Protocol
Controlling Hypertension After Severe Cerebrovascular Event:

the CHASE study

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重症脑血管病患者急性期血压管理研究
Controlling Hypertension After Severe Cerebrovascular Event (CHASE)

STUDY PROTOCOL

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# ABBREVIATIONS

| Abbreviation | Description |
|--------------|-------------|
| AE/SAE | Adverse events / Serious adverse event |
| AHA | American Heart Association |
| AIS | Acute ischemic stroke |
| ASA | American Stroke Association |
| CHD | Coronary heart disease |
| CT | Computed Tomography |
| CVT | Cerebral venous thrombosis |
| DBP | Diastolic blood pressure |
| EC | Executive Committee |
| ECG | Electrocardiography |
| ED | Emergency department |
| EF | Ejection Fraction |
| ESO | European Stroke Organization |
| FEV1 | Forced Expiratory Volume in the first second |
| GCP | Good Clinical Practice |
| GCS | Glasgow coma scale |
| ICU | Intensive care unit |
| ITT | Intention To Treat |
| MAP | Mean arterial pressure |
| MRI | Magnetic Resonance Imaging |
| mRS | Modified Rankin Scale |
| NHISS | National Institute of Health stroke scale |
| ICH | Intracerebral hemorrhage |
| PI | Principal Investigator |
| QCAC | Quality Control and Assurance Committee |
| RCT | Randomized controlled trial |
| SAH | Subarachnoid hemorrhage |
| SBP | Systolic blood pressure |
## CHASE PROTOCOL SYNOPSIS

| **Chinese Study Title** | 重症脑血管病患者急性期血压管理研究 |
|-------------------------|--------------------------------------|
| **English Study Title** | Controlling Hypertension After Severe Cerebrovascular Event |
| **Acronym**             | CHASE |
| **Trial Registration**  | - Registration Authority: ClinicalTrials.gov  
- Registration Number: NCT02982655  
- Registration Time: 30 November 2016 |
| **Study Design**        | Prospective, Multicenter, Single-blind, Randomized Controlled Trial |
| **Primary Study Objective** | To determine the therapeutic benefit of Individualized BP lowering treatment (10–15% reduction from admission level) compared with guideline-recommended BP lowering treatment (AIS: SBP ≤ 200 mmHg; ICH: SBP ≤ 180 mmHg) in reducing the proportion of severe stroke patients with a poor outcome (mRS ≥ 3) at day 90 of enrollment. |
| **Study Population**    | Acute severe stroke patients |
| **Sample Size**         | 500 participants randomized in a 1:1 ratio to |
either Individualized BP lowering treatment or guideline-recommended BP lowering treatment.

Selection of Subjects  

- Inclusion Criteria
  ① Age \( \geq 18 \) years;
  ② The randomly assigned BP-lowering regimen is able to be commenced within 72 h after the onset of stroke (ischemic or hemorrhagic), confirmed by a CT or MRI scan of the brain (if the precise timing of the onset of symptoms or signs of the qualifying event is unknown, then the time of onset will be taken as the last time the patient was known to be well);
  ③ GCS on admission \( \leq 12 \) or NIHSS on admission \( \geq 11 \);
  ④ There are at least two SBP measurements of \( \geq 150 \) and \( \leq 210 \) mmHg, recorded \( \geq 5 \) min apart (patients with an initial SBP \( < 150 \) mmHg may be randomized when the SBP fulfills entry criteria on rechecking up to 72 h after the onset of stroke);
  ⑤ Written informed consent is able to be obtained directly from the patient or an appropriate surrogate, based on local ethics committee recommendations.
Exclusion criteria

① Patients who have received thrombolytic therapy, embolectomy, or decompressive craniectomy for the current stroke;

② Patients with subarachnoid hemorrhage;

③ Known definite contraindication to acute BP lowering (e.g. known severe carotid, vertebral, or cerebral arterial stenosis, Moyamoya disease or Takayasu’s arteritis, high grade stenotic valvular heart disease);

④ Secondary to a structural abnormality in the brain (e.g. an arteriovenous malformation, intracranial aneurysm, tumor, or trauma);

⑤ Unstable vital signs and requiring the use of vasoactive agents;

⑥ Known existing dementia or prestroke disability (e.g. score 3–5 on the mRS);

⑦ Concomitant medical illness that would interfere with the outcome assessments and/or follow-up (advanced cancer; severe pulmonary dysfunction; severe cardiac dysfunction; severe hepatic failure; severe renal failure);

⑧ Patients who are currently participating
in other investigational trials;
⑨ Patients who are considered to have a high likelihood of not adhering to the study treatment or the follow-up regimen.

**Study Treatments**

- Individualized BP lowering group
  
  Antihypertensive treatments are to be initiated to reduce SBP to a range of 130–180 mmHg and by 10–15% from the admission level within 2 h after randomization. SBP in the Individualized BP-lowering group is to be maintained around the target level for one week with or without the use of hypertensive agents.

- Guideline-recommended BP lowering group
  
  Antihypertensive agents are to be administered if the SBP was > 200 mmHg in AIS or the SBP was > 180 mmHg in ICH. The goal is to maintain the SBP < 200 mmHg in ischemic stroke and < 180 mmHg in ICH for one week with or without the use of hypertensive agents.

**Primary Outcome**

Poor outcome (defined by mRS ≥ 3) at day 90 of enrollment.

**Statistical Analysis**

- Two-sided p values ≤ 0.05 will be
considered significant.

- Univariate and multivariate logistic regression analyses will be used to determine the effects of different BP lowering treatments on primary and secondary outcomes.
- A subgroup analysis of the primary outcome will be conducted.
- Statistical analysis will be mainly performed with SPSS software.

**Study Flowchart**

![Study Flowchart Diagram]

- Patients with acute stroke
- Meeting Exclusion criteria:
  - Received thrombolytic therapy, embolectomy, or decompressive craniectomy
  - Subarachnoid hemorrhage
  - Known definite contraindication to acute BP lowering
  - Secondary to a structural abnormality in the brain
  - Unstable vital signs
  - Known existing dementia or prestroke disability
  - Concomitant medical illness that would interfere with the outcome assessments
  - Participating in other investigational trials
  - Having a high likelihood of not adhering to the study treatment or the follow-up regimen
- Not meeting inclusion criteria:
  - Age ≥ 18 years
  - Within 72 h after the onset of stroke
  - GCS ≤ 12 or NIHSS ≥ 11
  - SBP ≥ 150 and ≤ 210 mm Hg
  - Consent acquired
- 500 patients to be randomized
  - 250 to be allocated to individualized BP lowering group
  - 250 to be allocated to guideline-recommended BP lowering group
- 7 day, hospital discharge evaluation and 90 day follow up
1. BACKGROUND

Severe stroke is a life-threatening cerebral vascular event which causes major neurological function deficits and leads to multiple organ dysfunctions, such as respiratory and circulatory failure. The mortality and disability rates of severe stroke are very high, and the therapeutic strategy in the acute stage determines the outcomes of severe stroke. During the early stage of severe stroke, the management of blood pressure (BP) is one of the most basic and crucial treatments in the intensive care unit (ICU). However, few studies with high evidence levels on the optimum goal of BP lowering treatment in patients with acute severe stroke have been conducted. Both large increase and reduction in BP were associated with a higher risk of early neurological deterioration, increased infarct volume, and poorer outcome at three months. The lack of clinical evidence on the BP lowering target often makes clinicians confused and unsure when they are handling with elevated BP in patients with acute severe stroke.

1.1 Potential harm caused by elevated BP in acute severe stroke

Elevated BP is one of the most common clinical manifestations in acute stroke, and it happens in more than 75% of stroke patients [1, 2]. An observational study on stroke indicated that every 10 mm Hg above 180 mm Hg of SBP raised 40% of neurological deterioration and 23% of poor outcome in stroke patients, whereas every 10 mm Hg below 180 mm Hg of SBP also raised 6% of neurological deterioration and 25% of poor outcome [3]. High BP may cause deterioration of cerebral edema, hemorrhagic transformation of infarction, cardiac complication, renal dysfunction, and many other serious conditions. However, lower BP level can reduce blood perfusion in multiple organs, especially in the brain, and exacerbate cerebral injury. Therefore, large increase and reduction in BP,
as well as rapid BP lowering, may raise the possibility of neurological deterioration and death. A rational and optimum strategy of BP management is required in acute stage of severe stroke.

1.2 Clinical researches on BP management in acute stroke

The management of BP in acute stroke has been a research hotspot for many years. However, the conclusions of these large clinical trials were conflicting, some supported BP lowering treatments, some opposed BP lowering treatments, and some had neutral results:

(1) Clinical trials that supported BP lowering: A German study published in 2003, the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) [4], assessed the safety of modest blood pressure reduction by candesartan cilexetil in the early treatment of stroke. ACCESS trial enrolled 342 stroke patients, and the target reduction of BP in the experimental group was 10% to 15% within 24 hours. This study found that the cumulative 12-month mortality and the number of vascular events differed significantly in favor of the candesartan cilexetil group, although there were no significant differences of BP between both groups in the first 7 days and in the subsequent 12 months of follow-up. The Controlling hypertension and hypotension immediately post-stroke (CHHIPS) study [5], published in 2009, included 179 stroke patients with SBP > 160 mm Hg. The target SBP in the experimental group was 145–155 mm Hg or a reduction in SBP of 15 mm Hg compared with SBP at randomization. CHHIPS study indicated that there was no evidence of early neurological deterioration with active treatment despite the significantly greater fall in SBP within the first 24 hours in this group compared with placebo, and there was no increase in serious adverse events reported with active treatment, but 3-month mortality was halved. However, both ACCESS and CHHIPS were not designed for severe stroke patients.
(2) Clinical trials that opposed BP lowering: The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST) [6], published in 2011, included 2029 stroke patients with SBP $\geq 140$ mm Hg from nine north European countries. Patients were randomly allocated to candesartan or placebo for 7 days. SBP on day 7 was reduced 14% in candesartan group and 11% in placebo group from the baseline level. Results of SCAST study showed a higher risk of poor outcome in the candesartan group, suggesting a harmful effect. SCAST study also excluded patients with severe stroke.

(3) Clinical trials with neutral results: The Effects of antihypertensive treatment after acute stroke in the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) [7], published in 2010, included 763 patients who were taking antihypertensive drugs before the onset of stroke. Patients were randomly assigned to either continue or stop pre-existing antihypertensive drugs for two weeks. SBP was reduced 6% from the baseline level in the continuation of antihypertensive drugs group within two weeks. No substantial differences were observed between groups in rates of serious adverse events, 6-month mortality, or major cardiovascular events. COSSACS study excluded patients with impaired consciousness.

The CATIS Randomized Clinical Trial [8], published in 2014, included 4071 stroke patients with elevated SBP, and evaluated the effect of immediate BP reduction on the clinical outcomes of patients with acute ischemic stroke. The treatment intervention aimed at lowering SBP by 10% to 25% within the first 24 hours after randomization, achieving a SBP less than 140 mmHg and DBP less than 90 mmHg within 7 days, and maintaining this level of BP control during the remainder of hospitalization. SBP was reduced 12.7% in the antihypertensive treatment group and 7.2% in control group from the baseline level within 24 hours.
The stroke patients enrolled in CATIS trial were not severe, and they had a median NIHSS score of only 4 at the randomization.

The intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT) [9], published in 2008, included 346 patients with ICH within 6 hours of onset, and assessed the safety and efficiency of intensive BP reduction. Patients were randomly assigned to early intensive lowering of BP (target SBP 140 mm Hg) or standard guideline-based management of BP (target SBP 180 mm Hg). This study showed that early intensive BP-lowering treatment was clinically feasible, well tolerated, and seemed to reduce haematoma growth in ICH, and a large randomised trial is needed to define the effects on clinical outcomes. In order to investigate whether rapid lowering of elevated BP would improve the outcome in ICH patients, INTERACT 2 trial was conducted [10]. It was published in 2013 and included 2839 patients with acute ICH. The median baseline GCS in this study was 14, the median baseline NIHSS was 10, and the median baseline hematoma volume was 11 ml. SBP was reduced 22.3% in intensive BP lowering group and 14.5% in control group from the baseline level within 6 hours. Results of INTERACT 2 study showed that intensive lowering of BP did not result in a significant reduction in the rate of death or severe disability in ICH patients, and an ordinal analysis of mRS indicated improved functional outcomes with intensive lowering of BP.

The above clinical trials had conflicting conclusions about the efficacy of BP lowering treatment in patients with acute stroke. Moreover, the whole populations or the majority of the populations included in those large multicenter randomized controlled trials (RCTs) were not patients with severe stroke.

1.3 Trial design for BP management in acute severe stroke
Factors that contribute to raised BP in acute stroke are multifaceted, such as history of hypertension, stroke severity, pressure response to hospital admission, infarct area related to BP adjustment, and increased intracranial pressure [11]. Raised BP later falls into the following types: without antihypertensive medications BP declines spontaneously; with antihypertensive medications BP does not decline, declines modestly (10–15% from baseline), or intensively (≥ 20% from baseline value) [12]. Considering the poor outcomes induced by excessive high BP, especially in severe stroke which is usually complicated with a larger increase in BP, a proper BP reduction treatment is reasonable and required theoretically. However, previous studies had conflicting conclusions about the target of BP reduction treatment in stroke patients, and prospective studies on the management of elevated BP in patients with acute severe stroke are lacking.

