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Optimizing Blood Pressure Management to Slow the Progression of Chronic Kidney Disease: A Comprehensive Review

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Abstract

Hypertension is both a cause and consequence of Chronic Kidney Disease (CKD), significantly accelerating its progression and increasing morbidity and mortality. Accurate Blood Pressure (BP) measurement and management are critical for mitigating these risks. This review examines the complex pathophysiology of hypertension in CKD and evaluates current BP management guidelines, including the 2017 AHA/ACC and 2021 KDIGO recommendations. Emphasis is placed on the importance of individualized treatment plans incorporating lifestyle modifications, RAAS inhibitors, calcium channel blockers, diuretics, and novel agents such as SGLT2 inhibitors. The review also explores emerging pharmacological therapies and their potential benefits. Effective BP control in CKD patients not only slows disease progression but also reduces cardiovascular risk, underscoring the need for a patient-specific approach to optimize clinical outcomes. Further research is required to refine treatment protocols and enhance therapeutic efficacy in this high-risk population.

Keywords: Chronic kidney disease • Hypertension • Blood pressure target • Blood pressure treatment

Introduction

Hypertension and Chronic Kidney Disease (CKD) are intricately interconnected. Individuals suffering from CKD commonly have hypertension, which, when left unmanaged, hastens the deterioration of kidney function. Hypertension is both a contributing factor and a consequence of CKD, significantly increasing risks of morbidity and mortality when both conditions coexist. The underlying mechanisms of high Blood Pressure (BP) in individuals with CKD are intricate. Ensuring precise measurement of BP is a fundamental initial step in identifying and controlling hypertension. Managing hypertension in CKD patients is crucial as it decelerates disease progression and reduces cardiovascular disease risk [1]. Current international recommendations lack a unanimous agreement on the most favourable blood pressure targets. Hence, it is crucial to comprehend the data employed in formulating these guidelines to determine the most effective approach to managing specific patients. In 2017, the AHA/ACC guidelines updated the definition and classification of hypertension and set a BP goal of 130/80 mmHg for most high-risk individuals, including patients with CKD [1]. The 2021 KDIGO guidelines recommend a stricter target SBP of 120 mmHg or lower for managing hypertension in CKD [2]. Other guidelines recommend less intensive BP targets [3,4]. Nonpharmacological interventions are efficacious in reducing BP in CKD; however, they are rarely sufficient for adequately controlling BP. Individuals diagnosed with CKD with hypertension may necessitate a combination of antihypertensive drugs to attain the desired BP target [1,2].

Pathophysiology of hypertension in chronic kidney disease

Hypertension and CKD are connected, and the pathophysiology of CKD-associated hypertension is complex and involves multiple mechanisms, including the following:

- **Sodium dysregulation:** This can be influenced by factors such as reduced eGFR, altered tubular function, and derangements in the Renin-Angiotensin-Aldosterone System (RAAS) [5].
- **Increased sympathetic nervous system activity:** CKD is associated with heightened sympathetic nervous system activity, leading to vasoconstriction, increased heart rate, and sodium retention [6].
- **Alterations in RAAS activity:** Increased production of angiotensin II, aldosterone, and other vasoactive substances can result in vasoconstriction, sodium retention, and long-term adverse effects on renal function and blood pressure regulation [7].
- **Endothelial dysfunction:** Decreased nitric oxide synthesis and elevated production of vasoconstrictor molecules such as endothelin-1 contribute to vasoconstriction and elevated blood pressure [8].
- **Inflammatory processes:** CKD increases the production of cytokines and chemokines. Chronic inflammation contributes to endothelial dysfunction, vascular remodeling, and increased peripheral resistance, leading to hypertension [8].
- **Arterial stiffness:** Structural changes in blood vessels and collagen deposition lead to increased systolic blood pressure [9].

Understanding these pathogenic mechanisms is crucial for managing hypertension in CKD. Therapeutic interventions often target these mechanisms, such as using RAAS inhibitors, volume control strategies, and sympathetic nervous system modulation to help manage BP and slow the progression of CKD.

