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Inspiration from strategy of blood pressure intervention in the elderly hypertensive patients for optimal blood pressure target

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Hypertension, as the leading modifiable risk factor for cardiovascular disease, represents the top cause of death, with the elderly as the most vulnerable population.[1] In China, >55% of citizens aged ≥65 years suffered from hypertension.[2] China will be faced with more severe blood pressure burden in the near future, as the elderly will expect to account for 30% of the total population by 2050.[3] For patients aged ≥60 years, isolated systolic hypertension is the most common hypertension subtype, which is defined as a systolic blood pressure (SBP) of ≥140 mmHg and a diastolic blood pressure of <90 mmHg.[4] Aging of the cardiovascular system leads to the increase in both large artery stiffness and arterial wave reflections to the heart, translating into the elevation of SBP.[5] However, treatment of older hypertensive patients remains challenging not only because the therapeutic goals often are difficult to reach due to differences in drug metabolism, use of multiple concomitant medications, and enhanced blood pressure variability in this population, but also because of the unclear blood pressure target. Current guideline-based recommendations of SBP targets remain inconsistent for the elderly, introducing uncertainty regarding optimal goals for hypertension treatment. The target is <150 mmHg in the American College of Physicians-American Academy of Family Physicians guideline,[6] 130 to 139 mmHg in the European guideline,[7] and <130 mmHg in the American College of Cardiology-American Heart Association guideline.[8] Thus, determining the optimal SBP target for older hypertensive patients is urgently required.

The *New England Journal of Medicine* published the results of the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial on September 30, 2021 (online published on August 30, 2021).[9] The STEP trial was a prospective, multicenter, randomized, controlled trial, sponsored by Fu Wai Hospital and the Chinese Academy of Medical Sciences.[9] This large scale clinical trial showed that for hypertensive patients aged 60 to 80 years old, an SBP target of 110 to <130 mmHg (intensive treatment) more effectively reduced the risk of primary outcome [hazard ratio (HR), 0.74; 95% confidence interval (CI), 0.60–0.92; $P = 0.007$], stroke (HR, 0.67, 95% CI, 0.47–0.97; $P = 0.007$), acute coronary syndrome (ACS) (HR, 0.67, 95% CI, 0.47–0.94; $P = 0.007$), and acute heart failure (HR, 0.27, 95% CI, 0.08–0.98; $P = 0.007$) than a target of 130 to <150 mmHg (standard treatment). The STEP trial from China complements some limitations of SPRINT and provided new evidence on the optimal target for intensive blood pressure control in older patients. This viewpoint deeply discusses the difference between SPRINT and STEP trials, analyzes the underlying possible reasons, and points out the gap field where future research is needed.

The STEP study was launched in 42 clinical centers that involved a total of 23 provinces, municipalities, and autonomous regions across China since January 2017. A total of 9624 elderly patients with hypertension were screened and 8511 patients aged 60 to 80 years old were randomly assigned to the intensive treatment group (4243 patients) or the standard treatment group (4268 patients). The two treatment strategies led to a rapid and sustained between-group difference in SBP levels. Throughout follow-up, the mean SBP was 126.7 mmHg in the intensive treatment group and 135.9 mmHg in the standard treatment group. This trial was stopped on December 31, 2020, with a median follow-up of 3.34 years, due to a clear cardiovascular benefit in the intensive treatment group at two consecutive interim analyses. The results revealed that the risk of primary outcome (composite of stroke, ACS, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or cardiovascular death) was reduced by 26% (95% CI, 8%–40%) in the intensive treatment group. The risk of secondary outcomes such as

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stroke, ACS, and acute decompensated heart failure also favored intensive treatment. Among adverse events, only hypotension occurred more often with intensive blood pressure control.

More importantly, the mean number of medications was modest in both treatment groups (intensive *vs*. standard: 1.9 *vs*. 1.5), with only an additional 0.4 classes of antihypertensive agents in the intensive treatment group, which implied a high cost-effectiveness of targeting SBP at <130 mmHg.

The SPRINT trial,[10] the SPRINT-Senior (a deliberately predesigned subgroup of patients aged ≥75 years),[11] and the STEP trial[9] have provided strong evidence regarding the benefits of intensive blood pressure control in older patients. The well-known landmark study SPRINT published in the New England Journal of Medicine in 2015 mainly focused on patients with high cardiovascular risk (one or more of the following: cardiovascular disease; chronic kidney disease; a 10-year cardiovascular risk of ≥15% based on the Framingham risk score; aged ≥75 years) to investigate whether intensive treatment (SBP target <120 mmHg), compared to standard treatment (SBP target <140 mmHg), could reduce the future cardiovascular risk[10]. The intervention period of this trial was terminated early with a median follow-up of 3.26 years, with (1) the risk of major adverse cardiac events reduced by 25%, (2) the risk of cardiovascular mortality reduced by 43%, and (3) the risk of all-cause mortality reduced by 27%.[10] According to the SPRINT final report, between-group differences were attenuated and were not significant outcomes during the observational post-intervention period.[12]

A predesigned subgroup analysis ($n = 2623$) of the SPRINT trial is the effect of intensive treatment in patients ≥75 years.[12] To astonish many, patients >75 years benefited, even to a greater extent, with a SBP target of <120 mmHg (with a 34% reduction in primary outcome and a 33% reduction in all-cause mortality). Many experts advocate the exquisite design and admirable novelty of SPRINT trial, claiming it as the foundation of the redefining of blood pressure target. However, critics did point out several limitations, which will be discussed in detail in a succeeding section of the article.[13] The STEP trial from China complements these limitations and provides new evidence on the optimal target for intensive blood pressure control in older patients.