(1) Supporting data for selection of treatment target for Individualized BP lowering: For ICH patients, 2015 guidelines from American Heart Association / American Stroke Association (AHA/ASA) recommended that for patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe and can be effective for improving functional outcome [13]. However, the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial [14], published in 2016, included 1000 ICH patients and showed that the treatment of participants with ICH to achieve a target SBP of 110 to 139 mm Hg did not result in a lower rate of death or disability than standard reduction to a target of 140 to 179 mm Hg, and the rate of renal adverse events within 7 days after randomization was significantly higher in the intensive treatment group than in the standard treatment group. For AIS patients, the latest guidelines from
AHA/ASA [15] recommended that lowering BP by 15% within 24 hours of onset was reasonable. Besides, previously we performed a retrospective preliminary study in stroke patients admitted to neurological intensive care unit (NICU) in Xijing Hospital in the last three years. A total of 302 patients were included, and 209 of them had SBP reduced from baseline level within 24 hours of onset. We found that NICU mortality

Table 1 Characteristics, interventions, and outcomes of patients with SBP reduced by > 15% and patients with SBP reduced by \(\leq 15\%\)

| Characteristics                          | Patients with SBP reduced from baseline level (n = 209) | Patients with SBP reduced by > 15% (n = 52) | Patients with SBP reduced by \(\leq 15\%\) (n = 157) | P 值 |
|-----------------------------------------|--------------------------------------------------------|-------------------------------------------|------------------------------------------------|------|
| Age, year, median (IQR)                | 59 (48 - 71)                                           | 60 (50 - 73)                              | 58 (47 - 70)                                    | 0.376|
| Female (%)                              | 74 (34.5%)                                             | 23 (44.2%)                                | 51 (32.5%)                                     | 0.125|
| Stroke type (%)                         | 148                                                   | 37 (71.2%)                                | 111 (70.7%)                                    | 0.939|
| AIS                                      |                                                       |                                           |                                               |      |
| ICH                                      | 55 (26.3%)                                             | 14 (26.9%)                                | 41 (26.1%)                                     |      |
| SAH                                      | 5 (2.4%)                                               | 1 (1.9%)                                  | 4 (2.5%)                                      |      |
| CVT                                      | 1 (0.5%)                                               | 0 (0.0%)                                  | 1 (0.6%)                                      |      |
| Prior hypertension (%)                  | 114 (54.5%)                                            | 38 (73.1%)                                | 76 (48.4%)                                     | 0.002|
| Prior diabetes (%)                      | 37 (17.7%)                                             | 9 (17.3%)                                 | 28 (17.8%)                                     | 0.931|
| Prior CHD (%)                           | 62 (29.7%)                                             | 13 (25.0%)                                | 49 (31.2%)                                     | 0.395|
| Time from onset to NICU admission, hr, median (IQR) | 70 (24 - 96)                                           | 48 (13 - 72)                              | 70 (24 - 113)                                  | 0.011|
| NIHSS on admission, median (IQR)        | 12 (6 - 19)                                            | 11 (6 - 22)                               | 12 (7 - 19)                                    | 0.847|
| GCS on admission, median (IQR)          | 13 (9 - 14)                                            | 14 (8 - 14)                               | 13 (9 - 14)                                    | 0.869|
| Body temperature, \(\vec{x}\pm s)     | 37.0\pm 0.7                                            | 37.1\pm 0.9                               | 36.9\pm 0.6                                    | 0.149|
| Heart rate on admission, \(\vec{x}\pm s) | 80.4\pm 20.3                                           | 82.3\pm 25.4                              | 79.8\pm 18.5                                   | 0.449|
| SBP on admission, mm Hg, \(\vec{x}\pm s) | 154.8\pm 25.6                                          | 175.1\pm 25.0                             | 148.1\pm 22.1                                  | <0.001|
| Any BP lowering treatments, (%)         | 72 (34.4%)                                             | 27 (51.9%)                                | 45 (28.7%)                                     | 0.002|
| Intravenous BP lowering treatment, (%)  | 45 (21.5%)                                             | 19 (36.5%)                                | 26 (16.6%)                                     | 0.002|
| Length of NICU stay, day, median (IQR)  | 10 (6 - 15)                                            | 8 (4 - 15)                                | 10 (6 - 15)                                    | 0.426|
| Death during NICU stay (%)              | 16 (7.7%)                                              | 8 (15.4%)                                 | 8 (5.1%)                                       | 0.016|
was significantly higher in patients with SBP reduced by > 15% than those with SBP reduced by ≤ 15%, and the rate of major disability at hospital discharge was also higher in patients with SBP reduced by > 15% than those with SBP reduced by ≤ 15% (table 1, figure 1).

Considering that a fixed target of BP lowering might not be proper for stroke patients with different severities, based on the previous studies and our retrospective study, we proposed an Individualized target, lowering BP by 10%-15% from the admission level, for patients with acute severe stroke. We aimed to investigate the effect of the Individualized BP lowering treatment on the outcomes of severe stroke compared with guideline-recommended BP lowering treatment, in order to provide clinical evidence for the BP management in patients with severe stroke.

(2) Supporting data for selection of treatment target for guideline-recommended Individualized BP lowering: 2015 Chinese guidelines for the management of patients with severe stroke [16] stated that so far there
was no sufficient clinical evidence to guide the management of elevated BP in patients with severe stroke. The latest Chinese guidelines for the early management of patients with AIS [17] recommended the use of hypertensive therapy when SBP is > 200 mmHg. 2006 European guidelines for the management of ICH [18] recommended the use of hypertensive therapy when SBP is ≥180 mmHg. 1999 Guidelines for the early management of ICH proposed by AHA/ASA [19] recommended to defer antihypertensive therapy in patients with SBP < 180 mmHg. 2007 Update of guidelines for the early management of ICH proposed by AHA/ASA [20] recommended to reduce BP when SBP is > 180 mm Hg or MAP is > 130 mm Hg. After the publication of INTERACT II [10], European Stroke Organization (ESO) and AHA/ASA updated the guidelines for ICH in 2014 [21] and 2015 [13] respectively, stating that in acute ICH within 6 hours of onset, intensive BP reduction (systolic target < 140 mm Hg in < 1 hour) is safe and may be superior to a systolic target < 180 mm Hg. However, studies investigating the efficacy and safety of rapid intensive BP reduction in patients with severe stroke are lacking. Besides, ATACH-2 trial [14], published in 2016, included 1000 ICH patients and showed that the rate of renal adverse events within 7 days after randomization was significantly higher in the intensive BP reduction group than in the standard treatment group, and the treatment to achieve a target SBP of 110 to 139 mm Hg did not result in a lower rate of death or disability than standard reduction to a target of 140 to 179 mm Hg. Therefore, the treatment target in the control group for patients with AIS is 200 mm Hg based on the Chinese guidelines, and the treatment target in the control group for patients with ICH is 180 mm Hg based on the Chinese, American and European guidelines published before 2014.
We aim to cooperate with tertiary hospitals in Shaanxi province to conduct a multicenter randomized controlled trial (RCT) called CHASE, dedicated to investigate whether Individualized antihypertensive treatment would lower the mortality and major disability in patients with severe stroke, in order to guide the optimum choice of a target for BP and improve the outcomes and quality of life.

2. STUDY OBJECTIVES

2.1 Primary objective

To determine the therapeutic benefit of Individualized BP lowering treatment (10–15% reduction from admission level) compared with guideline-recommended BP lowering treatment (AIS: SBP $\leq$ 200 mmHg; ICH: SBP $\leq$ 180 mmHg) in reducing the proportion of severe stroke patients with a poor outcome (mRS $\geq$ 3) at day 90 of enrollment.

2.2 Key secondary objective

To determine the therapeutic benefit of Individualized BP lowering treatment relative to guideline-recommended BP lowering treatment in reducing the proportion of severe stroke patients with a poor outcome (mRS $\geq$ 3) at hospital discharge.

2.3 Other secondary objectives

To determine the effects of the treatment on disability (evaluated by NIHSS, GCS, and Barthel index) at hospital discharge and the ability of activities of daily living at day 90 of enrollment (evaluated by Barthel index).

3. STUDY DESIGN

3.1 Overall design
This study has a multicenter, randomized, controlled, single-blind design. Patients will be randomized to two different arms: (1) intervention group (Individualized BP lowering), with an Individualized target for BP lowering during the first week of hospitalization (10–15% reduction from admission level); and (2) control group (guideline-recommended BP lowering), with a fixed target recommended by the guideline for BP lowering during the first week of hospitalization (AIS: SBP \( \leq 200 \text{ mmHg} \); ICH: SBP \( \leq 180 \text{ mmHg} \)). The CHASE trial is led by Xijing Hospital and involves a total of 26 tertiary regional medical centers in Shaanxi province, China. The CHASE will enroll 500 patients with acute severe stroke.

3.2 Clinical site personnel eligibility

All the participating sites should be tertiary hospitals, possess an adequate nurse-to-patient ratio, have a multidisciplinary stroke team and treatment protocols for common complications of stroke, be able to provide standard intensive care, and have rich experience in the management of severe stroke. All CHASE investigators are required to be trained in the protocol, Good Clinical Practice (GCP), and use of the GCS, NIHSS, Barthel index, and mRS if they had no recent certifications.

3.3 Blinding and unblinding

The participants are blind to the grouping results; the investigators are informed of the grouping results because they have to follow a specified strategy of BP management. In each research site, outcomes at hospital discharge and at day 90 of enrollment are assessed independently by a qualified researcher who does not participate in the treatment and is blind to the grouping results.
4. ETHICAL ISSUES

The CHASE study will be conducted according to Good Clinical Practice guidelines and the World Medical Association’s Declaration of Helsinki.

4.1 Institutional ethics committee approval

Based on Principles for ethical review of drug clinical trials formulated by China Food and Drug Administration, the ethics committee of the leading research site is responsible for the ethic censorship of the multicenter clinical trial. The ethics committee of Xijing Hospital, which is the leading research site in this trial, approved the scientificity and ethical rationality of this study. The Principal Investigator (PI) of each participating site is obliged to report any amendments in the protocol, serious adverse events (SAE), and progress of the trial to their Hospital Research Ethics Committee.

4.2 Consent

A signed consent form must be obtained from the participant. If the patient is not fully competent to give informed consent, for example because of a reduced level of consciousness or confusion, the patient’s next of kin or surrogate will be approached to provide informed consent on his or her behalf. An information statement will be given to the patient, and the responsible clinician will explain to the patient about the condition of illness, the purpose and meaning of the study, study protocol, possible benefits and risks, compensation for harms caused by the study, and confidentiality principles. Investigators are obliged to answer all the questions about this study raised by the patient or his/her surrogate. Every participant or their legally authorized representative has the right to withdraw voluntarily from the study at any time for any reason without
prejudice to his/her future medical care by the physician or at the institution. The collected data of the patient who has withdrawn the consent will not be used in any analysis in this study.

4.3 Confidentiality and privacy

All study investigators at the clinical sites have the responsibility to protect all personal identity and medical information at all time. All the medical records of study participants, such as consents, case report forms (CRF), and reports of laboratory tests, must be securely stored. Only de-identified data will be submitted to the Statistical Analysis Center. All digital data will be password-protected and stored in a firewall-protected secure environment. The trial sponsor, PI, Ethics Committees, Health and Family Planning Commissions are allowed to refer to medical records, in the course of monitoring data quality and adherence to the study protocol.

5. SELECTION AND ENROLLMENT OF SUBJECTS

5.1 Inclusion criteria

① Age $\geq 18$ years.

② The randomly assigned BP-lowering regimen is able to be commenced within 72 h after the onset of stroke (ischemic or hemorrhagic), confirmed by a CT or MRI scan of the brain (if the precise timing of the onset of symptoms or signs of the qualifying event is unknown, then the time of onset will be taken as the last time the patient was known to be well). Patients with ICH whilst on antithrombotic treatment (antiplatelet agents or anticoagulation), and patients with prior stroke are eligible.

③ GCS on admission $\leq 12$ or NIHSS on admission $\geq 11$. 
④ There are at least two SBP measurements of $\geq 150$ and $\leq 210$ mmHg, recorded $\geq 5$ min apart (patients with an initial SBP $< 150$ mmHg may be randomized when the SBP fulfills entry criteria on rechecking up to 72 hours after the onset of stroke.

⑤ Written informed consent is able to be obtained directly from the patient or an appropriate surrogate, based on local ethics committee recommendations.

5.2 Exclusion criteria

① Patients who have received thrombolytic therapy, embolectomy, or decompressive craniectomy for the current stroke.

② Patients with subarachnoid hemorrhage.

③ Known definite contraindication to acute BP lowering (e.g. known severe carotid, vertebral, or cerebral arterial stenosis, Moyamoya disease or Takayasu’s arteritis, high grade stenotic valvular heart disease).

④ Secondary to a structural abnormality in the brain (e.g. an arteriovenous malformation, intracranial aneurysm, tumor, or trauma).

⑤ unstable vital signs and requiring the use of vasoactive agents.

⑥ Known existing dementia or prestrike disability (e.g. score 3–5 on the modified Rankin scale).

⑦ Concomitant medical illness that would interfere with the outcome assessments and/or follow-up, such as:

1) Advanced cancer;

2) Severe pulmonary dysfunction (forced expiratory volume in 1 second $< 50\%$);

3) Severe cardiac dysfunction (ejection fraction $\leq 50\%$);

4) Severe hepatic failure (Child-Pugh score $\geq 7$);
5) Severe renal failure (glomerular filtration rate $\leq 30 \text{ mL/min}$ or serum creatinine $\geq 4 \text{ mg/dL}$);

8) Patients who are currently participating in other investigational trials.

9) Patients who are considered to have a high likelihood of not adhering to the study treatment or the follow-up regimen.

5.3 Study enrollment procedures

(1) Screening of Potential Subjects

Emergency department (ED) team will do the initial and rough screening, because all the patients with severe stroke are sent to the ED first. All subjects aged 18 years or older who present with clinical symptoms of acute stroke are screened for study eligibility. If ED personnel suspect an acute stroke, they should immediately call a stroke team member who participates in this study to the ED to evaluate the patient.

(2) Screening/Baseline Evaluations

After receiving report from ED, study investigators should arrive to the ED in an expeditious manner to evaluate the patient and determine potential study eligibility.

① Determination of time of onset

Stroke onset is defined as time of first symptoms or signs of neurological deficits. If stroke started during sleep, onset is recorded as time the subject was last known to be intact.

② Assessment of NIHSS and GCS score at the time of recruitment

The initial recruitment is based on the initial NIHSS and GCS. NIHSS is a 42-point scale, where higher scores indicate more severe neurological deficits. GCS is a 15-point scale (3 - 15), where lower scores indicate lower levels of consciousness. Intubated patients are rated none verbal
response in the verbal score of GCS. Stroke patients presenting with a NIHSS score of $\geq 11$ or a GCS score of $\leq 12$ are potential eligible subjects.

③ Measurement of BP

ED personnel must take two repeat measurements of BP at least 5 minutes apart using manual or automated cuff measurements at mid-biceps level. The mean of two measurements is recorded and used for the screening. The arm must also be horizontal at the level of the heart as denoted by the midsternal level in a supported position. All measurements must be recorded with subjects in recumbent position and with head of bed elevation not exceeding $15^\circ$.

④ Laboratory measurements and other procedures

The following pre-treatment tests and imaging should be measured as part of routine care upon ED presentation: routine blood tests, hepatorenal function routine tests, routine urine tests, electrocardiography (ECG), brain CT or MRI. When the complication of respiratory, cardiac, hepatic, or renal failure is suspected, forced expiratory volume in 1 second, ejection fraction, Child-Pugh score, or glomerular filtration rate should be assessed respectively.

(3)Process after screening

As soon as eligibility is confirmed, the subject or the legally authorized representative is asked to provide informed consent. A signed and dated informed consent is required prior to randomization. Any patient screened, but not randomized, is tracked on the screen failure log.

6. RANDOMIZATION

As soon as informed consent is provided, the investigator should acquire the result of randomization. A secure website (http://traillogin.applinzi.com) will be used to perform the centralized
randomization (computerized random numbers). Patients will be randomized into one of the two intervention arms (1:1): Individualized BP lowering group and guideline-recommended BP lowering group.

7. ALLOCATED STUDY TREATMENTS

As soon as the result of randomization is acquired, the allocated BP lowering treatment should be administered.

7.1 Individualized BP-lowering group

In patients who are assigned to receive Individualized regimen of BP reduction, antihypertensive treatments are to be initiated to reduce SBP to a range of 130–180 mmHg and by 10–15% from the admission level within 2 hours after randomization. SBP in the Individualized BP-lowering group is to be maintained around the target level for one week with or without the use of hypertensive agents. Table 2 presents the detailed management of BP in the first week after randomization.

7.2 Guideline-recommended BP-lowering group

In participants who were assigned to receive guideline-recommended treatment, antihypertensive agents are to be administered if the SBP is > 200 mmHg in AIS or the SBP is > 180 mmHg in ICH. The goal is to maintain the SBP < 200 mmHg in AIS and < 180 mmHg in ICH for one week.
Table 1 Management of blood pressure during the first week after randomization

| SBP level | Approaches |
|-----------|------------|
| **Individualized BP lowering group** | |
| Above the range* | Increase the dose of AHD, or use other stronger AHDs |
| In the range* | Maintain the regimen |
| Below the range* and above 100 mm Hg | Reduce the dose of AHD, or withdraw AHD |
| **Below 100 mm Hg** | |
| **Guideline-recommended BP lowering group** | |
| Above 200 mm Hg in AIS | Increase the dose of AHD, or use other stronger AHDs |
| Above 180 mm Hg in ICH | |
| Below 200 and above 100 mm Hg in AIS | Use the least dose of AHD to keep SBP not higher than 200 mm Hg in AIS, 180 mm Hg in ICH |
| Below 180 and above 100 mm Hg in ICH | |
| Below 100 mm Hg | Use vasopressor agents |

*10%-15% reduction from admission level and between 130-180 mm Hg. AHD antihypertensive drug, AIS Acute ischemic stroke, BP blood pressure, ICH intracerebral hemorrhage, SBP systolic blood pressure.

