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# MANAGING HYPERTENSION IN CHRONIC KIDNEY DISEASE PATIENTS: GOING BEYOND THE GUIDELINES

***[1]Devi Sri Jalasuthram, [1]Sahithi Gude, [1]Gayathri Kundeti, [1]Manasa Bonakala, [2]Pavani, [3]Padmalatha Kantamaneni**

[1]Pharm D V Year, Department of Pharmacy Practise, Vijaya Institute of Pharmaceutical Sciences for Women Enikepadu, Vijayawada – 521108, Andhra Pradesh, India.

[2]Assistant Professor, Department of Pharmacy Practise, Vijaya Institute of Pharmaceutical Sciences for Women Enikepadu, Vijayawada – 521108, Andhra Pradesh, India.

[3]Professor, Department of Pharmacy Practise, Vijaya Institute of Pharmaceutical Sciences for Women Enikepadu, Vijayawada – 521108, Andhra Pradesh, India.

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***Corresponding Author**
**Devi Sri Jalasuthram**
Pharm D V Year,
Department of Pharmacy Practise, Vijaya Institute of Pharmaceutical Sciences for Women Enikepadu,
Vijayawada - 521108,
Andhra Pradesh, India.

## ABSTRACT

Hypertension (HTN) and chronic kidney disease (CKD) are strongly related, having an overlapping cause and effect relationship. Blood pressure (BP) normally rises as kidney function diminishes, and prolonged elevations exacerbate the onset of renal disease. This review discusses current management concerns in HTN in CKD patients, such as altered circadian rhythm, timing of antihypertensive medication administration, BP objectives, diagnostic challenges in identifying secondary types of HTN, and the importance of salt restriction in CKD. HTN in CKD patients is frequently accompanied by a decline in the kidney's ability to eliminate salt. Addressing the salt sensitivity is crucial for managing HTN in CKD. In addition to the well-established use of an ACEI or angiotensin receptor blocker, dietary salt restriction and adequate diuretic therapy are the cornerstones of HTN management in CKD patients. Bedtime administration of antihypertensive drugs can reverse nocturnal blood pressure drops, and future clinical practice guidelines may propose bedtime dosing of one or more antihypertensive medications in CKD patients.

**KEYWORDS:** Chronic kidney disease, Anti-hypertensive, Hypertension, Circadian Rhythm, Blood pressure, Management.

## INTRODUCTION

CKD and hypertension (HTN) have overlapping and mixed cause-and-effect relationships. Decreases in kidney function are commonly accompanied with increases in blood pressure (BP), and prolonged elevations in BP exacerbate the progression of renal function decrease.[1] This adverse positive feedback loop between kidney function and blood pressure was discovered in early investigations with animal models of renal injury and later in clinical trials. In the Chronic Renal Insufficiency Cohort (CRIC), which included 3612 persons with CKD (mostly in the moderate stage), the prevalence of self-reported HTN was 86%, compared to 29% in the general population.[2,3] Furthermore, the prevalence of HTN increases, and controlling blood pressure becomes more difficult as CKD progresses.[4] A direct association exists between the relative risk of developing end-stage kidney disease (ESKD) and BP severity, indicating that increased blood pressure worsens kidney function.[5,6] In a major health screening registry, those with a baseline blood pressure close to 180/100 mm Hg were around 15 times more likely to develop ESKD than people with a baseline blood pressure close to 110/70 mm Hg.[5]

The interaction of CKD and HTN complicates treatment for both disorders. This article discusses current concerns in HTN in patients with CKD, such as changed circadian rhythm and timing of antihypertensive medication administration, BP targets, diagnostic difficulty in evaluating secondary types of HTN, and specialised HTN therapy options in patients with CKD.

