Transcript Details

This is a transcript of a continuing medical education (CME) activity accessible on the ReachMD network. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/raasi-therapy-diabetes-and-hyperkalemia-halting-therapy-not-only-option/12714/

Released: 07/15/2021
Valid until: 07/15/2022
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

RAASi Therapy, Diabetes, and Hyperkalemia: Halting Therapy Is NOT the Only Option

Announcer:
Welcome to CME on ReachMD. This activity, entitled “RAASi Therapy, Diabetes, and Hyperkalemia: Halting Therapy Is NOT the Only Option” is provided by Medtelligence.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Bakris:
This is CME on ReachMD. I’m George Bakris, and I’m joined today by my friend and colleague, Biff Palmer. Welcome, Biff.

Dr. Palmer:
Thank you, George. It’s nice to be here, today.

Dr. Bakris:
I’d like to start our program by sharing a case. We have a 63-year-old white woman with a history of diabetes, resistant hypertension and stage 3b chronic kidney disease. Her medications include candesartan, spironolactone, furosemide, metformin, glipizide, and really at reasonable doses. She also states that she’s been taking ibuprofen 2-3 times a day for recent knee pain from osteoarthritis. Her K is 5.3, her sodium is 137, and her blood pressure is 146/76 and her heart rate is 70. Her lungs are clear; she’s breathing fine. There is no significant pedal edema. And so, Biff, let me ask you – clearly, she has hyperkalemia, and often the first thing clinicians want to do is stop the RAAS inhibitors. Why is it important to continue the RAAS inhibitors?

Dr. Palmer:
You know, she’s really representative of the many patients that I think clinicians see in everyday practice. And, when you think about it, we recently had KDIGO clinical practice guidelines that really addressed why we should be utilizing ACE and ARB therapy at maximally tolerated doses in such individuals.

Two studies that really, support the KDIGO clinical practice guidelines are the IRMA 2 and INNOVATION trials. These are somewhat older trials, but what they looked at were two different angiotensin receptor blockers. One, irbesartan, and the other telmisartan, and what they found in these trials was that in diabetic individuals who had microalbuminuria, both of these agents were found to be effective in reducing the risk of patients progressing to overt diabetic nephropathy, as manifested by overt proteinuria.

And then we had the classic IDNT and the RENAAL study that showed in diabetic patients who had overt kidney disease, that is nephrotic-range proteinuria and reduced estimated GFR, that either irbesartan or losartan were able to reduce the doubling of the serum creatinine, end-stage kidney disease, or cardiovascular death. So I think based on these kinds of outcome trials, it makes a lot of sense that we should, in fact, try to maximize the dose of these classes of agents in our patients such as the one that you present.

Dr. Bakris:
And I also want to bring up the fact that this patient is also taking NSAIDs, which absolutely can confound potassium readings as elevations, and I think we need to go there, first, before we stop really, kind of, kidney and heart protective therapy. So we definitely don’t

want to stop the RAASi, especially in this patient, if it can be avoided. So can you tell us about some obstacles that you may face in a patient like this?

Dr. Palmer:
We do run into metabolic complications that oftentimes prompt physicians to want to lower the dose. And I think as you point out, that's really not the proper thing to do. Some of the more common reasons that perhaps impede physicians from utilizing maximal doses is soon after the administration of these drugs, you might see an increase in the serum creatinine concentration. But I think it's important to remember that most of the time, this is purely a hemodynamic-mediated increase. It doesn't represent structural injury. And a reasonable guideline is as long as the creatinine doesn't go up by more than 30%, and you verify that it's plateaued at that higher value, that that's not a reason to discontinue these drugs. And in fact, you want to continue them.

The other big reason of course, is that sometimes we see an increase in the plasma potassium concentration and as you point out in this individual, we look for various causes that might ameliorate that increase, in this case if we could minimize or use the lowest dose possible of that non-steroidal anti-inflammatory drug [NSAID], it's quite possible that the hyperkalemia would be improved.

Other things, of course, that we might take a look at is does the patient have an active infection? That will increase the risk of hyperkalemia in the setting of RAAS blocker, or if they're volume-depleted. So I think it's important to look at the patient and look for various causes that we can remove and would then allow us to use the maximally tolerated doses.

Dr. Bakris:
Biff, thank you very much. That was a nice evaluation.

I want to come back and emphasize a couple of points you made. And one is on this elevation of serum creatinine, everybody freaks out. We have excellent data now, and this dates back to 2000, but we have some recent trial data from the ACCORD trial, from the SPRINT trial, and from other trials, that are large outcome trials that have formed the basis of guidelines. All of those trials have had increases in serum creatinine, as much as 25% to 30%. And in fact, the outcome not only wasn't worse, it was better because of better blood pressure control and the agents being used, and I think physicians need to understand they're not causing AKI [acute kidney injury]. That's really a fallacy, and you really need to be careful in terms of stopping drugs because of fallacious reasoning or fear. I think that's really a big deal. If you're faced with hyperkalemia as a reason to be modifying drugs, there are many options that you have, and you just brought up a few, and there's others.

So I want you to speak now to the options for treating hyperkalemia rather than stopping RAASi therapy.

Dr. Palmer:
The first thing I often do if I see an elevation in the plasma creatinine, after first reviewing the medication list that the patient's on and, again, in this case, reducing the dose or discontinuing the NSAID if possible, I might consider maximizing the dose of diuretics. That would be particularly applicable if the patient still had uncontrolled hypertension or if on my exam they had peripheral edema. If the patient happened to be a little bit acidotic, there might be a role for sodium bicarbonate and we also would consider modifying the diet where applicable. In that regard, I would just point out just to blanketly discontinue all foods that happen to be enriched in potassium is not necessarily the best strategy.