7.3 Selection of antihypertensive drugs

As the trial is an assessment of BP management policies, there is some flexibility in the use of particular BP lowering agents to achieve BP targets. The selection of antihypertensive agents is based on the local availability; no specific agent is stipulated (both intravenous and oral agents can be used).

7.4 BP measuring and monitoring

Automatic BP cuff monitor is used for BP measuring and monitoring at mid-biceps level of the unaffected arm (right arm is chosen when both arms are affected or unaffected). All measurements are to be recorded with subjects in a recumbent position and with elevation of the head of the bed not exceeding 15°. BP measurements are to be taken on the following schedule:
① Every 5 minutes for the first 15 minutes after intravenous antihypertensive agent is started. Every 15 minutes for the remainder of the first hour, unless the dose is being adjusted (see next bullet point).

② Every 5 to 15 minutes during dose adjustments of intravenous antihypertensive agent.

③ At least every 30 minutes while receiving intravenous antihypertensive agent.

④ More frequent measurements are recommended if prominent BP changes are observed as determined by the treating physician.

⑤ Besides the above conditions, BP measurements are required to take according to the following protocol: During the first 24 hours after randomization, BP is recorded every 2 hours. On days 2 and 3, BP is recorded every 4 hours. During days 4–7, BP is recorded every 8 hours. On the day of hospital discharge, BP at 08:00 a.m. is recorded. The timetable of BP measurement is in the CRF. Three measurements of BP are required for each time point and the average is recorded.

7.5 Previous use of antihypertensive therapy in both groups

Patients who have been taking antihypertensive therapy prior to randomization will have their usual medication continued when oral administration is possible, unless the agents are considered to be inappropriate by the responsible physician (eg poor compliance, intolerance, or adverse events).

7.6 BP management after Day 7 or hospital discharge
The target SBP after Day 7 or hospital discharge is <140 mmHg, as per guideline-based recommendations for high risk vascular disease patients.

8. DISCONTINUATION OF ALLOCATED BP MANAGEMENT POLICY

The BP management in either group should be discontinued if any of the following occur:

① SAEs, which are in the opinion of the investigator, related to the trial protocol.

② The investigator feels it is in the subject’s best interest.

The investigator must not deviate from the protocol except the above situation occurs or the patient/surrogate chooses to withdraw consent to participation in the study. Follow-up data will be collected for all treated subjects except those who specifically withdraw consent for release of such information.

9. GENERAL PRINCIPLES OF MONITORING AND TREATMENT

9.1 Basic physiological function monitoring

The patient's heart rate and oxygen saturation are to be continuously monitored. The respiratory rate is to be measured hourly. Monitoring for BP refers to 7.4.

9.2 Neurological evaluation
A comprehensive neurologic examination must be performed at 2-hour intervals throughout the treatment period in other to detect neurological deterioration.

9.3 Definition and management of neurological deterioration

Neurological deterioration is defined as a decrease of $\geq 2$ on GCS or increase of $\geq 4$ points on NIHSS (from baseline) that is not related to sedation/hypnotic use and is sustained for at least 8 hours. After neurological deterioration is detected, related monitoring and management must be performed based on 2015 Chinese Guidelines for the early management of patients with severe stroke [16].

9.4 Other monitoring and management

During the study treatment and follow-up period, the standard management of acute severe stroke patients will be given according to 2015 Chinese Guidelines for the early management of patients with severe stroke [16]. Appropriate neuroimaging and neurophysiology examinations should be performed according to the patient’s condition. Efforts should be made to avoid, detect, and manage complications of stroke.

10. STUDY OUTCOMES

10.1 Primary outcomes

The primary outcome measurement is the proportion of participants with a poor outcome at day 90 of enrollment. Poor outcome is defined as major disability (unable to live independently, mRS $\geq 3$, see APPENDIX) or all-cause death.

10.2 Secondary outcomes
Key secondary outcome: will be the proportion of participants with a poor outcome (mRS $\geq 3$) at hospital discharge.

Other secondary outcomes:

① Neurological deficits at hospital discharge, defined by NIHSS (see APPENDIX);

② Level of consciousness at hospital discharge, defined by GCS (see APPENDIX);

③ Ability of activities of daily living at hospital discharge, defined by Barthel Index (see APPENDIX);

④ Ability of activities of daily living at day 90 of enrollment, defined by Barthel Index (see APPENDIX);

10.3 Safety outcome

The safety outcome will be the proportion of subjects who experienced any treatment-related SAEs during the first 7 days from randomization. The adjudication of site-reported relatedness of an SAE to treatment is performed by the Quality Control and Assurance Committee (QCAC). Moreover, neurological deterioration identified within 24 hours of randomization is a SAE. Neurological deterioration is defined as a 2 or more point decrease in the GCS or 4 or more point increase in the NIHSS from baseline measurements.

11. DATA COLLECTION AND FOLLOW-UP

At the time point of baseline screening, demographics, subtypes of stroke, medical history (e.g. AIS, ICH, coronary event, diabetes mellitus, and hypertension), physical examination, clinical scores (NIHSS, GCS, Barthel index, mRS), and vital signs are recorded. On day 1 and day 7, routine laboratory tests for stroke patients are assessed,
including blood routine, liver and renal function test, serum lipid, fasting glucose, urine routine, and electrocardiography. Co-morbidities on the day of screening and hospital discharge are recorded. Clinical scores on day 7, the day of hospital discharge, and day 90 are collected. During the whole hospitalization, BP, vital signs, and adverse events (AEs) are monitored, and concomitant treatments are documented. Table 3 presents all the variables measured at each time point of the study.

Table 3 Timing and content of study assessments

| Items                                | Day of Enrollment |
|--------------------------------------|-------------------|
|                                      | Screening | 1 | 2 | 3 | 4 | 5 | 6 | 7 | HD | 90 |
| Written Informed Consent             | ●         |   |   |   |   |   |   |   | ●  |    |
| Inclusion & exclusion criteria       | ●         |   |   |   |   |   |   |   | ●  |    |
| Demographics                         | ●         |   |   |   |   |   |   |   | ●  |    |
| Medical History                      | ●         |   |   |   |   |   |   |   | ●  |    |
| Physical examination                 | ●         |   |   |   |   |   |   |   | ●  | ●  |
| Blood pressure monitoring            | ●         | ● | ● | ● | ● | ● | ● | ● | ●  | ●  |
| Laboratory tests                     | ●         |   |   |   |   |   |   |   | ●  |    |
| NIHSS & GCS                          | ●         |   |   |   |   |   |   |   | ●  | ●  |
| Barthel Index & mRS                  | ●         |   |   |   |   |   |   |   | ●  | ●  |
| Vital signs monitoring               | ●         | ● | ● | ● | ● | ● | ● | ● | ●  | ●  |
| Comorbidities                        | ●         |   |   |   |   |   |   |   | ●  | ●  |
| Adverse events                       | ●         | ● | ● | ● | ● | ● | ● | ● | ●  | ●  |
| Use of antihypertensive agents       | ●         | ● | ● | ● | ● | ● | ● | ● | ●  | ●  |
| Concomitant therapies                | ●         | ● | ● | ● | ● | ● | ● | ● | ●  | ●  |

HD hospital discharge, GCS Glasgow Coma Scale, NIHSS National Institute of Health stroke scale, mRS modified Rankin Scale.

The 90-day outcomes are evaluated via telephone interviews at day 90 of enrollment (a delay of up to three days is acceptable). In cases when the patient is incapable to complete the interview, the first choice for a proxy is the spouse/live-in companion. Clinical scores at hospital discharge and on day 90 of enrollment will be assessed independently by
a trained research assistant at each participating site who is blind to the grouping results and does not participate in the treatment.

12. TREATMENT DEVIATIONS AND FAILURES

12.1 Inability to initiate allocated treatment

A subject may meet eligibility requirements and be randomized, and might be unable to proceed to the study treatment due to emergencies such as cardiac arrest, respiratory failure, severe hypotension, etc. Events like these may render the subject no longer medically fit to receive allocated treatment as determined by the site investigator or treating physician. Such events are expected to be uncommon. However, if the subject is randomized, he/she must complete the required study assessments and procedures through Day 90 unless the subject withdraws consent prior to that point.

12.2 Treatment failure

Spontaneous reduction in SBP in the guideline-recommended BP lowering group may result in their SBP entering the SBP range of the Individualized BP lowering group (10–15% reduction from admission level). Similarly, SBP may drop less than 10% from admission level even after an intensive treatment in the Individualized BP lowering group. If the goals of the assigned treatment cannot be met as defined earlier, the subject is considered a treatment failure but is considered in the original allocation group per the Intention To Treat (ITT) principle.

12.3 Deviations from the protocol

Investigators should not deviate from the protocol. A deviation from the protocol is defined when the subject has not received the allocated BP management strategy except the subject meets the discontinuation of allocated BP management policy (see section 8) or has medical
emergencies which render the subject no longer medically fit to receive allocated treatment. A deviation from the protocol will be determined by the QCAC. Patients with deviations from the protocol will be excluded from the study.

13. LOST TO FOLLOW UP

The 90-day outcomes are evaluated via telephone interviews at day 90 of enrollment (a delay of up to three days is acceptable). The subject is coded as lost to follow-up in the End-of-Study CRF when at least five attempts have been made to contact the patient over the course of two weeks and all methods have been tried and have failed.

14. MONITORING OF ADVERSE EVENTS

14.1 Definitions of adverse and serious adverse events

An adverse event is defined as any untoward event or complication that was not previously identified, or that occurs with greater frequency or severity than previously reported. The event occurs during the protocol intervention or during the follow-up period, and may or may not be considered related to the protocol intervention. As defined by the WHO International Drug Monitoring Center (1994), a SAE is any untoward medical occurrence that:

① Results in death;

② Is life threatening in the opinion of the attending clinician (ie the patient was at risk of death at the time of the event; it does not refer to an event that might hypothetically have caused death had it been more severe);
③ Requires inpatient hospitalization or prolongation of existing hospitalization;

④ Results in persistent or significant disability or incapacity;

⑤ Is an important medical event in the opinion of the attending clinician that is not immediately life-threatening and does not result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

14.2 Recording and reporting

All AEs, including SAEs, deaths and abnormal and clinically significant laboratory values, occurring to the subject from enrollment through Day 7 or hospital discharge (whichever occurs first) are recorded on the case report form. After Day 7 or discharge, only SAEs are collected and followed. For each event, date of onset, duration, severity, and relationship to the prescribed drug regimen are recorded. All SAEs should be reported to PI and the QCAC within 24 hours or as soon as the event is recognized. The time when a SAE has been reported, the approach how a SAE has been reported (via a written document, telephone, or fax), the person to whom a SAE has been reported, and the management and follow up of the reported SAE must be recorded.

14.3 Management and follow up

The QCAC will closely monitor all SAEs for any relationship to the study procedures and protocol and clustering of events at a particular site. The QCAC will submit all SAEs to the independent Statistical Analysis Center for review. The protocol will be amended or the study will be stopped earlier if an excess of particular SAEs appear to be protocol related. The managements of SAEs include no action taken, dose adjustment, suspension or termination of the allocated intervention, administration of
concomitant drugs, inpatient hospitalization or prolongation of existing hospitalization.

15. QUALITY CONTROL AND ASSURANCE

This study will be conducted in accordance with the guidelines of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP), and all relevant national and local regulations.

15.1 Oversight organization

The Quality Control and Assurance Committee (QCAC) is responsible for the assessment of site investigator clinical care and SAE review and adjudication for site-reported relatedness of an SAE to treatment and for the duration of the trial (if necessary).

15.2 Training of the study team

Training sessions about the protocol and related clinical scores will be held for all the research investigators before the commencement of CHASE study, in order to make sure the protocol will be understood correctly.

15.3 Monitoring of participating centers

The PI in each research site takes charge of quality control by supervising the conduct of the trial in accordance with the prespecified protocol, applicable guidelines and regulations. All participating sites will have monitoring visits via video conferencing after every ten patients are randomized, to verify consent, eligibility criteria, anomalous data, and reported serious AEs

16. STATISTICAL CONSIDERATIONS

16.1 Sample size
The sample size was set at 500 to provide at least 80% power to detect a 6% absolute risk reduction in the primary outcome for patients in the Individualized BP-lowering group compared to those in the guideline-recommended control group, using a two-sided significance test with 5% type I error. The following assumptions were made: a primary outcome of 60% in the control group will be reduced to 54% in the Individualized group; and there will be 10% non-adherence to the treatment protocol and loss to follow-up. The 60% incidence of unfavorable 90-day outcome is obtained from one Chinese study on severe stroke [22]. The 10% non-adherence rate and the absolute risk reduction in primary outcome are obtained from the INTERACT2 study and ATACH2 study which were designed to compare the effects of two different BP lowering strategies in acute stroke patients [10, 14].

16.2 Data analysis

16.2.1 Outcomes

Under the ITT principle, all patients who are randomized are included in the analysis of the original allocation group per the Intention To Treat (ITT) principle. Baseline and demographic characteristics such as gender, age, stroke type, medical history, GCS, NIHSS, SBP, etc, will be summarized by treatment group to assess comparability of treatment groups. The primary endpoint of death or dependency at 90 days will be analyzed by means of a chi-square test. Categorical secondary outcomes will preferably be analyzed by means of a Chi-square, and continuous variable will be analyzed using Student's t test or Mann-Whitney U test (whichever is proper). The proportions of SAEs will be analyzed by means of a chi-square test. Univariate and multivariate logistic regression analyses will be used to analyze the primary and key secondary outcomes and estimate adjusted odds ratios and associated 95% confidential intervals. Subgroup analyses will be carried out in patients with different
ages (≥65 years or <65), different stroke types (ICH or AIS), different SBP levels on admission (<180 or ≥180 mmHg), with or without history of hypertension, irrespective of whether there is a significant treatment effect on the primary outcome. Two-sided p values ≤ 0.05 will be considered significant. Statistical analysis will be performed with SPSS version 22 software (SPSS Inc., Chicago, IL, USA).

16.2.2 Handling of Missing Outcome Data

The multiple imputation method will be used as the primary approach. This is generally considered the least biased method since it incorporates the uncertainty to the imputed value. As a sensitivity analysis, we plan to impute the missing primary outcome data by assuming the missing mRS score at Day 90 to be unfavorable. If the treatment effect is robust, we expect analysis using these imputation methods would yield similar inferences, particularly if the missing data are minimal (<5%).

17. ORGANIZATION

This study is funded by the Shaanxi Province Key Research and Development Project (2017ZDCXL-SF-02-02), led by Xijing Hospital of Fourth Military Medical University, and conducted by 26 regional central hospitals in Shaanxi Province.