For groups where an office blood pressure of less than 140/90 mm Hg defines control, the total 24-hour mean blood pressure should be less than 130/80 mm Hg, with a mean daytime blood pressure of less than 135/85 mm Hg and a mean nighttime blood pressure of less than 120/70 mmHg.[7] Self-measured blood pressure at home matches the mean daily BP with ambulatory monitoring (<135/85 mm Hg).[8] Individuals who have an office blood pressure of less than 140/90 mm Hg but are not managed by home BP monitoring or 24-hour ambulatory monitoring are classed as masked HTN or masked uncontrolled HTN if they are taking antihypertensive medication.[7]

Masked uncontrolled HTN is more common among CKD patients, with rates ranging from 40% to 70%.[9,10] The chance of having disguised uncontrolled HTN increases with renal failure and the severity of proteinuria.[11] Without an examination of ambulatory or home blood pressure, masked uncontrolled HTN will be missed, putting this group of people at high risk for both cardiovascular events and dialysis commencement. 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, as well as a nearly 4-fold higher risk for dialysis initiation after a median of 5.2 years of follow-up, compared to the group controlled both at home and in the clinic. No increase in risk was observed in the group that was uncontrolled in the office but controlled at home.[12] During sleep, healthy people's blood pressure drops by 10% to 20%. A typical circadian pattern of blood pressure is characterised by a drop in nocturnal BP. Individuals whose blood pressure does not drop or rises at night are more likely to die than those who dip.[13,14] Furthermore, mean nocturnal systolic blood pressure predicts ESKD or mortality[15], and nondipping is linked with the severity of interstitial fibrosis and tubular atrophy as determined by kidney biopsy.[16] Therefore, the findings of Mojon and colleagues[17,18] that dipping patterns are muted in individuals with CKD are alarming and particularly significant for the management of HTN in patients with CKD.

A cross-sectional analysis and a small prospective investigation found that patients with CKD and HTN have a higher prevalence of nondipping.[9,19] In a subgroup of study participants in the African American Study of Kidney Disease and Hypertension (AASK) trial with baseline ambulatory blood pressure monitoring, nondipping prevalence rates reached 80%.[9] Nondipping was seen more commonly in later stages of CKD (60% in Stage 2, 80% in Stage 3, and 72% in Stage 4) in 232 Veterans with CKD (stages 2–5).[19]

However, Mojon and colleagues were the first to conduct a large-scale study of circadian blood pressure patterns in patients with HTN and CKD. The Hygia project, an ongoing prospective study aimed at assessing the impact of ambulatory blood pressure monitoring and HTN treatment time on cardiovascular risk, enrols patients with HTN from primary care centres in northwest Spain. Mojon and colleagues' cross-sectional investigation included 10,271 hypertension patients, 3227 of whom had CKD defined as an estimated GFR of less than 60 mL/min/1.73 m2 and/or a urine albumin-to-creatinine ratio of 30 mg/g or more. Patients with CKD had higher ambulatory systolic blood pressure, especially at night (mean

sleeping systolic BP 125.0 ± 17.9 vs 117.5 ± 13.1 mm Hg, P <.001), whereas overall diastolic blood pressure was lower (mean 48-hour diastolic BP 74.8 ± 11.6 vs 76.9 ± 9.5 mm Hg, P <.001).

Patients with CKD had a higher prevalence of nondipping (60.6% vs 43.2%, P <.001). The highest difference was noted in the riser pattern, where mean sleeping systolic BP was greater than mean awake systolic BP in 17.6% of patients with CKD vs 7.1% of patients without CKD.[17] Patients with CKD had higher ambulatory systolic blood pressure, notably at night (mean sleeping systolic BP 125.0 ± 17.9 vs 117.5 ± 13.1 mm Hg, P <.001), whereas overall diastolic blood pressure was lower (mean 48-hour diastolic BP 74.8 ± 11.6 vs 76.9 ± 9.5 mm Hg, P <.001). Patients with CKD were more likely to not dip (60.6% vs. 43.2%, P <.001). The most significant difference was seen in the riser pattern, where mean sleeping systolic BP was higher than mean awake systolic BP in 17.6% of patients with CKD compared to 7.1% of those without.[17] An excess of total body salt is also likely to contribute to arterial stiffness, which is measured by pulse pressure and has been linked to poor kidney function.[22] Although it is difficult to separate the effects of blood pressure reduction on arterial stiffness improvements from salt restriction.[22] The cause and effect link between total body salt and obstructive sleep apnoea is also unclear. However, considering the high frequency of salt overload and obstructive sleep apnoea in resistant HTN and CKD, the two are most likely linked.[24,25] Importantly, obstructive sleep apnoea may contribute to nocturnal hypertension and nondipping in those with CKD.

