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Resistant Hypertension in Chronic Kidney Disease
A Burden unto Itself

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CKD has long been known to be a risk factor for hypertension. Hypertension occurs in 60%–90% of patients with CKD, with higher prevalence occurring in later stages of CKD (1). Elevated BP, in turn, can worsen CKD, creating a feedback loop in which both disorders may inexorably progress. The interrelationship between CKD and hypertension reflects a complex interplay of physiologic factors, including endothelial dysfunction, dysregulation of the sympathetic nervous system, and excessive sodium retention leading to volume overload (1). The resulting feedback loop contributes to a distinctly elevated risk of difficult-to-control or resistant hypertension among patients with CKD.

Resistant hypertension is defined as BP that remains uncontrolled despite the use of at least three antihypertensive agents with different mechanisms of action taken at the highest tolerated dose (which may or may not require the use of a diuretic depending on the guideline) or the need for four or more antihypertensive agents to achieve adequate BP control (2,3). Resistant hypertension occurs more commonly among patients with CKD than the general population. As guidelines recommend more stringent systolic BP goals among patients with CKD (*e.g.*, the 2021 Kidney Disease Improving Global Outcomes [KDIGO] guidelines' target of <120 mm Hg [4]), the disproportionate prevalence of resistant hypertension in our patients will continue to increase.

Resistant hypertension carries substantial risk, and there is a dose-response relationship of the number of antihypertensive agents required to achieve adequate BP control with adverse kidney and cardiovascular outcomes. In the Chronic Renal Insufficiency Cohort, participants with resistant hypertension had a 66% higher risk of heart failure and a 24% higher risk of mortality compared with those with BP controlled on fewer agents (5). In the same cohort, participants with refractory hypertension, defined as uncontrolled BP despite five antihypertensive agents, had a 73% greater risk of progression of kidney disease and up to a 2.7-fold higher risk of adverse cardiovascular events compared with those with resistant hypertension (6). Accordingly, identification and appropriate management of resistant hypertension in patients with CKD are of the utmost importance to mitigate undue adverse outcomes.

In this issue of *CJASN*, An *et al*. (7) provide an expansive analysis of the prevalence of resistant hypertension and patterns of antihypertensive medication use among patients with CKD in two large US electronic health record–based cohorts: Kaiser Permanente of Southern California (KPSC; from 2014 to 2015) and the Veterans Health Administration (VHA; from 2018). More precisely, the authors evaluated the prevalence of apparent treatment-resistant hypertension—"apparent" due to frequent pseudoresistance, with the diagnosis of resistant hypertension limited by uncertain medication dosing and adherence as well as by suboptimal BP measurements inherent in any electronic health record–based study. Distinct from prior publications that evaluated the prevalence of resistant hypertension in CKD, which often used a BP threshold of <140/90 mm Hg to define resistant hypertension, the authors applied CKD-specific thresholds from recent guidelines (*i.e.*, the 2017 American College of Cardiology [ACC]/American Heart Association [AHA] BP threshold of <130/80 mm Hg and the KDIGO systolic BP threshold of <120 mm Hg).

Upon applying the ACC/AHA diagnostic BP threshold of <130/80 mm Hg, An *et al*. (7) observed that 39% of patients with CKD in KPSC had apparent treatment-resistant hypertension (28% were uncontrolled; *i.e.*, they met criteria for apparent treatment-resistant hypertension with their BP above the threshold for hypertension) and that 35% of patients with CKD in VHA had apparent treatment-resistant hypertension (29% were uncontrolled) (7). Applying the KDIGO target systolic BP threshold of <120 mm Hg, 48% of patients with CKD in KPSC and 55% of patients with CKD in VHA had apparent treatment-resistant hypertension. Similar to what is generally seen in patients with nonresistant hypertension, the prevalence of apparent treatment-resistant hypertension was higher among more advanced stages of CKD compared with earlier stages. Among patients with CKD stage 3a, 34% had apparent treatment-resistant hypertension in KPSC and 33% had apparent treatment-resistant hypertension in VHA. Alternatively, among patients with CKD stage 5, 60% had apparent treatment-resistant hypertension in KPSC and 37% had apparent treatment-resistant hypertension in VHA.

Interestingly, An *et al*. (7) observed that the most frequent antihypertensive medications prescribed in

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both cohorts were renin-angiotensin system inhibitors and β-blockers. Although β-blockers were prescribed in 76% of patients with apparent treatment-resistant hypertension in KPSC and 69% of patients in VHA, thiazide/thiazide-like diuretics were only prescribed in 45% of patients in KPSC and 30% of patients in VHA, and mineralocorticoid receptor antagonists were only prescribed in 8% of patients in both KPSC and VHA. Patients with controlled apparent treatment-resistant hypertension were more likely to be on thiazide/thiazide-like diuretics or mineralocorticoid receptor antagonists than those with uncontrolled apparent treatment-resistant hypertension.

