Debate: CON Position

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

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Despite its name, chronic kidney disease (CKD) is not a specific disease; CKD is a condition that indicates kidney damage and is associated with increased cardiovascular risk and, when damage is severe, an increased risk for end-stage renal disease (ESRD). Among patients with CKD, several studies have asked the question as to what level should blood pressure (BP) be lowered to. Although evidence indicates that BP control is important for treating CKD, there is little evidence that all people with CKD should have BP lowered to <130/80 mm Hg.

The evidence summarizing the level to which BP should be lowered to has emerged from observational studies, post-hoc analyses of trials and randomized controlled trials per se. Observational studies and post-hoc analyses of trials testing specific drugs (such as angiotensin receptor blockers) provide lower quality evidence with respect to developing recommendations as to the level to which BP should be lowered to among patients with CKD. In this context, it is important to distinguish observational from randomized controlled data.

Clinical trials that examine a specific level of BP intentionally lower BP to a specified target. Observational studies or post-hoc analyses of randomized trials can only analyze the level of BP achieved. The achievement of a lower BP may be due to patient characteristics. Those harder to control may have worse disease or may not take their drugs and therefore experience cardiovascular events. Studies that judge BP level by what was achieved

(instead of what was targeted) cannot prove causation and should be viewed with caution.

There are only three prospective randomized multi-center trials that have tested the notion how low BP should be targeted among patients with CKD. These trials were the Modification of Diet in Renal Disease (MDRD) [1], the African American Study of Kidney Disease (AASK) [2] and the Blood-Pressure Control for Renoprotection in Patients with Nondiabetic Chronic Renal Disease (REIN-2) Trial [3]. These trials are discussed in more detail below.

Modification of Diet in Renal Disease

The MDRD Study was a randomized controlled trial with 2 × 2 factorial design that tested the interventions of diet and BP among 840 patients with various chronic renal diseases [1]. Two studies were performed. In study 1, 585 patients with glomerular filtration rates (GFR) of 25–55 ml/min per 1.73 m² of body surface area were randomly assigned to a usual-protein diet or a low-protein diet and to a usual- or a low-BP group (mean arterial pressure, 107 or 92 mm Hg). In study 2, 255 patients with GFR of 13–24 ml/min per 1.73 m² were randomly assigned to the low-protein diet or a very-low-protein diet with a keto acid-amino acid supplement, and a usual- or a low-BP group (same values as those in study 1). An 18- to 45-month follow-up was planned, with monthly evaluations

of the patients. The mean follow-up was 2.2 years. In study 1, the projected mean decline in the GFR at 3 years did not differ significantly between the diet groups or between the BP groups. As compared with the usual-BP group, the low-BP group had a more rapid decline in the GFR during the first 4 months after randomization and a slower decline thereafter. There was no delay in the time to the occurrence of ESRD or death. In both studies, in post-hoc analyses, patients in the low-BP group who had more pronounced proteinuria at baseline had a significantly slower rate of decline in the GFR.

African American Study of Kidney Disease

AASK compared the effects of 2 levels of BP control and 3 antihypertensive drug classes on GFR decline in hypertension [2]. A 3×2 factorial trial design was used to randomize 1,094 African-Americans aged 18–70 years with hypertensive renal disease and GFR between 20 and 65 ml/min per 1.73 m² from 21 clinical centers throughout the United States. Participants were randomly assigned to 1 of 2 mean arterial pressure goals, 102–107 mm Hg (usual; n = 554) or 92 mm Hg or less (lower; n = 540), and to initial treatment with either a β -blocker (metoprolol 50–200 mg/d; n = 441), an angiotensin-converting enzyme inhibitor (ramipril 2.5–10 mg/d; n = 436) or a dihydropyridine calcium channel blocker (amlodipine 5–10 mg/d; n = 217). Open-label agents were added to achieve the assigned BP goals. Participants were followed up for 3–6.4 years. The main outcome measures were the following: rate of change in GFR (GFR slope), clinical composite outcome of reduction in GFR by 50% or more (or 25 ml/min per 1.73 m²) from baseline, ESRD or death. Three primary treatment comparisons were specified: lower versus usual BP goal, ramipril versus metoprolol, and amlodipine versus metoprolol. Achieved BP averaged (SD) 128/78 (12/8) mm Hg in the lower BP group and 141/85 (12/7) mm Hg in the usual BP group. The mean (SE) GFR slope from baseline through 4 years did not differ significantly between the lower BP group [–2.21 (0.17) ml/min per 1.73 m² per year] and the usual BP group [–1.95 (0.17) ml/min per 1.73 m² per year; p = 0.24], and the lower BP goal did not significantly reduce the rate of the clinical composite outcome (risk reduction for lower BP group = 2%; 95% CI: –22 to 21%; p = 0.85). Thus, no additional benefit of slowing progression of hypertensive nephrosclerosis was observed with the lower BP goal.

