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Addressing CKM Mortality & Morbidity in Patients With CKD and T2D: The Role of Combined ns-MRA & SGLT2i Therapy

Announcer:
Welcome to CE on ReachMD. This activity, titled “Additive Effects of non steroidal-MRA and SGLT2 inhibitor: Efficacy and Safety in the CONFIDENCE Trial” is provided by Medcon International

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Chapter 1

Dr. Agarwal:
Hi. I'm Dr. Rajiv Agarwal, professor emeritus of medicine at Indiana University School of Medicine, and a practicing nephrologist at the VA Medical Center, also in Indianapolis. I'm really excited to bring you a 3-part discussion series featuring insights from both nephrology and cardiology. We'll be exploring new opportunities for improving outcomes in patients with chronic kidney disease and type 2 diabetes.

I'm delighted to be joined by Dr. Amy Mottl, professor of medicine at University of North Carolina, Chapel Hill, and Dr. Muthiah Vaduganathan, a cardiologist at Brigham and Women's Hospital in Boston, affiliated with the Harvard Medical School.

The recent release of the CONFIDENCE results at the ERA gives us a unique opportunity to interpret these data and consider what it means for clinical practice.

Dr. Mottl:
So I just wanted to start by talking a little bit about the background of CKD and diabetes. As we all know, it's extremely common. About 1 in 3 people with type 2 diabetes have CKD, and it's a really heterogeneous disorder. People have decline in GFR and rise in urine albumin-creatinine ratio at very different rates, but both of these entities really contribute to the cardiovascular disease and even mortality in people with type 2 diabetes. In fact, CKD has been shown to be the primary factor in type 2 diabetes that brings the increased mortality.

And while we've been looking for other surrogate markers, albuminuria really remains the primary risk marker for progression of kidney disease, cardiovascular disease, and mortality. And hence the American Diabetes Association guidelines recommend annual monitoring of UACR in all people with diabetes and that we really use this as a target in order to reduce the albuminuria and hence reduce the cardiovascular and kidney risk.

Dr. Agarwal:

Great. So we're going to talk now about the CONFIDENCE trial.

The CONFIDENCE trial was designed to test the hypothesis that compared to monotherapies, when we start 2 therapies simultaneously, which is finerenone and empagliflozin on top of ACE and ARB, can we reduce albuminuria more, compared to monotherapies at 180 days? So we are looking at, first, a comparison of the combination versus finerenone and then the combination versus empagliflozin. And we have to declare victory on each 1 of these 2. These are 2 separate primary endpoints, and we have to show victory on both of them to show that this is really working.

So what we did was we designed the trial of using an intermediate endpoint of UACR reduction. And we took people, a broad category of people, with a eGFR between 30 and 90 and UACR between 100 and 5,000. And then we looked at the outcome of UACR reduction.

Now, most people believe that there would be an additive effect of these drugs. So that wasn't the only reason that we were doing the trial; we wanted to show the safety of this treatment.

What was remarkable was that the reduction in UACR happened very early, at day 14. We already saw a 30% reduction with the combination group. It kept on dropping at day 30, at day 90, until day 180. And at day 180, there was a 52% reduction in UACR in the combination group, there was a 29% reduction in the empagliflozin group, and a 32% reduction in the finerenone group. And each of the comparisons was significant with a P value of less than 0.001. So the combination was superior to finerenone by 29%, and the combination was superior to empagliflozin by 32%. The P values are significant.

Now, we stopped the IP, or investigational product, at day 180 and we measured the UACR at 210 days, and there was reversal of the albuminuria effect, which is what we expect. In other words, these are not drugs that are curing a disease; they will work only as long as you take the drugs.

It is very important also to point out that in heart failure literature, especially in FINEARTS, what the group has shown is that during that period in which the drugs are withdrawn, the clinical cardiovascular events go up. So it's very important to continue to take these therapies if you are on these therapies.

