COMMENT

Which blood pressure threshold indicates a therapeutic benefit for patients with chronic kidney disease?

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The optimal blood pressure (BP) goals for patients with hypertension and chronic kidney disease (CKD) continue to be debated. The 2017 American Heart Association/American College of Cardiology (AHA/ACC) guidelines modified the definition/classification of hypertension and introduced an intensive BP target of <130/80 mmHg for most individuals at high risk of cardiovascular disease, including patients with CKD [1]. The 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended an even tighter systolic BP target of <120 mmHg for the management of hypertension in CKD [2]. Which, therefore, is the BP threshold that indicates a therapeutic benefit in this high-risk patient population?

In this issue of *Hypertension Research*, Suzuki et al. [3] reported the results of a large retrospective observational study that aimed to explore the association of BP with the risk of developing cardiovascular disease in 188,837 Japanese adults with dipstick proteinuria and an estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2. These individuals were categorized into 4 groups following the classification of hypertension that was introduced in the 2017 AHA/ACC guidelines. During a mean follow-up period of 1050 days, 7039 individuals reached the pre-specified primary cardiovascular outcome, defined as the composite of myocardial infarction, angina pectoris, stroke, and heart failure. The analysis was conducted separately for individuals who were not taking BP-lowering medications

($n = 173,833$) and those who were receiving anti-hypertensive treatment ($n = 15,004$) [3]. Among drug-naive individuals, compared with the category of normal BP, the multivariable-adjusted hazard ratio (HR) for the primary cardiovascular outcome was 1.07 [95% confidence interval (CI): 0.97–1.17] in the category of elevated BP, 1.30 (95% CI: 1.21–1.40) in stage 1 hypertension and 2.17 (95% CI: 2.01–2.34) in stage 2 hypertension [3]. Among drug-treated individuals, compared with the reference category of patients with a normal BP range, the multivariate-adjusted HR for the composite cardiovascular outcome was 1.00 (95% CI: 0.82–1.23), 0.97 (95% CI: 0.83–1.14) and 1.19 (95% CI: 1.02–1.38) in those with elevated BP, stage 1 and stage 2 hypertension, respectively [3]. This dose–response relationship was consistent in the restricted cubic spline analysis. In the subgroup of drug-naive individuals, the cardiovascular risk was progressively increased after the cutoff point of 120/80 mmHg. Among individuals taking BP-lowering medications, an indication of increased cardiovascular risk was observed only when the BP levels were >140/90 mmHg [3].

One approach to define hypertension and identify the optimal therapeutic targets is to evaluate BP levels in relation to the risk of adverse health outcomes, as done in the large observational study of Suzuki et al. [3]. Among individuals taking BP-lowering medications, this analysis showed that the category of stage 1 hypertension, as defined in the 2017 AHA/ACC guideline, does not identify patients at higher risk of developing cardiovascular disease [3]. If we assume that this risk association is causal, then the intensive BP target of 130/80 mmHg that was established in the 2017 AHA/ACC guideline may not be suitable for the treatment of hypertension in patients with proteinuric CKD. Taking into consideration that an inherent limitation of observational studies is their inability to provide direct cause-and-effect risk associations, a more reliable approach to define the BP threshold of therapeutic benefit is the

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evaluation of data from randomized trials demonstrating reductions in the risk of adverse health outcomes with intensive BP-lowering protocols.

