Real-World Associations Between Renin-Angiotensin-Aldosterone System Inhibition Therapy, Hyperkalemia, and Outcomes: A Clinical and Scientific Call to Action

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In this issue of the Journal of the American Heart Association (JAHA), Linde and colleagues have further expanded the growing and compelling data demonstrating the cardiovascular and mortality benefits of adherence to guideline-recommended doses of renin-angiotensin-aldosterone system inhibition (RAASI) therapy. Although this is a retrospective review, the patient population in this study is robust with more than 191,000 chronic kidney disease (CKD) and 21,000 congestive heart failure (CHF) patients. Remarkably, the authors note on more than one occasion that the recommended dosing for the CKD patients was derived from CHF recommendations, given that there are no current guidelines for CKD management. Of note, the mean duration of RAASI withdrawal for hyperkalemia in CKD and CHF exceeded 867 and 690 days, respectively!

The authors focus on the difficulty in maintaining adherence to RAASI, namely, that hyperkalemia remains a barrier to maintenance of optimal dosing of RAASI. As such, it is important that we review and highlight the complex relationships between mortality and hyperkalemia, algorithms for appropriate circulatory potassium level monitoring, and consider the currently available treatments for managing hyperkalemia that allows for optimal RAASI. Finally, it is important to highlight potential future research programs aimed at strategies to maintain normokalemia in order to achieve and maintain optimal RAASI dosing.

Mortality and Hyperkalemia: Complex Relationships

The benefits of adherence to RAASI therapy in patients with CKD and CHF are profound. Therapy with RAASI reduces all-cause mortality in patients with CHF with reduced ejection fraction. In the management of CKD, RAASI use has been shown to reduce proteinuria and slow estimated glomerular filtration rate decline. However, because of RAASI mechanisms of action through either reduction in aldosterone production or inhibition of aldosterone activity, RAASI use increases the risk for the development of hyperkalemia. In the setting of CKD and CHF without RAASI, hyperkalemia can also occur, particularly during acute reduction in kidney function or when acute changes in dietary potassium take place. Given the life-threatening nature of hyperkalemia, this is a significant component of management in these complicated patients. With the overarching concern for patient safety as it relates to hyperkalemia, stopping RAASI tends to receive more attention than timely restarting of RAASI medications in these vulnerable patient populations.

In CKD, urinary potassium excretion is reduced as estimated glomerular filtration rate declines. In patients with normal kidney function, 90% of dietary potassium is excreted by the kidney. In contrast in individuals with advanced CKD, the kidney excretes only 70% with the remainder being excreted by the gastrointestinal tract. Despite reduction in total body potassium in patients with advanced CKD, internal homeostasis of potassium becomes dysregulated in a variety of conditions that are also present in many CKD and CHF patients, increasing the risk of hyperkalemia. Most significant, diabetes mellitus, particularly insulin requiring, can result in larger fluctuations in serum potassium concentration because of poor intracellular potassium uptake in the absence of insulin. In CHF, decreased effective arterial blood volume promotes proximal tubular sodium reabsorption, which will decrease sodium delivery to the distal tubules and impair the secretion of potassium. Although aldosterone is the key regulator of external potassium homeostasis and urinary potassium excretion, in decompensated CHF where effective arterial blood volume is significantly reduced, the prerenal state and avid sodium retention results in inadequate distal sodium delivery to exchange with potassium. Although increases in
serum creatinine consistent with prerenal azotemia can occur in this setting, no change in serum creatinine is required for inadequate sodium–potassium exchange distally.

Importantly, hyper- and hypokalemia have been shown to independently contribute to mortality in several observational studies. Collins and colleagues published data in 2017 from >900 000 patients demonstrating that all-cause mortality continuously increased with potassium values above or below the 4.0 to 5.0 mEq/L range. As well, in a large meta-analysis of population-based evaluations of dietary sodium and potassium intake, reduced potassium intake associates significantly with patient mortality. With all of these concerns, how do we rectify the competing risks and benefits of RAASi therapy and hyperkalemia in CHF and CKD patients?

Clinical Approach for Monitoring

First, appropriate monitoring of patients at the initiation and shortly after the commencement of therapy with RAASi is critical. Careful monitoring and cautious dose adjustment are absolutely essential to successfully maintain high-risk patients on maximal RAASi therapy.

