Supplementary Online Content


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eFigure 1. Treatment Algorithm for Blood Pressure Reduction Group

eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods. Detailed Design and Methods

1. Eligibility Criteria

The CATIS recruited patients with ischemic stroke onset within 48 hours confirmed by brain computed tomography (CT) or magnetic resonance imaging (MRI). Systolic blood pressure $>220$ and diastolic blood pressure $>120$ mm Hg have been recommended as blood pressure cut-points for antihypertensive treatment in acute ischemic stroke by established clinical guidelines (1-3). In CATIS, we focused on lowering systolic blood pressure in acute stroke patients and recruited patients with systolic blood pressure $\geq 140$ and $<220$ mm Hg. Intravenous thrombolytic therapy, such as intravenous recombinant tissue plasminogen activator (rtPA) is rare in Chinese patients with acute ischemic stroke. According to data from China National Stroke Registry, only 12.6% of acute ischemic stroke patients were eligible for thrombolytic treatment, 2.4% were treated, and 1.6% were treated with intravenous rtPA (4). Because of different blood pressure lowering requirements in patients with intravenous rtPA, we excluded them from CATIS.

Inclusion Criteria

- Age $\geq 22$ years
- Ischemic stroke onset within 48 hours confirmed by imaging (CT scan or MRI)
- Systolic blood pressure $\geq 140$ and $<220$ mm Hg and diastolic blood pressure $\geq 80$ mm Hg
- No contraindications to antihypertensive treatment
- Able and willing to sign informed consent by patients or their direct family members

Exclusion criteria

- Hemorrhagic stroke
- Severe heart failure (NY Heart Association class III and IV), myocardial infarction, unstable angina, atrial fibrillation, aortic dissection and cerebrovascular stenosis (>70%)
- Patients in a deep coma
- Diastolic blood pressure $>120$ mm Hg
- Resistant hypertension (systolic blood pressure $\geq 170$ mm Hg despite use of $\geq 4$ antihypertensive medications for $\geq 6$ months)
- Intravenous thrombolytic therapy (such as intravenous rtPA)
- Current pregnant women
- Unable to participate in the follow-up examination (i.e., living more than 30 kilometers away from participating hospital)

2. Randomization

Randomization was conducted centrally at the Study and Data Coordinating Center at Tulane University in the US and Soochow University in China. Randomization was stratified by participating hospitals and use of antihypertensive medications. In each stratum, patients were randomly assigned to the blood pressure lowering or the control group within each block. The block size was randomly selected from 4, 6, and 8. The randomization schedules for each participating hospital stratified by the use of antihypertensive medications were generated by a SAS program (SAS PROC PLAN) and concealed until an eligible participant was ready for randomization. The study physician called a 24-hour phone number at the Study and Data Coordinating Center to obtain the assignment for each participant.

3. Sample size considerations

The sample size calculation is based on the primary outcome (combination of death within 14 days after randomization and major disability at 14 days or at the time of discharge, if that occurred before 14 days). We calculated sample size based on the following assumptions:

- Significance level of 0.05 for a two-sided test;
- Statistical power of 90%;
- Event rate in the control group of 35% based on data from the CATIS-vanguard phase, which is more conservative than those reported from previous studies (5);
- Absolute risk reduction of 5%, which has been recommended as clinically meaningful risk reduction in acute stroke trials (6).

We estimated that 1,842 patients are required for each group based on a likelihood ratio test, and planned to recruit 4,000 patients (2,000 for each group) in the CATIS trial to accommodate potential withdrawals. In addition,
we have 80% statistical power to detect a 20% proportional reduction in the combined outcome of mortality and dependency over 3 months of follow-up (23.4% in control group from the CATIS-vanguard phase) based on a two-sided likelihood ratio test at the significance level of 0.05.

4. Antihypertensive Treatment

After the study participants were randomly assigned into the active antihypertensive treatment group and the usual care control group, all home blood pressure medications were discontinued. The active treatment group received antihypertensive medications according to the study protocol, and the control group received standard care according to the China National Guidelines for Prevention and Treatment of Cerebrovascular Diseases without antihypertensive treatment during hospitalization (3). Patients with unstable angina and atrial fibrillation were excluded because these conditions were indications for use of β-blockers and/or calcium channel blockers.

