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See related article, "Quantifying Postdonation Risk of ESRD in Living Kidney Donors," on pages 2749–2755.

BP Targets in CKD, Mortality, and SPRINT: What Have We Learned?

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Control of hypertension has long been a fundamental part of the care for patients with CKD. The vast majority of patients with CKD develop disturbances in sodium balance and pressor mechanisms that lead to higher arterial pressures as GFR declines.[1] Higher BP interacts with both classic cardiovascular (CV) risk factors, which are common in patients with CKD, and additional novel risk factors unique to CKD to increase risk for CV events above that for individuals without CKD. Recognition of this higher risk led the Joint National Committee 7 (JNC 7) in 2003 to designate CKD a CV "risk equivalent" of manifest CV disease and recommend an empirical BP target of <130/80 mm Hg.[2]

However, optimal goals of BP therapy for individuals with CKD have been controversial. The relationship between BP and CV events in patients with incident CKD is complex and may differ by patient age. Several large observational studies identify a U- or J-shaped curve with rising mortality for patients with CKD as systolic BP (SBP) falls <120 mm Hg and/or diastolic BP falls <60 mm Hg.[3,4] For patients >75 years old, higher SBP adds minimal demonstrable risk at all.[3,4] Treatment trials in CKD, including the Modification of Diet in Renal Disease (MDRD) Trial and the African-American Study of Kidney Disease (AASK), specifically tested the hypothesis that intensive BP reduction would slow the rate of decline in GFR. Both of these trials failed to show benefit in patients who were not proteinuric.[5,6] Intensive antihypertensive therapy to a target SBP of 120 mm Hg compared with a conventional target of 140 mm Hg in patients with diabetes who are hypertensive enrolled in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial also failed to show a benefit regarding overall CV events or mortality, and indeed, the results suggested caution with intensive BP reduction because of increased risks of hypotension and AKI.[7] These observations together led the committee selected for the JNC 8 in 2014 to raise the evidence-based BP target to 140/90 mm Hg in patients <60 years old with CKD (and 150/90 mm Hg for older individuals) because of the lack of prospective data to support lower goals.[8]

Cheung *et al.*[9] now report in this issue of the *Journal of the American Society of Nephrology*, in the article "Effects of intensive BP control in CKD"—an analysis from a preidentified CKD subset of patients enrolled in the Systolic BP Intervention Trial (SPRINT). This is the largest randomized trial to date (n=2646 subjects with eGFR between 20 and 59 ml/min per 1.73 m^2) to assess different BP targets on CV and kidney outcomes in patients with CKD. The trial targeted older subjects (mean age of 71.9 years old; 43.9% aged >75 years) considered at increased CV risk with SBP between 120 and 180 mm Hg. It excluded patients with diabetes, proteinuria >1 g/d, polycystic kidney disease, prior stroke, and symptomatic heart failure or ejection fraction <35%. Importantly, multiple BP readings were obtained at 1-minute intervals and averaged at each visit using an automated oscillometric unit (Omron Healthcare 907) after the patient had been seated quietly for 5 minutes alone (unattended automated BP measurement). SBP targets of 140 mm Hg in the standard group and 120 mm Hg in the intensive group were rapidly

achieved, with average values being 136.9±0.2 and 123.0± 0.2 mm Hg, respectively, after 1 year and an average SBP difference of 12.3 mm Hg between the groups. Antihypertensive drug requirements were low, with an average of two drugs in the standard group and 2.9 drugs in the intensive group. The overall SPRINT results have been reported previously. The trial was stopped early because of the observation of significantly reduced overall and CV mortality and CV composite end points in the intensive compared with the standard group.[10] This observed mortality benefit was also seen in the CKD cohort reported here when considered alone. No specifically different interactions were observed between those with and without CKD in these outcomes. All-cause mortality was 2.21%/yr in the standard group and 1.61%/yr in the intensive group ($P=0.04$). The primary composite CV disease and all-cause death outcomes were significantly lower in the intensively treated participants aged ≥75 year old with CKD. After adjustment for multiple comparisons, the beneficial effects of intensive SBP reduction persisted and were even more pronounced in older individuals. It should be emphasized that few cases of progressive CKD and/or ESRD occurred in patients in this cohort over the 3.3-year duration of the study. However, intensive SBP reduction was associated with a higher risk of a 30% fall in eGFR, which was not evident for higher levels (*e.g.*, 40% or 50% reduction). The fall in eGFR developed early and was followed by a minor ongoing annual decrement in eGFR in parallel with a similar fall in the standard group. The authors argue that the early decrement in eGFR likely reflected a functional rise in creatinine associated with more intensive diuretic therapy and/or renin-angiotensin-aldosterone system blockade. No differences were observed in incident albuminuria.

