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### Potassium Binders in Heart Failure: Who, When, and How

Announcer:

Welcome to CME on ReachMD. This activity, entitled "Potassium Binders in Heart Failure: Who, When, and How" is provided by Medtelligence and is supported by an independent educational grant from Vifor Pharma.

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Dr. Piña:

We as clinicians often struggle to optimize guideline-directed medical therapy, or as we know it as GDMT, in heart failure, which means that our patients are at increased risk for poor outcomes. Renin-angiotensin-aldosterone system, or RAAS as we know it, those inhibitor therapies are frequently lowered in response to episodes of hyperkalemia. But what if there were a better way to lower potassium levels so that our patients could still reach those target doses of RAASi inhibitor? Welcome to CME on ReachMD. I'm Dr. Ileana Piña, and joining me today is Dr. Patrick Rossignol from France, my good friend. Patrick, welcome to the program, great to have you.

Dr. Rossignol:

Thank you very much Ileana, my pleasure.

Dr. Piña:

So, the use of potassium binders is a relatively new tool for cardiologists, but you are a nephrologist, my friend, and you've had more experience using them than any of us. Can you tell us which patients with heart failure may benefit from treatment with a potassium binder?

Dr. Rossignol:

Actually, Ileana, hyperkalemia is an imminent risk for patients on RAAS inhibitor therapeutics. Hyperkalemia is especially prevalent in heart failure patients with comorbid conditions, such as chronic kidney disease and diabetes, diabetic nephropathies. It is of utmost importance to appropriately monitor serum potassium in order to retrieve the best benefits of shift consistently in measured cardiovascular outcome trials, which repeatedly showed that RAAS inhibitors reduced mortality rate in heart failure. It is also important to reach guideline-recommended dosing of RAAS inhibitor therapeutics, since maximizing RAASi therapy improves outcomes. However, there is a true dilemma here, because the initial reaction is to lower RAASi in reference to hyperkalemia, and Swedish registry and data showed that 47% of patients discontinued MRA after hyperkalemia, and unfortunately, treatment is not being reintroduced after a year or so, and this may ultimately lead to heart failure worsening. And this data were actually confirmed within the framework of the ESC Heart Failure Registry, gathering data for more than – almost 10,000 patients with heart failure.

Dr. Piña:

So, it is so important to monitor the potassium levels. That's something that we can't get away from, especially in patients when they start reaching that four and a half, 4.5, where clinicians start to get worried. So, I have a patient case here, and it's a patient of ours from clinic, and I call it the Zone of Uncertainty because people are uncertain as to what to do. So this patient's potassium is now 4.9, and

you knowing me, it's a heart failure patient. Does this patient meet that hyperkalemia threshold, and what would be the threshold to do some intervention?

Dr. Rossignol:

Well, Ileana, several definitions might be considered, either in the US or in Europe. If I consider the ESC guideline definitions, hyperkalemia was proposed to be defined as mild hyperkalemia if between 5 and 5.5 millimoles per liter, moderate hyperkalemia between 5.5 to 6 millimoles per liter, severe hyperkalemia above 6 millimoles per liter. Therefore, to answer your question, your patient did not reach the threshold to define hyperkalemia, which may trigger intervention. However, I should mention that the U-shaped relationship between serum potassium and outcomes was repeatedly showed across epidemiology course studies, with an ideal of around 4.2 millimoles per liter in heart failure patients. This means that patients with hypokalemia and patients with hyperkalemia ultimately experience poor outcomes.

Dr. Piña:

So I like the way the European Guidelines have outlined, you know, the mild, the moderate, and the severe, because I think, again, it gives clinicians a little bit of a guide as to what to do with the numbers. Managing the diet is also important. What do you do with the diet?

Dr. Rossignol:

Well, diet recommendations are key, because we all know that food may contain lots of potassium, but we also acknowledge that acid food, like fruits, contain potassium, and we certainly don't want to deprive our patients. Too restrictive diet restriction may not be sustainable in the long run, which is a measurable limitation for diet restrictions. Another possibility will be to consider loop diuretics uptitration, but there are some disadvantages in this approach. Indeed, uptitration may lead to worsening renal function due to dehydration, and this may also lead to another condition of the renal system, which we don't want in our patients. Another possibility might be step down – don't titrate RAASi, which might be unfortunate in the long run, since epidemiological studies repeatedly showed that those patients who do not reach target doses ultimately experience worse outcomes.

Dr. Piña:

That a great point. Well, let's go back to our patient, Patrick. So the patient still is not at that level of 5. But he's getting close, and I decided, because there was some history about this, to start getting our preauthorization, which you know in the United States, we sometimes have to get preauthorization to get a medication covered, even though it – it may be in our formulary, but this is for outpatient care. And I worry that the potassium may go up and I'm not ready for it. And I really hate to pull back the drugs. So at the next visit, the patient comes back. Now the potassium is 5.3. Now what would you do with this patient? Is this the right time to give him the potassium binder?