Diagnosis of hypertension in CKD

Accurate BP measurement is crucial as timely diagnosis and proper management of hypertension can delay or prevent CKD progression. BP measurement can be classified into standardized office measurement using an automated oscillometric device or manual sphygmomanometer, or out-of-office BP measurement using a 24-hour ambulatory BP monitor or home BP monitor. A study by Myers MG, et al. found that the mean clinic BP measured using an automated BP device is comparable to the 24-hour ambulatory BP monitor, while manual blood pressure measurements in clinic can result in significantly elevated BP [10]. A meta-analysis involving 7116 participants

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across 26 studies found that the mean automated office systolic BP is around 10 mmHg lower than that of the manual office BP, while the systolic and diastolic BP from ambulatory BP monitoring are similar to automated office BP measurements [11]. Appropriate BP cuff size is also important for accurate BP measurement: BP cuff sizes that are too small will lead to an overestimation of BP, while inappropriately large BP cuff sizes can cause underestimation of blood pressure [12]. To minimize errors in blood pressure measurements in clinic, the American Heart Association recommends a comprehensive set of instructions to standardize BP measurement [13].

Blood pressure control effects on kidneys and cardiovascular system

Hypertension is the leading modifiable risk factor for renal and cardiovascular outcomes, and these conditions are inseparably connected. Effective BP management mitigates cardiac and renal hazards. High BP is a significant risk factor for coronary heart disease, stroke, heart failure, atrial fibrillation, CKD, heart valve diseases, aortic syndromes, and dementia, according to large cohort studies [14]. Both systolic and diastolic hypertension, either individually or in combination, influence the risk of adverse cardiovascular events [15]. However, some authors propose that isolated diastolic hypertension does not correlate with composite kidney outcomes, composite cardiovascular events, or all-cause mortality [16]. A more substantial reduction in blood pressure to 133/76 mm Hg, as opposed to 140/81 mm Hg, has been linked to reduced cardiovascular and renal complications [17]. In the diabetic population, intensive BP reduction to 125/73 mmHg significantly reduces stroke and macroalbuminuria, although other outcomes such as renal outcomes, all-cause mortality, heart failure, microalbuminuria, and cardiovascular events did not experience statistically significant reductions [18]. Combined results from the SPRINT, MDRD, AASK, and REIN-2 trials indicate that an intensive BP target reduces macroalbuminuria and cardiovascular complications in CKD patients, but a less intensive BP target is recommended to prevent progression to ESKD. This evidence is extremely beneficial as CKD is a major cardiovascular risk factor [19,20].

Target of BP in the treatment of hypertension in CKD

Hypertension and CKD patients' ideal BP targets are still contested. The 2017 AHA/ACC guidelines redefined hypertension and set a target of <130/80 mmHg for high-risk adults, including those with CKD [1]. The 2021 KDIGO guidelines suggest a tighter systolic BP target of <120 mmHg for managing hypertension in CKD [2].

To ascertain the optimal therapeutic targets and define hypertension, one must assess BP levels in correlation with the risk of adverse health outcomes. This analysis revealed that the stage 1 hypertension category, as defined in the 2017 AHA/ACC guideline, does not identify patients at increased risk of developing cardiovascular disease among those taking BP-lowering medications. Assuming this risk association is causal, the 2017 AHA/ACC guideline's intensive BP target of 130/80 mmHg may not be appropriate for the management of hypertension in patients with proteinuric CKD [21].

Two landmark trials, MDRD and AASK, randomly assigned nondiabetic CKD patients to attain an intense (about 125/75 mmHg) or conventional (140/90 mmHg) BP objective. Both trials showed no improvement in renal outcomes with tighter BP management until the end of their randomized phase. Intensive BP-lowering results were linked to slower GFR deterioration in individuals with severe proteinuria (>1 g/day) at baseline in a subgroup analysis of the MDRD [22,23].

