Editorial

# Identifying the optimal blood pressure target for ideal health

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## INTRODUCTION

Hypertension is a major public health concern, affecting more than one billion adults worldwide and about 300 million in China[1,2]. Abundant epidemiological studies have proven that antihypertensive treatment is effective in both preventing the development of and delaying the progression of cardiovascular (CV) and/or cerebrovascular disease.[3-4] However, the optimal blood pressure (BP) target that is protective against cardio-cerebrovascular disease risk remains controversial. A number of unresolved scientific issues still remain to be explored.

## CURRENT CLINICAL GUIDELINES IN THE UNITED STATES AND EUROPE

The Eighth Joint National Committee (JNC 8) recommended a systolic blood pressure (SBP) goal of less than 150 mmHg and a diastolic blood pressure (DBP) goal of less than 90 mmHg in the general hypertensive population aged 60 years or older. For the general hypertensive population younger than 60 years of age and those with chronic kidney disease (CKD) or diabetes mellitus (DM), an SBP goal of less than 140 mmHg and a DBP goal of less than 90 mmHg is recommended.[5] Of note, only those recommendations for the general population aged 60 years or older were based on "Grade A" evidence, that is, supported by sufficient evidence from randomized controlled trials (RCTs). The other recommendations were based on "Grade E" evidence, or that of expert opinion. The JNC 8 clearly stated an absence or insufficiency of substantial evidence regarding BP goal recommendations for these two populations. However, the Clinical Practice Guidelines for the Management of Hypertension in the Community promulgated by the American Society of Hypertension and the International Society of Hypertension (ASH/ISH)[6] as well as the 2013 Guidelines for the Management of Arterial Hypertension promulgated by the European Society of Hypertension and the European Society of Cardiology (ESH/ESC)[7] have both recommended initiating pharmacologic therapy when BP is 150/90 mmHg or greater and maintaining a BP below that value for the general population aged 80 years or older. Moreover, the BP goals recommended for patients with DM differed between the JNC 8 and the ESH/ESC: the latter recommending a BP goal of less than 140/85 mmHg. Therefore, controversies remain in terms of identifying the optimal BP targets for the prevention of end organ diseases, because of the absence of strong evidence produced from high-quality and precisely designed RCTs.

## OPTIMAL BP TARGETS FOR ELDERLY HYPERTENSIVE PATIENTS

Establishing an ideal BP target for the elderly hypertensive population is a challenge. First, there is no uniform consensus on the definition of "elderly." As mentioned previously, the JNC 8 recommended a BP goal of less than 150/90 mmHg for the population aged 60 or older, which is

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10 mmHg higher than that of the JNC 7 (SBP less than 140 mmHg) and was based on expert opinion. Although the ESH/ECS recommended the same goal as the JNC 8, the cut-off age identified in the ESH/ESC hypertension management guidelines is 80 years of age as opposed to 60 years for the JNC 8. Notably, there was no consensus in either guideline regarding the BP treatment goal for the population aged 60–80 years. It remains to be determined whether a BP goal of less than 140 mmHg or less than 150 mmHg is more appropriate for this age group of hypertensive patients.

Evidence used to support the lower BP target (<140 mmHg) in the hypertensive population aged 60–80 years in the ESH/ESC hypertension guidelines was mainly based on a subanalysis of the FEVER study, where data suggested that for hypertensive patients older than 65 years of age, those in the felodipine treatment group whose SBP was lowered to a mean of 139.7 mmHg compared with those in the placebo group whose mean SBP was 145.5 mmHg showed a significantly reduced risk of stroke, CV events, cardiac events, and all deaths by about 40–50%[8]. In fact, almost all previously conducted successful trials on elderly hypertensive patients recruited patients with a baseline SBP of 160 mmHg or greater, and in most, the mean baseline SBP was greater than 170 mmHg, with an achieved SBP of 140 mmHg or greater.[9] To date, there is a lack of RCTs to support that a BP target of less than 140 mmHg would be most beneficial to the elderly population with hypertension.