The mean change in potassium was about 0.19 in the finerenone group and about 0.26 or so in the combination group. And it stayed elevated for most of the 180 days. When we stopped the drug, it came back to baseline. What is interesting is that there was about an 18% relative risk reduction in hyperkalemia risk in people who received the combination compared to finerenone group. We also had an improvement in blood pressure, about a 7.4 mm decline in the combination group. In terms of the eGFR slope declines, there were also a little bit more, about a 6-mL decline. The mean GFR was about 54 and you had a 6-mL decline. But this decline was reversible at day 180. When we stopped the drug, the GFR went to baseline. So this is not a permanent decline in GFR; it's a hemodynamic decline.

But when we look at people who have acute kidney injury reported by the investigators, we had 5 events in the combination group, 3 in the finerenone, and none in the empagliflozin group. So 8 out of 800 people actually experienced acute kidney injury, so very low incidence. And we were encouraged by the fact that there was not much danger in the use of these combination therapies compared to the components.

Amy, how would you interpret these results?

Dr. Mottl:
I think it gives us solid data with which to counsel our patients that we can safely start these medications together. And we often talk about how time is nephrons and so waiting 3 to 6 months between visits and starting one therapy versus another, especially for our rapid progressors, can really make a difference. I also think it shows us that putting them together mitigates some of the hyperkalemia that we do see with finerenone.

So I'll turn it over then to Dr. Vaduganathan to talk a little bit about FINEARTS.

Dr. Vaduganathan:
Absolutely. FINEARTS-Heart Failure, as a reminder to our audience, was a large, global, randomized trial of the nonsteroidal mineralocorticoid receptor antagonist finerenone among patients with heart failure with mildly reduced to preserved ejection fraction.

And the trial itself evaluated this therapy in this broad population for its cardiovascular effects and showed an important reduction in heart failure events and cardiovascular death.

However, there were interesting issues related to the kidney in that there was no apparent effect on the long-term decline in GFR or kidney function over time. And this was in contrast to what was observed with previous trials of patients with type 2 diabetes and chronic kidney disease in the FIDELITY program. And so there were new analyses that were presented at the ERA Congress to help bring this together to understand why there might have been deferring effects.

Now, FINEARTS-Heart Failure was a lower kidney risk population. On average, the average albuminuria levels, UACR levels, was only about 18 mg/g, and about only half of patients had a GFR that was less than 60. And so in this relatively low-risk population, it was difficult to show a true kidney outcome benefit, including a change in slope in GFR over time.

However, if you take higher-risk individuals, let's say UACR above 300 mg/g, which was represented in the trial, might you actually see similar effects to what was previously seen? And that was the focus of a dedicated analysis. And in fact, Dr. McCausland presented data that GFR slope was, in fact, modified to a significant degree in that high-risk population, and to a clinically significant degree. And so this suggests that perhaps it's all about the baseline risk of the population, and that if patients are at sufficient risk for kidney disease progression, they may benefit from therapies like finerenone to slow that kidney disease progression.

There was a second analysis that was also presented in FINEARTS-Heart Failure, again, to put together what we already know from the finerenone program in kidney disease. Rajiv, you have shown beautiful data about the mediating role of albuminuria, and, Dr. Mottl, you just shared that albuminuria is such a critical marker for screening and detection. But might it also be a surrogate or a mediator for outcome benefit of our patients? And might clinicians be able to follow these markers in clinical practice to ensure that patients are truly benefiting from a heart and kidney perspective?

And so in FINEARTS-Heart Failure, UACRs were serially measured. And the intent was to understand, could it actually forecast the ultimate benefit that was seen with respect to heart failure events? And it did actually mediate a portion of the benefits. Now, it's not a majority of the benefit, but a portion of the benefit was mediated, and that was independent of other characteristics that were measured in these patients. So it does suggest that the effects on the kidney might be really critical to understand as a window for cardiovascular protection with this therapy.

Dr. Agarwal:
So before we wrap up, let's each share one takeaway from this first chapter. I'll start with you, Amy, what's the key takeaway from your side?

