Optimal Systolic Blood Pressure Levels for Primary Prevention of Stroke in General Hypertensive Adults

Findings From the CSPPT (China Stroke Primary Prevention Trial)

Fangfang Fan,* Ziwen Yuan,* Xianhui Qin,* Jianping Li, Yan Zhang, Youbao Li, Tao Yu, Meng Ji, Junbo Ge, Meili Zheng, Xinchun Yang, Huihui Bao, Xiaoshu Cheng, Dongfeng Gu, Dong Zhao, Jiguang Wang, Ningling Sun, Yundai Chen, Hong Wang, Xiaobin Wang, Gianfranco Parati, Fanfan Hou, Xiping Xu, Xian Wang, Gang Zhao, Yong Huo

Abstract—We aimed to investigate the relationship of time-averaged on-treatment systolic blood pressure (SBP) with the risk of first stroke in the CSPPT (China Stroke Primary Prevention Trial). A post hoc analysis was conducted using data from 17 720 hypertensive adults without cardiovascular disease, diabetes mellitus, and renal function decline from the CSPPT, a randomized double-blind controlled trial. The primary outcome was first stroke. Over a median follow-up duration of 4.5 years, the association between averaged on-treatment SBP and risk for first stoke followed a U-shape curve, with increased risk above and below the reference range of 120 to 130 mm Hg. Compared with participants with time-averaged on-treatment SBP at 120 to 130 mm Hg (mean, 126.2 mm Hg), the risk of first stroke was not only increased in participants with SBP at 130 to 135 mm Hg (mean, 132.6 mm Hg; 1.5% versus 0.8%; hazard ratio, 1.63; 95% confidence interval, 1.01–2.63) or 135 to 140 mm Hg (mean, 137.5 mm Hg; 1.9% versus 0.8%; hazard ratio, 1.85; 95% confidence interval, 1.17–2.93), but also increased in participants with SBP <120 mm Hg (mean, 116.7 mm Hg; 3.1% versus 0.8%; hazard ratio, 4.37; 95% confidence interval, 2.10–9.07). Similar results were found in various subgroups stratified by age, sex, and treatment group. Furthermore, lower diastolic blood pressure was associated with lower risk of stroke, with a plateau at a time-average on-treatment diastolic blood pressure <80 mm Hg. In conclusion, among adults with hypertension and without a history of stroke or myocardial infarction, diabetes mellitus, or renal function decline, a lower SBP goal of 120 to 130 mm Hg, as compared with a target SBP of 130 to 140 mm Hg or <120 mm Hg, resulted in the lowest risk of first stroke. (***Hypertension*****. 2017;69:697-704. DOI: 10.1161/HYPERTENSIONAHA.116.08499.)**

● **Online Data Supplement**

Key Words: general hypertensives ■ goal blood pressure ■ hypertension ■ primary prevention ■ stroke

Hypertension is an important public health challenge, affecting over 1 billion adults worldwide (≈300 million in China).[1,2] The Global Burden of Disease, Injuries, and Risk Factor study in 2013 reported that high systolic blood pressure (SBP) was one of the leading risk factors for death and disability-adjusted life-years in most countries.[3]

Received September 23, 2016; first decision September 30, 2016; revision accepted January 22, 2017.

From the Department of Cardiology, Peking University First Hospital, Beijing, China (F.F., J.L., Y.Z., Y.H.); Department of Neurology, Xijing Hospital, the Fourth Military Medical University, Xi'an, China (Z.Y., G.Z.); National Clinical Research Center for Kidney Disease; State Key Laboratory for Organ Failure Research; Renal Division, Nanfang Hospital, Southern Medical University, Guangzhou, China (X.Q., Y.L., F.H., X.X.); Institute for Biomedicine, Anhui Medical University, Hefei, China (X.Q., T.Y.); Shanghai Institute of Cardiovascular Diseases, Department of Cardiology, Zhongshan Hospital (M.J., J.G.), and Institutes of Biomedical Sciences (M.J., J.G.), Fudan University, Shanghai, China; Department of Cardiology, Beijing Chaoyang Hospital, Capital Medical University, China (M.Z., X.Y.); Department of Cardiology, Second Affiliated Hospital, Nanchang University, China (H.B., X.C.); Department of Epidemiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (D.G.); Department of Epidemiology, Capital Medical University Beijing Anzhen Hospital–Beijing Institute of Heart, Lung & Blood Vessel Diseases, China (D.Z.); Centre for Epidemiological Studies and Clinical Trials, Ruijin Hospital, The Shanghai Institute of Hypertension, Shanghai Jiaotong University School of Medicine, China (J.W.); Department of Cardiology, Peking University People's Hospital, Beijing, China (N.S.); Department of Cardiology, Chinese People's Liberation Army General Hospital, Beijing, China (Y.C.); Centers for Metabolic Disease Research, Temple University School of Medicine, Philadelphia, PA (H.W.); Department of Population, Family and Reproductive Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD (Xiaobin Wang); Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Istituto Auxologico Italiano, Milan, Italy (G.P.); Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy (G.P.); and Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Peking University, Beijing, China (Xian Wang).

This article was sent to Marc L. De Buyzere, Guest Editor, for review by expert referees, editorial decision, and final disposition.

*These authors contributed equally to this work.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.116.08499/-/DC1.

Reprint requests to Yong Huo, Department of Cardiology, Peking University First Hospital, Beijing, China, E-mail huoyong@263.net.cn or Gang Zhao, Department of Neurology, Xijing Hospital, Forth Military Medical University, Xi'an, China, E-mail zhaogang@fmmu.edu.cn or Xian Wang, Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Peking University, Beijing, China, E-mail xwang@bjmu.edu.cn

Several randomized trials support the use of blood pressure (BP)–lowering drugs to reduce the risk of cardiovascular disease (CVD). A meta-analysis of 61 prospective studies, including 1 million adults with no previous vascular disease at baseline who were subsequently followed for ≈14 years, showed a linear relationship between SBP and cardiovascular risk down to 115 mm Hg.[4] However, although the most appropriate targets for SBP lowering have long been debated in high-risk patients,[5–8] such as those with diabetes mellitus or a history of CVD, or renal disease, few studies[9–11] have focused on optimal SBP levels in hypertensive adults without such diseases. According to the 2013 European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension, an SBP goal of <140 mm Hg was recommended, primarily based on data from 3 trials with noted limitations.[12] As a result, the Eighth Joint National Committee recommended a goal of SBP <140 mm Hg in the general population both for those aged ≥60 years or <60 years, though this recommendation was merely based on evidence graded as Expert Opinion-Grade E.[13]

Data from the CSPPT (China Stroke Primary Prevention Trial)[14] showed that during a median follow-up duration of 4.5 years, the combined use of enalapril and folic acid, compared with enalapril alone, significantly reduced the risk of first stroke by 21% among hypertensive adults without a history of stroke or myocardial infarction (MI) in China. The mean SBP was highly comparable between the 2 treatment groups at baseline and during follow-up. This current post hoc analysis of the CSPPT aimed to investigate the relationship between time-averaged on-treatment SBP and the risk of first stroke in hypertensive adults with normal renal function and without CVD or diabetes mellitus.

Methods

Participants

The methods and primary results of the CSPPT trial have been reported elsewhere.[14] Briefly, the CSPPT was a multicenter, randomized controlled trial conducted from May 19, 2008, to August 24, 2013, in 32 communities in the Jiangsu and Anhui provinces in China to test the hypothesis that therapy with enalapril and folic acid is more effective in reducing first stroke than that with enalapril alone among Chinese adults with hypertension. Eligible participants were men and women aged 45 to 75 years with hypertension, defined as seated resting SBP ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg at both the screening and recruitment visits, or who had previously taken antihypertensive medication. The major exclusion criteria included history of physician-diagnosed stroke, MI, heart failure, postcoronary revascularization, and congenital heart disease.

