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Challenges of managing hyperkalemia in patients with cardiorenal disease while maintaining RAASi therapy

Dr. Savarese:
Today, we are discussing challenges of managing hyperkalemia in heart failure patients with CKD while maintaining RAASi therapy.

This is the list of my disclosure.

So why do we need to talk about hyperkalemia? Hyperkalemia is extremely frequent among cardiorenal patients. Here, you see how frequent it is in several different conditions. So you see that in advanced CKD we have a prevalence of 50%, hemodialysis more than 25%, heart failure 40%, and this will be very much the focus today, diabetes around 17, hypertension between 8 and 17, and in the general population, it's between 2 and 3%.

The problem with hyperkalemia is that it's not only very frequent, but it's also recurrent. What does it mean? It means that whether a patient with CKD, for example, with heart failure, get a first hyperkalemic event, it will be very much likely they will get a second one. And then there will be a third one, and the third one will happen a little bit earlier as compared to the timeframe between the first and the second event. So hyperkalemia is frequent and it's recurrent.

Here, we see those patient characteristics which are linked with hyperkalemia, and they are also linked actually with recurrent hyperkalemia. So heart failure is clearly a reversible risk factor for hyperkalemia in patients with CKD, as well as CKD is a reversible risk factor for hyperkalemia in patients with heart failure. It's very interesting to see that in both conditions, as soon as the eGFR gets lower, actually the risk of hyperkalemia increases.

Other reversible factors associated with the incidence of hyperkalemia and recurrent hyperkalemia is actually diabetes. And of course, use of treatments which affect potassium homeostasis like spironolactone and RAASi. And I say reversible risk factor; we should really consider these irreversible risk factors, because patients should never withdraw these treatments, but we should try to find other strategies to address hyperkalemia while patients are on spironolactone and RAASi.

Another important point is that the risk of hyperkalemia actually increases together with the severity of heart failure. So you see that in patients with higher NYHA class actually, the risk for hyperkalemia is higher.

There is another important factor. Here, you see an analysis on around 45,000 of the heart failure patients from the Swedish Heart Failure Registry, and you see how common it is that a CKD and type 2 diabetes are co-prevalent in patients with heart failure across the entire ejection fraction. Around 50% of patients had CKD alone, around 24% had type 2 diabetes, and 13% had actually both of them.

Hyperkalemia in a similar cohort from Sweden, this is data from SwedeHF linked with the SCREAM registry, actually had an incidence of 25% when hyperkalemia was defined as a potassium over 5, and around 10% when it was defined as a potassium over 5.5; that's moderate/severe hyperkalemia. And you clearly see in this study that, of course, hyperkalemia is associated with increased risk of mortality. But it's very important to highlight that at least part of that association, so increased risk of mortality be linked to hyperkalemia is actually mediated by the fact that we withdraw in clinical practice very often guideline-directed medical treatments for heart failure, but also for CKD, because of hyperkalemia or because of the fear for hyperkalemia.

And this is a survey which have been performed with the Heart Failure Association of the European Society of Cardiology, where it's immediately clear that, according to physicians, according to 45% of them, actually hyperkalemia is a major barrier to the implementation of GDMT; in this case, of course, RAASi. And in case of an hyperkalemic event, we also see in this survey that, unfortunately, 60% of physicians will react, directly discontinuing MRA without giving an attempt even to novel potassium binders.

Once again comorbidities are, of course, linked to actually the likelihood of getting implemented GDMT. These are data from the EVOLUTION Heart Failure study, where you see that implementation was limited over the time, but it was even more limited in patients with type 2 diabetes and in patients with CKD. And this is very, very important, because actually this condition, as we saw, are extremely relevant and frequent in patients with heart failure.

And you see clearly here that CKD is actually one major barrier to the implementation of GDMT very often perceived. Why do I say perceived? There is no reason why patients with an eGFR between 30 and 45 should not receive a RAASi or an MRA. But you see in this study that as soon as renal function gets lower, actually the likelihood of receiving a GDMT decreases. And this is true even for eGFR ranges, where we know that MRA and RAASi are effective and they are safe.

Very important to note that whether patients get discontinued an MRA because of an hyperkalemic event, for example, it's very unlikely that they will restart later. That's why we should not discontinue. And it was also observed the same study, actually, that patients discontinuing MRA were at higher risk of mortality. So discontinuing MRA, unfortunately, is frequent following an hyperkalemic event, and it's associated with worse outcome.

And is it really needed? We tend to discontinue MRA in patients with an eGFR of less than 30. And if you check this study from the Swedish Heart Failure Registry, you see that whether patients can undergo a regular check of potassium and creatinine level, even if they have an eGFR of less than 30, and they are already on MRA when they get such a low eGFR, actually, the use of MRA doesn't get associated with any safety issue. So probably we should really discontinue MRA in those patients who are very much in need of discontinuation, and not all patients with eGFR less than 30 are in need of discontinuation.