Experimental animal models have demonstrated that HTN caused by generating kidney injury is connected with a diminished ability of the kidney to eliminate salt. For example, dogs with approximately 70% loss of kidney tissue acquire HTN within a few days of increasing dietary salt consumption, but HTN resolves when the increased salt intake is discontinued.[26] When these experiments are combined with computer models of blood pressure that identify salt and water balance in the kidney as the primary long-term regulator of blood pressure, it is reasonable to attribute a large portion of HTN in CKD to impaired salt excretion, which is exacerbated by excess salt intake.[27] Many CKD-related conditions can impair salt excretion, including decreased renal mass, sympathetic nervous system activation, renin-angiotensin-aldosterone imbalance, altered sodium chloride handling in the distal nephron, endothelial dysfunction, or a combination of the aforementioned conditions.

High dietary salt intake not only exacerbates HTN in CKD patients, but it may also directly impair kidney function. High salt diets in rats lead to prolonged increases in transforming growth factor-β levels in the kidney, which are linked to renal fibrosis.[28] A high salt diet inhibits renal autoregulation, exposing the glomerulus to increased filtration pressures.[29] Over time, increased glomerular filtration pressure causes glomerular sclerosis and nephron loss. Few clinical trials have been conducted to investigate the effects of salt intake on renal function. However, a recent systematic analysis discovered that high salt intake was related with worsening kidney function, defined as a decrease in creatinine clearance, doubling of serum creatinine, or progression to ESKD, in all four cohort studies that compared low and high sodium intake.[30] The related deterioration of both HTN and CKD in the presence of high salt intake emphasises the need of salt restriction in the treatment of HTN in patients with CKD.

Since 2011, eight clinical practice guidelines for treating HTN have been developed.[31,32,33,34,35,36,37] Although opinions differ in areas lacking substantial randomised controlled studies, the majority of people agree on a target blood pressure of less than 140/90 mm Hg. The Eighth Joint National Committee panellists limited their analysis to long-term randomised controlled studies with concrete outcomes in adult HTN study populations.[35] This research found insufficient evidence to propose a lower blood pressure goal of less than 140/90 mm Hg in either CKD or diabetes mellitus. The Kidney Disease Improving Global Outcomes BP task group broadened its evidence base beyond long-term randomised controlled trials in HTN, including meta-analyses, systematic reviews, and selected randomised controlled trials with outcomes relevant to kidney disease progression.[34] A review of the evidence base supported a lower blood pressure goal of less than 130/80 mm Hg for those with CKD and moderate-to-severe albuminuria (e.g., urine albumin-to-creatinine ratio > 30 mg/g), with or without diabetes. However, this advice was based on evidence comparable to expert opinion. As summarised in the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative commentary of the Kidney Disease Improving Global Outcomes guidelines and succinctly stated in a systematic review, the available evidence is inconclusive but does not prove that a blood pressure target of less than 130/80 mm Hg improves clinical outcomes more than a target of less than 140/90 mm Hg in adults with CKD.[38.39]

The guidelines focus on establishing a therapy BP threshold, however overtreatment of HTN in CKD patients may be harmful. In a cohort of nearly 650,000 Veteran Americans with CKD, extremes of both high and low blood pressure were associated with higher morality, with patients with high pulse pressures having the highest mortality rates. The authors suggest that it may not be favourable to reach an optimum systolic BP (<130 mm Hg) in patients who already have low diastolic BP (<70 mm Hg).[40]

CKD alone can produce antihypertensive drug resistance; however, patients who remain uncontrolled despite optimal doses of three distinct medication classes, including a diuretic, should be evaluated for a secondary cause of HTN.[41] When applying the suggested screening procedures described in the American Heart Association's scientific statement on resistant HTN in 2008 to the CKD population, minor alterations are required.

Revascularisation (e.g., angioplasty or stenting) for atherosclerosis-related renal artery stenosis (RAS) was viewed negatively due to high rates of serious complications and a lack of overall efficacy in improving kidney function or lowering blood pressure as seen in the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) and Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR) trials.[42,43] However, it was argued that patients with severe atherosclerotic-related RAS could still benefit from revascularisation. The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) experiment investigated this hypothesis. Patients with CKD Stage 3 or higher, HTN requiring 2 or more antihypertensive drugs, and more than 60% RAS by angiography did not benefit from revascularisation in addition to pharmacological therapy with candesartan, hydrochlorothiazide, and the combo amlodipine-atorvastatin. Specifically, no difference was found in a composite end goal of cardiovascular and kidney events over a median of 43 months of follow-up, with kidney artery dissection being the most common complication in 11 of 495 individuals.[44]