Before starting or changing RAASI dose, it is necessary to completely review prescribed (eg, trimethoprim or β-blockers, both shown to increase serum potassium) and over-the-counter medications (such as nonsteroidal anti-inflammatory agents), in addition to assessing intravascular volume status. Having an accurate assessment of the patient’s ideal weight is helpful in this regard. Patients significantly lower than their target body weight may already be sodium avid and not provide the distal sodium delivery needed to support potassium excretion. Patients who are significantly greater than their target body weight may have cardiac decompensation, which will reduce renal blood flow, activate the RAAS, and reduce distal sodium delivery. It is important to avoid starting or increasing RAASI dose until patients are optimized with regard to intravascular volume, with stable kidney function, and when other medications that increase serum potassium have been stopped or reduced as much as possible. Clearly starting RAASI in the setting of hyperkalemia is not advisable. Repeat laboratory testing 10 to 14 days after delaying or after starting or changing RAASI dose is important and should include close monitoring once a stable RAASI dose is achieved. The intervals for monitoring should be tailored to the patient’s history and comorbidities but at a minimum at least every 4 months.

Strategies for Potassium Lowering

When hyperkalemia is identified, it should be treated, and all attempts should be made to maintain RAASI dosing quickly if normokalemia can be achieved with these strategies. When RAASI is withheld for acute management of hyperkalemia, attention to resuming the medication must be maintained. If a source of hyperkalemia is clearly identified and treated, RAASI should be resumed within as early as 72 hours.

Medication reconciliation and discontinuation or reduction of medications known to cause hyperkalemia is a key initial management step. Nonsteroidal anti-inflammatories, trimethoprim, pentamidine, azole antifungals, and heparin have all been associated with hyperkalemia and should be discontinued if possible.

Reduction in dietary potassium intake can also be extremely helpful. In advanced CKD stage 4 (estimated glomerular filtration rate between 30 and 15 mL/min) or stage 5 (estimated glomerular filtration rate <15 mL/min) populations, the recommendation is to restrict potassium intake to <2.4 g/d. Support from dietitians who understand foods rich in potassium (citrus fruits, melons, spinach, kale, seaweed, kelp, figs, and avocado, for example) are an important support mechanism. They also have experience in identifying high-risk salt substitutes that should be avoided. While many of these foods are featured heavily in dietary approaches for improving cardiovascular health in patients with normal kidney and cardiac function such as the DASH diet used for blood pressure control, in these more ill patients with CHF and CKD, these approaches no longer can be used.

Loop and thiazide diuretics are both potent when it comes to potassium lowering. Diuretics act to increase delivery of fluid and sodium to the distal nephron, which both stimulate potassium secretion. Furthermore, the volume contraction caused by diuretics serves to increase circulating aldosterone levels, and high aldosterone levels also promote potassium secretion in the distal nephron. Long-term volume contraction may not be desirable for all patients, so close monitoring of renal function and intravascular volume status must be in place when these medications are prescribed.

Fludrocortisone for patients with aldosterone deficiency (as seen in many patients with CKD) and sodium bicarbonate for patients with metabolic acidosis can both help to prevent recurrent hyperkalemia. Use in the broader population, and particularly in the CHF population because of propensity for the medications to cause volume expansion, is unclear at this time.

Recently, 2 new oral potassium-binding agents have been developed and approved for physician use. In 2015, the US Food and Drug Administration approved patiromer, a polymer that exchanges potassium for calcium, as a therapy for management of hyperkalemia. In the past year, the US Food and Drug Administration approved sodium zirconium cyclosilicate, a polymer that exchanges potassium for sodium and hydrogen, as a therapy for management of hyperkalemia.
Both have been shown to be safe and effective for long-term management of hyperkalemia. They have not been shown to cause bowel necrosis as older agents have and are seen to be much more tolerable in terms of gastrointestinal side effects such as diarrhea. Additionally, there are small pilot data demonstrating that over a 4-week period in a group of CHF patients, patiromer use allowed for continued spironolactone use.\textsuperscript{10} Cost and need to time hours away from administration of other oral medications remain limitations.

**Future Directions**

We propose that if normokalemia with serum potassium $\geq 5.0$ mEq/L can be achieved with diet and drug modifications, treatment with optimal and maximal RAASi dosing should be continued. Compelling modeling data from Evans and colleagues demonstrate that the treatment of hyperkalemia that allows for continued RAASi use leads to longer life expectancy, delayed progression to end-stage renal disease, quality-adjusted life year gains, and cost savings in CKD populations.\textsuperscript{11}

The available data do not yet provide conclusive evidence of the potential impact on maintaining normokalemia with potassium binders to allow for RAASi use. We need further clinical studies of patients with CHF and advanced CKD taking chronic RAASi in order to evaluate the safety and tolerability with long-term use of potassium binders for the maintenance of normokalemia.

**Disclosures**

None.

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