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KDIGO Conversations in Nephrology: Benefits of RASi Utilization

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode is titled Benefits of RAASi Utilization. For disclosure information, please go to kdigo.org/podcasts. Here's your host, Dr. Roberto Pecoits-Filho.

Dr. Roberto Pecoits-Filho:
Hello and welcome to the KDIGO Conversations in Nephrology. I am Dr. Roberto Pecoits-Filho and Senior Research Scientist at Arbor Research Collaborative for Health, and a Professor of Medicine at the Pontifical Catholic University of Parana. Joining me to discuss the benefits of drugs that block the Renin-Angiotensin-Aldosterone System is Dr. Catherine Clase. Dr. Clase is a nephrologist, and a Professor of Medicine at McMaster University, and the Editor-in-Chief of the Canadian Journal of Kidney Health and Disease. Catherine and I share the passion for this area of our specialty, and I had the privilege of co-chairing the KDIGO Controversies Conference on the Management of Dyskalemias in Kidney Disease with her. Catherine, welcome to the program.

Dr. Catherine Clase:
Thank you, Roberto. It's great to participate in this, to be working with you again, and to participate in this discussion on RAAS Blockade.

Dr. Roberto Pecoits-Filho:
All right, so let's get started. Seems like as time goes by, the Renin-Angiotensen-Aldosterone inhibitors or RAASi, as I will refer from now on in this episode, are still very important therapies in kidney and cardiovascular disease, which is actually emphasized by the current revised guidelines in nephrology and cardiology. Now what's the main evidence-based reasons to the use of RAASi as a cardioprotective therapy?

Dr. Catherine Clase:
I think that's a great place to start reviewing the randomized evidence here. So when I think about the strongest, or perhaps the most prevalent indication or reason to use RAASi, it would be cardiovascular protection in people with cardiovascular disease, or in people who have diabetes, and evidence of end-organ damage. So high risk vascular population looking at a cardioprotective outcome. And this goes back to the HOPE Study 20 years ago, in which RAASi reduced major cardiovascular events, which I'm going to call Mace by 3% over five years. So it's a large effect, high certainty directly applicable to people with CKD G1 to G3, who have established cardiovascular disease or high risk diabetes. So in summary for cardioprotection, strong evidence, large effect.

Dr. Roberto Pecoits-Filho:
This is a great summary about the benefits of RAASi from a general perspective. Now, it seems that there is also robust evidence in heart failure specifically, right?

Dr. Catherine Clase:
Yes, that's right. So that evidence is actually older and even more compelling. It's specific to heart failure with reduced ejection fraction. And a good example here would be, say the SAVE trial 30 years ago. In this trial RAASi reduced cardiovascular events, but actually reduced death from all causes by 5%, which was a number [inaudible 00:03:15] of 20. So that's really the strongest indication based on the magnitude of the effect, and because we have here an effect on all cause mortality, which is relatively unusual in trials, even trials of cardiovascular outcomes.

Dr. Roberto Pecoits-Filho:

Interesting. So KDIGO revisited the role of RAASi in patients with diabetic and nondiabetic kidney disease. Is there something new in this area?

Dr. Catherine Clase:
When I think about this area, I'm really going back again to evidence that was generated some time ago. I think about the GSEN study. I think about the efficacy and nephropathy study, and fortunately there's a wonderful meta-analysis, an individual patient meta-analysis of those studies. And what they show is that for people with proteinuric kidney disease, there was a reduction in kidney replacement therapy, that's dialysis or transplant. That's the really clinically important outcome in this area. But having said that these were trials of proteinuric patients. Most of those studies had main proteinuric baseline of one gram a day or more. And in a subgroup analysis within this study, the benefit in terms of kidney replacement therapy was limited to people who had waistline proteinuria with more than 500. So that's why we have a recommend, the strongest level of recommendation in the KDIGO blood pressure guidelines for 2021.

