Is Chronic Kidney Disease in Type 2 Diabetes Preventable?

Michael Blaha: Thank you for joining this podcast on the link between type 2 diabetes and chronic kidney disease (CKD). We'll also discuss taking a multidisciplinary approach to managing people with type 2 diabetes at risk for chronic kidney disease progression.

This podcast is a continuation of our series focused on reducing cardiovascular deaths, heart attacks, heart failure, kidney disease, and strokes among people living with type 2 diabetes and is based on the collaborative initiative between the American Heart Association and the American Diabetes Association, Know Diabetes by Heart. This series is brought to you by our founding sponsor, Nova Nordisk, and national sponsor, Bayer.

My name is Michael Blaha, I'm a preventive cardiologist and Professor of Cardiology and Epidemiology, and also Director of Clinical Research for the Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease. Joining me today is Richard Pratley, a board-certified internal medicine physician and Medical Director at the AdventHealth Diabetes Institute, and Senior Investigator of the Diabetes Program Lead at the Translational Research Institute.

Let's get started. I think we should start off by talking about the definition of CKD, right? Because I think that gets confused. I think some people think CKD, that just means creatinine. So Rich, let's talk about the definition of CKD, what do we need to know about that right now?

Richard Pratley: Well, thanks, Mike. It's indeed a pleasure to be here with you on this podcast. This is a really important topic, and I think we've got some room to go to improve our care of people with chronic kidney disease. So, very basically, we can define chronic kidney disease in two different ways. One is by the creatinine, or the EGFR actually, so using the creatinine, we calculate the Estimated Glomerular Filtration Rate (EGFR). We're now using equations that don't take into account race, and that's important to note. The EGFR can be really broken down into several categories of increasing severity, but the important number to note is that people with an EGFR below 60 are considered to have chronic kidney disease, at least stage three.

The other way we can diagnose chronic kidney disease is through the presence of
protein in the urine, albuminuria. Now, this is done differently. The EGFR is a blood test, the proteinuria is, of course, a urine test, and this is done with a spot test. It can be early in the morning, or it can be anytime during the day, so it's a protein to creatinine ratio that we're collecting there. There are various strata for having proteinuria. People with normal function have a urine protein or albumin to creatinine ratio of less than 30, mild proteinuria is 30 to 300 or so, and then more severe is above 300.

It's important to realize that these two abnormalities can occur independently of one another, and they independently predict risk of progression of chronic kidney disease. Now, you can have chronic kidney disease without the presence of albuminuria, but albuminuria is more common in patients with diabetes.

Now, to make sense of this, the KDIGO (Kidney Disease Improving Global Outcomes) group has allowed us to classify chronic kidney disease according to both the EGFR and the albuminuria. So, you create a matrix, if you will, that takes into account both EGFR as well as proteinuria. We can grade the severity of chronic kidney disease by the severity of the diminution in EGFR as well as the presence of proteinuria.

Michael Blaha: That's a really great point. I think increasing attention to, like you said, the dual nature of CKD that we need to be thinking about. I don't think enough people are looking at urines of our patients. Would you agree? I think amongst my cardiology colleagues, we're probably under appreciating the albuminuria piece.

Richard Pratley: Yeah, so that's exactly the point. We do a pretty good job of measuring EGFR in patients, of course, because it's one of the complete metabolic panel parameters that are typically collected. Not so good with measuring urine protein levels, that should be done at least yearly in patients with diabetes, and the data would suggest in our country that a large majority of people don't get this measured on a regular basis. We don't even know what their entire risk spectrum is for chronic kidney disease. That's definitely a gap.

Michael Blaha: Yeah, no question. That's a great point. Let's move and talk about the prevalence of CKD and diabetes, because, of course, CKD is very prevalent in diabetes. And before this I pulled a few statistics, which I think tell the story a little bit, at least to me. I'm going to read some of these statistics and get your impression here, but I read that there's 700 million people with diabetic kidney disease worldwide now, 40% of people with diabetes have prevalent kidney disease, and that 50% of all people with end-stage renal disease have diabetes. I think that helps put things in perspective. So Rich, let's talk about the prevalence of CKD and diabetes, and then what to make of the connection to glycemic control or other diabetes care issues.

