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Review Article

# Management of Hypertension in Patients with Chronic Kidney Disease and End-stage Renal Disease

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## Abstract

Elevated blood pressures (BP) are common in patients with impaired kidney function. Hypertension (HTN) not only can be a consequence of chronic kidney disease (CKD) but it is also the most important risk factor for progressive decline of renal function in CKD leading to end-stage renal disease (ESRD). Hence, identification and management of HTN is essential for reducing morbidity and mortality resulting from both, i.e., cardiovascular events and renal failure. A combination of healthy lifestyle measures, dietary sodium restriction, and appropriate fluid management along with individualized antihypertensive regimen can achieve BP targets. Patients on renal replacement therapy also require optimized dialysis prescriptions in addition to the above measures. Finally, home measurement of BP and adherence to treatment is central for having a successful outcome. In this review, we discuss the benefits of BP control, measurement techniques, controversies regarding target pressures, rationale of current guidelines, and specific issues in management in patients with CKD and ESRD.

**Key words:** Hyperfilteration, renin–angiotensin, endothelial dysfunction

## Introduction

There is plenty of evidence in scientific literature that clearly demonstrates that elevated blood pressure (BP) levels reduce life expectancy. Hypertension (HTN) is a major contributor to one or more target organ damage, including of the heart, brain, eyes, and kidneys. Historically, major focus of HTN management was to prevent morbidity and mortality resulting from cardiovascular and cerebrovascular diseases. In the recent past multiple factors, i.e., role of the kidney in pathophysiology of HTN, increased prevalence of HTN in kidney diseases, and rapid deterioration of renal function in patients with uncontrolled HTN has led to increased awareness of benefits of BP management.

About 10% of world population have some form of renal dysfunction and HTN is the most common comorbidity affecting 65–95% of patients with chronic kidney disease (CKD).[1] Prevalence and severity of HTN and hence the incidence of end-organ damage increases with declining renal function.[2] Elevated BP can occur as a consequence of CKD but is also a risk factor for CKD progression. Interaction between HTN and CKD is complex and pathophysiologically it is difficult to determine which process precedes the other. Age, race, obesity, diabetes mellitus, and cardiovascular disease are common risk factors for both HTN and CKD.[3] Coexistence of both is known to greatly increase the risk of cardiovascular and cerebrovascular events. Therefore, control of HTN is the first priority in the management of CKD both to slow CKD progression and prevent other target organ(s) damage.

HTN accelerates kidney injury as impaired renal autoregulation allows transmission of high systemic pressures to the glomeruli, leading to hyperfiltration and accelerated glomerulosclerosis.[4] On the other hand, renal injury can cause HTN, by multiple mechanisms including decreased sodium excretion, poor volume control, enhanced activity of the sympathetic nervous system (SNS) and renin–angiotensin aldosterone system (RAAS), and endothelial dysfunction, etc.[5] HTN in this population is usually resistant or refractory requiring multiple antihypertensive agents of different mechanism of

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actions. Detailed discussion of pathogenesis can be found elsewhere.

This article reviews various issues, i.e., importance of home and ambulatory BP monitoring (ABPM), controversies and various recommendations regarding BP target levels, and implications of a most recent trial in relation to patients with CKD. Finally, we conclude by discussing current practice and suggestions in the management of high BP in patients with CKD and in patients with end-stage renal disease (ESRD) undergoing dialysis.

