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What's the Consensus on Cardiorenal Protection for CKD in T2D?

Announcer:
Welcome to CME on ReachMD. This activity, titled "What's the Consensus on Cardiorenal Protection for CKD in T2D?" is provided by Medtelligence.

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[Chapter 1]

Dr. Laubscher:
Achieving optimal outcomes when treating patients with chronic kidney disease and type 2 diabetes remains challenging, with a multidisciplinary approach and multiple medications required to prevent progressive decline in renal function and cardiovascular events. So what are the latest clinical trials and guidelines telling us on how to best treat these patients to improve outcomes?

This is CME on ReachMD, and I'm Dr. Tessa Laubscher, a family physician and diabetes specialist in Canada.

Dr. Bakris:
And I am Dr. George Bakris, a nephrologist, clinical trialist, and professor of medicine at the University of Chicago Medicine in Chicago, Illinois.

Dr. Kosiborod:
And I'm Dr. Mikhail Kosiborod, cardiologist at Saint Luke's Mid America Heart Institute in Kansas City.

Dr. Laubscher:
So our first topic is going to look at the clinical impact of the latest clinical trials in a patient with type 2 diabetes, identified with established CKD [chronic kidney disease]. George, will you start us off by describing a clinical case of a patient with type 2 diabetes and established CKD and tell us how recent clinical trials have impacted our therapeutic choices and how this data supports the updates to clinical practice guidelines on CKD and diabetes?

Dr. Bakris:
So this is a 52-year-old female, with a 12-year history of diabetes and a 15-year history of hypertension, and she presents to you for management of both conditions. Her blood pressure is 138/86, heart rate's 86, and her physical exam is really unremarkable. Her labs include a hemoglobin A1c of 7.6. Her potassium is fine, with a K of 4.3, and her estimated GFR is 47. Her urine albumin and creatinine excretion is 176 mg/g.

Her current meds include telmisartan 80 a day, amlodipine 5 a day, metformin 1 g in the morning and 500 mg in the evening, the SGLT2 [sodium-glucose cotransporter-2] inhibitor canagliflozin 100 mg a day, and she's on a statin of atorvastatin 40 mg a day for elevated cholesterols in the past. And she's been on these medications for the last 6 months when the labs were drawn, so that's what you're seeing.

If you look at the current recommendations based on the data from the clinical trials, she is still not maximized because while she's on

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the maximal dose of an ARB [angiotensin II receptor blocker], and she is on an SGLT2, we now know that the 3rd pillar of therapy, if you will here, is to add a nonsteroidal mineralocorticoid receptor antagonist [MRA], namely finerenone, based on 2 very large trials, 1 renal, 1 cardiovascular. The FIDELITY analysis pools the 2 together, and so you've got over 13,000 patients demonstrating that the finerenone added to the ARB or ACE [angiotensin-converting enzyme] inhibitor provides additional protection, and the SGLT2 is further stimulating benefit across the board.

So we really have 3 pillars of therapy, taking a page out of the heart failure model, for supporting the slowing of diabetic kidney disease progression and reducing cardiovascular events.

Dr. Kosiborod:
Well, that sounds really good, George. I would just add, from my standpoint, is that, you know, this patient has pretty a significant degree of kidney dysfunction, right? So essentially bordering on a CKD stage 3B with persistent albuminuria which is still in the microalbuminuria category, but really bordering now on macroalbuminuria. It's getting close to, you know, 250 mg/g, even though it's currently below that, despite the fact that the patient is getting reasonably good and one would say, you know, until recently, state-of-the-art therapy for diabetes-related CKD with albuminuria, which is a combination of angiotensin receptor blocker and a SGLT2 inhibitor. And the thing to point out here is that we're kind of concentrating on the kidney outcomes here, but of course, because the patient's significant CKD, diabetes, and persistent albuminuria, this patient's also at risk for cardiovascular events as well. And we know that, you know, especially from FIGARO trial, but really from combination of FIDELIO and FIGARO, that there is not just a reduction in progression of kidney disease, but also a significant reduction in the risk of composite of cardiovascular events driven in large part by hospitalizations for heart failure. So there are actually lots of different reasons to consider intensification of therapy in a patient like this, in part because of the risk of kidney disease progression.

