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Management of Heart Failure: Time to Consider New Options?

Announcer:
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Dr. Stack:
We know that derangements in potassium levels are common in patients with heart failure and are associated with poor clinical outcomes. Now, whether this is due to the direct effect of elevated serum potassium levels remains a subject of debate. But concerns and fear by physicians about hyperkalemia clearly lead to suboptimal use of inhibitors of the renin-angiotensin-aldosterone system, and this can negatively affect patient outcomes. So how do we as physicians best manage these risks? So, welcome to CME on ReachMD. I’m Dr. Austin Stack from the University of Limerick in Ireland, and joining me today to discuss how we can best manage hyperkalemia and heart failure and ensure our heart failure patients get the full benefit of RAASi therapy is Dr. Mikhail Kosiborod from the University of Missouri-Kansas [City] in the United States.

Dr. Kosiborod:
Hi, Austin. It’s really good to be with you today.

Dr. Stack:
The goal in the outpatient setting is to optimize RAAS inhibitor therapy while normalizing serum potassium levels and correcting any imbalances in potassium homeostasis. Mikhail, what options do we have available to manage elevations in serum potassium?

Dr. Kosiborod:
One, of course, is dietary intervention. So one of the things we can do is to try to convince our patients to adhere to low-potassium diets, and the problem, of course, is that those diets are very difficult to adhere to. The other option is using high doses of loop diuretics and, you know, that’s not something that we as cardiologists, and certainly heart failure cardiologists, particularly favor, partly because we want to use the absolute minimum dose of loop diuretics that we can get away with while keeping the patient adequately decongested. We know that using larger or higher doses of loop diuretics can really cause issues with renal hemodynamics. It can rev up counterregulatory hormones and actually, in some cases, may make things worse. So that’s not an option that we like, and frankly, it’s also not especially effective in every patient because a response to that from a potassium homeostasis standpoint is variable.

The last one that I will mention in terms of chronic management of hyperkalemia is potassium binders, and really the only one we had available until a few years ago was sodium polystyrene sulfonate, or SPS. And there are issues there as well, the biggest of which is that it’s really difficult to tolerate chronically. So SPS has been associated with very frequent incidents of gastrointestinal side effects, things like constipation and diarrhea. So patients generally do not tolerate it for more than just a few doses or a few days. There are also potential concerns about more rare significant gastrointestinal side effects. Those tend to happen mostly in hospitalized patients but, you know, I think for all effect and purposes, it’s hard to see most patients being able to tolerate SPS for perhaps, you know, 6-7

days. That's what the data will tell us. And so it's not a great option for chronic hyperkalemia management. And then, finally, SPS also is a potential significant sodium load, which we would like to avoid in patients that have heart failure with reduced ejection fraction and are sodium sensitive.

So I would say up until recently, the options were very limited, which is why when you actually look at the data and what happens in registries and what happens in real-world clinical practice is that what people end up going through – people, I mean, clinicians end up going through as options in those that's going to work and kind of maybe easiest and more straightforward is to down-titrate or discontinue RAAS inhibitors.

Dr. Stack:
A key question that you may have is when do we start the potassium binder in order to optimize RAASi therapy? And the consensus from the European Society of Cardiology is that an approved potassium-lowering agent is recommended once serum potassium levels exceed 5 millimole per liter in order to achieve the optimal or recommended dose of RAAS inhibitor therapy. Now, we've a brief animation for you here to show how patiromer and SZC work. So let's take a look at this over the next minute.

Announcer:
Hyperkalemia is a serious condition that is common in those with heart failure and chronic kidney disease. Total body potassium is balanced by multiple mechanisms, including those within the gastrointestinal, or GI, and renal systems. Specifically, the kidneys and renin-angiotensin-aldosterone system, or "RAAS," play a primary role in potassium homeostasis. Disturbances in RAAS, due to comorbid disease and/or guideline-recommended therapies, can impair renal potassium clearance, leading to elevations in serum levels. Novel potassium binders, patiromer and sodium zirconium cyclosilicate, or SZC, are designed to remove potassium from the GI tract. In the lumen of the distal colon, where potassium levels are highest, patiromer microbeads exchange calcium for potassium with a high binding capacity. SZC crystals exchange sodium or hydrogen for potassium within the GI tract. These binders help maintain normal potassium levels when hyperkalemia is present.