## BP Measurement

### In-Office Versus Home BP Monitoring

In-office measurements should be accurate if done in a standardized manner by a trained clinical staff even though it is more time-consuming than single conventional BP measurement done routinely. Out-of-office measurements may not be always available; consequently, most treatment decisions must still be based primarily on in-office readings. Recent reports indicate that home BP monitoring is superior to in-office BP readings in predicting adverse clinical outcomes in CKD patients, more so in patients undergoing dialysis.[6,7] Patients who use home BP monitoring are more likely to have target BP levels as well as having a near-dry weight as compared to those who are treated based only on in-office measurements.[8] This may be due to improved self-motivation and better adherence to salt water and antihypertensive regimens.[9]

### Manual versus Automated BP Measurements

Evidence now supports that home and ABPM can better predict the risk of cardiovascular events both in general population and in patients with CKD as compared to in-office measurements.[10,11] However, there remains a question of consistency and accuracy of these measurements. Adequate patient training and a standardized approach with the use of validated automated oscillometric device might be more reliable than manual auscultatory methods and may provide reproducible measurements when done repeatedly.[12,13]

### ABPM

24-h ABPM provides additional information about nocturnal measurements and BP variability.[14] Normal circadian BP rhythm and nocturnal BP is often abnormal in CKD and is usually characterized by either loss of the normal nocturnal fall (10–20%) in systolic BP (SBP) and diastolic BPs (DPBs) (non-dippers) or even a paradoxical rise in nocturnal BP (risers).[15,16] Exact underlying mechanism is not known, but high nocturnal BP is associated with reduced diuresis in day and enhanced pressure natriuresis at night.[17] The average level of nocturnal BP has been linked to both cardiovascular disease and CKD progression; however, evidence supporting that a reduction in BP variability leads to improved outcomes is currently lacking.[18,19] In addition, ABPM is diagnostic for white-coat HTN and masked HTN, the later appears to be remarkably prevalent in CKD.[20]

### Target BP in CKD

Optimal goals of BP therapy for individuals with CKD have been controversial. In addition to prevention of cardiovascular and cerebrovascular events as in general population, the rationale for treatment of HTN in CKD is to slow on-going renal injury and to delay progression to ESRD.[21,22] Another important factor is the presence of proteinuria. Patients with proteinuria have poorer outcomes.[23] These patients may require more aggressive BP management to prevent morbidity and mortality as compared to those without proteinuria.[24] The relationship between BP and cardiovascular events in patients with CKD is complex. Large observational studies have identified U- or J-curve phenomena with increase in mortality in patients with CKD at SBP <120 mmHg and/or DBP <60 mmHg.[25,26] Guidelines that have proposed recommendations for CKD population are based on data obtained mainly from two randomized controlled trials, e.g., the modification of diet in renal disease study and the African American Study of Kidney Disease and HTN.[27,28] Both trials were negative, failing to show benefit from lower BP targets of 125–130/75–80 mmHg compared to <140/90 mmHg either in reducing cardiovascular events or slowing progression of CKD to ESRD. *Post hoc* analyses of both studies, however, suggested a benefit of intensive BP treatment in the subgroup with significant proteinuria. None of these studies included patients with diabetes mellitus. Subsequent meta-analyses yielded conflicting results regarding the potential effect of BP reduction on the development of ESRD.[29,30] The Action to Control Cardiovascular Risk in Diabetes trial of patients with type 2 diabetes mellitus and normal renal function failed to show cardiovascular or mortality benefit of a lower BP target (i.e., SBP of <120 vs. <140 mmHg).[31] Intensive control group had greater number of serious adverse effects such as hypotension and acute kidney injury.

The 2012 KDIGO guideline target of <140/90 mmHg in patients with CKD without proteinuria was based on limited clinical trial evidence.[32] For patients with proteinuria, they set a target of <130/80 mmHg but acknowledged that this decision was based solely on expert opinion. While disagreement remains most consensus guidelines for CKD, set SBP targets mostly to <140 mmHg and DBP between 80 and 90 mmHg [Table 1].[32-40] The 2014 NICE CKD guideline recommends drug therapy for BPs of ≥140/90 mmHg in patients without proteinuria and ≥130/80 mmHg in patients with proteinuria to target of 120–139/<90 mmHg and 120–129/<80 mmHg in patients without and with proteinuria, respectively.[39]

Most recent data comes from analysis of CKD subset ($n$ = 2646 patients with estimated glomerular filtration rate [eGFR] of 20–59 ml/min per 1.73 $m^2$) of SBP Intervention Trial (SPRINT).[41,42] Till date, this is the largest randomized