Dr. Mottl:
I think it's the fact that our patients are at such high risk, not only for progressive kidney disease and cardiovascular disease and death, and that we really don't have time to sit and wait and sequentially add on therapies. And for patients who meet these criteria, I think that we can do this safely. The mean age was the 65 to 67 across the 3 different groups. And so this was not a young population. And so I think that also shows us that even in older individuals, who I think we worry a little bit more about, that they can tolerate this simultaneous initiation.

Dr. Agarwal:
And Muthu, what would you say?

Dr. Vaduganathan:
That this up-front combination, the simultaneous approach, is not only safe but reaches our clinically relevant targets faster. And that speed is actually very relevant, even in a CKD population, which has traditionally been viewed in this chronic lens. But up front, those cardiovascular risks are still borne, and so in those first months, where we traditionally would delay sequencing in a second therapy, those patients may experience early cardiovascular events that are potentially preventable with up-front, simultaneous initiation of therapy.

So CONFIDENCE, I think, does provide us as clinicians, confidence with using this approach, and we're hoping that it can stimulate interest in speeding up the process of implementation for this high-risk population.

Dr. Agarwal:
So you might not get second chances if you're sequencing. Get them out of harm's way quickly, and you can use albuminuria to diagnose and also look at the response to the treatment.

So in the next chapter, we'll turn our attention to how we identify the patients who are most likely to benefit from the combination therapy. Stay tuned.

Chapter 2

Dr. Agarwal:

In Chapter 1, we reviewed key findings from the CONFIDENCE trial that were recently presented at ERA. Now we are exploring the clinical characteristics that help us identify patients who may benefit from combination therapy.

So how do we tailor therapy? And I'll start with you, Amy. How do you look at tailoring therapy given now we have results of the CONFIDENCE trial?

Dr. Mottl:
Yeah, thanks, Rajiv. Our patients are so heterogeneous in terms of their risk factors. I think it's critical to tailor things according to what their blood pressure and their glycemic control and their body mass index are. For people who are very hyperglycemic, have A1c's above 8 or even 9, I tend to start a GLP-1 agonist first, because we know that those are the most effective in A1c reduction.

Barring that or somebody who really wants to lose weight, I will start – starting now – simultaneous initiation of nonsteroidal MRA finerenone and an SGLT2 inhibitor together. I expect that there will be patients who are uncomfortable starting 2 drugs at the same time. And then I think it's really the toss of a coin as to which 1 you start first, but I think it's important to have a plan in place. And I'll often say, okay, start this medicine for 2 weeks and see how your blood pressure is doing and how you're feeling, and then let me know, and we can then start the second agent as well. So I think it's really all about shared decision-making. What are the patient's priorities? What are their risk factors, etc.?

Dr. Agarwal:
Cardiology has done this for a long time with the HFrEF. How do you see CONFIDENCE changing, or do you see how we can apply the learnings from cardiology into nephrology?

Dr. Vaduganathan:
Yeah, thank you, Rajiv. So HFrEF, heart failure with reduced ejection fraction, is a fairly finite population. It's about 6 million Americans, for instance, have heart failure, and about 3 million have heart failure with reduced ejection fraction. And that's a group of patients that's uniformly almost high risk. They face high risk of near-term mortality and heart failure hospitalizations, and so we treat them with an aggressive treatment course, similar to almost chemotherapy, in which we're, up front, using multiple drug therapies to help ameliorate that risk.

Now, CKD is likely a broader-risk population. There's a lot of variability in risk as Dr. Mottl shared. And so I think that tailoring might be based on some of the phenotypic characteristics, as was just shared, but might also be based on risk itself. And so early implementation of combination therapy might especially be in those at highest risk for kidney disease and cardiovascular disease progression.

So those might be identified by simple measures. For instance, those with the highest degrees of albuminuria. Or we have now validated clinical risk scores and clinical tools that can help risk stratify patients. And so KFRE, Klinrisk, CKD-PC all are validated tools in practice that we can use to help dissect the population to see who should we start with implementation in. And those patients, I think, we can share those numbers at the bedside, and they may actually be much more open if they see that, "Oh, I am at high risk for near-term disease progression," to actually start more than 1 therapy at that clinic visit.

