Early versus delayed antihypertensive treatment in patients with acute ischaemic stroke: multicentre, open label, randomised, controlled trial

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ABSTRACT

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Introduction

Elevated blood pressure is common among patients with acute stroke and is associated with increased risk of long term disability and death.[1 2] Several randomised controlled trials have compared early antihypertensive treatment versus no antihypertensive treatment or intensive antihypertensive treatment versus standard antihypertensive treatment on clinical outcomes among patients with acute stroke.[3-8] Most of these trials included a mix of patients with either acute ischaemic or haemorrhagic stroke and reported no e ect of early antihypertensive treatment on clinical outcomes.[3 4 6] A meta-analysis of 13 randomised controlled trials

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that included 12 703 patients with acute ischaemic stroke showed that antihypertensive treatment within three days of symptom onset did not a ect the risk of functional dependency or death at 90 days.[9] In the enhanced control of hypertension and thrombolysis stroke study (ENCHANTED),[7] antihypertensive treatment targeting a systolic blood pressure of 130-140 mm Hg within an hour of randomisation did not improve functional status at 90 days among patients who had an acute ischaemic stroke within six hours of onset and receiving intravenous thrombolysis therapy. Furthermore, in the ENCHANTED-2 trial, more intensive antihypertensive treatment targeting an systolic blood pressure of less than 120 mm Hg within an hour of randomisation was associated with increased risk of major disability at 90 days among patients with acute ischaemic stroke who had persistently high systolic blood pressure (≥140 mm Hg) after successful reperfusion with endovascular thrombectomy.[8] These two trials indicate that intensive blood pressure reduction within the first few hours of acute ischaemic stroke onset do not improve functional outcomes, and may even worsen them.[7 8]

Although many mechanisms may cause increased blood pressure in the acute phase of ischaemic stroke, most patients have a previous history of hypertension.[3 5 7 10] Several randomised controlled trials have shown that blood pressure lowering reduces the risk of recurrent stroke among patients with a history of stroke.[11-13] However, the optimal timing for initiating blood pressure lowering after acute ischaemic stroke remains uncertain.[10 14 15] In the China antihypertensive trial in acute ischaemic stroke (CATIS),[16] we observed a potential beneficial e ect of blood pressure lowering on death and major disability, recurrent stroke, and vascular events among patients with acute ischaemic stroke who received treatment between 24 h and 48 h after stroke onset in a subgroup analysis. In this CATIS-2 trial, we aimed to test whether early antihypertensive treatment that started within the first 24-48 h of ischaemic stroke onset would result in a lower risk of a composite outcome of dependency or death (modified Rankin Score ≥3) at 90 days compared with delayed antihypertensive treatment starting on day eight after randomisation.

Methods

Trial design and participants

CATIS-2 is a multicentre, randomised, open label, endpoint trial conducted in 106 hospitals in China. The details of the study design and methods were published previously.[17]

In brief, we recruited patients (age of ≥40 years) with acute ischaemic stroke, diagnosed by computed tomography or magnetic resonance imaging of the brain, within 24-48 h of symptom onset and with an elevated systolic blood pressure of between 140 mm Hg and 219 mm Hg. We excluded individuals with an systolic blood pressure of 220 mm Hg or higher or diastolic blood pressure of 120 mm Hg or higher because these patients require immediate antihypertensive treatment.[14 15] We also excluded patients with haemorrhagic stroke, extracranial or intracranial artery stenosis (≥70%) on both sides or the a ected side based on imaging studies, severe stroke (National Institutes of Health (NIH) stroke scale score ≥21), deep coma, modified Rankin score of 3 or more, severe heart failure, acute myocardial infarction or unstable angina, aortic dissection, or di cult-to-control hypertension. Additionally, we excluded patients with atrial fibrillation (because they might require beta blocker or calcium channel blocker treatment) and patients treated with intravenous thrombolytic treatment or endovascular thrombectomy at baseline (because of di erent requirements for blood pressure control in this group) (supplementary table S1).

The trial was approved by the ethics committeees of Beijing Tiantan Hospital and all participating institutes in China and by the Institutional Review Board of Tulane University in the US. Informed consent was signed by patients or their representatives. An independent data and safety monitoring board met annually to review the accumulating data for safety and to monitor the trial for either superiority or inferiority of early antihypertensive treatment on clinical outcomes.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to the early treatment group or the delayed treatment group using a web-based system managed by the Study and Data Coordinating Center at Beijing Tiantan Hospital. The randomisation schedule was generated using PROC PLAN in SAS version 9.4 (SAS Institute, Cary, NC) and concealed centrally at the Study and Data Coordinating Center. Randomisation was stratified by participating hospitals with a random block size of 4, 6, and 8.