The committee's decision to exclude a lower BP treatment goal in the JNC 8 guidelines was mostly based on evidence from two trials from Japan. Both the JATOS[10] and the VALISH[11] trials recruited elderly Japanese hypertensive patients, and their results showed that subjects who achieved SBP values below 140 mmHg on a tight BP controlled regimen compared with subjects with SBP values above 140 mmHg did not demonstrate a benefit in reducing CV events. What's more, in the JATOS trial, an increased risk of CV events was observed for participants aged 75 years or older in the strict BP control group compared with those in the mild BP control group.

## OPTIMAL BP TARGETS FOR HYPERTENSIVE PATIENTS WITH DIABETES MELLITUS

The HOT (Hypertension Optimal Treatment) study[12] is frequently cited as important evidence in support of the optimal BP target currently recommended for patients with diabetes. The trial enrolled 18,790 patients aged 50–80 years from 26 countries, with DBP between 100 and 115 mmHg, who were randomly assigned to one of the three targeted DBP groups: ≤90, ≤85, or ≤80 mmHg. During the treatment with follow-up period of 3.8 years, patients with DM experienced a 51% reduction in major CV events and about a 30% reduction in all stroke for the target DBP ≤ 80 mmHg group compared with the target DBP ≤ 90 mmHg group (major CV events: *P* value for trend = 0.005, all stroke: *P* value for trend = 0.34). CV mortality was also significantly lower in the DBP ≤ 80 mmHg group than in each of the other groups; however, risk of other endpoints showed no significant difference. Another commonly cited study to support the current recommendation is the UKPDS[13] (UK Prospective Diabetes Study Group). The data did suggest that a BP goal of less than 150/85 mmHg brought a significant decrease in risk for all cardiovascular disease (CVD); however, it provided no additional evidence to support a lower BP target. The recommendation of an SBP target of less than 140 mmHg is partly based on the evidence from the ABCD[14] (Appropriate Blood Pressure Control in Diabetes) study, which enrolled patients aged 40–74 years and whose results indicated that the effects of intensive therapy lowered the incidence of all-cause mortality when compared to moderate therapy (5.5% *vs*. 10.7%, *P* = 0.037; the average achieved BP: 132/78 mmHg *vs*. 138/86 mmHg). However, the sample size was too small (less than 500 patients), CV endpoints were merely secondary outcomes, and the results regarding various hard endpoints were different. Additionally, a recent PROBE (Prospective Randomized Open-label Blinded End-point Trial) trial, the ACCORD[15] study (Action to Control Cardiovascular Risk in Diabetes), which compared an SBP goal of less than 140 mmHg with a lower SBP goal of less than 120 mmHg, failed to find a significant reduction in incidence of major CV events in patients with diabetes whose SBP achieved an average of 119 mmHg, compared with patients whose SBP remained at an average of 133 mmHg. The inconsistent results from these four studies indicate that high-quality randomized trials are still needed to clarify both age-specific and gender-specific BP targets for hypertensive patients with DM.

## OPTIMAL BP TARGETS FOR HYPERTENSIVE PATIENTS WITH CHRONIC KIDNEY DISEASE

For hypertensive patients with CKD, evidence regarding the optimal BP target is insufficient and often clouded with uncertainty regarding the respective effect of antihypertensive treatment and renin–angiotensin system (RAS) blockers on CKD[16]. The current recommendation of a BP goal of less than 140/90 mmHg for these patients is mostly based on three trials.[17-19] The AASK (African American Study of Kidney Disease and Hypertension) study,[17] a 3-by-2 factorial design, enrolled 1,094 African American patients aged 18–70 years who had hypertensive

CKD. Patients were randomly assigned to receive either intensive BP control (a mean BP target of less than 92 mmHg) or standard control (a mean BP target of 102–107 mmHg). After 3–6.5 years of follow-up, although mean BP was significantly lower in the intensive control group than in the standard control group (130/78 mmHg *vs.* 141/86 mmHg), there was no significant difference in the risk of the primary outcome (progression of CKD), and this remained even after extended follow-up, for which the corresponding average BPs were 131/78 and 134/78 mmHg, in the intensive and standard control groups, respectively. The other two studies, the MDRD study[18] (Modification of Diet in Renal Disease) and the Rein-2 study[19] also failed to show that BP treatment to attain a BP goal of 140/90 mmHg or less significantly lowered CVD or renal endpoints. Actually, we found two additional studies [20,21] that attempted to explore the effects of an SBP goal of 130 mmHg or less; however, both studies found no meaningful information because of a failure of the tightly controlled group to achieve the BP goal .Evidence remains insufficient to support a lower BP target for the population with CKD, and more exploration is needed to fill this gap.

