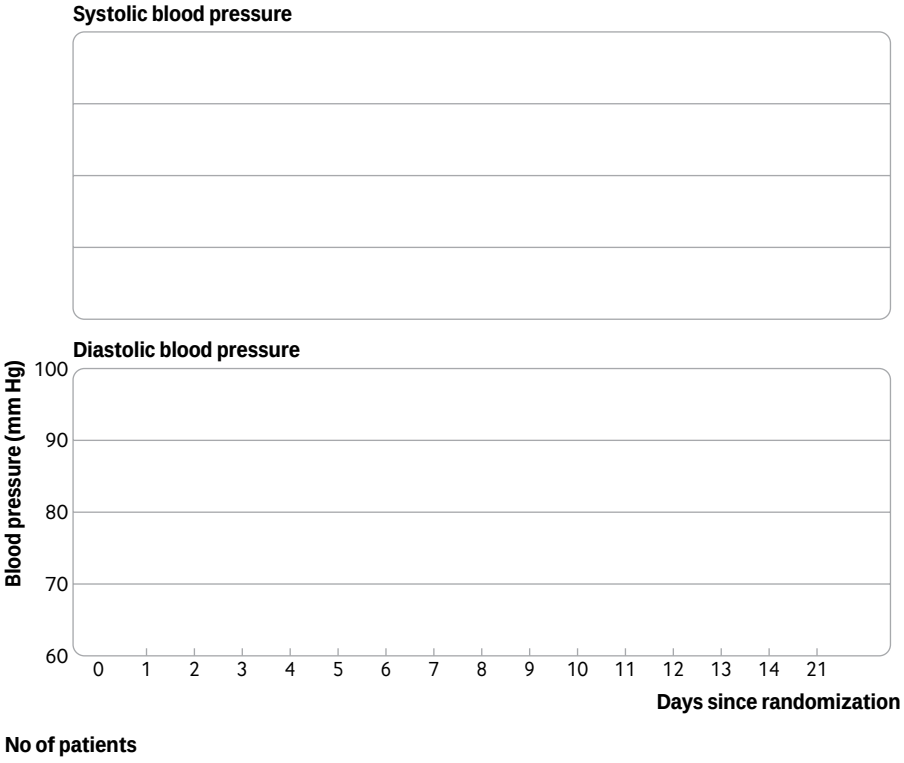
that included 12 703 patients with acute ischaemic stroke showed that antihypertensive treatment within three days of symptom onset did not affect the risk of

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Hg or more at each of two time points spaced six hours apart during the intervention, the participant would have been withdrawn from the trial.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



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-effects regression analysis was used to test the group differences in mean blood pressure changes between the early and delayed treatment groups with a significance level of 0.004 (0.05/14 tests). Mixed-effects 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 effect in the mixed-effects 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 differences in the entire distribution of modified Rankin score were compared using the Wilcoxon rank-sum test. Ordinal logistic regression was used to estimate the effect 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 effect 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.

Table 2 | 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=2408)	Delayed antihypertensive treatment (n=2394)	Group difference (95% CI)	P value
Mean SBP (SD) at baseline, mm Hg				
Sc	. (.)	. (.)	. (. .)	<0.00
Da c	. (0.)	. (.)	. (. .)	<0.00
Mean absolute change (SD) in SBP from baseline at hour 24, mm Hg				
Sc	. (.)	. (.)	. (. .)	<0.00
Da c	.0 (.0)	. (.)	. (. .)	<0.00
Mean relative change (SD) in SBP from baseline at hour 24, %				
Sc	. (.)	. (0.)	. (. .)	<0.00
Da c	. (.)	. (.)	. (.0 .)	<0.00
Mean SBP (SD) at day 7 or discharge, mm Hg				
Sc	. (.)	0. (.)	. (. 0.)	<0.00
Da c	0. (.)	. (.)	. (. .)	<0.00
Mean SBP (SD) at day 14 or discharge, mm Hg				
Sc	. (.)	. (.)	. (. 0.)	0.00
Da c	. (.)	0. (.)	. (. 0.0)	0.0
Mean SBP (SD) at day 90, mm Hg				
Sc	. (.)	. (.)	. (. 0.)	<0.00
Da c	. (.)	. (.)	.0 (. 0.)	<0.00
Mean SBP (SD) at day 0 or discharge, mm Hg				
Sc	. (.)	.0 (.)	0. (. 0.)	<0.00
Da c	. (.)	. (.)	0. (0. 0.0)	0.0