Dr. Bakris:
So, Mikhail, you made some very important points that I want to emphasize. Number 1 – microalbuminuria or high albuminuria, which is what this person has, is a risk marker for heart failure, and there's a very nice review in JACC [*Journal of the American College of Cardiology*], just published last month, that I recommend all the listeners read. So clearly there's room to play with, and clearly there's room to go down. So that's number 1. I might add – and I didn't mention this earlier – but when we started therapy, or when this person started therapy, her albumin–creatinine ratio was in the neighborhood of 700. So there's definitely been improvement, but very clearly, as we now know, when you add finerenone to this mix, you can almost normalize albuminuria, and I have cases in my own office where we've reduced albuminuria by 85% with triple therapy. That is an important marker. If you're not measuring it, you need to measure it because otherwise, you really don't know the true state of the kidney function, and as Dr. Kosiborod points out, clearly it is a marker of heart failure. And so you're getting a twofer here. You're adding one drug, but you're getting renal and cardiovascular benefits. So clearly, we have room to go, in terms of doing that. So there is a reason to do it here, and the indication – because a lot of clinicians ask me this, well, how do I know when to add finerenone or not – the answer is, if you have albuminuria at any level when you have this setting, you need to add finerenone. It's as simple as that.

Dr. Laubscher:
So thanks very much, George and Mikhail. That was really interesting, and as a family physician diabetes specialist, one of the biggest fears I see of people living with diabetes is end-stage kidney disease and dialysis. Previously, we didn't have many options to prevent this, but the latest data using nonsteroidal MRAs has changed the landscape completely, and I would encourage all primary care providers and generalists to review the ADA [American Diabetes Association]/KDIGO [Kidney Disease: Improving Global Outcomes] consensus recommendations, and if you're short on time, there is a 1-page summary of the top 10 takeaways from the KDIGO 2022 CPG [Clinical Practice Guidelines] on diabetes and CKD. It's really worth reading.

[Chapter 2]

Dr. Laubscher:
So for our second topic, we're going to move on to further discussion of the ADA/KDIGO consensus document and other guidelines and the implications to patients with type 2 diabetes and early-onset CKD, so stages 1 and 2.

I'll turn to Mikhail for this. Would you mind sharing a case of a patient with type 2 diabetes and early CKD and discuss how the current guidelines influence your treatment approach? And can you comment on how this approach differs from the one George presented in terms of the CKD status of the 2 patients?

Dr. Kosiborod:
Thanks for this, and this is actually very timely because this patient that we just evaluated recently in our cardiometabolic center is a 50-year-old gentleman, who has a 10-year history of type 2 diabetes, and a number of kind of multimorbid conditions, if you will, including

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significant obesity with a BMI [body mass index] of 42, hypertension, coronary disease, with a remote history of percutaneous intervention. Currently asymptomatic from a coronary disease standpoint, as well as, symptomatic heart failure with preserved ejection fraction, with New York Heart Association class 2 level symptoms, who's presenting for management of heart failure. But of course, there are obvious multimorbidities kind of on a background. The current medications include low-dose aspirin, a high-intensity statin, 100 mg of losartan daily, amlodipine 5 mg daily, furosemide 40 mg daily, and empagliflozin 10 mg daily, and the patient's also on semaglutide, 2 mg once a week, for management of type 2 diabetes. Patient's blood pressure is 123/75, and the exam at rest is unremarkable. And the laboratory evaluations reveal a well-controlled hemoglobin A1c of 6.2%, a well-controlled LDL cholesterol of 40 mg/dL, and eGFR [estimated glomerular filtration rate] of 79, but urine albumin–creatinine ratio of 874. So here is a patient who is receiving quite well-constructed regimen of medications for a number of comorbidities and has had what appears to be a reassuring kidney function with eGFR of 79, but despite the fact that this patient is on high-dose angiotensin receptor blocker, as well as an SGLT2 inhibitor – and also, I should add a GLP-1 [glucagon-like peptide-1] receptor agonist, which certainly being evaluated currently in clinical trials for potential role in the prevention of kidney disease progression. But we know also, in a number of trials, that patients with type 2 diabetes have been shown to reduce albuminuria.

