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https://reachmd.com/programs/cme/potassium-binders-as-enablers-of-raasi-therapy-diamond-topline-results/13260/

Released: 02/22/2022
Valid until: 02/22/2023
Time needed to complete: 15 minutes

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Approaching Optimal RAASi Therapy with Use of Potassium Binders: DIAMOND Topline Results

Announcer:
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Dr. Butler:
Guidelines give strong recommendations to the use of RAAS [renin-angiotensin-aldosterone] inhibitors to reduce mortality and morbidity in heart failure patients. But unfortunately, patients are often treated with low doses, or not treated at all, because RAAS inhibitors increase potassium levels and can cause hyperkalemia.

There has been considerable clinical evidence for the use of potassium binders in the management of hyperkalemia in patients with heart failure, the most recent being the DIAMOND trial, which recently released topline results. So what is the value of these topline results and the total body of evidence for management of hyperkalemia, and what does this mean for our patients with heart failure?

This is CME on ReachMD, and I'm Dr. Javed Butler.

Dr. Anker:
My name is Stefan Anker, and I'm very happy to be here with you, Javed, and yeah, let's go into this.

Dr. Butler:
Great. Great to have you, Stefan. So as I mentioned, hyperkalemia is a real problem in these patients because it can lead to reduction of necessary therapies. We have seen evidence for the use of potassium binders to manage hyperkalemia and to enable patients to stay on recommended heart failure therapy. So with that context, can you tell us what is the DIAMOND study, and what do we expect to learn from it?

Dr. Anker:
Yeah, thank you so much. Well, the DIAMOND study is, first of all, a study investigating patiromer, which is a potassium binder, and doing this in the context of patients with chronic heart failure. The idea was to really investigate whether using patiromer, you can have an impact on the overall fate of heart failure patients with regards to their morbidity and mortality events, but even more so, with regards to the ability that they receive the best possible guideline-recommended therapy, particularly with MRAs [mineralocorticoid receptor antagonists] and RAASis in general, and that they do not experience toxicity events related to hyperkalemia, which is very frequently seen as, really, a problem for practicing physicians. And all of this be done in a randomized, controlled trial, which is, of course, complex.

With regards to the trial design, the complex part comes because, really, you are talking about the question of whether or not you randomize patients from the get-go with patiromer versus placebo or whether you first establish a situation where you have optimized the therapy according to the guideline with the help of patiromer in a run-in phase, where everybody is treated, and then you randomize them to actually being taken off the medicine or continue to receive the medicine and see what impact that makes on toxicity events, on

enablement of a full dose of MRAs, and then also, of course, on morbidity and mortality events. And so this option was taken – this option with a run-in phase where everybody's treated – and a randomized phase where people are then taken off medication in a randomized way. And we now, at least, have seen the topline results.

Dr. Butler:
So that's a great background. Now we have recently seen that COVID-19 has impacted a lot of trials. So how did the DIAMOND trial fare in terms of COVID-19?

Dr. Anker:
Well, thank you for asking, because that had a big impact on the overall conduct of the study. The study was planned originally to recruit 2,000 and a few hundred patients in order to investigate just morbidity and mortality with the cardiovascular death and heart failure hospitalization being the focus and the primary endpoint and then investigating all sorts of other things. Recruitment was slow, and particularly in some countries, it was really not possible to start the trial, so it's not only a slow recruitment, but also a relatively slow rollout of the trial around the world in those countries already then affected by COVID. And then, of course, we – and this is something we see in all heart failure trials – the event rates for hospitalization, which was the original kind of key component of the primary endpoint, are going down simply because people avoid hospitalizations, and they get managed with their heart failure in the ambulatory setting. So relatively too few events, relatively to the plan's too-slow recruitment, and so there was the need to do something about a trial and adjust it.

And actually, in the middle of last year, we came together, reviewing all of this, and we decided we should change the focus of the trial and its endpoints. And we did this, and the design paper of the study is out, and so we turned the trial really a little bit around and focused on potassium, focused on the durable enablement of MRA therapy and RAASi therapy in general and on toxicity-related events, on the background, of course, of the more morbid events with morbidity and mortality. But changing this trial really also meant that the power of the trial, of course, was dramatically changed. And instead of more than 2,000 patients, we now needed only 850 or so patients, and indeed, then could stop the trial middle of last year when we had a sufficient number of patients recruited for these new, revised set of endpoints that are COVID, essentially, adjusted.

Dr. Butler:
Yeah, you know, what you say is so important, because it's one thing to have sort of low event rate and maybe the trial going longer, but in this particular case, when you know that these patients either have hyperkalemia or are at higher risk, and then on top of that you are giving therapies that may exacerbate that problem and then not have close follow-up, close labs, the investigational drugs just aren't sent, I mean, that's really a problem. So I can totally understand how the study thought process evolved.

For those just tuning in, you're listening to CME on ReachMD. I am Dr. Javed Butler, and here with me today is Dr. Stefan Anker. We are discussing the topline results from the DIAMOND trial, and the role of potassium binders as enablers of optimal heart failure therapy.

So with that being said, what do you think DIAMOND trial potentially brings to our clinical understanding of the potassium binders for the management of our heart failure patients with hyperkalemia?

