Target Blood Pressure for Cardiovascular Disease Prevention in Patients with CKD

Alex R. Chang [1,2] *and Lawrence J. Appel*[3]

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Two recent publications have reignited debate about BP goals in patients with CKD—results from the Systolic Blood Pressure Intervention Trial (SPRINT) and the American College of Cardiology/American Heart Association (ACC/AHA) 2017 BP guidelines (1,2). The latter declares a class 1 (strong) recommendation for a BP goal of <130/80 mm Hg in adults with CKD, regardless of albuminuria (2). This recommendation differs from the Kidney Disease Improving Global Outcomes 2012 Guidelines and 2014 BP guidelines from the panel members appointed to the Eighth Joint National Committee (Figure 1). Given these inconsistent guidelines, there is an urgent need for the nephrology community to assess optimal BP goals for not just CKD progression but also, risk of cardiovascular disease (CVD) and death.

The SPRINT randomized 9361 nondiabetic adults ≥50 years old with systolic BP (SBP) 130–180 mm Hg and elevated CVD risk to a target SBP<120 versus <140 mm Hg (1). Other major exclusion criteria included diabetes, stroke, proteinuria >1 g/d, polycystic kidney disease, symptomatic heart failure, and left ventricular ejection fraction <35%. The SPRINT was stopped early, because interim analyses found that intensive BP lowering reduced the risk of CVD by 25% and the risk of all-cause death by 27%. Intensive BP lowering also increased risks of eGFR decline ≥30%, syncope, and electrolyte abnormalities. Importantly, the beneficial effects of intensive BP lowering did not vary by eGFR<60 ml/min per 1.73 m^2. Among 2646 adults with eGFR of 20–59 ml/min per 1.73 m^2, intensive BP lowering tended to reduce risk of CVD by 19% (hazard ratio [HR], 0.81; 95% confidence interval [95% CI], 0.63 to 1.05) and all-cause death by 28% (HR, 0.72; 95% CI, 0.53 to 0.99) (3).

Individuals with diabetes were excluded from the SPRINT, because such patients were studied in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial, which randomized 4733 adults with type 2 diabetes, SBP of 130–180 mm Hg, elevated CVD risk, and creatinine ≤1.5 mg/dl to a target SBP<120 versus <140 mm Hg (4). In the ACCORD Trial, intensive BP lowering did not significantly decrease the risk of CVD (HR, 0.88; 95% CI, 0.73 to 1.06). However, the ACCORD Trial was likely underpowered, because the observed CVD event rate was only 2.1% per year, approximately one half of the expected event rate of 4% per year used in sample size projections. In the subgroup of 1726 (36%) adults with CKD (1325 stage 1 or 2 and 401 stage 3), the HR for CVD was 0.86 (95% CI, 0.67 to 1.11) (4).

Malhotra *et al.* (5) conducted a meta-analysis of 18 randomized BP trials with mortality data in adults with stage 3–5 CKD. A more intensive BP decreased the risk of all-cause death by 14% (odds ratio, 0.86; 95% CI, 0.76 to 0.97); the effect of more intensive BP lowering tended to be greatest in trials that achieved the largest SBP difference (≥12 mm Hg: odds ratio, 0.76; 95% CI, 0.62 to 0.93). However, some trials compared BP treatment with placebo without specific BP targets, and the heterogeneity in the approach to BP goals precluded the authors from making firm conclusions on optimal BP goals. Although this meta-analysis included the aforementioned BP studies and several others, it did not include extended follow-up data of the African-American Study of Kidney Disease and Hypertension (AASK) and the Modification of Diet in Renal Disease (MDRD) Trial, which support a long-term mortality benefit with intensive BP lowering. In a combined analysis of post-trial follow-up data of the AASK and the MDRD Trial, individuals randomized to the intensive BP lowering arms had a 13% reduced risk of death (relative risk, 0.87; 95% CI, 0.76 to 0.99) (6).

One concern with intensive BP lowering is that intensive SBP lowering may result in low diastolic BP (DBP), resulting in impaired myocardial perfusion. In a *post hoc* analysis of the SPRINT, low baseline DBP was associated with increased risk of CVD, consistent with prior observational studies (7). However, more relevant are analyses of trial results showing that the effects of intensive BP lowering on risk of CVD did not differ by quintiles of baseline DBP. In the lowest quintile of baseline DBP (mean DBP of 61±5 mm Hg), the HR for the primary CVD outcome associated with the intensive BP group was 0.78 (95% CI, 0.57 to 1.07), suggesting that the association between low DBP and risk of CVD in observational studies may be driven by underlying patient characteristics rather than by BP level or treatment.