Richard Pratley: Well, this is a really great topic because I think CKD is underappreciated. We have about 32-35 million people with diabetes living in this country. There are actually estimated to be 37 million people who have chronic kidney disease. So, of course, diabetes is not the only cause of chronic kidney disease, but it is the leading cause of chronic kidney disease. It's estimated that it accounts for, as you said, almost
40% of the cases. If you add in hypertension, which is common with diabetes, that accounts for almost 60% of all of the cases. So, diabetes is a leading cause of end-stage renal disease in patients with chronic kidney disease, and that's really an important thing to be aware of. But it's not just, of course, the risk of end-stage renal disease that we're worried about. That's a serious complication, but that's not what really is the most serious complication, which is cardiovascular disease. I think we need to focus on the cardiovascular risk, which, of course, is what this program is about.

Michael Blaha: Yeah, there's no question that CKD is an extremely potent risk factor for cardiovascular disease and heart failure, really the composite of all the cardiovascular events that we care about, including things like atrial fibrillation as well. I still think it's relatively underappreciated as a risk factor. I think we worry about chronic kidney disease a lot in terms of tolerance of our heart failure medications, or maybe other decisions, but really appreciating it as an independent risk factor, I'm not sure is fully communicated out in the community yet. Because clearly CKD is a risk factor for CVD, but clearly CVD risk factors are risk factors for CKD. So, it's this bidirectional relationship that makes it so important, right? A patient with diabetes is more likely to get CKD, and clearly, the more likely to get CKD, the more cardiovascular risk factors they have.

Richard Pratley: I think it's a common patient population. It's not rare, and one of the issues, I think, is that we don't recognize it enough. If we're looking down our labs on people and they have a reasonable, good, EGFR, we tend to just bypass that and focus on things like our LDL cholesterol, and other factors, in their A1C, for example, in our patients with diabetes.

It's important to realize that once the EGFR goes below 45, those individuals are at higher risk for developing, as you mentioned, both heart failure as well as atherosclerotic cardiovascular disease. It identifies, independently, a high-risk patient population. When we see CKD, we should be thinking cardiovascular disease, and then conversely, when we see patients with cardiovascular disease, they almost always have some element of chronic kidney disease.

It's also true that if patients have albuminuria, that's an independent risk factor for
cardiovascular risk and for heart failure. That's the importance of screening for both of these elements of kidney function. One of the problems that we have, however, in our practices is that people aren't getting screened. I think we touched upon that earlier, but there's a statistic that only about 48% of people with severely reduced kidney function, who were not yet on dialysis, are even aware that they have CKD. There are a couple of problems. One is we're not screening; we're not diagnosing and putting that into the chart, and then third, we're not talking to people about the importance of chronic kidney disease. There are many gaps in care that I think we still need to address.

Michael Blaha: Clearly, some of those are related to difficult issues around access to care, and social determinants of health like race, ethnicity, access to insurance and specialty care, et cetera. The list goes on. This is something that we need to be thinking about in our practices, clearly.

Let's start to talk a little bit about the main topic today, which is prevention. Is this chronic kidney disease and Type 2 diabetes preventable? So maybe, Rich, let me ask you for a quick comment or two about RAAS (renin-angiotensin-aldosterone system) inhibition, before we start getting into modern pillared therapy for CKD.

Richard Pratley: Yeah, well, it's not just RAAS inhibition, but first of all, I think there's pretty good data that if we can control glycemia in patients with diabetes, we can reduce the risk for developing chronic kidney disease. That data goes all the way back in Type 1 diabetes, to the DCCT trial, we've seen it in the UKPDS, ACCORD, and other studies. Now, in these studies, they typically didn't measure harder outcomes like progression to end-stage renal disease, for example. But we are convinced that glycemia control can help reduce progression of chronic kidney disease.