According to the SPRINT study, targeting a systolic BP of <120 mmHg in 9361 nondiabetic patients with high cardiovascular risk showed a 25% relative risk reduction in fatal and nonfatal cardiovascular events and a 27% relative risk reduction in all-cause mortality. A subgroup analysis of 2624 SPRINT participants with eGFR <60 ml/min/1.73 m^2 at baseline found that rigorous BP-lowering had the same cardioprotective effect for both CKD and non-CKD patients [24].

Based on different definitions, inclusion criteria in the above-mentioned studies, and different targets, further investigations are warranted to examine the benefit-to-risk ratio of intensive BP-lowering protocols in CKD patients [20].

Non-pharmacologic treatment of hypertension in CKD

The management of hypertension in individuals with chronic kidney disease predominantly involves pharmacological intervention. However, non-pharmacological interventions effectively lower blood pressure. Alongside administering medicines, hypertension management should also entail dietary and exercise modifications. In particular, a low-sodium diet (less than 5g/day) coupled with moderate-intensity physical activity for a minimum of 150 minutes per week is essential for this patient cohort [4].

The efficacy of salt reduction in lowering blood pressure and albuminuria, which may delay the progression of CKD and the risk of cardiovascular events in the long term, is well-established [5]. According to Heerspink HJ, et al., the effectiveness of RAAS inhibitors prescribed specifically for this group of patients can be augmented by a low-sodium diet [25]. Individualized treatment plans are necessary since certain CKD etiologies, such as salt-wasting kidney disease, do not benefit from these recommendations.

Regular physical activity helps manage blood pressure, improve weight control, and enhance strength and mental health without adversely impacting kidney function in the general population and CKD patients [26]. Other lifestyle modifications, including weight loss, decreased alcohol consumption, and adherence to a heart-healthy diet, have been proposed as adjuncts to blood pressure reduction in individuals with CKD [4].

Pharmacological treatment of hypertension in CKD

Hypertension and CKD are closely interlinked pathophysiologic states. Sustained hypertension can lead to worsening renal function, and progressive decline in renal function can worsen blood pressure control. Elevated blood pressure has detrimental effects on the cardiovascular system and several other vital organs. Pharmacological treatment is required to control and achieve the blood pressure target, thus helping to slow down CKD progression and decrease cardiovascular complications [4].

A comprehensive understanding of the available information is essential for delivering individualized management and meeting BP targets. The management guidelines for hypertension in patients with CKD have undergone significant transformations over the past two decades. For instance, substantial modifications have occurred between the KDIGO 2012 and KDIGO 2021 clinical practice guidelines for managing blood pressure in CKD [5].

The selection of antihypertensive drugs must be individualized. RAAS inhibitors are the preferred treatment for CKD and hypertension patients with albuminuria. Second-line agents include diuretics and calcium channel blockers. Failure to meet BP goals with the maximum dose of triple therapy (RAS inhibitors, calcium channel blockers, and diuretics) is termed resistant hypertension; consider mineralocorticoid receptor antagonists and spironolactone for these patients. However, spironolactone increases the risk of hyperkalemia. In such cases, chlorthalidone, a thiazide-like drug, can reduce hyperkalemia risk. These therapies are based on ACC 2017, KDIGO 2021, ESC 2021, and ISH 2020 guidelines [5].

Role of RAAS inhibitors in the management of hypertensive CKD

Hypertension significantly contributes to the pathogenesis of CKD, as uncontrolled hypertension accelerates CKD progression, and progressive renal impairment exacerbates hypertension through volume expansion and increased systemic vascular resistance. The Renin-Angiotensin-Aldosterone System (RAAS) is crucial for controlling BP. The RAAS regulates blood volume and systemic vascular resistance through its coordinated action on the kidneys and cardiovascular system. An inappropriate activation of the RAAS can result in hypertension. The intra-renally produced angiotensin II regulates tubular sodium transport and glomerular hemodynamics. Intrarenal RAAS activation is seen in diabetics during early nephropathy, which is a primary etiology of CKD [27].

