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The Role of Potassium Binders in Optimal HF Management: Discussing the DIAMOND Study

Announcer:
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Dr. Piña:
In patients with heart failure, rapid initiation, and up-titration of the guideline-directed medical therapy, or as we call it, GDMT, is really crucial to patient outcomes. Despite this, there are considerable gaps in the use of GDMT due to the risk of hyperkalemia. This is especially true for our patients who have multiple comorbidities, which is obviously very common in this syndrome, such as CKD [chronic kidney disease] and diabetes.

Today we are exploring the clinical evidence of the use of potassium binders in the management of hyperkalemia for patients with heart failure. The most recent study results we have are from the DIAMOND trial. So how can we support evidence-based decision-making to address the concerns of hyperkalemia while maintaining guideline-directed medical therapy in patients with heart failure?

This is CME on ReachMD, and I'm Dr. Ileana Piña. Dr. Anker, would you like to introduce yourself?

Dr. Anker:
My name is Stefan Anker. Thank you for having me. I'm a heart failure cardiologist from Berlin in Germany at Charité medical school and really have a great pleasure being here with you to discuss this topic.

Dr. Piña:
Dr. Butler.

Dr. Butler:
Very much the same here. I'm a heart failure cardiologist and delighted to be here with you. I'm practicing in Dallas, Texas.

Dr. Piña:
Dr. Pitt, do you want to introduce yourself, please?

Dr. Pitt:
Yes, I'm Dr. Bertram Pitt, at the University of Michigan School of Medicine, and have been involved with heart failure and MRAs [mineralocorticoid receptor antagonists] over the last several decades.

Dr. Piña:
So, Dr. Pitt, as I've just mentioned, hyperkalemia is a real problem in these patients because it can lead to a reduction in necessary therapies, and we always try to avoid reducing those necessary therapies. What are some of the challenges we all face when trying to maintain GDMT in heart failure?

Dr. Pitt:
Well, I think everyone knows that the steroidal MRAs, eplerenone and spironolactone, are a class 1 indication in heart failure and reduced ejection fraction [HFrEF] and have been shown to reduce total mortality and total hospitalizations. Now, despite the fact that they are a class 1 indication and have shown a reduction in mortality, hospitalization, and healthcare costs, their use is really suboptimal. For instance, the recent US Get With the Guidelines heart failure registry shows there's a tremendous underuse of MRAs, but this is also seen in Europe in the Danish registry and in many other registries. In the US Get With the Guidelines registry, in fact, even people with a GFR [glomerular filtration rate] over 90 had suboptimal use, but once it got down to a GFR of less than 45, only about 26% of people were using a steroidal MRA. The reason, obviously, is the fear of hyperkalemia, but once they start an MRA, these MRAs are stopped, and that's because of an increase in potassium or a drop in eGFR [estimated glomerular filtration rate]. And the drop in eGFR scares people, but it's really hemodynamically mediated. So, there is this tremendous underuse of MRAs, and we know from several studies that if you don't use an MRA in a person with HFrEF, then there is an increase in mortality, increase in hospitalization, increase in healthcare cost, and obviously, we're doing our patients a disservice. So, this fear has really driven this underuse and created a tremendous opportunity, and if you have a history of hyperkalemia or hypokalemia, the use is even less. So, I think there is a tremendous opportunity because of this suboptimal use of MRAs. Thank you.

Dr. Piña:
Thank you, Bert, and I always recommend that if the patient's in the hospital, why not start it in the hospital a day or 2 before, because then it gives you a chance to actually see what happens to the creatinine and the potassium, and I think people would be much more comfortable sending the patients home on it once they have seen some data. But I agree with you.

Dr. Pitt:
Well, obviously, that's a very good strategy. But unfortunately, it isn't happening.

Dr. Piña:
I agree, and it's very frustrating. I just saw 2 patients exactly with what you are describing in the post-discharge clinic.