Masking patients and treating physicians to whether antihypertensive medications would be started or stopped at randomisation was not practical. However, the study coordinators who collected study data, the neurologists who evaluated patients, and the endpoint adjudication committee members were all masked to patients' treatment assignments.

Procedures

Demographic characteristics and medical history were collected at enrolment. Stroke severity was assessed using NIH stroke scores (ranging from 0 to 42, with higher scores indicating a more severe neurological deficit) by trained neurologists at baseline, 14 days or hospital discharge, and 90 day follow-up visits. Computed tomography or magnetic resonance imaging of the brain was done according to a standard protocol to confirm the diagnosis of ischaemic stroke in all trial participants. Blood pressure measurements were obtained from participants in a supine position by trained nurses using an automated device (Omron HBP-1300 professional blood pressure monitor) and one of four cu sizes (paediatric, regular adult,

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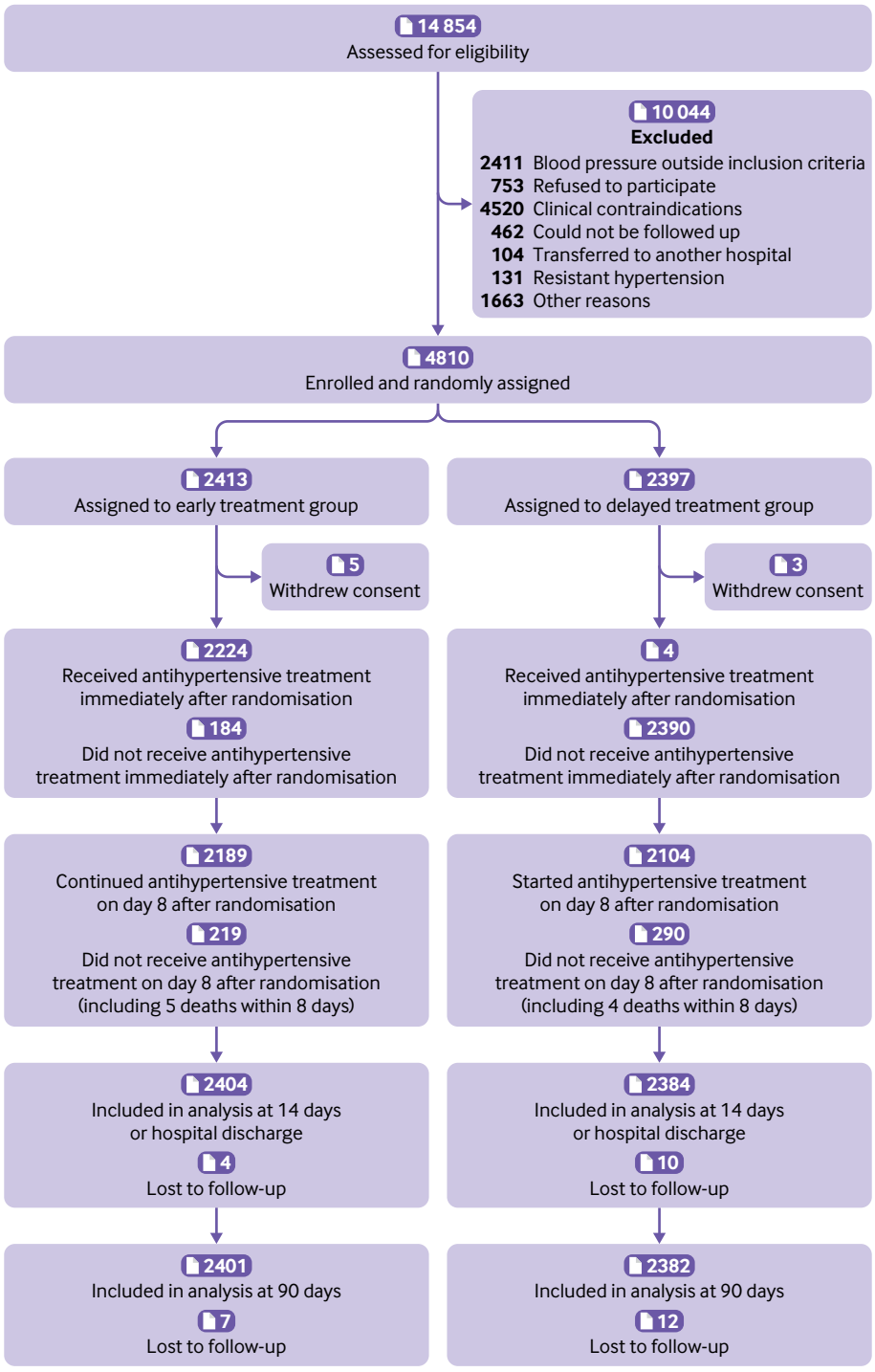

