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Breaking the Cycle: Addressing Hyperkalemia in CKD and Heart Failure to Optimize RAASi Therapy

Announcer:
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Dr. Kosiborod:
For patients with chronic kidney disease, or CKD, as well as heart failure, the potential threat of hyperkalemia is common. Join us today as we explore chronic hyperkalemia management in patients with heart failure, or CKD, using concomitant therapies, including renin-angiotensin-aldosterone inhibitors, or RAASi therapy, and potassium binders.

This is CME on ReachMD, and I'm Dr. Mikhail Kosiborod.

Dr. Greene:
And I'm Dr. Steven Greene.

Dr. Kosiborod:
Let's start by just discussing this question of, I guess you could say it should be obvious to everyone, but it's still good to talk about guideline-directed medical therapy and why do we use it in people with heart failure, especially when it comes to RAASi or renin-angiotensin-aldosterone system inhibitors in people with heart failure and CKD.

Dr. Greene:
I think important to understand for both patients with heart failure and/or CKD, RAASi inhibitors, including ACE inhibitors for example, angiotensin-receptor and neprilysin inhibitors for people with heart failure, and mineralocorticoid receptor antagonists, these are foundational therapies for these patients. I mean, just for example, heart failure with reduced ejection fraction, we talk about the four pillars of therapy. Two of those four pillars are RAASi therapies with ACE/ARB/RNA or MRA. And important to understand that these therapies don't just work like a modest amount, for example. They are overwhelmingly effective in the sense that they reduce the endpoint of all endpoints, all-cause mortality, for example in our patients with heart failure with reduced ejection fraction. And then, even with heart failure with ejection fractions above 40%, you know we now have very recent data with nonsteroidal mineralocorticoid receptor antagonists, which historically this has been a heart failure population with very limited treatment options.

I think it's fair to say that hyperkalemia and how we think about these patient populations, is unfortunately something that we've gotten used to. And even with our newer therapies, we have to learn how to live with it and mitigate that risk.

Dr. Kosiborod:
So, you already alluded to the fact that we're in this situation where we know these treatments can significantly improve really meaningful clinical endpoints, adverse events both in people with CKD and heart failure, but there is this kind of competing issue with

the fact that they raise potassium levels. And they just do that because that's how they work, and while minor elevations in potassium most clinicians nowadays don't get overly anxious about, certainly, once potassium levels go above the threshold, above 5 1/2 or 6 depending on your specialty and your level of tolerance for potassium elevations, can potentially trigger a lot of anxiety, a lot of worry in clinicians, because certainly, the last thing we want is somebody to have an untoward effect because potassium levels are so high.

And so, for a long time we've had this dilemma, which is we want our patients to be on these treatments, the RAASi treatments, to address potassium levels. And of course, one of the biggest problems is the people at the highest risk of developing hyperkalemia as well as kidney disease are exactly the kind of people that would also benefit the most from this treatment. So, there is this paradox of people at the highest risk of not being treated, or that would have the greatest benefit of RAASi treatment itself, also are the ones that are most likely to experience this side effect of elevated potassium levels.

Dr. Greene:
Unfortunately, as you alluded to, Mikhail, the people who need the help the most, in the sense that they have the worst outcomes, they're less likely to get these evidence-based therapies. And I think another point that you alluded to as well was, sure, there of course is true risk of hyperkalemia with these therapies, but there's also this fear of hyperkalemia that gets embedded into clinical practice, and I think, really just fuels so much clinical inertia and therapeutic hesitancy.

Dr. Kosiborod:
For those just tuning in, you are listening to CME on ReachMD. I'm Dr. Mikhail Kosiborod, and here with me today is Dr. Stephen Greene. We're discussing how clinicians can manage hyperkalemia in chronic kidney disease and heart failure while maintaining RAASi therapy.

Dr. Kosiborod:
For a long time there's been this controversy in the field about, well, if somebody developed hyperkalemia, we know that's high risk, but is it the potassium that's actually responsible for that risk? Or is it just a risk marker because it's a high risk patient? I have my own ideas about that. But what I think is not controversial is that the knee-jerk reaction typically tends to be to down-titrate or discontinue the RAASi treatment. And I guess in the past, that was at least somewhat understandable because there were relatively limited options for what to do.

So, what are some of the things that we've had traditionally? Low potassium diet, which tends to be pretty low in terms of adherence from patients. Not easy to maintain long-term. We don't like using diuretic therapy just to lower potassium levels, right? We decongest patients with diuretics since they have heart failure. We manage volume issues in the setting of CKD, but you don't want to volume deplete someone just to lower the potassium level and rev up their hormones, because you're doing that just for the sake of potassium. So, that's not always very practical or appropriate clinically. And the older versions of the potassium binders, like sodium polystyrene sulfonate, or SPS, what we know in the US as KAYEXALATE. That, while OK in the short-term, from a general tolerability standpoint, has not been well-tolerated by patients long-term, mostly due to things like diarrhea, constipation, or the gastrointestinal tolerability issues.

But now we have more than one of novel potassium binders that, at least from a GI tolerability standpoint, appear to be better, and that therefore may be appropriate for chronic use. And we know from trials that have been done with these agents that they effectively lower potassium levels. But the question is, can they actually be used to enable RAASi? And that's a concept that needs to be tested in clinical trials, asked and answered. And we now have clinical trials that actually have looked at that.

So, one of these is called the DIAMOND trial with patiromer, one of these novel potassium binders. Why don't you tell us a little bit about DIAMOND and what lessons we learned from that?