Dr. Agarwal:
Let me ask you, in a person with type 2 diabetes, the average age here is 67 and the median UACR is like 574, if I recall correctly. And the low end, maybe the lowest quartile, may be 100 and 110, something like that. Is there any low-risk population? When we say high

risk, is there any low risk here for cardiovascular disease?

Dr. Vaduganathan:
No. In a CONFIDENCE-like population, we are actually considering simultaneous initiatives and early combination therapy in all individuals. It is really probably those who are in the community with really low or no levels of albuminuria, perhaps with just some, perhaps, age-related reductions in GFR, where they may have relatively low rates of disease progression from the kidney standpoint, and maybe sequencing might be a more acceptable approach in that population.

Dr. Mottl:
I think it's important to point out, we've looked at the different KDIGO categories for kidney and cardiovascular risk. And with SGLT2 inhibitors and with combination therapy, people are at such high risk with type 2 diabetes. I don't think there is a no-risk category for people unless they have normal GFR and normal ACR, obviously.

So I think the one caveat might be for patients who are extremely elderly or have minimal ability to participate in daily life and are very frail. I think that those people might be the only ones where you might be a little bit more cautious in starting simultaneous therapy and tailoring their medicine, depending on how much polypharmacy they have on board, appropriately.

Dr. Agarwal:
I think that this is probably a way that we are getting into the future. But in terms of the risk, we can actually reduce the risk of hyperkalemia if started simultaneously, right? We are not increasing the risk. You can make a case that you can start with half dose of each therapy instead of full dose. Instead of sequencing, you can still do simultaneous. You can half dose and then full dose at week 1 or week 2, whatever you prefer. And so everybody starts with a low-dose combination to a full-dose combination, potentially.

eGFR monitoring, I think that's more potentially for the physician, because that's where they might pull the trigger and say that, no, this is not for you, because your creatinine bumped. And I think if we looked at it in combination with a UACR reduction, you might actually find that, oh, this person is more protected than harmed by the eGFR change.

So the decision support tools, particularly for the primary care, may be very important, and especially when they're treating people with, say, eGFR of 70, the risk of hyperkalemia is essentially nonexistent in those individuals. If they're K of 4, how can you get really hyperkalemic with that kind of a thing? And albuminuria, which is very little.

eGFR monitoring, if you go from, say, a creatinine of 0.9 to 1.1, you might actually have a 20% reduction in an elderly woman, but that's probably not clinically relevant. I would keep on going and say you have had such a big reduction in UACR. So I think that the treatment targets for the vast majority, if we're looking at a population level, not what a cardiologist or nephrologist sees but what the population of type 2 diabetes that exist, it might be more safe than dangerous. Because in the CONFIDENCE trial, we are taking really an advanced disease, with a mean GFR of 54 and a UACR of like 574, something like that. I think we have come to it, but seems like we want to identify and refine how we apply to a broader population.

So before we close, I'd like to invite each one of you to share one practical insight or key message from this chapter that you'd like our audience to remember.

Amy, I'll start with you.

Dr. Mottl:
One of the things that we haven't talked about is the GFR decline that we see with starting any of these strict 4-pillar drugs; they all have that same effect. And I think telling patients and telling other providers up front to expect this change and explain to them that it's probably a positive change due to decrease in intraglomerular hypertension and that they should not worry about it. So I think telling them what to expect is really important.

Dr. Agarwal:
Muthu?

Dr. Vaduganathan:

I think the point you made, Rajiv, about that these therapies are safer together is such a critical point because it arms clinicians with information that, typically, patients always assume that if you start 2 medicines at once, it would be unsafe. And here, we actually have 2 therapies that actually make one another safer, and that is a critical, critical item that can be shared at the bedside or in the clinic to help convince patients and clinicians that this is the right approach for their patients.

