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Maximally Tolerated or Suboptimal Therapy? Clinical Perspectives on Rechallenging RAASi Therapy

Announcer:
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Dr. Piña:
In the treatment of our patients with heart failure, RAASi [renin-angiotensin-aldosterone system inhibitor] therapy, especially the use of MRAs [Mineralocorticoid receptor antagonists], is often delayed despite being a crucial part of medical therapy. Whether due to misplaced caution or clinical inertia, the evidence is clear that the suboptimal use of these therapies leads to poorer outcomes for our patients. So how can we approach this clinical stigma surrounding the use of MRAs, and what strategies can we employ to better ensure the very best medical therapy, possibly, for our patients with heart failure.

This is CME on ReachMD, and I am Dr. Ileana Piña, and with me is Dr. Patrick Rossignol, a wonderful friend from the University of Nancy in France. Patrick, welcome.

Dr. Rossignol:
Thank you very much, Ileana. Very pleased to meet you today.

Dr. Piña:
Let's talk about these things. You and I have had these conversations before, so let's use a patient case that unfortunately we see more often than we would like to. So, let's say we have a 62-year-old woman with a history of heart failure with reduced ejection fraction, so HFrEF, 36% ejection fraction and CKD [chronic kidney disease], with a GFR of 37. So, this is in your camp. Three weeks after a hospitalization for an acute exacerbation of heart failure, she comes to your clinic for follow-up. Currently on furosemide, lisinopril, carvedilol, and atorvastatin. Vitals are stable, but her serum potassium is 5 mEq/L. What do you see as one of the main issues in the medical management of this patient, and what factors contribute to this?

Dr. Rossignol:
First of all, one may notice that this patient is neither receiving an SGLT2 [sodium-glucose co-transporter 2] inhibitor, nor an MRA, while both drugs are universally graded with a 1A. Actually, such recommendations are obviously more recent for SGLT2 inhibitors. Concerning MRAs, registry data repeatedly showed that suboptimal and underuse of MRAs are associated with worse outcomes. Major hurdles throughout MRA use encompass hyperkalemia, worsening renal function on CKD. While our patient is indeed presenting with CKD, but some potassium does not meet a hyperkalemia definition. However, many physicians could be reluctant to initiate an MRA owing to the risk of developing hyperkalemia in this CKD setting. Strikingly, recent analysis from the Get With the Guideline Registry, published 2021, in JACC by Patel observes that evidence-based medical therapies, including those without EGFR [estimated glomerular filtration rate] restrictions, were suboptimally used in patients with comorbid HFrEF and CKD, even at levels of EGFR where such therapies would not be contraindicated by kidney dysfunction.

Furthermore, there was a marked decrease in prescription rates of triple therapy associated with low EGFR categories. Patel rightly concluded risk treatment paradox exists in the management of patients with HFrEF and comorbid kidney disease, such as patients with the highest mortality actually treated with lesser disease-modifying medical therapies.

Dr. Piña:
So, these are really important points, and I like hearing that a potassium of 5 is really, to you, certainly not hyperkalemia, but it would be for a lot of physicians. So, I think your points are extremely well taken.

Now, what evidence-based approach should we use in rechallenging RAASi therapy? Let's say that this patient gets her lisinopril, for example, taken away because her potassium is fine. What do we know about the data of rechallenging a patient? And just because the potassium has been higher at one point, does that mean it's going to be forever?

Dr. Rossignol:
We should keep in mind that dynamic management was implemented in the major trials, such as RALES, EMPHASIS, and EMPHASIS-HF. In other words, the study drug could be temporarily discontinued in case of hyperkalemia and resumed to the highest tolerated dose as soon as the potassium got back to the normal. The latest 2022 AHA/ACC/HFSA guidelines acknowledge that the development of worsening renal function or hyperkalemia is often a reflection of acute clinical change or progressive disease, prompting careful evaluation of the on-time medical regimen and other causes of hyperkalemia, in addition to all things MRA. Furthermore, the ESC heart failure guidelines propose practical guidance with quasi-algorithmic tables and the use of MRAs in patients with heart failure with reduced ejection fraction as a function of potassium and EGFR in order to get the highest tolerated doses to the patients. Obviously, thorough serum potassium monitoring is indeed warranted in patients who are treated with an MRA, and the ESC heart failure guidelines recommend to check blood chemistry at 1 and 4 weeks after starting increasing dose, and at 8 and 12 weeks, 6, 9, and 12 months, and 4 monthly thereafter. Second, close potassium monitoring is especially warranted under potassium-lowering agents.