4.1. Blood pressure treatment goals and timeline

Blood pressure-lowering treatment started immediately after randomization. The target treatment goals were:

*Step 1 (within 24 hours after randomization)*

To lower systolic blood pressure by 10 to 25% (but systolic blood pressure not lower than 126 mm Hg and diastolic blood pressure not lower than 80 mm Hg) within the first 24 hours after randomization based on the participant’s admission blood pressure levels.

*Step 2 (within 7 days after randomization)*

To achieve systolic blood pressure below 140 mm Hg and diastolic blood pressure below 90 mm Hg and maintain these blood pressure levels afterwards during hospitalization.

Except for antihypertensive treatment, the intervention group received the same usual care as the control group according to the China National Guidelines for Prevention and Treatment of Cerebrovascular Diseases (3). We encouraged trial participants to stay in the hospital for at least 10 days. After discharge, patients in both groups were prescribed antihypertensive drugs according to clinical guidelines (3). It would be unethical to withhold antihypertensive treatment in stroke survivors based on the current evidence (7).

4.2. Antihypertensive agents

The CATIS was designed to test blood pressure reduction strategies — lowering systolic blood pressure by 10-25% within the first 24 hours and achieving systolic blood pressure <140 and diastolic blood pressure <90 mm Hg within 7 days after randomization — rather than test the efficacy of specific antihypertensive drugs. Several antihypertensive agents, including intravenous angiotensin-converting enzyme inhibitors (ACE-I, enalapril, first-line), calcium channel blockers (CCB, second-line) and diuretics (third-line) were used in the intervention group. Based on the literature, ACE-I and angiotensin type-1 receptor blockade might provide better neurovascular protection (8-10), and ACE-I could reduce blood pressure after acute stroke without reducing cerebral blood flow (11). In addition, based on experience from previous trials (12) and our pilot study, intravenous antihypertensive agents are preferable over oral agents because of their quick effect and easy administration to stroke patients. Enalapril is the only intravenous ACE-I agent approved by the Chinese FDA and available on the market. Changzhou Pharmaceutical Co. Ltd donated intravenous enalapril to the CATIS. The study physicians selected second-line CCB and third-line diuretics based on the availability of these medications in their hospitals.

4.3. Treatment algorithm

All participants in the intervention group received antihypertensive medications in a staged sequence. Based on patients’ baseline blood pressure level, the first-line medication (intravenous enalapril) can be used alone or in combination with second-line medications (CCB) and third-line medications (diuretics) to achieve the target systolic blood pressure lowering of 10 to 25% within the first 24 hours after randomization according to the treatment algorithm (Figure S1). The dosage and number of medications were titrated to achieve systolic blood pressure below 140 mm Hg and diastolic blood pressure below 90 mm Hg within 7 days and maintain this blood pressure level afterwards.

At any step above, if the blood pressure target is achieved, medication was continued at the same dosage and titrated to maintain the target blood pressure level. If the blood pressure target is not achieved by the above treatment algorithm, medications were titrated up to the maximum dosage in the order of ACE-I, CCB and diuretics before adding another blood pressure agent. A 4th agent can be added if needed.
4.4. Safety considerations

Study physicians closely monitored stroke patients during the intervention. If systolic blood pressure reduction was more than 25%, or systolic blood pressure <126 mm Hg, or diastolic blood pressure <80 mm Hg, we titrated down or temporarily withheld antihypertensive medications. Patients who experienced severe conditions during the intervention, such as worsened neurologic status, acute myocardial infarction, and heart failure, were withdrawn from the trial. Stroke patients with mean systolic blood pressure ≥220 or diastolic blood pressure ≥120 mm Hg during the intervention were withdrawn from the trial. Study physicians collected endpoint data for all withdrawn patients if possible. In addition, the Data and Safety Monitoring Board examined blinded data every 6 months.

4.5. Masking

The treating physicians and nurses were not masked to patients’ randomization assignments because of the different blood pressure treatment goals for each arm. Data on blood pressure were also unmasked because they were management tools for attaining the specific treatment targets. However, patients were masked to their group assignments. In addition, the neurologists who conducted the neurological and functional assessments at baseline and follow-up examinations were masked to patients’ assignments. The members of the Outcome Assessment Subcommittee were also masked to patients’ randomization. The personnel at the clinical laboratories and the CT/MRI laboratories were masked to patient randomization.