Dr. Greene:
Yeah, absolutely, Mikhail. I think DIAMOND really solidified in my mind this concept that novel potassium binders like patiromer can really be used for enablement for getting our patients on therapy.

So, just in brief, so DIAMOND was a clinical trial of patients with heart failure with reduced ejection fraction that either had active hyperkalemia or a history of hyperkalemia. And the way the trial worked is that there was a run-in period where people were on suboptimal RAASi therapy at baseline, but they were used at the run-in period as a patiromer-facilitated up-titration to optimal high levels of RAASi MRA dosing.

And then, all people who completed the run-in, they were then randomized one to one to either, patiromer continuation versus patiromer withdrawal. Now, just as some more information, just to put some more color to the DIAMOND trial, so, this was initially planned as a cardiovascular outcome trial with the primary endpoint of cardiovascular death or cardiovascular hospitalization, and the thought being

that if you could use patiromer to enable enough continuation of high use or RAASi therapy, that you would translate to improve cardiovascular outcomes.

Unfortunately, the COVID pandemic happened and that really impacted the operations of this trial, slowed enrollment. So, the trial was adapted prior to unblinding and whatnot, to have the primary endpoint, instead, be change in serum potassium. But there are also some really key secondary endpoints that were also evaluated, looking at the risk of hyperkalemic events during follow-up of greater than 5.5. Also, reduction in MRA dosing, if that had to happen, that was one of the other key endpoints.

So, just again, just to put some more specifics into what DIAMOND showed. So, a couple key things. One key thing was, what happened in the run-in period. So, people in this trial were, of course, by definition either actively hyperkalemic or a history of hyperkalemia that got in the way of being on RAASi therapy. So, these are patients we see all the time in clinical practice that are unfortunately, not on MRA and RAASi.

What the run-in period showed is that when you did a strategy of patiromer enablement using patiromer up to 3 times a day to really ramp up the doses of RAASi and MRA and get people on high levels of therapy, 85% of the patients that entered the run-in period were able to get to those target high levels of RAASi and MRA therapy.

But then, during the double-blind period where patients were randomized either to a continuation of patiromer, versus withdrawal of patiromer, the people who continued patiromer had about a 30 to 35% lower chance of developing hyperkalemia greater than 5.5 during that period, and also, importantly, had about a 30 to 35% lower risk of discontinuing or de-escalating MRA dosing. So, essentially, if you kept people on patiromer, you are able to have a much higher chance of continuing those very high levels of RAASi MRA dosing that you were able to get to at the end of the run-in period.

So, to me, this really hits home at, really, proof of concept that, yes, enablement can be a viable strategy for getting people on RAASi MRA dosing, and that doesn't need to be either/or, maintain normal kalemia or initiate MRA or RAASi therapy. You can do both, and I think DIAMOND is really proof of concept for this.

Dr. Kosiborod:
Well, thanks, Steve. That was a great summary of DIAMOND, and I will also remind folks that I think, in part because it was initially designed as an outcome trial, even though the trial was stopped immaturely, actually both because of the issues with enrollment from COVID-19 pandemic, but also lower than expected event rates, it still ended up with more than 800 patients, by far the largest clinical trial experience to date with trying to address that issue of RAASi enablement in people with heart failure with reduced ejection fraction.

There are other trials ongoing and there will be more data coming out on this particular topic. But it's a very, I would say, hefty contribution from DIAMOND in large part because it’s a very large trial for testing a concept that we're talking about, which is RAASi enablement. And it was an interesting way to actually manage hyperkalemia, because as we said, in some patients this was used because they already had high potassium levels. But in many patients, it was kind of more of a prophylactic use. Regardless, I think, of how you use it in practice, and I think most of us probably in practice would use it more as a reactive way to treat hyperkalemia, as in proactive. It clearly, as you said, was a proof of concept that in fact, potassium binders, that can be used chronically and well-tolerated, can effectively enable this treatment.

Dr. Greene:
We want to use it proactively to prevent hyperkalemia in people that have already declared themselves as high risk, or again, use it reactively. I mean, at the very least, we know we have this as a very effective treatment option for preventing hyperkalemia or treating it if we do run into it. So, very important.

Dr. Kosiborod:
Sounds good. Well, this has certainly been an enlightening conversation, but before we wrap up, I'd like for both of us to provide a final take-home message for our audience.

So, I guess the way I would summarize it best, Steve, from my standpoint kind of as a take-home message is, we have extremely solid evidence both in CKD and heart failure that RAASi treatments have a substantial effect on morbidity and mortality. They are frequently underused in this patient population, especially those that are most vulnerable to risks, but also most likely to benefit. And for a long time we had very limited treatment options. Those treatment options appeared to have broadened recently and we have already some evidence that they can be used to enable optimization of RAASi in people with heart failure, like in the DIAMOND trial, for example, and there will be more data in the future.

Dr. Greene:
I think this fear of, well, it's either initiate or enhance GDMT, or maintain normal kalemia. It has to be one or the other. That's really a

false dichotomy I think right now with what we have with novel potassium binders, that we can do both, whether you have that high risk patient who's had hyperkalemia in the past and you want to prophylactically start a potassium binder to ensure they get on appropriate therapy. Or you just want to rechallenge that patient, but know that if they do develop hyperkalemia again, in your back pocket you have available potassium binders to really treat that hyperkalemia and help enable them persisting on that therapy.

Dr. Kosiborod:
Well, thank you, Steve. Unfortunately, that's all the time we have today. So, I want to thank our audience for listening and to thank you, Steve, for joining me and for sharing all of your valuable insights and expertise. It was great speaking with you today.

Dr. Greene:
No, always great, Mikhail. Great seeing you.

Announcer:
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