The STEP participants are relatively healthier compared to the SPRINT population with high cardiovascular risk. The annual event rates for the primary outcome in the intensive treatment group and the standard treatment group observed in the STEP trial (intensive *vs*. standard: 1.0% per year *vs*. 1.4% per year) were lower than those observed in SPRINT (intensive *vs*. standard: 1.8% per year *vs*. 2.4% per year), which is also consistent with lower cardiovascular risk in Asian populations than in U.S. and European populations.

Blood pressure measurement approaches were different between SPRINT and STEP trials. Among the limitations of SPRINT, first and foremost, a considerable proportion of follow-up office blood pressure values were measured with an automated blood pressure monitor, with clinical staff unattended (a technology rarely used in the current clinical practice). It has been suggested that the blood pressure values reported in SPRINT may correspond to conventional office SBPs in the 130 to <140 mmHg, and 140 to <150 mmHg, ranges in the intensive *vs*. standard treatment groups, respectively.[7] Thus, translation of the conclusions of SPRINT to the real-world situations was doubted. In STEP, office blood pressure was measured by a trained trial staff member (physician or nurse), which was consistent with the most-used clinical practice.

The STEP trial showed that a SBP target of 110 to <130 mmHg significantly reduced the risk of stroke by 33%, but similar results were not observed in SPRINT. The risk reduction of primary outcome in SPRINT was largely attributed to a significant alleviation of heart failure, which was considered as "soft endpoint," deemed less convincing than "hard endpoints" such as stroke. The higher incidence of stroke in China compared with the Western countries may illustrate the difference. It should be noted that both trials excluded persons with a history of stroke, and further trials to assess the cardiovascular benefits of intensive blood pressure control in this population are needed, given the high burden of hypertension and stroke worldwide.

In the STEP trial, intensive treatment did not have a significant effect on the risk of cardiovascular mortality or all-cause mortality. However, the SPRINT trial revealed significantly reduced risks of the two. The inconsistency might be partially explained by differences in the trial design and eligibility criteria, the SBP targets, or the geographic location along with the racial and ethnic background of the trial population.

Target to <120 mmHg led to a significantly increased incidence of serious adverse events including hypotension, syncope, and acute kidney injury or acute renal failure in SPRINT. Due to the increasing arterial stiffness and losses in arterial compliance with age, excessive blood pressure reduction in the elderly could result in ischemia and injury of important organs. The STEP trial targeting to <130 mmHg did not increase the incidences of dizziness, syncope, and renal outcomes. Although patients in the intensive group had a slightly higher risk of hypotension (SBP <110 mmHg) (intensive *vs*. standard: 3.4% *vs*. 2.6%), most of these hypotension events only occurred in the first 6 months of the trial and were alleviated after adjusting the therapeutic doses.

Although SPRINT showed that controlling SBP to <120 mmHg was associated with cardiovascular benefits, such a low target resulted in the significant increase of medication numbers (intensive *vs*. standard: 2.8 *vs*. 1.8), which increases not only the incidence of adverse reaction but also medication costs and clinic visits. In STEP, participants began treatment with olmesartan medoxomil (angiotensin receptor blocker [ARB]) tablets, or amlodipine besylate (calcium channel blocker [CCB]) tablets, as an initial therapy, not including hydrochlorothiazide. In the intensive treatment group, 50% of the participants

received two-drug therapy (ARB + CCB), 10% added received hydrochlorothiazide (ARB + CCB + hydrochlorothiazide), and the mean number of medications administered per patient was 1.9 (intensive *vs*. standard: 1.9 *vs*. 1.5). A lower incidence of adverse events in STEP can at least partially be illustrated by fewer medication numbers due to appropriate target and efficient antihypertensive strategy.

As the editorial of *the New England Journal of Medicine* described,[14] the concept pursued from SPRINT that SBP targets below currently accepted levels provide real clinical benefits with relative safety was confirmed by STEP. While comments on a SBP target of <120 mmHg remain yet debated, a SBP target of <130 mmHg is uniformly deemed as an appropriate and safe recommendation for hypertension management in older patients. Current guidelines should revise the optimal SBP target, at least moving forward in the recommendations for general older hypertensive patients.

At present, STEP trial is still continuing to ensure the long-term effects of intensive blood pressure control. We must recognize that STEP also has some limitations. As a randomized controlled trial with strict inclusion and exclusion criteria, the study situation did not fully match the real world elderly population with hypertension. In addition, for hypertensive patients aged >80 years complicated with stroke, heart failure, and renal function injury, more clinical evidence is needed to determine the individualized antihypertensive therapeutic strategies and blood pressure targets. Several other issues (such as the effects of intensive blood pressure control on quality of life, cost effectiveness, and long-term clinical outcomes) could be addressed in future research. Determining the optimal SBP target for the elderly can be strenuous and consuming, but every little progression is worthy and is supposed to produce gigantic social profits in the present and future, with enormous and unceasingly mounted numbers of older patients.

Conflicts of interest

None.

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