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Synergy of Guideline-Directed Medical Therapies in Heart Failure to Optimize Patient Outcomes

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Synergy of Guideline-Directed Medical Therapies in Heart Failure to Optimize Patient Outcomes” is provided by Medtelligence.

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Dr. Butler:
Renin-angiotensin-aldosterone system inhibition [RAASi] is the foundation of guideline-directed medical therapy [GDMT] for heart failure patients. However, due to practice gaps, the benefits of RAASi therapy are not enjoyed by a significant proportion of the population requiring its use. This is especially true for patients with comorbid conditions. Hyperkalemia is a common adverse effect of RAASi therapy that needs to be anticipated and mediated so that the optimal dosing of necessary medications can occur. Maximizing guideline-directed medical therapy in the face of hyperkalemia remains a key clinical challenge that if not handled properly can result in increased morbidity and mortality.

This is CME on ReachMD, and I am Dr. Butler.

Dr. Kosiborod:
I’m Mikhail Kosiborod, cardiologist at Saint Luke’s Mid America Heart Institute in Kansas City.

Dr. Weir:
And I’m Dr. Matthew Weir, and I work in Baltimore, Maryland.

Dr. Butler:
Today, we are going to go through a case and discuss different treatment approaches to optimize guideline-directed medical therapy while managing hyperkalemia. So let’s dive right into it.

This is a patient with CKD, stage 3b, recurrent hyperkalemia, potassium levels around 5. You cannot increase the diuretic dose because of the creatinine issues and the fact that the patient is actually optimally decongested.

So, Dr. Kosiborod, let me start with you and ask your approach to the management of a patient like this when you are trying to optimize the RAASi therapy but have issues with CKD and hyperkalemia.

Dr. Kosiborod:
Well, thank you, Javed, and of course this is a very common clinical scenario. We have a patient with heart failure and reduced ejection fraction [HFrEF], somebody who also has a concomitant chronic kidney disease, which is so common in our patients with HFrEF, and his borderline potassium levels that, of course, occur in patients with heart failure and kidney disease, especially advanced kidney disease.

And to your question, I think the critical important issue here is that you've got to, first and foremost, make sure the patient's optimized on guideline-directed medical therapy, which has the 4 pillars of fundamental disease-modifying treatments in HFrEF. Those include RAAS blockers, renin-angiotensin system blockers, or ARNI; beta-blockers; MRAs, the mineralocorticoid receptor antagonists; and SGLT2 inhibitors. And as it happens, at least several of these classes of medications may further increase potassium levels as you make sure, the clinicians, that you get patients on GDMT, on those 4 pillars, and you also then make sure, after the patient is receiving all 4 pillars, that they're also receiving optimal doses. This is exactly the patient that's likely to develop further elevations in potassium levels. So, first thing, make sure patient's receiving GDMT and optimize GDMT. Second, monitor potassium levels carefully because this patient's high risk for developing hyperkalemia. And third is, if hyperkalemia does develop, then figure out what can be done to make sure a patient can continue to stay on optimal GDMT, because we know that's what has been shown to improve survival and reduce hospitalizations and, at least with some classes of the medications, also improve quality of life.

So in the past we, of course, had very limited options of what to do if potassium levels continue to progressively elevate. It would typically mean dietary modifications or, unfortunately, what's frequently done is down-titration or discontinuation of the classes of medicines that can increase potassium levels, most notably RAAS blockers, ARNI, or MRAs – or sometimes all of the above – and that, we know, is not optimal because patients that have that therapy down-titrated, discontinued, have a higher associated risk of poor outcomes.

Dr. Butler:
So, yeah, I completely agree with you. I mean, and again, just to put it in perspective, just a potassium of 5 by itself is not necessarily a reason not to optimize medical therapy. The question is whenever you try and then the potassium goes up, and that's when you are facing this challenge, whether to go up on the dose and do something else to manage hyperkalemia or cut back on the doses.

Dr. Weir, what do you think?

