

Intensive Blood Pressure Targets and Kidney Disease

Tara I. Chang¹ and Mark J. Sarnak²

Clin J Am Soc Nephrol 13: 1575–1577, 2018. doi: <https://doi.org/10.2215/CJN.02010218>

Introduction

In November 2017, the American College of Cardiology/American Heart Association (ACC/AHA) released new guidelines that lowered BP targets to <130/80 mm Hg for virtually all adults, including patients with CKD. These guidelines were largely on the basis of results from the Systolic BP Intervention Trial (SPRINT), which randomized participants at relatively high risk for cardiovascular disease to an intensive (<120 mm Hg) versus standard (<140 mm Hg) systolic BP target. Participants in the intensive BP group had lower rates of cardiovascular events and death, and results did not differ by baseline CKD (defined *a priori* as eGFR<60 ml/min per 1.73 m²; *P* interactions ≥0.30) (1). However, the effect of more intensive BP lowering on kidney-related outcomes remains controversial.

BP Targets and Development of Incident CKD

Among the SPRINT participants without baseline CKD, intensive BP lowering resulted in a 3.5-fold higher rate of incident CKD defined as a ≥30% reduction to <60 ml/min per 1.73 m² (2). Like SPRINT, the Action to Control Cardiovascular Risk in Diabetes BP (ACCORD BP) Trial tested the effect of systolic BP target <120 versus <140 mm Hg on cardiovascular outcomes but in patients with type 2 diabetes mellitus (3). The ACCORD BP Trial enrolled participants with mean baseline eGFR of 91.6 ml/min per 1.73 m², which by the study's end, was lower in the intensive versus the standard BP group (74.8 versus 80.6 ml/min per 1.73 m²; *P*<0.001), and more participants in the intensive BP group had eGFR<30 ml/min per 1.73 m² (4.2% versus 2.2%; *P*<0.001) (3).

Whether the larger fall in eGFR with intensive BP lowering reflects a reversible hemodynamic effect or a true acceleration to incident CKD is difficult to determine within the relatively short follow-up period of clinical trials, but there are some reassuring signals. In the SPRINT participants without baseline CKD, the difference in eGFR between randomized groups stabilized after month 18 at 4.5 ml/min per 1.73 m² (2). Of the 140 participants who developed incident CKD in the intensive group, 25% had improved eGFR in follow-up and no longer met the definition of incident CKD; none developed ESKD during the 3.3 median years of follow-up. In the ACCORD BP Trial, incident ESKD did not differ between randomized groups (2.5% versus 2.4%; *P*=0.93).

BP Targets and Progression of CKD among Patients with Existing CKD

The Modification of Diet in Renal Disease (MDRD) Study and the African American Study of Kidney Disease and Hypertension (AASK) targeted mean arterial pressure ≤92 mm Hg (equivalent to approximately 125/75 mm Hg) versus mean arterial pressure of 102–107 mm Hg (the latter is equivalent to approximately 140/90 mm Hg). Neither trial showed a benefit of intensive BP control on CKD progression during the trial phase. However, with extended post-trial observational follow-up, more intensive BP control was associated with a lower rate of ESKD in the MDRD Study (4) and in AASK a lower rate of the composite end point of ESKD, doubling of serum creatinine, or death in those with proteinuria (5). A meta-analysis incorporating these studies and others concluded that, in patients with CKD and proteinuria, more intensive BP control may slow CKD progression (6), consistent with the 2012 Kidney Disease Improving Global Outcomes guidelines that recommended a BP target <130/80 mm Hg in patients with proteinuria.

Among the SPRINT participants with baseline CKD (mean eGFR of 47.9 ml/min per 1.73 m² and median albuminuria of 13.3 mg/g), there was no difference in the occurrence of a ≥50% decline in eGFR or ESKD between randomized groups. Admittedly, only 31 participants reached this end point, limiting the statistical power (7). Using the 6-month values as baseline, the intensive BP group had a larger decline in eGFR (−0.47 versus −0.32 ml/min per 1.73 m² per year), but no differences were found in the incidences of a ≥30%, ≥40%, or ≥50% decline in eGFR between the randomized groups. These results suggest no longer-term harm from intensive BP lowering but no overt benefit on slowing CKD progression in patients without significant proteinuria. More definitive answers may be provided by a limited extension of the SPRINT (the SPRINT Alzheimer's, Seniors and Kidney Study), which will collect additional creatinine and albuminuria measurements.