Dr. Anker:
Yeah, well, of course, you know that we can't discuss the results in detail here beyond saying what the press release said, that the primary endpoint of the study was met. And that means, basically, that potassium levels are, of course, affected, and we have to assume in a positive way. With the potassium binder in these patients, we can basically make an impact on potassium in real life using a potassium binder in this context of such a trial in the randomized space.

But then there was another important aspect – and this is stated in the press release as well – that during the run-in phase, actually it was seen that surprisingly many – and the number 85% was publicly mentioned also – that surprisingly many patients with a history of hyperkalemia or with current hyperkalemia – this is the patients we included in the trial – that they can actually tolerate a full dose of RAASi therapy despite physicians thinking previously that they couldn't tolerate it. But with the protection of a potassium binder, they indeed were able to tolerate the up-titration in the run-in phase, which was not a randomized phase. Everybody got exposed to this, so it's more like you might almost say like a registry of, really, that attempt to optimize therapy. But in this registry of more than 1,000 patients, 85% with a history of hyperkalemia, with current hyperkalemia, could tolerate full RAASi therapy when protected.

Dr. Butler:

You know, so this obviously was not part of the randomized study, but these results are probably equally important, as the randomized part, because if you talk to the clinicians, there is a general sense that patients who develop hyperkalemia sort of have a phenotype, right? So they're sicker – heart failure patients – more comorbidity, maybe more older, maybe lower GFR. The hyperkalemia, even if you were to take care of it, there are other reasons, like changes in creatinine and blood pressure and dizziness, that you will never be

able to optimally treat. But what you're saying is that that perception is just not true, and in these patients with documented hyperkalemia, either right now or in the past, 85% of the patients were able to be optimized on guideline-directed medical therapy, so that's actually pretty important.

Dr. Anker:
I think that gives a practical message that do not give up on patients receiving full guideline-recommended therapy at the full dose, which is the evidence-based dose, that we should all try to practice for our patients as the medicine they receive. And do not give up on this. You can achieve this, admittedly with some extra protection. But within a few weeks, you get these patients on the right dose that actually is known to improve their survival.

Dr. Butler:
So that's great. So in a similar sort of theme with whatever time we have left in this program, I'd like to discuss with you sort of this issue of clinical hesitancy towards the initiation and up-titration of RAAS inhibitor therapy and the strategies that a clinician may be able to employ to optimize therapy in our patients with heart failure/reduced ejection fraction, right? So can you make some comments about this hesitancy and how people may be able to overcome it?

Dr. Anker:
Well, first of all, of course you're right in saying that this is vulnerable patients. The elderly, in particular those with kidney dysfunction, and one group you didn't mention, I would like to add, diabetic patients. 30%-40% of patients with heart failure have diabetes, and so they are certainly amongst those that very often have the problem of hyperkalemia when you start new therapies, when you up-titrate, particularly MRAs.

And hyperkalemia is a problem. In the extreme forms, it can be life-threatening. Certainly, it's something that is an acute illness, often resulting in intensive care or at least a hospitalization kind of admission. And so we need to do something about this. We have a dilemma here, that this problem is there; it's looming. Versus the mandate to give the patient the best possible care according to the guidelines that is including, then, all the RAASi inhibitors and MRAs. And in that daily dilemma, where you are short of time – in COVID times now, particularly – have a problem that you can't so easily take lab values. You want to up-titrate, basically, an MRA. You should actually have, after 3, 5, 7, 9 days, at least 2 or 3 potassium assessments in the next 2 weeks.

And how do you want to do that, really, in the COVID time, when you try to reduce the number of visits? So in that scenario, having a mode of action by a drug that basically takes 100% care of the risk of hyperkalemia, that actually could be a very practical, useful thing for a clinician to have at their hand. But let's not forget, this was only the run-in phase. The randomized phase, we only know the headline result, that potassium values indeed were lower in those patients receiving patiromer. And there's other very interesting secondary endpoints, and we hope to learn very soon what the results for those are.

Dr. Butler:
You know, I find this whole notion of "first, do no harm" pretty interesting because, obviously, that's the cornerstone of sort of how clinicians think, and that's exactly how we should think, that first, do no harm. Except that I think this issue is much more nuanced because not giving appropriate therapy is actually, in a way, doing harm as well. So it's not only avoiding side effects but also improving patients' outcomes.

So can you, Stefan, share with us one take-home message that you have for our audience?

Dr. Anker:
Well, I believe that the DIAMOND study – diamonds are valuable – that the DIAMOND study results will be valuable, and I really look forward to the presentation that I believe yours truly is going to have, hopefully, at the American College of Cardiology if the trial is accepted for presentation there. And if not, then, of course, very soon thereafter in Europe at the European Heart Failure meeting; I really look forward to this. We should all be able to learn a lot from this study for the practical management of how best to resolve that dilemma of up-titration of RAASi therapy, preventing harm from hyperkalemia; maybe we can have both – no hyperkalemia and full therapy with RAASis.

Dr. Butler:
Really well said. So thank you very much. And unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Professor Anker, for joining me and for sharing all of your valuable insights. It was really great speaking with you today.

Dr. Anker:
Thank you so much.

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