Invited Commentary

The Ideal Blood Pressure Target for Patients With Chronic Kidney Disease—Searching for the Sweet Spot

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Hypertension is the number 1 cardiovascular risk factor, and its treatment prevents major cardiovascular events and lowers mortality. Most patients with chronic kidney disease (CKD) have hypertension, and CKD is characterized by extremely high cardiovascular disease rates. It is thus not surprising that antihypertensive therapy is a universal part of CKD management, and its benefits are broadly accepted. Notwithstanding the general consensus about the pathophysiologic relevance of hypertension, there has been controversy in the medical community regarding the ideal therapeutic blood pressure (BP) target in patients with CKD. Fueling this controversy are concerns about the presence of a J-curve and the paucity of dedicated randomized clinical trials (RCTs) testing the effects of BP lowering to levels that approach physiologic normalcy (ie, <120/80 mm Hg). These uncertainties are further accentuated when assessing the effects of antihypertensive therapy on all-cause mortality, which includes deaths with causes entirely unrelated to hypertension.

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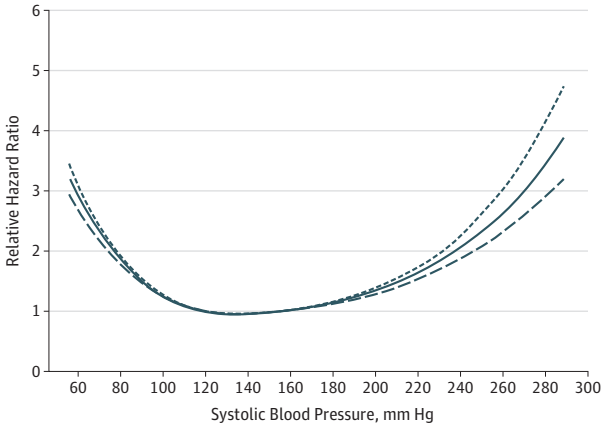
In this issue of *JAMA Internal Medicine*, Malhotra et al[1] attempt to address the vexing issue of all-cause mortality benefit vs harm associated with intensive vs less intensive BP lowering in hypertensive patients with CKD by performing a meta-analysis of RCTs that included patients with estimated glomerular filtration rates (eGFRs) below 60 mL/min/1.73 m^2 and not undergoing renal replacement therapy. The authors analyze published and unpublished data from 18 RCTs on 15 924 patients with CKD exposed to various BP lowering interventions. The mean systolic BP (SBP) achieved in the more intensive vs less intensive BP control arms were 132 vs 140 mm Hg, respectively, with more intensive treatment resulting in a 14% lower risk of all-cause mortality. The results did not show substantial heterogeneity and were consistent in various subgroup analyses. In addition, larger decreases in SBP showed a trend toward more benefit in a meta-regression analysis. This study is a valuable addition to our knowledge about hypertension therapy in CKD, but its interpretation still requires caution, for several reasons.

First, the question of whether a normal BP target (as most would define intensive BP control) is beneficial in patients with CKD remains unanswered. The meta-analysis includes RCTs that used various BP targets, and Malhotra et al[1] define "intensive" as the lower target in each individual study. The mean overall intensive SBP of 132 mm Hg in the meta-analysis actually falls within the clinical target recommended by most current guidelines (ie, <140 mm Hg) and is also within the range that has been associated with the best outcomes in large observational studies (**Figure**).[2] One could therefore interpret the results of this meta-analysis as solidifying existing evidence about the benefits of lowering BP to a range of 130 to 140 mm Hg but not as proof that truly intensive BP lowering (ie, to a target <120 mm Hg) is beneficial. Another aspect of this question concerns the BP levels achieved in the SPRINT study,[3] in which the intensive treatment target was an SBP of lower than 120 mm Hg, but which used a measurement method different from that used in routine clinical practice. When the measurement method is translated to that used in clinical practice, SBP levels might be substantially higher (up to 10-15 mm Hg).[4] Using a higher value for the SBP in SPRINT would increase the mean SBP estimated in the meta-analysis and might also affect the result of the subgroup analysis, which implies equally beneficial effects from more intensive BP lowering in RCTs using various target BP levels (including <120 mm Hg).

The second question concerns the external validity of RCTs assessing hypertension control in CKD. The observed absolute mortality rate was substantially higher in large cohort studies[5] than it was in patients enrolled in the RCTs included in the meta-analysis by Malhotra et al.[1] The much higher all-cause mortality rate in the general CKD population may be due to causes that are unaffected by BP lowering (eg, infections or malignant conditions). Thus the real-life efficiency of BP lowering may be diluted, and intensive control may even have deleterious effects in some cases. A further concern is that lumping all patients with an eGFR below 60 mL/min/1.73 m^2 together under the umbrella of CKD risks mixing different populations that may very well have divergent responses to BP lowering.

Figure. Mortality Hazard Ratios Associated With Various Baseline Systolic Blood Pressures



The illustrated cohort consisted of 651 749 US veterans, each with an estimated glomerular filtration rate lower than mL/min/1.73 m^2. This graph was adapted from Kovesdy et al.[2]

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It is possible that intensive BP lowering may have a diminishing benefit along with an increase in the incidence of adverse outcomes such as acute kidney injury in patients with more advanced CKD (eg, eGFR <30 mL/min/1.73 m^2). The assessment of this hypothesis in secondary analyses of the SPRINT study is pending.

Finally, we must remember that the highest risks of hypertension occur in those with extremely elevated BP levels (Figure), and the benefits accrued with treating SBP to levels below about 140 mm Hg are much smaller. In one of the first ever RCTs assessing the impact of antihypertensive therapy in previously untreated patients (mean baseline BP of 186/121 mm Hg), the beneficial effect of treatment (vs placebo) was massive, resulting in a number needed to treat (NNT) to prevent 1 adverse event of 2.8, and an NNT to prevent 1 death of 17.5.[6] In contrast, more intensive vs less intensive BP lowering resulted in an NNT to prevent 1 death of 167 based on the absolute risk reduction estimated in the meta-analysis by Malhotra et al[1] and an NNT to prevent 1 composite renal failure event of 250 based on the results of another meta-analysis.[7] These diminishing absolute benefits have to be weighed against the increased likelihood of adverse effects and the higher costs associated with more intensive BP lowering.

In conclusion, the meta-analysis by Malhotra et al[1] suggests that lowering elevated BP to a target of below 140 mm Hg and possibly closer to 130 mm Hg improves all-cause mortality in patients with CKD. There are still numerous open questions requiring further research about the benefits of treating SBP to even lower levels, especially in patients with more advanced stages of CKD.

ARTICLE INFORMATION

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