Achieving blood pressure control targets in hypertensive patients of rural China – A pilot randomized trial

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Abstract

Background: This study aimed to test the feasibility and titration methods to achieve specific BP control targets in hypertensive patients of rural China.

Methods: A randomized, controlled, open-label trial was conducted in Rongcheng, China. We enrolled 105 hypertensive participants aged over 60 years, and who had no history of stroke and cardiovascular disease. The patients were randomly assigned to one of three systolic BP target groups: standard: 140 - <150mmHg; moderately intensive: 130 - <140mmHg; and intensive: <130mmHg. Patients were followed for 6 months.

Discussion: The optimal target for SBP lowering is still uncertain worldwide and such information is critically needed, especially in China. However, in China the rates of awareness, treatment and control are only 46.9%, 40.7% and 15.3%, respectively. It is challenging to achieve BP control in the real world and it is very important to develop population-specific BP control protocols that fully consider the population’s characteristics, such as age, sex, socio-economic status, compliance, education level and lifestyle. This randomized trial showed feasibility and safety of the titration protocol to achieve desirable SBP targets (<150, <140, and <130mmHg) in a sample of rural Chinese hypertensive patients. The three BP target groups had similar baseline characteristics. After 6 months of treatment, the mean SBP measured at an office visit was 137.2mmHg, 131.1mmHg, and 124.2mmHg in the three groups. Home BP and central aortic BP measurements were also obtained. At 6 months, home BP measurements (2 hours after drug administration) showed a mean SBP of 130.9 mmHg in the standard group, 124.9 mmHg in the moderately intense group, and 119.7 mmHg in the intensive group. No serious adverse events were recorded over the 6-month study period. Rates of adverse events including dry cough, palpitations, and arthralgia were low and showed no significant differences between the three groups. This trial gained real world experience and laid the foundation for a future large-scale BP target study.

Trial registration: Feasibility Study of the Intensive Systolic Blood Pressure Control; ClinicalTrials.gov Identifier: NCT02817503. Registered 29 June 2016 - Retrospectively registered, https://www.clinicaltrials.gov/ct2/results?cond=&term=02817503&cntry=&state=&city=&dist=
Background

Hypertension is highly prevalent in the world, particularly in China [1-3] and is a leading modifiable cause of end organ damage, including stroke, cardiovascular disease and chronic kidney disease [4-8]. Clearly, achieving optimal blood pressure (BP) control is critically important to prevent hypertension induced end-organ diseases. Yet, questions and challenges persist to attaining this goal. First, there is still no consensus on what is the optimal BP target in the general population for the primary prevention of stroke and cardiovascular disease for people over 60 years of age. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) [9] recommended initiating pharmacologic treatment to lower BP to achieve a systolic blood pressure (SBP) target of <150mmHg and a diastolic blood pressure (DBP) target of <90mmHg for the general population aged ≥60 years, and a SBP target of <140mmHg and a DBP target of <90mmHg for people < 60 years of age. The results of the Systolic Blood Pressure Intervention Trial (SPRINT) [10] in which the investigators targeted a systolic blood pressure of less than 120mmHg, as compared to less than 140mmHg, renewed interest on more intensive antihypertensive therapies directed towards a lower BP target among patients at high risk for cardiovascular events but without diabetes. The SPRINT trial showed lower rates of fatal and nonfatal major cardiovascular events and death in the lower BP target group, which subsequently led to a revision of the definition of hypertension in the American Hypertension Association Guidelines in 2017 [11]. Opponents argued that over-reduction of BP could lead to adverse events such as severe hypotension and end organ hypo-perfusion or ischemia in some patients, particularly those with a pulse pressure > 60mmHg and a diastolic pressure < 60mmHg [12]. Thus, the optimal target for BP control remains a controversial topic and requires further evidence to weigh the benefits and risks.

Second, it is well observed that hypertensive patients are heterogeneous by age, sex, race, ethnicity, risk factors and co-morbidities. As such, when setting BP control targets, it is important to carefully consider these factors, with the understanding that one size does not fit all. For example, there are several unique characteristics that are specific to hypertensive populations in China, including folate insufficiency, a high rate of the MTHFR C677T genotype mutation and a high rate (74.45%) of
hyperhomocysteinemia (HHcy) [13-15].

Third, in real world practice, achieving BP control and attaining optimal target in a high-risk population, such as rural Chinese, remain a challenge. Recent surveys showed that the rates of awareness, treatment and control are only 46.9%, 40.7% and 15.3%, respectively in China [2-3]. Thus, there is an urgent need for evidence-based guideline to inform clinical and public health practice and policy in rural China.