And this is why we think that we have very clear evidence to use RAAS inhibition to prevent kidney failure in people who have CKD and A3 albuminuria. In people with diabetes, the evidence comes from different trials, but it's similar. So we have IDNT and we're now looking at people with macroalbuminuria or A3 as we call it now. Looking at outcomes of doubling of creatinine or kidney replacement therapy. And then when we think about people with diabetes and A2 albuminuria or microalbuminuria, we can go back to the HOPE Study and look at the cardiovascular outcome, which was reduced. So for this reason, people with A3 albuminuria and CKD or A2 albuminuria and diabetes, these again are recommended when we look at the KDIGO guidelines.

Dr. Roberto Pecoits-Filho:
Still in this area of the blood pressure management in CKD, there has been some controversies in the final report of the guidelines prepared by KDIGO. Can you comment on the decision?

Dr. Catherine Clase:
Absolutely. So the biggest area of controversy, I think, is the use of RAAS Blockade in people with A2 CKD. We can say that somebody with CKD and A2 is at high cardiovascular risk. We can say that most of these patients, or perhaps all of these patients are at sufficiently high risk. That we should consider them like participants in the HOPE Study and that they should be taking RAAS Blockade because of the cardiovascular benefit. And I think that's a very good argument, but it's not the same kind of directness of evidence that we have seen when we talked about the previous categories of reasons to use RAAS Blockade. When we look at the kidney progression, again, the data that we have are much less clear. We have some evidence from the TRANSCEND Study, some evidence from the AASK Study. But again, we do not have that consistency of direct evidence that leads to the highest level of recommendation, and KDIGO reflects this controversy by using the word suggests quite appropriately in my mind.

The other thing that KDIGO's consumed with, of course, is hypertension in people who don't have CKD or who have A1 CKD. In that setting, it's not known really whether there's a special role or a special benefit for RAAS Blockade, but we can certainly recognize that RAAS inhibition is going to be a useful tool in our toolbox when we're treating people with hypertension, particularly when we start to apply the results of the SPRINT Study, we're looking at a blood pressure target of less than 120. Why are we doing that? Because cardiovascular outcomes were reduced by 0.5% in the SPRINT Study. That's a number needed to treat of 200, bigger than the numbers we've talked about before. But if you and your patient come together and make a patient-centered decision that you're going to go for SPRINT target, the next thing you need to know is that that's going to take about three meds on average rather than two meds.

And when we're using three different classes of medication, having RAAS Blockade as one of those classes of medication is obviously going to be very useful. There's further evidence now about a lower blood pressure target from the recently published STEP Study out of China, they have a composite outcome of MACE heart failure and atrial fibrillation, but they found that over three years that was reduced by fully 1% and long term kidney outcomes were equivalent. So we now have two studies pushing us towards that lower blood pressure target. And what I tend to do is approach this in a patient-centered way. I tend to say, "Are you're prepared to take more drugs to have your blood pressure lower because we think it's better."

Dr. Roberto Pecoits-Filho:
Well, thanks for that, Catherine. Let's change from the evidence and guidelines to the real world clinical practice. I'm always striked by the under utilization of RAASi that we see in different real world, the cohorts. For instance in the US, it seems like 50% of people discontinue RAASi within five years of starting. What do you think are the challenges in applying this evidence?

Dr. Catherine Clase:
I think that's really a very important point that people are starting and then they're stopping. We know from a recent study that when we look at prevalent patients in the US, again, only 50% of people with proteinuric CKD, for example, are actually actively on RAAS inhibition. And when we look at the risk factors for being in that situation, they are past AKI, past hyperkalemia and not being under the care of a nephrologist.

Dr. Roberto Pecoits-Filho:
For those just turning in, you are listening to the KDIGO conversations in nephrology. Our topic today is the benefits of RAASi utilization. I'm Dr. Roberto Pecoits-Filho and I'm speaking with Dr. Catherine Clase. Catherine, coming back to the discussion about the under utilization of RAASi in the real world, what do you think are the practical challenges of using this class of drugs in 2021?

