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Implementing the latest evidence on novel potassium binders for achieving long-term goals

### Dr. Wong:

Hi everyone. I'm Aaron Wong from the United Kingdom. It's my great pleasure here to share with you some practical considerations when implementing latest evidence of novel potassium binders for achieving long-term goals.

These are my disclosures.

So we know that RAASi therapy is a foundational therapy recommended by multiple organization in national as well as international guidelines in the treatment for heart failure, CKD, and type 2 diabetes. However, what is actually recommended and what is actually prescribing? There's a substantial gap between this recommendation and the actual real-world prescribing pattern. Many registry data has highlighted that there is a big gap of RAASi prescription in real life. So a lot of these patients, they are either not on RAASi therapy or they are not on the dosing recommended by all these international guidelines.

The dosing of RAASi therapy is really important because it can translate into a better outcome, and many registry data has also highlighted that discontinuation of RAASi therapy can lead to adverse outcomes, even up to two- to threefold increased risk of adverse events, particularly in patients with heart failure and CKD.

So if you know that what the guidelines is recommending is what it's actually prescribing, there is a big gap. So what are the common reasons for stopping or not optimizing therapy? So hyperkalemia, renal dysfunction, hypotension, and age are by far the commonest reasons for not optimizing therapy. Recent trials have shown that patients who are older with increased frailty index, they do derive benefits from standard heart failure therapies, particularly with regards to the quality of life. Hypotension can be a hindrance for us to initiate and optimize RAASi therapy, and we should try to stop all the non-prognostic, antihypertensive agents to allow room for initiating and optimizing RAASi therapy.

In the past, some of us may have thought that RAASi therapy are nephrotoxic, but actually RAASi therapy, they are nephroprotective. Studies have shown that patients with a lower GFR who are on RAASi therapy, they actually do better than those with a higher GFR without RAASi therapy. And lastly, recurrent hyperkalemia can be a barrier for us to optimizing RAASi therapy. Indeed, in 2024, a recurrent hyperkalemia, recommended by many guidelines, should not be the main reason for not optimizing RAASi therapy.

So this is a very interesting study from the ESC Heart Failure Long-Term Registry. The authors highlighted that the levels of potassium do correlate with poorer outcome. A low potassium and a high potassium are not good for our patient. However, when they performed a mediation analysis of this, including discontinuation and not starting RAASi therapy into the analysis, they discovered that hyperkalemia is no longer the risk factors for mortality, but hyperkalemia, in fact, is a marker for not initiating and discontinuation of RAASi therapies. It's actually the discontinuation of RAASi therapy that translates into the worst outcome in patients with hyperkalemia.

So as a physician, when we are confronted with a problem of hyperkalemia, and on the other hand, we thought that these patients should benefit from the RAASi therapy, so what should we do? So the temptation here is to stop or reduce the RAASi therapy. However, this registry data and recent international guidelines suggested that stopping or reducing RAASi therapy are harmful to our patients, and

we should try our best to optimize RAASi therapy as much as possible.

So I'm just going to present to you a real case. This is one of my patients from last year who presented with the standard heart failure signs and symptoms, with a high NT-proBNP level of 4,500 with a very low ejection fraction of 10%. So the patient was admitted to the cardiac ward, and the patient was offloaded with IV diuretics, and we started the patient on 4-pillars therapy, as per guidelines. So when the patient was discharged and followed up, we continued to up-titrate the RAASi therapy. As you can see here, when the eplerenone dose was increased to 50 mg once a day, we can see a spike of potassium levels and a slight worsening of kidney function. So in this situation, the patients are not on optimal guidelines-recommended therapy yet for heart failure, following an admission with decompensated heart failure.

So may I ask you a question? What would you do in this scenario? Would you stop the eplerenone and just keep watch on the kidney function? Or would you stop both eplerenone and sacubitril valsartan and keep watch on the kidney function? Or would you, because of the potassium of 5.9, would you even admit the patient for the management of acute hyperkalemia? And lastly, would you think about starting the patient on the novel potassium binders and continue to optimize RAASi therapy?