As a prelude to a large trial of blood pressure targets, this pilot randomized trial aimed to test the feasibility of a BP control protocol designed to effectively and safely manage hypertensive patients and achieve prespecified systolic BP targets in hypertensive patients of rural China. It is the hypotheses whether it has the feasibility of achieved mean blood pressure levels in each of the treatment groups of this present trail. In order to explore various possibilities and the low rates of awareness, treatment and control of Chinese population, a three groups design (i.e, 140 - < 150mmHg; 130 - < 140mmHg; <130mmHg) was made in this pilot study. Furthermore, different modalities for obtaining BP measurements [routine office visits, home blood pressure measurement (HBPM), and central aortic systolic pressure (CASP)] were also included as part of the trial.

Methods

Study design and oversight

The study was a randomized, controlled, open-label trial conducted in Rongcheng, Shandong, China. The trial consisted of 3 stages: (1) screening, (2) recruitment and randomization to specific BP targets, and (3) anti-hypertension treatment titrated to achieve assigned BP target. The study was approved by the ethics committee of the Second Affiliated Hospital of Nanchang University, China and is registered in the clinical trial website (ClinicalTrials.gov Identifier: NCT02817503). All participants provided written, informed consent.

Study population

Inclusion Criteria

1. Hypertensive patients aged 60 years or older.

2. Current SBP ≥ 150mmHg but <180mmHg (within the previous two weeks) not
regularly treated with antihypertensive drugs.

3. If currently regularly treated with antihypertensive drugs (at least 10 days on antihypertensive drugs within the previous two weeks), BP must meet the following criteria:

\[ \text{SBP} \geq 140 \text{mmHg} \text{ but } <170 \text{mmHg}, \text{ if regularly (no less than 10 days) taking 1 type of antihypertensive medication within the previous two weeks;} \]

\[ \text{SBP} \geq 130 \text{mmHg} \text{ but } <160 \text{mmHg}, \text{ if regularly (no less than 10 days) taking 2 types of antihypertensive medications within the previous two weeks;} \]

\[ \text{SBP} \geq 130 \text{mmHg} \text{ but } <150 \text{mmHg}, \text{ if regularly (no less than 10 days) taking 3 types of antihypertensive medication within the previous two weeks.} \]

For patients who were taking a fixed-dose-combination (FDC), this treatment was considered as two types of drugs if the dose of each component of the FDC was equal to or higher than the routine therapeutic dose.

4. Serum homocysteine (Hcy) \( \geq 10 \mu\text{mol/L} \), or the patient is taking enalapril-folic acid;

5. Subject has read, agreed to, and signed a written, informed consent form.

Exclusion Criteria

1. History of physician diagnosed stroke, myocardial infarction, heart failure, revascularization, or malignancy;

2. History of physician diagnosed secondary hypertension;

3. Undergoing regular renal dialysis or has been diagnosed with end-stage kidney disease;

4. Congenital or acquired organic heart disease;

5. Severe somatic disease preventing the participant from completing the trial, or the patient is incapable of participating, as judged by the investigators;

6. Contraindications or intolerance to ACEIs (including enalapril-folic acid) or, a history
of severe adverse effects to ACEIs;

7. Abnormal laboratory test results and/or clinical manifestations rendering the patient unsuitable to participate as judged by the investigators.

Randomization and Interventions

During the screening stage, each participant completed a physical examination and questionnaire interview on lifestyle and history of disease and medication use. Laboratory tests included fasting lipid profile and plasma homocysteine. Eligible participants were randomized, in a 1:1:1 ratio, to a systolic BP target of 140-150 mmHg (the standard-treatment group [Group A]), 130-140 mmHg (the moderately-intensive treatment group [Group B]) or less than 130 mmHg (the intensive-treatment group [Group C]) with a fixed block size of 9. Study personnel were aware of the study-group assignments, but participants were not.

After the participants underwent randomization, their baseline antihypertensive regimens were adjusted on the basis of the study-group assignment. The treatment algorithms were similar to those used in the SPRINT trial [10]. These algorithms and our formulary are listed in the supplemental material (Supplemental Table 1). All major classes of antihypertensive agents were included in the formulary and were provided at no cost to the participants. For all participants, the initial therapy was a daily oral dose of 1 tablet of enalapril–folic acid (containing 10mg of enalapril and 0.8 mg of folic acid). Other drugs, including CCBs (amlodipine preferred), diuretics (hydrochlorothiazide preferred), and β-blockers, were allowed, in order to achieve the SBP target. For those who couldn’t tolerate enalapril-folic acid well, other types of antihypertensive agents could be used as alternative choices. If the target BP level was not achieved during the titration or follow-up periods, adjustment of drug type and dosage was carried out according to the protocol.

