Renal Consult

Renal Consult is edited by **Jane S. Davis, CRNP, DNP,** a member of the *Clinician Reviews* editorial board, who is a nurse practitioner in the Division of Nephrology at the University of Alabama at Birmingham and is the communications chairperson for the National Kidney Foundation's Council of Advanced Practitioners (NKF-CAP); and **Kim Zuber, PA-C, MSPS, DFAAPA,** a semi-retired PA who works with the American Academy of Nephrology PAs and is a past chair of the NKF-CAP. This month's responses were authored by **Cynthia Smith, DNP, CNN-NP, APRN, FNP-BC,** who practices at Renal Consultants, PLLC, in South Charleston, West Virginia, **Rebecca V. Rokosky, MSN, APRN, FNP-BC,** who is Sub Investigator in the Clinical Advancement Center, PPLC, in San Antonio, Texas, and **Shannon M. Rice, MS, PA-C,** who is in the Division of Nephrology and Hypertension, Department of Medicine, at the University of California, San Diego.

New Drugs to Treat Hyperkalemia

Q I have heard talk about the development of new drugs to treat hyperkalemia. What is the status of these?

Hyperkalemia is a commonly seen electrolyte imbalance in clinical practice. Risks associated with moderate-to-severe hyperkalemia include potentially fatal cardiac conduction abnormalities/arrhythmias, making identification and management critical. An in-depth discussion of hyperkalemia diagnosis can be found in our March 2017 CE/CME activity (2017;27[3]:40-49).

Risk factors for hyperkalemia include excess intake or supplementation of potassium, type 2 diabetes, liver cirrhosis, congestive heart failure (CHF), and chronic kidney disease (CKD). The kidneys excrete 90% to 95% of ingested potassium, and the gut excretes the rest. Normal kidneys take six to 12 hours to excrete an acute potassium load. As kidney function decreases, risk for hyperkalemia increases.[1] Hyperkalemia rates as high as 26% have been observed in patients with CKD stages 3 to 5 (glomerular filtration rate [GFR], < 60 mL/min).[2]

> RAAS therapy plays an important role in CKD management—but hyperkalemia can necessitate a dose reduction or discontinuation.

Renin-angiotensin-aldosterone system (RAAS) inhibitors—including ACE inhibitors (ACEis), angiotensin-receptor blockers, and aldosterone agonists—are associated with hyperkalemia. While RAAS therapy can play an important role in the management of CKD and cardiovascular disease (CVD), the development of hyperkalemia can necessitate a dose reduction or discontinuation of these medications, limiting their therapeutic benefit. Other medications that elevate risk for hyperkalemia include NSAIDs, heparin, cyclosporine, amiloride, triamterene, and nonselective ß-blockers.[1]

Therapeutic options for nonurgent treatment of hyperkalemia are limited. In addition to reducing or discontinuing associated medications, strategies include use of diuretics (as appropriate), treatment of metabolic acidosis, and dietary restrictions (ie, limiting high-potassium foods).[1] Pharmacologically, there has been one (less than ideal) option—until recently.

Sodium polystyrene sulfonate (SPS), an ion-exchange resin approved in 1958, can be used to treat hyperkalemia.[3] It comes in an enema and an oral form; the former has a faster onset, but the latter is more effective, with an onset of action of one to two hours and a duration of four to six hours.[1] However, each gram of SPS contains 100 g of sodium, and the typical dose of SPS is 15 g to 60 g.[4] The resulting increase in sodium load can be a concern for patients with CHF, severe hypertension, or severe edema.[5]

Data from randomized controlled trials (RCTs) are limited; however, one double-blind RCT investigated the effect of SPS on 33 patients with CKD and mild-to-moderate hyperkalemia (potassium level, 5 mEq/L to 5.9 mEq/L). The researchers found that patients who took 30 g/d of SPS for seven days experienced a 73% reduction in serum potassium, compared with a 38% reduction in patients who took a placebo. Of note, more gastrointestinal issues were observed in the SPS group.[6]

Additionally, a retrospective chart review of 14 patients with CKD and heart disease found low-dose SPS to be safe and effective when used as a secondary measure for hyperkalemia prevention in those taking RAAS therapy.[7] However, a systematic review found that SPS use with and without

concurrent sorbitol may be associated with serious and fatal gastrointestinal injuries.[8] In 2011, the FDA issued a black box warning regarding increased risk for intestinal necrosis when SPS is used with sorbitol.[9] In 2015, the FDA recommended separating SPS from other oral medications by at least six hours, due to its potential to bind with other medications.[10]

Patiromer, a new potassium binder, was approved by the FDA in 2015. This sodium-free, nonabsorbed, spherical polymer uses calcium as the exchange cation to bind potassium in the gastrointestinal tract. Its onset of action is seven hours, with a 24-hour duration of action. It is not approved for emergency use. There are no renal dosing adjustment considerations with patiromer.