Fig 1 | Recruitment, randomisation, and follow-up in a trial of early versus delayed antihypertensive treatment in patients with acute ischaemic stroke. Clinical contraindications (n=45) included history of atrial fibrillation (n=), NIH stroke scale score ≥ 1 (n=1 1) at baseline assessment, modified Rankin score ≥ at baseline assessment (n=4), severe heart failure defined as ejection fraction < 5% (n=11), kidney failure defined as estimated glomerular filtration rate < mL/min/1. m (n=1), intravenous thrombolytic treatment or mechanical thrombectomy (n=11 5), all cause dementia (n=4), mental disorders (n=), history of cancer (n=1) or other conditions (n=1 15)

large adult, or thigh) based on participant arm circumference according to a standard protocol.[18] Three blood pressure measurements were obtained at baseline; every three hours after randomisation for the first 24 h; every eight hours from day two until day 14 or hospital discharge; and at 21 day and 90 day follow-up visits.

Interventions

All eligible participants discontinued home antihypertensive medications at the baseline examination if they were taking these drugs. The early treatment group received antihypertensive medications immediately after randomisation aimed at lowering systolic blood pressure by 10%–20% within the first

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Table 1 | Baseline characteristics of study participants in a trial of early versus delayed antihypertensive treatment in patients with acute ischaemic stroke

Characteristics	Early antihypertensive treatment (n= 4)	Delayed antihypertensive treatment (n= 94)
Mean age, years	64.0 (10.2)	63.5 (10.3)
Sex, no. (%):		
Male	1559 (64.7)	1563 (65.3)
Female	849 (35.3)	831 (34.7)
Median time from onset to randomisation, hours	36.2 (9.2)	36.2 (10.3)
Mean blood pressure at baseline, mm Hg:		
Systolic	162.9 (14.9)	162.8 (14.9)
Diastolic	91.8 (9.9)	91.8 (10.0)
Median NIH stroke scale score*	3 (2-5)	3 (2-5)
Medical history, no. (%):		
Hypertension	1918 (79.7)	1911 (79.8)
Diabetes mellitus	605 (25.1)	561 (23.4)
Dyslipidaemia	82 (3.4)	67 (2.8)
Stroke	617 (25.6)	619 (25.9)
Transient ischaemic attack	8 (0.3)	12 (0.5)
Coronary heart disease	200 (8.3)	181 (7.6)
Current smoking, no. (%)	829 (34.4)	815 (34.1)
Current alcohol drinking	545 (22.6)	528 (22.1)
Medications at baseline, no. (%):		
Antihypertensive	1265 (52.5)	1275 (53.3)
Antidiabetic	504 (20.9)	456 (19.1)
Lipid lowering	155 (6.4)	163 (6.8)
Antiplatelet	248 (10.3)	239 (10.0)
Cause of stroke, no. (%):		
Large artery atherosclerosis	1212 (50.3)	1154 (48.2)
Small artery disease	1026 (42.6)	1045 (43.7)
Others	170 (7.1)	195 (8.1)
Median time from onset to intervention, days; hours	1.5 (1.2-1.8); (36.0 (28.0-44.0))	8.5 (8.2-8.9); 204.1 (196.7-212.6))

Data are mean (standard deviation), no. (%), or median (interquartile range). NIH=National Institutes of Health.
*Scores on the NIH stroke scale range from 0 to 42, with higher scores indicating more severe neurological deficits.

24 h, reaching an average reading within seven days for systolic blood pressure of less than 140 mm Hg and for diastolic blood pressure of less than 90 mm Hg, and maintaining this blood pressure level during the 90 day follow-up. The delayed treatment group discontinued all antihypertensive medications after randomisation and restarted antihypertensive therapy on day eight aimed at reaching and maintaining a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg during the 90 day follow-up. During the first seven days, a study physician could give patients temporary antihypertensive treatment based on their clinical judgment if a patient's systolic blood pressure rose to 200 mm Hg or more. If a stroke patient's mean systolic blood pressure was 220 mm Hg or more or had a diastolic blood pressure of 120 mm Hg or more at each of two time points spaced six hours apart during the intervention, the participant would have been withdrawn from the trial.

