Hypertension Management in Transition: From CKD to ESRD

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Hypertension is present in ~90% of patients in late-stage CKD. There are scarce data focusing on the transition period between CKD Stages 4 and 5 (end-stage kidney disease) as it relates to hypertension evaluation and management. Here, we propose that a combination of the principles used in the management of patients with CKD Stages 4 and 5 be applied to patients in this transition. These include the use of out-of-office blood pressure (BP) monitoring (eg, home BP), avoidance of excessively tight BP goals, emphasis of sodium restriction, preferential use of blockers of the renin-angiotensin system and diuretics, and consideration of the use of beta blockers.

Key Words: Hypertension, CKD

The prevalence of hypertension (HTN) in CKD Stages 4 and 5 is ~90%, and most studies of the general CKD population show that only a small fraction of these patients have their pressure well controlled.[1] Although the average man or woman with CKD spends a relatively short amount of time with Stage 5 disease (eg, 7.4 months in a clinical trial environment[2]) before progressing to dialysis or transplantation, it is a time where rates of cardiovascular (CV) mortality and morbidity increase and begin to mirror those of the dialysis population.[3] It is also a time of significant change for patients, as their dialysis providers are often different from their usual clinic providers, and medication adjustments are frequent as contact with health care providers increases. This "unstable" population has characteristically been excluded from most clinical trials,[4,5] thus, much of our treatment strategy stems from conventional wisdom, clinical experience, and extrapolation from populations that have been studied more extensively (eg, early CKD, ESRD, or subjects without any renal disease). Despite this significant limitation, this review will describe an outline for the assessment and treatment of HTN in patients who are transitioning from advanced CKD to ESRD.

HYPERTENSION BURDEN AND BLOOD PRESSURE ASSESSMENT

Before aggressive attempts at treatment, accurate assessment of blood pressure (BP) is critical to appropriate management of patients in transition. Isolated daytime BP measurements at infrequent intervals during clinic visits are often used to initiate and guide therapy. Discordance between out-of-office and in-clinic readings is highly prevalent in the CKD and dialysis population, and studies using ambulatory blood pressure monitoring (ABPM) have highlighted this difference. In a large study of African Americans with hypertensive kidney disease,[6] masked HTN (elevated readings at home but not at clinic) was present in 43% of patients, whereas white coat HTN occurred in 2.2%. In another cohort of white patients with CKD due to various causes in which CKD stages were reported, the rates of masked HTN and white coat HTN in Stages 4 and 5 patients were 14% and 13%, respectively.[7]

Out-of-office measurements were also useful and accurate in prognostication of adverse events. Gabbai and colleagues[8] found that HTN on ABPM predicted both adverse renal and CV outcomes, independent of clinic BP in the African American Study of Kidney Disease. In a multicenter Italian study of CKD patients, subjects with HTN on ABPM and normal clinic BP (ie, "masked" uncontrolled HTN) had an increased risk of CV and renal events and all-cause mortality (hazard ratio (HR) 3.17, 3.93, 3.45, respectively), whereas the risk of these events in those with in-clinic HTN only (ie, normal ABPM) was not statistically significant.[7] A meta-analysis of trials using ABPM in CKD patients showed that 30% of patients who were thought to be uncontrolled on treatment in clinic were actually normotensive at home, and 40% of those felt to be controlled were hypertensive at home.[9] Of note, only 1 of the trials reviewed actually enrolled patients with an average glomerular filtration rate (GFR) in the CKD 4 range (mean GFR 17.6).[10] Similarly, in the dialysis population, it seems that both ABPM and self-measurements at home are more accurate in diagnosing HTN and more predictive of adverse CV outcomes, when compared to in-center measurements during dialysis sessions.[11] In addition, there are data showing that home BP is superior to clinic BP to achieve BP control in hemodialysis patients.[12] Therefore, in advanced CKD, relying on office measurements alone seems to mischaracterize the BP control of a significant proportion of patients with CKD. Although there are practical difficulties in routinely using out-of-clinic BP measurements to guide antihypertensive therapy in all patients nearing dialysis, the limitations and pitfalls of relying solely on in-clinic measurements should be understood and taken into account.

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Despite the lack of data showing the superiority of home BP or ABPM to guide the treatment of HTN, we believe there may be value based on prognostic studies and data on the increased patient engagement with use of home BP.[13] This is in agreement with the recent recommendations of the US Preventive Services Task Force released in October 2015 (http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/high-blood-pressure-in-adults-screening?ds=1&s=hypertension). We use home BP routinely and follow the European protocol for data acquisition and collection[14]; that is, 7 days of twice daily readings, preferably in duplicate at each time. We use the outcome-based reference value of 130/85 mm Hg[15] as equivalent to a clinic BP target of 140/90 mm Hg. In patients in whom home BP is not possible or unreliable, we perform 24-hour ABPM (Table 1).

