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Elevated Creatinine and AKI Are NOT Synonymous: Optimal RAASi Therapy Is Always the Goal

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Elevated Creatinine and AKI Are NOT Synonymous: Optimal RAASi Therapy Is Always the Goal” is provided by Medtelligence.

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Dr. Bakris:
When treating our patients with heart failure and CKD, we should continue RAASi therapy if at all possible. Today, we’re looking at a case presentation to discuss how we manage RAASi therapy in the presence of elevated creatine levels in hyperkalemia.

This is CME on ReachMD. I’m George Bakris and I’m joined today by my friends and colleagues, Biykem Bozkurt and Robert Toto. Welcome.

Dr. Bozkurt:
Thank you, George, it’s wonderful to be here.

Dr. Toto:
Thanks George, glad to be here with you.

Dr. Bakris:
Glad to have you. I’d like to start our program today by sharing a case. We have a 73-year-old African American man with a history of type 2 diabetes, poorly controlled hypertension, and stage 3a CKD and heart failure with reduced ejection fraction, or HFrEF, with an LV ejection fraction of 30%. His medications include carvedilol twice daily, valsartan, spironolactone, and furosemide, metformin, as well as glipizide for his diabetes.

Biykem, does this therapy, at present seem appropriate for the patient with HFrEF based on published guidelines?

Dr. Bozkurt:
Partially, George. As we can see, some of the listed medications such as carvedilol and spironolactone are appropriate as a class in patients with heart failure with reduced EF. Furosemide would be appropriate if the patient is congested. Valsartan alone could have been appropriate if we knew that the patient was ACE inhibitor or ARNi intolerant, but we don’t know that. And thus, he should be considered for ARNi. He should also be considered for SGLT2 inhibitor, which now is, with the evidence, indicated for patients with heart failure with reduced EF, regardless of diabetes. And because he has diabetes, his glucose-lowering agents needs to be changed to SGLT2 inhibitor, and depending on his symptoms, signs, and blood pressure, all the doses of guideline-directed therapies should be optimized.

Dr. Bakris:
Very good. Well, let me tell you, he experienced shortness of breath over the past 3 days and gained 3 kilos and popped into the emergency room last night. His GFR is 53 at baseline. His potassium is 4.7 and his serum creatinine is 1.5. Otherwise, his labs are

okay.

He had pulmonary edema on chest X-ray, ECG – no acute changes. BP was 148/76 and his heart rate was 78 in sinus rhythm. His oxygen sat was 94 and he was given IV Lasix 80 mg and admitted to the hospital, where he got 80 twice a day of Lasix. Continued diuresing, ended up with 800 mL of negative fluid balance over 24 hours. Now, his morning labs, his creatinine is now 1.7, his GFR is 45, his K^+ is 5.1 and his hemoglobin A1C is 7.3. On morning rounds, the hospitalist stops the valsartan and the spironolactone based on his EGFR and serum creatinine. Cardiology consult is pending; no other changes overnight and he still has mild congestion on auscultation.

So, Bob, what do you think about this stuff about stopping the RAASi therapy?

Dr. Toto:
Well, I think it's premature, and I don't think it's necessary given the changes in his creatinine and potassium, which as you pointed out were the, were the reasons why those were held. I think that it's important to understand that when the patient like this comes in with chronic kidney disease in HFrEF and is congested, of course diuretics are necessary and they were used. That's going to contribute to an increase in the serum creatinine based on the basis of change in volume. But it's also likely that his blood pressure dropped some given that he has poorly controlled hypertension in the past, and the combination of volume depletion from the diuretic that's acute, meaning effective just by the, Lasix and the RAAS blockade that he was on. His creatinine is expected to go up. The increase in potassium is mild. I don't think that would necessitate having to stop either the RAAS blockade or the mineralocorticoid receptor antagonist. These elevations are not serious, and the patient's going to need to continue on therapy for his heart and his kidney disease. We know that, for example, that patients with chronic kidney disease don't auto-regulate normally, so if the blood pressure drops for whatever reason, his GFR may also go down as a result of blood pressure changes alone. So it's important to recognize the physiologic changes that you expect with the pharmacological intervention here and that really it's appropriate and it's going to need to be continued in order to manage the patient.

