Consequences of Overinterpreting Serum Creatinine Increases when Achieving BP Reduction

Balancing Risks and Benefits of BP Reduction in Hypertension

Hala Yamout[1,2] *and George L. Bakris*[3]

Clin J Am Soc Nephrol 13: 9–10, 2018. doi: https://doi.org/10.2215/CJN.11811017

[1]Department of Medicine, Division of Nephrology, St. Louis University Medical Center, St. Louis, Missouri; [2]John Cochran Division, Veterans Affairs St. Louis Health Care System, St. Louis, Missouri; and [3]American Society of Hypertension Comprehensive Hypertension Center, University of Chicago Medicine, Chicago, Illinois

Correspondence: Dr. George L. Bakris, ASH Comprehensive Hypertension Center, University of Chicago Medicine, 5841 South Maryland Avenue, MC 1027, Chicago, IL 60637. Email: gbakris@medicine.bsd.uchicago.edu

Hypertension is a known risk factor for cardiovascular (CV) death as well as the second most common cause of ESRD in the United States. Systolic BP reductions to levels below 140 mm Hg and even 130 mm Hg are associated with a slower decline in kidney function over the spectrum of kidney disease severity (1).

Multiple trials in patients with nondiabetic CKD have formally tested the hypothesis that a lower BP is associated with a slower decline in kidney function, but all have failed to show a slowed progression (2). An exception may be among those with 1 g or more of proteinuria, where *post hoc* analyses suggest slower CKD progression at lower pressures. In these trials, only hyperkalemia was noted as a kidney-related safety issue in the lower BP groups in these trials (3).

The Systolic Blood Pressure Intervention Trial (SPRINT) was a multicenter, randomized study with 9361 participants that examined whether a systolic BP <120 mm Hg reduced CV events more than standard treatment to <140 mm Hg. The primary outcome was a composite of CV events or death from CV disease. The trial was stopped early for overwhelming CV event reduction in the intensive BP group; however, this group also had higher risk of adverse events, specifically hypotension, electrolyte abnormalities, and AKI.

The paper by Magriço *et al.* (4) in this issue of the *Clinical Journal of the American Society of Nephrology* evaluates the magnitude of BP reduction in the context of kidney function decline in the subset of patients without CKD. The primary end point that they used was a decline as defined in the SPRINT protocol of ≥30% reduction in eGFR to <60 ml/min per 1.73 m^2 on two consecutive laboratory determinations collected at 3-month intervals (5). It should be noted that this definition of percentage reduction in eGFR is accepted as only preliminary evidence of reduced kidney function. What is needed to confirm harm to kidney function is to stop the therapy, which in most patients, involved a blocker of the renin-angiotensin system and a long-acting thiazide-like diuretic to see if eGFR returns to baseline. When this was done in other long-term studies, eGFR did return to baseline even after 6 years of treatment in one study, and it was associated with long-term benefits in another (6,7).

The authors evaluated the association of change in eGFR as a complication of the magnitude of BP reduction from baseline with the desired systolic BP goal. The authors categorized the mean arterial pressure change from baseline to the lowest recorded BP as <20 mm Hg (baseline systolic BP of 129 mm Hg), 20 to <40 mm Hg (baseline systolic BP of 143 mm Hg), and ≥40 mm Hg (baseline systolic BP of 161 mm Hg) among those with stages 1 and 2 CKD in the intensive treatment group of the SPRINT. They note a relationship between the magnitude of drop in BP and risk of decline in eGFR. Although this association seems a reasonable conclusion, one must carefully examine the following: (*1*) the baseline level of eGFR and (*2*) the duration of previously uncontrolled BP. These are key factors that would distinguish true reduction in kidney function from a hemodynamic resetting of eGFR. Clearly, from these data, there is no evidence of permanent kidney injury. These are important variables to assess and confirm before drawing any conclusions about kidney injury.

A review of kidney physiology shows that, although systolic BPs within the range of 80–150 mm Hg should maintain GFR, acute large changes in BP can be associated with acute changes in kidney autoregulation and subsequent reductions in kidney plasma flow and GFR (8). Moreover, as the authors note, agents used to lower BP (*i.e.*, renin-angiotensin system blockers and diuretics) contribute to accentuated drops in GFR. However, in some studies, an early and sustained fall in eGFR portended a better kidney outcome in patients with CKD and those with stage 2 CKD (7,9). Hence, it would be misleading and inappropriate to view a hemodynamic resetting of kidney function as injury.

This analysis ignores physiologic adaptation and treats the numbers as if they are truly verified, implying injury without long-term follow-up, which is an overstatement at best. The clinical consequences of such analyses result in patients not receiving proper treatment of BP to avoid a rise in creatinine, a hemodynamic consequence of both the Δ change in systolic BP and medications used to achieve the goal. This results in patients being denied the opportunity of CV mortality and morbidity reduction afforded by lower pressures.

In those with advanced CKD, not the group reported by Magriço *et al.* (4), a >20% sustained reduction in eGFR early during treatment resulted in worse kidney outcome over time, regardless of intensity of BP

reduction (10). This change in eGFR may simply reflect severe underlying atherosclerotic disease in the kidney, making it very susceptible to small intra-arterial changes, because this is not seen in large outcome studies (11).

CV disease remains a leading cause of mortality and morbidity, and its risk factors, especially uncontrolled BP, should be aggressively managed. Patients should not be denied such management because of fear that eGFR will fall. It is clear that, apart from in those hospitalized with heart failure and those with advanced CKD, manifesting >20% increases in serum creatinine when BP is lowered does not significantly affect long-term kidney outcomes. Hence, the CV risk reduction far outweighs the CKD progression risk.

Disclosures

None.

References

1. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, Woodward M, MacMahon S, Turnbull F, Hillis GS, Chalmers J, Mant J, Salam A, Rahimi K, Perkovic V, Rodgers A: Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: Updated systematic review and meta-analysis. *Lancet* 387: 435–443, 2016
2. Upadhyay A, Earley A, Haynes SM, Uhlig K: Systematic review: Blood pressure target in chronic kidney disease and proteinuria as an effect modifier. *Ann Intern Med* 154: 541–548, 2011
3. Lazich I, Bakris GL: Prediction and management of hyperkalemia across the spectrum of chronic kidney disease. *Semin Nephrol* 34: 333–339, 2014
4. Magriço R, Bigotte Vieira M, Viegas Dias C, Leitão L, Neves JS: BP reduction, kidney function decline, and cardiovascular events in patients without CKD. *Clin J Am Soc Nephrol* 13: 73–80, 2018
5. Wright JT Jr., Whelton PK, Reboussin DM: A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 374: 2294, 2016
6. Ruggenenti P, Remuzzi G: Dealing with renin-angiotensin inhibitors, don't mind serum creatinine. *Am J Nephrol* 36: 427–429, 2012
7. Bakris GL, Weir MR: Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? *Arch Intern Med* 160: 685–693, 2000
8. Palmer BF: Renal dysfunction complicating the treatment of hypertension. *N Engl J Med* 347: 1256–1261, 2002
9. Holtkamp FA, de Zeeuw D, Thomas MC, Cooper ME, de Graeff PA, Hillege HJ, Parving HH, Brenner BM, Shahinfar S, Lambers Heerspink HJ: An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. *Kidney Int* 80: 282–287, 2011
10. 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
11. Adams PL, Adams FF, Bell PD, Navar LG: Impaired renal blood flow autoregulation in ischemic acute renal failure. *Kidney Int* 18: 68–76, 1980

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

See related article, "BP Reduction, Kidney Function Decline, and Cardiovascular Events in Patients without CKD," on pages 73–80.