This study was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (Federal Wide Assurance number: FWA00001263). All participants gave written informed consent prior to data collection.

Intervention and Follow-Up

Eligible participants, stratified by methylenetetrahydrofolate reductase (*MTHFR*) *C677T* genotypes (CC, CT, or TT), were randomly assigned, in a 1:1 ratio, to 1 of 2 treatment groups: a daily oral dose of 1 tablet containing 10 mg enalapril and 0.8 mg folic acid (single tablet combination; the enalapril–folic acid group) or a daily oral dose of 1 tablet containing 10 mg enalapril only (the enalapril only group). All study investigators and participants were blinded to the randomization procedure and the treatment assignments. During the trial period, concomitant use of other antihypertensive drugs (mainly calcium channel blockers or diuretics) was allowed, but not B vitamins. Participants were scheduled for follow-up every 3 months. At each follow-up visit, vital signs, study drug compliance, concomitant medication use, adverse events, and possible end point events were documented by trained research staff and physicians.

Seated BP measurements were obtained by trained research staff after the patients had been seated for 10 minutes by using a mercury manometer and using the standard method and appropriately sized cuffs. Triplicate measurements on the same arm were taken with at least 2 minutes between readings. The mean SBP and DBP of the 3 independent measures were used in the analyses.

Outcomes

The primary outcome was a first nonfatal or fatal stroke (ischemic or hemorrhagic), excluding subarachnoid hemorrhage and silent stroke. Secondary outcomes included a composite of cardiovascular events consisting of cardiovascular death, MI, and stroke and first ischemic stroke (fatal and nonfatal). All of the study outcomes were reviewed and adjudicated according to standard criteria by an independent End Point Adjudication Committee.

Statistical Analysis

Time-averaged on-treatment SBP was calculated for each participant using all of the post-baseline SBP results up to the last visit before the date of primary outcome or death or the end of follow-up in those patients without events. Participants with a history of diabetes mellitus or under treatment for diabetes mellitus at baseline were classified as having diabetes mellitus. Estimated glomerular filtration rate was calculated using the equation provided by the Chronic Kidney Disease Epidemiology Collaboration.[15]

Baseline characteristics are presented as mean (continuous variables) or percentage (categorical variables) as appropriate, stratified by time-averaged on-treatment SBP categories (120, 120–130, 130–135, 135–140, and ≥140 mm Hg). Outcomes in various groups of on-treatment SBP were compared using the Kaplan–Meier method and log-rank test. Multivariable Cox proportional hazard regression models were used to evaluate the role of on-treatment SBP on the risk of outcomes, and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated to evaluate the risks. Consistency of the results in various subgroups (sex, age, and study treatment groups) was also explored using Cox proportional hazard regression models.

A 2-tailed $P<0.05$ was considered to be statistically significant in all analyses. Empower(R) (www.empowerstats.com; X&Y solutions, Inc., Boston MA) and R software, version 3.1.2 (http://www.r-project.org) were used for all statistical analyses.

Results

Study Participants and Baseline Characteristics

The total sample of the CSPPT was 20 702. At baseline, 2288 participants with diabetes mellitus or with missing data on fasting glucose (n=361), 327 participants with estimated glomerular filtration rate <60 mL/min per 1.73 m^2 or with missing data on estimated glomerular filtration rate (n=5), and 1 participant without an SBP measurement during the follow-up period were excluded. A total of 17 720 participants constituted our final analysis set.

At baseline, 324, 3062, 3178, 3435, and 7720 participants had time-averaged on-treatment SBP <120 mm Hg, ≥120 and <130 mm Hg, ≥130 and <135 mm Hg, ≥135 and <140 mm Hg, and ≥140 mm Hg, respectively. Baseline characteristics of participants according to time-averaged on-treatment SBP categories (<120, 120–130, 130–135, 135–140, and ≥140 mm Hg) are summarized in Table 1. Participants with lower on-treatment BP tended to have younger age, lower body mass

Table 1. Characteristics of the Study Participants by Time-Averaged On-Treatment Systolic Blood Pressure Categories*

Characteristics	Total (n=17 720)	Time-Averaged On-Treatment SBP, mm Hg					P Value
		<120 (n=324)	120–130 (n=3062)	130–135 (n=3178)	135–140 (n=3436)	≥140 (n=7720)	
Age, y	59.9 (7.5)	58.2 (7.6)	58.7 (7.3)	59.3 (7.3)	59.8 (7.5)	60.7 (7.6)	<0.001
Male, N (%)	7307 (41.2)	124 (38.3)	1227 (40.1)	1344 (42.3)	1458 (42.4)	3154 (40.9)	0.145
Body mass index, kg/m^2	24.8 (3.7)	24.5 (3.4)	24.5 (3.5)	24.8 (3.7)	24.8 (3.6)	24.9 (3.8)	<0.001
Current smoking, N (%)	4268 (24.1)	68 (21)	647 (21.1)	755 (23.8)	840 (24.5)	1958 (25.4)	<0.001
Treatment group, N (%)							
Enalapril	8859 (50)	167 (51.5)	1550 (50.6)	1567 (49.3)	1699 (49.4)	3876 (50.2)	0.746
Enalapril–folic acid	8861 (50)	157 (48.5)	1512 (49.4)	1611 (50.7)	1737 (50.6)	3844 (49.8)	
Baseline blood pressure, mm Hg							
Systolic	166.5 (20.2)	149.1 (17.4)	156.1 (16.4)	161.1 (16.8)	164.6 (17.1)	174.4 (21)	<0.001
Diastolic	94.1 (11.8)	90.4 (10.5)	92 (10.7)	93.2 (10.9)	93.4 (11.3)	95.8 (12.6)	<0.001
Time-averaged on-treatment blood pressure, mm Hg							
Systolic	139.5 (11.3)	116.7 (3.0)	126.2 (2.7)	132.6 (1.4)	137.5 (1.4)	149.6 (8.6)	<0.001
Diastolic	83.2 (7.6)	76.1 (5.0)	79.3 (5.6)	81.3 (6.1)	82.6 (6.5)	86.0 (8.3)	<0.001
Laboratory results							
Fasting glucose, mmol/L	5.4 (0.7)	5.3 (0.6)	5.3 (0.7)	5.4 (0.7)	5.4 (0.7)	5.4 (0.7)	<0.001
Total cholesterol, mmol/L	5.5 (1.1)	5.3 (1.1)	5.4 (1.1)	5.5 (1.1)	5.5 (1.1)	5.5 (1.1)	0.008
HDL cholesterol, mmol/L	1.4 (0.4)	1.3 (0.3)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)	0.079
Triglycerides, mmol/L	1.6 (0.9)	1.5 (0.8)	1.6 (0.8)	1.6 (0.8)	1.6 (0.9)	1.6 (0.9)	<0.001
Creatinine, μmol/L	65.0 (13.6)	65.1 (13.5)	64.6 (13.3)	65.4 (13.7)	65.2 (13.5)	64.9 (13.6)	0.143
eGFR, mL/min per 1.73 m2	94.3 (11.3)	95.0 (11.0)	95.3 (11.0)	94.4 (11.4)	94.4 (11.2)	93.8 (11.4)	<0.001
Medication use, N (%)							
Antihypertensive drugs	7925 (44.7)	149 (46)	1346 (44)	1402 (44.1)	1491 (43.4)	3537 (45.8)	0.108
Lipid-lowering drugs	127 (0.7)	1 (0.3)	34 (1.1)	34 (1.1)	13 (0.4)	45 (0.6)	<0.001
Antiplatelet drugs	499 (2.8)	9 (2.8)	83 (2.7)	99 (3.1)	107 (3.1)	201 (2.6)	0.470

eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein; and SBP, systolic blood pressure.
*For continuous variables, values are presented as mean (SD).

index, higher folate levels, and lower serum fasting glucose, total cholesterol, triglycerides, creatinine, and homocysteine concentrations.

