Inhibitors of the renin-angiotensin-aldosterone system (RAAS) prescribed at maximally tolerated doses are a critical part of clinical practice guidelines for management of patients with chronic kidney disease (CKD), congestive heart failure with reduced ejection fraction, and a recent myocardial infarction. These drugs interfere with the hormonal system regulating kidney excretion of potassium and commonly cause hyperkalemia. Patients at greatest risk for this complication are those with CKD who commonly have diabetes and/or coexisting cardiovascular disease. Development of hyperkalemia poses a therapeutic dilemma, since these patients derive the greatest benefit with respect to cardiovascular disease and progression of CKD.

Common management strategies to address hyperkalemia are to either down-titrate the dose or discontinue RAAS inhibitors altogether. In a retrospective analysis of a large database, development of hyperkalemia led to discontinuation in 30% and down-titration in 50% of those receiving submaximal and maximal doses of RAAS inhibitors, respectively. This approach of discontinuation or dose reduction was associated with more rapid progression of CKD, cardiovascular events, and mortality than patients receiving maximally tolerated doses. These data highlight challenges clinicians face as they balance the risk of hyperkalemia and benefits of RAAS inhibitors in patients with underlying cardiovascular disease.

In this issue of AJKD, Leon et al provide data directly relevant to this challenge. In a retrospective cohort study of 2 separate populations in Canada, the authors examined the association between discontinuing RAAS inhibitors in response to development of hyperkalemia and all-cause mortality as a primary outcome. Secondary outcomes included cardiovascular mortality, fatal and nonfatal cardiovascular events, and dialysis initiation. The mean potassium concentration was 5.7–5.8 mEq/L and estimated glomerular filtration rate (eGFR) was 41 mL/min/1.73 m² in each group. Discontinuation of RAAS inhibitors was associated with higher all-cause mortality, higher cardiovascular mortality, and increased risk of dialysis initiation. Submaximal doses of RAAS inhibitors were associated with lower risk of all-cause and cardiovascular mortality when compared to discontinuation of therapy; however, those receiving maximal doses of RAAS inhibitors had the highest survival benefit. The uniformity of data in 2 separate cohorts strongly supports maintaining RAAS inhibitors at maximally tolerated doses after an episode of hyperkalemia whenever possible.

Clinicians should assess baseline risks and consider more frequent monitoring when trying to narrow the gap between guideline-based recommendations for optimization of RAAS inhibitors and changes in practice patterns following development of hyperkalemia. In both Canadian cohorts, lower eGFR was commonly present in those who discontinued therapy. In general, hyperkalemia is uncommon in CKD until the eGFR falls below 15-20 mL/min/1.73 m². Amplification of the basolateral membrane area, increases in adenosine triphosphatase sodium/potassium pump activity, increased sodium delivery, and apical sodium transport in the distal nephron are all adaptive changes leading to increased capacity for potassium secretion. Changes in serum potassium concentration and mineralocorticoids independently mediate these adaptive structural and functional changes, which occur as kidney function declines.

Development of hyperkalemia with more modest reductions in eGFR occurs with superimposed decreases in distal sodium delivery (decompensated congestive heart failure), direct injury to the distal nephron (tubulointerstitial disease), and abnormalities of the renin-angiotensin-aldosterone cascade. More than 50% of the participants in the study by Leon et al had diabetes mellitus, a concurrent medical condition where hyporeninemic hypoaldosteronism is common and hyperkalemia is an early occurrence, often with eGFRs ranging from 20 to 60 mL/min/1.73 m². Decreased mineralocorticoid levels commonly result from reduced plasma renin and angiotensin II activity. However, plasma renin may be normal or even increased, yet aldosterone remain low secondary to a postreceptor defect specific to angiotensin II in zona glomerulosa cells. Decreased prostaglandin production can impair both renin release and interfere in the stimulatory effect of angiotensin II on release of aldosterone in the adrenal gland. Increased levels of natriuretic peptides secondary to volume expansion also exert inhibitory effects on both renin and aldosterone release and contribute to hyporeninemic hypoaldosteronism in patients with diabetes mellitus.

