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Invited Commentary

What we learned from STEP that we didn't already know from SPRINT

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ABSTRACT

Background: In view of the aging population, the target value for treatment in elderly hypertensive patients is today a clinically relevant problem.

Methods: STEP and SPRINT studies enrolled elderly subjects with exclusion of previous stroke patients. However, STEP enrolled subjects at lower cardiovascular risk than SPRINT.

Results: In Chinese hypertensive patients aged 60–80 years enrolled in the STEP study, intensive blood pressure treatment (systolic blood pressure target of 110–130 mmHg) reduced the primary composite cardiovascular endpoint and stroke with no effect on cardiovascular death and renal harm, two endpoints significantly affected in SPRINT.

Conclusion: Differences with SPRINT are the lower cardiovascular risk and CKD prevalence of STEP population.

In light of the aging of the population, the target value for treatment in elderly hypertensive patients is a highly relevant clinically problem. In the SPRINT study [1], intensive systolic blood pressure (SBP) control, with target of less than 120 mmHg, was shown to reduce cardiovascular death although increasing the incidence of renal failure. The recently published STEP study [2] showed that the SBP target of 110 to less than 130 mmHg may reduce the primary composite cardiovascular outcome, with no renal harm. The study offers important lessons for identifying the patient best suitable for intensive treatment.

The Systolic Blood Pressure Intervention Trial (SPRINT) [1], performed on patients without diabetes, showed impressive cardiovascular benefits with intensive SBP control (target <120 mmHg), as compared with standard SBP control (target <140 mmHg). The National Heart, Lung, and Blood Institute (NHLBI), the primary sponsor, stopped the study after a median follow up of 3.26 years because more intensive versus less intensive treatment of SBP reduced the primary combined endpoint (myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) (HR 0.75; 95% Cl 0.64–0.89), all-cause mortality (0.73; 0.60–0.90), and cardiovascular mortality (0.57; 0.38–0.85). Stroke incidence was not modified by intervention (0.89; 0.63–1.25). These results prompted the American College of Cardiology - American Heart Association to modify the guideline to suggest a target of less than 130 mmHg [3]. However, intensive SBP lowering in the SPRINT study also increased the incidence of chronic kidney disease (≥30% reduction in eGFR to <60 ml/min/1.73 m^2) among patients without renal impairment at baseline (eGFR ≥60% ml/min/1.73 m^2) [1]. In a secondary analysis of the Action to Control Cardiovascular Risk in Diabetes blood pressure trial (ACCORD BP, which enrolled high-risk persons with type 2 diabetes aged over 40 years) and SPRINT [4], intensive SBP lowering in patients without renal impairment at baseline increased the risk of incidental chronic kidney disease in people with and without type 2 diabetes, the risk of incidental chronic kidney disease being higher in individuals with type 2 diabetes [4]. On the basis of these studies, the European guideline considers a blood pressure target of less than 140/90 mmHg in these conditions, with no attempt to go lower than 130/80 mmHg [5], the target adopted by US hypertension guidelines [3].

In patients with CKD at baseline enrolled in SPRINT, intensive BP lowering treatment did not affect the main kidney outcome (≥50% reduction in eGFR from baseline or ESRD) (0.90; 0.44–1.83) although it increased the incidence of acute renal failure (1.46; 1.10–1.95, $p < 0.01$) [6]. In this subgroup intervention was associated with a small reduction in all-cause death (0.72; 0.53–0.99, $p < 0.04$). The number needed to treat (66 for primary CV outcome; 28 for all cause death) and to harm (35 for acute kidney failure) were remarkably similar. Among in the subgroup of patients with CKD over 75 years of age, targeting an SBP<120 mmHg compared with <140 mmHg reduced rates of both the primary composite outcome (0.64; 0.45–0.92, $p < 0.01$) and all-cause death (0.64; 0.43–0.96, $p < 0.03$) although no information was provided for acute kidney failure. These results in CKD patients are consistent with a large meta-analysis showing that more intensive versus less intensive BP control resulted in 14% lower risk of all-cause mortality (OR, 0.86; 95% CI, 0.76–0.97, $p < 0.01$) in chronic kidney disease stages 3–5 [7]. The more recent guidelines of the International Society of Hypertension adopt this position suggesting a target lower than 130/80 mmHg in patients with CKD [8].

Given this background, the STEP study, sponsored by FuWai Hospital and the Chinese Academy of Medical Sciences, now offers interesting data that enrich and complement the information provided by SPRINT. The trial was stopped early (median follow-up of 3.34 years) on the basis of a clear cardiovascular benefit in the intensive-treatment group. The SBP target of 110 to less than 130 mmHg was indeed associated with a reduction of the primary outcome, a composite of stroke, acute coronary syndrome (acute myocardial infarction and hospitalization for unstable angina), acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes (HR 0.74; 95% Cl 0.60–0.92), and secondary endpoints such as stroke (0.67; 0.47–0.97), acute coronary syndrome (0.67; 0.47–0.94), or acute decompensated

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heart failure (0.27; 0.08–0.98). Secondary endpoints not modified by intervention were coronary revascularization (0.69; 0.40–1.18), atrial fibrillation (0.96; 0.55–1.68), and death from cardiovascular causes (0.72; 0.39–1.32).