5. Study Outcomes

5.1. Outcomes within 2 weeks

- The primary outcome was a combination of death within 14 days after randomization and major disability at 14 days or at the time of discharge, if that occurred before 14 days.
- The secondary outcome was neurological dysfunction (modified Rankin scale and NIH Stroke Scale, NIHSS). Since the development of the initial CATIS protocol, ordinal analysis of modified Rankin scores has been recommended for acute stroke trials. Therefore, we analyzed the ordered 7-level categorical score of the modified Rankin scale as an outcome of neurological functional status (13,14).
- An additional secondary outcome was blood pressure change during 14 days in the hospital.

5.2. Outcomes at 3-month post-treatment follow-up

- The primary outcome was a combination of all-cause mortality and major disability at 3 months.
- The secondary outcomes included the following variables at 3 months:
  - All-cause mortality
  - Recurrent fatal and non-fatal stroke
  - Combined vascular disease events (vascular deaths, non-fatal stroke, non-fatal myocardial infarction, coronary revascularization, hospitalized or treated angina, hospitalized or treated congestive heart failure, and hospitalized or treated peripheral arterial disease)
  - Neurological functional status measured by NIHSS and modified Rankin scale
  - Systolic and diastolic blood pressure at 3 months

Modified Rankin Scale score description (15,16):

- 0 No symptoms at all
- 1 No significant disability despite symptoms; able to carry out all usual duties and activities
- 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
- 3 Moderate disability; requiring some help, but able to walk without assistance
- 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- 5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention
- 6 Dead

6. Training and Quality Control

All investigators, study physicians, study neurologists, and research nurses participated in central training/certification and re-training/recertification annually throughout the trial. The study physicians were trained on how to use antihypertensive medications in a staged sequence according to study protocol using the treatment algorithm. Investigators and research staff were trained on the study outcome assessments, including blood pressure measurements, neurological dysfunction assessments (NIHSS and modified Rankin scale), and clinical data collection. At the training sessions, interviewers were given detailed instructions on administration of the study questionnaire. All blood pressure observers participated in a special training session on the use of a standardized
protocol for measurement of blood pressure. Satisfactory performance during a written test on knowledge of preparing study participants for blood pressure measurement, selecting correct cuff size and using standard techniques for blood pressure measurement during a standardized videotape examination, and during concordant measurements of blood pressure with an instructor was required for certification as a blood pressure observer.

Study site visits were conducted every six months or more often if needed at each participating hospital. Investigators and research staff from the Study and Data Coordinating Center traveled to each participating hospital to assess adherence of clinical staff to the study protocol, the consistency in protocol implementation between sites, and the administration and management of each site with respect to communication and decision-making. The site visits also provided feedback on performance regarding recruitment, blood pressure treatment, and data completeness. These visits provided opportunities for investigators and research staff to discuss and evaluate solutions related to critical issues in the study.

All data were double-entered through a web-based data system. All data were first entered at local hospitals and then sent to Soochow University Department of Epidemiology where the second entry was conducted. The two independent databases were sent to Tulane University’s Department of Epidemiology for final data check and quality control.

7. Statistical Analysis Plan

Data were analyzed according to participants' randomized treatment assignments regardless of their subsequent medications (intent-to-treat analysis). Two-sided P-values were calculated and the significance level was assessed at .05. The proportions of participants with the primary and secondary outcomes at 14 days or discharge and at 3-month post-treatment follow-up were compared between the treatment and control groups using a χ² test. Logistic regression analysis was used to estimate the unadjusted odds ratios and 95% confidence intervals associated with blood pressure reduction compared to usual control. In a sensitivity analysis, odds ratios were adjusted for important confounders (baseline age, gender, systolic blood pressure, NIHSS score, time from onset of stroke to randomization, and use of antihypertensive medication). The median and inter-quartile range of Rankin’s scale scores were calculated for the two comparison groups and the difference was tested using a Wilcoxon rank-sum test (17). Ordinal logistical regression was used to estimate the effect of blood pressure reduction on the full range of the modified Rankin scale (18).