Time-Averaged On-Treatment SBP and Risk of Primary and Secondary Outcomes

The mean time-averaged on-treatment SBP levels were 116.7, 126.2, 132.6, 137.5, and 149.6 mm Hg, respectively, for participants with on-treatment SBP at <120, 120 to 130, 130 to 135, 135 to 140, and ≥140 mm Hg.

Over a median follow-up duration of 4.5 years, the association between time-averaged on-treatment SBP and risk of first stroke followed a U-shaped curve, with increased risk above and below the reference range of 120 to 130 mm Hg (Figure 1; Figure S1 in the online-only Data Supplement). Compared with participants with time-averaged on-treatment SBP at 120 to 130 mm Hg (mean, 126.2 mm Hg), the risk of first stroke was not only increased in participants with SBP at 130 to 135 mm Hg (mean, 132.6 mm Hg; 1.5% versus 0.8%; HR, 1.63; 95% CI, 1.01–2.63) or 135 to 140 mm Hg (mean, 137.5 mm Hg; 1.9% versus 0.8%; HR, 1.85; 95% CI, 1.17–2.93), but also increased in participants with SBP <120 mm Hg (mean, 116.7 mm Hg; 3.1% versus 0.8%; HR, 4.37; 95% CI, 2.10–9.07). Similar results were observed for the composite cardiovascular events and ischemic stroke (Table 2).

In other words, even compared with those with usual control of SBP (130–140 mm Hg), participants with a tighter SBP control (120–130 mm Hg) were associated with lower first stroke risk. Compared with those with on-treatment SBP at 135 to 140 and 130 to 135 mm Hg, the risk of first stroke in participants with on-treatment SBP at 120 to 130 mm Hg was reduced by 46% (1.9% versus 0.8%; HR, 0.54; 95% CI, 0.34–0.86) and 39% (1.5% versus 0.8%; HR, 0.61; 95% CI, 0.38–0.99), respectively. Furthermore, compared with those with uncontrolled SBP (≥140 mm Hg), a significantly lower risk of first stoke was observed in those with usual control of SBP (versus 135–140 mm Hg; 4.4% versus 1.9%; HR, 0.48; 95% CI, 0.37–0.64; versus 130–135 mm Hg; 4.4% versus 1.5%; HR, 0.43; 95% CI, 0.31–0.58; Table S1). Moreover, only 0.7% of the participants used the lipid-lowering drugs

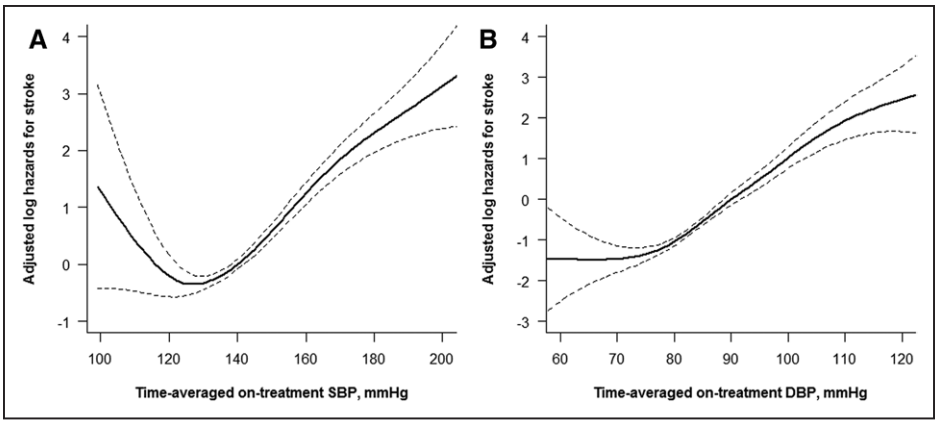

Figure 1. The association between time-averaged on-treatment systolic blood pressure (SBP) or diastolic blood pressure (DBP) and risk for first stroke.

at baseline. Excluding these participants did not substantially change the results (Table S2).

Stratified analyses were performed by sex, age (<60 versus ≥60 and <65 versus ≥65 years), and study treatment group. The lowest risk of first stroke was observed in participants with time-averaged on-treatment SBP at 120 to 130 mm Hg in all of the subgroups. There were no significant interactions in any of the subgroups (P>0.05 for all comparisons; Figure 2; Table S3).

Time-Averaged On-Treatment DBP and Risk of Primary and Secondary Outcomes

The mean time-averaged on-treatment DBP level was 75.3, 84.5, and 94.9 mm Hg, respectively, for participants with on-treatment DBP at <80, 80 to 90, and ≥90 mm Hg.

Compared with those with on-treatment DBP at <80 mm Hg, a significantly increased risk of first stroke was observed in those with DBP at 80 to 90 mm Hg (2.6% versus 1.6%; HR, 2.14; 95% CI, 1.65–2.77) or ≥90 mm Hg (5.4% versus 1.6%; HR, 5.55; 95% CI, 4.04–7.62). Similar results were observed for the composite cardiovascular events or ischemic stroke (Table 3).

More importantly, a lower on-treatment DBP was associated with a higher on-treatment pulse pressure (Table S4). However, we did not observe a U-shaped association between on-treatment DBP and risk of first stroke (Figure 1). There was no significant difference in the risk of first stroke between those with on-treatment DBP at 70 to 80 mm Hg and at <70 mm Hg (Table S4).

Discussion

The current analysis was the first study to investigate the relationship between time-averaged on-treatment SBP and the risk of first stroke in hypertensive adults with normal renal function and without CVD or diabetes mellitus. Our results suggest that a tight SBP control (120–130 mm Hg) was related to a lower risk of stroke, compared with usual control of SBP (135–140 or 130–135 mm Hg). Most importantly, an increased stroke risk was observed in those participants with a further reduction in SBP (<120 mm Hg). Furthermore, lower time-averaged on-treatment DBP was associated with a lower risk of stroke. Therefore, the increased stroke risk of those with on-treatment SBP <120 mm Hg could not be explained by the combined lowest time-averaged on-treatment DBP levels (76.1 mm Hg; Table 1).