The study is strengthened by its broad generalizability to real-world populations of patients with CKD and hypertension by the use of electronic health record–derived data obtained during routine outpatient care across two distinct health care systems. Limitations of the study include the risk of misclassification of resistant hypertension due to (*1*) inadequate BP measurement, (*2*) the inability to derive whether participants were on optimally tolerated doses of medications, and (*3*) the inability to confirm medication adherence by directly measuring antihypertensive medication levels in the serum or directly observing administration of therapy. Additionally, patients may have been treated with medications for common indications other than hypertension (*e.g.*, use of a renin-angiotensin inhibitor for proteinuria or heart failure, a β-blocker for atrial fibrillation or management after a myocardial infarction, or a diuretic for heart failure), which could further result in erroneous classification of resistant hypertension, particularly among those who met criteria by being on four or more agents but had well-controlled BPs.

In clinical practice, resistant hypertension engenders major diagnostic and therapeutic challenges. Nonadherence occurs in 50%–80% of patients with apparent treatment-resistant hypertension, likely driven by complex antihypertensive regimens and the desire to avoid medication side effects (*e.g.*, urinary frequency from diuretics) (2,8). Difficulty obtaining accurate and representative BP readings further complicates diagnosis and management of resistant hypertension, resulting in both over- and undertreatment. Routine clinic BPs are subject to the "white coat effect" and inappropriate technique. Guidelines recommending repeated BP readings obtained on an empty bladder using appropriate positioning after 5 minutes of rest are seldom followed. The authors of this study reported that providers in the KPSC and VHA health systems are instructed to measure BP using standardized approaches (7). However, this is not representative of usual patient care in the community. Accordingly, nephrology clinics are well overdue to transform our expectations of BP measurement during routine patient care. Standardized office BP measurement using an automated office BP device with appropriate technique is feasible to implement and is necessary in order to apply BP treatment thresholds safely and appropriately (8). Furthermore, ambulatory and home BP monitoring are underutilized tools that offer an even greater opportunity for accurate, highly prognostic readings outside of the clinic setting (3).

Clinician inertia and nonevidence-based prescribing practices are also important factors contributing to the high prevalence and inadequate management of resistant hypertension in patients with CKD. The authors of this study observed that the majority of patients with apparent treatment-resistant hypertension had uncontrolled BPs (7), which is likely at least in part due to inadequate escalation of therapy. Furthermore, antihypertensive prescribing patterns in both cohorts leaned heavily on the use of β-blockers in patients with apparent treatment-resistant hypertension, with much less frequent use of thiazide/thiazide-like diuretics and very few patients treated with mineralocorticoid receptor antagonists (7). These findings are similar to our prior work evaluating patients without CKD with apparent treatment-resistant hypertension in VHA (9). We observed that only 14% of patients with new-onset apparent treatment-resistant hypertension were ever treated with mineralocorticoid receptor antagonists over a 20-year period, whereas 64% were treated with β-blockers at the time of diagnosis with apparent treatment-resistant hypertension. These findings demonstrate prescribing practices in opposition to guidelines for the treatment of resistant hypertension, which recommend optimizing diuretic therapy and adding mineralocorticoid receptor antagonists prior to β-blockers on the basis of high-quality evidence (2,3). Although the risk of hyperkalemia was historically a reasonable barrier to using mineralocorticoid receptor antagonists in patients with resistant hypertension and CKD, this should be less of a deterrent as safe and tolerable potassium binders are increasingly available. Furthermore, recent randomized controlled trial evidence supports greater adoption of thiazide-like diuretics in patients with advanced CKD (with or without loop diuretics), which can have a substantial effect on difficult-to-control BPs in these patients (10).

In conclusion, the study by An *et al*. (7) highlights the growing prevalence of apparent treatment-resistant hypertension among patients with CKD and the need for much greater attention to distinguishing these patients from those with nonresistant hypertension. Our current approach to the diagnosis and management of resistant hypertension in patients with CKD represents an alarming gap in adherence to best practices. The enormous burden of resistant hypertension in CKD underscores the need for improved BP measurement and wider implementation of existing evidence-based treatment as well as novel therapeutic regimens specific to the pathophysiology of patients with CKD.

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Author Contributions

J.B. Cohen and R. Shulman wrote the original draft and reviewed and edited the manuscript.

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