Participants were seen weekly for the first month, every 2 weeks for the next two months, and once a month thereafter for a total of 6 months, totaling to eleven follow-up visits. For participants in the Group A and B, medications were adjusted to target SBP of 145 to 149mmHg and 135-139mmHg, respectively. For participants in Group C, medications were adjusted to target SBP of less than
130mmHg. The dose was reduced if SBP was under the target on two consecutive visits. Dose adjustment was based on the mean of three blood-pressure measurements at an office visit. Self-monitored HBPM were recorded by using an electronic sphygmomanometer (Kingyield, Shenzhen, China). Additional, CASP was also conducted at office visits by using a central aortic systolic pressure monitor device (A-pulse CASPro, Jianzi, Singapore). Lifestyle modification, like sodium restriction, smoking cessation were encouraged as part of the management strategy for all study participants. The participants’ retention and adherence to treatment were also monitored at each follow-up visit.

Outcomes and Study measurements

Primary outcome was achieved mean blood pressure levels in each of the treatment groups. Secondary outcome was the difference between carotid-femoral pulse wave velocity (cf-PWV), 3D carotid artery ultrasound, and Ankle-brachial index (ABI) of each treatment groups. BP measurements at an office visit were with the patient seated and rested quietly for 10 minutes; the measurements were made with the use of an electronic sphygmomanometer (Kingyield, Shenzhen, China). Self-monitored HBPM were recorded by using an electronic sphygmomanometer (Kingyield, Shenzhen, China). Participants were trained on the use of the electronic sphygmomanometer for HBPM according to the protocol. Before formally recording any BP values, the patients underwent 10 days of continuous training conducted by the investigators to ensure that each participant mastered the method. The participants were requested to continuously measure BP at three-time points per day (in the morning after urination and before breakfast and medication, 2 hours after taking antihypertensive medication, and in the evening) for weeks 12, 16, 20 and 24 and to record values on a HBPM self-test registration form. All data were collected 7 days before the office visit. The main objective of the HBPM protocol was to assess the reproducibility and reliability of a 7-day self-monitoring prior to an office visit day. CASP was also conducted at office visits at Weeks 6, 12, and 24 by using a central aortic systolic pressure monitor device (A-pulse CASPro, Jianzi, Singapore).

Epidemiological, clinical and laboratory data were obtained at baseline. Data on carotid-femoral pulse wave velocity (cf-PWV), 3D carotid artery ultrasound, and Ankle-brachial index (ABI) were all obtained at baseline and 6-month visit. Medical records and electrocardiograms were obtained for
documentation of events. Serious adverse events (SAE) were defined as events that were fatal or life-threatening, that resulted in clinically significant or persistent disability, that required or prolonged a hospitalization, or that were judged by the investigator to represent a clinically significant hazard or to cause harm to the participant, that might require medical or surgical intervention to prevent one of the other events listed above. Any condition on a short list of monitored conditions would be reported as an adverse event if it was evaluated in a hospital emergency department: hypotension, syncope, injurious falls, electrolyte abnormalities, and bradycardia.

Statistical Analysis
According to previous large-scale RCT studies, the rate of achieved mean blood pressure levels in the target window is around 60%, assuming that the rate of achieved mean blood pressure levels in this feasibility present study is 70-80% and the significance level of bilateral test $\alpha = 0.05$. With an enrollment target of 30 participants of each group, we estimated that the trial would have 80% power to detect the difference between groups. Anticipated a loss to follow-up, so 35 participants were included of each group. Continuous variables were presented as mean±SD and categorical variables as frequency (%). The baseline population characteristics of the three BP groups were compared using Kruskal Wallis test or $\chi^2$ tests. Similarly, incidence of adverse events (AE) that were likely caused by the drug or intensive BP control was compared among the three BP target groups. Systolic and diastolic BP was compared between 0 and 6 month points by paired t tests within each treatment group. Change in systolic and diastolic BP (6 month BP minus baseline BP) was compared among the three treatment groups. Epidata 3.1 was used to build the database; double entry mode and error checking were adopted. Data were analyzed using Empower (R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA).

