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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Looking Beyond Diabetes: The Role of SGLT2i and MRAs in Cardiorenal Disease

Announcer:
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Dr. Kosiborod:
Hello, everyone, and welcome to today's Expert Perspective program. I am Dr. Mikhail Kosiborod, cardiologist at Saint Luke's Mid America Heart Institute, and it's my pleasure to speak with you today about the important topic of optimizing guideline-directed medical therapy [GDMT] in patients with heart failure and reduced ejection fraction [HFrEF] and management of hyperkalemia.

We know that optimization of guideline-directed medical therapy is a key goal of care in patients with heart failure and reduced ejection fraction, and we now have quadruple therapy – meaning 4 pillars of disease-modifying therapies – which include renin-angiotensin-aldosterone system inhibitors [RAASi] – that's ACE [angiotensin-converting enzyme] inhibitors, ARBs [angiotensin receptor blockers], and ARNI [angiotensin receptor neprilysin inhibitor] – as well as mineralocorticoid receptor antagonists [MRAs], beta-blockers, and SGLT2 [sodium glucose transporter type 2] inhibitors.

The guidelines for management of patients with heart failure and reduced ejection fraction are very clear in regards to introducing and optimizing rapidly these 4 pillars in patients with HFrEF. Here you can see the 2021 European Society of Cardiology Heart Failure Association guidelines, which give Class I level recommendation to all of the therapies that I just mentioned. The American guidelines, also very consistent with that. These were just issued earlier in 2022 from American Heart Association, American College of Cardiology, and Heart Failure Society of America. And again, you can see that all of these 4 pillars have the highest level recommendation, meaning that unless there is a contraindication of patient didn't tolerate therapy, if you're not using these, you're not really practicing optimal medical care for your patients.

Now, despite the fact that the clinical trial evidence is extremely strong in terms of the impact of these 4 pillars on those important outcomes that I just mentioned, they continue to be systemically underused across the Atlantic – both in the United States and in Europe. And especially when we look at the current management in real-world clinical practice from large registries in the United States, we see consistent underuse of these treatments. And these extend to renin-angiotensin-aldosterone system inhibition, as well as other guideline-recommended therapies, including beta-blockers and especially mineralocorticoid receptor antagonists.

We also see that there is a substantial gradient in that suboptimal use when we look at the patient's underlying kidney function as measured by eGFR [estimated glomerular filtration rate]. While that gradient is relatively minor for medications that don't have any significant effect on kidney function, such as beta-blockers, we see a very large gradient when it comes to renin-angiotensin-aldosterone system inhibitors, including ACE inhibitors and ARBs, ARNI, and especially mineralocorticoid receptor antagonists, where the use is suboptimal to begin with, but it drops off dramatically as eGFR declines. We also see it when we look at triple therapy, which includes ACE inhibitor, ARB, or ARNI, beta-blockers, mineralocorticoid receptor antagonists, where patients with lower eGFR have a dramatic underuse of these therapies.

Now, what are the reasons that we see this gradient across eGFR and general underuse of guideline-recommended therapies such as MRAs, in particular? We, of course, know that patients treated with MRAs, especially if their eGFR is low, would be at higher risk of developing hyperkalemia. And we know that hyperkalemia is associated with a higher risk of adverse events, including death, especially as the potassium levels go above 5 mEq/L, and of course, the higher the potassium levels, the greater the degree of association with adverse events. One of the key questions here is whether hyperkalemia actually is a cause of those adverse outcomes or whether it's just a risk marker.

Now, do we actually have evidence that patients with heart failure and reduced ejection fraction treated with MRAs who give out hyperkalemia still benefit from those agents? And the answer is absolutely yes. We have this data from MRA trials, including EMPHASIS-HF, where it's very clear that even those patients that develop hyperkalemia on eplerenone still do better, still have better outcomes than those patients that are treated with placebo. We also know from observational data that there is a very clear association between guideline-directed medical therapy, and specifically MRAs, being down-titrated to discontinued and subsequent increased risk of adverse outcomes.

So in this particular study, whether we look at patients with CKD [chronic kidney disease], heart failure, diabetes, or the entire population, we see that those patients that are on submaximal dose – and especially those that have had their MRAs discontinued – have much higher risk of subsequent adverse events than patients that are optimally treated.

Now, you can ask, you know, what am I supposed to do as a clinician if my patient with HFrEF is on ACE inhibitor, ARB, or ARNI and MRAs and develops hyperkalemia? What are my treatment options? There are a number of approaches that could be considered, and I think if you look at overall approach from expert consensus as well as that outline in the guidelines, is that you certainly should look at other options first, especially if hyperkalemia is mild or moderate and not severe, before down-titration or discontinuation of GDMT. That includes low-potassium diet and eliminating offending agents that don't provide cardiovascular benefit such as NSAIDs [nonsteroidal anti-inflammatory drugs] and trying to maintain RAASi treatment and, of course, monitoring potassium and kidney function carefully.

It's also acknowledged that in some patients, using novel potassium binders such as patiromer and sodium zirconium cyclosilicate [SZC] may be an option, and there are certainly patients where using potassium binders may be quite reasonable before RAASi treatment is down-titrated or discontinued.

2022 AHA/ACC/HFSA guidelines, there is a level 2B recommendation for use of potassium binders in patients with heart failure that experience hyperkalemia and are taking RAASi. That means that there is some evidence suggesting that benefit may outweigh risk, but of course, there needs to be additional evidence in that regard. Right now it's rated as 2B, which is considered a relatively weak level of evidence. In the 2021 ESC Heart Failure Association guidelines, it's acknowledged that kidney dysfunction and hyperkalemia are major causes of underuse for GDMT – especially RAASi and especially MRAs – and administration of potassium binders, such as patiromer or SZC, may allow enabling of a RAASi and optimization of RAASi in a larger proportion of patients.

