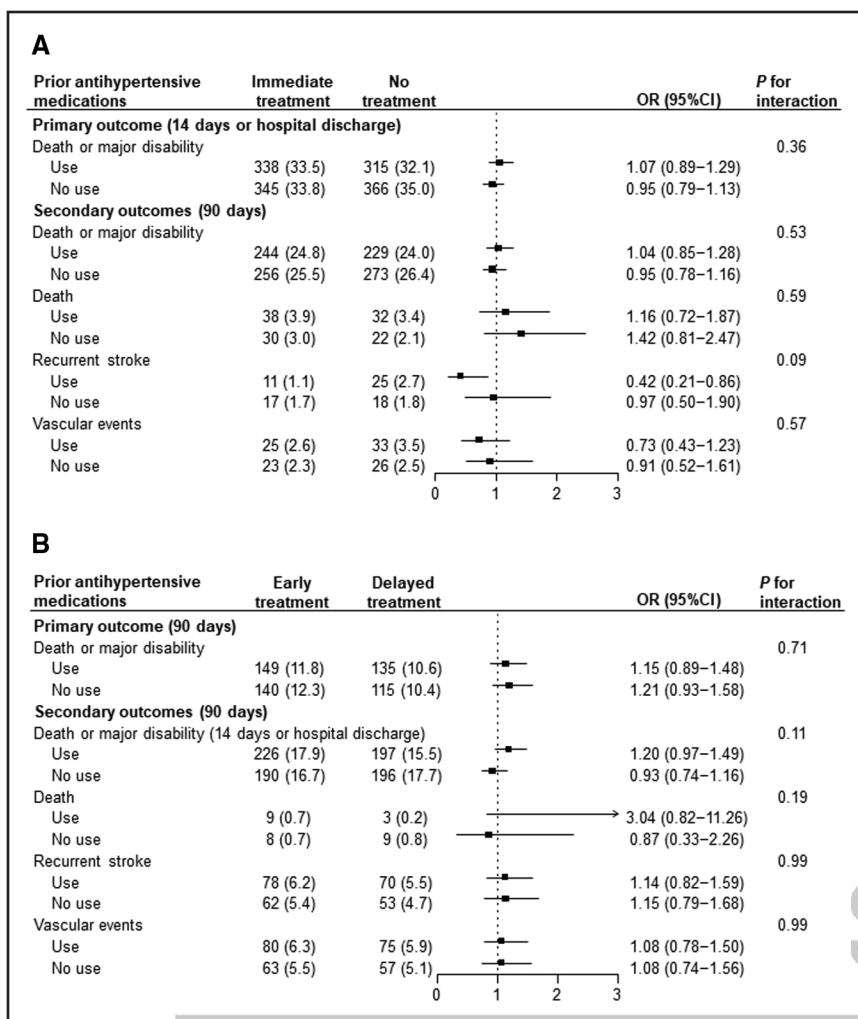
At the 90-day follow-up visit, among participants who had already taken antihypertensive medications, early antihypertensive treatment (24–48 hours) compared with delayed treatment (8 days) was not significantly associated with the primary outcome of death or major disability (OR, 1.15 [95% CI, 0.89–1.48]). Similarly, the primary outcome was not different between the early treatment group and the delayed treatment group among participants without prior antihypertensive medication use (OR, 1.21 [95% CI, 0.93–1.58];  $P_{\text{interaction}} = 0.71$ ; Figure 3).

The ordinal logistic regression showed that early antihypertensive treatment compared with delayed treatment was not associated with the odds of a higher mRS score at 90 days, regardless of existing antihypertensive medication use ( $P_{\text{interaction}} = 0.44$ ; Figure 4). The Kaplan-Meier

curves showed that no significant difference in secondary outcomes between the early treatment and the delayed treatment group was observed (all log-rank  $P > 0.05$ ; Figure 4; Figures S2 and S3). Likewise, the secondary outcomes including death, recurrent stroke, and major vascular events within 90 days were not significantly different between the 2 treatment groups among participants with and without prior antihypertensive medication use history (all  $P_{\text{interaction}} > 0.05$ ; Figure 3; Figure S4).