So I'm going to share with you what I did in this situation. I started the patient of sodium zirconium cyclosilicate 10 g 3 times a day to normalize the potassium level. As you can see here, within 24 hours, the potassium level dropped from 5.9 to 4.9, so I didn't pause the RAASi therapy. In fact, I up-titrated the sacubitril valsartan the following day, with the help of sodium zirconium cyclosilicate as an enabler for me to do so. So within 2 to 3 months since this serious admission with decompensated heart failure, the patient is now on the optimal 4-pillars therapy for heart failure with reduced ejection fraction, with the help of sodium zirconium cyclosilicate as an enabler to achieve that.

So let's go through some of the major guidelines. So the KDIGO, the kidney guidelines, and the cardiology ESC/AHA guidelines, they all recommended using 1 of the 2 novel potassium binders as an enabler to allow a maintenance and optimization of RAASi therapy in both heart failure and CKD. The latest KDIGO guideline suggested that we should try our best to maintain RAASi therapy. So we should correct acidosis, we should correct fluid overload with diuretics, and we should think about using the novel potassium binders. Reducing the dose or stopping the RAASi treatment should be the last resort.

So we are very lucky, in the last couple of years, we have 2 compounds, 2 new novel potassium binders that in clinical trials have shown that they are very, very good to maintain potassium levels when they are on the binders. When this binder was stopped at the end of the trial, you can see a rebound hyperkalemia. That indicates that these patients do have a genuine risk of recurrent hyperkalemia.

So this is the study from the DIAMOND study, showing that with the use of patiromer, which not just controlled the potassium levels, but allowed continuation of a prespecified high-dose MRA in this group of patients. For sodium zirconium cyclosilicate, both in clinical trials and also in the real-world setting, also show that with the use of the binders as an enabler, the majority of patients we can continue on RAASi therapy as much as possible.

So in the recently published ZORA meta-analysis of K binder and RAASi therapy is not just showing that the discontinuation of RAASi therapy translates to adverse cardiorenal outcome, but this real-world evidence also shows that with the use of sodium zirconium cyclosilicate, 74% of these patients can actually maintain on this prognostically important RAASi therapy.

So the Delphi consensus consists of a group of expert cardiologists and nephrologists. They're all recommending that hyperkalemia should be recognized as a predictable, treatable, and a manageable side effect of optimal heart failure and CKD therapy, and RAASi discontinuation or dis-escalation should be the last resort. And we should think about using the novel potassium binders to optimize the RAASi therapy in patients with heart and renal failure.

So prior to considering using these novel potassium binders as an enabler to optimize RAASi therapy, what should we do? We should always do the basics first, review the cause of heart failure and kidney failure, and think about what causes the hyperkalemia. Are there any reversible causes of hyperkalemia? If there are not, we should then think about a strategy to overcome the risk of recurrent hyperkalemia. We should review the medication, review the patient's diet, and perform a very thorough clinical assessment of our patient. If the patient is overloaded, we may use higher doses of loop diuretics. If the patient is acidotic, we may then think about a strategy to correct the acidosis. We should also think about what types of heart failure the patient has, because there would be a different impact of RAASi therapy in the different types of heart failure.

And lastly, we should always involve the patients and the patient carer in the discussion. There's no point giving the patient medication, but the patients do not know how to take it or they are not compliant with it. So I think it's important to explain to the patient the importance of taking the K binders and the importance of taking the RAASi therapy, and what should they do or the carer do when these

get changed. So I think it's really important to highlight that collaboration, not just with the patient, but sometimes we may even need to ask our friends as a nephrologist, as a diabetologist, and then we work together as a team to deliver a high level heart failure and renal care to our patients. So guidelines like that in your local setting may be beneficial.

This is one of our local guidelines of giving recommendation of how to adjust sodium zirconium cyclosilicate dosing and RAASi therapy in a patient who has been stabilized on this medication. And we also give recommendation about the frequency of how regular we need to check the potassium levels and the kidney function. So this would empower other allied healthcare professionals to have the confidence to continue to prescribe these K binders and RAASi therapy in this group of patients.

So in conclusion, we highlighted that the RAASi therapy are the cornerstone treatment for patients with heart and kidney failure, and they are recommended by international guidelines. Hyperkalemia can be a barrier to optimize RAASi therapy. However, we do have novel potassium binders to act as an enabler for us to get over this barrier to allow us to optimize the lifesaving therapies RAASi therapy for our patient. So a selective use of the potassium binders in a selective group of patients can translate into a better uptake of guidelines-recommended RAASi therapy, and also the guideline-recommended dosing as well.

So thank you very much for your attention.