Another major concern about intensive BP lowering is whether an acute decrease in GFR is purely hemodynamic or carries long-term adverse consequences. In a *post hoc* analysis of the Secondary Prevention of Small Subcortical Strokes Trial, Peralta *et al.* (8)

[1]Kidney Health Research Institute and [2]Department of Epidemiology and Health Services Research, Geisinger Health System, Danville, Pennsylvania; and [3]Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, Maryland

Correspondence: Dr. Alex R. Chang, Geisinger Health System, 100 North Academy Avenue, Danville, PA 17822. Email: achang@geisinger.edu

	ACC/AHA 2017	JNC-8 2014	KDIGO 2012
Stage 3–5 CKD without albuminuria*	< 130/80 mmHg	< 140/90 mmHg	< 140/90 mmHg
Stage 1–5 CKD with albuminuria*	< 130/80 mmHg	< 140/90 mmHg	< 130/80 mmHg

*albuminuria is defined as albumin excretion rate ≥ 30 mg/24 h, approximately equivalent to urine albumin/creatinine ratio ≥ 30 mg/g.

Figure 1. | Recent guidelines have different target blood pressure recommendations for patients with CKD. ACC, American College of Cardiology; AHA, American Heart Association; JNC-8, Eighth Joint National Committee; KDIGO, Kidney Disease Improving Global Outcome.

examined the effect of intensive BP control (SBP target <130 versus 130–149 mm Hg) on kidney function in 2610 adults with a recent lacunar stroke. Consistent with the SPRINT, individuals randomized to the goal of SBP<130 mm Hg had an increased risk of eGFR decline ≥30% (8). Interestingly, the association between eGFR decline ≥30% during the first year and risk of CVD or death varied by BP target. In the SBP<130 mm Hg group, eGFR decline ≥30% was not associated with increased risk (HR, 0.83; 95% CI, 0.51 to 1.35), whereas in the SBP=130–149 mm Hg group, eGFR decline ≥30% was associated with increased risk (HR, 1.62; 95% CI, 1.05 to 2.51). This suggests that an acute decrease in eGFR secondary to intensive BP lowering may not necessarily translate into future increased CVD/mortality risk. Confirmation is needed in other trials with longer-term follow-up to fully understand potential risks or benefits.

It is important to emphasize that findings from intensive BP trials may not be generalizable to every patient with CKD. Data are more limited for those with diabetes or stage 4+ CKD, and benefits of intensive BP control are uncertain in frail patients. Consideration of albuminuria status as a prognostic indicator of CVD risk could identify patients who may derive the greatest benefits of intensive BP lowering. Although the effects of intensive BP lowering on CVD risk are similar by level of albuminuria (6,9), the absolute risk reduction can be expected to be highest among those with albuminuria due to the strong association between albuminuria and CVD. In an analysis of 4515 diabetic adults with CKD in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Trial, treatment with perindopril-indapamide resulted in the greatest CVD absolute risk reduction in patients with stage 3+ CKD and albuminuria (9).

Another concern is that BP measured in the "real world" setting often differs from that measured in trials, which typically involve careful protocols to standardize measurements. In a trial that randomized clinics to continue manual BP measurements or switch to automatic oscillometric BP devices (mean of five BP readings separated by 2-minute intervals), measurement by automatic oscillometric BP device was associated with 5.4-mm Hg lower SBP than manual BP (10). Such evidence has led to speculation that a target SBP goal <130 mm Hg measured in typical clinics may be similar to the SBP goal <120 mm Hg in the SPRINT.

Overall, we believe that the current body of literature on intensive BP lowering in CKD supports the ACC/AHA 2017 BP guideline of a BP goal <130/80 mm Hg for patients with CKD. However, clinicians should manage patients considering overall CVD risk, frailty, and potential risks of treatment (*e.g.*, hyperkalemia, hypokalemia, hyponatremia, AKI, and syncope). Trials are needed to determine optimal strategies for measuring BP accurately and implementing more intensive BP control in real world settings.

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Disclosures

None.

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