Debate: PRO Position

People with Chronic Kidney Disease Should Have a Blood Pressure Lower than 130/80 mm Hg

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Blood pressure (BP) is a carefully regulated physiological variable and a critically important measure of overall general health in humans. Clinicians are increasingly concerned with BP diagnosis and management because of its high prevalence in their practice population and the beneficial impact that BP lowering interventions can have on their patients at risk. For more than a century, it has been well established that chronic elevation of BP, hypertension, is associated with tissue injury and organ damage that can be both debilitating and fatal.

For more than 50 years, investigations into the epidemiology, mechanisms and treatment of hypertension have dominated the cardiovascular literature. During this period of time, the definition of hypertension (the magnitude of elevation above normal) has changed considerably. In addition, some have suggested that abnormal elevation of BP alone should not be considered the only definition of hypertension because it is often associated with metabolic derangements that may be associated with increased risk for cardiovascular events including stroke and heart attack as well as progressive kidney disease. For example, an apparently abnormal albumin excretion rate in the setting of hypertension increases risk for cardiovascular mortality beyond BP elevation alone. Information based on epidemiological investigation, prospective observational studies and clinical trials suggest that lower BP levels signify better health or at least re-

duced risk for cardiovascular and kidney diseases in the general population. In particular, it has been recommended by several major national and international organizations that achieving and maintaining a systolic BP level <130 mm Hg in those with hypertension and diabetes or kidney disease, or those with multiple cardiovascular risk factors, is a desirable goal [1–4]. The purpose of this paper is to review the evidence for this recommendation that a systolic BP goal of <130 mm Hg is desirable for all people including those in the general community and those with and those at risk for kidney disease.

Rationale for a Systolic BP Goal <130 mm Hg

The rationale for recommending systolic BP <130 mm Hg is strongly supported by meta-analysis including observational, epidemiological and clinical trials published by Lewington et al. [5]. In this evaluation of more than 1 million people, this group of investigators was able to clearly discern that elevation in systolic BP >115 mm Hg was associated with increased risk for both coronary and stroke mortality. Moreover, for those in the age range of 40–69 years, a 20-mm Hg increase in BP above this threshold was associated with a more than twofold doubling in risk for mortality and the relationship held for each decade of life within this range. This and other in-

formation led the Joint National Committee VII group to modify the definition and staging of hypertension in which the category of prehypertension (systolic BP of 120–139 mm Hg) was created. Based on the Lewington observation and recommendation of the JNC VII on prevention, detection evaluation and treatment of high BP, it would clearly be desirable to achieve and maintain a systolic BP below and perhaps well below 130 mm Hg in people at risk for adverse cardiovascular outcomes [1].

Evidence for Achieving and Maintaining a Systolic BP Goal <130 mm Hg

Observational Studies

Several observational studies support the benefit of systolic BP <130 mm Hg in patients at risk for kidney disease. Evaluation of outcomes of men screened for the Multiple Risk Factor Intervention Trial revealed a strong graded relationship between systolic BP and end-stage renal disease (ESRD) during an average of 16 years of follow-up. A systolic BP level >120 mm Hg was associated with increased risk for ESRD among this cohort [6]. In addition, Hsu et al. [7] examined the relationship between BP and ESRD events among 316,675 adult Kaiser members from the Northern California Kaiser Permanente group, all of whom had an estimated glomerular filtration rate (GFR) of ≥ 60 ml/min/1.73 m² and no proteinuria or hematuria on routine urine testing. They found that compared to those with a systolic BP <120, there was a 62% increase in risk for ESRD. The risk increased for each decile of systolic BP and it was concluded that even a modest elevation in BP is an independent risk factor for ESRD. Analysis of the relationship between systolic BP elevation and ESRD has also been evaluated prospectively in the population of Okinawa. In this analysis of 98,759 subjects observed over a 7-year period by Tozawa et al. [8], systolic BP levels >120 mm Hg showed a graded increase in risk for future ESRD. Taken together, these observational data provide strong evidence supporting systolic BP level <130 mm Hg as a reasonable and beneficial, if not optimal, goal for preventing or slowing kidney disease.

Clinical Trials

Powerful evidence from clinical trials supports lower systolic BP <130 mm Hg for preservation of renal function in patients with chronic kidney disease (CKD). The Modification of Diet in Renal Disease (MDRD) Study included 840 individuals with CKD of varying etiology, ex-

cluding type 1 diabetes mellitus. Among individuals with proteinuria assigned to the aggressive BP goal of <92 mm Hg, the rate of decline was significantly slower as compared to those assigned to less aggressive BP control. In addition, careful analysis of BP, rate of decline in GFR and proteinuria revealed that the rate of decline in GFR was directly related to both systolic and mean arterial pressure, with higher pressure associated with a more rapid decline in GFR. Moreover, in long-term follow-up of the original trial cohort, the incidence of ESRD was significantly lower in those assigned to the more aggressive BP goal than those assigned to the usual BP goal [9]. Long-term follow-up of this cohort further demonstrated the benefit of an aggressive BP target on progression of kidney disease [10].