17.1 Executive Committee (EC)

Overall responsibility includes the execution of the study design, protocol, data collection and analysis plan, as well as publications. The EC has the right to appoint new members and co-opt others to add to the integrity of the conduct of the study and analyses. The members of EC are as follows:

Wen Jiang (Chair, PI), Xijing Hospital, Fourth Military Medical
University, Shaanxi Stroke Association, The Shaanxi Cerebrovascular Disease Clinical Research Center, Xi’an, China
Li Li, Xijing Hospital, Fourth Military Medical University, The Shaanxi Cerebrovascular Disease Clinical Research Center, Xi’an, China
Hongzeng Li, Tangdu Hospital, Fourth Military Medical University, Xi’an, China
Changhu Xue, Xianyang Central Hospital, Xianyang, China
Chaohui Song, Tongchuan Mining Hospital, Tongchuan, China
Ding’an Li, Hanzhong Central Hospital, Hanzhong, China
Fang Yang, Xijing Hospital, Fourth Military Medical University, Xi’an, China
Feng Fu, Shaanxi 215 Hospital, Xianyang, China
Hua Lv, Shaanxi Provincial People’s Hospital, Xi’an, China
Jun Zhou, Shangluo Central Hospital, Shangluo, China
Kangjun Wang, Hanzhong Central Hospital, Hanzhong, China
Wei Zhang, Tangdu Hospital, Fourth Military Medical University, Xi’an, China
Yi Liu, Ankang Central Hospital, Ankang, China
Xiangjun Yuan, Weinan Central Hospital, Weinan, China
Xiaocheng Wang, Yulin No.2 Hospital, Yulin, China
Xinlai Wang, Xi’an Central Hospital, Xi’an, China
Yongqiang Li, Baoji Central Hospital, Baoji, China

17.2 Quality Control and Assurance Committee (QCAC)

Overall responsibility includes monitoring of the execution of the study, regular quality inspection in participating sites, monitoring of blinded response variables and SAEs. When early dramatic benefits or potential harmful effects have been shown, the QCAC will report to the
EC on recommendations to continue or temporarily halt recruitment to the study. The members of QCAC are as follows:

Fang Yang, Xijing Hospital, Fourth Military Medical University, Xi’an, China
Wen Li, Xijing Hospital, Fourth Military Medical University, Xi’an, China
Yuan Che, Shaanxi Stroke Association, Xi’an, China
Xiai Yang, Ankang Central Hospital, Ankang, China

17.3 Statistical Analysis Center
Overall responsibility is to make statistical analysis plan and conduct statistical analysis. The members of Statistical Analysis Center are as follows:

Lei Shang, Department of Health Statistics of The Fourth Military Medical University, Xi'an, China
Jingjing Zhao, Xijing Hospital, Fourth Military Medical University, Xi’an, China
Qiong Gao, Xijing Hospital, Fourth Military Medical University, Xi’an, China

17.4 Participating Centers
A total of 26 hospitals will participate in this study:
Xijing Hospital: Wen Jiang, Fang Yang, Fang Yuan, Li Li, Lijie Bi, Lijuan Liu, Mengmeng Hu, Jingya Wei, Gengyao Hu, Yuanfang Zhao
Shaanxi 215 Hospital: Feng Fu, Dingfeng Wu, Jie Yang, Xiaoning Li, Haiyan Zhai, Fupeng Fang, Lifang Zhu, Lin Li, Min Zhang
521 Hospital of NORINCO Group: Zhuanhui Li, Ni Zhang, Xing Wang, Xin Ma, Yuanyuan Wei, Li Xue, Fei Yan, Changfu Cui
Ankang Central Hospital: Yi Liu, Tao Chen, Jiaming Gong, Xingsheng Wang, Guixi Shen, Yan Li, Xingjun Zou, Derong Hu, Xiang Qu, Yun Chen, Xue Zhao, Xiaomei Yang, Quanwei Jin, Jianghong Ma
Baoji Central Hospital: Yongqiang Li, Junwen Wang, Dong Luo, Lijun Wang
First Affiliated Hospital Xi'an Jiaotong University: Jin Qiao, Guogang Luo, Kang Huo, Chen Chen, Dan Zhu
Hanzhong Central Hospital: Ding’an Li, Kangjun Wang, Zheng Chen, Heng Wang, Ruirui Bai, Rong Chen, Jing Li, Chang Chai, Baoxia Tian, Feng He, Ying Yang, Senling Zhang, Nan Yang, Qiang Wu, Jian Li, Benkui Li, Jian Wang
Tangdu Hospital: Wei Zhang, Hongzeng Li, Peng Guo, Chuan Li, Min Zhang, Jinjin Shen, Rong Yan
Tongchuan Mining Hospital: Chaohui Song, Hongyan Zhao, Zhongyi Li, Yuan Shao, Doumin Li
Tongchuan People's Hospital: Chengkai Wang, Changpeng Song, Siwen Chen, Zhemin Qiao, Shuang Lu, Qianmeng Ren, Ruixiu Wang, Yanhua Niu, Longfei Zhang, Xiuxia Cai, Xueyan Zhang
The First Affiliated Hospital of Xi'an Medical University: Bei Zhang, Shijun Zhang, Yulan Bai, Yanan Bai, Fangfang Yu, Wei Wei, Tong Yuan, Li Xue
Shaanxi Provincial People's Hospital: Hua Lv, Wei Di, Wenxiu Wang, Le Wang, Qiang Zhang, Xiansong Cheng, Jiankuan Shi, Ni Ma, Jingyan Li
Shangluo Central Hospital: Jun Zhou, Juan Li, Yuting Ji, Baodan Lei, Fei Qu
Weinan Central Hospital: Xiangjun Yuan, Jirong Liu, Xiaohong Wei,
Huijuan Shang, Xiaodong Yuan, Ying Li, Jing Li, Yanling Song, Xiaorong Yang, Ke Lei, Huimin Cui
Xi’an 141 Hospital: Qiuwu Liu, Dongjing Zhu, Yanhui Dong, Lihe Yin, Jialing Li
Xi’an Central Hospital: Xinlai Wang, Hui Lei, Zhiqin Liu, Yi Jiang, Gemin Zhu, Yu’e Yan, Yanzhi Zhou
Xi’an Gaoxin Hospital: Yi Jia, Tao Wu, Saibing Liu, Jingmei Chen
Xi’an No.3 Hospital: Mingze Chang, Yanling Yin, Lu Zhao, Haojun Ma, Meng Jiao
Xi’an No.4 Hospital: Aixiang Zhang, Tao Lei, Juan Li, Gang Guo, Qiubo Qiao, Man Wang
Xi’an No.9 Hospital: Junxian Gao, Xiaolin Wu, Qiang Ma, Chao Wei, Zheng Fang, Fei Chen
Xi’an Traditional Chinese Medicine Hospital: Hai lin, Gang Liu, Fang Mi, Yan Wei, Shunqing Lu, Guoyan Fang
Xi’an XD Group Hospital: Jianbo He, Huiqi Li, Qiang Guo, Hang Su, Jiemin Zhai, Li Yao, Juanjuan Sha, Heng Zhang, Liang Shi, Juanli Zhang, Haiguo Wang
Xianyang Central Hospital: Changhu Xue, Jun Wu, Tao Han, Ting Fu, Jie Zhang, Tingting Li, Gaowen Liu, Lin Su
Yan’an University Affiliated Hospital: Yongcai Qu, Li Ma, Xuejun Gao, Yingying Liu, Xibin Gao, Yajun Gao, Junyan Yang
Yulin No.1 Hospital: Yaling Ma, Yingjuan Hou, Wenzong Wang, Tao Lv, Liang Liu, Yajuan Li, Xumei Ma, Xianda Cui, Haixia Wu
Yulin No.2 Hospital: Xiaocheng Wang, Bingdong Feng, Hufei Chang, Rong Zhao, Xiaoping Wang, Cunjun Yang, Rongrong Guo, Donghong He, Jian Zhang, Quan Jing, Caiqin Bai, Yumei Wang, Min Sheng, Shuxia Shen, Jun
Hao, Xue Li, Chunyan Yang, Yongping Yu

18. PROTOCOL AMENDMENTS

Protocol amendments will be agreed upon with the CHASE Study Group, Sponsor and Funding Body before submission for ethical approval. Following ethical approval, protocol modifications will be communicated with relevant parties such as the trial investigators, the trial registry, and, if required, trial participants.

19. PUBLICATION AND DISSEMINATION POLICY

Publication of all the reports from the study (research article, abstract, or conference communication) will be in the name of CHASE Study Group. The results of this trial will be disseminated to a wide clinical audience (patients, health professionals, policy makers, and the general public) through publication in a high-impact international scientific journal.
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APPENDIX

Glasgow Coma Scale (GCS)

| Name       | Sex | Age | ID | Diagnosis          | Response                                      | Score |
|------------|-----|-----|----|--------------------|-----------------------------------------------|-------|
| Response   |     |     |    |                    |                                               |       |
| Eye        |     |     |    |                    | Opens eyes spontaneously                      | 4     |
|            |     |     |    |                    | Opens eyes in response to voice               | 3     |
|            |     |     |    |                    | Opens eyes in response to pain                | 2     |
|            |     |     |    |                    | No opening of the eye                         | 1     |
| Verbal     |     |     |    |                    | Oriented, converses normally                  | 5     |
|            |     |     |    |                    | Confused, disoriented                         | 4     |
|            |     |     |    |                    | Inappropriate words                           | 3     |
|            |     |     |    |                    | Incomprehensible sounds                       | 2     |
|            |     |     |    |                    | No verbal response                            | 1     |
| Motor      |     |     |    |                    | Obeys commands                                | 6     |
|            |     |     |    |                    | Localizes to pain                             | 5     |
|            |     |     |    |                    | Withdrawal from pain                          | 4     |
|            |     |     |    |                    | Decorticate posturing accentuated by pain     | 3     |
|            |     |     |    |                    | Decerebrate posturing accentuated by pain     | 2     |
| Total:     |     |     |    |                    |                                               |       |

Rater: Date:
### National Institutes of Health Stroke Scale (NIHSS)

| Name                              | Sex | Age | ID | Diagnosis                                         | Total score | Score |
|-----------------------------------|-----|-----|----|---------------------------------------------------|-------------|-------|
| **1a. Level of Consciousness:**   |     |     |    | Only one level can be chosen.                     |             |       |
|                                   |     |     |    | 0 = Alert; keenly responsive.                     |             |       |
|                                   |     |     |    | 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. |             |       |
|                                   |     |     |    | 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). |             |       |
|                                   |     |     |    | 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic. |             |       |
| **1b. LOC Questions:**            |     |     |    | Month, age                                        |             |       |
|                                   |     |     |    | 0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly. Aphasic and stuporous patients will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause will score 1. |             |       |
| **1c. LOC Commands:**             |     |     |    | Open and close the eyes and then to grip and release the non-paretic hand. |             |       |
|                                   |     |     |    | 0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly. |             |       |
| **2. Best Gaze:**                 |     |     |    | Only horizontal eye movements will be tested.    |             |       |
|                                   |     |     |    | 0 = Normal.                                       |             |       |
|                                   |     |     |    | 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. |             |       |
|                                   |     |     |    | 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver. |             |       |
| **3. Visual:**                    |     |     |    | Upper and lower quadrants are tested.             |             |       |
|                                   |     |     |    | 0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. |             |       |
|                                   |     |     |    | 3 = Bilateral hemianopia (blind including cortical blindness). Near death scores 1. |             |       |
| **4. Facial Palsy:**              |     |     |    | Ask or use pantomime.                             |             |       |
|                                   |     |     |    | 0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). |             |       |
|                                   |     |     |    | 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face). |             |       |
| **5. Motor Arm:**                 |     |     |    | The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). |             |       |
|                                   |     |     |    | 0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. |             |       |
|                                   |     |     |    | 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. |             |       |
|                                   |     |     |    | 5a. Left Arm                                      |             |       |
|                                   |     |     |    | 5b. Right Arm                                    |             |       |
| **6. Motor Leg:**                 |     |     |    | Hold the leg at 30 degrees                       |             |       |
|                                   |     |     |    | 0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. |             |       |
|                                   |     |     |    | 6a. Left Leg                                      |             |       |
|                                   |     |     |    | 6b. Right Leg                                    |             |       |
| **7. Limb Ataxia:**               |     |     |    | Ataxia is absent in the patient who cannot understand or is paralyzed. |             |       |
|                                   |     |     |    | 0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. |             |       |
| **8. Sensory:**                   |     |     |    | Pinprick                                          |             |       |
|                                   |     |     |    | 0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss. |             |       |
|                                   |     |     |    | 2 = Severe to total sensory loss.                 |             |       |
| **9. Best Language**              |     |     |    | Name and read.                                    |             |       |
|                                   |     |     |    | 0 = No aphasia; normal. 1 = Mild-to-moderate aphasia. 2 = Severe aphasia. |             |       |
|                                   |     |     |    | 3 = Mute, global aphasia; no usable speech or auditory comprehension. Coma scores 3. |             |       |
| **10. Dysarthria**                |     |     |    | Read or repeat words                              |             |       |
|                                   |     |     |    | 0 = Normal. 1 = Mild-to-moderate dysarthria.      |             |       |
|                                   |     |     |    | 2 = Severe dysarthria.                            |             |       |
| **11. Extinction / Inattention**  |     |     |    |                                                   |             |       |
|                                   |     |     |    | 0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space. |             |       |
# Modified Rankin Scale (mRS)

| Name | Sex | Age | ID | Diagnosis |
|------|-----|-----|----|-----------|
| Score | Description |
| 0 | No symptoms. |
| 1 | No significant disability. Able to carry out all usual activities, despite some symptoms. |
| 2 | Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities. |
| 3 | Moderate disability. Requires some help, but able to walk unassisted. |
| 4 | Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted. |
| 5 | Severe disability. Requires constant nursing care and attention, bedridden, incontinent. |
| 6 | Dead. |

**Total score:**

**Rater:**

**Date:**
# Barthel Index of Activities of Daily Living

| Name | Sex | Age | ID | Diagnosis |
|------|-----|-----|----|-----------|
|      |     |     |    |           |

## Item | Description | Score |
|-------|-------------|-------|
| **Bowels** | 0 = incontinent (or needs to be given enemas). 5 = occasional accident. 10 = continent. |
| **Bladder** | 0 = incontinent, or catheterized and unable to manage alone. 5 = occasional accident. 10 = continent |
| **Grooming** | 0 = needs to help with personal care. 5 = independent face/hair/teeth/shaving (implements provided) |
| **Toilet use** | 0 = dependent. 5 = needs some help, but can do something alone. 10 = independent (on and off, dressing, wiping). |
| **Feeding** | 0 = unable. 5 = needs help cutting, spreading butter, etc., or requires modified diet. 10 = independent. |
| **Transfer** | 0 = unable, no sitting balance. 5 = major help (one or two people, physical), can sit. 10 = minor help (verbal or physical). 15 = independent. |
| **Mobility** | 0 = immobile. 5 = wheelchair independent, including corners. 10 = walks with help of one person (verbal or physical) > 50 yards. 15 = independent (but may use any aid; for example, stick) > 50 yards |
| **Dressing** | 0 = dependent. 5 = needs help but can do about half unaided. 10 = independent (including buttons, zips, laces, etc.). |
| **Stairs** | 0 = unable. 5 = needs help (verbal, physical, carrying aid). 10 = independent. |
| **Bathing** | 0 = dependent. 1 = independent (or in shower). |

**Total score:**

| Rater: | Date: |
|--------|-------|
Funding: Shaanxi Province Key Research and Development Project (2013KTZB03-02-02 and 2017ZDCXL-SF-02-02)