A recent meta-analysis[16] found that intensive BP-lowering treatment provided greater vascular protection did than standard regimens. However, after randomization, the mean SBP was 133 and 140 mm Hg, respectively, in the intensive BP-lowering treatment group and in the standard treatment group. In other words, most of the patients in the standard treatment group had uncontrolled SBP (≥140 mm Hg). The Cardio-Sis,[17] ACCORD (Action to Control Cardiovascular Risk in Diabetes),[18] and SPRINT (Systolic Blood Pressure Intervention Trial)[19] are 3 randomized trials designed to assess the efficacy of tight SBP control on cardiovascular outcomes, compared with usual SBP control (130–140 mm Hg). In the Cardio-Sis trial,[17] a total of 1111 nondiabetic patients aged ≥55 years with SBP of ≥150 mm Hg were randomly assigned to a target SBP of <140 mm Hg (usual control; n=553) or <130 mm Hg (tight control; n=558). The tight SBP control was associated with lower stroke or transient ischemic attack risk (HR, 0.44; 95% CI, 0.13–1.42). However, because the average SBP was 135.6 mm Hg in the usual control group and 131.9 mm Hg in the tight control group at the end of the study (2-year trial), the Cardio-Sis trial was not able to provide informative data on the supposed benefit of an SBP target <130 mm Hg. The ACCORD and SPRINT trials aimed to compare the benefits of treatment for SBP to a target of <120 mm Hg with treatment to a target of 130 to 140 mm Hg on hypertension-related complications. As compared with the usual SBP control (ACCORD: ≈130–135 mm Hg; SPRINT: ≈135–140 mm Hg), the tight SBP control resulted in lower rates of stroke (overall: HR, 0.75; 95% CI, 0.58–0.97; ACCORD: HR, 0.59; 95% CI, 0.39–0.89; SPRINT: HR, 0.89; 95% CI, 0.64–1.09).[18,19] It is noteworthy that the number of patients with stroke in SPRINT was low with no significant difference between the 2 groups, the reason for which possibly being that SPRINT was stopped prematurely because of an expected significant difference in the soft end point heart failure (HR, 0.62; 95% CI, 0.45–0.84) because of the larger doses of diuretics throughout the treatment. However, although an average of 3 different antihypertensive drugs were used in the tight SBP control group, the average SBPs were 119.3 and 121.4 mm Hg, respectively, in the ACCORD and SPRINT

Table 2. Comparisons of Primary and Secondary Outcomes by Time-Averaged On-Treatment Systolic Blood Pressure Categories

On-Treatment SBP Categories, mm Hg	Outcomes, N (%)	HR (95% CI)	
		Model 1	Model 2
Primary outcome			
First stroke			
<120	10 (3.1%)	3.92 (1.89–8.14)	4.37 (2.10–9.07)
120–130	26 (0.8%)	Ref	Ref
130–135	48 (1.5%)	1.73 (1.07–2.79)	1.63 (1.01–2.63)
135–140	65 (1.9%)	2.13 (1.35–3.35)	1.85(1.17–2.93)
≥140	339 (4.4%)	4.90 (3.28–7.30)	3.83 (2.54–5.76)
Secondary outcomes			
Composite of stroke, myocardial infarction, or death from cardiovascular causes			
<120	13 (4.0%)	4.41 (2.30–8.46)	4.93 (2.57–9.47)
120–130	30 (1.0%)	Ref	Ref
130–135	57 (1.8%)	1.78 (1.14–2.77)	1.67 (1.07–2.60)
135–140	77 (2.2%)	2.17 (1.42–3.31)	1.88 (1.22–2.87)
≥140	379 (4.9%)	4.71 (3.25–6.84)	3.67 (2.51–5.38)
Ischemic stroke			
<120	10 (3.1%)	5.48 (2.55–11.79)	6.22 (2.89–13.40)
120–130	19 (0.6%)	Ref	Ref
130–135	38 (1.2%)	1.86 (1.07–3.22)	1.72 (0.99–2.98)
135–140	51 (1.5%)	2.23 (1.32–3.78)	1.92 (1.13–3.26)
≥140	267 (3.5%)	5.07 (3.18–8.09)	3.80 (2.36–6.13)

Model 1 was adjusted for age, sex, study centers, and study treatment groups. Model 2 was adjusted for age, sex, study centers, study treatment groups, MTHFR C677T polymorphism, body mass index, smoking, systolic and diastolic blood pressure, eGFR levels, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, folate, and homocysteine levels at baseline. CI indicates confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MTHFR, methylenetetrahydrofolate reductase; and SBP, systolic blood pressure.

studies. These results indicate that many of the participants did not reach the goal of an SBP of <120 mm Hg and instead had an SBP of 120 to 130 mm Hg even in the tight SBP control group. Furthermore, the BP measurement method used in SPRINT has resulted in lower BP values than those routinely obtained by research staff in the clinic, and the strict BP target of <120 mm Hg might actually be higher if using routine BP.[20] Consistently, even compared with those with usual control of SBP (130–135 or 135–140 mm Hg), those in the tighter SBP control group (120–130 mm Hg) significantly reduced their risk of first stroke in the CSPPT. In fact, even with a conservative BP goal of 140/90 mm Hg, the control rate of BP in hypertensive adults was only ≈50% and 9.4%, respectively, in the United States and China.[2,21] Therefore, based on the results from ACCORD, SPRINT, and the findings from the post hoc analysis of the CSPPT, and in consideration of the current challenges associated with stricter SBP control, the treatment goal to lower SBP to 120 to 130 mm Hg (rather than <120 mm Hg) is more reasonable and accessible in a high-risk population and especially in subjects without CVD, diabetes mellitus, and renal function decline, like the participants included in this subanalysis of CSPPT.

Most importantly, the CSPPT first found that the risk of first stoke was significantly increased in participants with on-treatment SBP <120 mm Hg, compared with those with on-treatment SBP at 120 to 130 mm Hg. Consistently, in previous post hoc analyses of antihypertensive treatment trials, an SBP <120 mm Hg was also associated with an increased risk for cardiovascular death (relative risk, 4.06; 95% CI, 2.11–7.80) and stroke (relative risk, 2.12; 95% CI, 0.77–5.84; versus >120 mm Hg; IDNT [Irbesartan Diabetic Nephropathy Trial]),[22] recurrent stroke (HR, 1.29; 95% CI, 1.07–1.56; versus 130–140 mm Hg; PROFESS trial [Prevention Regimen for Effectively Avoiding Second Strokes]),[23] and all-cause mortality (versus 120–130 mm Hg; INVEST [International Verapamil SR-Trandolapril Study]).[24] Moreover, an SBP <120 mm Hg, compared with the standard treatment, was associated with significantly increased risks of serious adverse events, such as hypotension, syncope, electrolyte abnormality, or estimated glomerular filtration rate <30 mL/min per 1.73 m^2, in ACCORD[18] and hypotension, acute kidney injury or acute renal failure, hypokalemia, or hyponatremia in SPRINT.[19] However, there was a rather low number of participants and especially a low number of stroke events (n=10) in the group with SBP <120 mm Hg. Therefore, in this light, our results can be viewed as hypothesis generating. Confirmation of our findings in a large-scale randomized trial is essential.

In fact, although the U-shaped phenomenon has been shown in several previous studies, some trial analyses have raised the point that the U shape applies largely to the coronary circulation but not to the cerebral circulation.[25–28] The CSPPT provides further evidence that a U shape may also exist for first stroke. Furthermore, there has been speculation that the U-shaped effect observed in these trials may be because of a form of reverse causality, whereby the low BPs were actually because of the existing increased baseline cardiovascular risk or poor health. However, this seems unlikely in the CSPPT because only participants without stroke and major coronary heart disease were enrolled. Furthermore, participants with on-treatment SBP of <120 mm Hg had lower cardiovascular risk, including younger age, lower body mass index, and lower serum fasting glucose, total cholesterol, triglycerides, and creatinine levels. In addition, the U-shaped relationship between SBP and the risk of first stroke persisted even after controlling for baseline covariates. Further analysis of the ACCORD and SPRINT trials could provide more evidence about the risks and benefits associated with an on-treatment SBP of <120 mm Hg in high-risk populations.