The African-American Study of Kidney Disease and Hypertension Trial enrolled 1,089 African-Americans with hypertension and CKD, among whom approximately 700 participated in a 5-year prospective cohort follow-up study (AASK cohort study). Among proteinuric subjects who participated in the trial and cohort, the rate of end-stage kidney disease was significantly less in those managed with aggressive (mean achieved systolic BP: 128 mm Hg) versus usual (mean achieved systolic BP: 141 mm Hg) BP control during the trial phase [11].

Bakris et al. [12] demonstrated an increased risk for ESRD among subjects with a baseline systolic BP >130 mm Hg among 1,513 subjects enrolled in the Reduction in Endpoints in NIDDM with the Angiotensin Receptor Blocker Losartan (RENAAL) Trial. Moreover, they demonstrated an approximate 7% increase in risk for every 10-mm Hg increase in systolic BP above a value of 130 mm Hg in this cohort and concluded that achieving a systolic BP goal <130 mm Hg in people with type 2 diabetes mellitus and nephropathy can postpone dialysis. Pohl et al. [13] found that kidney disease progression was 2.2 times more likely in those with an achieved systolic BP >149 mm Hg as compared to those with an achieved systolic BP <134 mm Hg among 1,590 hypertensive patients with type 2 diabetes enrolled in the Irbesartan Diabetic Nephropathy Trial. Moreover, they found that progressive lowering of systolic BP to 120 mm Hg was associated with improved kidney and subject survival not dependent on baseline kidney function. They concluded that a systolic BP target in the range of 120–130 mm Hg was appropriate for patients with type 2 diabetic nephropathy.

In a long-term cardiovascular and renal (surrogate) endpoint trial in patients with type 2 diabetes, Gaede et al. [14] demonstrated that intensive multiple risk factor intervention, including aggressive lowering of systolic BP

from 150 to approximately 130 mm Hg, was associated with a 50% decrease in mortality and slowing of progression of albuminuria as compared to conventional intervention and BP control. In this study, 50% of the study subjects randomized to intensive control achieved a systolic BP <130 mm Hg as compared to <10% in the conventional group. This is further evidence that BP <130 mm Hg contributes to improvement of cardiovascular and renal outcome in type 2 diabetes.

In a meta-analysis of individual patient level data from 1,860 patients with nondiabetic CKD, Jafar et al. [15] evaluated the association of systolic and diastolic BP and urine protein excretion with kidney disease progression. They found that both baseline and follow-up systolic BP between 110 and 129 mm Hg were associated with the lowest risk for kidney disease progression. Furthermore, they demonstrated that for a systolic BP $\geq$ 130 mm Hg, risk ratios for ESRD were higher for baseline levels than for follow-up levels.

Two recent studies provide additional support for more aggressive BP control among those with type 2 diabetes mellitus. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial investigated the effect of aggressive BP treatment to a systolic value <120 as compared to the usual BP goal <140 mm Hg on the occurrence of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes among 4,733 patients with type 2 diabetes. The mean achieved systolic BP in the aggressive control group was 119.3 mm Hg as compared to 133.5 mm Hg in the usual control group. Overall, there was no difference in cardiovascular events; however, there was a significant reduction in risk for stroke in those assigned to achieve a systolic BP of <120 mm Hg [16]. The Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) Trial evaluated the effect of BP lowering on renal events among 11,140 patients with type 2 diabetes mellitus. Study subjects were randomly assigned to fixed combination perindopril-indapamide or placebo and fol-

lowed for a mean of 4.3 years regardless of starting BP. Lower BP was associated with significant reduction in risk for developing microalbuminuria and macroalbuminuria. Lower systolic BP levels down to $\leq$ 110 mm Hg were associated with progressively lower event rates. The authors concluded that BP lowering in type 2 diabetes provided kidney protection even when initial systolic BP was 120 mm Hg [17]. There was no identifiable systolic BP threshold below which a renal benefit was lost.

Summary and Conclusion

The optimal BP for adults to preserve and maintain optimal cardiovascular health is not known. Treatment of hypertension according to current definitions by the JNC VII committee is strongly advised. Evidence from both observational studies and clinical trials supports a systolic BP goal of <130 mm Hg for preserving renal function and reducing cardiovascular morbidity in those with kidney disease and diabetes. Still, there are no large-scale rigorously designed and conducted randomized controlled trials in patients with kidney disease aimed at directly comparing the effect of more aggressive versus less aggressive systolic BP targets on renal and cardiovascular outcomes. The ACCORD trial in patients with type 2 diabetes did not show overall beneficial effects of more aggressive BP lowering on cardiovascular outcomes, although the stroke rate was significantly reduced by this therapy. The Systolic Pressure Intervention Trial (SPRINT) is a novel large-scale trial in the development process. It will examine whether more versus less aggressive systolic BP control will improve cardiovascular and renal outcomes in a large cohort of nondiabetics in the United States. This trial will include a large proportion of patients with CKD and it should provide important new evidence on the optimal BP goal and how to achieve such a goal in this patient population.

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