Trial registration: NCT02982655

重症脑血管病患者急性期血压管理研究
Controlling Hypertension After Severe Cerebrovascular Event (CHASE)

STUDY PROTOCOL

Leading research site: Xijing Hospital

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Version 1.1 – 30 January 2018
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# ABBREVIATIONS

| Abbreviation | Description |
|--------------|-------------|
| AE/SAE       | Adverse events / Serious adverse event |
| AHA          | American Heart Association |
| AIS          | Acute ischemic stroke |
| ASA          | American Stroke Association |
| CHD          | Coronary heart disease |
| CT           | Computed Tomography |
| CVT          | Cerebral venous thrombosis |
| DBP          | Diastolic blood pressure |
| EC           | Executive Committee |
| ECG          | Electrocardiography |
| ED           | Emergency department |
| EF           | Ejection Fraction |
| ESO          | European Stroke Organization |
| FEV1         | Forced Expiratory Volume in the first second |
| GCP          | Good Clinical Practice |
| GCS          | Glasgow coma scale |
| ICU          | Intensive care unit |
| ITT          | Intention To Treat |
| MAP          | Mean arterial pressure |
| MRI          | Magnetic Resonance Imaging |
| mRS          | Modified Rankin Scale |
| NHISS        | National Institute of Health stroke scale |
| ICH          | Intracerebral hemorrhage |
| PI           | Principal Investigator |
| QCAC         | Quality Control and Assurance Committee |
| RCT          | Randomized controlled trial |
| SAH          | Subarachnoid hemorrhage |
| SBP          | Systolic blood pressure |
CHASE PROTOCOL SYNOPSIS

Chinese Study Title 重症脑血管病患者急性期血压管理研究

English Study Title Controlling Hypertension After Severe Cerebrovascular Event

Acronym CHASE

Trial Registration
- Registration Authority: ClinicalTrials.gov
- Registration Number: NCT02982655
- Registration Time: 30 November 2016

Study Design Prospective, Multicentre, Single-blind, Randomized Controlled Trial

Primary Study Objective To determine the therapeutic benefit of Individualized BP lowering treatment (10–15% reduction from admission level) compared with guideline-recommended BP lowering treatment (AIS: SBP ≤ 200 mmHg; ICH: SBP ≤ 180 mmHg) in reducing the proportion of severe stroke patients with a poor outcome (mRS ≥ 3) at day 90 of enrollment.

Study Population Acute severe stroke patients

Sample Size 500 participants randomized in a 1:1 ratio to
either Individualized BP lowering treatment or
guideline-recommended BP lowering
treatment.

Selection of Subjects

- Inclusion Criteria
  ① Age $\geq$ 18 years;
  ② The randomly assigned BP-lowering regimen is able to be commenced within 72 h after the onset of stroke (ischemic or hemorrhagic), confirmed by a CT or MRI scan of the brain (if the precise timing of the onset of symptoms or signs of the qualifying event is unknown, then the time of onset will be taken as the last time the patient was known to be well);
  ③ GCS on admission $\leq$ 12 or NIHSS on admission $\geq$ 11;
  ④ There are at least two SBP measurements of $\geq$ 150 and $\leq$ 210 mmHg, recorded $\geq$ 5 min apart (patients with an initial SBP $<$ 150 mmHg may be randomized when the SBP fulfills entry criteria on rechecking up to 72 h after the onset of stroke);
  ⑤ Written informed consent is able to be obtained directly from the patient or an appropriate surrogate, based on local ethics committee recommendations.
Exclusion criteria

1. Patients who have received thrombolytic therapy, embolectomy, or decompressive craniectomy for the current stroke;
2. Patients with subarachnoid hemorrhage;
3. Known definite contraindication to acute BP lowering (e.g. known severe carotid, vertebral, or cerebral arterial stenosis, Moyamoya disease or Takayasu’s arteritis, high grade stenotic valvular heart disease);
4. Secondary to a structural abnormality in the brain (e.g. an arteriovenous malformation, intracranial aneurysm, tumor, or trauma);
5. Unstable vital signs and requiring the use of vasoactive agents;
6. Known existing dementia or prestroke disability (e.g. score 3–5 on the mRS);
7. Concomitant medical illness that would interfere with the outcome assessments and/or follow-up (advanced cancer; severe pulmonary dysfunction; severe cardiac dysfunction; severe hepatic failure; severe renal failure);
8. Patients who are currently participating
in other investigational trials;
⑨ Patients who are considered to have a high likelihood of not adhering to the study treatment or the follow-up regimen.

**Study Treatments**

- Individualized BP lowering group

Antihypertensive treatments are to be initiated to reduce SBP to a range of 130–180 mmHg and by 10–15% from the admission level within 2 h after randomization. SBP in the Individualized BP-lowering group is to be maintained around the target level for one week with or without the use of hypertensive agents.

- Guideline-recommended BP lowering group

Antihypertensive agents are to be administered if the SBP was > 200 mmHg in AIS or the SBP was > 180 mmHg in ICH. The goal is to maintain the SBP < 200 mmHg in ischemic stroke and < 180 mmHg in ICH for one week with or without the use of hypertensive agents.

**Primary Outcome**

Poor outcome (defined by mRS \( \geq 3 \)) at day 90 of enrollment.

**Statistical Analysis**

- Two-sided p values \( \leq 0.05 \) will be
Univariate and multivariate logistic regression analyses will be used to determine the effects of different BP lowering treatments on primary and secondary outcomes.

A subgroup analysis of the primary outcome will be conducted.

Statistical analysis will be mainly performed with SPSS software.

**Study Flowchart**

- Patients with acute stroke
  - Not meeting inclusion criteria:
    - Age ≥ 18 years
    - Within 72 h after the onset of stroke
    - GCS≤12 or NIHSS≥11分
    - SBP ≥ 150 and ≤ 210 mm Hg
    - Consent acquired
  - Meeting Exclusion criteria:
    - Received thrombolytic therapy, embolectomy, or decompressive craniectomy
    - Subarachnoid hemorrhage
    - Known definite contraindication to acute BP lowering
    - Secondary to a structural abnormality in the brain
    - Unstable vital signs
    - Known existing dementia or prestroke disability
    - Concomitant medical illness that would interfere with the outcome assessments
    - Participating in other investigational trials
    - Having a high likelihood of not adhering to the study treatment or the follow-up regimen

- 500 patients to be randomized
  - 250 to be allocated to individualized BP lowering group
  - 250 to be allocated to guideline-recommended BP lowering group

- 7 day, hospital discharge evaluation and 90 day follow up
1. BACKGROUND

Severe stroke is a life-threatening cerebral vascular event which causes major neurological function deficits and leads to multiple organ dysfunctions, such as respiratory and circulatory failure. The mortality and disability rates of severe stroke are very high, and the therapeutic strategy in the acute stage determines the outcomes of severe stroke. During the early stage of severe stroke, the management of blood pressure (BP) is one of the most basic and crucial treatments in the intensive care unit (ICU). However, few studies with high evidence levels on the optimum goal of BP lowering treatment in patients with acute severe stroke have been conducted. Both large increase and reduction in BP were associated with a higher risk of early neurological deterioration, increased infarct volume, and poorer outcome at three months. The lack of clinical evidence on the BP lowering target often makes clinicians confused and unsure when they are handling with elevated BP in patients with acute severe stroke.

1.1 Potential harm caused by elevated BP in acute severe stroke

Elevated BP is one of the most common clinical manifestations in acute stroke, and it happens in more than 75% of stroke patients [1, 2]. An observational study on stroke indicated that every 10 mm Hg above 180 mm Hg of SBP raised 40% of neurological deterioration and 23% of poor outcome in stroke patients, whereas every 10 mm Hg below 180 mm Hg of SBP also raised 6% of neurological deterioration and 25% of poor outcome [3]. High BP may cause deterioration of cerebral edema, hemorrhagic transformation of infarction, cardiac complication, renal dysfunction, and many other serious conditions. However, lower BP level can reduce blood perfusion in multiple organs, especially in the brain, and exacerbate cerebral injury. Therefore, large increase and reduction in BP,
as well as rapid BP lowering, may raise the possibility of neurological deterioration and death. A rational and optimum strategy of BP management is required in acute stage of severe stroke.

1.2 Clinical researches on BP management in acute stroke

The management of BP in acute stroke has been a research hotspot for many years. However, the conclusions of these large clinical trials were conflicting, some supported BP lowering treatments, some opposed BP lowering treatments, and some had neutral results:

(1) Clinical trials that supported BP lowering: A German study published in 2003, the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) [4], assessed the safety of modest blood pressure reduction by candesartan cilexetil in the early treatment of stroke. ACCESS trial enrolled 342 stroke patients, and the target reduction of BP in the experimental group was 10% to 15% within 24 hours. This study found that the cumulative 12-month mortality and the number of vascular events differed significantly in favor of the candesartan cilexetil group, although there were no significant differences of BP between both groups in the first 7 days and in the subsequent 12 months of follow-up. The Controlling hypertension and hypotension immediately post-stroke (CHHIPS) study [5], published in 2009, included 179 stroke patients with SBP > 160 mm Hg. The target SBP in the experimental group was 145–155 mm Hg or a reduction in SBP of 15 mm Hg compared with SBP at randomization. CHHIPS study indicated that there was no evidence of early neurological deterioration with active treatment despite the significantly greater fall in SBP within the first 24 hours in this group compared with placebo, and there was no increase in serious adverse events reported with active treatment, but 3-month mortality was halved. However, both ACCESS and CHHIPS were not designed for severe stroke patients.
(2) Clinical trials that opposed BP lowering: The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST) [6], published in 2011, included 2029 stroke patients with SBP ≥ 140 mm Hg from nine north European countries. Patients were randomly allocated to candesartan or placebo for 7 days. SBP on day 7 was reduced 14% in candesartan group and 11% in placebo group from the baseline level. Results of SCAST study showed a higher risk of poor outcome in the candesartan group, suggesting a harmful effect. SCAST study also excluded patients with severe stroke.

(3) Clinical trials with neutral results: The Effects of antihypertensive treatment after acute stroke in the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) [7], published in 2010, included 763 patients who were taking antihypertensive drugs before the onset of stroke. Patients were randomly assigned to either continue or stop pre-existing antihypertensive drugs for two weeks. SBP was reduced 6% from the baseline level in the continuation of antihypertensive drugs group within two weeks. No substantial differences were observed between groups in rates of serious adverse events, 6-month mortality, or major cardiovascular events. COSSACS study excluded patients with impaired consciousness.

The CATIS Randomized Clinical Trial [8], published in 2014, included 4071 stroke patients with elevated SBP, and evaluated the effect of immediate BP reduction on the clinical outcomes of patients with acute ischemic stroke. The treatment intervention aimed at lowering SBP by 10% to 25% within the first 24 hours after randomization, achieving a SBP less than 140 mmHg and DBP less than 90 mmHg within 7 days, and maintaining this level of BP control during the remainder of hospitalization. SBP was reduced 12.7% in the antihypertensive treatment group and 7.2% in control group from the baseline level within 24 hours.
The stroke patients enrolled in CATIS trial were not severe, and they had a median NIHSS score of only 4 at the randomization.

The intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT) [9], published in 2008, included 346 patients with ICH within 6 hours of onset, and assessed the safety and efficiency of intensive BP reduction. Patients were randomly assigned to early intensive lowering of BP (target SBP 140 mm Hg) or standard guideline-based management of BP (target SBP 180 mm Hg). This study showed that early intensive BP-lowering treatment was clinically feasible, well tolerated, and seemed to reduce haematoma growth in ICH, and a large randomised trial is needed to define the effects on clinical outcomes. In order to investigate whether rapid lowering of elevated BP would improve the outcome in ICH patients, INTERACT 2 trial was conducted [10]. It was published in 2013 and included 2839 patients with acute ICH. The median baseline GCS in this study was 14, the median baseline NIHSS was 10, and the median baseline hematoma volume was 11 ml. SBP was reduced 22.3% in intensive BP lowering group and 14.5% in control group from the baseline level within 6 hours. Results of INTERACT 2 study showed that intensive lowering of BP did not result in a significant reduction in the rate of death or severe disability in ICH patients, and an ordinal analysis of mRS indicated improved functional outcomes with intensive lowering of BP.

The above clinical trials had conflicting conclusions about the efficacy of BP lowering treatment in patients with acute stroke. Moreover, the whole populations or the majority of the populations included in those large multicentre randomized controlled trials (RCTs) were not patients with severe stroke.

1.3 Trial design for BP management in acute severe stroke
Factors that contribute to raised BP in acute stroke are multifaceted, such as history of hypertension, stroke severity, pressure response to hospital admission, infarct area related to BP adjustment, and increased intracranial pressure [11]. Raised BP later falls into the following types: without antihypertensive medications BP declines spontaneously; with antihypertensive medications BP does not decline, declines modestly (10–15% from baseline), or intensively (\(\geq 20\%\) from baseline value) [12]. Considering the poor outcomes induced by excessive high BP, especially in severe stroke which is usually complicated with a larger increase in BP, a proper BP reduction treatment is reasonable and required theoretically. However, previous studies had conflicting conclusions about the target of BP reduction treatment in stroke patients, and prospective studies on the management of elevated BP in patients with acute severe stroke are lacking.