As noted, the Eighth Joint National Committee recommended different SBP control goals for participants aged <60 and ≥60 years.[13] However, the lowest risk of first stroke was found in participants with on-treatment SBP at 120 to 130 mm Hg in all of the age subgroups (<60 versus ≥60 and <65 versus ≥65 years) in the CSPPT. Furthermore, the greater beneficial effect on the primary outcome (the first occurrence of MI, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) was observed in the intensive BP control group (versus standard BP control group) among

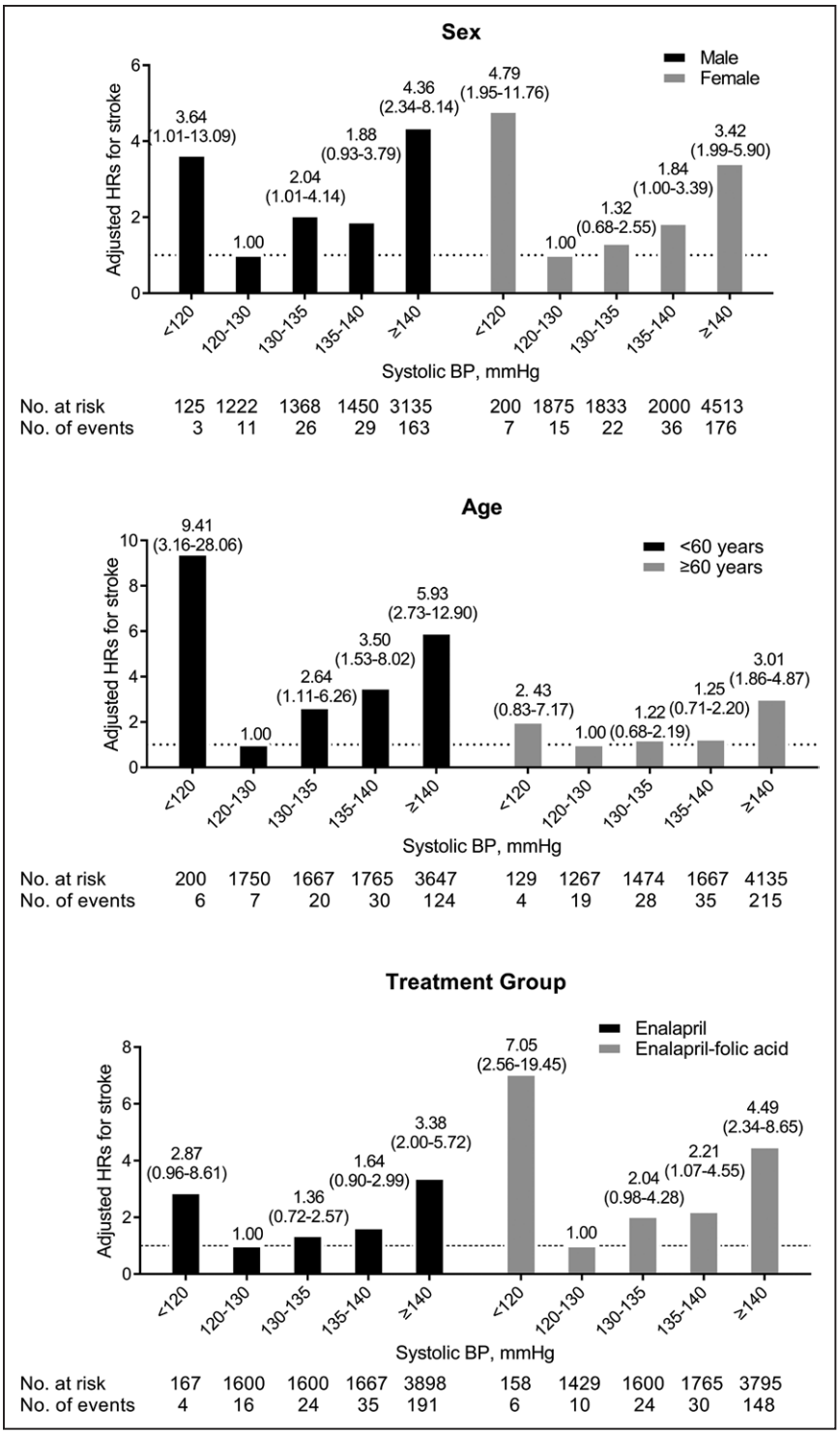

Figure 2. Comparisons of first stroke by time-averaged on-treatment systolic blood pressure (SBP) categories in different subgroups. HR indicates hazard ratio.

participants aged ≥75 years (HR, 0.67; 95% CI, 0.51–0.86 versus <75 years, HR, 0.80; 95% CI, 0.54–1.00) in the SPRINT trial.[19] These results consistently suggest that older participants with hypertension may also benefit from stricter SBP control.

The CSPPT was conducted in Chinese adults without preexisting stroke or MI. Our findings in patients with SBP <120 mm Hg and low cardiovascular risk extend on similar previous results. This study also had several limitations. First, this was a post hoc analysis of a randomized clinical trial that did not randomize participants to different on-treatment SBP groups. This could have led to possible confounding because of differences between the SBP groups both at baseline and during follow-up. Although we adjusted our analysis for baseline confounders, we cannot exclude the possibility that unmeasured confounding may explain some of our findings. Second, just as in the Cardio-Sis study,[17] we did not measure glycosylated hemoglobin A1c or perform glucose tolerance tests at baseline. Third, the CSPPT was underpowered for assessing the association between on-treatment BP and the

Table 3. Comparisons of Primary and Secondary Outcomes by Time-Averaged On-Treatment Diastolic Blood Pressure Categories

On-Treatment DBP Category, mm Hg	Outcome, N (%)	HR (95% CI)	
		Model 1	Model 2
Primary outcome			
First stroke			
<80	99 (1.6%)	Ref	Ref
80–90	225 (2.6%)	2.09 (1.64–2.66)	2.14 (1.65–2.77)
≥90	164 (5.4%)	5.79 (4.41–7.61)	5.55 (4.04–7.62)
Secondary outcomes			
Composite of stroke, myocardial infarction, or death from cardiovascular causes			
<80	121 (2.0%)	Ref	Ref
80–90	252 (2.9%)	1.95 (1.56–2.44)	1.97 (1.55–2.50)
≥90	183 (6.0%)	5.47 (4.25–7.04)	5.18 (3.86-6.95)
Ischemic stroke			
<80	83 (1.4%)	Ref	Ref
80–90	180 (2.1%)	1.98 (1.52–2.59)	1.98 (1.49–2.63)
≥90	122 (4.0%)	5.17 (3.81–7.02)	4.72 (3.31–6.72)

Model 1 was adjusted for age, sex, study centers, and study treatment groups. Model 2 was adjusted for age, sex, study centers, study treatment groups, MTHFR C677T polymorphism, body mass index, smoking, systolic and diastolic blood pressure, eGFR levels, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, folate, and homocysteine levels at baseline. CI indicates confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MTHFR, methylenetetrahydrofolate reductase; and DBP, diastolic blood pressure.

risk of first hemorrhagic stroke or nonstroke events in the composite of cardiovascular events. Fourth, a time-averaged on-treatment BP of 120 to 130 mm Hg or <120 mm Hg in our current study is not exactly the same as BP management with a strict goal of SBP control of 120 to 130 mm Hg or <120 mm Hg. Furthermore, our current study could not evaluate whether the effect of having a decreasing average over time in the interval 120 to 130 mm Hg was more important than consistently being at target 120 to 130 mm Hg. The time-averaged on-treatment BP reflects the effect of long-term control of the on-treatment office BP. The major problem with time-averaged on-treatment BP is the difficulty in implementing it shortly after the start of treatment. It will take some time to have a good idea of a patient's time-averaged on-treatment BP in a prospective context. Furthermore, we cannot neglect the modifying effect of visit-to-visit BP variability. In the current study, SBP variability, which was defined as the standard deviation of all post baseline SBP results up to the last visit before the date of primary outcome or death or the end of follow-up in those patients without events, was also significantly associated with the risk of stroke (per SD increase of the SBP SD: HR, 1.64; 95% CI, 1.27–2.13). However, further adjustment for BP variability did not substantially change our results (Table S5). The other important limitation is that we could not evaluate the effect of 24-hour ambulatory BP in the present study. Overall, the CSPPT was not specifically designed to determine the office BP goal for the prevention of CVD. Our current results merely indicated the possible beneficial or detrimental effect when the long-term mean on-treatment BP was reduced to a certain level. Therefore, confirmation of our findings in a large-scale clinical trial of participants who are randomized to different on-treatment SBP targets is essential.

