

## RENAL DENERVATION IN CKD PATIENTS: PATHOPHYSIOLOGICAL RATIONALE, CLINICAL EVIDENCE, AND CONTEMPORARY PERSPECTIVES

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### ABSTRACT

Hypertension is a central driver of cardiovascular morbidity and progressive renal dysfunction in patients with chronic kidney disease (CKD), yet optimal blood pressure control remains challenging, particularly in advanced disease stages. Resistant hypertension is common in CKD, reflecting complex interactions among volume overload, neurohormonal activation, sympathetic overactivity, and vascular dysfunction. This narrative review synthesizes contemporary evidence on the pathophysiological mechanisms underlying hypertension in CKD, diagnostic challenges related to blood pressure assessment, and integrated therapeutic strategies. Particular emphasis is placed on the evolving role of device-based interventions, especially renal denervation, as an adjunctive therapy for carefully selected patients with resistant hypertension. We review current data supporting renal denervation, discuss patient selection considerations, and highlight unresolved questions regarding long-term efficacy and safety in CKD populations. Special clinical contexts, including dialysis, kidney transplantation, and older adults, are addressed, along with common misconceptions that contribute to therapeutic inertia. By integrating mechanistic insights with emerging clinical evidence, this review aims to inform a more individualized, patient-centered approach to hypertension management in CKD and to clarify the potential clinical niche of renal denervation within contemporary treatment paradigms.

**Keywords:** Chronic Kidney Disease, Hypertension, Renal Denervation, Resistant Hypertension

### ABSTRAK

*Hipertensi merupakan pendorong utama morbiditas kardiovaskular dan disfungsi ginjal progresif pada pasien dengan penyakit ginjal kronis (CKD), namun kontrol tekanan darah yang optimal masih menjadi tantangan, terutama pada stadium penyakit yang lebih lanjut. Hipertensi resisten sering ditemukan pada CKD, mencerminkan interaksi kompleks antara kelebihan volume, aktivasi neurohormonal, peningkatan aktivitas simpatis, dan disfungsi vaskular. Tinjauan naratif ini mensintesis bukti terkini mengenai mekanisme patofisiologis yang mendasari hipertensi pada CKD, tantangan diagnostik terkait penilaian tekanan darah, serta strategi terapi terintegrasi. Penekanan khusus diberikan pada peran intervensi berbasis perangkat yang terus berkembang, terutama denervasi ginjal, sebagai terapi tambahan pada pasien terpilih dengan hipertensi resisten. Kami meninjau data terkini yang mendukung denervasi ginjal, membahas pertimbangan seleksi pasien, serta menyoroti pertanyaan yang belum terjawab terkait efektivitas dan keamanan jangka panjang pada populasi CKD. Konteks klinis khusus, termasuk dialisis, transplantasi ginjal, dan populasi usia lanjut, juga dibahas,*

*bersama dengan kesalahpahaman umum yang berkontribusi terhadap inersia terapeutik. Dengan mengintegrasikan wawasan mekanistik dan bukti klinis yang berkembang, tinjauan ini bertujuan untuk mendukung pendekatan manajemen hipertensi pada CKD yang lebih individual dan berpusat pada pasien, serta memperjelas potensi posisi klinis denervasi ginjal dalam paradigma terapi kontemporer.*

**Kata Kunci:** Penyakit Ginjal Kronis, Hipertensi, Denervasi Ginjal, Hipertensi Resisten

## INTRODUCTION

Hypertension is a central and modifiable determinant of adverse outcomes in chronic kidney disease (CKD), contributing directly to both cardiovascular morbidity and progressive renal dysfunction. Even modest elevations in systolic blood pressure have been associated with accelerated decline in estimated glomerular filtration rate, left ventricular hypertrophy, and increased risk of heart failure and stroke, highlighting hypertension as a key driver rather than a mere comorbidity in CKD progression.<sup>1,2</sup>

Hypertension affects the majority of individuals with CKD across all stages of renal impairment, reflecting a bidirectional relationship in which declining kidney function promotes blood pressure elevation, while uncontrolled hypertension further exacerbates renal injury.<sup>3</sup> This self-perpetuating interaction complicates clinical management and exposes the limitations of conventional blood pressure treatment strategies in this population.<sup>4</sup>

Despite its clinical relevance, optimal blood pressure control in CKD remains difficult to achieve. Resistant hypertension is disproportionately prevalent, driven by volume overload, altered drug pharmacokinetics, neurohormonal activation, and diagnostic challenges such as white coat or pseudo resistance.<sup>2</sup> These factors are further compounded by therapeutic inertia and uncertainty regarding treatment escalation in advanced CKD and dialysis settings.<sup>5</sup>

This narrative review synthesizes current evidence on the pathophysiology, diagnosis,

and management of hypertension in CKD, with particular emphasis on individualized treatment strategies and emerging device based therapies such as renal denervation. A structured literature search was conducted using major electronic databases, including PubMed and Scopus, covering articles published between 2019 and 2025. The search strategy combined keywords related to chronic kidney disease, hypertension, resistant hypertension, and renal denervation. A total of approximately 46 relevant articles were identified, of which the most pertinent and high-quality studies were selected to inform this review.