Results
Characteristics of the participants
105 participants were enrolled between December 2015 and January 2016. Participants were randomized into three groups with different BP targets (Figure 1). Baseline characteristics are shown in Table 1. The mean age of the population was 68.4±5.5 years. 31.4% of the participants were male,
and 20% were former or current smokers. 15.2% of the participants had a history of diabetes. The percentage of SBP >150mmHg; >140 but <=150mmHg; and >130 but <=140mmHg at enrollment was 41.0%, 45.7%, and 13.3%, respectively. Aspirin and statins use was 5.7% and 20.0%, respectively. There were no significant differences in baseline characteristics among the three groups (P>0.05).

**BP titration and antihypertensive drug use**

The mean SBP at the end of 6 month visit in the standard-BP control group (A), the moderately intensive-BP control group (B) and the intensive-BP control group (C) was 137.2mmHg, 131.1mmHg and 124.2mmHg, while the corresponding DBPs were 77.6mmHg, 74.9mmHg and 71.5 mmHg, for each group, respectively (Figure 2A).

The mean number of antihypertensive drugs prescribed at baseline enrollment were 1.4, 1.4, and 1.5 among the standard-BP control group (A), the moderately intensive-BP control group (B) and the intensive-BP control group (C), respectively, and, at the end of 6 month visit, were 1.4, 2.2, and 2.5, respectively (Figure 2B). The distribution of anti-hypertension drugs used in different groups was shown in Figure 2C.

Decreased SBP and DBP was expressed as ΔSBP and ΔDBP (which equals to SBP at Week “x” –SBP at Week “0”), respectively. After 6 months of anti-hypertensive treatment, the absolute decrease in SBP in the Group A, B, C was 9.5mmHg, 16.1mmHg and 26.4mmHg, respectively, while the absolute decrease in DBP was 9.7mmHg, 13.6mmHg and 18.2mmHg, respectively (Table 2).

After 6 months of treatment, for the standard-BP control group (A), 83% achieved SBP<150mmHg (29% of participants had a mean SBP in the BP target window of 140mg-150mmHg, but 14% were in the 130-140mmHg window and 40% were in the <130mmHg group). For the moderately intensive-BP control group (B), 80% achieved SBP<140 (37% of participants had a mean SBP in the target window of 130-140mmHg, but 43% were in the <130mmHg group). For the intensive-BP control group (C), 73% of participants had a mean SBP <130mmHg (6% of participants had a mean SBP in the target window of 140-150mmHg, and 18% were in the target window of 130-140mmHg). (Supplemental Fig.2)
**HBPM and CASP**

In this study, 98 participants (93%) agreed to self-monitor their blood pressure using an electronic sphygmomanometer for HBPM; and 94 of the 98 participants completed the HBPM according to protocol, including 29 males (30.9%) with a mean age of 71.0 (±5.2) years and 65 females (69.1%) with a mean age of 67.2 (±5.0) years. There was a consistent trend between office visit BP and HBPM (2 hours after taking medication) among the three BP control groups at each titration period (Supplemental Figure 1A). CASP was also measured at Weeks 6, 12, 24. Consistent trends were also observed between CASP and office visit BP among the three groups at each titration period (Supplemental Figure 1B). CASP was generally lower than that of office visit BP (Supplemental Table 2). At the end of 6 months titration, the difference in SBP between CASP and office visit BP was -7.1 ± 8.0 in the standard-BP control group (A); -9.6 ± 8.2 in the moderately intensive-BP control group (B); and -9.0 ± 9.0 in the intensive-BP control group (C).

**Adverse events (AE)**

There were no severe AEs recorded and no direct and close relationship between the occurrence of an AE and the BP titration. As shown in Table 3, there were no significant differences in AE occurrence, especially hypotension, between the intensive BP control group and the other groups.

**Discussion**

To our knowledge, this is the first randomized trial to test the feasibility and safety of the BP control protocol (including medication titration) to achieve three different BP control targets in rural Chinese hypertensive patients. This trial gained real world experience and laid the foundation for a future large-scale BP target study. Below we discuss what we learned from this trial and how it relates to the literature.

**BP Control Targets:** Given the lack of consensus on optimal BP targets in Chinese population, we chose three systolic BP targets based on American Heart Association previous and new BP guidelines [2,11,16] and findings from the two relevant trials: SPRINT and ACCORD [10,17]. Our goal was to evaluate how likely each of the BP targets can be safely achieved in rural Chinese hypertensive patients, a population with low BP control rate and at high-risk of stroke. Our ultimate goal of the
management of hypertension is for the prevention of end organ damage, including stroke, cardiovascular events, and renal dysfunction.