(1) Supporting data for selection of treatment target for Individualized BP lowering: For ICH patients, 2015 guidelines from American Heart Association / American Stroke Association (AHA/ASA) recommended that for patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe and can be effective for improving functional outcome [13]. However, the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial [14], published in 2016, included 1000 ICH patients and showed that the treatment of participants with ICH to achieve a target SBP of 110 to 139 mm Hg did not result in a lower rate of death or disability than standard reduction to a target of 140 to 179 mm Hg, and the rate of renal adverse events within 7 days after randomization was significantly higher in the intensive treatment group than in the standard treatment group. For AIS patients, the latest guidelines from
AHA/ASA [15] recommended that lowering BP by 15% within 24 hours of onset was reasonable. Besides, previously we performed a retrospective preliminary study in stroke patients admitted to neurological intensive care unit (NICU) in Xijing Hospital in the last three years. A total of 302 patients were included, and 209 of them had SBP reduced from baseline level within 24 hours of onset. We found that NICU mortality

Table 1 Characteristics, interventions, and outcomes of patients with SBP reduced by $>15\%$ and patients with SBP reduced by $\leq 15\%$

|                                | Patients with SBP reduced from baseline level (n = 209) | Patients with SBP reduced by $>15\%$ (n = 52) | Patients with SBP reduced by $\leq 15\%$ (n = 157) | $P$ 值 |
|--------------------------------|--------------------------------------------------------|-----------------------------------------------|--------------------------------------------------|-------|
| Age, year, median (IQR)        | 59 (48 - 71)                                           | 60 (50 - 73)                                  | 58 (47 - 70)                                     | 0.376 |
| Female (%)                     | 74 (35.4%)                                             | 23 (44.2%)                                    | 51 (32.5%)                                      | 0.125 |
| Stroke type (%)                | 148 (70.8%)                                            | 37 (71.2%)                                    | 111 (70.7%)                                     | 0.939 |
| AIS                             | 148 (70.8%)                                            | 37 (71.2%)                                    | 111 (70.7%)                                     |       |
| ICH                             | 55 (26.3%)                                             | 14 (26.9%)                                    | 41 (26.1%)                                      |       |
| SAH                             | 5 (2.4%)                                               | 1 (1.9%)                                      | 4 (2.5%)                                        |       |
| CVT                             | 1 (0.5%)                                               | 0 (0.0%)                                      | 1 (0.6%)                                        |       |
| Prior hypertension (%)          | 114 (54.5%)                                            | 38 (73.1%)                                    | 76 (48.4%)                                      | 0.002 |
| Prior diabetes (%)              | 37 (17.7%)                                             | 9 (17.3%)                                     | 28 (17.8%)                                      | 0.931 |
| Prior CHD (%)                   | 62 (29.7%)                                             | 13 (25.0%)                                    | 49 (31.2%)                                      | 0.395 |
| Time from onset to NICU admission, hr, median (IQR) | 70 (24 - 96)                                           | 48 (13 - 72)                                  | 70 (24 - 113)                                   | 0.011 |
| NIHSS on admission, median (IQR) | 12 (6 - 19)                                            | 11 (6 - 22)                                   | 12 (7 - 19)                                     | 0.847 |
| GCS on admission, median (IQR)  | 13 (9 - 14)                                            | 14 (8 - 14)                                   | 13 (9 - 14)                                     | 0.869 |
| Body temperature, $\bar{x}\pm$s | 37.0±0.7                                               | 37.1±0.9                                      | 36.9±0.6                                        | 0.149 |
| Heart rate on admission, $\bar{x}\pm$s | 80.4±20.3                                              | 82.3±25.4                                     | 79.8±18.5                                       | 0.449 |
| SBP on admission, mm Hg, $\bar{x}\pm$s | 154.8±25.6                                            | 175.1±25.0                                    | 148.1±22.1                                     | <0.001|
| Any BP lowering treatments (%)  | 72 (34.4%)                                             | 27 (51.9%)                                    | 45 (28.7%)                                      | 0.002 |
| Intravenous BP lowering treatment, (%) | 45 (21.5%)                                            | 19 (36.5%)                                    | 26 (16.6%)                                      | 0.002 |
| Length of NICU stay, day, median (IQR) | 10 (6 - 15)                                           | 8 (4 - 15)                                    | 10 (6 - 15)                                     | 0.426 |
| Death during NICU stay (%)      | 16 (7.7%)                                              | 8 (15.4%)                                     | 8 (5.1%)                                        | 0.016 |
was significantly higher in patients with SBP reduced by $> 15\%$ than those with SBP reduced by $\leq 15\%$, and the rate of major disability at hospital discharge was also higher in patients with SBP reduced by $> 15\%$ than those with SBP reduced by $\leq 15\%$ (table 1, figure 1). Considering that a fixed target of BP lowering might not be proper for stroke patients with different severities, based on the previous studies and our retrospective study, we proposed an Individualized target, lowering BP by 10%-15% from the admission level, for patients with acute severe stroke. We aimed to investigate the effect of the Individualized BP lowering treatment on the outcomes of severe stroke compared with guideline-recommended BP lowering treatment, in order to provide clinical evidence for the BP management in patients with severe stroke.

(2) Supporting data for selection of treatment target for guideline-recommended Individualized BP lowering: 2015 Chinese guidelines for the management of patients with severe stroke [16] stated that so far there
was no sufficient clinical evidence to guide the management of elevated BP in patients with severe stroke. The latest Chinese guidelines for the early management of patients with AIS [17] recommended the use of hypertensive therapy when SBP is > 200 mmHg. 2006 European guidelines for the management of ICH [18] recommended the use of hypertensive therapy when SBP is ≥180 mmHg. 1999 Guidelines for the early management of ICH proposed by AHA/ASA [19] recommended to defer antihypertensive therapy in patients with SBP < 180 mmHg. 2007 Update of guidelines for the early management of ICH proposed by AHA/ASA [20] recommended to reduce BP when SBP is > 180 mm Hg or MAP is > 130 mm Hg. After the publication of INTERACT II [10], European Stroke Organization (ESO) and AHA/ASA updated the guidelines for ICH in 2014 [21] and 2015 [13] respectively, stating that in acute ICH within 6 hours of onset, intensive BP reduction (systolic target < 140 mm Hg in < 1 hour) is safe and may be superior to a systolic target < 180 mm Hg. However, studies investigating the efficacy and safety of rapid intensive BP reduction in patients with severe stroke are lacking. Besides, ATACH-2 trial [14], published in 2016, included 1000 ICH patients and showed that the rate of renal adverse events within 7 days after randomization was significantly higher in the intensive BP reduction group than in the standard treatment group, and the treatment to achieve a target SBP of 110 to 139 mm Hg did not result in a lower rate of death or disability than standard reduction to a target of 140 to 179 mm Hg. Therefore, the treatment target in the control group for patients with AIS is 200 mm Hg based on the Chinese guidelines, and the treatment target in the control group for patients with ICH is 180 mm Hg based on the Chinese, American and European guidelines published before 2014.
We aim to cooperate with tertiary hospitals in Shaanxi province to conduct a multicentre randomized controlled trial (RCT) called CHASE, dedicated to investigate whether Individualized antihypertensive treatment would lower the mortality and major disability in patients with severe stroke, in order to guide the optimum choice of a target for BP and improve the outcomes and quality of life.

2. STUDY OBJECTIVES

2.1 Primary objective

To determine the therapeutic benefit of Individualized BP lowering treatment (10–15% reduction from admission level) compared with guideline-recommended BP lowering treatment (AIS: SBP ≤ 200 mmHg; ICH: SBP ≤ 180 mmHg) in reducing the proportion of severe stroke patients with a poor outcome (mRS ≥ 3) at day 90 of enrollment.

2.2 Key secondary objective

To determine the therapeutic benefit of Individualized BP lowering treatment relative to guideline-recommended BP lowering treatment in reducing the proportion of severe stroke patients with a poor outcome (mRS ≥ 3) at hospital discharge.

2.3 Other secondary objectives

To determine the effects of the treatment on disability (evaluated by NIHSS, GCS, and Barthel index) at hospital discharge and the ability of activities of daily living at day 90 of enrollment (evaluated by Barthel index).

3. STUDY DESIGN

3.1 Overall design
This study has a multicentre, randomized, controlled, single-blind design. Patients will be randomized to two different arms: (1) intervention group (Individualized BP lowering), with an Individualized target for BP lowering during the first week of hospitalization (10–15% reduction from admission level); and (2) control group (guideline-recommended BP lowering), with a fixed target recommended by the guideline for BP lowering during the first week of hospitalization (AIS: SBP ≤ 200 mmHg; ICH: SBP ≤ 180 mmHg). The CHASE trial is led by Xijing Hospital and involves a total of 26 tertiary regional medical centers in Shaanxi province, China. The CHASE will enroll 500 patients with acute severe stroke.

3.2 Clinical site personnel eligibility

All the participating sites should be tertiary hospitals, possess an adequate nurse-to-patient ratio, have a multidisciplinary stroke team and treatment protocols for common complications of stroke, be able to provide standard intensive care, and have rich experience in the management of severe stroke. All CHASE investigators are required to be trained in the protocol, Good Clinical Practice (GCP), and use of the GCS, NIHSS, Barthel index, and mRS if they had no recent certifications.

3.3 Blinding and unblinding

The participants are blind to the grouping results; the investigators are informed of the grouping results because they have to follow a specified strategy of BP management. In each research site, outcomes at hospital discharge and at day 90 of enrollment are assessed independently by a qualified researcher who does not participate in the treatment and is blind to the grouping results.
4. ETHICAL ISSUES

The CHASE study will be conducted according to Good Clinical Practice guidelines and the World Medical Association’s Declaration of Helsinki.

4.1 Institutional ethics committee approval

Based on Principles for ethical review of drug clinical trials formulated by China Food and Drug Administration, the ethics committee of the leading research site is responsible for the ethic censorship of the multicentre clinical trial. The ethics committee of Xijing Hospital, which is the leading research site in this trial, approved the scientificity and ethical rationality of this study. The Principal Investigator (PI) of each participating site is obliged to report any amendments in the protocol, serious adverse events (SAE), and progress of the trial to their Hospital Research Ethics Committee.

4.2 Consent

A signed consent form must be obtained from the participant. If the patient is not fully competent to give informed consent, for example because of a reduced level of consciousness or confusion, the patient’s next of kin or surrogate will be approached to provide informed consent on his or her behalf. An information statement will be given to the patient, and the responsible clinician will explain to the patient about the condition of illness, the purpose and meaning of the study, study protocol, possible benefits and risks, compensation for harms caused by the study, and confidentiality principles. Investigators are obliged to answer all the questions about this study raised by the patient or his/her surrogate. Every participant or their legally authorized representative has the right to withdraw voluntarily from the study at any time for any reason without
prejudice to his/her future medical care by the physician or at the institution. The collected data of the patient who has withdrawn the consent will not be used in any analysis in this study.

4.3 Confidentiality and privacy

All study investigators at the clinical sites have the responsibility to protect all personal identity and medical information at all time. All the medical records of study participants, such as consents, case report forms (CRF), and reports of laboratory tests, must be securely stored. Only de-identified data will be submitted to the Statistical Analysis Centre. All digital data will be password-protected and stored in a firewall-protected secure environment. The trial sponsor, PI, Ethics Committees, Health and Family Planning Commissions are allowed to refer to medical records, in the course of monitoring data quality and adherence to the study protocol.

5. SELECTION AND ENROLLMENT OF SUBJECTS

5.1 Inclusion criteria

① Age $\geq$ 18 years.

② The randomly assigned BP-lowering regimen is able to be commenced within 72 h after the onset of stroke (ischemic or hemorrhagic), confirmed by a CT or MRI scan of the brain (if the precise timing of the onset of symptoms or signs of the qualifying event is unknown, then the time of onset will be taken as the last time the patient was known to be well). Patients with ICH whilst on antithrombotic treatment (antiplatelet agents or anticoagulation), and patients with prior stroke are eligible.

③ GCS on admission $\leq$ 12 or NIHSS on admission $\geq$ 11.
④ There are at least two SBP measurements of $\geq 150$ and $\leq 210$ mmHg, recorded $\geq 5$ min apart (patients with an initial SBP $< 150$ mmHg may be randomized when the SBP fulfills entry criteria on rechecking up to 72 hours after the onset of stroke.

⑤ Written informed consent is able to be obtained directly from the patient or an appropriate surrogate, based on local ethics committee recommendations.

5.2 Exclusion criteria

① Patients who have received thrombolytic therapy, embolectomy, or decompressive craniectomy for the current stroke.

② Patients with subarachnoid hemorrhage.

③ Known definite contraindication to acute BP lowering (e.g. known severe carotid, vertebral, or cerebral arterial stenosis, Moyamoya disease or Takayasu’s arteritis, high grade stenotic valvular heart disease).

④ Secondary to a structural abnormality in the brain (e.g. an arteriovenous malformation, intracranial aneurysm, tumor, or trauma).

⑤ unstable vital signs and requiring the use of vasoactive agents.

⑥ Known existing dementia or prestrike disability (e.g. score 3–5 on the modified Rankin scale).

⑦ Concomitant medical illness that would interfere with the outcome assessments and/or follow-up, such as:

1) Advanced cancer;

2) Severe pulmonary dysfunction (forced expiratory volume in 1 second $< 50\%$);

3) Severe cardiac dysfunction (ejection fraction $\leq 50\%$);

4) Severe hepatic failure (Child-Pugh score $\geq 7$);
5) Severe renal failure (glomerular filtration rate $\leq 30$ mL/min or serum creatinine $\geq 4$ mg/dL);

8) Patients who are currently participating in other investigational trials.

9) Patients who are considered to have a high likelihood of not adhering to the study treatment or the follow-up regimen.

5.3 Study enrollment procedures

(1) Screening of Potential Subjects

Emergency department (ED) team will do the initial and rough screening, because all the patients with severe stroke are sent to the ED first. All subjects aged 18 years or older who present with clinical symptoms of acute stroke are screened for study eligibility. If ED personnel suspect an acute stroke, they should immediately call a stroke team member who participates in this study to the ED to evaluate the patient.

(2) Screening/Baseline Evaluations

After receiving report from ED, study investigators should arrive to the ED in an expeditious manner to evaluate the patient and determine potential study eligibility.

① Determination of time of onset

Stroke onset is defined as time of first symptoms or signs of neurological deficits. If stroke started during sleep, onset is recorded as time the subject was last known to be intact.

② Assessment of NIHSS and GCS score at the time of recruitment

The initial recruitment is based on the initial NIHSS and GCS. NIHSS is a 42-point scale, where higher scores indicate more severe neurological deficits. GCS is a 15-point scale (3 - 15), where lower scores indicate lower levels of consciousness. Intubated patients are rated none verbal
response in the verbal score of GCS. Stroke patients presenting with a NIHSS score of \( \geq 11 \) or a GCS score of \( \leq 12 \) are potential eligible subjects.

③ Measurement of BP

ED personnel must take two repeat measurements of BP at least 5 minutes apart using manual or automated cuff measurements at mid-biceps level. The mean of two measurements is recorded and used for the screening. The arm must also be horizontal at the level of the heart as denoted by the midsternal level in a supported position. All measurements must be recorded with subjects in recumbent position and with head of bed elevation not exceeding 15°.

④ Laboratory measurements and other procedures

The following pre-treatment tests and imaging should be measured as part of routine care upon ED presentation: routine blood tests, hepatorenal function routine tests, routine urine tests, electrocardiography (ECG), brain CT or MRI. When the complication of respiratory, cardiac, hepatic, or renal failure is suspected, forced expiratory volume in 1 second, ejection fraction, Child-Pugh score, or glomerular filtration rate should be assessed respectively.

(3) Process after screening

As soon as eligibility is confirmed, the subject or the legally authorized representative is asked to provide informed consent. A signed and dated informed consent is required prior to randomization. Any patient screened, but not randomized, is tracked on the screen failure log.

6. RANDOMIZATION

As soon as informed consent is provided, the investigator should acquire the result of randomization. A secure website (http://traillogin.applinzi.com) will be used to perform the centralized
randomization (computerized random numbers). Patients will be randomized into one of the two intervention arms (1:1): Individualized BP lowering group and guideline-recommended BP lowering group.

7. ALLOCATED STUDY TREATMENTS

As soon as the result of randomization is acquired, the allocated BP lowering treatment should be administered.

7.1 Individualized BP-lowering group

In patients who are assigned to receive Individualized regimen of BP reduction, antihypertensive treatments are to be initiated to reduce SBP to a range of 130–180 mmHg and by 10–15% from the admission level within 2 hours after randomization. SBP in the Individualized BP-lowering group is to be maintained around the target level for one week with or without the use of hypertensive agents. Table 2 presents the detailed management of BP in the first week after randomization.

7.2 Guideline-recommended BP-lowering group

In participants who were assigned to receive guideline-recommended treatment, antihypertensive agents are to be administered if the SBP is > 200 mmHg in AIS or the SBP is > 180 mmHg in ICH. The goal is to maintain the SBP < 200 mmHg in AIS and < 180 mmHg in ICH for one week.
Table 1  Management of blood pressure during the first week after randomization

| SBP level | Approaches |
|-----------|------------|
| Individualized BP lowering group | |
| Above the range* | Increase the dose of AHD, or use other stronger AHDs |
| In the range* | Maintain the regimen |
| Below the range* and above 100 mm Hg | Reduce the dose of AHD, or withdraw AHD |
| Below 100 mm Hg | Use vasopressor agents |
| Guideline-recommended BP lowering group | |
| Above 200 mm Hg in AIS | Increase the dose of AHD, or use other stronger AHDs |
| Above 180 mm Hg in ICH | |
| Below 200 and above 100 mm Hg in AIS | Use the least dose of AHD to keep SBP not higher than 200 mm Hg in AIS, 180 mm Hg in ICH |
| Below 180 and above 100 mm Hg in ICH | Use vasopressor agents |
| Below 100 mm Hg | |

*10%-15% reduction from admission level and between 130-180 mm Hg. AHD antihypertensive drug, AIS Acute ischemic stroke, BP blood pressure, ICH intracerebral hemorrhage, SBP systolic blood pressure.