But lastly, the other welcome tool to our armamentarium are the use of potassium-binding agents. For the last 50 years, the only one we had was sodium polystyrene sulfonate, but that was really not a viable strategy to use on a long-term basis because of its intolerability. But I think we now have two new agents that in fact are well tolerated and very efficacious.

Dr. Bakris:
Those are excellent points, and I think we need to look at options before we abandon therapy that we know can be life-changing. Everybody blows off the diet, and yet I think it's critically important. I've been able to change potassium in patients as much as 0.5 milliequivalents simply by modifying the diet and educating them on lower-potassium foods. So I don't know. What's your experience with that?

Dr. Palmer:
Sometimes, just in an almost reflexive manner we tell patients, "Okay, I want you to cut out these fruits and vegetables," a food group that we know is actually heart healthy. Fruits and vegetables that might be of higher fiber content would be less offensive as compared to, for example, something that was just fruits and vegetables with a lot of liquid in it, you know, strawberries, watermelon, those kinds of things, there the bioavailability of potassium is quite high. And so I think you have to be more nuanced and be more critical as to how you actually recommend the diet be modified. In that way, you can still enjoy some of the heart healthy benefits of those foods and perhaps minimize the degree of hyperkalemia.

Dr. Bakris:
Yeah. Absolutely. Excellent point.

This is CME on ReachMD. I'm Dr. George Bakris and I'm joined today by Dr. Biff Palmer. We're discussing management of RASi therapy in patients with CKD and diabetes who develop hyperkalemia.

Alright Biff, you also mentioned the newer potassium binders, let's talk about those a little bit more. How efficacious are they? What data do we have from trials? And how accessible are they to the clinicians? I find many clinicians are not even familiar with them, or they've heard about them but immediately dismiss them because they really have no experience with them.

Dr. Palmer:
Sure. I mean unlike that sodium polystyrene sulfonate, the two new agents that have now become available to our use are patiromer and zirconium cyclosilicate. These drugs have now been really looked at in prospective trials, and long-term trials really demonstrating their efficacy. For example, patiromer, which has now been out for several years is a polymer. It was shown in a trial called OPAL-HK to have a very effective efficacy in lowering the plasma potassium. And in a subsequent trial called the AMETHYST trial, that you're quite familiar with, showing that long-term use of that drug over a 1-year period, again, could control patients who had been previously hyperkalemic. And importantly in those two trials, I would mention that nearly 100% were on drugs that target the renin-angiotensin system and the use of this binding agent was able to maintain normokalemia.

With regards to the other product, zirconium cyclosilicate, again, a study in the *New England Journal* by Packham and with a subsequent long-term study by Spinowitz, again, a similar efficacy in being able to control patients who had been previously hyperkalemic. In those trials, once again, about two-thirds of subjects were receiving renin-angiotensin system blockers. So again, I think we really have very effective strategies to be able to maintain maximal doses of our ACE or ARB or aldosterone antagonist therapy and yet control the metabolic side effect, as opposed to having to give up on that strategy.

Dr. Bakris:
Yeah, very good point. Now, I'm going flip things a little bit, Biff, and talk about the new boys on the block, the non-steroidal mineralocorticoid receptor antagonist finerenone and our friends, the SGLT2 inhibitors. We know unequivocally that SGLT2 inhibitors reduce cardiovascular disease and the events, they reduce kidney disease progression, especially in diabetes, but even without. The hyperkalemia, we also know per very recent publications, with the SGLT2 inhibitors, if anything, they not only don't cause hyperkalemia, they seem to protect you against it. And then finerenone has about one-tenth the hyperkalemic risk that spironolactone has. Why don't you talk to us a little bit about that?

Dr. Palmer:
Let's just take the SGLT2 inhibitors, I mean, they've been shown to reduce the chronic kidney disease progression, the DAPA-CKD trial, more recently the CREDENCE trial. These drugs have been shown to reduce the progression of chronic kidney disease, not only in diabetic individuals, but in non-diabetic individuals. Moreover, these drugs have also been shown to provide cardiovascular protection, for example in patients who have high risk for cardiovascular disease. And a similar story seems to be unfolding with the finerenone, again in a chronic kidney disease, type 2 diabetic population, they were shown to reduce the risk of CKD progression, and also reduce the risk of cardiovascular events.

Dr. Bakris:
The fun is just beginning, I think, with these agents. We've turned into cardiologists now. We've got add-on therapies, just like they have for heart failure, which is – it's about time after 20 years.

Well, Biff, this has been a great interaction, but we're running out of time. Do you have any final take-home message for our audience?

Dr. Palmer:
I think the thing that I would like to really emphasize is that with our recent tools there's really no reason why we can't maintain drugs that target the renin-angiotensin system and be limited by side effects such as hyperkalemia. I think this is going to continue to play out as these new agents now become more commonplace, the utilization of SGLT2 inhibitors, not just to control the blood glucose, but to provide organ-protective effects, and then similarly with these new aldosterone receptor antagonists.

Dr. Bakris:
Absolutely. Couldn't agree more. We now have a class of agents that I affectionately refer to as "enablers." They enable the use of cardio-renal protective therapies and enable you to continue RAAS blockade or mineralocorticoid receptor blockade, or both, to clearly reduce heart failure mortality and also kidney disease progression. So don't dismiss these lifesaving agents, knowing that you have the ability to use potassium binders that are well tolerated over long-term periods of time, that can be used in concert with these agents to enable them to do what they have been proven to do.

I want to thank our audience and offer a special thank you to my colleague, Dr. Biff Palmer. Thanks for sharing your thoughts with us today. It was great having this discussion with you.

Dr. Palmer:
Well, thank you very much, George. It's always a pleasure.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Medtelligence.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Medtelligence. Thank you for listening.