The benefits of BP lowering were demonstrated in randomized controlled trials of hypertensive patients. The following trials contributed to the changes in the BP targets in the major hypertension management guidelines from 2000 to 2018: the Hypertension in the Very Elderly Trial (HYVET 2003) [18]; the Action to Control Cardiovascular Risk in Diabetes trial (ACCORD 2010) [17]; the Valsartan in Elderly Isolated Systolic Hypertension study (VALISH 2010) [19]; the Secondary Prevention of Small Subcortical Strokes trial (SPS3 2013) [20]; the Systolic Blood Pressure Intervention trial (SPRINT 2015) [10]; and the Heart Outcome Prevention Evaluation-3 trial (HOPE-3 2016) [21].

Of note, in contrast to the findings of “SPRINT”, which showed a benefit of tighter BP control, the ACCORD trial showed no significant difference in cardiovascular events and all-cause mortality between the intensive treatment (mean SBP 119.3 mmHg) and the standard treatment (mean SBP 133.5 mmHg); cardiovascular events and death from cardiovascular causes (HR 0.88, 95%CI 0.73-1.06, p=0.20). However, the cardiovascular events observed in the ACCORD trial were mainly ischemic heart disease, but the prevalence of cerebrovascular disease was significantly reduced in the intensive-treatment group (HR 0.59, 95%CI 0.39–0.89, p=0.01). There were important difference between the two trials. The ACCORD trial enrolled participants with diabetes exclusively, whereas SPRINT excluded participants with diabetes; in addition, the sample size differed (4733, ACCORD vs. 9361, SPRINT). The ACCORD trial also used a factorial design that included comparisons of standard and intensive glycemic and lipid treatment targets in the same trial. SPRINT enrolled an older cohort (mean age, 68 years vs. 62 years in the ACCORD trial), with 28% of the participants 75 years of age or older, and included participants with chronic kidney disease.

Limited data were available for Asian populations. A recent study among 248,8101 Koreans aged 20 through 39 years found that stage 1 hypertension (SBP, 130-139mmHg or DBP, 80-89mmHg) was associated with an increased risk of subsequent cardiovascular disease (Hazard ratio, 1.25 for men; 1.27 for women) during a median follow-up duration of 10 years. Among Koreans, young adults with hypertension, defined by the 2017 ACC/AHA criteria, may be at increased risk of cardiovascular
disease [22].

**Choice of Anti-Hypertension Drugs:** Drug choice is related to the clinical indications, cost, availability, insurance coverage, and patient preference. In the ACCORD trial, a strategy of treatment to specific SBP goals was tested, rather than testing any specific drug regimen. All major classes of antihypertensive drugs and many combination medications were provided by the study. All antihypertensive regimens were to include a drug class that had demonstrated efficacy in reducing cardiovascular events in participants with diabetes: diuretics, beta-blockers, calcium channel blockers (CCB), angiotensin converting-enzymes (ACE) inhibitors, or angiotensin receptor blockers (ARB). The treatment algorithms of SPRINT were similar to the ACCORD trial. The SPRINT investigators also prescribed other antihypertensive medications (not provided by the study). The protocol encouraged, but did not mandate, the use of drug classes with the strongest evidence for reduction in cardiovascular outcomes, including thiazide-type diuretics (encouraged as the first-line agent), loop diuretics (for participants with advanced chronic kidney disease), and beta-adrenergic blockers (for those with coronary artery disease). Chlorthalidone was encouraged as the primary thiazide-type diuretic, and amlodipine as the preferred calcium-channel blocker. In the International Verapamil-Trandolapril Study (INVEST) [23] patients were randomly assigned to either a calcium antagonist (verapamil sustained release) vs. a non-calcium antagonist (atenolol). Trandolapril and/or hydrochlorothiazide was administered to achieve blood pressure goals.

In this present trial, the antihypertensive drugs were provided at no cost to the participants; and all the antihypertensive regimens included drug classes that had been shown to result in a reduction in stroke or cardiovascular events [24]. For all participants, the initial therapy was a daily oral dose of 1 tablet of enalapril-folic acid (containing 10mg of enalapril and 0.8mg of folic acid) because the homocysteine level of all participants was >10μmol/L [25]. The next step used amlodipine or hydrochlorothiazide. β-blockers were also allowed, to achieve the SBP target.

