# Management of Hypertension in CKD: Beyond the Guidelines

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**Hypertension (HTN) and CKD are closely associated with an intermingled cause and effect relationship. Blood pressure (BP) typically rises with declines in kidney function, and sustained elevations in BP hasten progression of kidney disease. This review addresses current management issues in HTN in patients with CKD including altered circadian rhythm of BP, timing of antihypertensive medication dosing, BP targets, diagnostic challenges in evaluating secondary forms of HTN, and the role of salt restriction in CKD. HTN in patients with CKD is often accompanied by a decrease in the kidney's ability to remove salt. Addressing this salt sensitivity is critical for the management of HTN in CKD. In addition to the well-established use of an ACEI or angiotensin receptor blocker, dietary salt restriction and appropriate diuretic therapy make up the mainstay of HTN treatment in patients with CKD. Bedtime dosing of antihypertensive medications can restore nocturnal dips in BP, and future clinical practice guidelines may recommend bedtime dosing of 1 or more antihypertensive medications in patients with CKD.**

**Key Words:** Resistant, Hypertension, Blood pressure, CKD, Salt

## Introduction

CKD and hypertension (HTN) are closely associated with an overlapping and intermingled cause and effect relationship. Declines in kidney function are typically associated with rises in blood pressure (BP), and sustained elevations in BP hasten the progression of kidney function decline.[1] This detrimental positive feedback interaction between kidney function and BP was observed in early experiments with animal models of kidney injury and later in clinical trials. In the Chronic Renal Insufficiency Cohort (CRIC), which consists of 3612 adults with CKD (majority moderate stage), the prevalence of self-reported HTN was 86% compared with 29% in the general population.[2,3] Furthermore, the prevalence rate of HTN rises, and BP becomes more difficult to control with advancing CKD stage.[4] Worsening of kidney function as a consequence of an elevated BP is evident by a direct relationship between relative risk of developing end-stage kidney disease (ESKD) and BP severity.[5,6] In a large health screening registry, individuals with a baseline BP close to 180/100 mm Hg were approximately 15 times more likely to develop ESKD than individuals with a baseline BP close to 110/70 mm Hg.[5]

The interdependence between CKD and HTN complicates management of both diseases. This article addresses current issues in HTN in patients with CKD including altered circadian rhythm of BP and timing of antihypertensive medication dosing, BP targets, diagnostic challenges in evaluating secondary forms of HTN, and specialized management strategies of HTN in patients with CKD.

### *Defining BP Control by Ambulatory Monitoring in HTN*

For groups where an office BP less than 140/90 mm Hg defines control, the overall 24-hour mean BP should be less than 130/80 mm Hg with a corresponding mean daytime BP less than 135/85 mm Hg and mean night-time BP less than 120/70 mm Hg.[7] Blood pressure control using self-measured BPs at home is identical to mean daytime BP with ambulatory monitoring (<135/85 mm Hg).[8] Individuals with an office BP less than 140/90 mm Hg yet who are not controlled by home BP monitoring or 24-hour ambulatory monitoring are classified as masked HTN or masked uncontrolled HTN if he/she is receiving antihypertensive medications.[7] Table 1 summarizes definitions of common terms associated with HTN.

Masked uncontrolled HTN is more prevalent among individuals with CKD with rates ranging from 40% to 70%.[9,10] The likelihood of having masked uncontrolled HTN rises in proportion to kidney dysfunction and the extent of proteinuria.[11] Without an assessment of ambulatory or home BP, masked uncontrolled HTN will be missed, and this group of individuals is at a high risk for both cardiovascular events and initiation of dialysis. In a multicenter prospective study of 489 consecutive hypertensive patients with CKD, the group with masked uncontrolled HTN had a 3-fold higher risk for fatal and nonfatal cardiovascular events and a nearly 4-fold higher risk for dialysis initiation after a median of 5.2 years of follow-up, compared with the group controlled both at home and in the clinic. No increase in risk was seen in the group who was uncontrolled in the office yet controlled at home.[12]

### *Circadian Rhythm of BP in Patients With CKD*

In healthy individuals, BP falls by 10% to 20% during sleep. A fall in nocturnal BP characterizes a normal circadian pattern of BP. Individuals whose BP fails to drop or, instead, rises at night are at an increased risk of death

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compared with dippers.[13,14] In addition, mean nocturnal systolic BP predicts ESKD or death,[15] and nondipping is associated with the severity of interstitial fibrosis and tubular atrophy by kidney biopsy.[16] Therefore, the findings from Mojon and colleagues[17,18] that dipping patterns are blunted in individuals with CKD (Fig 1) is concerning and particularly relevant for management of HTN in patients with CKD.