Dr. Bakris:
These are excellent points, Bob. I want the audience to remember the kidney is a regulatory organ and will respond appropriately to the changes it sees in the environment and the orders it's being given, ie, diuresis, etc. And I couldn't agree more with what you said. I think it's important – people need to be not gun-shy. They need to understand what's going on and treat the patient and not worry about labs that could or could not be of issue.

Now, Biykem as a cardiologist, what are your thoughts on discontinuing RAAS blockade?

Dr. Bozkurt:
First and foremost, I find these reflex approaches to discontinuation of therapy highly inappropriate. In approximately one-third of acute decompensated heart failure patients, the therapies are withdrawn or held due to these changes in lab findings. The reflex approaches are detrimental because we know 75% of the time, when discontinued during hospitalization, these therapies are not reinstituted. We know these are lifesaving therapies. In patients with heart failure with reduced EF, we have strong evidence for reduction mortality and hospitalizations with ACE inhibitors supported by large-scale trials. We know that the initial rise in creatinine due to RAAS inhibition at the initiation phase is not associated with bad outcomes, and this is supported by the analyses showing that there is no difference in survival benefit among patients with or without a rise in creatinine after initiation of RAASi therapy. But we know, after withdrawal of these therapies, due to a variety of reasons, the outcomes are actually worse. We have this data from the registries.

Dr. Bakris:
Thank you very much. I want to remind the audience and encourage them to keep up with the literature. As Biykem just went through, there are at least, off the top of my head, 5 well-done analyses of multiple trials showing exactly what she said, published in the last 5 years. Unfortunately, a lot of them are in the cardiology literature, so the general medical population may not be aware of them. But the message that you've heard, not only from her, but also from Bob, is very clearly, which I fully agree with, doing exactly what they're recommending.

Now, Bob, what is your cutoff for the rise in serum creatinine when deciding when to stop RAASi therapy? And how often does this actually occur?

Dr. Toto:
OK. Well, thanks George. I support everything that you and Biykem said in terms of management and the evidence for it. And I also want to remind the audience that this rise in creatinine that we've see on the patient that you presented is not AKI, it's not acute kidney injury. But I think for an acute rise in creatinine, we get concerned when there's more than a 30% increase if there, for example, is a change in dose or a start, you know, when we start a RAAS blockade or up the dose of RAAS blockade.

So I think that it's relatively common. When you ask about how often does this happen that the creatinine goes up when you put somebody on RAS blockade, it's common. Unfortunately, it's also very common to stop RAASi therapy with these slight increases in creatinine. Which sometimes are accompanied by an increase in potassium, and I think that raises concern on the part of the practitioners. If the rise in creatinine doesn't exceed 30%, there's no reason to stop the RAASi therapy.

Dr. Bakris:
And let me just add to that, Bob. That 30% magic number was derived in a paper that I published with Dr. Matt Weir back in 2000, and this was an analysis that we carefully looked at and we derived that 30%. And that 30%, I must say, I'm very happy about, has sustained itself over the last 20-plus years in terms of other studies that have looked at this in terms of outcome.

Dr. Bozkurt:
Yes, we do see the rise in creatinine in, let's say, 30% to 40% of the patients, depending on the background, comorbidities, and baseline kidney dysfunction in patients hospitalized with acute decompensated heart failure. The rise in creatinine is associated with worse outcomes, but who does it happen in? The baseline medium, meaning this happens in advanced heart failure patients – but by the way, improvement in kidney function, Testani's group showed also the same, is associated with the same risk, and these are very similar patients, meaning those who have a variation in their creatinine are the type of patient with advanced heart failure that are advanced NYHA class with a lot of congestion. And we are taking snapshots in their delta changes in their creatinine at different time levels. It's not to say going up in creatinine versus coming down is associated with a different outcome; they are both bad. But the important thing to keep in mind is decongestion in those patients is associated with better outcomes than leaving them with residual congestion and having appropriate guideline-directed therapies associated with better outcomes than withdrawing therapy.

