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Hyperkalemia in CKD and HFrEF…What Am I Missing?

Announcer:
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Dr. Bakris:
Well, welcome, and happy to see you today, and I'm here with a panel of experts to discuss with you hyperkalemia, HFrEF, and really what are we missing in terms of management of hyperkalemia in situations where potassium is a critical variable, such as dialysis and HFrEF. I'm joined today by Lars Lund, noted cardiologist from Sweden, and Dr. David Bushinsky, a noted expert in kidney disease, and we are going to talk to you today about how the management of potassium should be done under ideal circumstances with what we have available.

Lars, let me start with you. HFrEF is a major issue. A lot of the therapies that help the heart clearly lead to increases in potassium. So, what are your thoughts on really idealizing the management of heart failure and taking potassium out of the equation?

Dr. Lund:
Right. It's a terrific question. So let me start by saying how important heart failure is, and in particular, heart failure with reduced ejection fraction, HFrEF, which has a high prevalence, a high incidence, and a high mortality rate and poor quality of life. We have good therapy in heart failure, including renin-angiotensin-aldosterone system inhibitors [RAASi], and in particular, mineralocorticoid receptor antagonists. But, a major problem, perhaps the biggest problem when it comes to heart failure therapy and implementation, is the very poor use of RAASi drugs in general, and very specifically, mineralocorticoid receptor antagonists. And the reasons for this are hyperkalemia, but there are many complex issues about hyperkalemia that I hope to be able to discuss today and will shed some practical light on how to handle hyperkalemia in heart failure with reduced ejection fraction.

Dr. Bakris:
Okay, very good. One of the biggest problems in managing patients with advanced kidney disease are dialysis patients, and there's a lot of poor adherence as you can imagine in these patients, especially dietary adherence. David, what are your thoughts on management of potassium in dialysis patients?

Dr. Bushinsky:
So, George, that's a great question. We've known since the landmark studies for sodium zirconium cyclosilicate and patiromer in the *New England Journal [of Medicine]*, that these agents bind potassium well in patients with chronic kidney disease, and even those on ACEs [angiotensin-converting enzyme inhibitors] and ARBs [angiotensin receptor blockers]. But, more recently, we've started to study how these agents work in dialysis patients.

Back in 2016 we did the first study with patiromer. Now, since it was the first study, it was a CRC study. We took on 6 patients, hyperkalemic, and admitted them to the CRC [clinical research center] and demonstrated that using patiromer, we had a marked

reduction in potassium before each of their dialysis treatments. So that was really the first study, use of partiromer. The next study, really, in 2019, which was published in JASN [Journal of the American Society of Nephrology], was a double-blind placebo-controlled study called DIALIZE. So, we moved from the CRC, using a different agent, SZC [sodium zirconium cyclosilicate], to a double-blind placebo-controlled study. They took hyperkalemic dialysis patients, gave half SZC, half placebo, and the goal was to reduce the potassium, especially during the long stretch between dialysis treatments, which tends to occur over the weekend, and they demonstrated that this agent was highly effective in lowering potassium. Then we moved from double-blind placebo-controlled studies to real-world studies, and the first one was really done by Kovesdy, and they did a chart review of a large dialysis provider. They took patients who were hyperkalemic, who had received an order for patiromer, studied them for a mean of 141 days. They studied 500 plus patients on patiromer, almost 9,000 patients on no potassium binder, and found that patiromer lowered potassium by half a milligram equivalent per liter, but more importantly, potassiums greater than 6 were cut in half after patiromer was used. So, we have a real-world study on patiromer lowering potassium on that critical day after the weekend. There are several other studies. Pinnell did a study in veterans published in *Medicine* and it really demonstrated again, in 460 veterans who were hyperkalemic, that they had almost a milli-equivalent fall in serum potassium when treated with patiromer. Real-world VA studies. And there've been others. Amdur did a study in a community dialysis center 2 weeks of no treatment, 12 weeks of patiromer, 2 weeks of no treatment, and demonstrated again a marked fall in serum potassium with patiromer. So, I think we have a fair amount of evidence that patiromer and SZC can be used in dialysis patients to lower serum potassium.

Dr. Bakris:
David, you gave us a nice summary and synopsis of all the literature, but can you give us an individual patient for example that you have treated this way and what the outcomes were?

Dr. Bushinsky:
So, George, thank you. This is a critical question in heart dialysis patients. Let me tell you about one individual who was just referred to us. Fifty-eight-year-old male, decades of poorly treated hypertension, obese, 2 prior MI's [myocardial infarction], had a CABG [coronary artery bypass graft], has heart failure with reduced ejection fraction, has LVEFs [left ventricular ejection fraction] of 30%. He's on, as you might imagine, beta blocker, carvedilol, he's on eplerenone, he's on dapagliflozin. And he was on 30 mg of lisinopril, but because of hyperkalemia, that's been reduced and his 10 mg was just stopped. So, we'd like to get him back, not only on the proper cardiac therapy, we'd like him to eat a heart-healthy diet, which as you know, contains an awful lot of potassium. So, we want to increase the lisinopril, we want to get him some good dietary counseling, so what did we do? We started him on patiromer. Again, we used patiromer because it exchanges potassium for calcium and that calcium goes on to bind a little bit of phosphorous, so you not only get a reduction in potassium, but a reduction in phosphorous and it will allow us, hopefully, to increase his lisinopril, which as has been mentioned, will clearly lead to enhanced survival. So, this is a critical problem hyperkalemia in dialysis patients. Most of our docs – primary care docs, even cardiologists and nephrologists – when they see that potassium starting to creep up, the first thing they do is stop the ARB or the ACE, and it's critical to educate people that they have a new tool, a tool that can bind the potassium and allow the use of these agents which will improve cardiac and renal survival.