7.3 Selection of antihypertensive drugs

As the trial is an assessment of BP management policies, there is some flexibility in the use of particular BP lowering agents to achieve BP targets. The selection of antihypertensive agents is based on the local availability; no specific agent is stipulated (both intravenous and oral agents can be used).

7.4 BP measuring and monitoring

Automatic BP cuff monitor is used for BP measuring and monitoring at mid-biceps level of the unaffected arm (right arm is chosen when both arms are affected or unaffected). All measurements are to be recorded with subjects in a recumbent position and with elevation of the head of the bed not exceeding 15°. BP measurements are to be taken on the following schedule:
① Every 5 minutes for the first 15 minutes after intravenous antihypertensive agent is started. Every 15 minutes for the remainder of the first hour, unless the dose is being adjusted (see next bullet point).

② Every 5 to 15 minutes during dose adjustments of intravenous antihypertensive agent.

③ At least every 30 minutes while receiving intravenous antihypertensive agent.

④ More frequent measurements are recommended if prominent BP changes are observed as determined by the treating physician.

⑤ Besides the above conditions, BP measurements are required to take according to the following protocol: During the first 24 hours after randomization, BP is recorded every 2 hours. On days 2 and 3, BP is recorded every 4 hours. During days 4–7, BP is recorded every 8 hours. On the day of hospital discharge, BP at 08:00 a.m. is recorded. The timetable of BP measurement is in the CRF. Three measurements of BP are required for each time point and the average is recorded.

7.5 Previous use of antihypertensive therapy in both groups

Patients who have been taking antihypertensive therapy prior to randomization will have their usual medication continued when oral administration is possible, unless the agents are considered to be inappropriate by the responsible physician (eg poor compliance, intolerance, or adverse events).

7.6 BP management after Day 7 or hospital discharge
The target SBP after Day 7 or hospital discharge is <140 mmHg, as per guideline-based recommendations for high risk vascular disease patients.

8. DISCONTINUATION OF ALLOCATED BP MANAGEMENT POLICY

The BP management in either group should be discontinued if any of the following occur:

① SAEs, which are in the opinion of the investigator, related to the trial protocol.

② The investigator feels it is in the subject’s best interest.

The investigator must not deviate from the protocol except the above situation occurs or the patient/surrogate chooses to withdraw consent to participation in the study. Follow-up data will be collected for all treated subjects except those who specifically withdraw consent for release of such information.

9. GENERAL PRINCIPLES OF MONITORING AND TREATMENT

9.1 Basic physiological function monitoring

The patient's heart rate and oxygen saturation are to be continuously monitored. The respiratory rate is to be measured hourly. Monitoring for BP refers to 7.4.

9.2 Neurological evaluation
A comprehensive neurologic examination must be performed at 2-hour intervals throughout the treatment period in other to detect neurological deterioration.

9.3 Definition and management of neurological deterioration

Neurological deterioration is defined as a decrease of $\geq 2$ on GCS OR increase of $\geq 4$ points on NIHSS (from baseline) that is not related to sedation/hypnotic use and is sustained for at least 8 hours. After neurological deterioration is detected, related monitoring and management must be performed based on 2015 Chinese Guidelines for the early management of patients with severe stroke [16].

9.4 Other monitoring and management

During the study treatment and follow-up period, the standard management of acute severe stroke patients will be given according to 2015 Chinese Guidelines for the early management of patients with severe stroke [16]. Appropriate neuroimaging and neurophysiology examinations should be performed according to the patient’s condition. Efforts should be made to avoid, detect, and manage complications of stroke.

10. STUDY OUTCOMES

10.1 Primary outcomes

The primary outcome measurement is the proportion of participants with a poor outcome at day 90 of enrollment. Poor outcome is defined as major disability (unable to live independently, mRS $\geq 3$, see APPENDIX) or all-cause death.

10.2 Secondary outcomes
Key secondary outcome: will be the proportion of participants with a poor outcome (mRS $\geq 3$) at hospital discharge.

Other secondary outcomes:
① Neurological deficits at hospital discharge, defined by NIHSS (see APPENDIX);
② Level of consciousness at hospital discharge, defined by GCS (see APPENDIX);
③ Ability of activities of daily living at hospital discharge, defined by Barthel Index (see APPENDIX);
④ Ability of activities of daily living at day 90 of enrollment, defined by Barthel Index (see APPENDIX);

10.3 Safety outcome

The safety outcome will be the proportion of subjects who experienced any treatment-related SAEs during the first 7 days from randomization. The adjudication of site-reported relatedness of an SAE to treatment is performed by the Quality Control and Assurance Committee (QCAC). Moreover, neurological deterioration identified within 24 hours of randomization is a SAE. Neurological deterioration is defined as a 2 or more point decrease in the GCS or 4 or more point increase in the NIHSS from baseline measurements.

11. DATA COLLECTION AND FOLLOW-UP

At the time point of baseline screening, demographics, subtypes of stroke, medical history (e.g. AIS, ICH, coronary event, diabetes mellitus, and hypertension), physical examination, clinical scores (NIHSS, GCS, Barthel index, mRS), and vital signs are recorded. On day 1 and day 7, routine laboratory tests for stroke patients are assessed,
including blood routine, liver and renal function test, serum lipid, fasting glucose, urine routine, and electrocardiography. Co-morbidities on the day of screening and hospital discharge are recorded. Clinical scores on day 7, the day of hospital discharge, and day 90 are collected. During the whole hospitalization, BP, vital signs, and adverse events (AEs) are monitored, and concomitant treatments are documented. Table 3 presents all the variables measured at each time point of the study.

Table 3 Timing and content of study assessments

| Items                        | Day of Enrollment |
|------------------------------|-------------------|
|                              | Screening 1 2 3 4 5 6 7 HD 90 |
| Written Informed Consent     | ●                 |
| Inclusion & exclusion criteria | ●               |
| Demographics                 | ●                 |
| Medical History              | ●                 |
| Physical examination         | ●                 |
| Blood pressure monitoring    | ● ● ● ● ● ● ● ● ● |
| Laboratory tests             | ●                 |
| NIHSS & GCS                  | ●                 |
| Barthel Index & mRS          | ● ● ● ● ● ● ● ● ● |
| Vital signs monitoring       | ● ● ● ● ● ● ● ● ● |
| Comorbidities                | ●                 |
| Adverse events               | ● ● ● ● ● ● ● ● ● |
| Use of antihypertensive agents| ● ● ● ● ● ● ● ● ● |
| Concomitant therapies        | ● ● ● ● ● ● ● ● ● |

HD hospital discharge, GCS Glasgow Coma Scale, NIHSS National Institute of Health stroke scale, mRS modified Rankin Scale.

The 90-day outcomes are evaluated via telephone interviews at day 90 of enrollment (a delay of up to three days is acceptable). In cases when the patient is incapable to complete the interview, the first choice for a proxy is the spouse/live-in companion. Clinical scores at hospital discharge and on day 90 of enrollment will be assessed independently by
a trained research assistant at each participating site who is blind to the grouping results and does not participate in the treatment.

12. TREATMENT DEVIATIONS AND FAILURES

12.1 Inability to initiate allocated treatment

A subject may meet eligibility requirements and be randomized, and might be unable to proceed to the study treatment due to emergencies such as cardiac arrest, respiratory failure, severe hypotension, etc. Events like these may render the subject no longer medically fit to receive allocated treatment as determined by the site investigator or treating physician. Such events are expected to be uncommon. However, if the subject is randomized, he/she must complete the required study assessments and procedures through Day 90 unless the subject withdraws consent prior to that point.

12.2 Treatment failure

Spontaneous reduction in SBP in the guideline-recommended BP lowering group may result in their SBP entering the SBP range of the Individualized BP lowering group (10–15% reduction from admission level). Similarly, SBP may drop less than 10% from admission level even after an intensive treatment in the Individualized BP lowering group. If the goals of the assigned treatment cannot be met as defined earlier, the subject is considered a treatment failure but is considered in the original allocation group per the Intention To Treat (ITT) principle.

12.3 Deviations from the protocol

Investigators should not deviate from the protocol. A deviation from the protocol is defined when the subject has not received the allocated BP management strategy except the subject meets the discontinuation of allocated BP management policy (see section 8) or has medical
emergencies which render the subject no longer medically fit to receive allocated treatment. A deviation from the protocol will be determined by the QCAC. Patients with deviations from the protocol will be excluded from the study.

13. LOST TO FOLLOW UP

The 90-day outcomes are evaluated via telephone interviews at day 90 of enrollment (a delay of up to three days is acceptable). The subject is coded as lost to follow-up in the End-of-Study CRF when at least five attempts have been made to contact the patient over the course of two weeks and all methods have been tried and have failed.

14. MONITORING OF ADVERSE EVENTS

14.1 Definitions of adverse and serious adverse events

An adverse event is defined as any untoward event or complication that was not previously identified, or that occurs with greater frequency or severity than previously reported. The event occurs during the protocol intervention or during the follow-up period, and may or may not be considered related to the protocol intervention. As defined by the WHO International Drug Monitoring Center (1994), a SAE is any untoward medical occurrence that:

1. Results in death;

2. Is life threatening in the opinion of the attending clinician (i.e. the patient was at risk of death at the time of the event; it does not refer to an event that might hypothetically have caused death had it been more severe);
③ Requires inpatient hospitalization or prolongation of existing hospitalization;

④ Results in persistent or significant disability or incapacity;

⑤ Is an important medical event in the opinion of the attending clinician that is not immediately life-threatening and does not result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

14.2 Recording and reporting

All AEs, including SAEs, deaths and abnormal and clinically significant laboratory values, occurring to the subject from enrollment through Day 7 or hospital discharge (whichever occurs first) are recorded on the case report form. After Day 7 or discharge, only SAEs are collected and followed. For each event, date of onset, duration, severity, and relationship to the prescribed drug regimen are recorded. All SAEs should be reported to PI and the QCAC within 24 hours or as soon as the event is recognized. The time when a SAE has been reported, the approach how a SAE has been reported (via a written document, telephone, or fax), the person to whom a SAE has been reported, and the management and follow up of the reported SAE must be recorded.

14.3 Management and follow up

The QCAC will closely monitor all SAEs for any relationship to the study procedures and protocol and clustering of events at a particular site. The QCAC will submit all SAEs to the independent Statistical Analysis Centre for review. The protocol will be amended or the study will be stopped earlier if an excess of particular SAEs appear to be protocol related. The managements of SAEs include no action taken, dose adjustment, suspension or termination of the allocated intervention, administration of
concomitant drugs, inpatient hospitalization or prolongation of existing hospitalization.

15. QUALITY CONTROL AND ASSURANCE

This study will be conducted in accordance with the guidelines of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP), and all relevant national and local regulations.

15.1 Oversight organization

The Quality Control and Assurance Committee (QCAC) is responsible for the assessment of site investigator clinical care and SAE review and adjudication for site-reported relatedness of an SAE to treatment and for the duration of the trial (if necessary).

15.2 Training of the study team

Training sessions about the protocol and related clinical scores will be held for all the research investigators before the commencement of CHASE study, in order to make sure the protocol will be understood correctly.

15.3 Monitoring of participating centers

The PI in each research site takes charge of quality control by supervising the conduct of the trial in accordance with the prespecified protocol, applicable guidelines and regulations. All participating sites will have monitoring visits via video conferencing after every ten patients are randomized, to verify consent, eligibility criteria, anomalous data, and reported serious AEs

16. STATISTICAL CONSIDERATIONS

16.1 Sample size
The sample size was set at 500 to provide at least 80% power to detect a 12% absolute risk reduction (15% relative risk reduction) in the primary outcome for patients in the Individualized BP-lowering group compared to those in the guideline-recommended control group, using a two-sided significance test with 5% type I error. The following assumptions were made: a primary outcome of 75% in the control group will be reduced to 63% in the Individualized group; and there will be 8% non-adherence to the treatment protocol and loss to follow-up. The 75% incidence of unfavorable 90-day outcome is obtained from one Chinese study and one Swiss study on severe stroke [22, 23]. The 8% non-adherence rate and the 15% relative risk reduction in primary outcome are obtained from the INTERACT2 study and ATACH2 study which were designed to compare the effects of two different BP lowering strategies in acute stroke patients [10, 14].

16.2 Data analysis

16.2.1 Outcomes

Under the ITT principle, all patients who are randomized are included in the analysis of the original allocation group per the Intention To Treat (ITT) principle. Baseline and demographic characteristics such as gender, age, stroke type, medical history, GCS, NIHSS, SBP, etc, will be summarized by treatment group to assess comparability of treatment groups. The primary endpoint of death or dependency at 90 days will be analyzed by means of a chi-square test. Categorical secondary outcomes will preferably be analyzed by means of a Chi-square, and continuous variable will be analyzed using Student's t test or Mann-Whitney U test (whichever is proper). The proportions of SAEs will be analyzed by means of a chi-square test. Univariate and multivariate logistic regression analyses will be used to analyze the primary and key secondary outcomes and estimate adjusted odds ratios and associated 95% confidential
intervals. Subgroup analyses will be carried out in patients with different ages (≥65 years or <65), different stroke types (ICH or AIS), different SBP levels on admission (<180 or ≥180 mmHg), with or without history of hypertension, irrespective of whether there is a significant treatment effect on the primary outcome. Two-sided p values ≤ 0.05 will be considered significant. Statistical analysis will be performed with SPSS version 22 software (SPSS Inc., Chicago, IL, USA).

16.2.2 Handling of Missing Outcome Data

The multiple imputation method will be used as the primary approach. This is generally considered the least biased method since it incorporates the uncertainty to the imputed value. As a sensitivity analysis, we plan to impute the missing primary outcome data by assuming the missing mRS score at Day 90 to be unfavorable. If the treatment effect is robust, we expect analysis using these imputation methods would yield similar inferences, particularly if the missing data are minimal (<5%).

17. ORGANIZATION

This study is funded by the Shaanxi Province Key Research and Development Project (2017ZDCXL-SF-02-02), led by Xijing Hospital of Fourth Military Medical University, and conducted by 26 regional central hospitals in Shaanxi Province.