So despite all of that, the patient still has a markedly elevated urine albumin–creatinine ratio of over 800. And I think it's an important case for similar reasons that we discussed before in case 1, which is this degree of albuminuria is a high-risk marker not just for kidney disease progression, but also cardiovascular events such as both atherosclerotic cardiovascular disease events and especially heart failure. And this patient already has a heart failure history, of heart failure with preserved ejection fraction, but certainly that level of urine albumin–creatinine ratio puts the patient at high risk for recurrent heart failure hospitalizations, and of course, heart failure events. But importantly here, you have a patient that's a prime candidate for additional risk-reducing strategies, and this eGFR of 79 should not fool you, because the rate of decline in somebody with urine albumin–creatinine ratio that's persistently high like this, and I suspect, even though we don't know for sure, but I suspect in this particular case, the urine albumin–creatinine ratio was probably much, much higher before the patient was initiated on ARB and SGLT2 inhibitor and possibly also with some roles here from a GLP-1 receptor agonist in reducing albuminuria as well. So this is somebody with undoubtably significant diabetes-related nephropathy and marked albuminuria. But again, just kind of what we see sometimes is a sense of complacency because eGFR is still okay, but we know if you look at it epidemiologically, this patient's kidney function is likely to decline quite precipitously over the next few years. And we have an opportunity to do something in addition to reduce the risk, and this is a patient with very high absolute risk of kidney function decline, as well as cardiovascular events.

So once again, if you look at the data from FIGARO, it's very clear that finerenone in this patient population can reduce the risk of cardiovascular events, including heart failure hospitalizations in particular as well as kidney disease progression, and it's a real opportunity here to intervene before the kidney function gets worse. I think if you, also look at the professional practice guidelines, professional organization recommendations, including ADA standards of care and KDIGO, a patient like that would be recommended to have additional risk-reducing strategies for prevention of kidney disease progression, and since the patient's already on very good medical therapy, with combination of ARB and empagliflozin, and also with a GLP-1 receptor agonist on board, consideration for nonsteroidal MRA is clearly something that should be considered very strongly here. So I think it's very illustrative of things that happen commonly in practice, where we see patients with persistent albuminuria despite what we consider to be state-of-the-art medical therapy and that it's very important not to be complacent just because eGFR is preserved.

So I maybe wanted to ask, George, your opinion on whether you agree with some of the things I just summarized and whether that patient is somebody that should be considered for additional risk-reducing strategies here.

Dr. Laubscher:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Tessa Laubscher, and with me today are Dr. George Bakris and Dr. Mikhail Kosiborod. We're discussing recently updated clinical practice guidelines and how best to address the use of nonsteroidal MRAs in patients with type 2 diabetes and CKD.

Dr. Bakris:

So I want to fully applaud you because this was an excellent therapeutic approach. I also want to applaud you and I want the audience to be aware that you measured albuminuria. You would have totally missed the boat, as you yourself pointed out, had you not measured that. I want to urge the audience to get a copy of the KDIGO Heat Map, which is published in many places and it's on the kidney.org website, and xerox it, put it in your exam rooms, and when the patient comes in, you show them where they are on the heat map.

If you pull out the heat map and this person – guess what? They're not going to be in red, but they're going to be in orange. That's not good. And the patient will figure out it's not good. And you need to then explain to them what you're going to do. It's very important that they understand what their level of kidney function is so they can help you. And believe me, I've seen it. We haven't published this, but

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I've seen it in my practice. It will improve adherence dramatically. So it's a big deal, and I recommend to do it.

Now, to the practical points. I would issue 2 points here of importance. One is fully agree with Mikhail, and here you can start with 20 mg – you don't need to mess around with 10. You can start with 20 mg of finerenone, which is what we did in the trials in people with this level of GFR. And you want to achieve 20 mg, not 10. You start with 10 if the GFR is low. But if the GFR is above 60, you start with 20. And you monitor the potassium in about a month, and if you have a problem, fine. You won't in this person because GFR is the key determining factor for whether you're going to have a problem with potassium or not.