Perspectives

In conclusion, a lower SBP goal of 120 to 130 mm Hg, as compared with the target SBP of 130 to 140 mm Hg or <120 mm Hg, resulted in the lowest risk of first stroke among adults with hypertension in China without a history of stroke or MI, diabetes mellitus, and renal function decline. Our data provide new evidence for setting a lower SBP goal than is currently recommended in general hypertensive patients for the primary prevention of stroke. This finding may have great implications for other hypertensive populations living in regions, such as China, where there is a higher risk of stroke than MI.

Acknowledgments

We thank Alberto Zanchetti, MD (Scientific Director, Istituto Auxologico Italiano IRCCS and Centro Interuniversitario di Fisiologia Clinica e Ipertensione, University of Milan, Milan, Italy), for his helpful review and comments on the article. No compensation was provided for these contributions.

Sources of Funding

This work was supported by Shenzhen AUSA Pharmed Co. Ltd. and national, provincial, and private funding, including support from the following: The Projects of National Natural Science Foundation of China (Grant No. 81473052 and Grant No. 81402735); National Key Research and Development Program 2016YFC0903100; National Key Technologies R&D Program, 2016 YFC0904900; NSFC Innovative Group grant, 81521003; The National Science and Technology Major Projects Specialized for "Major New Drugs Innovation and Development" during the 12th Five-year Plan Period: China Stroke Primary Prevention Trial (Grant No. zx09101105), Clinical Center Grant (Grant No. zx09401013); The Major State Basic Research Development Program of China (program 973; Grant No. 2012 CB517703); The National Clinical Research Center for Kidney Disease, Nanfang Hospital, Nanfang Medical University, Guangzhou, China; and The State Key Laboratory for Organ Failure Research, Nanfang Hospital, Nanfang Medical University, Guangzhou, China. The funding sources participated in the study design, but had no role in any of the following: the conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; or the decision to submit the article for publication.

Disclosures

Y. Huo reports grants from the National Science and Technology Major Project. F. Hou reports grants from the Major State Basic Research Development Program of China, Ministry of Science and Technology of the People's Republic of China, and State Key Laboratory for Organ Failure Research, Guangzhou, China. Prof Xu reports grants from National Science and Technology Major Projects of China, grants from National Natural Science Foundation of China. N. Sun reports grants from the Ministry of Science and Technology of the People's Republic of China and the Major State Basic Research Development Program of China. X. Qin reports grants from the National Natural Science Foundation and consulting fees from AUSA Research Institute, Shenzhen AUSA. The other authors report no conflicts.

References

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217–223. doi: 10.1016/S0140-6736(05)17741-1.

2. Wang J, Zhang L, Wang F, Liu L, Wang H; China National Survey of Chronic Kidney Disease Working Group. Prevalence, awareness, treatment, and control of hypertension in China: results from a national survey. *Am J Hypertens*. 2014;27:1355–1361. doi: 10.1093/ajh/hpu053.
3. GBD 2013 Risk Factors Collaborators; Forouzanfar MH, Alexander L, Anderson HR, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386:2287–2323. doi: 10.1016/S0140-6736(15)00128-2.
4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
5. Mancia G, Kjeldsen SE, Zappe DH, Holzhauer B, Hua TA, Zanchetti A, Julius S, Weber MA. Cardiovascular outcomes at different on-treatment blood pressures in the hypertensive patients of the VALUE trial. *Eur Heart J*. 2016;37:955–964. doi: 10.1093/eurheartj/ehv633.
6. Zanchetti A. Blood pressure targets of antihypertensive treatment: up and down the J-shaped curve. *Eur Heart J*. 2010;31:2837–2840. doi: 10.1093/eurheartj/ehq281.
7. Mancia G, Schumacher H, Redon J, Verdecchia P, Schmieder R, Jennings G, Yusoff K, Ryden L, Liu GL, Teo K, Sleight P, Yusuf S. Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET). *Circulation*. 2011;124:1727–1736. doi: 10.1161/CIRCULATIONAHA.110.008870.
8. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels–overview and meta-analyses of randomized trials. *J Hypertens*. 2014;32:2296–2304. doi: 10.1097/HJH.0000000000000379.
9. MRC trial on treatment of mild hypertension: principal results. Medical Research Council Working Party. *Br Med J*. 1985;291:97–104.
10. The effect of treatment on mortality in "mild" hypertension: results of the hypertension detection and follow-up program. *N Engl J Med*. 1982;307:976–980.
11. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A; FEVER Study Group. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. *J Hypertens*. 2005;23:2157–2172.
12. Mancia G, Fagard R, Narkiewicz K, et al; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–1357. doi: 10.1097/01.hjh.0000431740.32696.cc.
13. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–520. doi: 10.1001/jama.2013.284427.
14. Huo Y, Li J, Qin X, et al; CSPPT Investigators. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA*. 2015;313:1325–1335. doi: 10.1001/jama.2015.2274.
15. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
16. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet*. 2016;387:435–443. doi: 10.1016/S0140-6736(15)00805-3.
17. Verdecchia P, Staessen JA, Angeli F, de Simone G, Achilli A, Ganau A, Mureddu G, Pede S, Maggioni AP, Lucci D, Reboldi G; Cardio-Sis investigators. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet*. 2009;374:525–533. doi: 10.1016/S0140-6736(09)61340-4.
18. Cushman WC, Evans GW, Byington RP, et al; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585. doi: 10.1056/NEJMoa1001286.
19. Wright JT Jr, Williamson JD, Whelton PK, et al; SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015;373:2103–2116. doi: 10.1056/NEJMoa1511939.
20. Agarwal R. Hypertension: Rest before blood pressure measurement: a lesson from SPRINT. *Nat Rev Nephrol*. 2016;12:127–128. doi: 10.1038/nrneph.2016.2.
21. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA*. 2010;303:2043–2050. doi: 10.1001/jama.2010.650.
22. Berl T, Hunsicker LG, Lewis JB, et al; Collaborative Study Group. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. *J Am Soc Nephrol*. 2005;16:2170–2179. doi: 10.1681/ASN.2004090763.
23. Ovbiagele B, Diener HC, Yusuf S, Martin RH, Cotton D, Vinisko R, Donnan GA, Bath PM; PROFESS Investigators. Level of systolic blood pressure within the normal range and risk of recurrent stroke. *JAMA*. 2011;306:2137–2144. doi: 10.1001/jama.2011.1650.
24. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, Pepine CJ. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA*. 2010;304:61–68. doi: 10.1001/jama.2010.884.
25. Arima H, Chalmers J, Woodward M, Anderson C, Rodgers A, Davis S, Macmahon S, Neal B; PROGRESS Collaborative Group. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. *J Hypertens*. 2006;24:1201–1208. doi: 10.1097/01.hjh.0000226212.34055.86.
26. Sleight P, Redon J, Verdecchia P, Mancia G, Gao P, Fagard R, Schumacher H, Weber M, Böhm M, Williams B, Pogue J, Koon T, Yusuf S; ONTARGET investigators. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. *J Hypertens*. 2009;27:1360–1369. doi: 10.1097/HJH.0b013e32832d7370.
27. Bangalore S, Messerli FH, Wun CC, Zuckerman AL, DeMicco D, Kostis JB, LaRosa JC; Treating to New Targets Steering Committee and Investigators. J-curve revisited: an analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Heart J*. 2010;31:2897–2908. doi: 10.1093/eurheartj/ehq328.
28. Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP; PROVE IT-TIMI 22 Trial Investigators. What is the optimal blood pressure in patients after acute coronary syndromes?: Relationship of blood pressure and cardiovascular events in the PRavastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. *Circulation*. 2010;122:2142–2151. doi: 10.1161/CIRCULATIONAHA.109.905687.