However, it also is a minority of the effect that we can achieve with reducing our residual risk. We have, as you mentioned, good evidence that RAAS blockade, both with ACE (angiotensin-converting enzyme) inhibitors as well as angiotensin receptor blockade (ARB), can also reduce risk for progression of chronic kidney disease. But even with good glycemic control, and even with maximal RAS inhibition, there's still a substantial residual risk of progressing to chronic kidney disease. So clearly, we need new options for addressing chronic kidney disease and diabetes, and there's been some really exciting data in recent years about a couple of different classes of medications that suggests we might have a path forward. So, Mike, do you want to start us off on that?

Michael Blaha: Yeah, absolutely, because you're absolutely right. What an amazing time to be having this conversation because we can do more for our patients than ever. I think it was in January of 2014 that SGLT2 inhibitors hit the market, predominantly, of course, for their effect on reducing glycemia for diabetes. It wasn't long thereafter that there was a recognition that SGLT2 inhibitors can have favorable effects on kidney disease. And this, of course, was observed from early data with SGLT2 inhibitors, and it followed up with three dedicated kidney trials, which I'm going to
speak briefly about, which really established this class as, of course, kidney protective and additive to the things we've talked about, to glycemic control, risk factor control, and RAAS inhibition.

The first of those was the CREDENCE trial with canagliflozin, and as you mentioned, this was looking at a hard kidney disease endpoint, of a time to end-stage renal disease, doubling of creatinine, or renal or cardiovascular death. This was a dedicated study, once again, of patients with diabetes and chronic kidney disease, that showed a 30% relative risk reduction in this hard kidney outcome. This was the first hint that SGLT2 inhibitors have a solid effect on reducing kidney and cardiovascular outcomes in patients with chronic kidney disease.

This was followed quickly thereafter by the DAPA-CKD trial, in which a third of those patients didn't even have diabetes in the trial. This is starting to extend that SGLT2 inhibitor story to patients who don't have diabetes but have CKD. And in this case, there was a 44% reduction, a similar outcome to that in the CREDENCE trial.

And finally, most recently, EMPA-KIDNEY with empagliflozin, DAPA-CKD was, of course, with dapagliflozin. Empagliflozin in EMPA-KIDNEY, in a wide range of kidney disease that was enrolled, wide range of GFR values, and UACR values, showed a 28% reduction in kidney outcomes and cardiovascular and renal death, as well as a 14% reduction for any hospitalization in that trial, some of which was heart failure.

So really these are three pivotal trials that established SGLT2 inhibitors as kidney protective, and additive, because, of course, the patients in these trials were predominantly well-treated with standard of care, which includes RAAS inhibition, and of course, risk factor control. Rich, this established SGLT2 inhibitors as a critical part of the story of CKD and diabetes and preventing progression.

What I find so fascinating by this data is the fact that these drugs worked in patients that didn't have diabetes, and they worked just as well. So that tells me that the mechanism for the benefit is not glucose lowering. This goes along with my earlier comment that glucose lowering is important in patients with diabetes, but it's not the whole story. With SGLT2 inhibitors, we have some very specific mechanisms working through the kidney perhaps to decrease the glomerular pressure, and that seems to be a benefit, not just kidney progression, but as you mentioned, these important cardiovascular endpoints.

So, for the first time, we have a treatment that's going to be able to reduce risk of CKD progression, as well as the associated CVD risk, the atherosclerotic cardiovascular disease and heart failure risk. So that's pretty exciting, and these are meaningful benefits in this very high-risk population.

I also wanted to talk about another class of medications, though, that's recently been studied. That's the nonsteroidal mineralocorticoid receptor antagonists.

We've had, of course, medications like spironolactone and eplerenone for some time. Spironolactone is indicated for the treatment of hypertension, eplerenone for heart failure. But there's reasons to think that, just like with RAAS blockade having
general beneficial effects, that blockade through mineralocorticoid receptor antagonists could have similar benefits on the inflammatory and fibrotic process that underlies both chronic kidney disease and cardiovascular disease.

That was borne out in these couple of studies that were done with a new nonsteroidal mineralocorticoid receptor antagonist called finerenone. This program is a large program, enrolled about 13,000 patients in two different trials. One trial [FIDELIO-DKD] was focused on chronic kidney disease endpoints, and the second trial, the FIGARO-DKD study, was focused on a cardiovascular endpoint.