Outcomes

The primary endpoint of the CATIS-2 trial was a composite outcome of death within 90 days or functional dependency (modified Rankin score of 3-5) at 90 days after randomisation. Modified Rankin scores range from 0 to 6, with a score of 0 indicating no symptoms, a score of 5 indicating severe disability, and a score of 6 indicating death.[19] Secondary outcomes included ordinal modified Rankin score,[20] recurrent total stroke events, and major vascular disease events (ie, vascular deaths, non-fatal stroke, non-fatal myocardial infarction, coronary revascularisation, and admitted to hospital for angina and heart failure) at the 90 day follow-up visit, as well as categorical and ordinal modified Rankin score at 14 days or hospital discharge.

Trained research nurses and neurologists who were masked to treatment assignment conducted follow-up visits with participants at day 21 and day 90. Data for medical history, medication use, vascular events, blood pressure, NIH stroke scale, and modified Rankin score were collected. Death certificates were obtained for deceased participants, and hospital data were abstracted for all vascular events. A study wide endpoint adjudication committee, whose members were masked to participants' treatment assignments, reviewed and adjudicated vascular events based on established criteria.[21] Each case was independently adjudicated by two members; if a disagreement arose, a third reviewer was included to reach a consensus.

Adverse events were queried by research nurses during admission to hospital and follow-up visits. Serious adverse events included deaths and events that were fatal or life threatening, those that resulted in clinically significant or persistent disability, required admission to hospital again or prolonged a hospital stay, or were judged by the investigator to represent a clinically significant hazard or harm to the participant that might require medical or surgical intervention to prevent one of the other events listed above.[22] The association of serious adverse events to

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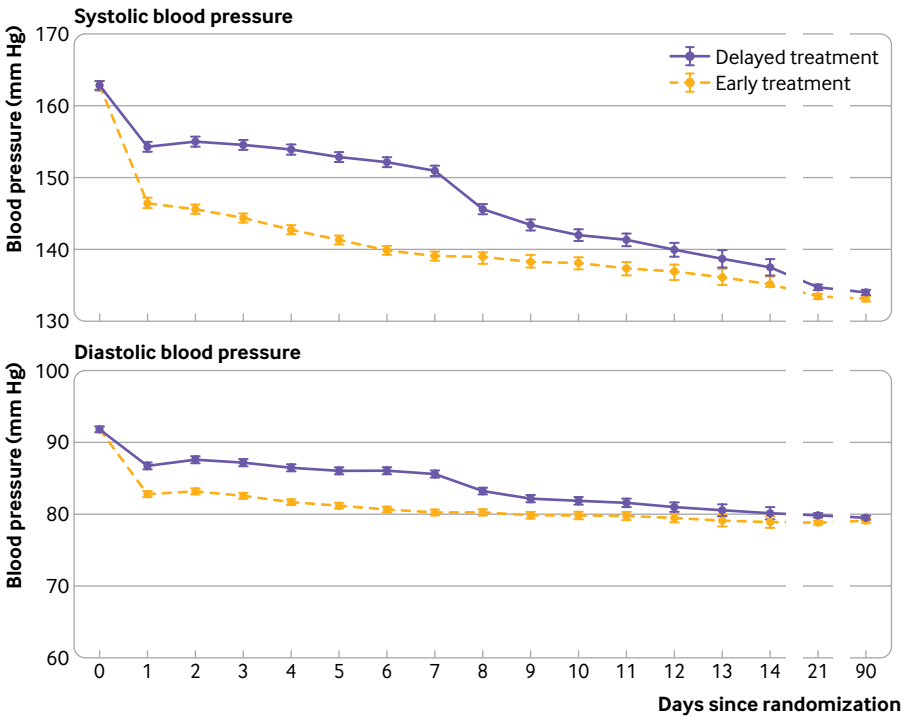

No of patients

Delayed treatment
2394 2280 2249 2243 2215 2176 2097 1985 1803 1561 1340 1115 860 511 424 2317 2298

Early treatment
2408 2309 2268 2248 2232 2180 2090 1922 1733 1454 1242 1038 820 490 424 2333 2310

Fig | Mean systolic and diastolic blood pressure since randomisation in a trial of early vs delayed antihypertensive treatment in patients with acute ischaemic stroke. Three blood pressure measurements were obtained every three hours for the first 4 h and then every eight hours during hospital admission until day 14 or hospital discharge. Additionally, three blood pressure measurements were obtained at 1 day and 9 day follow-up visits in all patients. Error bars represent 95% confidence intervals. Tinted regions indicate the timeframe from day to

the intervention was assessed by trial physicians and reviewed by the data and safety monitoring board and participating institutes' ethics committees.