Novelty and Significance

What Is New?

- Most of the current guidelines recommend lowering systolic blood pressure (SBP) to <140 mm Hg in all adults with hypertension.
- However, the level to which SBP should be controlled to maintain optimal health in general hypertensive adults without cardiovascular disease, diabetes mellitus, and renal function decline remains unclear.

What Is Relevant?

- Our data provide new evidence for a lower SBP goal than is currently recommended to general hypertensive patients for the primary prevention of stroke.
- Setting a new recommendation for a lower SBP goal may have great implications for other hypertensive populations living in regions such as China, where there is a higher risk of stroke than myocardial infarction.

Summary

Among adults with hypertension and without a history of stroke or myocardial infarction, diabetes mellitus, or renal function decline, we showed that a lower SBP goal of 120 to <130 mm Hg, as compared with the current target SBP of 130 to <140 mm Hg or <120 mm Hg, resulted in the lowest risk of first stroke.

Hypertension
Journal of the American Heart Association

Optimal Systolic Blood Pressure Levels for Primary Prevention of Stroke in General Hypertensive Adults: Findings From the CSPPT (China Stroke Primary Prevention Trial)

Fangfang Fan, Ziwen Yuan, Xianhui Qin, Jianping Li, Yan Zhang, Youbao Li, Tao Yu, Meng Ji, Junbo Ge, Meili Zheng, Xinchun Yang, Huihui Bao, Xiaoshu Cheng, Dongfeng Gu, Dong Zhao, Jiguang Wang, Ningling Sun, Yundai Chen, Hong Wang, Xiaobin Wang, Gianfranco Parati, Fanfan Hou, Xiping Xu, Xian Wang, Gang Zhao and Yong Huo

Hypertension. 2017;69:697-704; originally published online February 27, 2017;
doi: 10.1161/HYPERTENSIONAHA.116.08499
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

SUPPLEMENT MATERIAL

Title: Optimal systolic blood pressure levels for primary prevention of stroke in general hypertensive adults: findings from the China Stroke Primary Prevention Trial (CSPPT)

Running Title: Optimal blood pressures in general hypertensives

Correspondence and reprint requests should be addressed to:

Yong Huo, MD

Department of Cardiology, Peking University First Hospital

Beijing, China

Email: huoyong@263.net.cn

Phone: 86-10-83572283

Fax: 86-10-66137748

OR

Gang Zhao, MD

Department of Neurology, Xijing Hospital, Forth Military Medical University,

Xi'an, China

Email: zhaogang@fmmu.edu.cn

Phone: 86-29-84775361

Fax: 86-29-82551806

OR

Xian Wang, PhD

Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Peking University

Beijing, China

Email: xwang@bjmu.edu.cn

Phone: 86-10- 82801443

Table S1. Comparisons of first stroke by time-averaged on-treatment systolic blood pressure (SBP) categories

Table S2. Comparisons of primary outcome by time-averaged on-treatment systolic blood pressure (SBP) categories with the exclusion of participants using the lipid lowering drugs at baseline

Table S3. Comparisons of first stroke by time-averaged on-treatment systolic blood pressure (SBP) categories in different subgroups

Table S4. Comparisons of primary outcome by time-averaged on-treatment diastolic blood pressure (DBP) categories

Table S5. Comparisons of primary outcome by time-averaged on-treatment systolic blood pressure (SBP) categories with further adjustment for the standard deviance (SD) of the SBP during the treatment period

Figure S1. Kaplan-Meier curves of cumulative hazards for first stroke by the SBP categories

Table S1. Comparisons of first stroke by time-averaged on-treatment systolic blood pressure (SBP) categories

On-treatment SBP categories, mmHg	Adjusted* HR (95%CI)		
<120	2.68(1.35, 5.31)	2.36(1.21, 4.63)	1.14(0.60, 2.17)
120-130	0.61(0.38, 0.99)	0.54(0.34, 0.86)	0.26(0.17, 0.39)
130-135	Ref	0.88(0.60, 1.28)	0.43(0.31, 0.58)
135-140	1.14(0.78, 1.66)	Ref	0.48(0.37, 0.64)
≥140	2.35(1.72, 3.20)	2.07(1.57, 2.73)	Ref

*Adjusted for age, sex, study centers, MTHFR C677T polymorphism, study treatment groups, body mass index, smoking, systolic blood pressure and diastolic blood pressure, eGFR levels, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, folate and homocysteine levels at baseline.

Table S2. Comparisons of primary outcome by time-averaged on-treatment systolic blood pressure (SBP) categories with the exclusion of participants using the lipid lowering drugs at baseline

On-treatment SBP categories, mmHg	Outcomes, No.(%)	HR (95%CI)*
<120	10(3.1%)	4.34(2.09, 9.00)
120-130	26(0.9%)	Ref
130-135	48(1.5%)	1.63(1.01, 2.62)
135-140	63(1.8%)	1.77(1.12, 2.81)
≥140	337(4.4%)	3.75(2.49, 5.65)

*Adjustment for age, sex, study centers, study treatment groups, MTHFR C677T polymorphism, body mass index, smoking, systolic blood pressure and diastolic blood pressure, eGFR levels, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, folate and homocysteine levels at baseline.

Table S3. Comparisons of first stroke by time-averaged on-treatment systolic blood pressure (SBP) categories in different subgroups

On-treatment SBP categories, mmHg	Outcomes, No.(%)	Model 1	Model 2	*P* for interaction
		HR(95%CI)	HR (95%CI)	
Sex				0.692
Male				
<120	3(2.4)	2.94(0.82, 10.54)	3.64(1.01, 13.09)	
120-130	11(0.9)	Ref	Ref	
130-135	26(1.9)	2.14(1.06, 4.33)	2.04(1.01, 4.14)	
135-140	29(2.0)	2.16(1.08, 4.33)	1.88(0.93, 3.79)	
≥140	163(5.2)	5.56(3.01, 10.24)	4.36(2.34, 8.14)	
Female				
<120	7(3.5)	4.53(1.85, 11.12)	4.79(1.95, 11.76)	
120-130	15(0.8)	Ref	Ref	
130-135	22(1.2)	1.43(0.74, 2.75)	1.32(0.68, 2.55)	
135-140	36(1.8)	2.11(1.16, 3.86)	1.84(1.00, 3.39)	
≥140	176(3.9)	4.40(2.59, 7.47)	3.42(1.99, 5.90)	
Age, years				0.223
<60 years				
<120	6(3.0)	8.03(2.70, 23.90)	9.41(3.16, 28.06)	
120-130	7(0.4)	Ref	Ref	
130-135	20(1.2)	2.96(1.25, 7.00)	2.64(1.11, 6.26)	
135-140	30(1.7)	4.28(1.88, 9.75)	3.50(1.53, 8.02)	
≥140	124(3.4)	8.83(4.12, 18.90)	5.93(2.73, 12.90)	
≥60 years				
<120	4(3.1)	2.29(0.78, 6.74)	2.43(0.83, 7.17)	
120-130	19(1.5)	Ref	Ref	
130-135	28(1.9)	1.28(0.71, 2.29)	1.22(0.68, 2.19)	
135-140	35(2.1)	1.41(0.80, 2.46)	1.25(0.71, 2.20)	
≥140	215(5.2)	3.58(2.24, 5.73)	3.01(1.86, 4.87)	
Age, years				
<65 years				0.403
<120	7(2.6)	3.91(1.62, 9.43)	4.26(1.77, 10.28)	

