

# Target Blood Pressure for Cardiovascular Disease Prevention in Patients with CKD

Alex R. Chang<sup>1,2</sup> and Lawrence J. Appel<sup>3</sup>

*Clin J Am Soc Nephrol* 13: 1572–1574, 2018. doi: <https://doi.org/10.2215/CJN.02130218>

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  $\geq 50$  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  $\geq 30\%$ , syncope, and electrolyte abnormalities. Importantly, the beneficial effects of intensive BP lowering did not vary by eGFR <60 ml/min per 1.73 m<sup>2</sup>. Among 2646 adults with eGFR of 20–59 ml/min per 1.73 m<sup>2</sup>, 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  $\leq 1.5$  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 ( $\geq 12$  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  $61 \pm 5$  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)

<sup>1</sup>Kidney Health Research Institute and <sup>2</sup>Department of Epidemiology and Health Services Research, Geisinger Health System, Danville, Pennsylvania; and <sup>3</sup>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](mailto: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  $\geq$  30 mg/24 h, approximately equivalent to urine albumin/creatinine ratio  $\geq$  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  $\geq$ 30% (8). Interestingly, the association between eGFR decline  $\geq$ 30% during the first year and risk of CVD or death varied by BP target. In the SBP<130 mm Hg group, eGFR decline  $\geq$ 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  $\geq$ 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.

#### Acknowledgments

A.R.C. is supported by National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases grant K23 DK106515-01.

The content of this article does not reflect the views or opinions of the American Society of Nephrology (ASN) or the *Clinical Journal of the American Society of Nephrology* (CJASN). Responsibility for the information and views expressed therein lies entirely with the author(s).

#### Disclosures

None.

#### References

1. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT; SPRINT Research Group: A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 373: 2103–2116, 2015
2. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbigele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines [published online ahead of print November 13, 2017]. *Hypertension* doi:10.1161/HYP.000000000000066
3. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, Cushman WC, Hawfield AT, Johnson KC, Lewis CE, Oparil S, Rocco MV, Sink KM, Whelton PK, Wright JT Jr, Basile J, Beddhu S, Bhatt U, Chang TI, Chertow GM, Chonchol M, Freedman BI, Haley W, Ix JH, Katz LA, Killeen AA, Papademetriou V, Ricardo AC, Servilla K, Wall B, Wolfgam D, Yee J; SPRINT Research Group: Effects of intensive BP control in CKD. *J Am Soc Nephrol* 28: 2812–2823, 2017
4. Papademetriou V, Zaheer M, Dumas M, Lovato L, Applegate WB, Tsioufis C, Mottle A, Punthakee Z, Cushman WC; ACCORD Study Group: Cardiovascular outcomes in action to control cardiovascular risk in diabetes: Impact of blood pressure level and presence of kidney disease. *Am J Nephrol* 43: 271–280, 2016
5. Malhotra R, Nguyen HA, Benavente O, Mete M, Howard BV, Mant J, Odden MC, Peralta CA, Cheung AK, Nadkarni GN, Coleman RL, Holman RR, Zanchetti A, Peters R, Beckett N, Staessen JA, Ix JH: Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: A systematic review and meta-analysis. *JAMA Intern Med* 177: 1498–1505, 2017
6. Ku E, Gassman J, Appel LJ, Smogorzewski M, Sarnak MJ, Glidden DV, Bakris G, Gutiérrez OM, Hebert LA, Ix JH, Lea J, Lipkowitz MS, Norris K, Plath D, Pogue VA, Rostand SG, Siew ED, Sika M, Tisher CC, Toto R, Wright JT Jr, Wyatt C, Hsu CY: BP control and long-term risk of ESRD and mortality. *J Am Soc Nephrol* 28: 671–677, 2017
7. Beddhu S, Chertow GM, Cheung AK, Cushman WC, Rahman M, Greene T, Wei G, Campbell RC, Conroy M, Freedman BI, Haley W, Horwitz E, Kitzman D, Lash J, Papademetriou V, Pisoni R, Riessen E, Rosendorff C, Watnick SG, Whittle J, Whelton PK; SPRINT Research Group: Influence of baseline diastolic blood pressure on effects of intensive compared with standard blood pressure control. *Circulation* 137: 134–143, 2018
8. Peralta CA, McClure LA, Scherzer R, Odden MC, White CL, Shlipak M, Benavente O, Pergola P: Effect of intensive versus usual blood pressure control on kidney function among individuals with

- prior lacunar stroke: A post hoc analysis of the Secondary Prevention of Small Subcortical Strokes (SPS3) randomized trial. *Circulation* 133: 584–591, 2016
9. Heerspink HJ, Ninomiya T, Perkovic V, Woodward M, Zoungas S, Cass A, Cooper M, Grobbee DE, Mancia G, Mogensen CE, Neal B, Chalmers J; ADVANCE Collaborative Group: Effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease. *Eur Heart J* 31: 2888–2896, 2010
  10. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Grant FC, Kaczorowski J: Conventional versus automated measurement of blood pressure in primary care patients with systolic hypertension: Randomised parallel design controlled trial. *BMJ* 342: d286, 2011

Published online ahead of print. Publication date available at [www.cjasn.org](http://www.cjasn.org).

See related articles, “Intensive Blood Pressure Targets and Kidney Disease,” and “Defining Hypertension: Role of New Trials and Guidelines,” on pages 1575–1577 and 1578–1580, respectively.