[ ]BP=b d e e; CI=c de ce e a ; SD= a da d de a

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 efficacy 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

doi: 10.1136/bmj-2023-076448 | BMJ 2023;383:e076448 | the bmj

Table 3 | Primary, secondary, and safety outcomes in a trial of early versus delayed antihypertensive treatment in patients with acute ischaemic stroke

Outcomes	Early antihypertensive treatment	Delayed antihypertensive treatment	Odds ratio (95% CI)	P value
Primary outcome				
Dea h Γ aJ Γd ab a 0 da (RS c Ie / 0 (.0)		0/ (0.)	. (0. .)	0.0
f -), –1. (%)*				
Secondary outcomes at 90 days				
Med a –1 RS c Ie (IQR)	(0-)	(0-)		0.
O Id a1 RS c Ie			.0 (0. .)	0.
0 (–1 a a)	/ 0 (.)	/ (.)		
(–1 g –1 ca –1 d ab de e)	/ 0 (0.)	/ (.0)		
(gh d ab)	/ 0 (.)	/ (.)		
(de Ia e d ab Ie Γ g1 e he)	/ 0 (.)	/ (.)		
(de Ia e- e e Ie d ab Ie Γ g1 a .cIe	/ 0 (.)	/ (.)		
h da g)				
(e e Ie d ab , bed b d1 a d c1 –1 e1 –1)	0/ 0 (0.)	/ (0.)		
(dead)	/ 0 (0.)	/ (0.)		

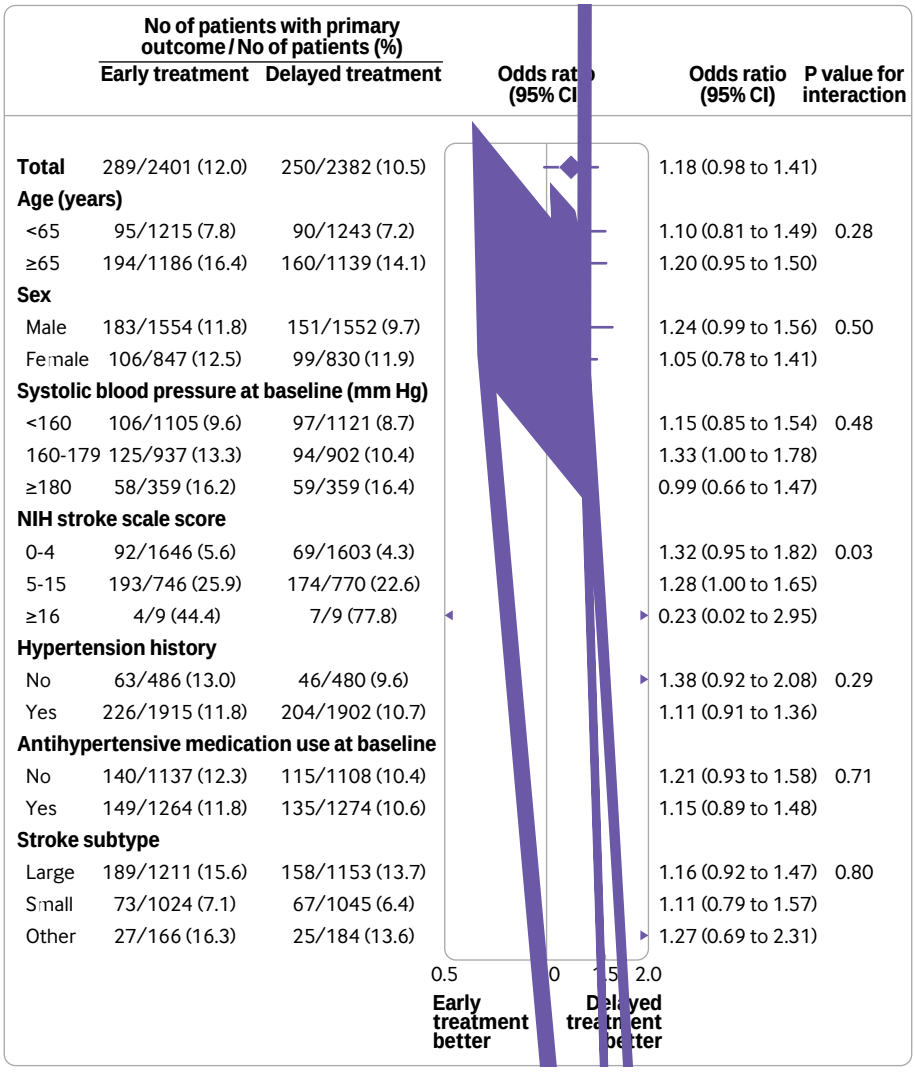
intravenous) in the early treatment group while four patients received antihypertensive medications (one intravenous) in the delayed treatment group (fig 1). At 24 h after randomisation, mean systolic blood pressure was reduced by 16.4 mm Hg (standard deviation 19.7) in the early treatment group and by 8.6 mm Hg (standard deviation 16.9) in the delayed treatment group with a net group difference of −7.8 mm Hg ((95% confidence interval −8.9 to −6.7), P<0.001) (fig 2, table 2). Approximate 51.0% (1177/2309) of patients in the early treatment group and 28.9% (659/2280) of patients in the delayed treatment group had a systolic blood pressure reduction of at least 10% within the first 24 h. At day seven, mean systolic blood pressure was 139.1 mm Hg in the early treatment group and 150.9 mm Hg in the delayed treatment group with a net systolic blood pressure difference of −11.9 mm Hg ((95% confidence interval −12.9 to −10.9), P<0.001). Additionally, 54.6% (1050/1922) of patients in the early treatment group and 22.4% (445/1985) in the delayed treatment group had blood pressure of less than 140/90 mm Hg (P<0.001 for group difference). After starting antihypertensive medications on day eight in the delayed treatment group, the difference in mean systolic blood pressure between the two groups narrowed to −2.3 mm Hg at day 14 and further narrowed down to −0.9 mm Hg at day 90. The most used antihypertensive medications were calcium channel blockers, followed by angiotensin-converting-enzyme inhibitors, angiotensin-II receptor blockers, and diuretics (supplementary table S2).