Dr. Toto:
I couldn't agree more with what Biykem said about the decongestion, and I think it's really important. And it goes back to what you were also saying, George, earlier, is that it's important to treat the patient and not just the numbers.

Dr. Bakris:
Yeah, I might add to Biykem's point, the original paper that talked about that increase in so-called AKI, and everything, the authors of that are epidemiologists. Moreover, they've recanted that observation based on future data that we're talking about right now. So even the people who proposed this are now saying it's not true. So be very careful.

For those just tuning in, you're listening to CME on ReachMD. I'm George Bakris and I'm joined today by Biykem Bozkurt and Robert Toto. We're looking at a patient case to help us navigate management of RAASi therapy in our patients with heart failure, CKD, and a rise in creatinine level with a goal of avoiding interruption of therapy, when possible.

Let's get back to our patient who is now seen by cardiology. A 2D echo, of course, is obtained, no significant changes, and the EF is still approximately 30%. The patient's discharged and his GFR is 53, creatinine is 1.5, his potassium is down to 4.7, he's still on Lasix 60 mg daily, and valsartan is switched to sacubitril/valsartan. He's restarted on spironolactone 12.5 daily and he's started on dapagliflozin 10 mg daily. He returns to the clinic in 3 weeks. K^+ is now 5.1, GFR is 49, creatinine is 1.6, BP is 140/76, and sacubitril/valsartan is increased. The patient has not made any changes related to his diet.

Biykem, how do you want to handle the burden of hyperkalemia in people with CKD and heart failure?

Dr. Bozkurt:
So I'm going to first talk about the burden of hyperkalemia because as to how we define hyperkalemia of K^+ over 5 versus 5.5 and over 6 matters, right? So if we look at the prevalence of hyperkalemia in the heart failure population, it varies. It ranges all the way from the 10% up to 40% if we're talking about patients with background CKD. In heart failure trials of patients with heart failure with reduced EF, the reported adverse events due to hyperkalemia ranges from 7% to 8% when treated with ACE inhibitors alone to 16% to 17% when also concomitantly treated with MRA to about 13% to 16% in the studies with ARNi. And in most recent studies with SGLT2 inhibitors, the adverse event rates with hyperkalemia were around 6% to 7% with optimal background therapy involving all the others. But when you look at K^+ over 5.5 in the DAPA-HF, it was 11%. So what that means is serious adverse event rates may be somewhere around 6%, 7% but K^+ over a certain level such as 5.5 in the overall trial population may be 11% to 15%.

Now, if we add the comorbidities to this, such as diabetes, then it becomes 15%, 20%. And if we add the CKD, then it starts going to the 17%. There is always an important "but." The RAAS inhibitors, though associated with hyperkalemia, still retain their benefit in patients with heart failure with reduced EF when they're able to be given without an interaction. So those individuals who are able to be treated with RAAS inhibitors, with or without hyperkalemia, have the same amount of benefit. Those who cannot be treated have worse outcomes.

Now, two comments, the new agents, the SGLT2 inhibitors and ARNi are associated with slowing of the progression of CKD. The eGFRs in the long run are better than the placebo arms, and the hyperkalemia risk and SGLT2 is not higher than the placebo.

Dr. Bakris:
Speaking of risk, we are no longer paralyzed to, at the prey, at the mercy of kayexalate. We have other issues and other ways of dealing with hyperkalemia and we certainly don't want to stop RAASi therapy, as we already talked about. So, Bob, give us an insight into this.

Dr. Toto:
So I think that's really a key point. We like to keep the patients on RAAS blockade, obviously, if we can, and if they're becoming hyperkalemic and since they're predisposed to hyperkalemia with these agents and given their kidney function and heart failure, there are things that we can do to avoid hyperkalemia. If they're taking salt substitutes, for example, or some other over-the-counter things such as juices that are high in potassium, NSAIDs being another relatively common drug that people use that can raise hyperkalemia in this setting. So managing it can be done by explaining to the patient what things they could avoid. Dietary restriction of potassium intake also can mitigate hyperkalemia to some degree. Dose adjustments of diuretics that are kaluretic, including the loop diuretics, may also help. Thiazides are, of course, also kaluretic, so adjustment of doses of those can also mitigate the hyperkalemia. And then in some circumstances, patients are academic. The addition of sodium bicarbonate to their regimen can help to eliminate potassium in the urine, although there is some sodium load associated with that. And then, as you point out, we have new potassium-binding agents beyond kayexalate that are available. These include patiromer and zirconium cyclosilicate, both of which have been shown to lower potassium in patients who are maintained on RAAS blockade including combination with an ACE inhibitor or angiotensin receptor blocker plus a mineralocorticoid receptor antagonist – and safely for at least a year. So these agents can be used chronically as oral therapy to mitigate hyperkalemia in our patients who we need to keep on these lifesaving drugs.

