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Diabetes and CKD: Strategies for Diagnosis and Treatment

Dr. Cheeley:
Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. Mary Katherine Cheeley. And joining us for a discussion on diabetes management in patients with chronic kidney disease is Dr. Ian de Boer. Dr. de Boer is a Professor of Medicine in the Division of Nephrology and the Director of the Kidney Research Institute at the University of Washington in Seattle.

Dr. de Boer, thanks for speaking with me today.

Dr. de Boer:
It's my pleasure. Thanks for having me. It's fabulous to be here.

Dr. Cheeley:
So let's jump in. I love this topic. Can you tell us a little bit about diabetic kidney disease and how it can develop?

Dr. de Boer:
Diabetic kidney disease is chronic kidney disease that occurs in someone with diabetes who doesn't have any other clear cause of kidney disease. And chronic kidney disease, just to remind folks, is defined as persistent kidney damage or reduced function. What does that mean? So persistent albuminuria, that's more than 30 mg/gm in a urine albumin-creatinine ratio, for example, or persistent low EGFR, less than 60 mL/min. And persistent means confirmed, repeated; generally, we like three months apart to rule out acute kidney. So when we use these definitions, we find out that about 30 or 40 percent of people with diabetes do develop diabetic kidney disease sometime during their disease process. That's true for both type 1 and type 2 diabetes. So it is common, and it can cause problems. They can progress to kidney failure that is treated with dialysis or kidney transplantation. Even if it doesn't, it markedly increases risks of cardiovascular events, like atherosclerotic cardiovascular events, heart failure, and arrhythmias. So it is a major complication of diabetes.

Dr. Cheeley:
So what are those early signs and symptoms that can send someone down the path of chronic kidney disease in patients with diabetes?

Dr. de Boer:
That's a key question, and there are no early signs or symptoms of diabetic kidney disease. I should clarify, there are no symptoms. It's asymptomatic in its early stages. People won't know that they have it unless they're screened for it, or what epidemiologists would call "case finding." Swelling can happen. Elevated blood pressure can happen. It's more common in people who have retinopathy, high hemoglobin A1C, and poor glycemic control, but there are no ways to know that you have diabetic kidney disease unless you test for it. And testing is quite easy. It's a urine albumin-creatinine ratio and an EGFR based on serum creatinine, and that screening is critical to identify people who have diabetic kidney disease.

Dr. Cheeley:
Once we find these folks, how do we treat them? What's available out there?

Dr. de Boer:
We've known for a couple of decades that renin angiotensin system inhibitors, either ACE inhibitors or angiotensin II receptor blockers, are effective for delaying the progression of chronic kidney disease for people who have diabetic kidney disease with albuminuria, and albuminuria is a potent risk factor for progression of kidney disease. So people who have albuminuria and diabetes should be treated with an ACE inhibitor or an ARB.

That's clearly not enough. We find that there's a lot of residual risk treating only with a RAS inhibitor, and so that's where these new classes of medications come in that are really revolutionizing the field. And I'll start with SGLT2 inhibitors, which, of course, were developed as control for glycemia for type 2 diabetes, but they are not really diabetes drugs in my mind. They are kidney drugs. They're also heart drugs. That's a whole other topic. But they have strong effects on the kidney. They work primarily in the kidney, and they markedly reduce the risk of progressive kidney disease. We're talking 30 percent reductions or more. They're more effective than RAS inhibitors, and their effects are complementary or additive to RAS inhibitors.

There are other agents also. So we have GLP-1 receptor agonists, which are very potent drugs for controlling glycemia and reducing weight, particularly in people with type 2 diabetes, and we're learning that they also have kidney benefits. The FLOW trial was the first trial to specifically look at how semaglutide affects kidney outcomes, and we've heard that it's been stopped early because it's positive, and we're looking forward to seeing those results. Those are already getting integrated into clinical care. And then we have another class of medication called nonsteroidal mineralocorticoid receptor antagonists, which currently the only drug available in that class is finerenone, which also improves kidney outcomes in these people.