TARGET BP

The Irbesartan in Diabetic Nephropathy Trial and long-term follow-up analyses of the Modification of Diet in Renal Disease and African American Study of Kidney Disease (AASK) trials all suggest that targeting goal BPs of less than 125 to 130/75 to 80 mm Hg is beneficial in patients with proteinuric CKD, both diabetic and nondiabetic.[16-18] It is relatively well established that achieving these targets leads to a slower decline in GFR, although without a significant effect on mortality or CV outcomes. However, none of the 3 clinical trials that proposed lower targets for BP control was able to demonstrate a difference when compared to the conventional target of 140/90 mm Hg.[19] Recent major guidelines have differed in their recommendations. The Kidney Disease Improving Global Outcomes recommends a goal of 130/80 mm Hg in the presence of albuminuria, whereas the evidence-based guidelines (also known as, "JNC 8"), and the European guidelines propose 140/90 mm Hg.[20,21] Multiple epidemiological studies of subjects with ESRD have shown a J-shaped association between BP and survival, noting that patients with lower BPs (below ~120/80 mm Hg) have higher mortality than those with higher levels.[22] Some studies find systolic blood pressures (SBPs) as high as 180 mm Hg to be protective in comparison. Similar data are available for patients with earlier stages of CKD.[23] However, an interesting recent long-term follow-up (19.3 years) report of the Modification of Diet in Renal Disease study indicates that randomization to a lower BP target (125/75 mm Hg during the trial) resulted in a 28% lower risk of death after ESRD was reached (HR 0.72, $P = .003$) and significant reductions in the development of heart failure and coronary disease at the time of reaching ESRD,[24] thus suggesting value of BP control during CKD that is only realized after very long follow-up. The exciting results of the recently published Systolic Blood Pressure Intervention Trial (SPRINT) showing significant reductions in mortality and CV events among patients randomized to a SBP target of 120 mm Hg (compared with 140 mm Hg) have, unfortunately, limited applicability to the CKD 5 population.

CLINICAL SUMMARY

1. Out-of-office BP is helpful to better assess the overall hypertension burden and improve treatment decisions.
2. Salt restriction and diuretics are essential to adequate BP control.
3. RAS blockers and beta-blockers, if well tolerated, are the preferred antihypertensive drugs.

However, these associative studies do not prove causation; no prospective studies have been performed that evaluate varying target BPs in dialysis or predialysis patients, and few have assessed the effect of antihypertensive medications. Patients progressing to dialysis are often volume-overloaded, and HTN is nearly universal; most of the subset of patients with lower or "controlled" BPs may represent those with comorbidities that carry a high risk of mortality, such as congestive heart failure or cirrhosis. Furthermore, a higher rate of mortality due to background diagnoses (eg, diabetes or smoking) precludes obtaining a beneficial signal from HTN control over relatively short periods of time.[25] A long-term study of a prevalent cohort of dialysis patients in Uruguay showed that late mortality (>5 years) was associated only with higher, not lower BPs.[26] Likewise, the association of mortality with SBPs < 120 mm Hg disappeared in those who survived greater than 2 years in a group of US-based patients.[27] Regardless of BP control or time on dialysis, the use of antihypertensives in ESRD is associated with improved survival, and meta-analyses of randomized controlled trials of various different BP-lowering drugs showed an overall reduction in mortality and CV events from their use.[28,29]

So, from a clinician's perspective, how should we proceed during this CKD or ESRD transition? Although many of these studies were in incident dialysis cohorts, none apply directly to advanced CKD. Given that many dialysis patients live longer or are bridged to transplant, it is likely that patients will still reap CV benefit from adequate BP control. Therefore, our opinion is that a target of 140/90 mm Hg is justified in this transition phase.

DIETARY SALT RESTRICTION AND DIURETIC USE

Salt reduction is essential in the management of HTN in CKD, and the more advanced the CKD, the more salt-sensitive BP becomes. In anephric patients, classic studies by Merril and colleagues[30] demonstrated that excess sodium accumulation was the primary cause of HTN in the "renoprival state" and that HTN in subjects with kidney disease was readily responsive to adequate sodium and water removal during dialysis.[31] A modest but significant reduction of 5/3 mm Hg was shown in a recent meta-analysis of a number of clinical trials for dietary sodium restriction on BP control in the general population.[32] This effect has been described across many populations with different characteristics, including age, gender, and race, and the response is observed in normotensive patients as well. Given this relatively mild effect