Dr. Agarwal:
Yeah. So I'm going to steal something from the heart failure literature, and it says some of all instead of all of some. And so you don't want to just do 1 or 2 therapies, give the max dose, but have a little bit. That's why I think if you are concerned that the patient might have an exaggerated response, such as the patient that you pointed out, Amy, very elderly, frail, etc., maybe we can start them on half dose of finerenone, half dose of empa. So like 5 and 5 and say, okay, in 2 weeks you can go to 10 and 10. And that might be a better way, because it may be the 5 and 5 is making each therapy safer, and you're still getting 2 on board.

In the next chapter, we'll shift our focus to collaborative care and explore how we can implement a multidisciplinary approach to reduce CKM risk. Stay tuned.

Chapter 3

Dr. Agarwal:
In Chapter 2, we discussed which patients might benefit most from combined nsMRA and SGLT2 inhibitor therapy and how to identify them. In Chapter 3, we are looking at the transition from a patient-level strategy to system-level implementation and care coordination.

So first of all, we'll ask about collaborative models and practice, who's involved, and how collaboration works in real-world care. So you know we have started this model of CKM, the metabolic, the cardiac, and the kidney model. And how does this multidisciplinary approach affect us all? And how can we collaborate to make this happen in the real-world care?

Dr. Vaduganathan:
I think conceptually, CKM is, in many ways, how we should be practicing medicine. It's ideal that we have collaborations. It's ideal that we have more eyes on the patient and more minds thinking about the patient and the best treatment approach.

Now, operationalizing this in practice is quite challenging. Actually, many institutions have resource scarcity, specialist scarcity, in which there is long wait times for seeing an endocrinologist, nephrologist, or cardiologist, so seeing them all jointly might be, actually, a challenging proposition. That is slowly changing. In some ways, this is starting with 2 specialties working together. For instance, there's cardiometabolic clinics that are established in which this seeing patients actually in a coordinated fashion, and it might not need to be necessarily at the same time, but at least that the same clinic has the capacity to be able to see complex individuals and seek expertise within that same clinic for the various specialties. That model has been efficiently rolled out nationwide and in many healthcare settings, and it is actually proving to be a very impactful way to approach care, that you can rapidly optimize patients.

Dr. Agarwal:
And, Amy, how has it been at your institution and your practice? How have they embraced SGLT2 inhibitors, for instance? And how have the specialties collaborated in a multidisciplinary way?

Dr. Mottl:
Yeah, we're actually about to launch our first triple-specialty clinic, so we will actually have a CKM clinic. And I've been involved in other multidisciplinary clinics, and patients absolutely love it because they can physically see their different physicians collaborating with one another and getting the same message at the same time.

We also, however, for years, have had a CPP, clinical practicing pharmacist, within our different clinics. So the same people who are in clinic and endocrinology, cardiology, and nephrology, so they are really the link between us. And so if I have a patient who I really want to get started on these numerous medications, I can refer them to the CPP, and they'll get them started, and they will be checking labs and titrating up and so forth. And then they can also see them when they're there in other clinics as well.

And I think in academia, this kind of a model can definitely work. I think in private practice, it probably is a little bit more difficult. And so then I think it's a matter of really good communication. If we are all within the same EMR system, and we can just shoot each other

messages, I think that really works well, but it definitely does take the effort. And I think that effort is very not only important but much appreciated by the patient, for them to feel safe that all of their physicians feel the same about starting these different medications.

Dr. Agarwal:
And one of the criticisms that I've heard is, again, “Doc, okay, you have taught me that the creatinine bump doesn't matter. I'm not going to do anything about it.” But the patient is going to go on the internet and say, “Oh, my GFR dropped. Your medication caused it. Why are you still giving me the medication?” And he goes to another specialist who hasn't heard about these benefits, and he stops it.

I've heard from various people that many people would stop these medications after taking them for a certain length of time. In other words, these medications work when you take it for the lifetime.

Dr. Mottl:
Yeah, I think talking to the patient before starting these medications, so that they know to expect the creatinine bump. And also, I'll even tell other providers, primary care that the GFR dropped this amount, and I'm really not worried about it; I think it's fine. And I think that settles a lot of angst.