Dr. Stack:
Now, patiromer and SZC were primarily studied in patients with chronic kidney disease, but also patients with heart failure were included in these clinical trials. Mikhail, what can you tell us about the efficacy of potassium binders in patients with heart failure?

Dr. Kosiborod:
So, let's kind of break it down by the two novel potassium binders and talk about the data that we have for those, and we'll start with patiromer. So patiromer is an exchange resin. It's a polymer that exchanges potassium for calcium. Because it's an exchange resin polymer, we think that it's most likely starting to work when it gets to the distal colon.

And so in OPAL-HK study of patiromer, what we learned is that in patients with mild to moderate hyperkalemia, it can effectively normalize potassium levels within a relatively brief period of time and then keep potassium levels in normal range for a period of about four weeks. And it was effective in bringing potassium levels to normal and maintaining them in a normokalemic range regardless of whether the patients had mild or moderate hyperkalemia.

The AMETHYST-DN study was a longer-term, open-label, single-arm study that looked at efficacy and safety of patiromer for up to one year, again, in patients with mild to moderate hyperkalemia, many of whom, of course, had chronic kidney disease and some of whom had heart failure. And again, what we observed was that patiromer was effective in normalizing potassium levels in that patient population and maintaining potassium levels in the normokalemic range for up to one year.

When it comes to tolerability and safety, what we observed in those studies is that it was well tolerated. The incidence of mild to moderate gastrointestinal adverse events was a bit higher than it was in the placebo, and there are no head-to-head comparisons, of course, with SPS, but if you kind of historically compare the data, it appears to be better tolerated from a gastrointestinal standpoint, certainly, than older binders like SPS. The one other factor that I will mention in terms of tolerability and safety is effect on electrolytes. Of course, when you give medication like a potassium binder, you would expect that a few patients may develop hypokalemia. So we did – those studies did show low incidence of hypokalemia. Most of those events were mild, and most of those events were easily corrected. And there were also some patients that developed low magnesium level, hypomagnesemia, but the clinical significance of those hypomagnesemic events remains unclear. So overall, I would say from a tolerability and safety standpoint, things look quite favorable.

When we look at SZC, sodium zirconium cyclosilicate, it's an inorganic crystal. It's not an exchange resin, and it has high affinity for potassium cations, doesn't appear to bind bivalent cations like magnesium or calcium. It exchanges potassium for sodium or hydrogen. And it's possible that it may start binding potassium in a – more of a higher portion or upper portion of the gastrointestinal tract, because it appears to have relatively quick outset of action. What we know from several trials now with SZC is that, again, it normalizes

potassium levels quickly. It maintains potassium levels in the normokalemic range regardless of patients' comorbidities or severity of hyperkalemia for up to four weeks in the HARMONIZE trial. And again, in a longer-term, single-arm, open-label study called ZS-005, we see that it can normalize potassium levels in patients with hyperkalemia – mild, moderate, and a few patients with severe hyperkalemia – maintains those potassium levels in the normal range over a long period of time, up to one year.

When we look at tolerability and safety, again, from a gastrointestinal standpoint, it appears to be well tolerated. The safety events essentially center around few patients developing hypokalemia. Again, these events are relatively uncommon and most of those patients – nearly all of those patients had mild hypokalemia that was easily corrected. And then with higher doses of SZC, there is increased incidence of edema, lower extremity edema.

Bringing it back to heart failure, I would say that there was definitely a proportion of patients in both patiromer studies and SZC studies that had heart failure, and these medications appear to be equally efficacious in patients with heart failure as they are in patients that did not have a history of heart failure. The problem is we don't know what kind of heart failure these patients had. They were not very well characterized in terms of the ejection fraction and the background medical therapy for heart failure. And so we definitely need more data that is specifically dedicated to the heart failure and reduced ejection fraction population because that's where we mostly use RAAS inhibitors.