BP Targets, AKI, and Rapid Kidney Function Decline

In the SPRINT and the ACCORD BP Trial, intensive BP lowering led to more frequent episodes of AKI (1,3), which is concerning given the known associations of AKI with adverse events, longer hospital

¹Division of Nephrology, Stanford University School of Medicine, Palo Alto, California; and

²Division of Nephrology, Tufts Medical Center, Boston, Massachusetts

Correspondence:

Dr. Mark J. Sarnak, Division of Nephrology, Tufts Medical Center, 800 Washington Street, Box 391, Boston, MA 02111. Email: msarnak@tuftsmedicalcenter.org

stays, and higher health care costs. However, in the 288 SPRINT participants with AKI, most had mild AKI, and >90% had AKI that resolved completely or partially; seven of 14 participants with AKI requiring dialysis continued to require dialysis after hospital discharge, but the proportion of patients with this most severe form of AKI was similar between randomized groups (8).

A *post hoc* observational analysis of the AASK and the MDRD Study (9) showed that participants in the intensive BP group with $\geq 20\%$ decline in eGFR during the first 3 months had significantly higher adjusted risks of ESKD compared with participants in the standard group with <5% decline in eGFR. These results suggest that large declines in eGFR during intensification of BP treatment may signal higher future ESKD risk, but whether relaxing BP targets in these patients reduces that risk is uncertain and may come at the cost of higher cardiovascular disease risk.

Conclusions

What should clinicians do? Despite the lack of definitive evidence that intensive BP lowering improves kidney outcomes, we agree with the ACC/AHA guidelines of targeting BP <130/80 mm Hg in most adults with CKD for the purpose of cardiovascular disease prevention. Patients with CKD are at high risk for cardiovascular events, and SPRINT, together with several other studies (10), showed that more intensive systolic BP control decreased cardiovascular events and death, including in patients with CKD. Although intensive BP control may lead to a slightly faster decline in eGFR and AKI, these adverse outcomes are often reversible, of low absolute magnitude, and of unclear clinical relevance. Thus, the benefit of intensive BP control will, in most circumstances, outweigh kidney and other adverse outcomes (Figure 1). The optimal frequency of kidney function monitoring is debatable, but more frequent

checks soon after intensification of the antihypertensive regimen or after a decline in eGFR are prudent.

Despite these general recommendations, several important caveats remain. All BP target trials to date excluded patients with advanced CKD, and thus, optimal BP targets in patients with CKD stage 4 or 5 remain unknown. SPRINT excluded patients with heavy proteinuria and diabetes mellitus. However, analyses from the other trials noted above support targeting BP <130/80 mm Hg for kidney protection among patients with proteinuria, and there is no *a priori* hypothesis as to why patients with diabetes mellitus would not benefit from the same lower BP target with regard to cardiovascular disease. Although the ACCORD BP Trial did not show a benefit for intensive BP control, the lower than expected event rate may have reduced the statistical power to detect significant differences, and the point estimates for cardiovascular events were similar to those in the SPRINT. Methods of BP measurement in the context of clinical trials often yield lower values than BP measured in routine clinical practice. Efforts to improve clinic BP measurement are needed, but targeting BP <130/80 mm Hg rather than systolic BP <120 mm Hg provides a buffer in translating the trial data to clinical practice. Guidelines cannot always keep up with science, because results from future studies will provide new data to consider, such as the forthcoming cognitive function results from the SPRINT. As always, we as clinicians need to incorporate individualized patient-specific risks and benefits when making BP treatment decisions.

Acknowledgments

T.I.C. and M.J.S. are members of the Kidney Disease Improving Global Outcomes BP Guideline Update Work Group. The views expressed in this manuscript are those of the authors and do not represent those of the Work Group.

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

The authors disclose the following potential conflicts that are not directly relevant to this article: T.I.C., consulting fees from Janssen, Novo Nordisk, and Fresenius Medical Center; M.J.S., steering committee for Akebia.

