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Challenges of managing hyperkalemia in HF patients with CKD while maintaining RAAS inhibitor therapy

Dr. Savarese:
Welcome, I'm Dr. Savarese from Karolinska Institute in Stockholm, Sweden, and today we will discuss challenges of managing hyperkalemia in heart failure patients with CKD while maintaining RAASi therapy.

This is the list for my disclosure.

Hyperkalemia is extremely frequent in patients with cardiorenal disease. Here, you can see like an overview of prevalence of hyperkalemia in patients with different cardiorenal metabolic diseases. You can see that in patients with heart failure reaches over 40%, in patients with CKD up to 50%, around 20% in patients with diabetes and hypertension. This clearly show that this is a very actual problem in our patients with cardiorenal disease.

And the problem is not only that hyperkalemia is frequent; it is also very much recurrent. What does it mean? For example, if we consider patients with heart failure, 40% of those might have a hyperkalemic event, might have a recurrent event. And even more might have a second event. And might even more a third event. And the time frame between one event and another will become shorter together with increasing numbers of hyperkalemic event. So assessing the risk and management of recurrent hyperkalemia is particularly important.

Which are the risk factors for recurrent hyperkalemia and hyperkalemia? Well, in patients with CKD, heart failure is a risk factor. In those with heart failure, CKD is an important risk factor. And overall, in patients we meet in our daily clinical practice, a declining eGFR is a risk factor for hyperkalemia and comorbidities such as, for example, diabetes.

More severe versus less severe heart failure is also associated with increased risk of hyperkalemia. And, very importantly, also spironolactone. So MRA use and ACE, which are lifesaving treatment in patients with heart failure and CKD, are associated with higher risk of hyperkalemia. But in any case, we should not consider this factor. So RAASi treatment is a reversible risk factor for hyperkalemia. We will see more in the remaining part of the presentation that we should consider this as irreversible risk factor for hyperkalemia, something which actually we should try to avoid discontinuing these treatments in order to reduce the risk of hyperkalemia. So this is a very important message to keep in mind.

So you see in this tally from the Swedish Heart Failure Registry we performed a few years ago, that actually the incidence of hyperkalemia is high in these patients. It's around 25% for getting any potassium measurement over 5 during 1-year follow-up. And what is also important is that there is an increased risk of mortality associated with a hyperkalemic event. So it's true that hyperkalemia is frequent, and it's true that it's associated with increased risk of mortality. But it's very important to remember that in clinical practice, unfortunately, many of us discontinue a RAASi therapy in patients with cardiorenal disease because of actual hyperkalemia or because of fear for hyperkalemia. And part of the association between hyperkalemia and poor outcome might be actually explained by the withdrawal of these treatments rather than the role of hyperkalemia per se in determining an increased risk of all-cause mortality.

I was speaking about fear for hyperkalemia. This leads the discussion to the barriers to the implementation of GDMT in clinical practice,

in particular of what concerns patients with heart failure. And you see in this survey we performed with the Heart Failure Association of the European Society of Cardiology, that actually hyperkalemia is listed among one of the most important and the most heavily perceived barriers to the implementation of GDMT.

Up to 50% of physician might say that hyperkalemia actually is an implementation of GDMT in their clinical practice. And if you look at the right side of this slide, you might also see that the way physicians react to hyperkalemia, their first strategy is actually, unfortunately, to withdraw MRA treatments in 54% of the cases. But we know very well, and we will see more later, that actually there are other strategies to handle hyperkalemia rather than discontinuing lifesaving treatments such as MRA, RAASi, ARNI in patients with GDMT, and we will see more about K binders in this survey, actually, around 20% were suggesting the use of a novel K binder as a strategy to the management of hyperkalemia.

And what is also concerning is that most physicians will react to a potassium level more than 5. So 25% will react with mild hyperkalemia, unfortunately most of the cases, by withdrawing lifesaving treatment, which I think might lead to increased risk of mortality, not because of hyperkalemia, but because of the withdrawal of lifesaving treatments. And we see in the study, again from Swedish registries, that after, unfortunately, a hyperkalemic event, 47% of physicians might discontinue an MRA, and 10% reduce their doses. And what is important is that 74% of patients who got discontinued or got MRA discontinued will not reinitiate the treatment over a follow-up of 1 year. So once it's withdrawn, it's likely not to be reintroduced.

In this slide, we also see that discontinuation of MRA is associated with increased risk of mortality. So once again, do not withdraw RAASi, but manage hyperkalemia in a different way. Very important focus of scientific societies and care in general in patients with heart failure is trying to understand how to handle patient profiles, and whether we understand that different treatments have a different role of potassium homeostasis, we can actually understand that we can prioritize some treatments rather than others, actually, to try to slightly decrease the risk of hyperkalemia.

If we considered the PARADIGM-HF trial, we see actually that patients on sacubitril/valsartan at lower potassium level as compared to those randomized to enalapril, and this allowed also higher use of MRA in those receiving sacubitril/valsartan. In the middle, you see that in the EMPEROR trials, patients receiving empagliflozin were less likely to discontinue an MRA, and this is slightly due to the lower risk of hyperkalemia in patients receiving SGLT2 inhibitors.

On the right, you see a meta-analysis of trials in the diabetes field on SGLT2 inhibitors where patients on SGLT2 inhibitors where at lower risk of hyperkalemia. When it comes to MRA, and this is particularly important during the ESC Congress, where we'll see more data on finerenone, is to actually consider that nonsteroidal MRA are linked to a lower risk of hyperkalemia as compared to eplerenone and spironolactone. So in the future, probably, we could also better use this drug and others to decrease the risk and in patients at risk or with hyperkalemia.