By integrating mechanistic insights with evolving clinical data, this review aims to support more effective and patient centered blood pressure management across diverse CKD populations. To our knowledge, this is among the first narrative reviews to provide a comprehensive and focused discussion on the role of renal denervation specifically in patients with CKD, bridging pathophysiological rationale with emerging clinical evidence in this high-risk population.

## PATHOPHYSIOLOGY OF HYPERTENSION IN CKD

Rather than a single mechanistic entity, hypertension in CKD represents a systems-level disorder driven by interdependent renal, neurohormonal, and vascular pathways. Impaired sodium excretion resulting from nephron loss remains a foundational mechanism, promoting extracellular fluid expansion and elevated cardiac output, particularly in early and intermediate CKD stages where overt edema may be absent.<sup>6</sup>

Superimposed on volume expansion, chronic activation of the renin-angiotensin-aldosterone system amplifies vasoconstriction and sodium retention while simultaneously accelerating vascular remodeling, myocardial fibrosis, and progressive nephron loss.<sup>7</sup> These pleiotropic effects explain why RAAS blockade remains central to both BP control and long-term renoprotection, even when antihypertensive effects appear modest.

Sympathetic nervous system overactivity further compounds hypertension severity, especially in advanced CKD. Afferent renal nerve signaling increases central sympathetic tone, perpetuating vasoconstriction, tachycardia, and renin release.<sup>8</sup> This neurohumoral amplification creates a self-reinforcing loop that underlies many cases of resistant hypertension and provides a mechanistic rationale for interventions targeting renal sympathetic pathways, including renal denervation.<sup>9</sup>

Vascular dysfunction acts as the final common pathway sustaining elevated systemic resistance. Endothelial injury, oxidative stress, arterial stiffness, and microvascular rarefaction impair vasodilatory capacity and exacerbate ischemic end-organ injury.<sup>10,11</sup> Uremic toxins and chronic inflammation further accelerate arteriosclerosis, linking renal dysfunction to disproportionate cardiovascular risk.

## **BLOOD PRESSURE ASSESSMENT AND RESISTANCE**

Accurate classification of hypertension in CKD hinges less on numerical thresholds than on methodological rigor. Traditional office BP measurements frequently misrepresent true BP burden due to white-coat and masked hypertension, phenomena that are particularly prevalent in CKD populations.<sup>12</sup> Consequently, reliance on clinic readings alone contributes to both under-treatment and overtreatment.

Ambulatory and home BP monitoring provide superior prognostic value, enabling

detection of nocturnal hypertension and non-dipping patterns that are strongly associated with cardiovascular and renal outcomes.<sup>13</sup> Ambulatory monitoring is therefore essential for confirming true resistant hypertension, defined as uncontrolled BP despite three or more agents including a diuretic, and for distinguishing it from pseudo-resistance related to nonadherence or measurement error.<sup>14</sup>

Volume assessment represents an equally critical but frequently underemphasized component of diagnosis. In dialysis-dependent patients, interdialytic weight gain and ultrafiltration rates exert dominant effects on BP variability, underscoring the inseparability of hemodynamic control and fluid management.<sup>15</sup> Without diagnostic clarity, intensification of pharmacotherapy risks perpetuating instability rather than achieving durable control.

## **INTEGRATED THERAPEUTIC APPROACHES**

Effective BP management in CKD requires coordinated application of lifestyle, pharmacologic, and interventional strategies, tailored to renal function and comorbidity burden.<sup>16</sup> Contemporary guidelines emphasize individualized targets, acknowledging both the high prevalence of resistant hypertension and the risks of overly aggressive BP lowering in advanced disease.<sup>17</sup>

Non-pharmacologic measures form the foundation of therapy. Dietary sodium restriction, fluid moderation, weight optimization, and physical activity improve BP control and enhance responsiveness to antihypertensive agents, particularly in volume-sensitive patients.<sup>18</sup> In dialysis populations, achieving and maintaining optimal dry weight remains the most powerful determinant of sustained BP reduction, supplemented by structured patient education to improve adherence.<sup>19</sup>