Dr. Catherine Clase:
The first thing to say is, I don't think this is a knowledge issue. I'm just quoting some evidence that suggests that though only 50% of people with proteinuric CKD are on RAAS Blockade, 90% have been on in the past. I think that people have got the message. I think that there are challenges facing maintaining people on RAAS Blockade and those challenges are changes in creatinine levels, hyperkalemia, and AKI. So I'm going to start just by talking about hyperkalemia. When we look at trial data, only small proportions of people develop hyperkalemia, but in clinical practice and routine care studies, it tends to be higher. So for example, in a Danish cohort, 16% of people started on RAASi developed hyperkalemia in the first six months, and 5% of people had hyperkalemia greater than six, and in 6% of people there was recurrent hyperkalemia. The other thing is that potassium in patients at high vascular risk seems to drift up over time.

So in the CREDENCE Study, for example, where most people would know, I think, that in the CREDENCE Study people were optimized on RASS Blockaded baseline. So this is a study of people who tolerate RAAS Blockade. The potassium level in CREDENCE over the 42 months of the study just drifts up slowly by an average of 0.3 millions per litter, which suggests that over time it may be harder to keep somebody on RAAS Blockade. So what can we do about the problem of hyperkalemia in the context of RAAS Blockade? There were obvious things like looking for prescribed or non-prescribed supplements and salt substitutions, look at coexisting medications like potassium-sparing diuretics, and look at MRA's unless they're being used for a specific indication and consider stopping those things. Very important to my mind is the use of a diuretic in this context. Usually I'll use a loop diuretic if the GFR's less than 30 and a thiazide if the GFR's above 30.

I want to talk a bit about thiazide because, I think they're key. There's a very strong evidence for using thiazides in hypertension in general. We have meta-analysis showing reductions in cardiovascular outcomes and in mortality. I also want to promote the use of chlorthalidone, particularly in this indication to lower potassium. The blood pressure lowering with chlorthalidone is superior to the blood pressure lowering of hydrochlorothiazide. And so is the potassium lowering probably by about 0.2. Looked at another way, the odds ratio for hypokalemia was 2.7 times that of hydrochlorothiazide in a US cohort. So 2.7 times as much hypokalemia with chlorthalidone as with hydrochlorothiazide suggesting it's a much more potent work when it comes to lowering potassium. So whereas this might be a caution for you if you are using it as monotherapy, when you are using it to reduce serum potassium, chlorthalidone is undoubtedly a better drug to use.

The other thing is that for many of these patients, if you're going for SPRINT target, you are going to need to prescribe more than one antihypertensive in any case. And in that case, the combination of RAASi inhibition with a thiazide diuretic is a very useful and evidence-based way to approach this. And you'll notice that I'm coming to the whole question of diet really right at the end, because I think these other things should be thought about first. And the reason for that is because we don't really have trials showing the effectiveness of diet. And we do actually have evidence showing that people's dietary potassium intake doesn't really correlate with their levels. However, using dietary restrictions to control potassium is standard of care and moving away from this is going to be challenging and needs to be done safely.

So what I'm doing is I'm thinking very much about substituting vegetables, not eliminating them so that people can still have the health benefits of eating vegetables and yet eat vegetables that are lower in potassium content. I also talk about the potassium content of meat as well. We know, for example in hemodialysis patients, that four out of the top five sources of potassium in their diet are actually meat products. Even unprocessed meat often contains injected additives and processed meat is even worse. So I would say if you're discussing diet, put the whole diet on the table and not to convey the impression that vegetables are particularly the demons when it comes to dietary content of potassium.

Dr. Roberto Pecoits-Filho:
Right. Are there any developments here that you would like to mention? What are your thoughts, for example, on potassium binders?

Dr. Catherine Clase:
Right. Well, most of our listeners will be aware that there are new potassium binders on the market. So let's just talk about the evidence space that we have here. The first thing to say is that for none of the potassium binders do we have outcome studies that include outcomes that are important to patients or what we used to call clinically important outcomes. For our old binder SPS, Kayexalate as it's soften called, we have a small trial showing efficacy for potassium outcomes, and then we have huge postmarketing experience for harms. We have two very large well-conducted observation studies looking at the magnitude of severe GI consequences of taking SPS.

And though it looks like there is a signal there, my general take home from those studies is actually one of reassurance because the absolute numbers are very small. And we turn to the new binders, we have a different situation.