### DISCUSSION

These prespecified subgroup analyses of 2 multicenter clinical trials explored the common clinical dilemmas: whether to administer early antihypertensive treatment and when to start or restart antihypertensive treatments in the acute phase of ischemic stroke, according to prestroke antihypertensive medication use. Several main findings emerged. In the CATIS, we first found that immediate initiation of preexisting antihypertensive treatment was not associated with decreased odds of death or major disability at 14 days or hospital discharge in patients using prior antihypertensive medications. Second, the CATIS-2 reported that compared with delayed antihypertensive treatment starting on day 8, early antihypertensive treatment at 24 to 48 hours did not reduce



**Figure 3. Effects of antihypertensive treatment on clinical outcomes in CATIS (China Antihypertensive Trial in Acute Ischemic Stroke) and CATIS-2 (China Antihypertensive Trial in Acute Ischemic Stroke II).**

**A**, The effects of immediate treatment vs no treatment in CATIS. **B**, The effects of early treatment vs delayed treatment in CATIS-2. OR indicates odds ratio.

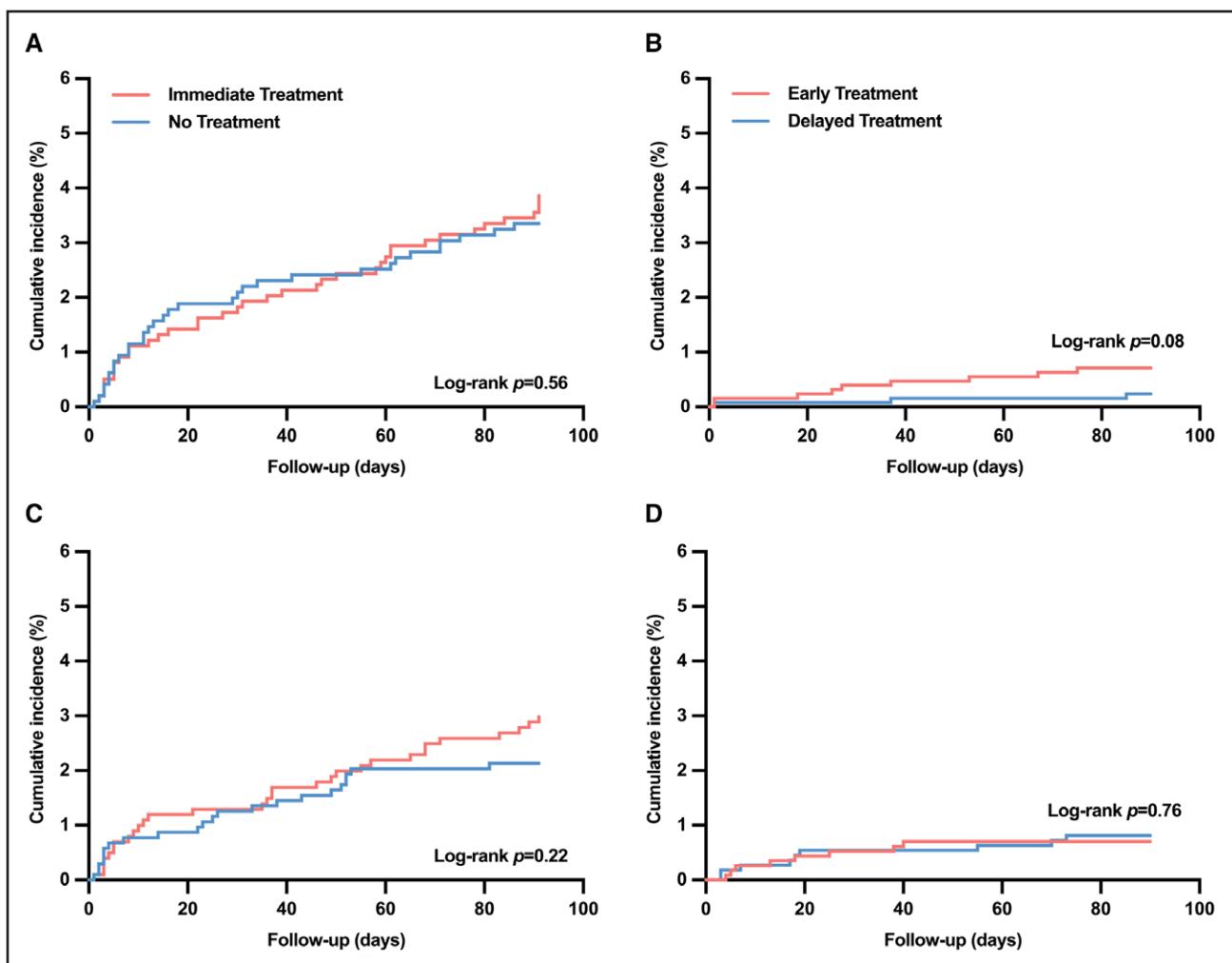


the odds of the primary outcome of death or major disability at 90 days in patients using prior antihypertensive medications. Furthermore, no antihypertensive treatment in the acute phase or delayed treatment did not increase the risk of clinical outcomes among patients without the use of any antihypertensive medications. These findings comprehensively evaluate early antihypertensive strategies in patients with or without prestroke antihypertensive medication use and contribute to better BP management after acute ischemic stroke.

