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Review Article

Treatment of Hypertension in the Different Stages of Chronic Kidney Disease

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Abstract

The blood pressure (BP) targets for patients with chronic kidney disease (CKD) to decrease the risk of cardiovascular outcomes and progression of renal disease remain unclear. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) published a clinical practice guideline on the management of BP in CKD patients not on renal replacement therapy, for both diabetic and non-diabetic population. KDIGO recommended the target BP of <140/90 mmHg for CKD patients without albuminuria and <130/80 mmHg for those with albuminuria. Since then, new data arising from recent clinical trials such as the 2015 Systolic BP Intervention Trial have added to the evidence base. As well as, the current recommendations from the American College of Cardiology/American Heart Association Clinical Practice Guideline in 2017 have made us reevaluate our BP targets and hypertension management in the CKD population.

Key words: Albuminuria, blood pressure, chronic kidney disease, dialysis, hypertension, renal replacement therapy

Introduction

Hypertension (HTN) is the chronic elevation of blood pressure (BP) sufficient to increase the risk of HTN-mediated organ damage and other related complications in the general population, particularly in the presence of comorbidities.^[1-4] It is the level of BP at which the benefits of lifestyle interventions or medical therapy outweigh the risks of treatment.^[5] In 2015, the global prevalence of hypertension (HTN) was estimated to be 1.13 billion.^[6] There is around 30–45% of adults worldwide diagnosed with HTN. Majority of those diagnosed with elevated BP are males. This is consistent across different countries regardless of socioeconomic status.^[7] The aging population, sedentary lifestyles, and obesity contribute to the rise of HTN cases globally, with an estimated increase in disease prevalence to close to 1.5 billion by 2025.^[8]

Interdependence of HTN and CKD

Chronic kidney disease (CKD) comprises a range of different pathophysiologic processes, leading to progressively irreversible

decline in estimated glomerular filtration rate (eGFR) over 3 months that have a great impact to overall health. Different stages of CKD have been defined based on the eGFR. The two main causes of CKD worldwide are diabetes and high BP.^[9]

The pathogenesis of HTN in CKD is an actual interplay of independent and interdependent mechanisms, where the kidney is both a contributor and the target organ. The relationship of HTN and CKD has been well established in several literatures.^[10] The dilemma to identify whether the HTN caused the kidney disease or the other way around could be challenging. Regardless of which came first, the degree of HTN among patients with kidney disease usually worsens with the severity of renal dysfunction. Kidney involvement in HTN is based on the findings of renal parenchymal changes, declines in kidney function with or without the presence of albuminuria that is independent predictors of increased cardiovascular (CV) risk and renal disease progression.^[11] All hypertensive patients with suspected kidney involvement should have an annual examination consisting of serum creatinine, eGFR, and urine albumin-creatinine ratio (UACR).^[1]

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HTN in patients with CKD across all stages can be produced by several mechanisms including volume expansion, abnormalities in renin secretion, and hyperactivity of the autonomic nervous system.^[12]

BP Target in CKD Patients

The primary goal in the management of HTN in CKD is to lessen CV events and delay the progression to end-stage renal disease (ESRD) that necessitates renal replacement therapy or kidney transplantation.^[13] However, the optimal BP level in the management of HTN in the CKD population remains uncertain despite the recent and robust source of trial data and clinical guidelines.^[2,14] The threshold for treatment has been continually refined as new research accumulates [Table 1].

It is also important to note that the type of BP measurement and monitoring for CKD patients are major factors to be considered in the HTN in CKD treatment strategy. Home BP measurements which correlate closer to ambulatory BP monitoring are superior to conventional office BP measurements and are hence more predictive of CV outcomes.^[15,16]

Focusing on the reduction of CV events, studies on both diabetic and non-diabetic patients with kidney disease have been facilitated throughout the years. The Action to Control CV Risk in Diabetes trial enrolled diabetic patients with mild CKD (creatinine <1.5 mg/dl) and subjected to an intensive systolic BP (SBP) goal of <120 mmHg versus a standard BP goal of <140 mmHg. There was a reduction of CV events in the diabetic patients, but this effect is small and statistically insignificant.^[17] A follow-up study also shows increased risk of adverse event associated with the intense BP-lowering strategy. Clinical studies on the non-diabetic CKD population also failed to show benefit of lowering BP thresholds to <130/80 mmHg compared to <140/90 mmHg in slowing CKD progression or significant impact on mortality or CV outcomes.^[18-21]

