Transcript Details

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

Nonsteroidal MRA & SGLT2i in People With CKD & T2D: Current Evidence and Rationale for Combination Therapy

Announcer:
Welcome to CME on ReachMD. This activity, titled Nonsteroidal MRA & SGLT2i in People With CKD & T2D: Current Evidence and Rationale for Combination Therapy is provided by MedCon International.

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Dr. Green:
Combining nonsteroidal mineralocorticoid receptor antagonists, or MRAs, with SGLT2 inhibitors may provide added benefits for people living with chronic kidney disease and type 2 diabetes. With new trial data emerging, we're now beginning to understand how this combination could help reduce persistent cardio-kidney-metabolic risk.

I'm Jennifer Green, an endocrinologist and clinical trialist at Duke University in Durham, North Carolina.

Dr. Heerspink:
Hello, everyone. My name is Hiddo Heerspink. I'm a clinical pharmacologist and clinical trialist at the University of Groningen in the Netherlands. It's our pleasure to discuss type 2 diabetes, chronic kidney disease, clinical management, and new clinical trial data from the CONFIDENCE trial.

Let's start by setting the stage with the clinical background. And, Jennifer, I would like to ask you: Why is early chronic kidney disease detection in patients with type 2 diabetes still such a challenge?

Dr. Green:
That is a wonderful question. I will preface this by saying it's not difficult to do. Essentially, what we need to do is we need to assess whether or not our patients have evidence of kidney disease through measurement of a creatinine and calculation of eGFR, as well as measurement of the urine albumin-to-creatinine ratio at least once a year. It is recommended for everyone with type 2 diabetes, and those recommendations are also not new.

I will give a US example. We're doing a pretty good job at measuring serum creatinine and calculating eGFR values in most people with type 2 diabetes annually in the United States. However, it's that urine albumin-to-creatinine ratio measurement that tends to fall through the cracks. It's not happening very often.

And I don't know if it's more of an issue of people just forgetting to do it, or sometimes I send my patients to the lab and they're unable to provide a sample, but I think we need to spend some time today really emphasizing the importance of understanding what that level

is, what it means, and how we can follow the uACR over time to assess if the therapies that we're introducing are having a beneficial effect.

Dr. Heerspink:
Yeah, so, Jennifer, it's interesting, isn't it? A creatinine measurement requires a venipuncture, and we can easily collect the urine. That can be done at home in the morning. It can be done during the day. But still, we find it so difficult to ask our patients to collect a little bit of urine and just measure the albumin-to-creatinine ratio.

Dr. Green:
Yes. And I think maybe there's just not a good understanding of the importance of that value, of knowing what it is. Traditionally, endocrinologists, we would look to see if our patient had an elevated urine albumin-to-creatinine ratio. We would make sure that they were on an ACE inhibitor or an ARB, and that their blood pressure was controlled. But beyond that, I would say endocrinologists probably did not use the information to alter care in any type of meaningful way. But we've really entered a new era of care for the person with type 2 diabetes and chronic kidney disease, and I hope we'll get that message out today.

Dr. Heerspink:
Exactly. And we have already started directly talking about albuminuria. But of course, we have other risk factors as well: blood pressure, hyperglycemia, hyperlipidemia. And we should, I think, control all these risk factors, and not only focus on albuminuria or only GFR; it's really that constellation of risk factors, obesity, for example, that should all be targeted. Because I believe that the Steno-2 trial beautifully demonstrated, already many years ago, that in type 2 diabetes patients, multiple risk factor targeting is the way going forward.

Now, even when we look at these multiple risk factors, there's still residual risk. And how should we think about this clinically? What can we do with this residual risk?

Dr. Green:
Yeah, so that's a very important question. And I do have a slide that I like to show that really very nicely demonstrates the positive impact that management of what we consider to be these traditional risk factors, so blood pressure, lipids, glycemia, on outcomes in the time period between about 1995 and 2005 and an increased emphasis on managing those really traditional, or maybe foundational risk factors very significantly reduced the risks of certain types of adverse outcomes in people with type 2 diabetes.

So for example, we saw significant reductions in rates of myocardial infarction, reductions in risk of stroke, but we didn't see much of a change in the risk of progression, for example, to end-stage kidney disease or for the incidence of heart failure hospitalizations.

So we know that these foundational, these traditional risk management approaches are highly important, but there are still metabolic physiologic drivers of adverse outcomes that are present in people with type 2 diabetes that are not fully addressed with these traditional therapies.

Dr. Heerspink:
In addition, we also have albuminuria. We already talked about it as a risk factor. And we know that now, with new therapies becoming available for the treatment of type 2 diabetes and chronic kidney disease, these new therapies like SGLT2 inhibitors, mineralocorticoid receptor antagonists, they reduce albuminuria. And the magnitude of the albuminuria reduction is directly related to the magnitude of residual risk reduction for cardio and kidney outcomes.

So it appears that we can use this change in albuminuria as a pharmacodynamic biomarker or to monitor the efficacy of the treatment and to monitor the risk of progression of individual patients.

But yet, despite the availability of these new therapies, we also recognize that there are still many patients with residual high albuminuria, which is still driving the risk of kidney and cardiovascular damage. And considering that residual risk, perhaps in the future, we should not only focus on the individual therapies but really think about combination treatments and trying to find the best combination for each individual patient.

And perhaps with that in mind, we can now turn over to the CONFIDENCE trial and also talk about what is the benefit of combining an

SGLT2 inhibitor together with a nonsteroidal MRA.