Compelling clinical trial evidence to demonstrate nephroprotection with lower BP targets is lacking. The Modification of Diet in Renal Disease (MDRD) [4] and the African American Study of Kidney Disease and Hypertension (AASK) [5] were 2 landmark trials that randomly assigned nondiabetic patients with CKD to achieve an intensive (approximately 125/75 mmHg) versus a standard (140/90 mmHg) BP goal. Until the completion of their randomized phase, neither of these 2 trials demonstrated an overall improvement in kidney outcomes with the achievement of tighter BP control [4;5]. However, a subgroup analysis of the MDRD suggested that intensive BP-lowering results were associated with a slower rate of decline in the GFR in patients who had more severe proteinuria (>1 g/day) at baseline [4]. The notion that proteinuria modifies the treatment effects of intensive BP-lowering was also supported by a post hoc analysis of the AASK [6]. After the termination of the trial phase, AASK participants were invited to participate in a post-trial cohort study. In the overall analysis of both trial and cohort phases of the AASK, there was no difference between the intensive-treatment and standard-treatment arms in the risk of progression of CKD [6]. However, a significant 27% relative risk reduction in the composite kidney outcome was observed in the subgroup of AASK participants who had a urinary protein-to-creatinine ratio of > 0.22 g/g at baseline [6]. Despite the fact that an indication of nephroprotection with intensive BP control was observed only in subgroup analyses, these low-quality data influenced the 2012 KDIGO guideline to provide a weak Level 2D recommendation for a tighter BP target of <130/80 mmHg in proteinuric CKD and a standard BP target of <140/90 mmHg for patients without proteinuric CKD [7].

Published in 2015, the Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that among 9361 nondiabetic patients with a high cardiovascular risk profile, targeting a systolic BP of <120 mmHg compared with < 140 mmHg provoked a 25% relative risk reduction in fatal and nonfatal cardiovascular events as well as a 27% relative risk reduction in all-cause mortality [8]. A prespecified subgroup analysis that included 2624 SPRINT participants with an eGFR of <60 ml/min/1.73 m^2 at baseline showed that the cardioprotective benefit of intensive BP-lowering did not differ between patients with or without CKD [9]. A subsequent subgroup analysis of 1723 SPRINT participants with a urinary albumin-to-creatinine ratio of ≥30 mg/g at baseline also showed that the beneficial effects of intensive BP control on cardiovascular events and all-cause death were similar irrespective of the presence of albuminuria

[10]. A slower progression of CKD was not associated with the lower systolic BP target in SPRINT [9]. It must be noted, however, that the prespecified kidney outcome, defined as the composite of sustained ≥ 50% decline in eGFR from baseline or end-stage kidney disease, occurred in only 15 patients in the intensive-treatment arm versus 16 patients in the standard-treatment arm [9]. Therefore, SPRINT was not adequately powered to detect the kidney protective effects of intensive BP-lowering.

Although SPRINT demonstrated a substantial cardioprotective benefit when systolic BP was targeted to levels <120 mmHg compared with <140 mmHg, the 2017 AHA/ACC guideline set the systolic BP target at 130 mmHg [1]. Most likely, this algebraic adjustment by 10 mmHg was performed in an attempt to counteract the expected mean difference between routine office BP recordings that are widely used in daily clinical practice and research-grade BP measurement methodology that guided the intensification of antihypertensive treatment over the course of the SPRINT trial. In SPRINT, office BP was measured under standardized conditions: multiple automated BP recordings taken after a prespecified 5-minute rest period in a quiet room and without the presence of an observer in the room [8]. In a diagnostic-test study that included 275 patients with CKD, office BP was measured with the research-grade technique that was used in SPRINT [11]. On the same day, office BP was also recorded without specification of a 5-minute seated rest [11]. The mean difference between research-grade and routine office systolic BP was −12.7 mmHg, but the 95% limits of agreement were wide, ranging from −46.1 mmHg to 20.7 mmHg [11]. These data indicate that algebraic manipulation of routine office BP of any degree is probably insufficient to counteract the large variability in BP levels from patient to patient. Perhaps the 2021 KDIGO guidelines take a clearer and more straightforward position on this crucial issue, recommending a systolic BP target of <120 mmHg (as in the intensive-treatment arm of SPRINT) with the use of standardized BP measurement methodology in the office environment [2].

Have the results of SPRINT conclusively answered the question of the optimal BP target for the management of hypertension in the entire spectrum of patients with CKD? The answer is probably no. The results of SPRINT are generalizable to patients with clinical characteristics similar to those of the patients who participated in that landmark trial. Notably, SPRINT excluded patients with diabetic kidney disease, polycystic kidney disease, proteinuria >1 g/day and eGFR <20 ml/min/1.73 m^2 [8–10]. Future research is needed to investigate the benefit/risk ratio of intensive BP-lowering protocols in these large subgroups of patients with CKD.

Compliance with ethical standards

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