Since RAAS plays a major role in BP modulation, it is a preferred target for pharmacological innovation in treating CKD. Consequently, current recommendations advise using multifocal inhibition of RAAS, either alone or in combination with other therapies, as the first-line antihypertensive medication. By reducing proteinuria and improving BP control, RAAS inhibitors have proven effective in slowing the progression of nephropathy to end-stage renal disease. However, a significant portion of patients with proteinuria develop hyperkalemia, necessitating stopping the medication or administering it at suboptimal doses to avoid hyperkalemia [28].

Calcium channel blockers and diuretics: Nephroprotective effects

The KDIGO 2021 and ESC/ESH 2018 guidelines agree that ACE inhibitors and ARBs should be the initial treatment for achieving target BP and slowing CKD progression. Regarding second-line or third-line treatments to be added when monotherapy fails to achieve the desired BP target or when RAAS inhibitors are inappropriate or intolerable, guidance is less specific, and clinicians must be guided by patients' clinical presentations. The choice of drugs such as Calcium Channel Blockers (CCBs), diuretics (thiazides or loop diuretics), and beta-blockers should consider the patient's volume status, comorbidities, potential drug interactions, and electrolyte imbalances [18].

CCBs are divided into Dihydropyridine (DHP-CCBs) and non-DHP-CCBs. Both reduce the contractility of vascular smooth muscle, resulting in vasodilation and consequently lowering BP. Non-DHP-CCBs show a higher effect on cardiac muscle, while DHP-CCBs work well for non-proteinuric patients as a first-line monotherapy or in combination. The metabolism of CCBs is mainly hepatic, not affected by renal function, making them suitable for CKD patients; however, side effects include peripheral edema [29-31]. DHP-CCBs, in combination with RAAS inhibitors, improve BP with an additional renoprotective effect of reducing proteinuria [32].

Diuretics are typically considered an add-on therapy to manage hypertension in CKD patients. They reduce BP by inducing acute natriuresis at the level of distal tubules of the nephron and the Loop of Henle, increasing urine output and reducing cardiac output. This impacts fluid overload, improving BP and consequently slowing CKD progression [33,34]. Additionally, the natural nocturnal drop in BP is lost as CKD progresses, but diuretics could help preserve tubular function [35].

Role of novel SGLT2 inhibitors as nephroprotective agents

In recent years, SGLT2 inhibitors have emerged as a novel therapeutic intervention for slowing CKD progression, particularly in individuals with type 2 diabetes. Beyond their primary function of glucose reduction, meta-analyses have evidenced significant reductions in both systolic and diastolic blood pressure. These BP-lowering effects are attributed to the indirect impact on blood pressure, stemming from their distinctive mechanism of action and consequential physiological alterations [36,37].

The mechanism by which SGLT2 inhibitors influence blood pressure involves an increase in the distal delivery of sodium to the macula densa, triggering tubuloglomerular feedback. This leads to vasoconstriction of the afferent arteriole, reducing intraglomerular pressure. Additionally, the diuretic effect of SGLT2 inhibitors, achieved through enhanced glucose excretion in the urine, contributes to blood volume loss [38].

Studies have indicated that SGLT2 inhibitors may reduce arterial stiffness, a crucial parameter reflecting arterial elasticity. The observed improvement in arterial function holds promise for contributing to more effective blood pressure control. Furthermore, there is evidence suggesting a potential inhibition of sympathetic nervous system activity associated with using SGLT2 inhibitors. The CREDENCE trial has shown that the blood pressure-lowering effect of canagliflozin was also seen in patients with resistant hypertension [39]. Although not explicitly approved for blood pressure reduction, these medications may aid in achieving blood pressure goals, particularly in individuals within 7-10 mm Hg of their target values [40].