Dr. Piña:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ileana Piña, and here with me today is Dr. Patrick Rossignol. We are discussing the challenges surrounding the use of MRAs and effective strategies to ensure the best medical therapy for all our patients with heart failure.

I love that last comment, because for the first time, we are actually seeing in the guidelines some recommendations about using the potassium-lowering agents that we have available. I think it's also important for the clinicians to hear that they need to ask the patient if they're taking potassium salts, because with heart failure we often say to the patients, "You have to cut down your salt intake. You have to cut down your sodium." And what do they do? They go buy salt substitute, which is, in fact, potassium salts. So that's a very important question to ask the patient, which they may not think of telling you, because they may not realize that that salt substitute is, in fact, potassium salts.

And we know that lowering potassium in foods doesn't always work, but I do go through the exercise of saying to patients, "There are foods that are very high in potassium." And we have in our own patient education booklet a whole page of listing of foods that are high in potassium, things like orange juice – even strawberries have a lot of potassium. So I think the better educated the patient is, the better they can handle it.

What do you think, Patrick, with what we now have in the guidelines and the potential for potassium binders that would actually support or even the word "enable" the ability to get these drugs on the patients?

Dr. Rossignol:
Yeah, you are totally right, Ileana. Indeed, the latest 2021 ESC Heart Failure guidelines stated that the administration of the K-lowering agents, patiromer or sodium zirconium cyclosilicate, may allow renin-angiotensin-aldosterone-system inhibitor initiation or up-titration in a larger proportion of patients. Furthermore, the latest 2022 heart failure guidelines – the US guidelines – acknowledge that in patients with heart failure who experience hyperkalemia – in other words, serum potassium level above 5 mmol/L – who are taking renin-angiotensin-aldosterone-system inhibitor, the effectiveness of potassium binders to improve outcomes by facilitating continuation of RAASi therapy's uncertain, and was therefore graded with a 2b B-R.

In this setting, importantly, the DIAMOND trial data just presented at the ACC meeting showed that in HFrEF patients, either hyperkalemic or prone to experience hyperkalemia owing to a history of hyperkalemia leading to RAASi reduction or discontinuation, optimal RAASi therapy was enabled in 85% of the patients during the run-in phase, while all patients were treated with patiromer. Secondly, during the double-blind, randomized, placebo result phase, patiromer used simultaneously reduced the risk of recurrent hyperkalemia and enabled guideline-recommended RAASi use. In our patient case, an MRA was indeed initiated at low doses, but a mild hyperkalemia occurred, which was successfully treated with patiromer, while MRA could be subsequently up-titrated to the target

dose.

Dr. Piña:
Yeah, this is a great case. I see these patients all the time, and they come in and the MRA is not on board. And what I would have done with this woman is started her on spironolactone, perhaps even at 12.5, depending upon how quickly she can come back to get her labs drawn or could she get her labs drawn in an outside laboratory. And I would start the SGLT2s then, too, because we do have some data that when the SGLT2 inhibitors are started, the potassium may actually drop some. And so we may be able to stay on it for a longer period of time. But I am very happy that the guidelines, for the first time, really talk about this as using it as an enabler to get the patients on the right drugs, because that's really what we want.

So, it's been a great conversation with you, Patrick, but before we wrap up, give me one good take-home message for the clinical audience that's with us today.

Dr. Rossignol:
Sure. Guideline-recommended therapy best practices, including proper biological monitoring, should be definitively implemented in our patients with heart failure.

Dr. Piña:
So, then, my final take-home message is really do whatever you can do to get the patients on the right drugs, because now we know that withdrawing the RAASi therapy is actually not beneficial and that there are curves that we have very clearly showing that the patients who get discontinued are as bad as the patients who are never started.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Rossignol, for joining me and for sharing all of your valuable insights. As usual, it was great speaking with you today.

Dr. Rossignol:
Thank you so much, Ileana. You're very welcome.

Announcer:
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