Whether preexisting antihypertensive treatment should be continued or stopped in the acute phase of ischemic stroke remains uncertain.<sup>11,19</sup> Continued use of antihypertensive medications may prevent unfavorable clinical outcomes among patients with ischemic stroke and help them transition to long-term antihypertensive therapy for secondary prevention.<sup>12,14</sup> However, early BP reduction may also decrease cerebral blood flow, increase the ischemic penumbra, and result in a larger infarct size, as patients with acute stroke are usually accompanied by impaired cerebral autoregulation.<sup>12</sup> The COSSACS trial reported that continuation of antihypertensive drugs did not reduce 2-week death or dependency, cardiovascular

event rate, and mortality at 6 months, nor did it increase adverse events among 763 patients with acute stroke.<sup>9</sup> Similarly, the ENOS trial recruited 2097 patients with acute ischemic or hemorrhagic stroke and demonstrated that continuing prestroke antihypertensive drugs did not improve functional outcome compared with stopping them temporarily but even worsened several secondary measures of outcome, including discharge destination, activities of daily living, and cognition.<sup>10</sup> A further meta-analysis of individual patient data from the COSSACS and ENOS trial also found no significant benefit with continuation of antihypertensive treatment in the acute stroke period.<sup>11</sup> However, due to the different pathophysiological mechanisms and treatment requirements between ischemic and hemorrhagic stroke, the efficacy of continuing prestroke antihypertensive medications should be tested specifically in patients with ischemic stroke.

A post hoc analysis of the COSSACS trial found that continuation of antihypertensive drugs might be associated with reduced 2-week death and dependency in patients with ischemic stroke confirmed on neuroimaging compared with the stop group (46 of 241 versus