Heterogeneity of effects in pre-specified subgroups, by age, gender, 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 was examined by testing for treatment-covariate interaction with the logistic regression analysis model by using P <.05. SAS programs (SAS Institute, Cary, NC) and STATA programs (Stata Corp, College Station, TX) were used for statistical analyses.
**eTable 1. Treatment of Patients With Acute Ischemic Stroke**

<table>
<thead>
<tr>
<th>Treatment, no. (%)</th>
<th>Antihypertensive Treatment (N = 2,037)ᵃ</th>
<th>Control (N = 2,033)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants</td>
<td>680 (33.4)</td>
<td>693 (34.1)</td>
<td>.63</td>
</tr>
<tr>
<td>Heparin</td>
<td>263 (12.9)</td>
<td>259 (12.7)</td>
<td>.87</td>
</tr>
<tr>
<td>Low-molecular-weight Heparin</td>
<td>438 (21.5)</td>
<td>438 (21.5)</td>
<td>.97</td>
</tr>
<tr>
<td>Antiplatelet Agents</td>
<td>1,993 (97.8)</td>
<td>1,962 (96.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1,709 (83.9)</td>
<td>1,671 (82.2)</td>
<td>.15</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>249 (12.2)</td>
<td>262 (12.9)</td>
<td>.52</td>
</tr>
<tr>
<td>Ozagrel</td>
<td>973 (47.8)</td>
<td>964 (47.4)</td>
<td>.82</td>
</tr>
<tr>
<td>Intravenous Fibrinolysis</td>
<td>52 (2.6)</td>
<td>46 (2.3)</td>
<td>.55</td>
</tr>
<tr>
<td>Urokinase</td>
<td>28 (1.4)</td>
<td>29 (1.4)</td>
<td>.89</td>
</tr>
<tr>
<td>Intravenous rtPA</td>
<td>12 (0.6)</td>
<td>10 (0.5)</td>
<td>.67</td>
</tr>
<tr>
<td>Dehydrants</td>
<td>811 (39.8)</td>
<td>806 (39.6)</td>
<td>.91</td>
</tr>
<tr>
<td>Mannitol</td>
<td>631 (31.0)</td>
<td>637 (31.3)</td>
<td>.81</td>
</tr>
<tr>
<td>Glycerol</td>
<td>242 (11.9)</td>
<td>247 (12.1)</td>
<td>.79</td>
</tr>
<tr>
<td>Glucose-lowering Agents</td>
<td>359 (17.6)</td>
<td>354 (17.4)</td>
<td>.86</td>
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<tr>
<td>Insulin</td>
<td>149 (7.3)</td>
<td>156 (7.7)</td>
<td>.66</td>
</tr>
<tr>
<td>Oral Hypoglycemic Agents</td>
<td>224 (11.0)</td>
<td>215 (10.6)</td>
<td>.67</td>
</tr>
</tbody>
</table>

ᵃ Treatment information was not provided for one participant in the antihypertensive treatment group.
eFigure 1. Treatment Algorithm for Blood Pressure Reduction Group

Start here

Is SBP= 200 mm Hg or on ≥ 2 BP agents

Yes

Enalapril 1.25 mg IV, every 6 hours, and Calcium channel blocker (CCB) PO, discontinue all home BP medications

6 hours later

Is SBP decreased 15% from baseline

Yes

Enalapril 1.25 mg and continue CCB

No

Is SBP decreased 15% from baseline

Yes

Continue treatment

No

Enalapril 2.5 mg + CCB and add diuretics

Is SBP <200 but ≥140 mm Hg or on ≥ 1 BP agents

No

Is SBP decreased 15% from baseline

Yes

Enalapril 2.5 mg and continue CCB

No

Enalapril 1.25 mg iv, every 6 hours, discontinue all home BP medications

6 hours later

Is SBP decreased 15% from baseline

Yes

Continue treatment

No

*Enalapril 2.5mg + CCB

*If SBP has not decreased 15% from baseline after an additional 6 hours (18 hours from baseline), diuretics will be added to the treatment regimen.

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eReferences


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