But, in these two trials, what they did, which was I think very clever, is to make the primary secondary endpoint the opposite. So, for example, when the primary endpoint was chronic kidney disease, the secondary endpoint was cardiovascular disease. And conversely, when the primary endpoint was cardiovascular disease, the key secondary endpoint was a kidney endpoint. These trials were run in similar ways, and in the totality of data, we can address both the CV as well as the CKD risks in these patients.

Enrolled are patients, a population at high risk, with established chronic kidney disease, so they all had albuminuria, many of them, in fact, most of them, had preexisting cardiovascular disease. These were people at high risk of progressing their CKD and also of atherosclerotic cardiovascular disease. When people were treated with this mineralocorticoid receptor antagonist (MRA), we saw improvements in albuminuria that were sustained over time. There were also changes in blood pressure in the people who underwent active treatment. But there were importantly no changes in hemoglobin A1C. This mechanism of action is not a glucose lowering mechanism.

So, we're again looking at a whole different mechanism of action. Now, importantly, these two trials showed that blockade of the mineralocorticoid receptor with a very specific nonsteroidal antagonists resulted in decreases in both kidney outcome, which is kidney failure, sustained 40% decrease in EGFR, or renal death, and a cardiovascular endpoint, which was the usual CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure.

And in the totality of data, when these two studies were put together, these two endpoints were very significant. And of course, one of the side effects of blockade of the mineralocorticoid system is the possibility of precipitating hyperkalemia. That was very rare in these trials, and almost nobody had to stop the medications because of hyperkalemia.

Now, interestingly, in these trials, a small minority of people were already treated with SGLT2 inhibitors, and we observed two things. One is that those who were on SGLT2 inhibitors still had a beneficial effect from mineralocorticoid receptor blockade. They still had an equivalent reduction in their CKD and CVD risk. The other thing that was, I thought, very interesting, is that having a SGLT2 inhibitor on board mitigated some of the risk of hyperkalemia with these drugs. I think that was a really cool outcome, that was, I guess, probably not so much expected in these
studies.

So now we have a couple of different classes, both the SGLT2 inhibitors and the mineralocorticoid receptor antagonists that have substantial benefits on reducing the progression of CKD, as well as the associated cardiovascular disease risk.

Michael Blaha: Yeah, and I think you brought some critical points here. I also wanted to second what you said there about the SGLT2 inhibitor, MRA combination. The SGLT2 seems to mitigate some of the effects of hyperkalemia, which is fascinating and important when we start to talk about combination therapy and putting together a treatment plan for our patients.

We've talked about screening, we've certainly talked about glycemic control and risk factor control, which, of course, includes blood pressure control. We've talked about RAAS inhibition, now, we've introduced the data on SGLT2 inhibitors and MRAs. So let's start to put this together, Rich. Our listeners have heard about a lot of options now. I think, let's talk about how to put together a treatment plan. You've hinted at the additive nature of these things, and so, what order, or what ways should we be making decisions about ways to proceed with our patients with diabetes and kidney disease in terms of bringing together all of this data on risk reduction?

Richard Pratley: Yeah, this is a great point, and I think I would actually even begin the discussion earlier, to just remind people the importance of screening, of getting the EGFR, of getting the urine albumin creatinine ratio, and making the diagnosis. If people aren't diagnosed, they're not going to get appropriate guideline directed therapy.

And importantly, in patients with diabetes, glycemic and blood pressure control, still are foundational therapies, so we have to focus on those things, but not at the expense of some of these other newer approaches. I'm just kind of following the ADA guidelines now, for the management of people with chronic kidney disease, and that includes screening and glucose control and blood pressure control.

Getting people on, not just a touch of ARBs, but on good doses of ARBs, and maximally tolerated doses, is important. In the clinical trials with ACEs and the ARBs, people are on high doses of the medication, and there does seem to be a dose dependent effect for the prevention.