Sample size and power

The sample size calculation was calculated on the following assumptions: a 25% event rate of the primary outcome in the delayed treatment group modelled on data from the CATIS trial,[5] a 21% event rate of the primary outcome in the early treatment group based on the assumption of a 15% proportional risk reduction associated with early antihypertensive treatment, 5% loss to follow-up, 85% statistical power, and a two-sided significance level of 0.05. Accordingly, the estimated sample size was 4776 participants (2388 in each randomisation group).

Statistical analysis

Intention to treat analyses were conducted. Linear mixed-e ects regression analysis was used to test the group di erences in mean blood pressure changes between the early and delayed treatment groups with a significance level of 0.004 (0.05/14 tests). Mixed-e ects logistic regression analysis was used to estimate odds ratios and 95% confidence intervals associated with early treatment compared with delayed treatment at a significance level of 0.05. Participating hospitals were included as a random e ect in the mixed-e ects models. In a sensitivity analysis, odds ratios were adjusted for baseline age, sex, systolic blood pressure, NIH stroke scale score, time from stroke onset to randomisation, history of hypertension, and antihypertensive medication use. Additionally, the median and interquartile range of modified Rankin score were calculated, and the di erences in the entire distribution of modified Rankin score were compared using the Wilcoxon rank-sum test. Ordinal logistic regression was used to estimate the e ect of early blood pressure reduction compared with delayed reduction on the full range of the modified Rankin score.[23] Furthermore, a per protocol analysis was conducted to assess the robustness of trial findings. We assessed the heterogeneity of the treatment e ect on the primary outcome in prespecified subgroups by age, sex, systolic blood pressure, NIH stroke scale score, history of hypertension, antihypertensive medication use, and subtypes of ischaemic stroke at baseline by adding an interaction term in logistic regression models. The Bonferroni correction method was used to adjust the critical value for interaction tests in these subgroup analyses.

In these analyses, pairwise deletion of missing data was used to preserve all information observed.

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Table | Blood pressure reduction during intervention in a trial of early versus delayed antihypertensive treatment in patients with acute ischaemic stroke

Characteristic	Early antihypertensive treatment (n= 4)	Delayed antihypertensive treatment (n= 94)	Group difference (95% CI)	P value
Mean BP (SD) at 24 h after randomisation, mm Hg				
Systolic	146.4 (19.1)	154.3 (16.8)	−7.9 (−8.9 to −6.9)	<0.001
Diastolic	82.8 (10.4)	86.7 (11.7)	−3.9 (−4.5 to −3.3)	<0.001
Mean absolute change (SD) in BP from baseline to 24 h after randomisation, mm Hg				
Systolic	−16.4 (19.7)	−8.6 (16.9)	−7.8 (−8.9 to −6.7)	<0.001
Diastolic	−9.0 (11.0)	−5.1 (11.4)	−3.9 (−4.5 to −3.3)	<0.001
Mean proportional change (SD) in BP from baseline to 24 h after randomisation, %				
Systolic	−9.7 (11.7)	−4.9 (10.2)	−4.8 (−5.4 to −4.2)	<0.001
Diastolic	−9.3 (11.5)	−5.1 (12.4)	−4.3 (−5.0 to −3.6)	<0.001
Mean BP (SD) at day 7 after randomisation, mm Hg				
Systolic	139.1 (13.9)	150.9 (16.4)	−11.9 (−12.9 to −10.9)	<0.001
Diastolic	80.2 (9.3)	85.6 (11.5)	−5.4 (−6.1 to −4.7)	<0.001
Mean BP (SD) at day 14 after randomisation, mm Hg				
Systolic	135.1 (11.3)	137.5 (11.9)	−2.3 (−3.9 to −0.7)	0.001
Diastolic	78.9 (8.4)	80.1 (8.9)	−1.2 (−2.4 to 0.0)	0.07
Mean BP (SD) at day 21 after randomisation, mmHg				
Systolic	133.5 (9.2)	134.7 (9.6)	−1.3 (−1.8 to −0.8)	<0.001
Diastolic	78.8 (7.2)	79.8 (7.7)	−1.0 (−1.4 to −0.6)	<0.001
Mean BP (SD) at day 90 after randomisation, mm Hg				
Systolic	133.1 (9.1)	134.0 (9.2)	−0.9 (−1.4 to −0.4)	<0.001
Diastolic	79.1 (7.3)	79.5 (7.4)	−0.4 (−0.8 to 0.0)	0.04

[i]BP=blood pressure; CI=confidence interval; SD=standard deviation.