120-130	17(0.7)	Ref	Ref	
130-135	38(1.6)	2.22(1.25, 3.93)	2.01(1.13, 3.56)	
135-140	40(1.6)	2.26(1.28, 3.98)	1.86(1.04, 3.30)	
≥140	205(3.9)	5.54(3.38, 9.08)	3.98(2.39, 6.62)	
≥65 years				
<120	3(5.2)	4.10(1.11, 15.16)	5.08(1.37, 18.86)	
120-130	9(1.4)	Ref	Ref	
130-135	10(1.3)	0.95(0.39, 2.33)	0.92(0.37, 2.26)	
135-140	25(2.6)	1.93(0.90, 4.14)	1.77(0.82, 3.83)	
≥140	134(5.5)	4.15(2.11, 8.17)	3.51(1.76, 6.99)	
Treatment Groups				0.719
Enalapril				
<120	4(2.4)	2.49(0.83, 7.46)	2.87(0.96, 8.61)	
120-130	16(1.0)	Ref	Ref	
130-135	24(1.5)	1.45(0.77, 2.73)	1.36(0.72, 2.57)	
135-140	35(2.1)	1.91(1.06, 3.45)	1.64(0.90, 2.99)	
≥140	191(4.9)	4.53(2.72, 7.56)	3.38(2.00, 5.72)	
Enalapril-Folic Acid				
<120	6(3.8)	6.34(2.30, 17.46)	7.05(2.56, 19.45)	
120-130	10(0.7)	Ref	Ref	
130-135	24(1.5)	2.17(1.04, 4.55)	2.04(0.98, 4.28)	
135-140	30(1.7)	2.47(1.21, 5.05)	2.21(1.07, 4.55)	
≥140	148(3.9)	5.47(2.88, 10.39)	4.49(2.34, 8.65)	

Model 1 was adjusted for age, sex, study centers and study treatment groups.

Model 2 was adjusted for age, sex, study centers, study treatment groups, MTHFR C677T polymorphism, body mass index, smoking, systolic blood pressure and diastolic blood pressure, eGFR levels, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, folate and homocysteine levels at baseline.

Table S4. Comparisons of primary outcome by time-averaged on-treatment diastolic blood pressure (DBP) categories

On-treatment DBP category, mmHg	Mean pulse pressure, mean(SD)	Outcome, No.(%)	Model 1	Model 2
			HR (95% CI)	HR (95% CI)
<70	68.1(12.2)	9(1.8%)	0.78(0.39, 1.55)	0.62(0.29, 1.36)
70-80	59.0(10.1)	90(1.7%)	Ref	Ref
80-90	54.7(9.6)	225(2.6%)	2.04(1.59, 2.62)	2.14(1.62, 2.82)
≥90	54.1(10.9)	164(5.4%)	5.66(4.28, 7.48)	5.16(3.67, 7.26)

Model 1 was adjusted for age, sex, study centers and study treatment groups.

Model 2 was adjusted for age, sex, study centers, study treatment groups, MTHFR C677T polymorphism, body mass index, smoking, systolic blood pressure and diastolic blood pressure, eGFR levels, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, folate and homocysteine levels at baseline.

Table S5. Comparisons of primary outcome by time-averaged on-treatment systolic blood pressure (SBP) categories with further adjustment for the standard deviance (SD) of the SBP during the treatment period

On-treatment SBP categories, mmHg	Outcomes, No.(%)	HR (95%CI)*
<120	10(3.1%)	2.70(1.02, 7.17)
120-130	26(0.8%)	Ref
130-135	48(1.5%)	1.68(0.99, 2.85)
135-140	65(1.9%)	2.17(1.32, 3.58)
≥140	339(4.4%)	4.27(2.71, 6.74)

*Adjustment for age, sex, study centers, study treatment groups, standard deviance (SD) of the SBP during the treatment period, MTHFR C677T polymorphism, body mass index, smoking, systolic blood pressure and diastolic blood pressure, eGFR levels, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, folate and homocysteine levels at baseline.

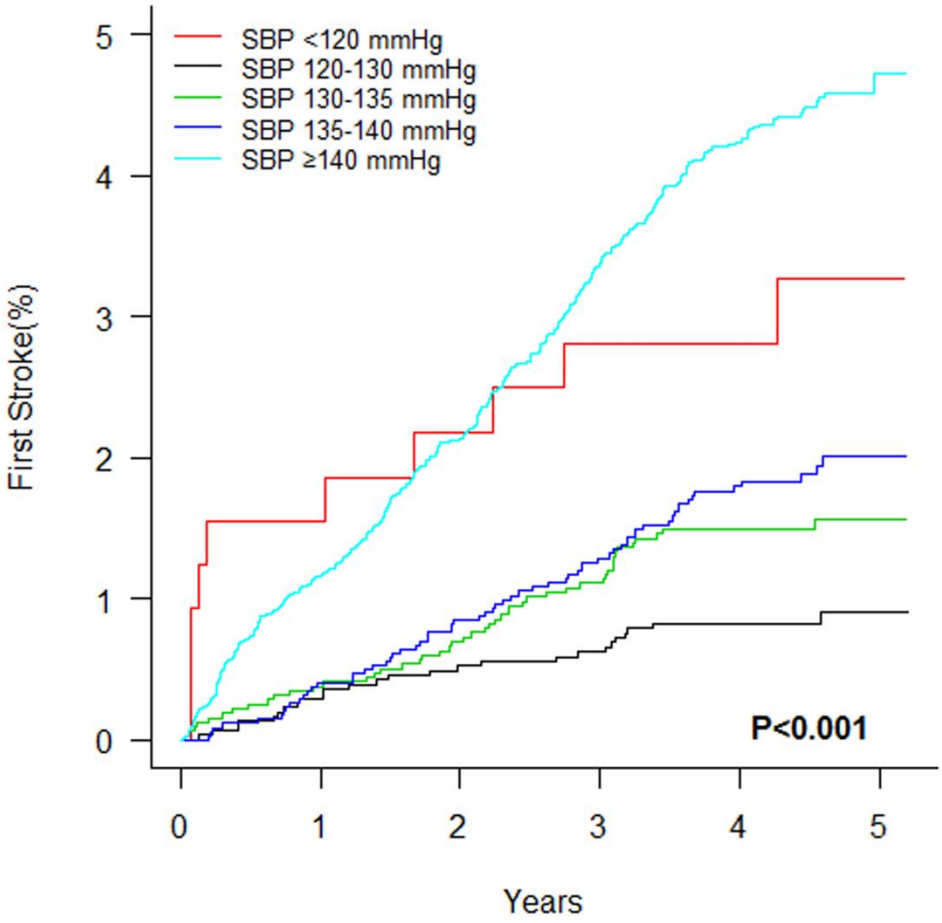

Figure S1. Kaplan-Meier curves of cumulative hazards for first stroke by the SBP categories