In RCTs, patiromer has been associated with a significant reduction in serum potassium in patients with CKD (with or without diabetes) taking RAAS therapy. The starting dose is 8.4 g/d mixed with water, taken with food; this can be increased by 8.4 g each week as needed, to a maximum dosage of 25.2 g/d. Patiromer binds between 8.5 mEq to 8.8 mEq of potassium per gram of polymer.

The original approval included a black box warning to take patiromer six hours before and after other medications, due to concern for binding with certain medications. However, after an additional study in 2016, the FDA removed this warning and approved a change in administration to three hours before and after taking other medications.

Use of patiromer is not advised in those with severe constipation, bowel obstruction/impaction, or allergies to any of its components.[11] Adverse reactions associated with patiromer include constipation (which generally improves with time), hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence. A 52-week RCT of 304 patients with CKD on RAAS found the most common adverse event to be mild-to-moderate constipation (6.3% of patients), with two patients discontinuing therapy as a result.[4] In clinical trials, 9% of patients developed hypomagnesemia (serum magnesium value, < 1.4 mg/dL). It is recommended that serum magnesium levels be monitored and supplementation offered, when appropriate.[11]

Sodium zirconium cyclosilicate (ZS-9) is among the potassium-lowering medications on the horizon. In 2016, the FDA accepted a new drug application for this insoluble, unabsorbed cation exchanger that also works in the GI tract and uses sodium and hydrogen as exchange cations.[12]

For now, however, dietary education remains a mainstay of treatment for patients with elevated serum potassium levels. It is particularly important to inform your patients that many salt substitutes and low-sodium products contain potassium chloride. They should therefore exercise caution when incorporating sodium-reducing components into their diet. **—CS**

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National Kidney Foundation™

The National Kidney Foundation Council of Advanced Practitioners' (NKF-CAP) mission is to serve as an advisory resource for the NKF, nurse practitioners, physician assistants, clinical nurse specialists, and the community in advancing the care, treatment, and education of patients with kidney disease and their families. CAP is an advocate for professional development, research, and health policies that impact the delivery of patient care and professional practice. For more information on NKF-CAP, visit **www.kidney.org/CAP**.

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When to Discontinue RAAS Therapy in CKD Patients

Q A speaker at a meeting I attended said that ACEis/ARBs can be used in all stages of CKD. But locally, our nephrologists discontinue use when the GFR falls below 20 mL/min. Who is correct?

Definitive data on whether to continue use of ACE inhibitors (ACEis) and angiotensin-II receptor blockers (ARBs) in patients with chronic kidney disease (CKD) is lacking.[1] At this time, it is difficult to prove that the renoprotective effects of renin-angiotensin-aldosterone system (RAAS) inhibitors are separate from their antihypertensive effects. Few studies have investigated the effects of RAAS therapy on patients with advanced CKD at baseline (CKD stage 4 or 5; glomerular filtration rate [GFR], < 30 mL/min).[2]

ACEis and ARBs are indicated for use in CKD patients with hypertension, proteinuria/albuminuria, heart failure with reduced ejection fraction, and left ventricle dysfunction post–myocardial infarction.[3] While these medications are the main pharmacologic therapy for reducing albuminuria in CKD patients, they increase serum creatinine by 20% to 30% and thereby decrease GFR.[2,4]

The decision to continue or discontinue ACEi/ARB use when patients reach CKD stage 4 or 5 is controversial. On one hand, risks associated with continuation include hyperkalemia, metabolic acidosis, and possible reduction in GFR. The decision to discontinue these medications may result in increased GFR, improved kidney function, and delayed onset of kidney failure or need for dialysis.[3,4] In a 2011 study examining outcomes in patients with stage 4 CKD two years after stopping their ACEis/ARBs, the researchers found that patients who were alive without renal replacement therapy were hypertensive but had the highest GFRs.[3]

On the other hand, ACEis/ARBs have been shown to reduce incidence of cardiovascular disease (CVD) in patients without CKD. It is widely known that patients with CKD have increased risk for CVD, though there is little data examining the effects of RAAS inhibitors on CVD in this population.[1] A recent study found a reduced risk for fatal CVD in peritoneal dialysis patients treated with ACEis.[5] Another study reported improved renal outcomes in nondiabetic patients with advanced CKD who were treated with ACEis.[6] The National Kidney Foundation/Kidney Disease Outcomes Quality Initiative *Clinical Practice Guidelines on Hypertension* currently state that with careful monitoring, most patients with advanced CKD can continue taking ACEis/ARBs.[7]

The decision to continue or discontinue ACE inhibitor/ARB use when patients reach CKD stage 4 or 5 is controversial.

More studies are needed to confidently close this controversial debate. Fortunately, the STOP-ACEi study, a three-year trial that began in 2014 in the UK, is examining the effects of ACEi/ARB use in patients with advanced CKD. It aims to determine whether discontinuation of ACEis/ARBs in these patients can help to stabilize or improve renal

function, compared to continued use. By maintaining good blood pressure control in these patients, the researchers hope to distinguish the antihypertensive effects from other potential benefits of the RAAS inhibitors.[2] The results of this trial may provide additional clarity for making decisions about ACEi/ARB treatment in our patients with advanced CKD. **—RVR, SMR** **CR**

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