BP Control for Renoprotection in Patients with Nondiabetic Chronic Renal Disease

The REIN-2 trials assessed the effect of intensified versus conventional BP control on progression to ESRD [3]. Participants had nondiabetic proteinuric nephropathies receiving background treatment with the angiotensin-converting enzyme inhibitor ramipril (2.5–5 mg/day), and were randomly assigned to either conventional (diastolic <90 mm Hg; n = 169) or intensified (systolic/diastolic <130/80 mm Hg; n = 169) BP control. To achieve the intensified BP level, patients received add-on therapy with the dihydropyridine calcium channel blocker felodipine (5–10 mg/day). The primary outcome measure was time to ESRD over 36 months of follow-up, and analysis was by intention-to-treat. Of 338 patients who were randomized, 3 (2 assigned intensified and 1 allocated conventional BP control) never took study drugs and were excluded. Over a median follow-up of 19 months (IQR 12–35), 38 of 167 patients (23%) assigned to the intensified BP control and 34 of 168 (20%) allocated conventional control progressed to ESRD [HR: 1.00 (95% CI: 0.61–1.64); p = 0.99]. The study was terminated early for futility. Among patients with nondiabetic proteinuric nephropathies receiving background angiotensin-converting enzyme inhibitor therapy, no additional benefit from further BP reduction by felodipine could be shown.

Should the level of proteinuria be considered in making clinical decisions? JNC VI guidelines recommended that among patients with CKD who have >1 g proteinuria/d, BP should be lowered to <125/75 mm Hg [4]. This guideline was based on the post-hoc analysis of the MDRD Study that demonstrated patients with >1 g/d proteinuria had greater progression of CKD when targeted to mean arterial pressure <107 mm Hg compared to <92 mm Hg [5]. The JNC VII guideline recognized the post-hoc nature of this analysis and removed the proteinuria-based recommendations [6]. No trial has a priori tested the notion that when patients with overt proteinuria are randomized to BP <130/80 mm Hg versus more, then greater reduction in ESRD, mortality or cardiovascular events will be seen.

In summary, among those with CKD, the AASK, MDRD and REIN-2 trials were notable by their absence of cardiovascular protection [1–3]. In fact, no trial among patients with CKD has demonstrated that a BP goal of <130/80 mm Hg saves lives, saves kidneys or reduces cardiovascular events.

Besides the absence of randomized trials, there are several other reasons why lowering BP to <130/80 mm

Hg may not be appropriate for all. First, comorbidities are common in CKD – one size does not fit all. Few people present to their physicians with CKD without other comorbid conditions. These conditions include the following: hypertension; diabetes mellitus; obesity; sleep apnea; atherosclerotic vascular diseases of the peripheral, coronary, cerebrovascular and renovascular circulations; myocardial infarction; stroke; and heart failure. Autonomic neuropathy often complicates diabetic nephropathy. Accordingly, the management of these patients is complicated. Increased arterial stiffness and autonomic neuropathy may provoke symptoms of orthostatic hypotension when BP is aggressively targeted.

Second, there are no data to support that patients with stage 5D CKD should have BP lowered to <130/80 mm Hg [7]. No trials have been conducted that have lowered BP to two different targets among these people. Although meta-analyses suggest that antihypertensive therapy may be of benefit in reducing cardiovascular events, no firm target exists to which BP should be lowered [8, 9].

Finally, white coat hypertension is common – treating white coat hypertension may be futile. Many patients with CKD in fact may have normal BP at home. In a me-

ta-analysis, approx. 20% of people with CKD had white coat hypertension [10]. These patients may, if aggressively targeted, demonstrate signs and symptoms of organ hypoperfusion. On the other hand, 5–10% of people with CKD have masked hypertension [10]. These patients may be missed completely if only clinic BP monitoring is performed. The latter patients also have increased cardiovascular events and progression to dialysis [11, 12].

One randomized trial among dialysis patients targeted therapy to either BP measured at home or to BP measured in the dialysis unit [13]. At the end of 6 months, only those patients who underwent home BP monitoring had improvement in ambulatory BP. These data suggest that home BP monitoring may be more valuable in ensuring hypertension control.

In conclusion, there is little evidence among patients with CKD that a BP goal of <130/80 mmHg saves lives, saves kidneys or reduces cardiovascular events. Nonetheless, BP control is important. Hypertension therapy should be individualized using home BP monitoring [14]. The precise targets must await randomized controlled trials.

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