Reconsidering α-Blockade for the Management of Hypertension in Patients With CKD

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Between 60% and 90% of individuals with chronic kidney disease (CKD) have hypertension, with a higher prevalence of hypertension as kidney function worsens. Compared with the general population, a disproportionate number of patients with CKD have treatment-resistant hypertension (elevated blood pressure despite treatment with at least 3 antihypertensives or requiring a fourth medication to achieve blood pressure control) and refractory hypertension (uncontrolled hypertension receiving ≥5 antihypertensives). Thus, patients with CKD often require multiple classes of medications to control their hypertension, though frequently have restricted options due to elevated risk for adverse effects. Most commonly, patients with advanced CKD are susceptible to hyperkalemia, limiting the use of renin-angiotensin-aldosterone system–inhibiting medications as kidney disease progresses and potentially requiring the use of third- or fourth-line agents. The distinctive challenges of treating hypertension in patients with CKD merit a better understanding of the risks and benefits associated with less commonly used antihypertensive agents, such as α-blockers, in this patient population.

In this issue of AJKD, Hundemer et al investigate the association of α-blockade with clinical outcomes (progression of CKD, cardiovascular events, and mortality) and safety events typically attributed to this class of antihypertensives (hospitalization for hypotension, syncope, falls, and fractures) across CKD stages. The authors leveraged robust province-wide clinical and prescription-dispensing data for all Ontario residents 66 years and older. During a maximum of 3 years of follow-up, they observed that initiation of α-blockade was associated with an 8% lower risk of cardiovascular events (hazard ratio [HR], 0.92; 95% CI, 0.89-0.95), 11% lower risk of death (HR, 0.89; 95% CI, 0.84-0.94), 14% higher risk of ≥30% decline in estimated glomerular filtration rate (eGFR; HR, 1.14; 95% CI, 1.08-1.21), and 28% higher risk of kidney failure requiring replacement therapy (HR, 1.28; 95% CI, 1.13-1.44) compared with initiation of non–α-blocking antihypertensives. In subgroup analyses, the lower risk of death was present only among patients with CKD, and patients with an eGFR < 30 mL/min/1.73 m² had the lowest risk of death when treated with α-blockade compared with non–α-blocking antihypertensives (HR, 0.71; 95% CI, 0.64-0.80). The results were similar across several sensitivity analyses, including upon restricting the cohort to individuals not on monotherapy, receiving 3 to 4 antihypertensives, or without prior cardiac disease. With regard to safety events, use of α-blockade was associated with elevated risk of hospitalization for syncope (among all participants) and hypotension (among those with higher eGFR).

The current study is strengthened by the authors’ approach to addressing confounding using high dimensional propensity score matching. Propensity score matching is an increasingly popular approach to addressing confounding in cohort studies. In standard propensity score matching, a score is calculated based on the likelihood of study participants to be in either exposure group. The score is then applied to generate a matched cohort that balances known clinical characteristics across exposure groups. This approach can be a helpful way to address measured (or known) confounders by indication for initiating different pharmacologic agents, such as when discrete clinical indications exist to select one agent over another. Despite clear benefits for addressing confounding, all matching approaches are prone to important limitations and misspecifications. Standard propensity score matching is particularly susceptible to inadequate matching, which can result in imbalance of some covariates across exposure groups. It is also susceptible to bias due to difficult-to-anticipate effects of investigator-selected covariates on the identification of matched pairs, which can result in inadvertently excluding participants with certain risk profiles, thus reducing the generalizability of the resulting cohort. In the current study, Hundemer et al used high dimensional propensity score matching, a data-driven approach to deriving a large number of potential covariates (in this instance, 207 covariates) for inclusion in propensity score models. Due to its multitiered empirical approach, high dimensional propensity score matching can help to overcome some of the biases and inadequate matching that can occur using more standard covariate selection approaches. Nonetheless, high dimensional propensity score matching is still susceptible to many of the methodologic misspecifications that can occur with any matching approach. Although some authors propose that high dimensional propensity score matching can overcome unmeasured confounding in retrospective cohort studies, this has not been adequately substantiated. This study provides unique insights into the management of hypertension in CKD, given that large-scale trials evaluating the safety and cardiovascular effectiveness of α-blockers (ie, ALLHAT and ASCOT) excluded patients with clinically significant CKD. ALLHAT and ASCOT demonstrated poor cardiac outcomes with α-blockers; however, several observational studies have shown the...
contrary. For example, in a propensity score–matched cohort study of US veterans with heart failure, in which 13% to 14% of patients had moderate to severe CKD, α-blocker use was associated with fewer heart failure admissions. Additionally, higher nonselective α-blockade doses and lower eGFR were both associated with lower mortality risk. Kidney outcomes were not assessed.

The physiologic basis for lower cardiovascular risk with α-blockade may be explained by inhibition of part of the neurohormonal activation pathway that promotes the development and progression of heart failure. In COMET, carvedilol was superior to metoprolol in reducing all-cause mortality in patients with chronic heart failure. The partial α-blocking effect of carvedilol may prevent cardiac remodeling by reducing systemic vascular resistance. Furthermore, α-blockers have been associated with improvement in lipid profiles and insulin resistance, which may mediate cardiovascular risk reduction. Regarding the higher risk for CKD progression among those who received α-blockers, the current study and a prior study published by the same authors demonstrated a higher incidence of hospitalizations for hypotension and syncope in older patients using α-blockers compared with other antihypertensive agents. This risk of hypotension may be the basis of progression of CKD. Low blood pressures can reduce afterload and prevent cardiac remodeling over time but can also result in kidney hypoperfusion, particularly in patients with stiffer vasculature (eg, those with underlying CKD). However, the authors’ prior and current studies were limited by a lack of blood pressure data. Hypotension was defined using diagnostic codes from inpatient hospitalizations in both studies. Thus, clinically significant hypotension and orthostasis not resulting in hospitalization would have been missed. That said, α-blockers are often well-tolerated in the general population. The “first-dose effect,” which can cause sudden severe symptomatic orthostatic hypotension, may be bypassed by using the extended-release dosage formulation and bedtime dosing.

In summary, this study from Hundermer et al sheds light on the potential cardiovascular benefit of α-blockers for the treatment of hypertension in older adults with CKD, balanced with elevated risk of CKD progression. The methodologic approach strengthens the authors’ conclusions about these relationships but cannot overcome unmeasured confounding. Lack of access to information on blood pressure control highlights the importance of future mechanistic investigations into these relationships, as outpatient hypotension could contribute to the observed outcomes. As nephrologists, we are hyperaware that cardiovascular diseases are the number 1 cause of mortality in patients with CKD. If these agents might mitigate that risk, perhaps we should give them stronger consideration when grasping for add-on therapies for the treatment of hypertension in our patients.

### Article Information

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### References