Dr. Laubscher:
Thank you, both George and Mikhail. I mean, Mikhail, that was a really great case, someone we see commonly in primary care and generalist care. And I'd just like to add from a diabetes point of view, I appreciate the fact that finerenone does not affect glucose levels, so there is no increased risk in this particular patient, of hyperglycemia, and there's no need to adjust other glucose-lowering medications, because you certainly encounter this with the addition of SGLT2s, and in Canada, where I practice, I've seen some nephrologists and cardiologists relax and to start SGLT2s because of uncertainty on how to adjust insulin in patients with good glycemic control.

[Chapter 3]

Dr. Laubscher:
So our final section and third topic is polypharmacy – and we're probably all aware these patients are on multiple medications – and what to do when adding a nonsteroidal MRA. So, George, I'll start with you. How do you approach polypharmacy, and what do you do to minimize the adverse drug side effects?

Dr. Bakris:
I personally have been and a group of us have been big proponents of a single-pill combination therapy. And we use this in the blood pressure area, and we have a lot of things to pick from, that have all been proven in outcome trials to be beneficial, and in a person like this, I absolutely would go with a single-pill combination where you can use, if you want, a diuretic since their GFR is good, along with an ARB at maximal dose, and that will reduce your pill count by one. There are combinations in the diabetes field, so you can use those if you want. Anything you can do to reduce the pill count counts. But the problem is, there are – believe it or not, there are people working on combinations now with an SGLT2 and finerenone. And there's at least 2 different companies that are working on this, and the hope is that this will be available within the next 2 years. But it's still a little early in the game, but that would be another way to approach this.

One thing I have to say – and we haven't talked about this, but it's very important – under no circumstances should you start all of these drugs together. In other words, finerenone, an SGLT2, an ARB – and give them all at once, because if you do, you're going to be horrified because the creatinine is going to go up significantly, especially if they're on diuretics. And then you're going to think you've crossed toxicity. The way to do this is to slowly bring them in, and so that within 6 weeks to 2 months, they're on all the therapies. Here, the cases we gave you, they're already on therapies; you can simply add, not a problem. But if you're starting fresh from scratch, you start with the ARB to get the blood pressure control, and then if glucose is an issue, you can use the SGLT2. If it's not an issue, you can use finerenone. That doesn't mean you forgot about the SGLT2 or finerenone; you add it later. How much later? You've got to give the kidney a chance to reacclimate. Usually about 2 weeks does it. And so by 6 weeks, you've paced yourself in there. Expect the GFR to drop a little bit; it's normal. You can get up to 25% reduction in GFR, and you still have positive outcomes.

Dr. Laubscher:
Thank you, that's really important guidance for our listeners. Mikhail, do you have anything to add?

Dr. Kosiborod:
You know, just a couple of things to what George said, which is, I mean, I think when you manage individuals, patients that have multimorbidity, like some of the cases that we've discussed, heart failure, kidney disease, atherosclerotic cardiovascular disease, hypertension, obesity, and so on, it's very important to focus on what I would call "high-value interventions." And what I mean by high-value interventions, are those where you address more than 1 issue with 1 treatment, right? And I think this is where medications like SGLT2 inhibitors, nonsteroidal MRAs, GLP-1 receptor agonists especially shine, because they really address multiple issues that the patient has. And you're really kind of hitting multiple problems with those interventions. You're not just treating the kidney disease, you're also treating cardiovascular disease. With SGLT2 inhibitors, for example, you're addressing CKD, heart failure, and diabetes. With finerenone, nonsteroidal MRAs, you are addressing CKD and the risk for, heart failure, the heart failure progression or potentially incident heart failure. As we've seen in the finerenone diabetes-related kidney disease program, with FIDELIO, FIGARO, and FIDELITY, GLP-1 receptor agonists, of course, are multifaceted agents that can provide better glycemic control, weight loss, cardiovascular benefit from atherosclerotic cardiovascular standpoint, and so on. So, you know, these high-value interventions really matter, and then, you

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know, if you explain that to the patient and you try to kind of highlight the fact that you're trying to, you know, kind of address multiple issues with these interventions that will have really multifaceted improvements, not just on 1 issue but on multiple issues, it does resonate with them.