References

1. Wright Jr. JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff Jr. DC, 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. Beddhu S, Rocco MV, Toto R, Craven TE, Greene T, Bhatt U, Cheung AK, Cohen D, Freedman BI, Hawfield AT, Killeen AA, Kimmel PL, Lash J, Papademetriou V, Rahman M, Rastogi A, Servilla K, Townsend RR, Wall B, Whelton PK; SPRINT Research Group: Effects of intensive systolic blood pressure control on kidney and cardiovascular outcomes in persons without kidney disease: A secondary analysis of a randomized trial. *Ann Intern Med* 167: 375–383, 2017
3. Cushman WC, Evans GW, Byington RP, Goff Jr. DC, Grimm Jr. RH, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F; ACCORD Study Group: Effects of

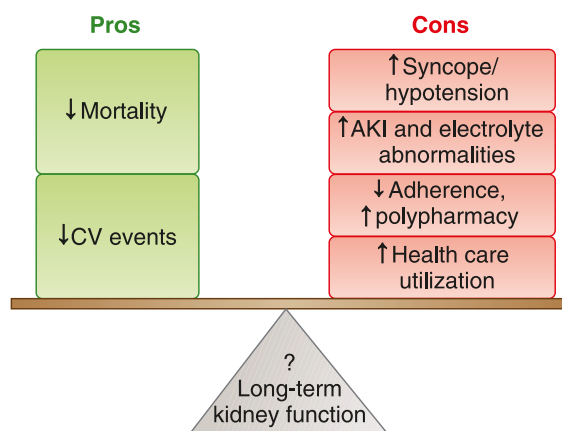


Figure 1. | The pros and cons of more intensive BP control need to be weighed in each patient. Although more intensive BP control can reduce rates of cardiovascular (CV) events and death, these benefits must be weighed against higher risks of potential adverse events, such as syncope, hypotension, AKI, or electrolyte disturbances. Intensive BP lowering also generally requires more medications, which can complicate adherence, and increase health care utilization, such as more frequent provider visits for medication titration. The association of intensive BP control with long-term kidney outcomes remains unknown.

- intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 362: 1575–1585, 2010
4. Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, Levey AS: The effect of a lower target blood pressure on the progression of kidney disease: Long-term follow-up of the modification of diet in renal disease study. *Ann Intern Med* 142: 342–351, 2005
 5. Appel LJ, Wright Jr. JT, Greene T, Agodoa LY, Astor BC, Bakris GL, Cleveland WH, Charleston J, Contreras G, Faulkner ML, Gabbai FB, Gassman JJ, Hebert LA, Jamerson KA, Kopple JD, Kusek JW, Lash JP, Lea JP, Lewis JB, Lipkowitz MS, Massry SG, Miller ER, Norris K, Phillips RA, Pogue VA, Randall OS, Rostand SG, Smogorzewski MJ, Toto RD, Wang X; AASK Collaborative Research Group: Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 363: 918–929, 2010
 6. Lv J, Ehteshami P, Sarnak MJ, Tighiouart H, Jun M, Ninomiya T, Foote C, Rodgers A, Zhang H, Wang H, Strippoli GF, Perkovic V: Effects of intensive blood pressure lowering on the progression of chronic kidney disease: A systematic review and meta-analysis. *CMAJ* 185: 949–957, 2013
 7. 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 Jr. JT, 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, Wolfgram D, Yee J; SPRINT Research Group: Effects of intensive BP control in CKD. *J Am Soc Nephrol* 28: 2812–2823, 2017
 8. Rocco MV, Sink KM, Lovato LC, Wolfgram DF, Wiegmann TB, Wall BM, Umanath K, Rahbari-Oskoui F, Porter AC, Pisoni R, Lewis CE, Lewis JB, Lash JP, Katz LA, Hawfield AT, Haley WE, Freedman BI, Dwyer JP, Drawz PE, Dobre M, Cheung AK, Campbell RC, Bhatt U, Beddhu S, Kimmel PL, Reboussin DM, Chertow GM; SPRINT Research Group: Effects of intensive blood pressure treatment on acute kidney injury events in the systolic blood pressure intervention trial (SPRINT). *Am J Kidney Dis* 71: 352–361, 2018
 9. Ku E, Bakris G, Johansen KL, Lin F, Sarnak MJ, Campese VM, Jamerson K, Gassman JJ, Smogorzewski M, Hsu CY: Acute declines in renal function during intensive BP lowering: Implications for future ESRD risk. *J Am Soc Nephrol* 28: 2794–2801, 2017
 10. 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

Published online ahead of print. Publication date available at www.cjasn.org.

See related articles, “Target Blood Pressure for Cardiovascular Disease Prevention in Patients with CKD,” and “Defining Hypertension: Role of New Trials and Guidelines,” on pages 1572–1574 and 1578–1580, respectively.