Optimizing Blood Pressure Control in Patients With Nondiabetic Glomerular Disease

Kausik Umanath, Julia B. Lewis, and Jamie P. Dwyer

Hypertension is a common problem among patients with glomerular disease and CKD. Optimal blood pressure targets for these patients have been the source of much debate. Careful review of the available data supports a blood pressure target of less than 140/90 mmHg. Consideration for a lower goal of less than 130/80 mmHg should be given for patients with heavy proteinuria. Renin-angiotensin system inhibitors should be used as the cornerstone of therapy for all patients with glomerular disease and CKD.

Key Words: Hypertension, CKD, Glomerular disease

Introduction

Hypertension complicates the management of most patients with CKD. Many seminal clinical studies over the past 4 decades have demonstrated that lowering blood pressure (BP) in individuals with hypertension reduces the risk of stroke and other cardiovascular (CV) events.[1-9] Analysis of data across these studies resulted in a guideline goal BP of less than 140/90 mmHg.[10] Unfortunately, patients with CKD were systematically excluded from many of these early BP trials. Thus, these early trials provided little information on the benefits of BP control on CV adverse outcomes in CKD patients or on preventing adverse kidney outcomes. However, CV disease is common in patients with CKD, and multiple observational studies have demonstrated a strong association among proteinuria, decreased glomerular filtration rate (GFR), and adverse CV events.[11] In addition, observational studies have demonstrated a strong association between higher achieved BP and faster declines in kidney function. Thus, several guidelines have recommended a BP target of less than 130/80 mmHg for patients with CKD on the basis of subgroup or post hoc analysis of trials examining different BP goals in CKD patients.[10,12-15]

There has recently been some controversy surrounding these targets.[16] For example, several small studies have suggested a J-shaped relationship between achieved BP and outcomes in the elderly, in individuals with vascular disease, and in CKD patients.[17-21] This debate has led to more recent guidelines for CKD patients that have recommended a BP target of less than 140/90 mmHg.[22] In this review, we will discuss the key clinical trials and evidence informing the clinician regarding optimal BP control in the patient with nondiabetic glomerular disease.

What Should the BP Goals Be in Nondiabetic CKD Patients?

Observational studies,[23-25] multiple small studies with surrogate outcomes,[26-29] and 3 randomized controlled trials (ie, the Modification of Diet in Renal Disease [MDRD] study, the African American Study of Kidney Disease and Hypertension [AASK], and the Ramipril Efficacy in Nephropathy 2 [REIN-2] study) form a body of evidence to determine appropriate BP goals in CKD patients. These 3 randomized trials merit careful review.

MDRD

The MDRD study randomly assigned 840 individuals with nondiabetic CKD to a mean arterial pressure (MAP) of 92 mmHg or less (roughly equivalent to 125/75 mmHg) vs 107 mmHg (roughly equivalent to 140/90 mmHg) and followed the rate of decline of GFR over 2.2 years. Over this time period, serial I^{125}-iothalamate GFR measurements were taken and analyzed to test the hypothesis that the lower MAP goal would reduce the rate of decline of GFR. When analyzed by the intention-to-treat design on the study population as a whole, there was no significant benefit seen in the lower MAP group in slowing the rate of decline of GFR. The study was not designed nor did it have a sufficient number of subjects to examine the effect of different BP goals on CV outcomes. In addition, analysis of other kidney outcomes, including doubling of serum creatinine (SCr), ESRD, and death, showed no difference between the 2 BP groups.[30] However, a subgroup analysis stratified by entry proteinuria demonstrated a slower rate of decline in kidney function for those subjects with greater than 3 g/24 hours (there were only 54 subjects in the subgroup with 3g/24 hours of proteinuria) who were randomized to the lower BP goal. In addition, when combined with

From Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI; Division of Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, TN; and Division of Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, TN.

K.U., J.B.L., and J.P.D. are supported in part by the National Institutes of Health Heart, Lung, and Blood Institute Systolic Blood Pressure INTervention Trial (SPRINT) HHSN268200900046 C.