**Feasibility:** Feasibility encompasses the likelihood of lowering BP to the prespecified target, the number of drugs required to achieve that goal, and whether patients can tolerate and comply to the regimen. In this trial, all patients completed the 6-month follow-up with the exception of only one
participant in the intensive BP control group (the patient had to travel out of town for an emergency). After six months of BP medication titration, 83%, 80%, and 73% of the patients attained a BP level below the specified SBP target for Group A, B, C, respectively. At baseline enrollment, the mean number of antihypertensive drugs prescribed were 1.4, 1.4, and 1.5 among the three groups. After 6 months of follow up, the number of drugs prescribed were 1.4, 2.2, and 2.5 (Figure 2B). In SPRINT the mean number of blood-pressure medications was 2.8 in the intensive treatment group and 1.8 in the standard treatment group. In the ACCORD study the mean number of medications after the first year was 3.4 (95% CI, 3.4 to 3.5) in the intensive therapy group and 2.1 (95% CI, 2.1 to 2.2) in the standard-therapy group.

In the process of BP medication titration, SBP fluctuated somewhat like Week 8, and we considered ambient temperature was a potential contributor [26]. As part of BP measurements, we also recorded the ambient temperature. As shown in Supplemental Fig. 3, ambient temperature was correlated with BP levels. On the other hand, between the Week 5 visit and Week 8 visit, there is a Spring Festival Holiday with sufficient rest time, which is also good for blood pressure control.

**Safety:** Safety issues were related to side effects of a specific anti-hypertensive drug used; safety surrounding the use of multiple drugs in combination; and safety related to the BP target and the corresponding risk of hypotension. The major side effects observed in the current study were cold symptoms, dry cough, and vertigo, all of which were similar between the three groups (Table 3). No SAE were recorded. The BP control protocols were overall safe without any major AE for all three target groups.

**Modality of BP Monitoring:** The current study tested different modalities of BP measurements: office visits, self-monitored HBPM, and CASP and examined their relationships. We found consistent pattern of BP control between HBPM and office visit BP measurements. In addition, there was a general 8-9mmHg difference between CASP and office visit BP.

**Strengths and limitations of this study**

This pilot randomized trial was the first step to address critical questions: what is the optimal BP control target and how to achieve it in Chinese population? This trial aimed to evaluate the feasibility
and safety to achieve prespecified BP targets (<150, <140, and <130mmHg) using a standard BP control protocol among hypertensive patients in rural China, which constitutes over 61.2% of Chinese population. This trial fully considered rural Chinese population’s characteristics such as socio-economic status, compliance, education level and lifestyle, which are quite different from western populations. This trial has following limitations: the sample size was small. The study had a short duration and was unable to evaluate long-term health outcomes. It was conducted in rural Chinese hypertensive patients, so generalization of the trial findings to other population requires caution. There are more left-behind women than men in rural China, so we have included more women. Salt intake is high in northern China, but apart from lifestyle modification, we haven’t accurately measured salt intake in this study.

Conclusion
The findings from this pilot trial suggest that all three BP targets (<150, <140, and <130mmHg) can be safely achieved in hypertensive patients in rural China without a history of stroke and cardiovascular events, using our BP control medication titration protocol. The next step would be to determine the long-term effects of different BP targets on end organ diseases, which would require both a large and longer term trial.

Declarations

**Trial status**

This pilot trial presented above has been completed.

_Ethics approval and consent to participate_

Ethics approval has been sought from the Ethics Committee of the Second Affiliated Hospital of Nanchang University, China [(2015)1217]. Written informed consent is obtained from the participants and their family members before screening.

_Consent for publication_

Not applicable.

_Acknowledgments_

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health center/clinic for facilitating the trial.

Authors’ Contributors

Xiao Huang, Lishun Liu, Yun Song, Lan Gao, Min Zhao, Chonglei Bi, Aiping Yue, Chongqian Fang, Genfu Tang, and Hai Ma were responsible for implement onsite. Xiao Huang drafted the manuscript. Ping Li, Jianping Li, Yan Zhang, Huihui Bao, Xianhui Qin, Yanqing Wu, Qinghua Wu, Yimin Cui, and Binyan Wang developed the methodological approach. Xiaoshu Cheng, Yong Huo, Xiping Xu, Xiao Huang, Guangliang Chen, Hong Wang, Gianfranco Parati, J. David Spence, Xiaobin Wang critically revised the protocol for important intellectual content. All authors contributed to the conception and design and approved the final version of the manuscript.