## NEW FINDINGS FROM RECENT STUDIES ON OPTIMAL BP TARGETS

It is noteworthy that recently published meta-analyses and clinical trials have provided new data regarding optimal BP targets, and consequently, these results raise new questions for further research. A recent meta-analysis[22] found that a tight BP-lowering treatment provided greater vascular protection than moderate treatment regimens. However, the mean SBP during treatment was 133 and 140 mmHg, respectively, in the tight BP-lowering treatment group and the moderate treatment group, that is, most of the patients in the standard treatment group had uncontrolled SBP (140 mmHg or greater).

Recently, two trials with a PROBE design, focusing on optimal BP targets attracted worldwide attention: the ACCORD study[15] and the SPRINT (The Systolic Blood Pressure Intervention Trial) study[23]. Both are randomized trials designed to assess the efficacy of tight SBP control (less than 120 mmHg) on CV outcomes, compared with usual SBP control (130–140 mmHg). The ACCORD study showed that throughout a mean follow-up of 4.7 years, the average SBP was 119.3 and 133.5 mmHg in the intensive treatment group and standard treatment group, respectively. Although the trial indicated a significant reduction of stroke (hazard ratio (HR): 0.59, 95% confidence interval (CI): 0.39–0.89) in the intensive treatment group, there were no statistically significant reductions for the primary outcomes of composite of CV death, nonfatal myocardial infarction, or nonfatal stroke. In contrast to the findings of the ACCORD study, the SPRINT study reported a mean SBP of 121.5 mmHg for the intensive treatment group and 134.6 mmHg for the standard treatment group. The intensive antihypertensive treatment lowered the relative risk by 25% for the primary outcome and the composite of outcomes including myocardial infarction, other acute coronary syndromes, stroke, heart failure, and death from CV causes compared to the standard treatment (HR: 0.75, 95%CI: 0.58–0.97). We believe that the following may explain the differences in results between the two trials. First, the ACCORD trial exclusively enrolled participants with diabetes, whereas the SPRINT trial excluded participants with diabetes. Additionally, participants enrolled in the SPRINT trial were relatively older (mean age of 68 years *vs.* 62 years in the ACCORD trial), with 28% of the participants with CKD and 28% of the participants aged 75 years or older. The data suggested that the greatest beneficial effect on the primary outcome was observed among the intensive treatment group among older patients (≥75 years: HR = 0.67; 95%CI: 0.51–0.86 *vs.* <75 years: HR = 0.80; 95%CI: 0.54–1.00). These results imply that patients even older than 75 years may well tolerate more intensive treatment and the benefits derived from more intensive treatment may inherently be different for patients with diabetes than those without, despite other risk factors of CVD. Second, the primary outcome of the SPRINT trial included heart failure, the risk of which was significantly lower in the intensive treatment group (HR: 0.62, 95%CI: 0.45–0.84). Available data reported that the mean number of BP medications administered throughout the trial in the intensive-treatment group and the standard treatment group was 2.8 and 1.8, respectively, and the dose of each class was larger in the intensive-treatment group, rendering it difficult to determine whether the reduction in the rate of heart failure in the intensive-treatment group was due to the intensive-treatment therapy or the larger doses of diuretics throughout the treatment. Third, the average SBP in the intensive-treatment group in the SPRINT trial was 121.5 mmHg, which was actually higher than the trial's BP goal of 120 mmHg and about 2 mmHg higher than that in the ACCORD trial. This implies that an SBP target of less than 130 mmHg may be more appropriate and attainable than a target of less than 120 mmHg. Fourth, the follow-up period for the SPRINT trial was shorter than that of the ACCORD trial. From the data shown, the number of renal events was small, and long-term effects of adverse events and any benefits associated with intensive antihypertensive treatment need to be prudently reevaluated. Findings from the SPRINT trial undoubtedly provide essential evidence to the benefits of intensive BP control, especially in elderly hypertensive patients. However, the SPRINT trial did not