**Table 1:** Guidelines for BP targets and treatment recommendations in patients with CKD

| Year | Guideline | Target BP in CKD without proteinuria* (SBP/DBP in mmHg) | Target BP in CKD with proteinuria (SBP/DBP in mmHg) | Recommended first-line medication |
|---|---|---|---|---|
| 2003 | JNC7 | <130/<80 | -/- | - |
| 2010 | ISHIB | <130/<80 | <130/<80 | Diuretic or CCB |
| 2012 | KDIGO | <140/<90 | <130/<80 | ACEI or ARB |
| 2013 | ESC/ESH | <140/- | <130/- | ACEI or ARB |
| 2013 | ADA | <140/<90 | -/- | - |
| 2014 | JNC8 | <140/<90 | <140/<90 | ACEI or ARB |
| 2014 | ASH/ISH | <140/<90 | <140/<90 | ARB or ACEI |
| 2014 | NICE | <140/<90 | <130/<80 | ACEI or ARB |
| 2015 | CHEP | <140/<90 | <140/<90 | ACEI; ARB if intolerant |

*Proteinuria is defined as either+1 (by dipstick); >500 mg protein per 24 h; or>200 mg albumin per 24 h. ACEI: Angiotensin-converting enzyme inhibitor, ADA: American Diabetes Association, ARB: Angiotensin receptor blocker, ASH/ISH: American Society of HTN/International Society of HTN, CHEP: Canadian HTN Education Program, CKD: Chronic kidney disease, ESC/ESH: European Society of Cardiology/European Society of HTN, ISHIB: International Society of HTN in Blacks, KDIGO: Kidney Disease Improving Global Outcomes, NICE: National Institute for Health and Care Excellence, JNC: Joint National Committee. HTN: Hypertension, DPB: Diastolic blood pressure

study assessing different BP targets (SBP target of 140 mmHg in the standard group and 120 mmHg in the intensive group) on the cardiovascular and renal outcomes in patients with CKD. Multiple BP readings were obtained by automated machine at 1-min intervals and averaged at each visit. Mean age of patients was 72 years. At the end of 1 year, SBP values of 136.9 ± 0.2 and 123.0 ± 0.2 mmHg were achieved in standard and intensive group, respectively. On an average of two in the standard group and three antihypertensive agents in the intensive group were required. The trial was stopped prematurely because of the significantly reduced (25% relative risk reduction) overall and cardiovascular mortality and composite end points in the intensive group. This observed mortality benefit was also seen in the whole CKD cohort and was even more pronounced in older patients with CKD. Intensive group had higher risk of a 30% fall in eGFR but not a 50% fall in eGFR. The fall in eGFR occurred early in the intensive group, but annual decrement in renal function was similar in both the groups. Few cases of progressive CKD and/or ESRD occurred in this cohort over the 3.3-year duration of the study. More intensive antihypertensive drug therapy was associated with increases in specific adverse events like hypo and/or hyperkalemia and acute kidney injury but not serious ones such as hypotension, syncope, and injurious falls. However, patients with diabetes, proteinuria more than 1 g/day, and autosomal dominant polycystic kidney disease were excluded from the study.

Taken together, data show probably a large number of uncomplicated CKD patients need to be treated intensively to achieve a moderate reduction in cardiovascular events and mortality that too at increased risk of adverse effects.[43,44] This goal might be challenging in clinical practice, especially with advanced CKD, diabetes, proteinuria, and with other comorbidities; who are more likely to have resistant HTN. Such individuals are likely to require more medications than the study participants even for liberal BP targets and hence will have higher risk of serious side effects. Ultimately, the net gain may be offset by adverse symptoms in many patients.