Another factor in those discontinuing therapy was age ≥72 years. Reduced mineralocorticoid activity is common in elderly patients owing to an age-related decline in release of renin and aldosterone combined with an increasing prevalence of comorbidities that impair kidney potassium secretion. Additionally, in those who
discontinued RAAS inhibitor therapy, a higher baseline serum potassium was present. Although age and eGFR are not modifiable, strategies are available to minimize the increase in potassium concentration associated with RAAS inhibitors use. Reviewing the patient’s medication profile and discontinuing medications impairing kidney potassium excretion is recommended. Although no differences were noted in those who continued or discontinued RAAS inhibitor therapy, a small percentage of both cohorts were taking drugs that interfere in kidney potassium excretion. Approximately 5%-10% of patients were taking nonsteroidal anti-inflammatory drugs, which—in addition to interfering in renin and aldosterone release through inhibition of prostaglandin synthesis, as noted previously—predispose to hyperkalemia by augmenting sodium reabsorption, thereby decreasing delivery to the distal nephron. Additionally, nearly half of patients were taking β-blockers. In the absence of a specific indication, a substitute agent is preferred, since these drugs lower plasma renin levels by interfering in the stimulatory effect of sympathetic nerves on juxtaglomerular cells. In addition, these drugs can exacerbate exercise and fasting-related hyperkalemia in CKD patients owing to unopposed α-adrenergic receptor stimulation caused by increased sympathetic outflow signaled by afferent nerve activity originating in the diseased kidneys.

Also noteworthy, nearly 5% of the patients in one cohort were taking potassium supplements. Salt substitutes and herbal remedies can be a hidden source of dietary potassium. Restricting dietary potassium is often prescribed following hyperkalemia, but this strategy creates a dilemma like that encountered when using suboptimal doses of RAAS inhibitors. Diets incorporating potassium-rich foods are rich sources of vitamins, minerals, and fiber, which provide multiple health benefits. Potassium-rich foods facilitate reductions in blood pressure, reduce risks for cardiovascular disease and stroke, mitigate the degree of metabolic acidosis, and slow CKD progression. Despite these health benefits, when patients present with hyperkalemia, clinicians reflexively counsel patients to avoid foods high in potassium. Instead, ensuring effective diuretic therapy and correcting metabolic acidosis, or prescribing one of the newer potassium-binding agents (patiromer or sodium zirconium cyclosilicate), may be better options. These drugs facilitate guideline-recommended doses of RAAS inhibitors in patients previously limited by development of hyperkalemia and potentially allow for liberalization of potassium in the diet.

When hyperkalemia develops in the setting of RAAS inhibitor therapy containing spironolactone, one may consider substitution with finerenone. Finerenone is a nonsteroidal mineralocorticoid receptor antagonist with a half-life of 2-3 hours in CKD patients. By contrast, spironolactone is a prodrug with biologically active metabolites possessing long half-lives and detectable in the urine several weeks after stopping therapy. Differences between these drugs are associated with less development of hyperkalemia when directly compared. Additional data suggest the frequency of hyperkalemia with RAAS inhibitors is reduced in the setting of sodium/glucose cotransporter 2 (SGLT2) inhibitors. Given the different mechanisms of action and the proven cardiovascular benefits of SGLT2 inhibitors, one could speculate combination therapy of inhibitors of RAAS and SGLT2 may facilitate using lower doses of RAAS inhibitors, thereby reducing the risk of hyperkalemia while preserving cardiovascular benefits.

In conclusion, this study demonstrates that maintaining optimal RAAS inhibitor dosing even in the setting of mild-to-moderate hyperkalemia is associated with reduced morbidity and mortality. Clinicians are encouraged to find alternative methods to reduce hyperkalemia should it become a limiting factor. Determining if medications can be changed if they precipitate hyperkalemia as well as considering novel drug combinations are excellent initial suggestions to manage hyperkalemia while preserving the health benefits of RAAS inhibitor usage.

Article Information
Authors’ Full Names and Academic Degrees: Biff F. Palmer, MD, and Deborah J. Clegg, PhD.
Authors’ Affiliations: Department of Medicine, Division of Nephrology, University of Texas Southwestern Medical Center, Dallas, Texas (BFP), and Texas Tech Health Sciences Center, El Paso, Texas (DJC).
Address for Correspondence: Biff F. Palmer, MD, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390. Email: biff.palmer@utsouthwestern.edu
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