Blood Pressure in Chronic Kidney Disease
Does the Emperor Have New Clothes?

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Hypertension represents the number 1 risk factor for cardiovascular morbidity and mortality worldwide, making its treatment a top public health priority. With continued lower-than-ideal awareness and control rates of hypertension, it is perhaps understandable and justifiable that the general attitude toward hypertension and its treatment has been bordering on the overzealous.

It is on this background that our thinking about blood pressure (BP)—lowering therapy in chronic kidney disease (CKD) and end-stage renal disease (ESRD) has been shaped for decades. Patients with CKD and ESRD represent some of the highest risk populations, and convictions about the unequivocal role of BP in causing renal and cardiovascular disease have until recently led to opinion-based recommendations to use more stringent treatment targets in these patients.

In this issue of the journal, Bansal et al present an analysis of the association of systolic BP (SBP) levels with all-cause mortality in patients with advanced stages of CKD enrolled in the Chronic Renal Insufficiency Cohort. In patients not on dialysis with estimated glomerular filtration rate <30 mL/min per 1.73 m², SBP was not associated with mortality; in a subgroup of these patients who advanced to ESRD and started receiving hemodialysis, predialysis SBP showed a U-shaped association with mortality, whereas higher interdialytic SBP was associated with a linear increase in the risk of mortality. By examining an extremely well-characterized prospective cohort, the biases for bias caused by measurement error or from unmeasured confounding in this study are diminished. The fact that essentially all examined patients received antihypertensive medications suggests that the observed SBP was the result of therapeutic interventions, which strengthens inferences about the potential effects of therapeutic BP lowering in this group. Examined separately, the findings in the predialysis and dialysis groups are by and large in line with previous observations. The relative contribution of SBP in the 110 to 170 mm Hg range to survival in CKD seems to be modest and may not be easily detectable in smaller studies (with much more robust associations being present above and below these thresholds). As for hemodialysis patients, the circumstances of their BP measurement (predialysis versus interdialytic) may have a major effect on its associations with outcomes.

Some of the results of the study by Bansal et al are more difficult to interpret. Their ESRD group was an extension of the CKD cohort, and if we premise that SBP is not associated with outcomes in CKD, why would it later become a potent risk factor in a subgroup of the same patients? A plausible answer is survivorship bias, but this raises questions about the generalizability of these findings to the wider ESRD population: Is this bias inherent to all those who progress to ESRD, or was it something specific to Chronic Renal Insufficiency Cohort participants? These findings suggest that a one-size-fits-all approach to hypertension management may not be appropriate in CKD and ESRD and should strengthen calls for more detailed and larger studies.

The wider implications of the study by Bansal et al and by other similar observational studies in patients with kidney disease are potentially significant. Causal inference requires proof from observational evidence (association between a risk factor and an outcome), biological plausibility (well-defined mechanisms of action), and evidence that a reversal of the risk factor is beneficial (efficacy and safety in randomized, controlled clinical trials). We now have mounting evidence that the observational association of SBP with mortality in CKD and ESRD is qualitatively different from that seen in patients with normal kidney function, thus denting the lower, the better concept that led to the stricter BP targets in CKD and ESRD. The negative physiological effects of lower BP levels in patients who have chronic diseases are now well established, by virtue of a diminished vascular autoregulation and consequent organ-hypoperfusion. Finally, there is now evidence from large clinical trials that stricter BP control in high-risk patients (eg, diabetics) is not as clearly beneficial as it was once thought. Clinical trials of BP lowering in CKD have failed to prove beneficial effects, but these trials were primarily designed to assess renoprotective effects of BP lowering. Clinical trial evidence for the effects of hypertension therapy in ESRD is also scant and of low quality. An observational modeling of strict versus usual SBP control in CKD suggested that the former was associated with higher mortality, but a traditional randomized controlled clinical trial will be needed to provide a conclusive answer to this vexing question. The Systolic Blood Pressure Intervention Trial (SPRINT) compares the effect of an SBP goal of <120 and <140 mm Hg, including for the first time patients with estimated glomerular filtration rate 20 to 59 mL/min (www.sprinttrial.org), with results expected after 2018.
As a result of the totality of the current evidence, most recent professional guidelines have backtracked on earlier recommendations on stricter BP control in patients with CKD and recommend the same BP targets as in other patient groups, occasionally advocating stricter control only in well-defined subgroups of patients, such as those with proteinuria. Perhaps the SPRINT will provide conclusive evidence about the merits of strict BP control in CKD although it is possible that the benefit of this strategy may be limited to only some end points (eg, strokes), which could mean that a more nuanced, individualized approach to antihypertensive therapy in CKD may be most beneficial. The recognition not only that uncontrolled hypertension is deleterious but also that overzealous BP lowering could be harmful should lead to a more balanced view of therapeutic goals in CKD and ESRD, which would only benefit our patients.

Disclosures
Dr Kovesdy is an employee of the US Department of Veterans Affairs. Opinions expressed are those of the author and do not represent the opinion of the US Department of Veterans Affairs.

References
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