Conflict(s) of Interest/Disclosure(s)

All authors have completed the ICMJE uniform disclosure form and have declared the following:

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Abbreviations

**SBP**: systolic blood pressure **DBP**: diastolic blood pressure **SPRINT**: Systolic Blood Pressure Intervention Trial **HHcy**: hyperhomocysteinemia **HBPM**: home blood pressure measurement **CASP**: central aortic systolic pressure **FDC**: fixed-dose-combination **SAE**: Serious adverse events

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Tables
Table 1 Characteristics of the participants at baseline according to BP control group
|                                | Total (140~<150mmHg) | A Standard (140~<150mmHg) | B Moderate (130~<140mmHg) |
|--------------------------------|----------------------|----------------------------|---------------------------|
| No.                            | 105                  | 35                         | 35                        |
| Age-yr                         |                      |                            |                           |
| overall                        | 68.4 ± 5.5           | 67.4 ± 4.9                 | 68.2 ± 5.8                |
| >=75 years of age              | 17 (16.2%)           | 3 (8.6%)                   | 6 (17%)                   |
| Baseline blood pressure-mmHg   |                      |                            |                           |
| Systolic                       | 149.6 ± 11.6         | 146.7 ± 8.6                | 147.2 ± 7.0               |
| Diastolic                      | 89.2 ± 9.7           | 87.3 ± 9.1                 | 88.5 ± 9.5                |
| BMI                            | 26.5 ± 3.4           | 25.8 ± 3.3                 | 26.9 ± 3.8                |
| Sex                            |                      |                            |                           |
| Male                           | 33 (31.4%)           | 11 (31.4%)                 | 11 (31.4%)                |
| Female                         | 72 (68.6%)           | 24 (68.6%)                 | 24 (68.6%)                |
| Smoking status                 |                      |                            |                           |
| Never                          | 84 (80.0%)           | 27 (77.1%)                 | 27 (77.1%)                |
| Former                         | 12 (11.4%)           | 6 (17.1%)                  | 3 (8.6%)                  |
| Current                        | 9 (8.6%)             | 2 (5.7%)                   | 5 (14.3%)                 |
| Diabetes history               | 16 (15.2%)           | 6 (17.1%)                  | 3 (8.6%)                  |
| Distribution of systolic blood pressure-no. % | | | | |
| >150 mmHg                      | 43 (41.0%)           | 11 (31.4%)                 | 12 (34.3%)                |
| >140,<=150 mmHg                | 48 (45.7%)           | 17 (48.6%)                 | 19 (54.3%)                |
| >130, <=140 mmHg               | 14 (13.3%)           | 7 (20.0%)                  | 4 (11.4%)                 |
| Antihypertensive drug use      | 1.4                  | 1.4                        | 1.4                       |
| Other medication usage         |                      |                            |                           |
| Statins                        | 6 (5.7%)             | 1 (2.9%)                   | 3 (8.6%)                  |
| Aspirin                        | 21 (20.0%)           | 6 (17.1%)                  | 7 (20%)                   |
| Laboratory results             |                      |                            |                           |
| Glucose (mmol/L)               | 6.5 ± 1.7            | 6.7 ± 1.8                  | 6.4 ± 2.0                 |
| Cholesterol (mmol/L)           | 5.5 ± 1.5            | 5.1 ± 1.8                  | 5.6 ± 1.0                 |
| Triglycerides (mmol/L)         | 1.8 ± 1.5            | 2.0 ± 2.2                  | 1.7 ± 1.1                 |
| LDL (mmol/L)                   | 4.1 ± 0.9            | 3.9 ± 0.9                  | 4.0 ± 0.9                 |
| HDL (mmol/L)                   | 1.5 ± 0.3            | 1.5 ± 0.3                  | 1.5 ± 0.3                 |
| Homocysteine (μmol/L)          | 10.4 ± 2.6           | 10.6 ± 3.2                 | 9.9 ± 1.9                 |
| MTHHR C677T                    |                      |                            |                           |
| CC                             | 24 (22.9%)           | 7 (20.0%)                  | 7 (20.0%)                 |
| CT                             | 52 (49.5%)           | 20 (57.1%)                 | 18 (51.4%)                |
| TT                             | 29 (27.6%)           | 8 (22.9%)                  | 10 (28.6%)                |
Data are mean (SD) or number (%). ACE=angiotensin-converting enzyme. ARB= angiotensin-II-receptor blocker. BMI= body mass index; MTHFR= methylenetetrahydrofolate reductase; LDL=Low-density lipoprotein; HDL=High-density lipoprotein *Difference between groups p<0.0001.