Additionally, 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.[24] The study outcome and baseline covariables—age, sex, systolic blood pressure, NIH stroke scale score, time from stroke onset to randomisation, history of hypertension, and antihypertensive medication use—were included in the analytical model for multiple imputation. Ten imputed datasets were generated and analysed using the statistical methods previously described here. The results from 10 imputed datasets were combined for inference. Statistical analyses were done using SAS software, version 9.4.

Protocol amendments

Due to covid-19 pandemic, the recruitment period was extended from two years to four years. Additionally, to reduce visiting time in clinics, the CATIS-2 Steering Committee and data and safety monitoring board decided to not collect data on the Montreal Cognitive Assessment and the 12-item Short Form-12 during three month follow-up visits. To be consistent with using ordinal logistic regression for the ordinal modified Rankin score scores, binary logistic regression was chosen to analyse the binary primary and secondary outcomes during the development of the statistical analysis plan.

Patient and public involvement

Patients or members of the public were not formally involved in the design, conduct, or analysis of the trial, nor in the writing or interpretation of study findings. This e cacy trial was conducted among patients with acute ischaemic stroke within 24-48 h of symptom onset. Therefore, the time and study site where the research took place limited the involvement of patients. Additionally, the trial was initiated before patient and public involvement became common, and funds or personnel to include patients or the public were not available. However, the study protocol, treatment plan, and manuscript were widely discussed among clinical practice neurologists. Furthermore, clinical practice neurologists will be involved in disseminating study findings to patients, members of the public, and healthcare professionals.

Results

Between 13 June 2018 and 10 July 2022, 14854 patients from 106 hospitals in China were screened; 4810 patients were enrolled; and 2413 patients were randomly assigned to the early treatment group and 2397 to the delayed treatment group (fig 1). During the 90 day follow-up, five patients withdrew consent and seven were lost to follow-up in the early-treatment group. Similarly, three patients withdrew consent and 12 were lost to follow-up in the delayed-treatment group. These patients were not included in the primary analysis.

Baseline characteristics of patients were similar between the two randomisation groups (table 1). The mean age was 63.7 years, 65.0% of patients were men, 79.7% had a history of hypertension, and 52.9% were taking antihypertensive medication at admission. Additionally, 25.7% of patients had a history of stroke, and 49.3% of patients had a large artery atherosclerosis stroke. The median time from symptom onset to randomisation was 36.2 h. The median time from symptom onset to intervention was 1.5 days (36.0 h) in the early treatment group and 8.5 days (204.1 h) in the delayed treatment group.

Blood pressure reduction

Immediately after randomisation, 2224 patients received antihypertensive medications (527

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multiple imputation for missing data, the odds ratio of dependency or death at day 90 associated with early antihypertensive treatment compared with delayed treatment was 1.17 ((0.98 to 1.40), P=0.084).

In the per protocol analysis, the odds ratios associated with early treatment compared with delayed treatment were 1.16 ((0.96 to 1.40), P=0.12) for dependency or death at day 90 and 1.16 ((0.90 to 1.49), P=0.25) for recurrent stroke at day 90 (supplementary table s5).

Adverse events

Serious adverse events occurred in 166 (6.9%) of 2401 participants in the early treatment group and 142 (6.0%) of 2382 participants in the delayed treatment group (P=0.17) (table 3). In the early treatment group, 17 deaths (0.7%) were reported and in the delayed treatment group, 12 deaths (0.5%) (P=0.36) were reported. Likewise, other serious adverse events were generally similar between the early treatment and delayed treatment groups (supplementary table S6).