Cotreatments

Other cotreatments for ischaemic stroke were balanced between the two randomisation groups (supplementary table S3). For example, in the early versus delayed treatment groups, 98.9% versus 98.8% of patients received antiplatelet drugs, 11.1% versus 11.0% received anticoagulant drugs, 25.5% versus 24.9% received antidiabetic drugs, and 97.3% versus 97.7% received lipid lowering drugs.

Primary and secondary outcomes

At day 90, 289 participants (12.0%) of 2401 in the early treatment group, compared with 250 (10.5%) of 2382 in the delayed treatment group, had died or experienced dependency (odds ratio 1.18 (95% confidence interval 0.98 to 1.41), P=0.083). The number needed to harm was 65 (95% confidence interval −400 to 30). The median modified Rankin



score was not significantly different between the two groups, and the odds of a higher modified Rankin score were not associated with early antihypertensive treatment compared with delayed treatment (table 3). Additionally, 140 (5.8%) of 2401 patients in the early treatment group and 123 (5.2%) of 2382 patients in the delayed treatment group experienced a recurrent stroke (odds ratio 1.14 (95% confidence interval 0.89 to 1.46), P=0.30). Likewise, 143 (6.0%) of 2401 patients in the early treatment group and 132 (5.5%) of 2382 patients in the delayed treatment group developed major vascular events (1.08 (0.85 to 1.38), P=0.53). The detailed causes for each secondary clinical outcome are presented in table S4.

At 14 days or hospital discharge, 416 (17.3%) of 2404 participants in the early treatment group, compared with 393 (16.5%) of 2384 individuals in the delayed treatment group, had died or experienced dependency (1.06 (0.91 to 1.24), P=0.44). The median modified Rankin score was not significantly different between the two groups, and the odds of a higher modified Rankin score were not significantly associated with early antihypertensive treatment compared with delayed treatment (table 3).

Subgroup and sensitivity analyses

At day 90, the odds ratio for the composite primary outcome of dependency or death were not significantly different across the prespecified subgroups by age, sex, systolic blood pressure, NIH stroke scale score, history of hypertension, antihypertensive medication use, and subtype of ischaemic stroke at baseline (fig 3).

We adjusted for important baseline covariates including age, sex, systolic blood pressure, NIH stroke scale score, time from stroke onset to randomisation, history of hypertension, and antihypertensive medication use. After adjustment, the odds ratios associated with early antihypertensive treatment compared with delayed treatment were 1.21 ((95% confidence interval 0.99 to 1.49), P=0.06) for dependency or death at day 90 and 1.14 ((0.89 to 1.46), P=0.31) for recurrent stroke at day 90. After

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 c i1(e lDC a1(2IIJO2Tw T4ffi.7r)0(e[par)-5((716 (7o(str)0(ok)1). I401)IIJO2Tw T[par)-5BT/,(ed in 1Tf0(ea)2(e.1s w T[dea7(oela ant 0cBT/linical outh ear Tw -10s0(eatm.2t)0(o amo.2[(o Tm[(wacuth ear8cBT/haemic0.25e tr). I04fi.7r)0(eou7i

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 effect 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 effect 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 difference 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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Competing interests:

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Web appendix: Online appendix