I'll bring up another scenario, which I think gets in the way a lot, is in the hospital. So frequently, RAS inhibitors, more than anything else, get stopped in the hospital. AKI episode, and then they just never get restarted again. And so I think education for our trainees in particular, but our hospitalists as well, that if they are stopped, that they can restart it on discharge and then have them follow up with one of their physicians to see how they're doing with it.

Dr. Agarwal:
So, Muthu, in cardiology, I've seen the term WRF, which is the worsening of renal function reported. Is that something which is often a trigger to stop treatment in heart failure?

Dr. Vaduganathan:
Yes, unfortunately, I think that the entire system of classifying GFR changes and creatinine changes needs to be relearned across our specialties, but especially outside of nephrology and more broadly in cardiology and primary care. And we've always been taught, and I think cardiologists have even been trained, that elevations in creatinine are a red flag, and that should prompt changes in therapy or therapeutic approaches and often signal safety issues. And here, now we have therapies that engage this system in such a way that those changes might actually reflect the very pharmacological action of the therapies and the pharmacological engagement of its sort of targets. And so in that setting, I think cardiologists really do need to relearn that, and terms like worsening renal function should be dropped and shouldn't be a reflection of these types of scenarios, and they should really be disconnected from other terms that might signal safety, like acute kidney injury.

Dr. Agarwal:
And we now see that we have effective treatments. And how do we encourage the long-term use of these treatments? I've seen some physicians say, “Oh, patient's UACR has dropped to less than 30. I'm going to stop these treatments. We have achieved a cure, and you don't need it anymore, because these are indicated for albuminuria, and albuminuria doesn't exist.” How do we make sure that the patients take these therapies for the long term for adherence and side effects and even the little bumps they have, like when they go in the hospital, somebody stops them, how do we get them back on track so they keep on having the benefits of these revolutionary treatments that we have discovered in the last 5 years?

Dr. Vaduganathan:
I think a reminder and education, broad education, that chronic kidney disease, much like many other chronic CKM, or cardio-kidney-metabolic, conditions, require lifetime or long-term therapies. For instance, if you're treating a patient with hypertension with a blood pressure-lowering therapy, stopping that therapy, it will, even if that therapy has achieved its intended purpose and the blood pressure is well controlled, will cause a rebound in that blood pressure. Same is true with anti-hyperglycemic therapies for diabetes, weight loss therapies or obesity medicines in the management of obesity. And so same is true for the management of heart failure and chronic kidney disease, even though those disease states sometimes might be more asymptomatic in terms of their disease progression. Here, we do see that once we stop these therapies, we can see a rise in, for instance, UACR levels, which signals that the risk has returned. And that's the risk not only of kidney disease progression, but also of cardiovascular events.

Dr. Agarwal:
So as we come to the end of this chapter, let's go around and highlight one takeaway that you think is the most important for clinical practice. I'll start with you, Amy.

Dr. Mottl:
Oh, I think it's education of the patient, telling them exactly what to expect, that they're going to be on these medicines for the duration of their life, and to make sure they understand why they're taking it. I actually write down when I print out their after-visit summary, these are your kidney medicines, and if anyone wants to stop them, you need to tell me.

Dr. Agarwal:
And Muthu?

Dr. Vaduganathan:
It's engaging in conversations just like this, because collaborative care models is going to be the future way that care is going to be delivered for broad-risk populations. Because ultimately, patients rarely will have 1 of these conditions in isolation. Patients are increasingly becoming older and more comorbid in many regions of the world, and so collaborative care models are the principal way that care will be delivered in the future.

Dr. Agarwal:
I think that educating the patient is really important.

I think we have come to the end of this chapter. Thank you to our audience for joining us throughout this 3-part series. And special thanks to Dr. Amy Mottl and Dr. Muthu Vaduganathan for today's thoughtful discussion on collaborative care and the 4-pillar strategy. We hope these conversations help support your efforts in delivering comprehensive, evidence-based care for patients with CKD and type 2 diabetes.

Dr. Mottl:
Thank you.

Dr. Vaduganathan:
Thank you so much.

Dr. Agarwal:
Thank you.

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