Till definitive clinical trial data are available, it is prudent to adhere to the current guidelines of target 130–140/<90 mmHg in patients with CKD without proteinuria and <130/80 mmHg in patients with proteinuria. There may be a tendency to maintain lower BP targets for those with more severe proteinuria provided patients are able to tolerate lower BP levels without developing symptoms. Conversely, targets may be loosened for those who are likely to develop symptoms of hypoperfusion, i.e., elderly or frail patients.

## Treatment of HTN in CKD

### Non-pharmacologic Therapy

As in general population, modifiable lifestyle factors including dietary salt restriction, weight loss, regular exercise, cessation of smoking, and alcohol ingestion are first steps in the management of HTN in CKD.[45] Sodium intake contributes to drug resistance, more so in patients with a reduced GFR. Accordingly, dietary sodium restriction of <100 mEq (2300 mg)/24 h is recommended in advanced CKD and ESRD and is particularly effective in patients with higher degree of proteinuria.[46,47]

### Pharmacologic Therapy

Individualization of treatment should be based on CKD stage, age, gender, existing comorbidities such as diabetes and cardiovascular risk status [Table 2].[48] Combination of long-acting drugs of different class that increases the renal sodium excretion and inhibit both RAAS and SNS activity provide synergistic effect with minimal side effects.[49,50] Most

antihypertensive agents can be used alone or in combination after consideration of their metabolism and dosing requirements according to the level of renal function. Avoidance of complex dosing regimens, use of combination pills, and consideration on cost improve compliance and adherence to therapy.[51] Bedtime administration of at least one of the drugs is associated with a better 24-h mean BP control and could induce the desired nocturnal dip in non-dippers.[52]

Most guidelines for patients with CKD recommend angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) as initial treatment or add-on to the current regimen.[53-55] RAAS blockade reduces intraglomerular pressure and thereby reduces hyperfiltration and proteinuria. A concurrent reduction in GFR results in an increase in serum creatinine of up to 30%, however, greater increases in serum creatinine should be investigated for other causes, i.e., volume contraction, nephrotoxic agents, or bilateral renal artery stenosis.[56,57] Combination of ACEI and ARB is discouraged following increased adverse effects of hyperkalemia and acute kidney injury in randomized trials as compared to use of ACEI or ARB therapy alone.[58-60] Similarly, combination of ACEI or ARB with an aldosterone antagonist is also generally discouraged.[55] Frequent monitoring of serum potassium and creatinine levels must be performed if at all these combinations are used as hyperkalemia will be more severe as renal function declines.[61] ACEIs and ARBs have been used in patients with CKD to delay progression. However, discontinuing RAAS blockade in patients with low levels of renal function might delay initiation of dialysis.[62] Most patients with CKD should have a diuretic as their first or second agent to manage volume and sodium retention.[63] In early CKD, a long-acting thiazide and in advanced CKD stages (i.e., eGFR of <30 ml/min/1.73 $m^2$), a loop diuretic may be effective in resistant HTN.[64,65] Addition of a diuretic might correct nocturnal non-dipping and restore the circadian rhythm of BP in CKD.[66] Dihydropyridine calcium channel blockers (CCBs) are more effective in lowering BP than non-dihydropyridine CCBs and can be used as monotherapy or in combination.[67] Long-acting CCB combined with ACEI or ARB might be more effective in slowing the progression of nephropathy, particularly in black race.[68] CCB induced lower extremity edema due to pre-capillary arterial dilatation is refractory to diuretics but responds to addition of ACEI. Beta-blockers are often used, especially when there is a coexisting cardiac disease.[69,70] Combined alpha and beta antagonists are the more effective agents in patients with CKD.[71] Alpha-blockers despite their possible favorable effect on BP and vascular remodeling have limited role due to common side effect of dizziness. Clonidine, a potent centrally acting agent but requires frequent dosing, has a significant side effect profile including rebound HTN which can be life-threatening. Vasodilators such as di-hydralazine or minoxidil are less preferred drugs due to a higher incidence of adverse effects and are usually reserved for refractory cases.