We just talked about the fact that the level of evidence was considered by the guideline developers to not yet be sufficient for anything more than the level 2B recommendation, but of course, the evidence base in this space continues to evolve. And in that regard, it's important to mention the DIAMOND trial, which was presented at the American College of Cardiology earlier in 2022, and to date, that so far is the largest study to look at use of potassium binders as potential enabling strategy for RAASi optimization in patients with heart failure and reduced ejection fraction who either have hyperkalemia or at risk of developing hyperkalemia.

So how was the DIAMOND trial designed? The study included patients with heart failure and reduced ejection fraction that were either hyperkalemic, meaning that they had a potassium level of greater than 5 mEq/L on RAASi at baseline, or they could be normokalemic but be at risk for developing hyperkalemia, and that was a serum potassium level between 4 and 5 and a prior history of hyperkalemia that previously led to RAASi reduction or discontinuation. These patients were subsequently initiated on open-label patiromer during the run-in phase, and during that run-in phase the goal was to optimize the RAASi treatment, including ACE inhibitors, ARB, or ARNI, as well as initiation and/or optimization of mineralocorticoid receptor antagonists. At the completion of the run-in phase, those patients that were able to be optimized on RAASi and MRA and were normokalemic were then randomized. This was a randomized withdrawal design, which means patients were randomly assigned to either continue the patiromer or to be withdrawn from patiromer and switched to placebo.

Here you can see that patients on patiromer had significantly lower potassium levels. The difference was in absolute terms, modest – about 0.1 mEq/L – but highly statistically significant. But of course, it's important to keep in mind that after patients were randomized to the continuation of patiromer or withdrawal of patiromer, the clinicians were free to adjust RAASi treatments in accordance with their clinical judgment, which means that in patients randomized to placebo, if the potassium levels increased, there was a much higher likelihood of down-titration or discontinuation of RAASi treatments, so these potassium levels certainly need to be interpreted in that context.

The outcomes that I think are probably more relevant to clinical practice are secondary endpoints, and as we can see, use of patiromer led to a significant reduction in the risk of hyperkalemia events. This was consistent for hyperkalemia events based on laboratory measurements in the central laboratory, where that risk was reduced by 37%, with a hazard ratio of 0.63, and it was also consistent for events that were reported by investigators – events of hyperkalemia, where the relative risk reduction was quite similar.

In addition, use of patiromer led to a significantly lower risk of reduction in MRA dose below target, where again, here we see a 37% relative risk reduction and a likelihood of MRA dose reduction. I will point out, however, that majority of patients, even of those that were on placebo, were actually able to be optimized and maintained on MRA, even when they were withdrawn from a potassium binder and switched to placebo. And what that means is that in clinical practice, patients that either had hyperkalemia or those at risk for hyperkalemia could actually be optimized on MRA treatment and maintained on MRA treatment over a long time period without the need to down-titrate or discontinue MRAs and without the need to actually reduce it below target dose.

So the clinical take-home message here is that in large proportion of patients like this, the fear of hyperkalemia, when overcome, can actually lead to optimization of guideline-directed medical therapy. And of course, if you use a potassium binder, the likelihood of maintaining optimal MRA therapy is significantly greater.

Now, it's important to keep in mind that there are other things that can be done in addition to using potassium binders to reduce the risk of significant hyperkalemia in patients with HFrEF. And the good news here is that using those 4 pillars, including SGLT2 inhibitors when combined with MRAs, may actually lead to lower risk of significant hyperkalemia. So what we see here is the risk of developing mild or moderate to severe hyperkalemia in patients treated with MRAs when they were assigned to either dapagliflozin or placebo in the DAPA-HF trial. And here, we see that, especially when it comes to moderate to severe hyperkalemia and the likelihood of developing potassium levels of greater than 6 mmol/L, there is a 50% lower risk of developing that significant hyperkalemia in patients assigned to dapagliflozin versus those assigned to placebo. So here, you can essentially accomplish both goals at the same time, getting patients on those 4 pillars – that quadruple therapy that we know will extend life and improve symptoms and functional limitations in this patient population – and at the same time, when SGLT2 inhibitors are combined with MRAs, also reducing the risk of significant hyperkalemia. So again, optimization of GDMT itself can actually lead to lower risk of hyperkalemia with MRAs. In fact, I think it's an important clinical message here.

So what are the concluding thoughts here? I think the take-home messages are, number one, optimization of guideline-directed medical therapy is critical. And we really want to do everything possible to try to get patients with HFrEF on optimal GDMT as rapidly as possible. Hyperkalemia can be a rate-limiting step and is an obstacle to GDMT optimization in a large proportion of patients, especially those with compromised kidney function, and we know that that's one of the key reasons why GDMT is not optimized, unfortunately, to this day in a large proportion of patients with HFrEF. The tools that we have in our armamentarium to optimize renin-angiotensin-aldosterone system inhibition, and especially MRAs, is increasing and now includes novel potassium binders, including patiromer and SZC. The guidelines are beginning to recognize that this is a potentially important tool in enabling optimal RAASi treatment in patients with HFrEF, and the evidence base is emerging in this space, with the recent DIAMOND trial clearly demonstrating that using potassium binders in a patient population like this with HFrEF that either have hyperkalemia or at high risk of developing hyperkalemia can help optimize GDMT use and especially MRA use while maintaining potassium levels in a safe range.

So with that, I will close. Thank you very much for watching the program and take care.

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