Not surprisingly, more intensive antihypertensive drug therapy to lower BP levels was associated with increases in specific adverse events, namely potassium disorders (both hypokalemia and hyperkalemia), and ARF. The authors argue that serious events from hypotension, syncope, and injurious falls did not differ between groups, although for the entire SPRINT, these were more common with intensive therapy. They present the numbers needed to treat over a 4-year period as 66 for a reduction in CV outcome events, 28 for death, and 61 for CV death. The numbers need to harm were 35 for ARF, 131 for hypokalemia, and 41 for hyperk6alemia.

How do these results add to the information that nephrologists and other clinicians apply to treating hypertension in patients with CKD? The facts that no such benefits were observed in subjects with diabetes enrolled in the ACCORD Trial treated to similar levels and that serious adverse effects were more clinically evident in that cohort give some pause to more intensive drug therapy. Some authors emphasize that the ACCORD Trial may have been underpowered to detect mortality benefits and that the outcomes observed generally were in the same direction of some small benefit with more intensive therapy,[11] albeit with higher risks for hypotension and syncope. Both the ACCORD Trial and the Secondary Prevention of Small Subcortical Stroke Trial[12] were heavily weighted to subjects with normal kidney function (mean eGFR was >80 ml/min per 1.73 m^2 in both).

The authors from the SPRINT argue that their "findings present the best available evidence to date in favor of intensive SBP reduction as a means to improve survival in patients with CKD and hypertension. . ."[9] At the very least, these data offer a persuasive counterpoint to the concern that the U-shaped curve reported in large observational cohorts might be associated with increased mortality with intensive antihypertensive drug therapy. The SPRINT data also confirm that progression of nondiabetic CKD with minimal proteinuria does not abate with lowering BP alone. In this regard, these data are consistent with the MDRD Trial and the AASK.

Should clinicians advance antihypertensive drug therapy in CKD with the goal of achieving 120 mm Hg SBP to lower CV mortality? Although data from the SPRINT, in fact, show a small reduction in CV events and mortality from treating large numbers with uncomplicated CKD, this effort will come at a price of increased drug use and some adverse events. The numbers needed to treat and harm are remarkably similar. One might argue that the population enrolled in the SPRINT was a limited subset of patients, most of whom are unlike many patients referred to nephrologists for CKD management with diabetes, proteinuria, and episodic circulatory congestion. Such individuals are likely to require more medications than the SPRINT participants for even less effective BP control. In a large cohort of subjects treated within the Kaiser system, >12% were considered to have "resistant hypertension," many of whom had the levels of eGFR and phenotypic characteristics similar to the participants in the SPRINT but required considerably more antihypertensive drugs.[13]

Taken together, the subset of the SPRINT population with CKD reported by Cheung *et al.*[9] does provide evidence of moderate CV benefit from achieving more intensive SBP reduction but at some cost. The use of multiple automated and undisturbed office BP readings has not yet become widely applied in practice. Some authors argue that, although such readings provide a valid estimate of ambulatory, daytime BP, they differ from conventional BP measurements recorded in study settings by 5–10 mm Hg.[14] Hence, the goal of 120 mm Hg translates closer to 130 mm Hg in most practice settings, which they recommend as a reasonable goal. Other authors emphasize the hazards, cost, and symptoms associated with more intensive therapy as a serious limitation, particularly for older individuals. They argue that the net gain may be offset by adverse symptoms in many patients treated outside the supportive environment of a clinical trial, such as the SPRINT.[15] Taken together, these results suggest that we may be approaching an equilibrium between small benefits and nearly equal adverse effects that warrant careful shared decision making between physicians and individual patients.

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DISCLOSURES

S.C.T. participates as a section editor for UpToDate and on the Data Safety Monitoring Board for Sentien Therapeutics. G.L.S. is the president of the American Hypertension Specialist's Certification Program.

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