Blood Pressure Targets in CKD

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With the release of the 2014 Guidelines for the Management of Hypertension in Adults, a significant amount of discussion has ensued around both the 9 major recommendations promulgated by the Panel and the nature of the evidence base used to formulate those recommendations. In this article, the author will review the data used to support the 2 recommendations made by the Panel that specifically addressed treatment goals (Recommendation 4) and desirable agents to use (Recommendation 8) in hypertensive patients with CKD. Most published recommendations are actually similar, and there is a general consensus that the blood pressure goal should be at least less than 140/90 mm Hg in CKD; some recommend a target of less than 130/80 mm Hg in patients with CKD who have significant proteinuria. This article represents the view of the author and should not be construed as Panel endorsement.

Key Words: Blood pressure target, Chronic kidney disease, Guideline

Introduction

Since 2008, a number of guidance documents have appeared in the medical literature providing recommendations for the management of high blood pressure (BP), including the most recent adult guidelines published earlier in 2014.[1] These are described in Table 1. The preeminence of BP as the single most important risk factor for premature death and disability in the world[2] warrants careful consideration of recommendations for target levels. Because drug therapies are not without risk, the most convincing strategy involved in the recommendation of a BP target is the demonstration of the point at which treatment benefits outweigh the risks with respect to important health outcomes. Because there are 2 numbers involved in BP measurement, and since for many years, the primary focus of BP recommendations was directed to the diastolic target value, there is less information available about systolic targets, particularly in CKD. Moreover, in patients with CKD, the presence of dipstick-detectable (+1 or greater, roughly analogous to a urine protein:creatinine ratio [UPCr] of .22) urine protein excretion adds an extra level of consideration. Finally, though some evidence informing the best treatment BP target in CKD is available, not all groups looking at the same data agree on exactly what the evidence shows. In this article, the evidence base for BP targets in CKD and drug treatment and the various recommendations for BP targets are compared in the hope of providing more light than heat in this still somewhat contentious area of clinical medicine.

Among the various guidelines appearing recently, the author is more familiar with the processes governing the development of recommendations 4 and 8 in the 2014 Evidence-Based Guideline for the Management of Hypertension in Adults (hereafter "*JAMA* 2014") published in *Journal of the American Medical Association* (*JAMA*) by the group originally empanelled as Joint National Committee (JNC) 8.[1] Recommendation 4 advised a treatment goal of less than 140/90 mm Hg and did not recommend an alternate goal in the presence of proteinuria. Recommendation 8 advised the use of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB; but not both at the same time) in the management of hypertension in CKD, either as initial or as add-on therapy, regardless of race or diabetes status. What was the thinking behind these recommendations?

The JAMA *2014 Definition of "CKD"*

The *JAMA* 2014 Panel defined CKD in a person with hypertension based on the entry criteria of the studies used in the evidence base. The main component of the definition was a measured or estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 in people younger than 70 years. If a urine albumin-to-creatinine ratio was greater than 30 mg to 1 g, then the definition was not restricted to an age or GFR limit.

Framing the Question of Treatment in Hypertensives With CKD

For the development of the BP target in CKD in the *JAMA* 2014 guideline, the Panel considered the basic criteria used to answer Critical Question 2 that asked: "Among adults, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?"

To address this question, and the other questions in *JAMA* 2014, the Panel considered studies using PICO criteria:

- Population: included adults aged 18 years and older.
- Intervention: antihypertensive pharmacologic therapy to a specified BP goal.
- Comparator: comparator group has a different BP goal than the intervention group or the comparator group has no stated BP goal.

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- Outcomes: overall mortality, cardiovascular (CV) disease-related mortality, CKD-related mortality, myocardial infarction, heart failure, hospitalization for heart failure, stroke, coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty, and coronary stent placement), peripheral revascularization (includes carotid, kidney, and lower extremity revascularization), ESRD (ie, kidney failure resulting in dialysis or transplant), doubling of creatinine, and halving of estimated GFR.