We also know when actually the finding the best therapy for our patients with HFrEF, that some treatments have no effect at all on potassium homeostasis and vericiguat is one on that. You see in the VICTORIA trial, no impact at all of vericiguat on potassium levels as compared to placebo. And on the right, you see same thing for omecamtiv mecarbil, although this is not approved at the moment in Europe and US. And then very importantly, nowadays we do have a treatment for actually treating patients with hyperkalemia and reducing the risk of recurrent hyperkalemia, which leads to the chance actually to foster better GDMT implementation, and we are talking about novel K binders.

This is the HARMONIZE study on SZC, where you can clearly see that the treatment was effective in reducing 98% of the cases. Here, we have patients with hyperkalemia indeed reduced potassium levels to normokalemia within 48 hours following the hyperkalemic event. So a treatment which works in acute phase of hyperkalemia. And then you also see that during the follow-up, the treatment was able to maintain normokalemia, which allows to implement GDMT in clinical practice. Even if we talk about heart failure or CKD, it doesn't matter.

During the extension phase of the trial, it was shown still very good maintaining effect on potassium levels, but as soon as the treatment was discontinued, actually, the potassium level went up once again, which means that these heart treatments to be used chronically.

We have also results on another novel K binder, which is patiromer. Patiromer has a slower onset of effect, so probably not the best treatment to be used to reduce potassium in the acute setting, but you can see works extremely fine as well for maintaining low potassium level in the chronic setting. And as soon as also in the study, in AMETHYST, actually the treatment was discontinued, actually, potassium level went up as well.

We have also data from real world where it's clearly shown that patients on SZC and on patiromer in real-world practice were able to maintain better RAASi use, meaning yes versus no or higher dose as compared to those who were not in treatment, which clearly I liked

the role of this treatment as an enabler for GDMT implementation. These data were true for SZC and for patiromer.

The DIAMOND trial is one of the most recent, which has been delivered for patiromer focusing on patients with heart failure with hyperkalemia or at risk of hyperkalemia. Patiromer, as compared to placebo, led to lower potassium levels, but even more importantly, it allowed to maintain MRA target dose in more cases and reduced the overall number of hyperkalemic events and also led to better implementation of RAASi over time. Once again, in this trial, you see very well how this treatment, in this case novel K binders, can lead to better GDMT implementation in clinical practice by reducing the risk of recurrent hyperkalemia.

More or less similar setting for the REALIZE case study, which is instead focusing on SZC, enrolling patients with hyperkalemia or at risk of hyperkalemia randomized to SZC plus spironolactone versus placebo plus spironolactone. The trial is ongoing and will tell us more about the role of this drug on important outcome and the role on GDMT implementation.

In current European guidelines on heart failure, the role of novel K binder is very clearly highlighted in patients who have a potassium level more than 5. A K binder may be initiated in order to optimize GDMT treatment while managing the risk of hyperkalemia. RAASi might be discontinued only in cases such as K level extremely high, such as potassium over 6.5. Also, the kidney guidelines highlight very clearly the role of potassium binders for the management of hyperkalemia, together with reviewing other drugs affecting potassium homeostasis, checking diet, using diuretics, and soluble bicarbonate.

So together with many colleagues from many European countries, we established the GUARDIAN-HK committee, which aims actually to provide guidance in daily clinical practice for the management of hyperkalemia. And we provide recommendation regarding duty of care, identifying patients at risk of hyperkalemia recurrence, and managing the risk of hyperkalemia recurrence.

When we meet in daily clinical practice a patient with hyperkalemia, the first step should be, of course, to try to reach normokalemia and to correct reversible precipitating factor for hyperkalemia. Once this is done, it's important to lead a proper risk assessment for hyperkalemia recurrence, which should be part of standard practice of physicians meeting these kind of patients. And all our care providers are actually responsible for evaluating the risk of recurrent hyperkalemia once they meet the patient with hyperkalemia.

There might be reversible causes, which might be identified, or there might be no reversible causes, which might be linked, of course, to the comorbidity burden and patient characteristics. It's important that the assessment of hyperkalemia recurrence should be performed while considering that RAASi should not be discontinued, but there are other strategies too for the patient at risk of hyperkalemia recurrence. And therefore, actually, RAASi should be considered, as I said at the beginning of this presentation, an irreversible factor for hyperkalemia.

Once the risk assessment has been performed and patients are at high risk of recurrent hyperkalemia, actually treatment should be started. And K binders actually are the ideal treatment for preventing other hyperkalemic event. And during treatment with a K binder, so the risk of hyperkalemia is under control, optimization of RAASi should be performed, and each medical encounter should be an opportunity for RAASi optimization. And it's important to remember that the treatment with a K binder should be indefinite because these patients might have a comorbidity burden, which actually sets them at chronic high risk of hyperkalemia.

And whether patients are on a K binder or they are at very low risk of hyperkalemia, no further follow-up for potassium level is necessary beyond the one which is performed in daily clinical practice for these kind of patients.

So to conclude, hyperkalemia is frequently recurrent and associated with poor outcome in patients with cardiorenal disease. Several comorbidities, such as CKD, heart failure, and diabetes, are irreversible risk factors for hyperkalemia. And also, MRA and RAASi use are risk factors for hyperkalemia, but these should be considered as irreversible risk factors as well because we should not discontinue with these treatments because of the risk of hyperkalemia. And recent oral potassium binders provide potassium reduction with potential to allow patients to avoid recurrence of hyperkalemia and maintain and increase the dose of RAASi therapy.

Thank you very much for your attention.