Given the cumulative evidence supporting the multifaceted cardiovascular benefits of SGLT2 inhibitors, recent research suggests considering their incorporation into the first-line antihypertensive regimen for individuals with diabetic nephropathy and concomitant hypertension. This strategic integration holds therapeutic implications and may enhance the attainment of blood pressure goals [40].

Role of beta-blockers, alpha-blockers and renal denervation in BP control in CKD patients

Beta-blockers are not recommended as the first line in controlling hypertension in CKD patients [41,42]. They can be used in treating resistant hypertension when spironolactone is not tolerated or contraindicated. In the PATHWAY-2 trial, they were not found to be superior to spironolactone or doxazosin in lowering systolic blood pressure over 12 weeks [43]. Beta-blockers are recommended in CKD patients with heart failure with reduced ejection fraction, atrial fibrillation, and angina or myocardial infarction [43]. Renal denervation studies like the SPYRAL-HTN-ON MED trial showed that renal denervation in CKD patients on antihypertensives caused a sustained blood pressure reduction of 10/5.9 mmHg during a 36-month follow-up. Renal denervation caused albuminuria regression and slowed the decline of eGFR in CKD stage 3-4 patients. Further trials are needed to assess its safety [44].

Alpha-blockers were shown to cause an 8% reduction in cardiovascular events in CKD patients, a 14% higher risk of eGFR decline by more than 30%, and an increased risk of renal failure needing dialysis by 28%. Alpha-blockers cause hypotension and syncope, especially in elderly patients. The decline in eGFR was linked to the hypotension caused by alpha-blockers and vessel stiffness due to CKD. They improved cardiovascular events by reducing insulin resistance and improving lipid profiles. The balance is delicate in CKD patients at risk of cardiovascular events [45].

Significant advancements and future prospects in the pharmacological therapy of hypertension in chronic kidney disease

Recently, emerging pharmacological therapies, such as non-steroidal mineralocorticoid receptor antagonists, have surged. Ocedurenone, a small molecule administered orally, is undergoing phase 3 trials (CLARION-CKD) for patients with uncontrolled hypertension in the US, Europe, and Asia. Ocedurenone aims to reduce blood pressure and lower hyperkalemia, making it potentially useful for CKD patients [46].

Another drug under development is aprocitentan, a dual endothelin receptor antagonist aiming to treat pulmonary arterial hypertension. Aprocitentan enhances the BP-lowering effects of other antihypertensives, including renin-angiotensin system blockers, thereby offering cardiovascular protection in patients with resistant hypertension [47]. Aldosterone synthase inhibitor Baxdrostat, undergoing phase 2 trials, aims to treat resistant hypertension. Baxdrostat is highly selective for aldosterone synthase and spares the cortisol pathway, thus lowering blood pressure. These novel medications require further investigation to assess their renal consequences [48].

Experts acknowledge that the use of these emerging drugs in advanced CKD is limited by safety concerns, particularly in hyperkalemia, and compounded by a lack of clinical evidence. It is rare to find patients with stage 4 CKD (eGFR <30 mL/min/1.73 m^2) on one medication; adherence to medication is an existing challenge in advanced CKD, which will be an additional burden with polypharmacy.

Conclusion

Hypertension significantly exacerbates the progression of Chronic Kidney Disease (CKD), leading to increased morbidity and mortality. Accurate Blood Pressure (BP) measurement and effective management are crucial in mitigating these risks. While the 2017 AHA/ACC guidelines recommend a BP target of 130/80 mmHg, the 2021 KDIGO guidelines suggest a more

stringent systolic BP target of <120 mmHg for patients with CKD. Both lifestyle modifications and pharmacological treatments are essential in achieving these targets. RAAS inhibitors remain the cornerstone of antihypertensive therapy for CKD, with additional roles for calcium channel blockers, diuretics, and newer agents like SGLT2 inhibitors. Emerging pharmacological therapies show promise but require further research. A nuanced, patient-specific approach is vital for optimizing outcomes, emphasizing the importance of individualized treatment plans to manage hypertension effectively and slow CKD progression.

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Conflict of Interest

No conflict of interest.

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