And the good news is those trials are on the way. So we have a DIAMOND trial with patiromer in patients with heart failure and reduced ejection fraction. That's actually a true heart failure outcome trial that's going to look at a primary endpoint of cardiovascular death or worsening heart failure. And then we have PRIORITIZE trial with SZCs that's currently ongoing. That's not an outcome trial, but it's looking more at the question whether using SZC in patients with HFrEF, heart failure with reduced ejection fraction, whether that can help optimize renin-angiotensin-aldosterone system inhibition while keeping potassium levels in a safe range. So, the good news is we have lots more data coming in the heart failure space with these agents.

Dr. Stack:
Mikhail, it's probably well worth reiterating, from those studies, and particularly the OPAL-HK, that absolutely one of the key outcomes was the normalization of serum potassium, which both of these novel potassium binders did effectively. But also in the OPAL-HK study, that 90% of patients in the patiromer group were able to continue and remain on maximal RAAS inhibition. And this is probably one of the key messages that we want to send out to the clinical community, that there's good evidence now that we can normalize serum potassium, we can treat serum potassium, and at the same time, ensure that patients are on maximal therapy to block the renin-angiotensin system. In other words, to get those good outcomes, both renal outcomes and cardiovascular outcomes. But as you rightly say, we need the specific outcome data, and hopefully the DIAMOND study and the PRIORITIZE-HF will give us the answers that we need over the coming years.

Mikhail, what other practical tips do you have for cardiologists in using these agents in heart failure?

Dr. Kosiborod:
I think while we don't have official kind of professional-cited guidelines for frequency of monitoring of potassium levels after initiation of potassium binders, I think taking a similar approach to what was done in clinical trials that have been done or a similar approach to what the guidelines recommend for monitoring after starting an MRA, for example, would be quite reasonable. So what do I do if I start the patient on potassium binder? I would normally check potassium level – well, kind of depends on where potassium was to begin with. Obviously, if it was really significantly elevated, I may be even more careful and do even more frequent checks. But in a normal situation when you're dealing with a patient that has mild to moderate hyperkalemia, you know, typically what I would do after I start a potassium binder, whether it's patiromer or SZC, is to frequently check potassium levels. Typically would be about a week after I start the potassium binder. And then, depending on what the results are, monitor it, you know, perhaps a couple of weeks afterwards and then one month after that as long as things are stable. Of course, if I'm combining use of potassium binder with up-titration of RAAS inhibitors, including MRAs, then you may need to monitor things a bit more frequently. The good news is that, you know, just like what we see in clinical trials for many patients, once they kind of settle in terms of their RAASi inhibition dose, MRA dose, and potassium binder dose, you know, and you've convinced yourself after monitoring them for a few months, you know, so initially every few weeks, once a month, then maybe every three months, that things are stable, of course the frequency of monitoring can be dialed down.

Dr. Stack:
I think that's a very good point, Mikhail, in terms of surveyance of patients on RAAS inhibitor therapy and certainly in terms of how often we should monitor them. Certainly, there's evidence from some of the population-based cohorts that, you know, we typically don't check potassium that often, even following the initiation of an ACE inhibitor. And data from the SCREAM cohort showed about 30 to 40% only had a potassium check in the first month following the initiation of a RAAS inhibitor. So clearly, what we do in clinical trials sometimes is not translated into clinical practice.

Dr. Kosiborod:
Now, I couldn't agree more, Austin. I mean, I think appropriate monitoring is absolutely critical. And then the good news, I would say also, is that both of the novel potassium binders, including patiromer and SZC, are titratable.

Dr. Stack:
I 100% agree. To my nephrology and cardiology colleagues, we need to utilize all available tools, including these novel potassium binders, to improve the care of our patients with heart failure.

Dr. Kosiborod:
Thanks very much, Austin. It was great to be with you.

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