The JAMA *2014 Definition of Important Health Outcomes*

The *JAMA* 2014 guideline Panel considered 3 clinical trials as evidence for Recommendation 4 that stipulated the presence of CKD and that tested 2 different goals. These 3 studies and their relevant characteristics are outlined in Table 2. In reviewing and summarizing these 3 studies, it is important to recall what the *JAMA* 2014 defined as important health outcomes as noted earlier in the PICO criteria.[1]

Three studies were selected because they had Fair to Good[1] quality evidence and included the Modification of Diet in Renal Disease (MDRD) study,[3] African American Study of Kidney Disease and Hypertension (AASK),[4] and the Ramipril Efficacy in Nephropathy 2 (REIN-2).[5]

The Modification of Diet in Kidney Disease

The MDRD trial tested 2 mean arterial pressure (MAP) levels separated by 15 mm Hg (≤92 mm Hg in the low and ≤107 in the usual BP groups for those ≤60 years; ≤98 mm Hg vs ≤ 113 mm Hg for those 61 years and older,[6] see Table 2) and found no difference after 2.6 years in slope of GFR in low vs usual pressure groups.[3] Importantly, the original report did not disclose the incidence of doubling of serum creatinine or halving of the GFR. The MDRD Investigators stated that ESRD (the occurrence of which resulted in removal of the subject from the study) "did not differ significantly in the diet groups or the blood pressure groups." Also, the Investigators stated "no significant differences in the number or causes of death or stopping points between the diet and the blood-pressure groups in either study." An important item in MDRD was that the halving of GFR was considered a "stopping point," and it was stated that "stopping points" did not differ between BP groups. Neither halving of GFR, death, or ESRD were different in the low vs the usual BP groups. The only espoused benefit of the low BP group was a less steep slope of GFR loss that was not specified as an Important Health Outcome in the *JAMA* 2014 Panel criteria. This study did not demonstrate a benefit with respect to the *JAMA* 2014 criteria for the lower BP target. Because it did not report separately on a higher than 140 mm Hg target (the 61 years and older group), one is left to assume that the known benefit (or anticipated consequences) of treating patients with CKD to the 140/90 mm Hg, but not to a lower goal, is reasonable based on this study.

CLINICAL SUMMARY

- Hypertension is a critical, modifiable factor in chronic kidney disease progression.
- The 2014 *JAMA* Guidelines for Hypertension (USA) recommend a target blood pressure of <140/<90 mmHg.
- Uncertainty remains about the optimal systolic BP target particularly in patients with proteinuria.

The African American Study of Kidney Disease and Hypertension

The AASK trial tested similar MAP levels to MDRD and had the largest number of subjects enrolled among the 3 CKD studies: 1094 participants.[4] Using an MAP of 102 to 107 mm Hg (about 140/90 mm Hg, the usual BP group), they compared this with an MAP of 92 mm Hg or less (about 125/75 mm Hg, the lower BP group). In the AASK trial, the primary events were ESRD, death, halving of GFR, and a composite of these. The AASK Investigators indicated that the lower BP target group did not differ significantly from the usual BP group. With respect to CV end points, the Investigators stated "The study was not powered to detect differences in the rate of myocardial infarction, stroke, or death. However, we found no evidence of differences in the rates of these events between the randomized BP groups." With respect to the proteinuria issue, the original study publication did not show a difference in the higher (UPCr > .22) proteinuria groups in the lower vs the usual BP target groups. The Investigators stated that "… with the exception of the acute slope, the BP comparison for the aforementioned outcomes was not significantly different within either the lower (baseline urinary protein-to-creatinine ratio ≤ .22) or higher (baseline urinary protein-to-creatinine ratio > .22) proteinuria strata." In the Methods section of the primary results article, the AASK Investigators considered a GFR "event" to be a reduction of GFR by 50% or a decline of 25 mL/min/1.73m^2 from the average of the 2 baseline values, and they stated that "the numbers of events (rate/participant year) for the main clinical composite (declining GFR events, ESRD, or death) were 173 (rate, .081) and 167 (rate, .076) in the lower and usual BP groups. After adjustment for the prespecified covariates, there were no significant differences between the BP groups in the risk of clinical composite outcome (risk reduction for the lower BP goal, 2%; 95% confidence interval, −22% to 21%; $P = .85$)." This author's read of the AASK study is that it did not demonstrate, as originally published, significant benefit with the lower BP target compared with a 140/90 mm Hg target.[4] This article also appears to support a 140/90 mm Hg target as opposed to something lower. In the years after the original randomized trial, a follow-up publication appeared that continued surveillance of the surviving AASK cohort observing that the group with the UPCr >.22 originally randomized to the lower BP target had a lower composite end point occurrence.[7] Keeping in mind that the opposite is the case in the larger, less proteinuric cohort randomized to the lower BP target (ie, the lower BP target group with less proteinuria