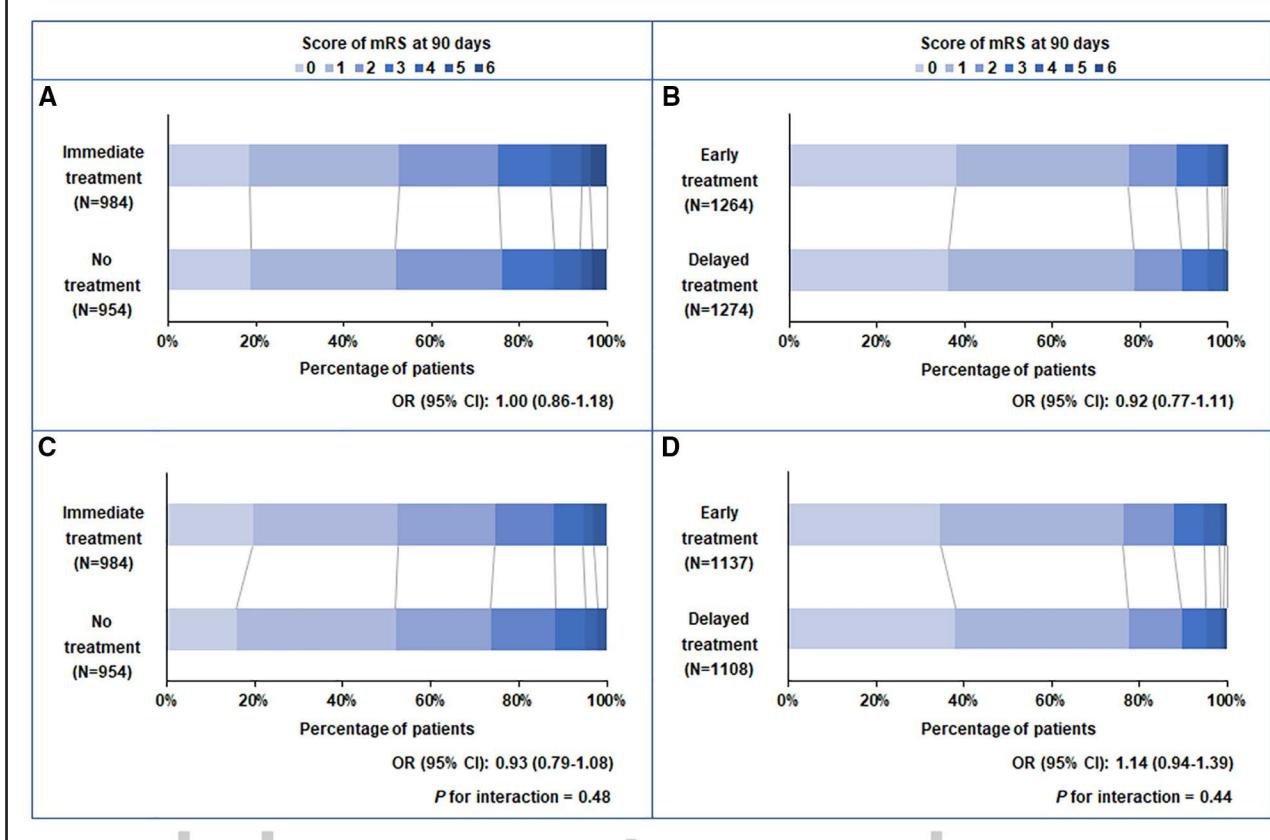


**Figure 4.** Kaplan-Meier survival curves of death in CATIS (China Antihypertensive Trial in Acute Ischemic Stroke) and CATIS-2 (China Antihypertensive Trial in Acute Ischemic Stroke II).

**A,** CATIS: use of prior antihypertensive medications. **B,** CATIS-2: use of prior antihypertensive medications. **C,** CATIS: no use of prior antihypertensive medications. **D,** CATIS-2: no use of prior antihypertensive medications.

55 of 203; relative ratio, 0.70 [95% CI, 0.51–0.99].<sup>9</sup> While the few included patients with ischemic stroke and underpowered COSSACS trial suggested that this might be a chance finding, our prespecified subgroup analysis of CATIS with large sample size of ischemic stroke did not identify a benefit for immediately continuous BP reduction, but also it did not increase the risk of unfavorable functional outcome in patients using prior antihypertensive medications, as well as those not using. We found that there was a tendency for immediate initiation of preexisting antihypertensive treatment to reduce the risk of recurrent stroke, but no significant interaction was observed. The clinical implication of these findings is that there may be no urgency to immediately administer prestroke antihypertensive therapy after ischemic stroke. However, when we should restart such early treatment for patients with a history of antihypertensive medication use is a commonly ignored issue by randomized evidence and clinical guidelines.

The hypertensive response following ischemic stroke is self-limiting, with most patients resolving within several days after the onset of stroke.<sup>20–22</sup> A secondary analysis of the ENOS trial demonstrated that continuing prior antihypertensive therapy in patients with predominantly ischemic stroke within 12 hours of symptom onset was associated with worse clinical outcomes across multiple domains, including functional outcome, death, disability, cognition, quality of life, and mood.<sup>23</sup> Recently, the INTERACT4 (Fourth Intensive Ambulance Delivered Blood Pressure Reduction in Hyper-Acute Stroke Trial) also reported that prehospital BP reduction in the ambulance within 2 hours had no benefit in patients with undifferentiated acute stroke but had an increased odds of poor functional outcome among patients with cerebral ischemia.<sup>24</sup> The guidelines for the early management of acute ischemic stroke indicate that reinitiating antihypertensive therapy within the first 48 to 72 hours after an acute ischemic stroke is safe but



**Figure 5. Distribution of modified Rankin Scale scores at 90 days in CATIS (China Antihypertensive Trial in Acute Ischemic Stroke) and CATIS-2 (China Antihypertensive Trial in Acute Ischemic Stroke II).**