Dr. Bakris:
No question about it. Biykem, I want to come to you because, at least in my circles with these new potassium binders, there's kind of a dual approach. One is calcium-based; that's patiromer. And one is sodium-based, which is ZS-9. Basically the argument is because of the sodium load, heart failure cardiologists are going to favor patiromer more because there's no sodium involved, and the nephrologists don't care because the sodium, there, if they're on dialysis, is going to get dialyzed off anyway. And so that's been kind of a proposal. Now, that's not what I'm seeing, but I'm just asking your opinion. What do you think about that?

Dr. Bozkurt:
There's no evidence of the absorption of the sodium and/or any of the biproducts that's contained in these products. Currently, we do have evidence form a variety of studies with – in the setting of patiromer, we had the OPAL and the PEARL-HF trials where it did effectively reduce the potassium levels. And PEARL-HF facilitated a higher use of mineralocorticoid receptor antagonist, namely spironolactone in a higher proportion of patients without worsening of heart failure. In the setting of the ZS-9, sodium zirconium, HARMONIZE-HF effectively showed reduction in potassium levels.

Now, what we need to see is facilitation of optimization of RAASi, be it MRA and ARNi as well as ACE inhibitors or ARBs, in a larger heart failure population demonstrating perhaps efficacy and a reduction of events with these agents, which currently, there are a variety of registries that are being conducted to be able to capture these data. In the meantime, we need to also recognize the background therapy in heart failure, as you alluded to, is changing with SGLT2 inhibition. I think the facilitation of being able to use other agents, such as MRA, there's also sub-group analyses was from the trials demonstrating that these agents allow us to use a higher proportion of patients remain on MRA after initiation when they have the SGLT2 therapies. So it doesn't look like this individual is with rapidly declining eGFR and thus a significant prediction of a rise in potassium. It looks like this borderline level may be managed with adjustment of background, stopping the NSAIDs, and optimization of the guideline-directed therapies and looking at his new baseline. If he's still hovering on the high range, 5.5 and so forth, again, yes, the binding agents, potassium-binding agents will facilitate continuation of RAAS inhibitors and have been associated with better outcomes.

Dr. Bakris:
Very good. Very good. Well, we're running short on time and so what I want to do is I want to provide each of you with one final take-home message. So Biykem, I'll go with you first.

Dr. Bozkurt:
Not every rise in creatinine is acute kidney injury or cardiorenal syndrome. So I'm hoping that this collaborative message is widely heard. And rise in creatinine is transient in a significant proportion of our patients and when successfully decongested, rise in creatinine is not associated with bad outcomes.

Dr. Bakris:
Excellent. Bob?

Dr. Toto:
Yeah, I agree with what Biykem said. My take-home message is optimize the RAAS blockade when you can, and not all patients may be able to tolerate. But with the addition of potassiu-binding agents now, we can control the potassium long-term and maintain our patients on RAAS blockade and not have to discontinue the RAAS blockade in these patients.

Dr. Bakris:
Very important point. And as you pointed out – I want the audience to walk away with this – we have enablers. The enablers are well-tolerated, daily potassium binders that can be taken. We're no longer in the era of kayexalate.

So that's it, friends. We're done; we're out of time. I want to thank our audience and offer a special thank you to my colleagues, Dr. Biykem Bozkurt and Dr. Robert Toto. Thanks for sharing your thoughts with us, today.

Dr. Bozkurt:
Thank you, it was a pleasure.

Dr. Toto:
Thanks, George

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