Discussion

Principal findings

CATIS-2 is the only randomised controlled trial to our knowledge that has aimed at comparing the e ect of early antihypertensive treatment versus delayed antihypertensive treatment on clinical outcomes among patients with acute ischaemic stroke. In our trial, mean systolic blood pressure in the early treatment group was reduced by 9.7% within the first 24 h after randomisation and reached 139.1 mm Hg on day seven. The net group di erence in systolic blood pressure was −11.9 mm Hg between the early treatment and delayed treatment groups. After antihypertensive treatment was initiated on day eight in the delayed treatment group, the mean systolic blood pressure di erence between the two randomisation groups narrowed to −2.3 mm Hg at day 14 and further narrowed down to −0.9 mm Hg at day 90. The composite primary outcome of dependency or death at day 90 was not significantly di erent between the two groups. No significant di erences were noted in the incidence of recurrent stroke, major vascular events, or serious adverse events. These results indicate that starting antihypertensive treatment within the first week of acute ischaemic stroke onset holds no advantage with alter treatment start dates.

Limitations

This study has several limitations. Firstly, the observed primary outcome rate of 10.5% in the delayed treatment group was substantially lower than the rate of 25.0% that we had used in the sample size calculation and therefore our trial was underpowered to test the hypotheses that early treatment is better than delayed treatment. However, our study was adequately powered to conclude that no meaningful benefit is likely from early intervention. We observed a 95% confidence interval of the odds ratio for the primary outcome, ranging from 0.98 to 1.41. The lower bound of the 95% confidence interval ruled out anything but the smallest benefit of 2% at a significance level of 0.05. Secondly, the blood pressure reduction noted during the first seven days in the early treatment group was moderate. However, in the ENCHANTED-2 trial published in 2022, the likelihood of poor functional outcome was greater in the more intensive treatment group than in the less intensive treatment group among patients with acute ischaemic stroke.[8] Thirdly, the study physicians and patients were not masked to randomisation assignment. However, all data collectors and outcome adjudication committee members were masked to randomisation assignment. Additionally, our trial excluded patients treated with intravenous thrombolytic treatment or endovascular thrombectomy at baseline, and thus our study results cannot be generalised to these patients. Furthermore, most patients in our study had mild-to-moderate symptoms, so the study findings might not be generalisable to patients with severe acute ischaemic stroke.

Comparison with other studies

Several previous clinical trials compared early antihypertensive treatment versus no antihypertensive treatment or specific antihypertensive agents versus placebo on clinical outcomes among patients with acute stroke.[3-6 25-28] In a meta-analysis of these trials, Lee and colleagues reported that antihypertensive treatment in early ischaemic stroke did not a ect risk of a composite of dependency or death at 90 days or at trial end (relative risk 1.04 (95% confidence interval 0.96 to 1.13), P=0.35).[9] Two clinical trials have tested the e ect of intensive blood pressure reduction within the first few hours of acute ischaemic stroke onset among patients who received intravenous thrombolysis treatment or endovascular thrombectomy.[7 8] In the ENCHANTED trial,[7] 2196 patients with acute ischaemic stroke who received intravenous thrombolysis treatment and had raised blood pressure were randomly assigned within six hours of symptom onset to receive intensive antihypertensive treatment (with an systolic blood pressure target of 130-140 mm Hg within one hour) or guideline based treatment (with an systolic blood pressure target 140-180 mm Hg over 72 h). The composite outcome of death and major disability at day 90 did not di er between groups (odds ratio 1.00 (95% confidence interval 0.84 to 1.20), P>0.99). In the ENCHANTED-2 trial,[8] 821 patients with persistently raised systolic blood pressure after successful endovascular thrombectomy were randomly assigned to a more intensive systolic blood pressure target <120 mm Hg or to a less intensive target of 140-180 mm Hg, with the goal of meeting the target within an hour and sustaining it for 72 h. Compared with the less intensive treatment, the more intensive treatment group had significantly higher odds of death or disability at 90 days (odds ratio 1.85 (95% confidence interval 1.36 to 2.51), P<0.0001).

Theoretically, increased blood pressure during acute ischaemic stroke might be advantageous (by improving cerebral perfusion of the ischaemic tissue), or it might

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be detrimental (by exacerbating cerebral oedema and haemorrhagic transformation of the ischaemic tissue).[1 29] Raised blood pressure in acute stroke can result from many causes, including history of chronic hypertension, disturbed cerebral autoregulation, damage or compression of the brain regions involved in blood pressure regulation, neuroendocrine disturbance, and non-specific mechanisms, such as anxiety and stress associated with hospital admission, severe headaches, and urinary retention.[10 30] In previous trials, investigators observed significant reductions in blood pressure within the first 24 h of ischaemic stroke onset in control groups that did not receive any antihypertensive treatment.[5 27 28] In the CATIS-2 trial, patients were recruited and randomised between 24 h and 48 h after stroke onset to avoid early transient blood pressure increase due to mental and physical stress.[10 29 30] We observed a moderate 16.4 mm Hg (9.7%) reduction in systolic blood pressure in the early treatment group 24 h after randomisation.