address optimal BP targets for other important subgroups, such as patients with diabetes, patients with a prior history of stroke, or those younger than 50 years of age. As in the ACCORD trial, the SPRINT trial only compared two BP targets (<120 mmHg *vs.* <140 mmHg).

## FURTHER EXPLORATION: RESULTS FROM THE CSPPT (CHINA STROKE PRIMARY PREVENTION TRIAL)

Current guidelines recommend a target BP of 140/90 mmHg for the general hypertensive population (defined as those at low-to-moderate CV risk) based on evidence from several RCTs, including OSLO,[24] HDFP-stratum1 (HDFP),[25] Australian-mild hypertension (AUS),[26] MRC-mild hypertension (MRC),[27] and FEVER.[28] All these trials achieved a target SBP of less than 140 mmHg with the exception of AUS, and three of the four studies demonstrated that patients benefited from a BP target of less than 140 mmHg. The HDFP-stratum1 study, however, enrolled mild hypertensive patients at high CV risk. Patients in the MRC trial had a significant reduction only for the primary endpoint of stroke and all CV events but not for coronary events and mortality from all causes. In the FEVER study, 42% of patients were accompanied by CVD and 13% were accompanied by diabetes. As a result, only the subanalysis of the FEVER study showed significant CV reduction through lowering SBP to 137 mmHg rather than 142 mmHg in uncomplicated patients free of CVD and DM.

Up to now, only one trial, Cardio-Sis,[29] which enrolled 1,111 nondiabetic patients aged 55 years or older with uncontrolled hypertension, compared a SBP goal of less than 140 mmHg to a lower one of less than 130 mmHg and supported a SBP goal of less than 130 mmHg in reducing the risk of the primary outcome (prevalence of electrocardiographic left ventricular hypertrophy) and composite CV endpoints (mainly coronary revascularization and new-onset atrial fibrillation). However, the reduction in the risk of the composite endpoint was mainly owing to the decrease in new-onset atrial fibrillation and coronary revascularization. Risks of stroke and overall mortality in the two BP treatment groups were not significantly different (usual *vs.* tight control: 1.6% *vs.* 0.7%, $P = 0.16$ for stroke or transient ischemic attack; 0.9% *vs.* 0.7%, $P = 0.70$ for death from any cause), and the mean BP was 135.6/78.7 mmHg in the usual-control group and 131.9/77.4 mmHg in the tight-control group, which was not under the target BP of 130 mmHg as designed.[29] Thus, firm evidence regarding BP targets aimed at general hypertensive individuals can only be obtained through an appropriately designed new trial.

Post hoc analyses of hypertensive patients without CVD, DM, end-stage renal disease (ESRD), or other severe somatic diseases of the China Stroke Primary Prevention Trial (CSPPT)[30] indicate that, in general hypertensive patients aged less than 60 years (the SBP target currently recommended by guidelines is below 140 mmHg), the risks of overall mortality and stroke were significantly reduced by 49% and 52%, respectively, for patients with mean SBP in the 125–135 mmHg group and the 135–145 mmHg group. Likewise, in general hypertensive patients aged 60 years or older (the SBP target currently recommended by guidelines is below 150 mmHg), the risk of mortality and stroke was reduced by 32% and 30%, respectively, for patients with mean SBP in the 135–145 mmHg group and the 145–155 mmHg group. It follows that a BP goal lower than that recommended by the existing guidelines may be associated with greater reduction in risk of not only stroke but also all-cause mortality in general hypertensive patients without DM, ESRD, or CVD.