Importantly, ASTRAL, STAR, and CORAL all evaluated revascularisation in atherosclerotic-related RAS but not RAS caused by fibromuscular dysplasia (FMD). Young women with severe HTN and a familial history of HTN at an early age, as well as an abdominal bruit on physical examination, will benefit from RAS identification and angioplasty (rather than stenting) of FMD-related renal artery narrowing. An RAS assessment by kidney duplex ultrasonography remains clinically useful for individuals with probable atherosclerotic disease. In addition to acquiring structural imaging of the kidneys, a diagnosis of RAS gives a

target for medical therapy and resolution of the cause of HTN. As a result, the key change in screening recommendations for RAS in resistant HTN following CORAL may be to discontinue angiography or contrast-containing imaging in older patients with a low risk of FMD-related RAS.

It should also be emphasised that no research has investigated the efficacy of kidney artery revascularisation in high-risk clinical presentations such as acute HTN coupled with flash pulmonary oedema. In these acute cases, renal artery stenting and/or angioplasty may be needed.

The existing evidence suggests a significant portion of salt sensitivity to HTN in CKD patients. As a result, teaching CKD patients on a reduced salt diet is crucial for achieving BP control while adhering to a basic BP medication regimen. In a double-blind placebo-controlled crossover experiment, 20 hypertensive persons with Stage 3 to 4 CKD were randomly assigned to a low sodium diet supplemented with nutritional education and 120 mmol of sodium or a low sodium diet plus matched placebo capsule. Participants followed each diet with capsules for two weeks, with a one-week washout period in between. The mean 24-hour urine sodium excretions were 168 mmol (95% confidence interval [CI], 146-219) and 75 mmol (95% CI, 58-112) for the high and low salt interventions, respectively. The low salt intervention reduced mean blood pressure by 9.7/3.9 mm Hg (95% CI, 4.5-14.8/1.3-6.4) by 24-hour ambulatory monitoring.[45]

When treating HTN in CKD, a small dietary sodium restriction can improve the effectiveness of antihypertensive drugs such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In a small randomised trial, 52 patients with nondiabetic nephropathy who were taking lisinopril 40 mg daily were randomly assigned to valsartan 320 mg daily or placebo, followed by a low sodium (target 50 mmol/d) or regular sodium (target 200 mmol/d) diet for four 6-week periods. The low and regular sodium interventions had mean urine sodium excretion of 106 and 184 mmol/d, respectively. This difference in dietary salt intake resulted in a greater BP reduction (7% vs 2%, P =.003) than the addition of the angiotensin receptor blocker to lisinopril 40 mg daily.[46]

Importantly, decreased dietary salt intake enhances the antiproteinuric action of diuretics and renin-angiotensin-aldosterone blocking agents. In 34 proteinuria patients with diabetes mellitus, adding a reduced salt diet to losartan monotherapy boosted mean baseline

proteinuria reductions from 30% to 55%. A low-salt diet combined with hydrochlorothiazide reduced proteinuria by 70% compared to the baseline.[47] A high salt diet, on the other hand, reduces the effectiveness of diuretics and renin-angiotensin-aldosterone blockers in terms of lowering blood pressure and proteinuria.

Concerns have been raised concerning the potential consequences of severely reducing dietary salt. In the Institute of Medicine's salt intake study, the committee discovered that studies relating health outcomes to dietary sodium intake had significantly varying methodologic quality, limiting their conclusions. Higher levels of sodium intake were related with an increased risk of cardiovascular disease in the general US population; nevertheless, the evidence was insufficient to advocate decreasing daily salt intake beyond 2.3 g/d. The committee did identify a subgroup at risk for adverse events from a low sodium diet (for example, individuals with heart failure with a reduced ejection fraction and receiving aggressive therapeutic regimens); however, this does not apply to the majority of people with HTN and CKD, who are at risk for salt-sensitive HTN.[48,49]