A cross-sectional analysis and small prospective study have shown an increased prevalence of nondipping among patients with CKD and HTN.[9,19] Prevalence rates for nondipping were as high as 80% in a subgroup of the study participants of the African American Study of Kidney Disease and Hypertension (AASK) trial with baseline ambulatory BP monitoring.[9] In 232 Veterans with CKD in stages ranging from 2 to 5, nondipping was detected more frequently in later stages of CKD (60% in Stage 2, 80% in Stage 3, and 72% in Stage 4).[19]

However, Mojon and others were the first to examine circadian BP patterns in patients with HTN and CKD on a large scale. The Hygia project, which is an ongoing prospective study aimed to assess ambulatory BP monitoring and HTN treatment time on cardiovascular risk, enrolls patients with HTN from primary care centers in northwest Spain. At the time of cross-sectional analysis by Mojon and colleagues, 10,271 hypertensive patients had been enrolled, of which 3227 had CKD defined by an estimated GFR less than 60 mL/min/1.73 $m^2$ and/or urine albumin-to-creatinine ratio of 30 mg/g or more. In patients with CKD compared with those without CKD, ambulatory systolic BP was higher, particularly at night (mean asleep systolic BP 125.0 ± 17.9 vs 117.5 ± 13.1 mm Hg, $P < .001$), whereas overall diastolic BP was lower (mean 48-hour diastolic BP 74.8 ± 11.6 vs 76.9 ± 9.5 mm Hg, $P < .001$). The prevalence of nondipping was higher in patients with CKD (60.6% vs 43.2%, $P < .001$); however, the largest difference was seen in the riser pattern where mean asleep systolic BP greater than mean awake systolic BP occurred in 17.6% of patients with CKD vs 7.1% of patients without CKD.[17] A comparison of the BP pattern between patients with and without CKD is displayed alongside a typical diurnal variation of plasma cortisol levels in Figure 1.

Although the mechanisms underlying sleep-related increases in BP and elevated pulse pressure in patients with CKD and HTN are not known, impaired long-term balance of salt and water by the kidney is an attractive hypothesis. High salt intake diminishes night-time dipping of BP in salt-sensitive HTN.[20] In a small clinical trial in patients with HTN and type 2 diabetes mellitus, the night-to-day ratio of mean BP by ambulatory monitoring correlated with 24-hour urine sodium excretion.[21] An excess of total body salt likely also contributes to arterial stiffness, which is approximated by pulse pressure and known to be associated with worsened kidney function.[22] Although it is difficult to disassociate BP-lowering effects on improvements in arterial stiffness with dietary restrictions of salt.[23] The cause and effect relationship between total body salt and obstructive sleep apnea also remains undefined. However, the 2 are likely related given the high prevalence for both salt excess and obstructive sleep apnea in resistant HTN and CKD.[24,25] Importantly, obstructive sleep apnea may contribute to nocturnal HTN and nondipping in individuals with CKD.

**CLINICAL SUMMARY**

- Ambulatory BP monitoring is needed to detect masked HTN and non-dipping, which are common in CKD.
- ACEIs or ARBs, appropriate diuretic therapy, and dietary salt restriction make up the foundation for the treatment of HTN in CKD.
- Bedtime dosing of at least one antihypertensive medication improves BP control in patients with CKD.

## *The Central Role of Salt in CKD and HTN*

Experimental animal models have shown that HTN brought on by inducing kidney damage is associated with a decreased ability of the kidney to remove salt. For example, dogs with about 70% loss of kidney tissue develop HTN within a few days when dietary salt is increased, yet HTN disappears when the increased salt intake is stopped.[26] When considering these experiments in combination with computer models of BP that identify salt and water balance in the kidney as the central long-term regulator of BP, one can reasonably attribute a large portion of HTN in CKD to an impaired salt excretion that is exacerbated by excess salt intake.[27] Many conditions associated with CKD can impair salt excretion, including reduced renal mass, sympathetic nervous system activation, renin-angiotensin-aldosterone imbalance, altered sodium chloride handling in the distal nephron, endothelial dysfunction, or some combination of the earlier mentioned conditions.

High dietary salt intake not only exacerbates HTN in patients with CKD but also has the potential to directly worsen kidney function. Rats receiving a high salt diet show sustained increases in kidney levels of transforming growth factor-β, polypeptides associated with kidney fibrosis.[28] High salt diet blunts kidney autoregulation, which exposes the glomerulus to higher filtration pressures.[29] Over time, the high glomerular filtration pressure leads to glomerular sclerosis and nephron loss. There are few clinical trials investigating salt intake on kidney outcomes. However, a recent systematic review found worsened kidney function, defined as a decline in creatinine clearance, doubling of serum creatinine, or progression to ESKD, associated with high sodium intake in all 4 cohort studies that compared a low and high sodium intake.[30] The associated worsening of both HTN and CKD in the setting of high salt intake highlights the importance of salt restriction in the management of HTN in patients with CKD.

## *Blood Pressure Target in CKD*

Starting in 2011, there have been 8 clinical practice guidelines published that address the treatment of HTN.[31-37] Although opinions differ in areas lacking large