The Continued Quest for Optimal BP Targets in Older Adults with Kidney Disease

Jessica W. Weiss

Since the landmark Veteran’s Affairs Cooperative Trials of the late 1960s to 1970s, hypertension management has played a central role in efforts to decrease cardiovascular risk (1,2). Given the prevalence of isolated systolic hypertension in older adults, later studies in older populations focused on systolic BP (SBP) targets; trials of older adults (mean age >60 years old) who were treated to specific BP goals showed decreased cardiovascular risk when SBP was controlled to <150 mmHg compared with higher targets (3–6). The value of more intensive SBP control (to levels well below 150 mmHg) continues to be the source of significant debate. Two studies among older Japanese adults failed to find a reduction in a composite cardiovascular outcome with lower versus higher targets (SBP<140 versus <150 mmHg or <160 mmHg) (7,8). Also, the recent Action to Control Cardiovascular Risk in Diabetes Trial did not find any difference in a composite cardiovascular outcome with more (SBP<120 mmHg) versus less intensive (SBP<140 mmHg) control among adults with diabetes (mean age =62 years old) (9). Importantly, the majority of these trials incorporated creatinine ceilings in their entry criteria, which resulted in the exclusion of patients who had anything beyond moderate reductions in eGFR. The lack of evidence to support the benefits of aggressive BP lowering for older adults led the Eighth Joint National Committee to recommend more liberal BP targets for adults ages >60 years old (<150/90 mmHg) (10). Of note, CKD-specific guidance within this report continued to recommend a lower BP target (<140/90 mmHg) for patients with CKD of all ages largely on the basis of expert opinion. The more recent Systolic Blood Pressure Intervention Trial (SPRINT) intentionally included adults with CKD as well as older adults to help address knowledge gaps about intensive BP lowering in these populations, although those with more severe reductions of eGFR were still excluded (11). The SPRINT found a lower risk of cardiovascular events and mortality among adults treated to SBP targets of <120 versus <140 mmHg in the overall analysis and across all subgroup analyses, including the CKD population; the contrast between these and previous trials to target BP trial results calls into question the appropriateness of recent guideline recommendations.

In this issue of the Clinical Journal of the American Society of Nephrology, Kovesdy et al. (12) add to the collective understanding of the relationship between BP and a wide range of clinical outcomes in older adults with incident CKD. In a large retrospective cohort of United States veterans, Kovesdy et al. (12) identified a U-shaped relationship between SBP and examined outcomes (mortality, incident coronary heart disease, incident stroke, and ESRD). Kovesdy et al. (12) found that both SBP≥140 and <120 mmHg were associated with an increased risk of all examined outcomes compared with SBP=130–139 mmHg, but the magnitude of risk associated with a given level of BP was attenuated with advancing age. For example, when SBP was ≥170 mmHg, the hazard ratios for mortality were 2.01, 1.68, 1.39, and 1.30 for ages 50–59, 60–69, 70–79, and ≥80 years old, respectively. Of note, for incident coronary heart disease and incident stroke, the hazard ratios were slightly higher in those ages ≥80 years old compared with those ages 70–79 years old when SBP =140–149 (1.3 versus 1.08 for coronary heart disease, respectively, and 1.23 versus 1.1 for stroke, respectively). Among adults ages ≥80 years old, however, the relative risk of these two outcomes remained relatively stable across SBP groups >140 mmHg, whereas the risk increased linearly with increasing SBP in younger patients. These results are consistent with an earlier study by Kovesdy et al. (13), which described a U-shaped relationship between BP and all-cause mortality (lowest risk of mortality seen in those with BP=130–159/70–89 mmHg) in a national cohort of veterans with CKD. In a previous study of older adults with CKD, we also described a U-shaped relationship between SBP and mortality (increased risk of mortality with SBP≥140 and <130 mmHg compared with 130–139 mmHg) among adults ages 65–70 years old but found no increase in risk of death at higher levels of SBP for those ages ≥70 years old (14). In our previous analysis (14) and in this study (12), there was not a definitive increase in the relative risk of mortality for adults ages ≥80 years old when SBP was 140–149 or 150–159 mmHg (confidence intervals included unity). Kovesdy et al. (12) expanded on this, however, via a more finely stratified analysis of higher SBP levels, which found an increase in relative risk of death even among those ≥80 years old when SBP was >160 mmHg. This suggests that a U-shaped relationship between BP and mortality was present even among the oldest participants but...
that the threshold where risk of death increases relative to SBP varied with age.