Albuminuria has been a focal point in defining intensity of BP-lowering strategies and published guidelines have exhibited disparities in BP goals for CKD patients. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) recommended the <130/80 mmHg target only for those with proteinuric CKD (ACR \geq 30 mg/g).^[1] The JNC-8 (2014) reports recommended BP of 140/90 mmHg, regardless of proteinuria.^[22] Based on the American College of Cardiology/American Heart Association (ACC/AHA) BP guidelines of 2017, the BP goal of <130/80 mmHg is a Class 1 recommendation in adults with CKD, regardless of albuminuria.^[3]

The SBP Intervention Trial (SPRINT) study was designed to measure the hypothesized difference in clinical outcomes of standard BP control (SBP < 140 mmHg) versus intensive BP lowering (SBP <120 mmHg).^[2] To date, the study is considered to be the biggest randomized trial ($n = 9361$) that evaluates the different BP targets on CV and renal outcomes in the non-diabetic, hypertensive population. The trial was prematurely terminated because the results showed that intensive BP-lowering decreased the risk of CV disease by 25% and the risk

of all-cause mortality by 27%. However, there was an increased risk of syncopal attacks, decline in eGFR, and electrolyte abnormalities with intensive BP lowering.

About 28% ($n = 2646$) of the total SPRINT cohort was diagnosed with CKD at baseline. The primary composite CV outcome was similar in patients who were treated with intensive and standard BP lowering (hazard ratio 0.81; 95% confidence interval [CI], 0.63–1.05) after a median follow-up of 3.3 years. The composite outcome of \geq 50% decrease in eGFR from baseline or occurrence of ESRD was no different from both treatment groups (HR, 0.90; 95% CI, 0.44–1.83). Furthermore, no significant difference was seen on the incidence of adverse events between the treatment and control group.^[23]

More recently released 2018 ESC/ESH Guidelines have taken the overall results of SPRINT into consideration. Addressing the issue of hypertensive patients with CKD (diabetic or non-diabetic), it is recommended to lower SBP to a range of 130–139 mmHg and that “individualized treatment” should be based on tolerability, impact on renal function, and electrolyte changes.^[24]

In patients with ESRD on maintenance dialysis, the pathogenesis of HTN is multifactorial and is confounded by a wide array of risk factors. The high-risk nature of these patients makes them often excluded in major clinical trials on intensive versus standard BP control. Thus, the optimal BP targets of these patients are still not established. The KDOQI guidelines have previously recommended a target SBP of <140 mmHg and SBP <130 mmHg, pre- and post-hemodialysis (HD), respectively, this is largely based on expert opinion.^[25] While there is a decrease in mortality noted in the general population with intensive BP control, observational studies on HD patients have noted an increase in mortality among those with SBP \leq 140 mmHg, among elderly patients and those with diabetes.^[26-31]

Drug Therapy

The renin-angiotensin-aldosterone system (RAAS) is recognized as the best modulator of BP and a determinant of HTN-mediated organ damage. Angiotensin II is the main effector of the RAAS that increases the vascular tone of the glomerular arterioles (afferent and efferent) in *in vivo* studies.^[32] Due to these changes, it is able to regulate the glomerular capillary pressure and filtration rate. Angiotensin II predominantly causes a vasoconstrictor efferent glomerular arterioles, leading to an increase in filtration fraction and glomerular hydraulic pressure. There is also an observed disruption on the size selectivity of the plasma proteins to the glomerular barrier.^[33] These changes lead to intracapillary HTN and increased ultrafiltration of plasma proteins that contribute to the onset of kidney disease and worsening of renal function.