The outcomes of STEP and SPRINT trials are almost identical, and this facilitates comparison. However, the STEP and SPRINT trials have different inclusion and exclusion criteria making the studied populations different. More precisely, three points are important. First, type 2 diabetes was an exclusion criterion in the SPRINT trial whereas patients with type 2 diabetes made up 19% of the STEP population. Second, STEP seems to have been careful to select a population without renal damage. More precisely, the prevalence of chronic kidney disease (CKD, defined in both studies as GFR <60 ml/min) was 2.4% in STEP versus 28.3% in SPRINT. Third, the STEP enrolled a single ethnic group, the Han Chinese population, whereas the SPRINT population included 31% African-ancestry patients.

The inclusion of patients with type 2 diabetes is crucial to make the data transferable to the Chinese clinical setting. However, in contrast to what was expected, notwithstanding the inclusion of patients with type 2 diabetes, the population enrolled by STEP proved to have a lower cardiovascular risk than subjects enrolled by SPRINT. More precisely, despite the presence of 19% of diabetic patients, the 10-year risk of patients assigned to conventional treatment in the STEP trial was markedly lower than what was observed in the SPRINT study with regards to total mortality (4.5% versus 13.8%), and CV mortality (1.8% versus 4.3%). In addition to differences in CKD, previous cardiovascular disease was less prevalent among STEP than SPRINT participants (6% and 20% respectively). In China the relative burden of ischemic heart disease and stroke is different from Western countries, myocardial infarction being less prevalent than stroke (the latter was an exclusion criterion in both studies). On the other hand, the enrolled populations reached similar blood pressure levels in the two studies and the 10-year risks of stroke, the endpoint most closely linked to blood pressure levels, were similar (5.0% versus 4.6% in STEP and SPRING respectively).

Patients with CKD (GFR<60 ml/min) made up 2.3% of the STEP population, so the study can say little about intensive BP treatment in CKD. The low prevalence of CKD in STEP is probably associated with the absence of acute kidney damage in the intensive treatment group. No information is available from subgroup analysis performed in the few patients with CKD at baseline because analysis was underpowered by low numbers. In STEP, intensive SBP reduction was not associated with an increase in the incidence of acute kidney damage compared to standard treatment. In contrast to SPRINT, the SBP target of 110 to less than 130 mmHg in the STEP trial was not associated with an increased incidence of kidney injury. The renal outcomes indeed show a more favorable response in STEP (OR of 0.90; 95% Cl 0.63–1.30 for a reduction of GFR of 30% or greater) compared to SPRINT which had an OR of 3.49 (95% Cl 2.44–5.10) for a 30% or greater reduction in GFR, the number needed to harm (NNH) for intensive treatment was 37 patients for 1 event. We cannot exclude that relative to SPRINT, the higher baseline eGFR in the STEP trial obligated a greater absolute decline to meet the eGFR of less than 60 ml/min per 1.73 m^2 threshold, which might have led to underestimation of incidental chronic kidney disease with intensive SBP lowering in the STEP trial. Of note, the incidence of hypotension increased significantly with intensive blood-pressure control in both trials.

The presence of an exclusively Chinese population offers additional consideration. As noted above, despite the lower risk of death, the 10-year risk of stroke in subjects assigned to conventional treatment is similar in the two studies. However, although the reduction in blood pressure obtained during intensive treatment was comparable in the two studies, even considering the different measurement strategies used, stroke reduction was an advantage for the intensive treatment in STEP (OR 0.67; 95% Cl 0.47–0.97) but not in SPRINT (OR 0.89; 95% Cl 0.64–1.23). To what could these differences be attributed? Extracranial carotid atherosclerotic stenosis is the most common vascular lesion found in stroke patients who are white. On the contrary, the prevalence of intracranial atherosclerotic stenosis was reported to account for 33%–67% of stroke or transient ischemic attack cases in China and other countries in Asia [9,10]. Despite the high prevalence of this high-risk disease, controversy exists regarding treatment of symptomatic intracranial atherosclerotic stenosis patients and the pattern of cerebral autoregulation. It is interesting to note that although this level of injury may be more sensitive to a reduction in blood pressure, stroke reduction remains a clear advantage of intensive SBP treatment in STEP.

In conclusion, in Chinese hypertensive patients aged 60–80 years enrolled in the STEP study, intensive SBP treatment (target of 110–130 mmHg) reduced the primary composite cardiovascular endpoint and stroke risk with no effect on cardiovascular death or renal harm, two endpoints significantly affected in SPRINT. Major differences with SPRINT are the lower baseline cardiovascular risk and CKD prevalence in the Chinese STEP population.

Declaration of competing interest

The author reports no relationships that could be construed as a conflict of interest.

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