Dr. Rossignol:

Yes, absolutely, Ileana, because now the patient reached the threshold of 5 millimoles per liter, which was used across clinical studies, which ultimately led to the approval of new potassium binders, patiomer and sodium zirconium cyclosilicates. I already discussed pros and cons of the possibilities, such as diet restrictions, which may deprive our patients from acid food, but needs to be considered, obviously, as a short-term option. But on the long run, it is not sustainable, in my opinion. Loop diuretics, we certainly don't want to over dialyze our patients. Dialysis, of course, is an option for end-stage kidney disease patients, but this was not your patient.

Dr. Piña:

So for those just joining us, this is CME on ReachMD. I'm Dr. Ileana Piña, and I'm speaking today with Dr. Patrick Rossignol from France – actually from Nancy – about potassium binders and heart failure. So we'll continue, Patrick. I think a lot of cardiologists are afraid of the ECG changes. That's what I was taught in school. You have to be careful with peaking T-waves, and then the QRS starts to widen, and that can happen with elevated potassium, but it's actually very rare; I've only seen maybe a handful of patients in my entire career. So there are two potassium binders available in the United States and in Europe, and that's patiomer and SZC, which we know as Z-9. I believe patiomer is the only one available in Australia, although it may be different now. I gave him patiomer because I had it on our formulary and I had already started using it, and SZC had not been approved at the time. Can you tell us about how these medications work? Because I think clinicians that are listening to us would like to know the mechanism of action.

Dr. Rossignol:

Well, for patiomer, it is a spherical, non-natural polymer where calcium is exchanged for potassium in the colon. What about side effects? I should mention here that hypomagnesemia might happen and should be assessed. What about ZS-9? It is a crystal lattice structure where sodium is exchanged for potassium. It begins working in small intestine, and with a measure of potassium bond within the colon, actually. The main side effects are edema and hypokalemia.

Dr. Piña:

So we see edema related to dosing. Have you seen that in the literature?

Dr. Rossignol:

Yes, indeed. There is a dual dependent increase in the edema rate, which, in my opinion, is not surprising since, as I mentioned, this drug is exchanging potassium versus sodium.

Dr. Piña:

So it's something that needs to be watched out for, for patiomer, I have found that the most common side effect is constipation. That's what the patients have complained about. So, in practice, it takes maybe two to three days to get a really significant drop in the potassium. Is that what you have seen?

Dr. Rossignol:

Yes, indeed. This was actually repeatedly shown across trial. And this led to get these drugs approved for the treatment of hyperkalemia, which is not emergent hyperkalemia. They are not approved to treat emergent hyperkalemia, only chronic management of hyperkalemia.

Dr. Piña:

And what about other medications? What do you tell them if they are asking you, "Can I take this with my other drugs?"

Dr. Rossignol:

Well, prescribing information notes that potassium binders should be taken two to three hours before or after other medications, and this suggests taking binder at a time when not taking something else, such as in the middle of the day, if other medications are q.d. or b.i.d., and importantly, Ileana, specifically patiomer can be taken with or without food. There is no difference, and this was demonstrated in a dedicated clinical trial.

Dr. Piña:

That's a very important point, because patients do want practical things to – around their medications. So I want to still point out that a healthy diet is really important, and we know that, you know, fruits and vegetables are very healthy, and we want them to be on them, but they are high in potassium. However, my experience has been that when you start a binder, you may be able to loosen up the potassium restrictions and still educate the patients and be judicious about it. So as we wrap up, Patrick, what are some pearls that you would like to give our colleagues?

Dr. Rossignol:

Well, Ileana, the first one relates to regular monitoring of serum potassium. We read in the literature that potassium and creatinine are, unfortunately, rarely properly monitored after the initiation of RAASi, MRA especially. We recently published a survey where home monitoring was implemented in heart failure patients post-discharge, and a number of significant hypokalemic or hyperkalemic episodes were identified, actually, which would have been overlooked should potassium not be monitored. Therefore, it is of primary importance to monitor potassium and creatinine so that our patients may cumulatively retrieve the best benefits of RAASi. Another possibility is to use, of course, potassium binders, but we discussed that already in order to maintain RAASi in patients initially hyperkalemic. And the last tip I wish I may share is an online calculator which is fully valuable, derived from the EPHESUS cohort, and validated using the EMPHASIS-HF cohort. And entering potassium levels on MRA use in the calculator, along with other patient features, is raising awareness of the importance of monitoring on the effect on patient outcomes. In other words, when you enter this data, which are really valuable, we see that those patients with normal potassium – we have seen that this may be reached by several potassium binders and maintain an MRA – experience better outcomes.

Dr. Piña:

Well, these tools are very important; I couldn't agree more with you. So as we wrap up here, we have some messages. First of all, do not stop the RAASi therapies if at all you can avoid it, because the patients can worsen. And then you don't know if it's a withdrawal of the drug or it's actually the disease getting worse. Do educate patients about their diet and foods that are high in potassium. Get some lists of foods and hand them to them in your office. We can get patients to those target doses with the use of potassium binders and the management of the diet. They go hand in hand. I want to thank Dr. Patrick Rossignol today for joining us and helping us better understand the role of potassium binders in the management of heart failure.

Dr. Rossignol:

Ileana, this was a pleasure.

Announcer:

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