This study (12) identified an increased risk of mortality with lower diastolic BP (DBP; DBP < 60 mmHg) but no association between higher levels of DBP (> 80 mmHg) and examined outcomes; this finding is consistent with previous work by Kovesdy et al. (13) and our group (14). The risk of isolated systolic hypertension increases as eGFR declines, and lower levels of DBP have been associated with increased risk of mortality and cardiovascular events (3,15–17). The comparative benefits of lowering SBP versus allowing DBP to stay > 60 mmHg, particularly among patients with renal disease, remain unclear.

High-quality observational data, such as those presented here by Kovesdy et al. (12), play a pivotal role in deciphering the relationship between BP and important outcomes in a subset of patients, older adults with CKD, who are unlikely to be comprehensively evaluated in a clinical trial. Those patient characteristics that make decisions about BP targets most challenging in a real-world clinic setting, including dementia, frailty, and poor functional status, are extremely common among older adults with CKD and portend a worse prognosis, including an increased risk of death (18–20); unfortunately, these characteristics often serve as indications to exclude these patients from trial populations. The majority of clinical trials of more versus less-intensive BP control in older adults, including the SPRINT, excluded adults with a prior diagnosis of dementia and excluded on the basis of criteria likely related to poor functional status, such as inability to sit or stand, presence of medical management problems, or residence in a skilled nursing facility (4–6,11,21).

In addition, clinical trials frequently exclude or limit inclusion of patients who have comorbidities that can influence the outcome of interest. In trials of BP management, this has often resulted in trial populations with a lesser burden of those severe comorbidities that may limit life expectancy and otherwise complicate everyday decisions about BP management. In trials of hypertension management, preexisting heart failure (especially symptomatic disease or New York Heart Association class 3/4), cancer, and diseases likely to limit life expectancy have been excluded by most major trials, including the SPRINT (5,7–9,11,21–23). Although observational cohort analyses cannot establish causation, age- and comorbidity-specific evaluations in real-world populations may provide a unique window into possible risks and benefits of hypertension management most pertinent to the older adult with complex comorbidity.

The observational nature of this study does impose some limitations, including the concern for residual confounding. In addition, although inclusion of frailty within this analysis would be ideal, use of a low body mass index/weight loss combined variable to identify frailty is complicated by the many clinical factors that can alter these characteristics—most notably, the use of diuretics for management of edema or heart failure. Furthermore, this variable alone is not an adequate surrogate for frailty, because even if truly representative of unintentional weight loss, weight loss alone speaks to only one factor in the most validated and accepted definition of frailty (24). Whereas frailty has been associated with an increased risk of mortality in previous studies, the presence of low body mass index/weight loss was not associated with increased risk of any examined outcome in this analysis (20). In addition, although the inclusion of the Charlson–Deyo comorbidity index in this analysis is commendable, because of its incorporation as a dichotomous variable this addition is unlikely to fully adjust or account for the role that comorbidity may play in the relationship between BP and examined outcomes (25,26). These results may also not be generalizable to women given that the cohort was comprised predominantly of men.

The results of this observational study provide novel insight into the complex relationships between BP and health outcomes and may be helpful in guiding the design of future trials to address the value of differing BP targets in older adults with CKD (12). These results may also add a note of caution to newfound enthusiasm for lower BP targets after the release of the SPRINT via the suggestion that harm may persist at upper and lower extremes of BP among populations more comorbid and complex than those evaluated in the setting of a clinical trial. Ideally, future studies may continue to expand our knowledge in this area with more detailed exploration of the potential modifying effect of comorbidity and frailty on the association between BP and outcomes in older adults. For now, a tailored application of available data to the constellation of comorbidities and health care priorities of a particular patient remains the best approach for individualized hypertension management among older adults with CKD.

Disclosures
None.

References
2. Anonymous: Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 213: 1143–1152, 1970


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

See related article, “Age and Outcomes Associated with BP in Patients with Incident CKD” on pages 821–831.