Dr. Green:
For those just tuning in, you're listening to CME on PACE CME and ReachMD. I'm Dr. Jennifer Green, and here with me today is Dr. Hiddo Heerspink. We're discussing the combination of nonsteroidal MRA and SGLT2 inhibitors in people with chronic kidney disease and type 2 diabetes.

Dr. Heerspink:
So maybe, Jennifer, you can give us an introduction to the CONFIDENCE trial and tell us why the trial was designed.

Dr. Green:
Absolutely. So this is, I think, very exciting new information that is available that can help inform how we apply the emerging data from recent clinical trials directly to the care of our patients.

And the clinical rationale for the design and conduct of the CONFIDENCE trial was really to understand more clearly whether or not combination therapy provides greater benefit than use of a single beneficial agent alone. So essentially, looking at whether or not treatment with both the nonsteroidal MRA and an SGLT2 inhibitor can improve outcomes, can improve markers of kidney disease and cardiovascular risk when given together. We can't automatically assume that. We know that there have been trials of the individual agents in people with type 2 diabetes and chronic kidney disease that demonstrated clear clinical outcomes benefits from use of the individual agents, but whether or not 2 are better than 1 was still a question. So that fundamentally is the rationale for the design of the CONFIDENCE trial.

In addition to that, in CONFIDENCE, as you'll talk about a bit further, we really looked at the safety of initiating both classes of drug at once.

Dr. Heerspink:
Yes, indeed, Jennifer. So this clinical trial was done in patients with type 2 diabetes and chronic kidney disease. They had high albuminuria, a median albuminuria level was around 800 mg/g creatinine, and they also had high blood pressure and BMI around 30 kg/m2. These patients were randomized to treatment with finerenone up-titrated to 20 mg or empagliflozin 10 mg per day or a combination. These patients were treated for 6 months, after which they discontinued the medication and were followed for another month.

Now the primary endpoint was the change in albuminuria from baseline. Of course, we would have loved to do this clinical trial using clinical kidney endpoints, but this is very difficult. In this population, a clinical trial using clinical kidney endpoints would require 41,000 individuals and was clearly not feasible. However, given the strong evidence between treatment effects on albuminuria and correlation with treatment effects on clinical kidney endpoints, albuminuria was considered to be the right endpoint for this trial.

And of course, when talking about efficacy, you should always balance efficacy with safety. So the safety at first events of special interest were, of course, hyperkalemia. And we know that both SGLT2 inhibitors and finerenone cause an acute dip in GFR, which is considered to be a hemodynamic effect and reflect the mode of action of these interventions, so we also carefully monitor GFR changes over time.

The trial was just recently finished, and we are very pleased to talk about the primary and secondary outcome results.

So, Jennifer, can you tell us what did we find in this trial?

Dr. Green:
Well, in the trial, just to sum it up, we found that 2 were better than 1 and that the simultaneous initiation of both the nonsteroidal MRA and the SGLT2 inhibitor reduced the urine albumin-to-creatinine ratio far more significantly than being treated with either agent alone.

Dr. Heerspink:
Yeah, isn't that interesting? With the combination, you get a 52% reduction in albuminuria; whereas, with finerenone or empagliflozin alone, you get a 30% reduction in albuminuria. So these effects are clearly additive. So when you combine the finerenone with

empagliflozin, you get additive effects, suggesting that the mode of action to prevent kidney failure with these agents are different, and that you can indeed use the combination.

Now, when we look at the safety, hyperkalemia as reported by the investigators was found in 11% of patients that were randomized to finerenone, 9% with the combination, 4% with empagliflozin. So we see fewer hyperkalemia events as reported by investigators with the combination compared to finerenone alone. And this was a little bit expected, because we knew that SGLT2 inhibitors reduce the incidence of hyperkalemia. So with the combination, you get additive efficacy, and you slightly reduce adverse events induced by finerenone alone. So both from an efficacy and safety perspective, an ideal combination, I would say.

GFR acutely declined as expected, reflecting the mode of action of these agents by 5.6 mL/min, 2.0 with with finerenone, 3.8 with with empagliflozin, but this acute effect on GFR is completely reversible directly when we stop the combination, so also indicating, again, that this effect most likely reflects a hemodynamic effect and certainly not a structural worsening of kidney function.

So we've discussed the data, and now it's a challenge to make sure that we implement these findings in clinical practice.

Jennifer, what do you think? Is this the right study, and should we now implement these findings in our clinical practice?

Dr. Green:
Well, that's a great question. Yes, I think we should. I think this trial makes me feel much more comfortable in initiating what I know are indicated therapies in my patients with type 2 diabetes and chronic kidney disease on the same day. I think the take-home message here is that these individuals should be treated with both classes of drugs and that we should feel comfortable and it is important to make sure that they take both classes and that there isn't a particularly long delay between the initiation of the second drug. So but that, again, it's a bit easier said than done, and we'll need to think about, first, the identification of individuals who will benefit from these agents and then take a systematic approach to the implementation of these therapies. And in an individual local practice or care setting, it may require that there is, for example, a local champion or perhaps a small team really focused on ensuring that patients are treated as per contemporary guidelines.

Dr. Heerspink:
I couldn't agree with you more, Jennifer. This is exactly what we have to do. We have evidence that these drugs work additive, and it's now up to the treating physician to either start a combination simultaneous or sequentially. But in these high-risk patients, we need combination treatments because they are more effective and can be used in a safe way.

I thank everyone for listening to this podcast by Jennifer Green and myself, Hiddo Heerspink. I hope you found this useful for your clinical practice, and I hope you will listen to us in the future again. There's a lot of clinical trials ongoing, and we'll see much more of these combination trials in the near future. Thank you for listening.

Dr. Green:
Thank you to everyone for joining what I think was a very exciting conversation.

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