So, Dr. Butler, we've seen considerable data over the years on the use of potassium binders to manage hyperkalemia and therefore enable RAASi [renin-angiotensin-aldosterone system inhibitor] therapy, which is what we like to do. The most recent data comes from our DIAMOND study. This was the purpose of the DIAMOND study. What have we really learned from it, Javed?

Dr. Butler:
Yeah, so as you mentioned, you know, there are sizable data in terms of potassium binders – novel potassium binders, patiromer and sodium zirconium cyclosilicate, in terms of managing potassium, maintaining normokalemia. But when it comes specifically to heart failure population and specifically to optimized medical therapy – RAAS inhibitors, MRAs, ACE [angiotensin-converting enzyme], ARB [angiotensin receptor blocker], ARNI [angiotensin receptor neprilysin inhibitor] – the data were relatively limited. And then the question is, how does it impact clinical outcome? So, the DIAMOND trial was specifically designed to answer all of these questions. So, patients who currently have hyperkalemia or may have had a history of hyperkalemia due to RAAS inhibitor therapy that led to compromise of RAAS inhibitor therapy or MRA therapy then went into an open-label phase where their RAAS inhibitor therapy was optimized with the use of patiromer. And those patients that got onto the optimal medical therapy were then randomized to either withdrawal of patiromer or continued patiromer, and then the idea was to long-term follow these patients for clinical outcomes.

So, the first learning that we had in this study design was actually the learning from the run-in phase, and that is that there are all of these concerns that, you know, even in patients with hyperkalemia, you may not be able to optimize RAASi therapy because of low blood pressure and GFR and creatinine and all those kind of stuff. But in this study, we found that about 85% of the patients, we were able to optimize medical therapy. So, this is actually a pretty interesting finding, although this was not a part of the randomized trial per se. But this run-in phase, that in 85% of the patients, with the use of potassium binder, patiromer, you can optimize RAAS inhibitor therapy was a really pleasant finding. So, then you go to the randomized phase, and the idea was to look for clinical outcomes. Well, then the reality hit with COVID. Many of the trials were impacted with COVID, and in this particular trial, it was not only an issue of the fact that enrollment slowed down, and the natural history changed; we didn't have as many hospitalizations and event rates. But here, remember that patients who are high risk, we are force up-titrating RAAS inhibitor therapy in that patient. So, it was very important for us to make sure that the patients continue to get their investigational therapy and have the routine follow-up for laboratory testing. And we couldn't do that. So, a decision was made to change the aim of the trial a little bit, from clinical outcomes to control of potassium and simultaneously optimization of RAASi therapy.

So, we completed the trial, and what we basically found was that you can get both things done simultaneously. And one problem in this field is you either have high potassium and optimal RAASi therapy or good potassium but not optimal RAASi therapy.

Dr. Piña:

Live with it.

Dr. Butler:
Yeah, so the question is how do you achieve both? So, our primary endpoint was serum potassium level control, which was significantly in favor of patiromer therapy. But then we really looked at our secondary outcomes. They were hierarchically tested statistically in sort of a sound manner – every possible combination that you can think of as a clinician. So first, time to first event of hyperkalemia. Total hyperkalemia events, first and recurrent. RAAS inhibitor use, the comprehensive RAAS inhibitor use, sort of putting in all the ACE, ARB, ARNI, beta-blocker, MRAs – all of those things together, and if you look at this total evidence, what we found is that while you're managing potassium, you're reducing the risk of hyperkalemia events and optimizing medical therapy and achieving better comprehensive medical therapy in these patients.

Dr. Piña:
So, you're really doing both. I often find that the fear of hyperkalemia may be even higher than the actual hyperkalemia, and so the drug gets avoided because of the fear. I think maybe repeating potassium is a good idea, how potassium is drawn. Is it sitting somewhere? There's so many things that can affect the potassium.