And then we have the SGLT2 inhibitors and the MRAs, both of which now are recommended for people with Type 2 diabetes and chronic kidney disease. So how do we decide? And I think where we're heading is that instead of choosing between different medications, because they work in tandem with one another, we really need to think of these as pillars of the management of chronic kidney disease and diabetes, and that people should be on these medications unless they can't be tolerated.

Michael Blaha: You bring up such a good point with this pillar's idea, and I think as a cardiologist,
and most of our cardiology colleagues in the heart failure space, have gotten used to this idea of pillars.

Richard Pratley: Yeah.

Michael Blaha: We now have four pillars for the care of patients with heart failure with reduced ejection fraction. I think that's led to tremendous increases in guideline directed care, at least in my observation, and there's some data to support that too. There's now a framework. I'll think about this, and once again, it's just as you mentioned, it's not this or that, or one choice, or one pillar or the other. Of course, that's why we call them pillars, you need all the pillars to hold up the structure. I think that's going to be very useful.

Could you talk a little bit more about this idea of pillars? For example, I guess, just the stigma of treating a patient like this. Is there a particular order? Or is there no preference in terms of order and so forth? Or is it really just get your patient on all of the pillars?

Richard Pratley: I think it's getting people on all of the pillars, but I recognize that people aren't excited about suddenly getting started on four different medications when they came into the office and they thought they were doing okay, because oftentimes people have no symptoms. It's oftentimes good if we stage the addition, but not wait for a year to be able to do this. Do this over a period of a few weeks, and convey to patients the necessity, the urgency, to get people on good therapy to protect their kidneys. Convince them that protecting their kidneys is a good thing. I think most people are actually pretty afraid of having to go on dialysis, and I think they will be engaged around things, particularly medications like finerenone and the SGLT2 inhibitors and ARBs, that are relatively easy to take, they're pretty well tolerated, and most people can do just fine on them.

Michael Blaha: You bring up a good point of how easy these medications generally are to use and to take. I found that in my practice.

Now, before we move on to who should be prescribing these medications, what should the team look like? That's really an important question. I wanted to give you a quick query on an important emerging area, which is GLP-1 receptor agonists, of course. Some of our patients are already taking GLP-1 receptor agonists, maybe patients have difficulty with weight loss and they're requesting these medications nowadays. And there is quite a bit of data from the registration CVOTs on GLP-1 receptor agonists showing potential for kidney benefit, and there is an ongoing dedicated kidney trial for GLP-1s. Can you tell us about that?

Richard Pratley: Yeah, so you're right, that there's data from the CVOTs to suggest that the GLP-1 receptor agonists decrease albuminuria, and there's also some data from pooled analysis to suggest that they might slow the rate of progression of EGFR decline. So that's very intriguing. The mechanism may be related to, again, decreasing inflammation, so a mechanism is similar to how ARBs and MRAs might work.
You're right, there is an ongoing trial called FLOW, which is investigating once weekly semaglutide in patients with chronic kidney disease that is fully recruited. About 3,500 patients are under study, and hopefully, in 2024, we'll hear more about that study. That's going to be a very important study because it'll be the first dedicated study of a GLP-1 receptor agonist for chronic kidney disease.

But apart from slowing progression of chronic kidney disease, GLP-1 receptor agonists have an important role to play in patients with chronic kidney disease. Because they work. They're very effective at lowering glucose levels, so that can help you meet this glycemic goal. And they do so without promoting hypoglycemia, which, of course, patients with chronic kidney disease are at higher risk for. So there's another check mark for GLP-1 receptor agonists.

They can also be used in people that have very poor renal function because they're not cleared by the kidney in the same way that other medications are. I've used the GLP-1 receptor agonists in people who are pre-dialysis, and even in some people who are on dialysis, to good effect. We have to be worried about the nausea that does happen sometimes when initiating therapy, and people with very poor renal function may be at a little bit of higher risk for that. We have to be careful that our patients don't develop vomiting and dehydration. But for the most part, they tolerate the medications well in my experience, and it's an important adjunct to therapy to control diabetes, as well as the cardiovascular risk, in this population.