Dr. Weir:
Well, this is a major clinical conundrum that we face. And that is mitigating potassium levels that might possibly interfere with using guideline-based medical therapy. And what I mean here is being able to utilize appropriate doses of either ACE, ARB, or ARNI coupled with MRA in an appropriate dose. And let's also remember, too, beta-blockers tend to increase serum potassium as well. So really, 3 of the 4 foundations that Dr. Kosiborod mentioned are drugs that tend to elevate serum potassium levels. And let's also agree, too, ramping up diuretic doses may not be the correct answer, especially if the patient's euvolemic, because causing volume depletion activates the very neurohormonal systems you are trying to dampen with these therapies.

Dr. Butler:
So, Mikhail, let me ask you one more question related to this patient. There is some emerging data on less risk of hyperkalemia with SLGT2 inhibitors, and that may actually facilitate other therapies. But what are your perspectives on that?

Dr. Kosiborod:
That's an excellent point, Javed, and I would say there are actually 2 things to keep in mind. There are 2 out of 4 guideline-directed therapies, Class 1, and indicated therapies in HFrEF actually have been shown to potentially mitigate some of the risk of hyperkalemia to an extent. So the first I'm actually going to mention sacubitril/valsartan, or ARNI, as compared to an ACE inhibitor in the PARADIGM-HF trial, was associated with or led to lower risk of significant hyperkalemia. That does not mean that you have no risk of hyperkalemia with ARNI; it just means you have less as compared to an ACE inhibitor, and presumably ARB, even though, of course, in the PARADIGM trial, the comparator was an ACE inhibitor. And then the second data, more recently emerging as you just pointed out, and it's actually coming from a variety of trials, but probably most notably and clearly demonstrated in the DAPA-HF secondary analysis, which is in DAPA-HF trial, of dapagliflozin versus placebo in patients with HFrEF. Patients that were on dapagliflozin concomitantly with MRA had a significantly lower risk of hyperkalemia, you know, clinically important hyperkalemia with potassium levels more than 6. So it's nearly, 50% lower risk of that significant hyperkalemia with dapagliflozin in conjunction with an MRA versus a placebo in conjunction with an MRA. So what that means is you can kind of have 2 for 1. You can really optimize therapy from a heart failure standpoint by using medications like ARNI and SGLT2 inhibitors while at the same time potentially mitigating the risk of significant hyperkalemia.

Dr. Butler:
So, great insights, Mikhail.

For those just tuning in, you're listening in to CME on ReachMD. I am Dr. Javed Butler, and here with me today are Drs. Matthew Weir and Mikhail Kosiborod. We are discussing how the synergy of guideline-directed medical therapies can optimize patients' outcomes in heart failure.

Matt, let me turn to you. So let's just, for the sake of discussion, assume that our patient has type 2 diabetes. And talking about novel

therapies, we are seeing all of these data are coming out with nonsteroidal MRAs and prevention of renal function deterioration as well as cardiovascular outcomes. Pertinent to our case, what would you say about therapies with those drugs?

Dr. Weir:
Well, Javed, this is an excellent question. And if you look at really all of the treatment algorithms for cardiorenal disease, we're looking at expanding the opportunities to people even with much lower GFRs. I mean, let's remember, the very vast majority of all the heart failure studies with reduced ejection fraction excluded patients with GFRs below 30.

So I think now that we're reaching out and trying to expand our capabilities of therapy even to the lower GFR patients, even those with diabetic kidney disease and reduced ejection fraction, you know, again, new drugs like finerenone have proven to be very helpful in this regard, but yet again, still tend to raise potassium by about 0.2 milliequivalents per liter, which could make some clinicians and some patients a little bit uncomfortable about that level of serum potassium. So we're still going to have to be attentive, focus on appropriate dietary measures, focus on avoiding nonsteroidal anti-inflammatory drugs, utilize potassium binders when we need to, so that we can mitigate chronic hyperkalemia, which is really the major barrier for us using many of these exciting new disease-modifying therapies.

Dr. Butler:
So very helpful. So Mikhail, let me turn back to you. You know, we have questioned a lot of things just in the past 5, 6 minutes. We talked about the importance of therapy. We talked about potential less risk with ARNIs, facilitation by SGLT2 inhibitor, diet, but let's touch on one last crucial topic as well, and that is these novel potassium binders, patiromer and sodium zirconium cyclosilicate. How will you approach these novel potassium binders in a person like this?