### Device Interventions

Renal denervation by radiofrequency ablation has resulted in significant reductions in BP in some but not all patients with CKD.[72,73] Similarly, baroreflex activation therapy using a pacing generator has been successful in limited uncontrolled studies in patients with CKD.[74] Even though procedures are safe in these patients, their effectiveness and reproducibility remain to be determined.[75,76]

## Treatment of HTN in ESRD

HTN in dialysis patients pose unique diagnostic, prognostic, and therapeutic challenges. Sodium and volume overload is the prominent mechanism of HTN in ESRD in addition to arterial stiffness, activation of RAAS and SNS, endothelial dysfunction, and the use of erythropoietin-stimulating agents.[77,78]

Due to the extreme variability of BP, diagnosis of HTN in ESRD is not straightforward. Recent recommendations suggest that diagnosis of HTN in patients on dialysis should ideally be made on the basis of either home BP measurements (≥135/85 mmHg) or 24/44-h ABPM (≥130/80 mmHg) but not on the basis of pre- or post-dialysis BP.[79] When neither ABPM nor home BP measurements are available the diagnosis can be made on the basis of average of interdialytic office BP measurements (≥140/90 mmHg) taken in a mid-week day free of hemodialysis.[80]

Non-pharmacological measures to reduce sodium and volume excess are fundamental for BP reduction in dialysis patients and individualized dialysis prescriptions should be strictly followed along with pharmacological interventions. Main measures include gradual supervised achievement of individual patients' dry weight, avoidance of short (i.e., <4 h) dialysis duration and minimization of inter- and intradialytic sodium gain by restriction of sodium intake to <65 mmol (1.5 g of sodium or 4 g of sodium chloride) per day, decreasing dialysate sodium toward pre-dialysis sodium in selected individuals, and avoidance of sodium-containing or sodium-exchanging drugs.[81-83]

Randomized trials clearly show that BP lowering is associated with reduced cardiovascular morbidity and mortality in dialysis patients.[84,85] All drug classes are useful except diuretics, which are ineffective in patients with ESRD [Table 2]. Multiple studies have supported efficacy of non-dialyzable long-acting beta-blockers, e.g., carvedilol and atenolol in lowering risk of sudden death, improving LV systolic function, and reducing the risk of all-cause hospitalization.[86,87] Dihydropyridine CCBs are potent agents even in volume-expanded state like in dialysis patients. In a study, amlodipine improved survival compared with placebo and was equally effective as ACEIs or ARBs in reducing LV hypertrophy.[88,89] Of note, all CCBs are non-dialyzable. The first-line use of ACEIs and ARBs in dialysis population is not supported by a meta-analysis of randomized trials.[90] However, ARBs, e.g., losartan, valsartan, and candesartan but not olmesartan reduced cardiovascular events and mortality

**Table 2:** Treatment considerations in patients with CKD and ESRD

| CKD Stages 1, 2* | CKD Stages 3, 4, and 5* | ESRD |
|---|---|---|
| Treatment recommendations similar to general population, i.e., select drug according to comorbidities, age, and ethnicity | Consider volume status, possible adverse effects of drugs, and tolerance to hypotension | Consider volume status, i.e., optimize dialysis prescription, increase dialysis duration, and/or frequency to achieve dry weight. |
| In addition, consider retarding the progression of renal disease | Consider stopping drugs that can cause decrease in GFR or hyperkalemia, i.e., ACEIs or ARBs | Stop or reduce dosage of drugs that have predominant renal excretion |
| Target BPs of 120-139/<90 and 120-129/<80 mmHg in patients without and with proteinuria, respectively | Monitor electrolytes and renal function frequently | Prefer use of drugs which are not removed in dialysis |
| Preferred drugs: | Preferred drugs: | Preferred drugs: |
| 1. ACEIs or ARBs | 1. Thiazide or loop diuretics | 1. Beta-blockers |
| 2. Thiazide diuretics | 2. Beta-blockers | 2. CCBs |
| 3. Beta-blockers | 3. CCBs | 3. ACEIs or ARBs |
| 4. CCBs | 4. Alpha-blockers | 4. Alpha-blockers |
| 5. Alpha-blockers | 5. Vasodilators | 5. Vasodilators |