The use of RAAS blockers, such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), has been the foundation of the treatment of elevated BP in patients with CKD with the additional benefit of slowing CKD progression and protection from CV outcomes. These have been supported by several studies in both the diabetic and non-diabetic population with kidney disease.^[34-36]

Table 1: Guidelines from various target blood pressure recommendations for patients with chronic kidney disease

CKD stages and presence of albuminuria	KDIGO (2012)	JNC-8 (2014)	ACC/AHA (2017)	ESC/ESH (2018), SBP
CKD stages 1–5 with albuminuria	<140/90	<140/90	<130/80	130–139
CKD stages 3–5 without albuminuria	<130/80	<140/90	<130/80	130–139

KDIGO: Kidney Disease: Improving Global Outcome, JNC-8: Eighth Joint National Committee, ACC/AHA: American College of Cardiology/American Heart Association, ESH: European Society of Hypertension, ESC: European Society of Cardiology, SBP: Systolic blood pressure, CKD: Chronic kidney disease

Table 2: Suggested antihypertensive medication in chronic kidney disease patients (predialysis and dialysis) and their prescribing order

Prescribing order	CKD (predialysis)	Dialysis patients
First	ACEi or ARB	ARB
Second	CCB	Beta-blockers (consider as first line for patients with established CV disease or at high risk)
Third	Diuretics	CCB

CKD: Chronic kidney disease, ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin II receptor blocker, CCB: Calcium channel blocker, CV: Cardiovascular

Dual RAAS blockade was previously believed to be more beneficial for both CV and renal outcomes as this would lead to a more extensive inhibition of angiotensin II production. Unfortunately, based on the results of the ONTARGET (Telmisartan, ramipril, or both in patients at high risk for vascular events trial)^[37] and ALTITUDE (Cardiorenal end points in a trial of aliskiren for Type 2 diabetes),^[38] there were more adverse events seen in the combination therapy such as an increased risk of hypotension, renal dysfunction, and hyperkalemia, with no additional benefit as compared to the controls.

There is currently a lack of strong evidence to support one drug class over another in the management of HTN in the dialysis population. The choice of antihypertensive therapy should be tailored to the individual patient basing on effective and safe BP lowering, CV protection, and consideration of drug pharmacokinetics altered by dialysis treatment.

In ESRD patients, ACEis and ARBs are effective at lowering BP.^[39,40] They are often recommended as first-line antihypertensive therapy for patients on dialysis basing on their trends on CV benefits seen with their use in the general population.^[41] It is important to consider that the choice of ACEis and ARBs is not interchangeable for dialysis patients, as there are important differences between in their important pharmacokinetic differences to be considered, particularly on renal clearance and drug removal during dialysis. Most ARBs are not dialyzed during conventional dialysis and may be preferred in these patients for sustained BP reduction [Table 2].^[42]

There are clinical trials that support the evidence that beta-blocking agents can provide the CV protection seen in the general population even to dialysis patients.^[43,44] Aside from their effects on addressing the overactivation of the sympathetic nervous system in hypertensive dialysis patients, they may have the potential benefit on CV protection through nitric oxide-

induced vasodilation and antioxidant properties.^[45] One of the studies to investigate this protective effect was a prospective, placebo-controlled trial with carvedilol. In this 2-year study, echocardiographic evidence showed a significant attenuation of pathologic remodeling of the left ventricle and higher ejection fractions in the treatment group compared to the placebo group. Furthermore, there were fewer hospital deaths recorded and hospitalization rates in the treatment group.^[43] A meta-analysis done in 2019 which included three randomized controlled trials (comparing β -blockers vs. placebo or another HTN drug) showed a significant association between β -blockers and reduced all-cause mortality, CV mortality, CV events, or hospitalizations among the 363 dialysis patients included in the studies analyzed.^[46]

An alternative antihypertensive drug in the management of HTN in CKD is the calcium channel blockers. They provide good BP lowering and are well-tolerated antihypertensive medications.^[45] Large trials specifically examining CCBs for HTN in CKD are lacking, but these drugs have often been used as an active comparator in landmark trials of ACEi and ARBs in CKD.^[19,34] They are effective antihypertensive agents in both CKD and ESRD.^[46]

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