Dr. Kosiborod:
Right. Well as you pointed out, Javed, the emergence of these novel potassium binders really gives us a new potential treatment option which we didn't previously have because not only are they efficacious in lowering potassium levels, but also tend to be well tolerated, including chronically, over an extended period of time, something that we just didn't have available to us before with all the therapies, like Kayexalate, really not being a chronic treatment option because of gastrointestinal tolerability issues. So the question is how would you use it clinically in a patient like this? So I think as we mentioned earlier, the first order of business is make sure the patient is optimized on GDMT. And some of the things that you could potentially capitalize on are things like potential use of ARNI and SGLT2 inhibitors to mitigate the risk of hyperkalemia.

But let's say a patient's potassium increases anyway, and now you're dealing with somebody who had a baseline potassium level of 5, and now the potassium level is what we would normally say moderately elevated – you know, let's say 5.7, 5.8. And it's kind of slowly moving in the wrong direction, and of course, different clinicians have different levels of tolerability for potassium levels, and it's certainly going to make some people nervous, as Matt just mentioned. So in the past, really the only thing one could do is dietary intervention, that Matt already said earlier, and then, really, after that it's down-titration and discontinuation of renin-angiotensin-aldosterone system inhibitors, including MRAs, which is really not optimal, because we know that these medications provide benefit to patients with HFrEF, regardless of the potassium levels. We know this from clinical trials of those medications, of the MRAs.

So now we have another treatment option. So let's say you're faced with a clinical dilemma, essentially, one additional treatment option that could be entertained now is using either patiromer or sodium zirconium cyclosilicate to normalize potassium levels or significantly lower potassium levels as you are optimizing GDMT, in case potassium levels continue to be elevated or elevate further, as you're optimizing GDMT.

Dr. Butler:
So great, great cardiology perspective. Matt, nephrologists see a lot of hyperkalemia. Can you give us a nephrologist's perspective on these novel potassium binders, both for chronic hyperkalemia management as well as enablement of RAASi therapy?

Dr. Weir:
Sure, I'd be delighted to. I think, you know, the real opportunity, moving forward, is that we are going to have the same opportunities in chronic kidney disease now that we've had already with heart failure, and that is more than a renin-angiotensin system blocking drug. We're going to have SGLT2 inhibitors. We're going to have these newer nonsteroidal mineralocorticoid receptor antagonists. So we will continue to have a balance between mitigating potassium and using these exciting new therapies, which we know improve clinical outcomes. And so, clearly, we're going to need to develop experience with chronic hyperkalemia management, and I think the cornerstone of that, beyond, obviously, dietary recommendations and avoiding medicines like nonsteroidals, is to utilize some of the novel, newer potassium binders, which we know have long-term safety and efficacy data.

Dr. Butler:
Well, thank you both. This has been an important conversation. Before we wrap up, maybe I can request both of you to give one take-

home message. Dr. Weir, let me start with you.

Dr. Weir:
Use guideline-based medical therapy and mitigate potassium problems.

Dr. Butler:
Dr. Kosiborod?

Dr. Kosiborod:
I think, probably in closing, what I will say is that there was a very important recent publication in the journal *The Lancet* that tried to estimate just how much of a benefit we can provide to patients with heart failure with reduced ejection fraction if you use all of the evidence-based fundamental therapies in HFrEF. And we're talking about more than 6 years of life that we can give somebody who has HFrEF and is age 65 years or older. That's a remarkable gift, and at least some of these treatments, patients won't just live longer, but feel better. But in order to do that, you have to use them, and in order to use them and use them safely, you know, it first of all, of course, requires a lot of emphasis in your clinical practice.

Dr. Butler:
Well, I cannot agree more with both of you, but unfortunately, that's all the time we have today. So I want to thank our audience for listening in, and thank you both, to Dr. Weir and Dr. Kosiborod, for joining me and for sharing your valuable insights and thoughts. It was a great time speaking with you today.

Dr. Weir:
Great pleasure. Thank you.

Dr. Kosiborod:
Thank you.

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