*Stages 1, 2, 3, 4, and 5 with GFR of≥90, 60–89, 30–59, 15–29, and<15 ml/min/1.73 $m^2$. CKD: Chronic kidney disease, ESRD: End-stage renal disease, GFR: glomerular filtration rate, ACEIs: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, CCBS: Calcium channel blockers

**Table 3:** Pathophysiology and management of intradialytic HTN in patients with ESRD

| Pathophysiologic mechanism | Possible interventions |
|---|---|
| Extracellular volume overload | Increase ultrafiltration, achieve dry weight Increase duration and/or frequency of dialysis<br>Restrict dietary salt and water |
| Increased cardiac output | Adrenergic receptor blockers (β-blockers) |
| Electrolyte imbalance | Ensure adequate intradialytic sodium balance<br>Reduce dialysate calcium concentration |
| Activation of RAAS | ACEI Angiotensin II receptor blockers |
| Sympathetic overactivity | ACEI Angiotensin II receptor blockers<br>Adrenergic receptor blockers (α-blockers and/or β-blockers) Increase duration and/or frequency of dialysis |
| Endothelial cell dysfunction and peripheral vasoconstriction | Antioxidants, statins, L-arginine, sevelamer<br>Increase duration and/or frequency of dialysis |
| Removal of antihypertensive medications by hemodialysis | Switch to non-dialyzable ones<br>(e.g., long-acting CCB, carvedilol, angiotensin II receptor blockers) |
| Use of erythropoiesis-stimulating agents | Decrease dosage Lower hematocrit if high. |

ESRD: End-stage renal disease, HTN: Hypertension, RAAS: Renin–angiotensin aldosterone system, CCB: Calcium channel blockers

compared with treatment in dialysis patients and are preferred over ACEIs for sustained BP reduction.[91-93]

Intradialytic HTN is defined as an increase in mean arterial BP of 15 mmHg or more during hemodialysis that is resistant to ultrafiltration.[94,95] It has a prevalence of 5–15% among patients on hemodialysis and is associated with adverse outcomes including higher mortality.[96,97] Mechanism remains elusive and hence management remains empiric and problematic as very few guidelines addresses this issue.[98] Potential pathophysiologic mechanisms and possible interventions are shown in Table 3.[99]

## Conclusions

HTN is a major risk factor for target organ damage, cardiovascular and cerebrovascular events, and hence a major contributor of morbidity and mortality both in patients with CKD and patients on dialysis. Elevated BP can be a consequence of a progressive decline in renal function. On the other hand, it is the most important risk factor for CKD progression leading to ESRD. Standardized out-of-office BP measurements better predict the risk of cardiovascular events than the usual practice of in-office measurements. Automated home readings and ABPM better characterize these patients, may help clinicians to optimize disease management. Mostly, current guidelines recommend BP target of <140/90 mmHg in most patients with CKD, with a suggestion based on expert opinion only to maintain a target of <130/80 mmHg for patients with proteinuria. Recent randomized trial showed moderate reduction in the cardiovascular events with an intensive systolic target of <120 mmHg in uncomplicated population, but no benefit was observed in relation to CKD progression to ESRD. Although the major adverse effects such as hypotension and falls were similar, incidence of hyperkalemia and acute kidney injury increased in the group with stricter target. Taken together, lowering of systolic

target to <120 mmHg should not be applied to patients with CKD, and it seems prudent to continue to adhere to the existing guidelines. Multiple pathophysiologic processes contribute and their individual contributions might differ in patients. Hence, medication regimens need to be individualized and optimized. Lifestyle measures, dietary recommendations, drug and dialysis regimen adherence, and home monitoring of BP are essential components for successful management of HTN in patients with CKD and in patients with ESRD on dialysis.

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