Pharmacologic therapy should be selected according to proteinuria, cardiovascular risk, and CKD stage.<sup>14</sup> RAAS inhibitors remain first-line agents, supported by diuretics for volume control and calcium channel blockers for systolic hypertension.<sup>20</sup> B-blockers serve important roles in patients with coronary disease or arrhythmias, while mineralocorticoid receptor antagonists such as finerenone offer additional benefit in resistant hypertension, albeit with heightened hyperkalemia risk requiring close monitoring.<sup>21</sup>

### **RENAL DENERVATION AND DEVICE-BASED THERAPY**

Renal denervation has re-emerged as a potential adjunct for resistant hypertension, particularly relevant in CKD where sympathetic overactivity is pronounced.<sup>22</sup> By disrupting afferent and efferent renal sympathetic signaling, RDN directly targets a central mechanism of BP elevation.<sup>1</sup> RDN can safely reduce both office and ambulatory BP in patients with moderate-to-severe CKD, including selected dialysis-dependent individuals, without accelerating renal function decline.<sup>2</sup> These effects appear durable over intermediate follow-up, although robust randomized data remain limited. Careful patient selection is essential. Candidates should demonstrate confirmed medication adherence, persistent uncontrolled BP, and suitable renal artery anatomy, as vascular calcification and structural abnormalities are common in CKD and may limit procedural feasibility.<sup>23-25</sup> Ongoing trials are expected to clarify long-term safety, durability, and the optimal clinical niche of RDN.

### **SPECIAL RENAL POPULATIONS**

Hypertension in dialysis patients is nearly ubiquitous and multifactorial, driven by volume overload, arterial stiffness, and sympathetic activation.<sup>22,26</sup> Ambulatory and interdialytic BP monitoring provide superior assessment, while excessive ultrafiltration should be avoided to prevent intradialytic

hypotension.<sup>15</sup> In kidney transplant recipients, hypertension is influenced by immunosuppressive regimens, chronic allograft dysfunction, and residual native kidney activity. RAAS blockade is often favored for antiproteinuric effects, supplemented by calcium channel blockers, diuretics, or mTOR inhibitors according to graft function and comorbidity profile.<sup>2</sup> Older adults with CKD represent a distinct phenotype characterized by isolated systolic hypertension, frailty, and heightened susceptibility to orthostatic hypotension. Individualized BP targets, regular medication review, and emphasis on non-pharmacologic strategies are critical to minimizing adverse events while preserving cardiovascular benefit.<sup>27,28</sup>

### **CONTROVERSIES AND CLINICAL BARRIERS**

Despite accumulating evidence, misconceptions continue to impede optimal BP management in CKD. Overreliance on office BP readings and underutilization of ambulatory monitoring contribute to diagnostic misclassification and therapeutic inertia.<sup>29,30</sup> Unwarranted discontinuation of RAAS inhibitors due to modest creatinine rises remains common, despite guideline recommendations supporting continued use unless hyperkalemia or symptomatic hypotension occurs.<sup>17</sup> Similarly, fear of intradialytic hypotension should not overshadow the prognostic importance of pre-dialysis hypertension, which is more strongly linked to mortality.<sup>15</sup> Therapeutic inertia persists as a critical barrier, often driven by misattribution of uncontrolled BP to nonadherence alone. Overcoming this requires structured assessment, multidisciplinary collaboration, and judicious consideration of adjunctive interventions, including device-based therapies, in appropriately selected patients.<sup>31</sup>

### **CONCLUSION**

Hypertension in chronic kidney disease represents a multifactorial and self-

reinforcing disorder that substantially amplifies cardiovascular risk and accelerates renal function decline. Effective management requires accurate blood pressure assessment, rigorous volume control, and individualized integration of lifestyle, pharmacologic, and, in selected cases, device-based interventions. Renal denervation offers a mechanistically appealing adjunct for patients with confirmed true resistant hypertension, particularly in CKD populations characterized by persistent blood pressure elevation despite optimized pharmacologic therapy and verified adherence. This distinction is critical, as emphasized earlier, to avoid misclassification related to pseudo resistance or measurement limitations. In carefully selected patients with documented sympathetic overactivity, renal denervation may provide additional and sustained blood pressure reduction, although its role should continue to be guided by evolving clinical evidence and long term safety data. Overcoming diagnostic limitations, therapeutic inertia, and persistent misconceptions is essential to improving outcomes. A multidisciplinary, patient-centered approach remains central to optimizing blood pressure control and mitigating the long-term burden of cardiovascular and renal complications in this high-risk population.

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