In general, when GFR decreases, greater diuretic dosages are required to produce a natriuretic response. Diuretic dosing can be especially difficult in the late stages of CKD, when the risk of over diuresis and the resulting accelerated progression to dialysis outweighs the benefit of improved blood pressure control. This is exacerbated in patients with hypoalbuminemia because less protein-bound loop diuretic is accessible for tubular secretion. Furthermore, the short-acting impact of many loop diuretics reduces their effectiveness in long-term blood pressure regulation. For these reasons, doctors have revisited the use of thiazide diuretics as an alternate or supplemental drug to loop diuretics in severe CKD (estimated GFR < 30 mL/min/1.73 m2), when they were previously thought to be useless.[50]

In 2012, Dussol and colleagues conducted a double-masked, randomised crossover trial of furosemide and hydrochlorothiazide in 23 patients with CKD stages 4 and 5. After 3 months of treatment, hydrochlorothiazide at 25 mg dose reduced mean supine blood pressure by the same amount as furosemide 60 mg (from 101 mm Hg to 94 and 93 mm Hg, respectively; P <.05). The combination of the two study drugs significantly reduced mean supine blood pressure to 86 mm Hg (P <.01).[51] This prospective experiment, as well as previous observational studies, give some evidence for the efficacy of thiazide diuretics, which are frequently used in combination with a loop diuretic in severe CKD.[50] Chlorthalidone, a

long-acting thiazide used in many big clinical studies of HTN, has double the potency of hydrochlorothiazide at comparable doses and may be effective in advanced CKD.[52]

In patients with excess volume, a thiazide plus a loop diuretic may be the most beneficial combination.

Multiple clinical trials have demonstrated that taking at least one antihypertensive drug before sleep improves nocturnal blood pressure dipping,[53,54,55] and night-time medication dosing has been linked to lower cardiovascular risk.[56,57] Hermida and colleagues conducted a prospective, open-label experiment in which 661 people with HTN and CKD were randomly assigned to receive antihypertensive medicines all morning or at least one at night. Ambulatory blood pressure monitoring for 48 hours was performed at baseline and at least once a year. After 5.4 years of follow-up, patients who took at least one medication at bedtime had an adjusted risk of cardiovascular death, myocardial infarction, and stroke that was roughly one-third that of patients who took all of their antihypertensive medications in the morning (adjusted hazard ratio, 0.28; 95% CI, 0.13-0.61).[56] In addition, bedtime dosing was linked to better ambulatory blood pressure control (56% versus 45%, P =.003). Based on the findings of similar trials in diabetes mellitus patients, the American Diabetes Association includes a level A recommendation to provide one or more antihypertensive drugs before bedtime in its 2013 guidelines for diabetes treatment.[31] Similar recommendations have yet to reach other guideline-producing groups, but given both the impaired circadian pattern of BP in CKD patients and the increased cardiovascular risk associated with CKD, future HTN management guidelines in CKD patients will most likely include recommendations for bedtime medication dosing.

Mineralocorticoid antagonists have become an essential fourth-line BP drug in the treatment of refractory HTN due to impressive blood pressure reductions for those on three or more antihypertensive medicines.[41,58,59] Patients in the later stages of CKD are more likely to have resistant HTN; nevertheless, the dangers of hyperkalaemia and acute renal injury have limited the use of mineralocorticoid antagonists in advanced CKD. In patients with refractory HTN and CKD Stage 3, mineralocorticoid antagonists increased serum potassium levels by an average of 0.4 mEq/L and serum creatinine concentrations by 1.5 to 1.8 mg/dL.[60] In protein uric CKD with HTN, spironolactone successfully lowers blood pressure and urine protein levels.[61] However, patients with a baseline serum potassium level of more than 4.6 mEq/L should proceed with caution when commencing spironolactone. Spironolactone is not

recommended for patients with acute renal damage or creatinine clearances of less than 10 mL/min. Eplerenone, a more specific mineralocorticoid antagonist, is not recommended for usage when creatinine clearance is less than 30 mL/min. Finer none, which binds to the mineralocorticoid receptor with a higher affinity than eplerenone, is currently in clinical studies for FDA approval in the treatment of heart failure and protein uric diabetic nephropathy.

## CONCLUSION

HTN may be the first indicator of kidney impairment in some types of CKD (for example, polycystic disease), and proper HTN management reduces both cardiovascular and renal outcomes. Impaired BP dropping during sleep, salt-sensitive HTN in animal models of renal disease, and exaggerated BP responses to dietary salt reductions all emphasise the relevance of salt in patients with CKD and HTN.

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