Implications of the study

Our study provides novel information about early blood pressure management in patients with acute ischaemic stroke in several ways. Previous clinical trials have shown that early antihypertensive treatment within 48 h of symptom onset had a neutral e ect on dependency or death, recurrent stroke, and vascular events.[9] Our findings further show that delaying antihypertensive treatment to eight days after stroke onset did not increase the risk of these clinical outcomes. Actually, early antihypertensive treatment was associated with an increased odds ratio of 1.18, with the lower 95% confidence interval limit at 0.98, very close to the null. Our study might suggest a potential harmful e ect associated with early antihypertensive treatment in patients with acute ischaemic stroke.

According to the subgroup analysis of the CATIS trial, blood pressure lowering between 24 h and 48 h after stroke onset might reduce odds of dependency or death, recurrent stroke, and vascular events compared with no treatment among patients with acute ischaemic stroke.[5] Our study results did not support these observations. Additionally, previous trials did not provide antihypertensive treatment after 7-14 days following the acute phase of ischaemic stroke.[5 7 25-28] Consequently, patients in the antihypertensive treatment group usually had lower blood pressure levels compared with those in the control group during the 90 day follow-up period. In our study, patients in both groups received the same antihypertensive treatment after the first seven days following stroke onset, resulting in similar blood pressure reduction over 90 days. Therefore, the only intervention di erence between the two comparison groups was whether antihypertensive treatment was received in the first seven days.

Furthermore, almost all previous antihypertensive trials in acute ischaemic stroke either excluded or recruited very few patients with minor stroke, despite patients with these events representing more than 70% of all referrals of acute ischaemic stroke in routine practice.[31] In our study, 68% of the participants had an NIH stroke scale score of less than 5, which was very similar to data from the China National Stroke Registry.[32] Thus, our study results may be more generalisable to routine clinical practice than previous trials. The length of hospital stays in patients with acute ischaemic stroke varied by the severity of the disease, treatment received, practice patterns, and other determinants.[33 34] Among patients with fewer than seven days in hospital, antihypertensive treatment can reasonably be prescribed at discharge for long term blood pressure control.

Conclusions

Early antihypertensive treatment did not reduce the odds of dependency or death at 90 days among patients with mild-to-moderate acute ischaemic stroke, systolic blood pressure between 140 and less than 220 mm Hg, and who did not receive intravenous thrombolytic treatment. Therefore, initiation of antihypertensive treatment might not be beneficial in the week following acute ischaemic stroke onset.

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C r , r : YZ, YWa, and JH all contributed equally. LL, XX, YZ, YWa, and JH conceived and designed the study. LL, XX, AW, YW, JL, XN, DL, ZZ, PW, SS, CZ, TX, DW, G-CW, DS, YM, YWa, and YZ supervised the data collection. LL, XX, YP, C-SC, YZ, YWa, and JH analysed and interpreted the data. LL, XX, and JH drafted the manuscript. All authors revised the manuscript for important intellectual content and approved the final submitted version. LL, XX, YP, C-SC, and JH accessed and verified the data. Corresponding authors had full access to all the data in the study, acted as guarantors for the study, and had final responsibility for the decision to submit for publication. All authors vouch for the

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completeness and accuracy of the data and for the fidelity of the trial to the protocol. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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E r : The CATIS-2 trial was approved by the ethics committees of Beijing Tiantan Hospital and all participating institutes in China and by the Institutional Review Board of Tulane University in the US. All participants provided informed consent.

D : Data from this study can be requested from LL (lipingsister@gmail.com) and YP (panys2000@163.com) after publication of this study. Deidentified participant data, the data dictionary, and other specified datasets can be requested. The study protocol, statistical analysis plan, and informed consent form will also be made available on request. Specific requests for data will require the submission of a proposal with a valuable research question as assessed by the study steering committee and may require a data access agreement be signed.

The corresponding authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

D , : Findings from this study will be disseminated to the trial participants through a plain language summary included in the trial newsletter. Following the embargo, the results will be publicised through mainstream media and social media platforms of the institute through which the trial was conducted. The work will be presented at scientific conferences and clinical meetings and grand rounds.

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Web appendix: Online appendix

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