17.1 Executive Committee (EC)

Overall responsibility includes the execution of the study design, protocol, data collection and analysis plan, as well as publications. The EC has the right to appoint new members and co-opt others to add to the integrity of the conduct of the study and analyses. The members of EC are as follows:
Wen Jiang (Chair, PI), Xijing Hospital, Fourth Military Medical University, Shaanxi Stroke Association, The Shaanxi Cerebrovascular Disease Clinical Research Centrc, Xi’an, China  
Li Li, Xijing Hospital, Fourth Military Medical University, The Shaanxi Cerebrovascular Disease Clinical Research Centrc, Xi’an, China  
Hongzeng Li, Tangdu Hospital, Fourth Military Medical University, Xi’an, China  
Changhu Xue, Xianyang Central Hospital, Xianyang, China  
Chaohui Song, Tongchuan Mining Hospital, Tongchuan, China  
Ding’an Li, Hanzhong Central Hospital, Hanzhong, China  
Fang Yang, Xijing Hospital, Fourth Military Medical University, Xi’an, China  
Feng Fu, Shaanxi 215 Hospital, Xianyang, China  
Hua Lv, Shaanxi Provincial People’s Hospital, Xi’an, China  
Jun Zhou, Shangluo Central Hospital, Shangluo, China  
Kangjun Wang, Hanzhong Central Hospital, Hanzhong, China  
Wei Zhang, Tangdu Hospital, Fourth Military Medical University, Xi’an, China  
Yi Liu, Ankang Central Hospital, Ankang, China  
Xiangjun Yuan, Weinan Central Hospital, Weinan, China  
Xiaocheng Wang, Yulin No.2 Hospital, Yulin, China  
Xinlai Wang, Xi’an Central Hospital, Xi’an, China  
Yongqiang Li, Baoji Central Hospital, Baoji, China

17.2 Quality Control and Assurance Committee (QCAC)

Overall responsibility includes monitoring of the execution of the study, regular quality inspection in participating sites, monitoring of blinded response variables and SAEs. When early dramatic benefits or
potential harmful effects have been shown, the QCAC will report to the EC on recommendations to continue or temporarily halt recruitment to the study. The members of QCAC are as follows:

Fang Yang, Xijing Hospital, Fourth Military Medical University, Xi’an, China
Wen Li, Xijing Hospital, Fourth Military Medical University, Xi’an, China
Yuan Che, Shaanxi Stroke Association, Xi’an, China
Xiai Yang, Ankang Central Hospital, Ankang, China

17.3 Statistical Analysis Centre
Overall responsibility is to make statistical analysis plan and conduct statistical analysis. The members of Statistical Analysis Centre are as follows:

Lei Shang, Department of Health Statistics of The Fourth Military Medical University, Xi'an, China
Jingjing Zhao, Xijing Hospital, Fourth Military Medical University, Xi’an, China
Qiong Gao, Xijing Hospital, Fourth Military Medical University, Xi’an, China

17.4 Participating Centers
A total of 26 hospitals will participate in this study:

Xijing Hospital: Wen Jiang, Fang Yang, Fang Yuan, Li Li, Lijie Bi, Lijuan Liu, Jingjing Zhao, Mengmeng Hu, Jingya Wei, Gengyao Hu, Yuanfang Zhao

Shaanxi 215 Hospital: Feng Fu, Dingfeng Wu, Jie Yang, Xiaoning Li, Haiyan Zhai, Fupeng Fang, Lifang Zhu, Lin Li, Min Zhang

521 Hospital of NORINCO Group: Zhuanhui Li, Ni Zhang, Xing Wang, Xin Ma, Yuanyuan Wei, Li Xue, Fei Yan, Changfu
Cui
Ankang Central Hospital: Yi Liu, Tao Chen, Jiaming Gong,
Xingsheng Wang, Guixi Shen, Yan Li, Xingjun Zou,
Derong Hu, Xiang Qu, Yun Chen, Xue Zhao, Xiaomei
Yang, Quanwei Jin, Jianghong Ma
Baoji Central Hospital: Yongqiang Li, Junwen Wang, Dong Luo,
Lijun Wang
First Affiliated Hospital Xi'an Jiaotong University: Jin Qiao,
Guogang Luo, Kang Huo, Chen Chen, Dan Zhu
Hanzhong Central Hospital: Ding’an Li, Kangjun Wang, Zheng Chen,
Heng Wang, Ruirui Bai, Rong Chen, Jing Li, Chang
Chai, Baoxia Tian, Feng He, Ying Yang, Senling Zhang,
Nan Yang, Qiang Wu, Jian Li, Benkui Li, Jian Wang
Tangdu Hospital: Wei Zhang, Hongzeng Li, Peng Guo, Chuan Li,
Min Zhang, Jinjin Shen, Rong Yan
Tongchuan Mining Hospital: Chaohui Song, Hongyan Zhao, Zhongyi
Li, Yuan Shao, Doumin Li
Tongchuan People's Hospital: Chengkai Wang, Changpeng Song,
Siwen Chen, Zhemin Qiao, Shuang Lu, Qianmeng Ren,
Ruixiu Wang, Yanhua Niu, Longfei Zhang, Xiuxia Cai,
Xueyan Zhang
The First Affiliated Hospital of Xi'an Medical University: Bei Zhang,
Shijun Zhang, Yulan Bai, Yanan Bai, Fangfang Yu, Wei
Wei, Tong Yuan, Li Xue
Shaanxi Provincial People's Hospital: Hua Lv, Wei Di, Wenxiu
Wang, Le Wang, Qiang Zhang, Xiansong Cheng, Jiankuan
Shi, Ni Ma, Jingyan Li
Shangluo Central Hospital: Jun Zhou, Juan Li, Yuting Ji, Baodian Lei,
Fei Qu
Weinan Central Hospital: Xiangjun Yuan, Jirong Liu, Xiaohong Wei, Huijuan Shang, Xiaodong Yuan, Ying Li, Jing Li, Yanling Song, Xiaorong Yang, Ke Lei, Huimin Cui
Xi'an 141 Hospital: Qiwu Liu, Dongjing Zhu, Yanhui Dong, Lihe Yin, Jialing Li
Xi'an Central Hospital: Xinlai Wang, Hui Lei, Zhiqin Liu, Yi Jiang, Gemin Zhu, Yu’e Yan, Yanzhi Zhou
Xi'an Gaoxin Hospital: Yi Jia, Tao Wu, Saibing Liu, Jingmei Chen
Xi'an No.3 Hospital: Mingze Chang, Yanling Yin, Lu Zhao, Haojun Ma, Meng Jiao
Xi'an No.4 Hospital: Aixiang Zhang, Tao Lei, Juan Li, Gang Guo, Qiubo Qiao, Man Wang
Xi'an No.9 Hospital: Junxian Gao, Xiaolin Wu, Qiang Ma, Chao Wei, Zheng Fang, Fei Chen
Xi'an Traditional Chinese Medicine Hospital: Hai lin, Gang Liu, Fang Mi, Yan Wei, Shunqing Lu, Guoyan Fang
Xi'an XD Group Hospital: Jianbo He, Huiqi Li, Qiang Guo, Hang Su, Jiemin Zhai, Li Yao, Juanjuan Sha, Heng Zhang, Liang Shi, Juanli Zhang, Haiguo Wang
Xianyang Central Hospital: Changhu Xue, Jun Wu, Tao Han, Ting Fu, Jie Zhang, Tingting Li, Gaowen Liu, Lin Su
Yan'an University Affiliated Hospital: Yongcai Qu, Li Ma, Xuejun Gao, Yingying Liu, Xibin Gao, Yajun Gao, Junyan Yang
Yulin No.1 Hospital: Yaling Ma, Yingjuan Hou, Wenzong Wang, Tao Lv, Liang Liu, Yajuan Li, Xuemei Ma, Xianda Cui, Haixia Wu
Yulin No.2 Hospital: Xiaocheng Wang, Bingdong Feng, Hufei Chang, Rong Zhao, Xiaoping Wang, Cunjun Yang, Rongrong Guo, Donghong He, Jian Zhang, Quan Jing,
Caiqin Bai, Yumei Wang, Min Sheng, Shuxia Shen, Jun Hao, Xue Li, Chunyan Yang, Yongping Yu

18. PROTOCOL AMENDMENTS

Protocol amendments will be agreed upon with the CHASE Study Group, Sponsor and Funding Body before submission for ethical approval. Following ethical approval, protocol modifications will be communicated with relevant parties such as the trial investigators, the trial registry, and, if required, trial participants.

19. PUBLICATION AND DISSEMINATION POLICY

Publication of all the reports from the study (research article, abstract, or conference communication) will be in the name of CHASE Study Group. The results of this trial will be disseminated to a wide clinical audience (patients, health professionals, policy makers, and the general public) through publication in a high-impact international scientific journal.
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APPENDIX

**Glasgow Coma Scale (GCS)**

| Name     | Sex      | Age | ID | Diagnosis               | Score |
|----------|----------|-----|----|-------------------------|-------|
| **Response** |          |     |    |                         |       |
| Eye      |          |     |    |                         |       |
| Opens eyes spontaneously |          |     |    |                         | 4     |
| Opens eyes in response to voice |          |     |    |                         | 3     |
| Opens eyes in response to pain |          |     |    |                         | 2     |
| No opening of the eye |          |     |    |                         | 1     |
| Verbal   |          |     |    |                         |       |
| Oriented, converses normally |          |     |    |                         | 5     |
| Confused, disoriented |          |     |    |                         | 4     |
| Inappropriate words |          |     |    |                         | 3     |
| Incomprehensible sounds |          |     |    |                         | 2     |
| No verbal response |          |     |    |                         | 1     |
| Motor    |          |     |    |                         |       |
| Obeys commands |          |     |    |                         | 6     |
| Localizes to pain |          |     |    |                         | 5     |
| Withdrawal from pain |          |     |    |                         | 4     |
| Decorticate posturing accentuated by pain |          |     |    |                         | 3     |
| Decerebrate posturing accentuated by pain |          |     |    |                         | 2     |
| No motor response |          |     |    |                         | 1     |
| **Total:** |          |     |    |                         |       |
| **Rater:** |          |     |    |                         |       |
| **Date:** |          |     |    |                         |       |
### National Institutes of Health Stroke Scale (NIHSS)

| Items                                      | Score |
|--------------------------------------------|-------|
| **1a. Level of Consciousness:**            |       |
| Only one level can be chosen.              |       |
| 0 = Alert; keenly responsive.              |       |
| 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. |       |
| 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). |       |
| 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic. |       |
| **1b. LOC Questions:**                     |       |
| Month, age                                 |       |
| 0 = Answers both questions correctly.      |       |
| 1 = Answers one question correctly.        |       |
| 2 = Answers neither question correctly.    |       |
| Aphasic and stuporous patients will score 2. |       |
| Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause will score 1. |       |
| **1c. LOC Commands:**                      |       |
| Open and close the eyes and then to grip and release the non-paretic hand. |       |
| 0 = Performs both tasks correctly.         |       |
| 1 = Performs one task correctly.           |       |
| 2 = Performs neither task correctly.       |       |
| **2. Best Gaze:**                          |       |
| Only horizontal eye movements will be tested. |       |
| 0 = Normal.                                |       |
| 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. |       |
| 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver. |       |
| **3. Visual:**                             |       |
| Upper and lower quadrants are tested.      |       |
| 0 = No visual loss.                        |       |
| 1 = Partial hemianopia.                    |       |
| 2 = Complete hemianopia.                   |       |
| 3 = Bilateral hemianopia (blind including cortical blindness). Near death scores 1. |       |
| **4. Facial Palsy:**                       |       |
| Ask or use pantomime.                     |       |
| 0 = Normal symmetrical movements.          |       |
| 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). |       |
| 2 = Partial paralysis (total or near-total paralysis of lower face). |       |
| 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face). |       |
| **5. Motor Arm:**                          |       |
| The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). |       |
| 0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. |       |
| 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. |       |
| 5a. Left Arm                               |       |
| 5b. Right Arm                              |       |
| **6. Motor Leg:**                          |       |
| Hold the leg at 30 degrees                 |       |
| 0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. |       |
| 6a. Left Leg                               |       |
| 6b. Right Leg                              |       |
| **7. Limb Ataxia:**                        |       |
| Ataxia is absent in the patient who cannot understand or is paralyzed. |       |
| 0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. |       |
| **8. Sensory:**                            |       |
| Pinprick                                   |       |
| 0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss. |       |
| 2 = Severe to total sensory loss.          |       |
| **9. Best Language:**                      |       |
| Name and read                              |       |
| 0 = No aphasia; normal. 1 = Mild-to-moderate aphasia. 2 = Severe aphasia. |       |
| 3 = Mute, global aphasia; no usable speech or auditory comprehension. Coma scores 3. |       |
| **10. Dysarthria:**                        |       |
| Read or repeat words                       |       |
| 0 = Normal. 1 = Mild-to-moderate dysarthria. |       |
| 2 = Severe dysarthria.                     |       |
| **11. Extinction / Inattention:**           |       |
| 0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space. |       |
## Modified Rankin Scale (mRS)

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

**Total score:**

**Rater:**

**Date:**
# Barthel Index of Activities of Daily Living

| Name | Sex | Age | ID |
|------|-----|-----|----|
| **Diagnosis** | | | |
| **Item** | **Description** | **Score** |
| Bowels | 0 = incontinent (or needs to be given enemas). 5 = occasional accident. 10 = continent. | |
| Bladder | 0 = incontinent, or catheterized and unable to manage alone. 5 = occasional accident. 10 = continent | |
| Grooming | 0 = needs to help with personal care. 5 = independent face/hair/teeth/shaving (implements provided) | |
| Toilet use | 0 = dependent. 5 = needs some help, but can do something alone. 10 = independent (on and off, dressing, wiping). | |
| Feeding | 0 = unable. 5 = needs help cutting, spreading butter, etc., or requires modified diet. 10 = independent. | |
| Transfer | 0 = unable, no sitting balance. 5 = major help (one or two people, physical), can sit. 10 = minor help (verbal or physical). 15 = independent. | |
| Mobility | 0 = immobile. 5 = wheelchair independent, including corners. 10 = walks with help of one person (verbal or physical) > 50 yards. 15 = independent (but may use any aid; for example, stick) > 50 yards | |
| Dressing | 0 = dependent. 5 = needs help but can do about half unaided. 10 = independent (including buttons, zips, laces, etc.). | |
| Stairs | 0 = unable. 5 = needs help (verbal, physical, carrying aid). 10 = independent. | |
| Bathing | 0 = dependent. 1 = independent (or in shower). | |
| **Total score:** | | |
| **Rater:** | **Date:** |
## Summary of changes

| Number | Page | Section | Version 1.0 | Version 1.1 |
|--------|------|---------|-------------|-------------|
| 1      | 33   | 16.1    | The sample size was set at 500 to provide at least 80% power to detect a 6% absolute risk reduction in the primary outcome for patients in the individualized BP-lowering group compared to those in the guideline-recommended control group, using a two-sided significance test with 5% type I error. The following assumptions were made: a primary outcome of 60% in the control group will be reduced to 54% in the individualized group; and there will be 10% non-adherence to the treatment protocol and loss to follow-up. The 60% incidence of unfavorable 90-day outcome is obtained from one Chinese study on severe stroke [22]. The 10% non-adherence rate and the absolute risk reduction in primary outcome are obtained from the INTERACT2 study and ATACH2 study which were designed to compare the effects of two different BP lowering strategies in acute stroke patients [10, 14]. | The sample size was set at 500 to provide at least 80% power to detect a 12% absolute risk reduction (15% relative risk reduction) in the primary outcome for patients in the individualized BP-lowering group compared to those in the guideline-recommended control group, using a two-sided significance test with 5% type I error. The following assumptions were made: a primary outcome of 75% in the control group will be reduced to 63% in the individualized group; and there will be 8% non-adherence to the treatment protocol and loss to follow-up. The 75% incidence of unfavorable 90-day outcome is obtained from one Chinese study and one Swiss study on severe stroke [22, 23]. The 8% non-adherence rate and the 15% relative risk reduction in primary outcome are obtained from the INTERACT2 study and ATACH2 study which were designed to compare the effects of two different BP lowering strategies in acute stroke patients [10, 14]. |