Address correspondence to Jamie P. Dwyer, MD, MCN S-3223, Division of Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, TN 37232. E-mail: Jamie.dwyer@vanderbilt.edu

1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2014.01.006

the 103 subjects who entered the study with between 1 and 3 g of proteinuria in 24 hours, a benefit was seen for the lower MAP goal in this collection of 157 subjects. The 1- to 3-g/24-hour group did not show statistical significance on its own. Of note, there was more frequent use of renin-angiotensin system (RAS) inhibitors in the lower MAP group, which raises the potential of confounding because these agents are known modifiers of kidney disease progression.[31] Despite these caveats, these results were used to support a BP goal of less than 130/80 mmHg in CKD patients with more than 1 g of proteinuria per day. In a post hoc observational study, MDRD subjects were followed for outcomes of ESRD (dialysis requirement or transplantation) or mortality 7 years after the primary study concluded. Of note, subjects over this 7-year period no longer had BP controlled to goals as in the original study. Subjects randomized to the lower BP group had a lower rate of ESRD and death despite no further BP intervention.[32] The observational study did not stratify analyses by entry proteinuria. This follow-up data generate the hypothesis that a lower BP goal in CKD patients may reduce the rate of progression of kidney disease.

CLINICAL SUMMARY

- Hypertension complicates the management of many patients with CKD.
- Recent controversy has sparked debate about appropriate blood pressure targets.
- Proteinuric patients might need tighter BP control.
- Agents which block the renin-angiotensin system are the cornerstone of therapy.

AASK

In the AASK study, 1094 African-American subjects with hypertensive nephrosclerosis and a GFR between 20 and 65 mL/minute per 1.73 m^2 were randomized to a MAP of 92 mmHg or less vs 102 to 107 mmHg (usual care) and followed for 3 to 6.4 years. There was no significant benefit of the lower MAP goal in slowing the rate of decline in GFR. There was also no benefit to the lower MAP group for the other clinical endpoints of doubling of SCr, ESRD, and mortality. It is interesting to note that, unlike the MDRD study, when subgroup analysis was done stratifying by the degree of proteinuria upon entry to the study, no benefit was seen in any subgroup.[33] AASK study participants entered a cohort phase at the conclusion of the main study and were followed for an additional 5 years. Subjects were treated based on the results of the main study to a goal MAP of 107 mmHg until national guidelines dictated a goal BP of less than 130/80 mmHg. Analysis of the cohort phase of the study showed a benefit for those originally randomized to intensive BP control in those subjects with an entry protein-to-creatinine ratio of more than 0.22.[34] The long-term follow-up data in the AASK study generate a hypothesis that a lower BP goal may have late manifesting benefit in CKD patients in preventing kidney disease progression. However, the absence of any benefit in the trial by the intention-to-treat design while subjects actually had separate BP goals brings this conclusion into some question.

REIN-2

The REIN-2 study sought to evaluate if intensive BP control (<130/80 mmHg) as compared to conventional therapy (diastolic BP < 90 mmHg) in subjects with nondiabetic proteinuric nephropathies would reduce the rate of ESRD. This study was unique in that the investigators mandated fixed-dose background therapy with ramipril in both arms of the study. Three-hundred and thirty-eight patients were randomized 1:1 into the study and were followed for a median time of 19 months. There was no additional benefit of the more intensive BP target in terms of progression to ESRD.[35] Thus, the results of REIN-2 do not support a lower BP goal for patients with CKD.

Optimal BP Targets

Outside of the 3 major studies discussed, observational studies, and multiple small studies with surrogate outcomes, there are few other studies to guide BP targets in CKD patients. First, many of the seminal hypertension studies systematically excluded CKD patients. Thus, we are left with MDRD, AASK, and REIN-2 as the major randomized controlled trials specifically designed for CKD patients assessing the potential benefits of the lower BP goals. There are a couple of critical points when judging the weight of the evidence in selecting a BP target for CKD patients. The AASK and MDRD studies targeted MAP. This means that one could have a range of systolic blood pressures (SBPs) that would still generate a MAP that is at goal for the study. Thus, targeting a MAP of 92 mmHg with resultant SBPs in a range of 98 to 154 is a distinctly different intervention when compared with targeting all patients to a specific SBP goal (Fig 1).

Several observational studies[23-25] and multiple small studies[26-29] showed the benefit of lower BP targets with respect to kidney and CV outcomes. However, given their observational design, small size, and surrogate endpoints, they did not have the ability to conclusively provide evidence for a lower BP goal. The 3 major prospective randomized controlled trials discussed above unfortunately did not show a benefit for kidney outcomes upon primary analysis (Table 1). The current debate surrounding the lower BP goals for proteinuric CKD patients stems from the secondary analysis of the