Michael Blaha: Great point, so perhaps a fourth pillar, we'll have to see what the FLOW study shows. Now, of course, all of these drugs potentially have heart failure benefit too, and this makes sense. Of course, we talked about the bidirectional nature of CKD, CVD, particularly heart failure. So most recently we saw some favorable symptomatic data with GLP-1 receptor agonists and HFpEF, and of course we have established data on SGLT2 inhibitors and HFpEF, as well as a very important ongoing trial called FINEARTS-HF with finerenone and HFpEF. So, this is really an exciting area where we're seeing CKD, diabetes, CVD, but also heart failure, particularly HFpEF, come together in a way that we've seen clinically. We know these things overlap in our patients, but now the therapies are coming together, and the mechanisms are coming together too.

I want to come back to the call to action. We've made the point that we're not doing as well as we should both in screening and implementing therapy. And certainly, part of this has to do, unfortunately, with the fractured care model that sometimes our patients experience. Who's managing my kidneys? Is it my primary care doctor? Is it my cardiologist? Is it my endocrinologist? Is it my nephrologist? Or maybe they're not even seeing some of those specialists. So, let me open, Rich, to you, for some comments about how do we do this better? What are the gaps in terms of the structure of our care, or in our healthcare systems, and how do we improve things?

Richard Pratley: Well, I really do believe that we need to help support our primary care colleagues to do this. Thirty-seven million people with chronic kidney disease, there are not
enough nephrologists to see all these people, there are not enough endocrinologists, and there are likely not even enough cardiologists, to see all of these people and make sure they're on therapy. We need to engage with our primary care colleagues, get them to understand the importance of screening, and also understand these pillars of therapy, which are fundamentally primary care medications, blood pressure control, SGLT2 inhibitors, and now the MRAs. These are very easy to use in primary care and people shouldn't be afraid of using them and using them in combination.

We need to, not just in primary care, but in all of our practices where we touch these people, make sure that people are on guideline directed therapy, which now does include, in addition to glycemic and blood pressure control, ARBs for blood pressure control and CKD prevention, SGLT2 inhibitors, and MRAs, for people that have established CKD. The data is very strong for all of those interventions. And then, make sure that people have adequate scheduled follow-up, it's not a set it and forget it kind of disease. We need to make sure that people are achieving their targets, that they're staying on their therapies, and address any concerns that they have.

Michael Blaha: Such great points, I think we'll wrap up here. I'm going to wrap up with just a quick call to action for all our listeners. I hope we have listeners across the spectrum, of people who care for diabetes and chronic kidney disease, as you mentioned, from primary care to subspecialists, we all have a role. Speaking to my cardiology colleagues, we have a role. We absolutely have a role, especially given the fact that what we've talked about today in terms of preventing CKD completely overlaps with preventing cardiovascular outcomes, MACE outcomes, but also heart failure outcomes, and cardiovascular mortality too. So, very important, I think it's very important just to communicate with our colleagues. I've had great success contacting my nephrology colleagues, or contacting my primary care referrals, and saying, "I am starting this medication," or "I think this patient should be started on a new pillar of care," and we've worked together, and we've got the patient on the correct medication.

Always, I think a call to action for team-based care and open lines of communication with these patients. But I think we are out of time today. We could go on forever. Thank goodness we have so much to talk about nowadays with all the great data. That's what's fun about this area, in terms of diabetes and CKD, and it is preventable.

Let me conclude this podcast, and we want to hear from you. So, if you have a suggestion for future content, email knowdiabetesbyheart@diabetes.org. It's our mission to reach as many listeners as possible with this potentially lifesaving information.

If you enjoyed this podcast and you're listening on iTunes or Google Play, don't forget to leave us a rating, and subscribe. Thank you very much for listening and stay tuned for upcoming podcasts. Rich, thank you for joining me, I learned a lot today, and I hope our listeners did too.
Richard Pratley: Well, thanks, Michael. I just want to leave on a positive note. It's a great time to be caring for people with diabetes and chronic kidney disease because we have things that work. So, let's get together and implement them.

Michael Blaha: Absolutely. All right, thank you so much.