For those of you just tuning in, we are listening to CME on ReachMD, and I'm Dr. Ileana Piña. I'm here today with my good friends, Dr. Bert Pitt, Javed Butler, and Stefan Anker. We're discussing the management of hyperkalemia in our patients with heart failure, and the recently released results of the DIAMOND trial.

So, Dr. Anker, what are your thoughts on what we have learned today, and the clinical implications, and how are you going to use it in your clinic?

Dr. Anker:
Yeah, thank you so much. I personally believe that the DIAMOND study will open in heart failure an approach to using medicines that we didn't have there before, and that is the enablement of therapy.

Dr. Piña:
That's an important word.

Dr. Anker:
Make other therapies feasible by giving something that protects the patient, and you spoke about fear – maybe even as anxiolytic to the –

Dr. Piña:
To the doctor.

Dr. Anker:
– to the physician, and so we need to learn from other fields of medicine. In cancer, we are using antiemetic drugs to –

Dr. Piña:
All the time.

Dr. Anker:
– enable chemotherapy. And let's not forget, even in cardiology, we are using proton pump inhibitors to enable some anticoagulants. They were never tested for outcomes other than safety events, and here –

Dr. Piña:
Nor were they asked for outcomes.

Dr. Anker:
Yeah, and now we have the same thing in the DIAMOND study. We know it makes the use of RAASi therapy, A, more successful in keeping patients where the guidelines want our patients to be, which is ideally at the maximum tolerated, trial-recommended dose, but at least 50%, and second, make it more safe in using them to have less hyperkalemia events. And so, this is really opening up a new avenue of caring for our heart failure patients, and I'm very positive about it, and I'm very happy that, already, the guidelines in the US just came out the other day –

Dr. Piña:
There's some mention of it in there, for the first time.

Dr. Anker:

Yeah, 2b recommendation, and this is a good sign.

Dr. Piña:
It's the first time. And the European guidelines have had some of this before.

Dr. Anker:
We had a verbal mentioning there, because we didn't have the result of the DIAMOND study yet.

Dr. Piña:
Now you can go back and tweak that one. Very good.

Well, this has certainly been a fascinating conversation, but before we wrap up, I want to hear from each of you a take-home message with the audience. Let's start with you, Dr. Pitt.

Dr. Pitt:
Well, I think we've heard a lot, but a lot of us have been focused on developing new drugs for heart failure, but I think it's very clear from the DIAMOND study that if we can use patiromer, we can use 1 of the 4 pillars of approved drugs, the steroidal MRAs, and really have a great effect in reducing mortality, hospitalization for heart failure, and eventually healthcare cost. So, this is really an important advance. Thank you.

Dr. Piña:
Thank you, Bert. Dr. Butler, what is your take-home message?

Dr. Butler:
Well, my take-home message would be that, obviously, there is no doubt that these therapies are lifesaving and improve patients' outcomes, so there's no debate or argument there, and that we have to give these therapies, and global guidelines give it a class 1 recommendation, so that's a settled debate. The issue is that there are a whole lot of reasons for which people are not on optimal medical therapy, and I think with the results of this trial, hyperkalemia should be stricken off that list, that there is nobody who should not receive optimal medical therapy because of hyperkalemia. Now realizing, obviously, accessibility and all of those real-life issues come in, but short of an alternate reason, hyperkalemia by itself should not be a reason to not optimally treat our patients.

Dr. Piña:
So, we should see registries doing better if this is, in fact, the case.

Dr. Anker:
Yeah, I would like to extend on what Javed just said, and simply go home and say, "Okay, hyperkalemia is an issue, but it's a manageable issue." And just do it.

Dr. Piña:
Yeah, I often wonder if we even believe how good these drugs are, and I think the COVID pandemic sort of taught us how good the drugs are that we use, the guideline-directed medical therapy. So, believe it, embrace it, and now we're giving you another tool to get the patients on it.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening, and I want to thank Dr. Pitt, Dr. Butler, and Dr. Anker for joining me today and sharing all their valuable insights. It was great speaking with you today. Have a great day.

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