Dr. Bakris:
Yeah. I think I agree with you. I think the data is irrefutable. I mean, these agents are enablers of therapy.

Dr. Lund:
For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Lars Lund and here with me today are Dr. David Bushinsky and Dr. George Bakris. We're discussing how best to discuss hyperkalemia in our challenging patients with CKD [chronic kidney disease] and heart failure.

Dr. Bakris:
And, speaking of enablers of therapy, Lars, I'm going to come back to you because, as you know, there was a very large trial in heart failure that was stopped early unfortunately, but it was testing whether binders could actually affect outcomes, and why don't you tell us a little bit about that.

Dr. Lund:
Yeah, so let's put this in a little bit of perspective. We talked about trials and studies of potassium binders in dialysis, and let's remember that potassium binders are effective in reducing potassium and maintaining normal normokalaemia over the long term, at least a year, in patients with CKD and/or diabetes, and/or hypertension, and/or heart failure, and/or dialysis. So, broadly throughout the imaginable indications. Now, when it comes to heart failure in particular, the trial you're referring to, which is the DIAMOND trial, which was a 1,200-patient trial where patients had heart failure and hyperkalemia. And these patients were all patients who were treated with patiromer during a run-in period, and this resulted in 85% of patients being able to be up titrated and initiated on all RAASi medications to target

doses. Then there was a randomized withdrawal period in which the patients who were randomized to placebo then had a very high incidence of having to reduce or eliminate treatment, primarily with MRAs [mineralocorticoid receptor antagonists]. So, DIAMOND shows in a randomized placebo-controlled fashion that a potassium binder lowers and maintains potassium, enables the use of life-saving heart failure therapy. What it did not show, but what we can assume, is that this enablement of heart failure therapy translates into improved outcomes. So, to put this in context, remember that the problem – that hyperkalemia is caused, to a great extent, from the syndromes and diseases that we treat. Now, that's because, what's the consequence of hyperkalemia? We often see these U-shaped curves showing that the risk of poor outcomes is high with hypokalemia and with hyperkalemia. We know that. So, we need to maintain normokalaemia. But interestingly in heart failure when we look at this U-shaped relationship, hypokalemia is really harmful, it causes ventricular arrhythmias and in severe hypokalemia can cause arrhythmic death. The hyperkalemia is less harmful in itself, but very harmful because it's a marker of RAASi discontinuation and nonuse. So, at any given time, hyperkalemia in heart failure is present only in about 5% of patients, but during a year it occurs in more than 25% of patients. So, many of our patients will, during a year, have problems with hyperkalemia, and not only is the use at any given time low, but the discontinuation rate is exceedingly high. So, among patients who would live longer with an MRA, only 30% are treated, and among those 30% approximately 70% have it discontinued within a year. So, this is a massive problem and creates a massive need for enablement. So, with the DIAMOND trial we showed that a potassium binder, patiromer, can achieve full-dose MRA, defined in this setting as 50mg a day, in 85% of patients and prevent having to reduce the dose or discontinue MRAs. So, the enablement strategy is very important, and it's very commonly accepted in other clinical settings; for example, where we perform stent placement and revascularization in cardiology, we routinely use proton pump inhibitors to enable anticoagulation. Even though that hasn't been shown directly to improve mortality down the line. Similarly, in oncology we use antiemetics of course to enable the use of chemotherapy. But it's been slow in heart failure to consider the use of potassium binders to enable the use of MRAs, but that is a critical niche to improve implementation of life-saving heart failure therapy, and the DIAMOND trial shows that.

Dr. Bakris:
Lars, thank you very much. That was right to the point, and I'm going to summarize now really in the context following your lead in terms of there are many patients who can't take RAAS blockade, for whatever reason, primarily hyperkalemia, the clinician is afraid. You are not maximizing this person's therapy under the guise of, well, you can't because hyperkalemia is preventing you. We are giving you solutions to allow the patient to get life-saving therapy. This is true for the kidney in slowing diabetic kidney disease, this is true in heart failure, you've heard, this is true in dialysis patients. So, hyperkalemia should not be an excuse. It is treatable. It is eminently available. The newer agents do not have anywhere near the profile that the old Kayexalate used to have. You can take these agents daily, or you can take them 3 times a week to manage potassium to allow the patient to not only have an ACE inhibitor or an ARB, but also mineralocorticoid receptor antagonist which now protects the kidney and the heart. So, again, use these agents to the best of your ability because they are enablers of proper therapy and don't deny the patient therapy.

So, Lars, what would you tell the audience in terms of what you want them to take home?

Dr. Lund:
Okay, great question. So I can summarize this briefly. Hyperkalemia is a big problem in heart failure and it's now treatable with novel potassium binders. The reason it's a problem is not primarily because it's harmful in itself, but because it causes non-use of renin-angiotensin-aldosterone system inhibitors, primarily MRAs. MRAs reduce mortality by more than 30% in patients with heart failure, but they are not used. With potassium binders there's data to support enablement of MRA use, and this enablement will translate into improved outcomes for our patients.

Dr. Bakris:
Lars, David, thank you very much. It's a pleasure talking today. I hope the audience got something out of this and I wish you all a good day. Thank you.

Dr. Lund:
Thank you, George.

Dr. Bushinsky:
Thanks, George.

Announcer:
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