We have trials of several 100 patients. We don't have patient-important outcomes, but we have lots of data showing potassium outcomes and also showing non-discontinuation of RAAS Blockade, that it's possible to keep people on RASS BLockade by using these binders. We also know that the adverse effects in those trials, though they're not negligible, are probably acceptable, but of course, what we don't have here is the phase four experience, that post-marketing experience about the real harms. So in my own practice, I continue to use SPS over time. I think we'll need to look at the observational evidence that's emerging about harms, and we'll also need to look at cost and cost effectiveness. So that's one new area. And then the other thing that I find really exciting is, literally just published this month, on SGLT2 inhibitors. And I'm grateful to you for pointing this evidence out.

Many populations that benefit from RAAS inhibition have now been shown to also benefit from SGLT2 inhibition. And the new evidence is that in CREDENCE, at least, with canagliflozin, there was a reduction in a variety of different potassium related adverse outcomes by 22 to 34%. So that's quite a big risk reduction we're seeing in high potassium related outcomes. And interestingly and almost magically there's no difference in mean potassium and there's no increase in hypokalemia. So really it's possible that when we add an SGLT2 inhibitor, and I wouldn't add it for potassium alone, but if you add it for one of the many indications for SGLT2 inhibition, that that is going to make it easier to avoid these upwards excursions of potassium that lead to a patient being identified as hypokalemic and that lead to RAAS Blockade being stopped.

Dr. Roberto Pecoits-Filho:
Interesting to hear that there are multiple strategies other than diet that we can use for controlling potassium. I think our patients would also be happy to hear about that. Are there any other particular challenges in keeping people on RAASi?

Dr. Catherine Clase:
Yes. There were two other things that I'd like to mention. The first is acute kidney injury. So we aren't certain based on observational data when we have an episode of acute kidney injury, we should restart people on RAAS Blockade. But given this uncertainty and given the wealth of randomized evidence that we have for benefit in those specific situations I was talking about, my personal preference is to assess the risk for a current AKI. If it's truly extreme, if a patient is coming into emergency with a high output ileostomy and with current hypovolemic shock, then I might not restart it. But if their risks for AKI are the same as their risks for progressive kidney disease and for cardiovascular disease, then I do tend to restart RAAS Blockade after AKI. The second issue is changing creatinine, particularly changing creatinine with starting. We've all come to recognize that the idea that we should stop RAAS Blockade if there's a change of more than 30% is actually not evidence-based. For sure, a large excursion in creatinine, a large change in creatinine like that, is a bad prognostic marker.

Multiple studies show this, but what we don't have is evidence that that change is then associated with a reduced stability to benefit from the RAAS Blockade itself. The other thing we know is that in general, for RAAS Blockade associated changes, when we repeat the creatinine in another couple of weeks, it tends to go back towards baseline in about 50%. So unless the change in creatinine is truly extreme, what I suggest is following the trajectory, stop the RAAS Blockade only if it's progressive and when you stop it, if the creatinine doesn't improve and your hypothesis doesn't look as if it's correct, then that's another great situation where you can consider restarting RAAS Blockade.

Dr. Roberto Pecoits-Filho:
These are great points, Catherine. Are there any final message you'd like to leave with our listeners?

Dr. Catherine Clase:
I'd like to go back to when you are prescribing this, think what the indications are, the magnitude of the benefit. And remember that for many of the patients that we're treating, cardiovascular outcomes are more numerous than kidney outcomes, even for nephrologists. And then the second thing is to think about the residual risk, even though these are quite drugs and they would use risk consistently and by a large effect, we know that risk is still high for many patients. And we now have strong evidence to use additional therapies, like SGLT2 inhibitors and MRA's for many of the same indications as RAASi as add-on therapies. So I'm always thinking about that.

Dr. Roberto Pecoits-Filho:
That's a great way to round out our discussion today. I want to thank my guest, Dr. Catherine Clase for joining me. Catherine, it was great having you in the program.

Dr. Catherine Clase:
Thank you for having me. It's been an honor to participate.

Dr. Roberto Pecoits-Filho:

I am Dr. Roberto Pecoits-Filho. To access this and other episodes of the series visit kdigo.org/podcast. Thanks for listening.

Announcer:
This episode was provided by KDIGO and supported by Vifor Pharma.