Table 2 ΔSBP and ΔDBP at each follow up visit

|       | ΔSBP* | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 8 | Week 10 |
|-------|-------|--------|--------|--------|--------|--------|--------|---------|
| A #   | 0.5   | -1.1   | -7.4   | -4.7   | -3.5   | -13.2  | -7     |
| B     | -1.4  | -4.6   | -10.8  | -9.9   | -8     | -16.3  | -7.9   |
| C     | -5.3  | -12.1  | -18.1  | -14.6  | -14.4  | -25.1  | -18.5  |
| ΔDBP  |       |        |        |        |        |        |        |         |
| A     | -4.1  | -5.4   | -6.1   | -3.9   | -4.1   | -15.3  | -11.7  |
| B     | -3.8  | -6.9   | -8.2   | -8.2   | -7.2   | -16.7  | -12.6  |
| C     | -6.5  | -10.2  | -13.1  | -11    | -11.7  | -21.2  | -20.2  |

*ΔSBP =SBP (Week “x”) – SBP (Week 0); ΔDBP =DBP (Week “x”) –DBP (Week 0)

#A =Standard Group      B= Moderately Intensive Group C= Intensive Group

Table 3 Adverse events among the three blood pressure control groups

Supplementary File Legends

**Supplemental Figure 1 Comparison of office visit SBP with HBPM and CASP**

Panel A: 94 participants completed the HBPM according to the protocol. There was a consistent trend between office visit BP and HBPM (2 hours after taking medication) among the standard BP control group, the moderate BP control group, and the intensive BP control group at each titration period.

Panel B: CASP was also measured at Weeks 6, 12, and 24. There was a consistent trend between CASP and office visit BP among the standard BP control group, the moderate BP control group, and the intensive BP control group at each titration period.
| Adverse Event (Number of patients Rate (%)) | Standard BP control | Moderate BP control |
|--------------------------------------------|---------------------|---------------------|
| Cold Symptoms                               | 7 (21%)             | 9 (26%)             |
| Dry Cough                                   | 5 (15%)             | 5 (14%)             |
| Vertigo                                     | 3 (9%)              | 3 (9%)              |
| Arthralgia                                  | 0                   | 1 (3%)              |
| Epigastric Pain                             | 1 (3%)              | 1 (3%)              |
| Palpitations                                | 0                   | 0                   |
| Drug Allergy                                | 1 (3%)              | 0                   |
| Skin Disease                                | 0                   | 1 (3%)              |
| Blurred Vision                              | 0                   | 0                   |
| Hypotension                                 | 0                   | 0                   |
| Total                                       | 17 (49%)            | 20 (57%)            |

**Supplemental Figure 2 Mean SBP in the target window of three treatment groups at each visit**

After 6 months of titration, for the standard-BP control group, 29% of participants had a mean SBP in the target window of 140mg-150mmHg, 14% were in the 130-140mmHg window and 40% were in the <130mmHg group; for the moderate-BP control group, 37% of participants had a mean SBP in the target window of 130-140mmHg, and 43% were in the <130mmHg group; for the intensive-BP control group, 73% of participants had a mean SBP in the <130mmHg group.

**Supplemental Figure 3 SBP fluctuated in the process of BP titration and ambient temperature recorded**

In the process of BP medication titration, SBP did not always decrease, but fluctuated in the middle. Ambient temperature affected BP control.

**Figures**
Figure 1

Design and flow chart of the feasibility study
Figure 2

Mean systolic BP of three treatment groups during the study visits Panel A: Mean SBP during the treatment period in the standard-BP control group, the moderate-BP control group, and the intensive-BP control group was 137.2mmHg, 131.1mmHg, and 124.2mmHg, respectively while the corresponding DBP was 77.6mmHg, 74.9mmHg and 71.5 mmHg in each of the three groups, respectively, by the end of 6 months of follow-up. Panel B: The mean number of antihypertension drugs prescribed at enrollment was 1.4, 1.4, and 1.5 among the standard-BP control group, the moderate-BP control group, and the intensive-BP control group, respectively. After 6 months of follow-up, the mean number of drugs prescribed was 1.4, 2.2, and 2.5, per group, respectively. Panel C: The distribution of anti-hypertension drugs used in different groups.

Supplementary Files
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