A note on the concept of "residual risk" as proposed by an analysis of all major trials with regards to antihypertensive agents[31,32]: this report has demonstrated the "residual risk" in trials on patients at high CV risk, that is, although intensive therapies including lipid-lowering or antiplatelet agents reduced the total risk of CV events, a high initial risk still remains high. On the contrary, in trials that enrolled hypertensive patients with low to moderate risk, the "residual risk" often significantly decreased, implying that it is more appropriate and more beneficial to initiate antihypertensive treatment earlier. Taken together, and based on the current evidence, it is important to explore other BP targets tailored to patient characteristics with the goal to maximize the benefits for cardio-cerebral-vascular endpoints and minimize the risk of adverse events associated with hypertension episodes.

## NEW INSIGHT FROM THE CSPPT

China is a country with a high prevalence of hypertension and stroke. In fact, stroke is the leading cause of death in China and the second leading cause of death in the world.[33] In contrast to the United States, the prevalence of elevated serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels among hypertensive patients in China are significantly lower, whereas the level of plasma homocysteine in China is about 50% higher than that in the United States.[34] Elevated plasma homocysteine is a known modifiable risk factor for CVD. On the basis of previous research, each 5 μmol/L elevation in homocysteine level is associated with approximately a 33% higher risk of ischemic heart disease and a 59% higher risk of stroke. In contrast, each 3 μmol/L reduction in plasma homocysteine by folate treatment is typically

associated with approximately a 16% lower risk of ischemic heart disease and a 24% lower risk of stroke.[35] Moreover, a recent report based on a study conducted in China hypertensive adults showed that the risk of stroke and stroke death was increased with elevated plasma total homocysteine levels.[36] Additionally, an elevated plasma homocysteine level may result in a twofold increase in risk for stroke when accompanied by other conventional CV risk factors, especially hypertension.[37,38] To a large extent, this may explain the high incidence of stroke in China. In the CSPPT, 20,702 eligible hypertensive participants without a history of physically diagnosed stroke and/or myocardial infarction, stratified by the MTHFR C677T genotypes (CC, CT, or TT), were randomly assigned in a 1:1 ratio to receive a daily oral dose of one tablet containing either 10 mg of enalapril and 0.8 mg of folic acid (single-pill combination; the enalapril–folic acid group) or a daily oral dose of one tablet containing 10 mg of enalapril only (the enalapril group). The mean follow-up time was 4.5 years. This trial found that enalapril–folic acid therapy, compared with enalapril alone, significantly reduced the risk of first stroke by 21% (HR = 0.79, 95%CI: 0.68–0.93), reduced the risk of ischemic stroke by 24%, and reduced the risk of composite CV events, including CV death, myocardial infarction, and stroke by 20%.[30] Epidemiological data indicates that inadequate folate intake is very prevalent in China, especially in northern regions with high stroke incidence. Therefore, folic acid supplementation is an important therapy for the primary prevention of stroke in all hypertensive patients in China. In addition, the CSPPT also showed that among participants with the CC or CT genotypes, both the highest risk of stroke and the greatest benefit of folic acid therapy were found in those with the lowest baseline folate levels. However, for individuals with the TT genotype, the greatest benefit of folic acid therapy was found in those with the highest baseline folate levels, implying that patients with the TT genotype may require a higher dosage of folic acid supplementation to overcome a biological insufficiency. These results also suggest that precise and targeted therapy may be another critical issue for the optimal BP goal in antihypertensive treatment.

The exploration of the most appropriate BP target has become an important and pressing public health task worldwide. In China, hypertension has a different effect on the risk of CVD from that of western populations. Also, diverse therapeutic methods should be considered for different populations because of significant dissimilarities in ethnicity, environment, nutritional status, and lifestyle. It is imperative to carry out research that focuses on the unique clinical features of Chinese hypertensive patients in order to reduce the risk of stroke and CV events and provide evidence-based guidelines for BP targets in China. To fill these persisting gaps in current knowledge, high-quality studies for hypertensive patients with initial low or moderate CV risk are warranted to test the hypothesis that a lower SBP treatment goal compared to the current available recommendation may bring greater benefits, which will provide sufficient high-quality evidence to inform optimal management of hypertension in China and in other populations with similar characteristics.

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## Conflict of Interest

None declared.

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