And the other thing that I do frequently is take very careful look at patients' medication list and carefully assess whether there are any interventions, any treatment that the patient is on that provides very little value or may, in fact, be harmful in some ways. I mean, that's not uncommon. You know, one great example is nonsteroidal anti-inflammatory drugs. You know, sometimes patients have to be on them because they're in a lot of pain due to arthritis or other issues, but I can't tell you how frequently it is that I see NSAIDs on the list and I ask the patient what they're taking the NSAIDs for, and they say, "Oh, well, I had, you know, pain due to arthritis, you know, a year ago." "Well, are you still having pain?" "No." "Have you tried to reduce the dose of medication, maybe wean yourself off of it?" "No, haven't tried that." "Well, how about we try and see what happens, and if you're no longer having a pain problem, maybe you don't need to be on this medication that otherwise has some pain control and provides very little, if any, value. And in fact could potentially be harmful from a cardiovascular and kidney standpoint." There are many other examples like that. So I think identifying high-value interventions and trying to peel away things that are of low value or may even be harmful is, I think, a worthwhile approach in complex patients like this.

Dr. Laubscher:
So all really good points, and I think a key part of this adherence issue is patient education, and what I've found is when patients understand why they're taking the medicines, as both George and Mikhail have emphasized, it makes a big difference. And we are in a unique place now, but it does take medications and multiple combinations to prevent CKD and these cardiovascular events.

Well, this has been an interesting and informative conversation. But before we wrap up, George and Mikhail, do you have any take-home messages that you would like to share with our audience today?

Dr. Bakris:
I think the big take-home message from me is we now have – taken from the cardiologists dealing with heart failure – pillars of therapy. That concept now can be applied to prevention or slowing of kidney disease progression, certainly in diabetes, with the nonsteroidal MRAs along with the SGLT2s and the ARBs. And I think using those drugs well and wisely, as we've talked about, will really make a dent in the progression of kidney disease progression. That, and patient education so they can help you, and using the KDIGO Heat Map as part of that education so that they know exactly what's going on.

Dr. Kosiborod:
And from my standpoint, I think, especially for my cardiology colleagues, but really anyone that's managing these patients with multimorbidity and diabetes-related kidney disease, it's really, really important to measure albuminuria, as we've discussed before. Otherwise, you actually miss a lot of patients that could benefit from additional risk reduction, could be at risk for both cardiovascular events and kidney events. It's important to keep in mind that this is a very inexpensive test that's widely available all over the world. It's easy to get, and it can give you really good prognostic information, not just about the risk of worsening kidney function over time, but also risk of cardiovascular events – both ASCVD [atherosclerotic cardiovascular disease] events and heart failure events.

And the second take-home point to kind of reemphasize what George just said, focus on high-value interventions and try to look carefully at the medication list and peel away the medications that may be unnecessary or even harmful, and that can really help kind of get the best outcomes for the patients, especially complex patients such as those we reviewed.

Dr. Bakris:
You heard it here. A cardiologist is telling you to measure the kidney product. Do it.

Dr. Laubscher:

Thank you, George, for emphasizing that. And my final take-home is just echoing what George said, and for those of you who are not familiar with KDIGO, this is the KDIGO Heat Map. You can download it from the internet, and I've found it really has changed my practice in terms of counseling patients and advocating for combination and multiple medications in diabetes and CKD.

So unfortunately that is all the time we have today, so I'd like to thank our audience for listening and a big thank you to Dr. George Bakris and Dr. Mikhail Kosiborod for joining me and sharing your valuable insights and expertise. It was great speaking with you today. Thank you.

Dr. Bakris:

Thank you.

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Dr. Kosiborod:

Thanks for having me.

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