We should not forget that some treatments might help some other treatments and work as an enabler for GDMT. For example, sacubitril valsartan is associated to lower increasing potassium level as compared to RAASi, and therefore might act as an enabler for MRA use. And this is even more clear with SGLT2 inhibitors, as you see in this analysis from the EMPEROR trial, where patients actually on empagliflozin were very much less likely to discontinue an MRA probably due to the fact that SGLT2 inhibitors decrease potassium – the risk of hyperkalemia.

And very important, SGLT2 inhibitors are relevant in the field also because they are a treatment for CKD. So you can see in the EMPA-KIDNEY and the DAPA-CKD that actually SGLT2 inhibitors reduced the risk of renal outcome in very broad populations. So reason more actually to use SGLT2 inhibitors in this population.

And one more treatment which might help us to fight against the risk of hyperkalemia is finerenone. Finerenone is indeed associated with increase in potassium levels, which are lower as compared to eplerenone, as shown in this randomized controlled trial.

Don’t forget that some other treatments we use for heart failure actually are not really linked with any change in renal function and potassium level, and this is indeed the case of vericiguat and omecamtiv mecarbil, which might be a very important weapon when we handle patient profiles with impaired renal function and very high risk of hyperkalemia.

But we are very lucky nowadays because we have a very good treatment to try to enable the use of RAASi and MRA in patients with heart failure. And these are, of course, the novel K binder. And we see here data from the HARMONIZE trial, this is on SZC, and you can see in this population with hyperkalemia that SZC 10 g was very effective in reducing, within 48 hours, levels of potassium. As well, it was very effective at maintaining potassium levels over time, and this was also observed in the long-term follow-up of this randomized controlled trial.

We see more data this time from AMETHYST-DN trial. And here, you see another novel K binder, patiromer. It takes a little bit longer to decrease potassium level, but very good as well to maintain potassium levels in a range where we can implement GDMT over time. And once again, we see data from randomized controlled trial as well from registries, where it's very clear that novel K binder works very well as enablers. So they work very well in maintaining same RAASi dose over time in patients at risk or with an episode of hyperkalemia. Similar findings actually from the PEARL-HF study.

The most recent trial which has delivered findings in the field has been the DIAMOND trial. The DIAMOND trial was addressing a population with HFrEF, so the ones we see in our daily clinical practice, and had as a primary outcome hard outcomes, which is very helpful to try to get treatment in the guidelines. But unfortunately, due to several issues, and among those also COVID, the primary outcome was changed to be changes in potassium levels with actually patiromer as compared to placebo in a population characterized

by HFrEF, as I said, mild to moderate renal impairment, high potassium level over 5 while treated with heart failure medication or with history of hyperkalemia. And you see that potassium level were slightly reduced by patiromer in a way that the primary outcome was met. And very, very important, the secondary outcome of this analysis, where it was shown that patiromer was effective in maintaining MRA target dose and in achieving better implementation of RAASi therapy and in reducing next hyperkalemic events.

The REALIZE-K study actually testing SZC is also addressing a similar population with HFrEF, NYHA class II/IV, and ejection fraction it is less than 40 and patients on GDMT on no or low dose of MRA. And in this study, in the open-label run-in phase, actually patients with potassium level between 5 and 6 were considered, as well as in the cohort number, 2 patients with normal kalemia, but at risk of hyperkalemia. Two different strategies were tested; in the first cohort, SZC was started on day 1, and the up-titration with spironolactone was started when normal kalemia was achieved. Whereas in the second cohort, the one with normal kalemia but at risk of hyperkalemia, actually the initiation of spironolactone happened at day 1, and SZC was implemented whether hyperkalemia developed. The trial is ongoing, and at this point after a selection of patients, actually patients were indeed randomized to SZC or placebo, and the primary outcome of the trial is actually defined by having a potassium between 3 and 5 assessed by a central laboratory and being on spironolactone equal or more than 20 mg, and not using any rescue therapy for hyperkalemia at month 6.

We should not forget our recommendations for trying to implement GDMT by using novel K binders. According to European Society of Cardiology Guidelines on Heart Failure, whether potassium levels are more than 5 and there is need of optimizing GDMT, actually, a K binder should be started to enable the implementation of GDMT.

And what do the nephrologists say? The nephrologists say, actually, that in case of hyperkalemia, among the different approaches, important one are, of course, novel potassium binders. Other one are, for example, diuretics, also changing diet habits and so on.

We should not forget as well that in case of normal kalemia, but with an eGFR decrease less than 30, together with initiation of medication, actually, we should just go on with the optimization of therapies without really focusing too much on a small decrease in eGFR.

So to conclude, hyperkalemia is frequently recurrent and associated with poorer outcome in patients with cardiorenal disease, several comorbidities such as CKD, heart failure, and diabetes, and therapies such as MRA and RAASi are risk factors for hyperkalemia, but I would say they are irreversible risk factors. Also use of MRA and RAASi is an irreversible risk factor. We should never discontinue treatment, should try to apply other strategies for optimizing GDMT while actually trying to get low potassium levels, and actually novel K binders are the perfect treatment for enabling GDMT in patients with heart failure.

Thank you so much for your attention.