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Individualized Management of Hyperkalemia: The Role of Potassium Binders in Patients With Cardiorenal Disease

Dr. Kelepouris:
Let's review some key insights also from Kidney Week 2025 in Houston, Texas, about managing our patients with hyperkalemia.

This is ReachMD, and I'm Dr. Ellie Kelepouris.

The issue is hyperkalemia versus RASi use, the catch-22 of managing diseases that benefit from RASi therapy. But as a consequence of RASi and the possibility of hyperkalemia, we tend to avoid or discontinue proven RASi therapies that have proven, really, to have renal protective and also cardiovascular protection, and that's the catch-22.

Hyperkalemia is a leading reason for not starting RASi blockade and the major reason for discontinuation of RASi in chronic kidney disease. The data are really incontrovertible, that 13% of patients who really should start RASi are not starting on RASi, and 66% of patients who really need RASi for renal and cardiovascular protection, RASi is stopped during their treatment because of the possibility and also because hyperkalemia ensues.

So treatment of hyperkalemia in patients on guideline-directed medical therapy with chronic kidney disease and heart failure have recently been updated by the European Society in 2025, along with the KDIGO guidelines in 2024 that are currently being reviewed. Guidelines recommend that RASi inhibition should be discontinued as a last resort because RASi blockade has proven to be beneficial both in cardiovascular mortality, hospitalization, CKD progression, and some new data on proteinuria reduction and reduction of NT-proBNP levels in patients with heart failure.

So what are the therapeutic agents for treatment of hyperkalemia in general and also particularly in patients who are being given RASi blockade agents for their renal protective and cardiovascular protective effects?

There are no prospective head-to-head studies being conducted among potassium binders, but there are 2 available oral potassium binders, which we use in clinical practice. The first is patiromer. The counterion to exchange for potassium in patiromer is a calcium. The second one is sodium zirconium cyclosilicate, and the counterion to exchange with potassium is sodium.

There's an important difference here. In the counterion calcium exchange for sodium with patiromer, there is no sodium delivered to the patient. There are some scattered cases of transient hypercalcemia, but no change in calcium balance has been reported.

With sodium zirconium cyclosilicate, the starting dose is 10 grams TID, and the maintenance dose really can be 10 grams a day, but the TID dose really has what we know now and what has been reported in the literature as a sodium signal.

What does that mean? That means that sodium delivery to the patient may lead to edema and also to exacerbations of heart failure in patients who are really at risk for heart failure.

As a result of these new findings with the sodium loading being implicated in the side effects of both edema and heart failure episodes resulting in hospitalization—so that's the important thing here. Taking care of patients, really, we have to be wary of causing hospitalizations in these patients. And in fact, to address this, the European Society and Australian and Japanese societies have added worsening heart failure as one of the side effects with sodium zirconium cyclosilicate use in their new guidelines in 2025.

We talked about sodium as being the counterion for potassium with sodium zirconium silicate. And why is that important? It's important because we've been increasingly recognizing, in clinical trials, particularly starting in 2022 through March of 2025, in clinical studies looking at patiromer versus sodium cyclosilicate. An independent claims analysis in the prioritized heart failure study of SZC versus placebo. A similar study by Nihar Desai, published in September 2024, of patiromer versus SZC, the REALIZE-K study, SZC versus placebo, published in November 2024. And finally, in March 2025, most recently, as a pharmacovigilance event, increasing hospitalization for heart failure with sodium zirconium cyclosilicate is really being reported. As nephrologists, we have to be aware that patients with advancing chronic kidney disease, particularly in stage IV, are thought to be almost similar, if not very similar, to patients with HFpEF. What does that mean? That means that our patients with advancing CKD are at risk for heart failure and hospitalizations related to heart failure and edema with sodium loading.

And RCTs with sodium zirconium cyclosilicate have shown this dose-related increase in adverse events and, potentially, they are related to sodium. There's the HARMONIZE trial, HARMONIZE and the PRIORITIZE, as well as a REALIZE-K study, that have shown compared to placebo, that sodium zirconium cyclosilicate dosage has a dose-dependent addition of sodium to patients who are receiving this agent, which results in heart failure exacerbations, hospitalizations, and edema.

Because of this sodium signal, there has been updated language on SZC, sodium zirconium cyclosilicate, and really in a pooled analysis of 3 placebo-controlled clinical studies in non-dialysis patients, patients with preexisting heart failure are experiencing worsening of heart failure, which occurs at a frequency of 13% on SZC, and 5.7% on placebo. Most cases have resolved with appropriate clinical management without withdrawal of SZC. But patients with preexisting heart failure, particularly those in whom an increased sodium intake may lead to fluid overload and decompensation, should be monitored for manifestations of worsening heart failure. And this might include symptoms such as dyspnea, edema, rapid weight gain. And as physicians, we really need to be aware of this side effect, and we need to optimize management of our patients with heart failure and advanced CKD as per standard clinical practice.

KDIGO in 2024 has come up with a guideline on managing hyperkalemia while on ACE and ARBS. The clinical pearl here is that hyperkalemia is associated with use of RASi, both ACEs and ARBS, but can often be managed by measures to reduce the serum potassium level rather than decreasing the dose or stopping RASi. That's a very important practice point because we need to be aware of this and to consider dose reduction or discontinuation of ACEs or ARBs, really as a last resort therapeutic interventions. We need to start with a potassium-restricted diet, which may work in part in early CKD. But in advancing CKD, we do really need to use other measures to control serum potassium if it's elevated rather than stopping RASi, which are really cornerstones of management for renal protection and cardiovascular protection in our patients.

To further bring that point home that heart failure is increasingly being recognized with sodium loading, particularly in potassium binder use for the treatment of hyperkalemia related to RASi block, what the REALIZE-K study showed, very importantly, that NT-proBNP at 6 months post-randomization was higher with SZC versus placebo.

Patiromer, whose counterion is not sodium but is calcium, NT-proBNPs at screening and week 18 post-randomization from the DIAMOND hyperkalemia study has shown a decrease in pro-NT-proBNP when using patiromer in those patients.

So what are tips for good multidisciplinary care? I think it's very important that healthcare team members and patients must share the same goal. We know from PROMs, patient-related outcomes measures, that shared decision-making is really very important. Education provided to the patient must be consistent among healthcare team members, and really, guideline-directed medical therapy is really our goal.

So treatment options should be personalized based on underlying CKD stage, the presence of heart failure, and the presence of edema.

So there are several key takeaways here. The takeaway is that RASi blockade confers cardiovascular and renal protection to patients with chronic kidney disease and heart failure. We're increasingly recognizing that advancing CKD is almost a model of HFpEF and that

those patients are predisposed to edema and heart failure exacerbations and hospitalizations. We need to be cognizant of the fact that hyperkalemia should not be a signal to de-escalate RASi blockade dosing but to think about measures such as using potassium binders to continue RASi blockade in our patients.

So my time is up. Thank you so much for tuning in.