Ordinal logistic regression was used to estimate odds ratios (ORs) and 95% CIs. **A.**, CATIS: use of prior antihypertensive medications. **B.**, CATIS-2: use of prior antihypertensive medications. **C.**, CATIS: no use of prior antihypertensive medications. **D.**, CATIS-2: no use of prior antihypertensive medications.

not effective to prevent death or functional disability.<sup>25-27</sup> The CATIS-2 investigated the optimal timing for initiating BP lowering after acute ischemic stroke and found that early antihypertensive treatment (at 24–48 hours) versus delayed treatment (at day 8) did not reduce the odds of dependency or death at 90 days. This current subgroup analysis of CATIS-2 confirmed the neutral efficacy of early antihypertensive treatment on unfavorable outcomes regardless of the use of prior antihypertensive medications.

The early transient raised BP after acute stroke can be caused by chronic hypertension or responses to physical and psychological stresses from brain ischemia, while active BP intervention may cause insufficient cerebral perfusion of the ischemic tissue.<sup>28,29</sup> In this prespecified subgroup analysis of 2 large clinical trials, no immediate BP intervention or delaying treatment to 8 days after stroke onset did not increase the risk of adverse clinical outcomes in patients with a history of antihypertensive medication use, also for those without. Our study provided comprehensive evidence on the efficacy of early antihypertensive treatment and extended the recommendations of existing clinical guidelines specifically to

patients with acute ischemic stroke.<sup>25</sup> The findings suggested that preexisting antihypertensive therapy could be withheld in the first few days after stroke onset until the patients are medically and neurologically stable, for patients with ischemic stroke who are already taking antihypertensive medications.

Our study should be interpreted in light of several limitations. First, both CATIS and CATIS-2 did not recruit participants treated with intravenous thrombolytic treatment or endovascular thrombectomy, which may limit the generalizability of the findings.<sup>6,7</sup> Second, the 2 subgroups analyses have some inherent limitations, including multiple comparisons and loss of statistical power. The findings cannot provide a definite answer to guide clinical patient care and should be validated in future, specially designed clinical trials. Third, the history of antihypertensive medication use was self-reported, which might not enroll all patients using prior antihypertensive medications and might cause misclassification. In addition, most included participants have mild-to-moderate stroke (with a lower median National Institutes of Health Stroke Scale score, 3 or 4); therefore, the study findings might not be generalizable to patients with severe ischemic stroke.

In conclusion, the prespecified subgroup analyses of the CATIS and CATIS-2 indicated that early antihypertensive treatment had neutral effects on clinical outcomes compared with no treatment or delayed treatment among patients with acute ischemic stroke, regardless of existing antihypertensive treatment.

## PERSPECTIVES

Based on 2 large clinical trials (CATIS and CATIS-2), this study comprehensively evaluated early antihypertensive strategies in patients with or without prestroke antihypertensive medication use. The findings confirmed the neutral efficacy of early antihypertensive treatment on unfavorable outcomes regardless of the use of prior antihypertensive medications. On the other hand, no immediate BP intervention or delaying treatment to 8 days after stroke onset did not increase the risk of adverse clinical outcomes in patients with a history of antihypertensive medication use, also for those without. This study contributes to better BP management after acute ischemic stroke, but further clinical trials are still needed to confirm our findings.

## ARTICLE INFORMATION

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### Author Contributions

C. Zhong, J. Chen, T. Xu, Yilong Wang, J. He, Yongjun Wang, Y. Zhang, L. Liu, and X. Xie contributed to the conception and design of the study. C. Zhong, Ming Wang, D. Liu, Y. Wei, Mengxing Wang, Y. Peng, and Y. Pan contributed to the acquisition and analysis of data. C. Zhong, Ming Wang, J. He, and X. Xie contributed to drafting the text or preparing the figures. All authors interpreted data, contributed to critical revisions, and read and approved the final version of the article. The corresponding authors attest that all listed authors meet authorship criteria and have full access to all the data in the study.

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### Disclosures

None.

### Supplemental Material

Tables S1–S2

Figure S1–S4

Supplemental 1-CATIS Protocol

Supplemental 2-CATIS-2 Study Protocol

Supplemental 3-CATIS-2 Statistical Analysis Plan

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