And then I should note that when we're treating people who have diabetic kidney disease, we're of course concerned about the kidney, but I noted early on that people with diabetic kidney disease also have high cardiovascular risk, and so we need to orient our therapy towards reducing that high cardiovascular risk. And happily, all the drugs that I've mentioned—RAS inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, finerenone—they all also reduce cardiovascular risk, so we're getting two birds with one stone with each of these drugs. And these patients should also be treated with statins for example. Almost all of them are high risk for cardiovascular disease and should be on a statin and other drugs that improve cardiovascular outcomes.

Dr. Cheeley:
For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. Mary Katherine Cheeley, and I'm speaking with Dr. Ian de Boer about managing diabetes and patients with chronic kidney disease.

So let's jump back in because this is where I really think the meat of our conversation is going to come in. If we continue to focus on our treatment strategies, how would you tailor medication regimens for patients with diabetes throughout the varying stages of chronic kidney disease?

Dr. de Boer:
It's a great question. I think it's critical to keep your eye on the prize, and that is what is really going to improve clinical outcomes here and prioritize the medications that are going to do that. And I should note also it's not just medications. Lifestyle therapies are important here too. So weight loss, regular physical activity, healthy diet, et cetera, is critical as a foundation of care for all of these patients. But then prioritizing the drugs that are going to make a difference, and those are the ones that we talked about.

So let's start this time with SGLT2 inhibitors, a low dose of an SGLT. We should note that these benefits are not dose dependent. A low dose is enough to have the clinical kidney and cardiovascular benefits, it's something that needs to be instituted right away, and it's not dependent on someone's glycemia. Even if their hemoglobin A1C is a goal, for example, for the clinical benefits, they need to have an SGLT2 inhibitor on board, and we can build on top of that. Similarly, if you have albuminuria, a RAS inhibitor is another foundational drug that should be used. And then we need to layer on top of that additional drugs that might have benefits for intermediate or clinical outcomes.

Dr. Cheeley:
How do you handle it when you have a patient that their kidney function continues to decline? When do you change their drug therapy?

Dr. de Boer:
It's a great question. When kidney function declines, clearance of many of these drugs does change, and the effectiveness of some of these drugs in some ways does change, and so you have to consider each one. So most drugs that we've discussed can be continued.

Renin angiotensin system inhibitors can be continued indefinitely at any eGFR, even onto dialysis or kidney transplantation, as long as there aren't problems with hyperkalemia or other issues. SGLT2 inhibitors now we know are basically the same. We talk about an initiation threshold of 20 mL/min of eGFR for starting. That's the threshold above which they've been proven to be beneficial. Below that we just don't know, and so we don't start below that. But if an eGFR falls below 20 on therapy, there's no need to stop. That's what the clinical trials do, and those drugs can be continued. GLP-1 receptor agonists are great drugs for low eGFR. Many of them—it depends on the specific drug—but many of them can be continued at any eGFR and even for patients treated with dialysis or kidney transplantation.

So it does vary by drug. You just have to know the indications and the changes. And I would say in general people are, perhaps, more worried about this than they need to be. Most of these drugs are safe when they're tolerated for each patient who's using them, even as the eGFR falls.

Dr. Cheeley:
A lot of these patients have some challenges, so what's the key challenges that you have in managing patients with diabetic kidney disease, and what can we do to overcome them?

Dr. de Boer:
Well, I think in the broad view, there are several big challenges. One is finding patients. I noted this is an asymptomatic disease. We are totally reliant on screening or case finding to identify these people. We do a good job as a population testing for eGFR. It's one of our routine blood tests. But urine albumin-creatinine ratio testing is not sufficient. Only about half of people in the United States with diabetes who should be tested are tested each year, and if we don't find these people, we don't know to treat them, so that is the first issue.

The second issue that I can think of is implementing these therapies. We know they work. We also know from research studies that we're not doing it as frequently as we should be, so we need to do what the guideline suggests.

And then another challenge that I want to bring up is the issue of residual risk. So these patients are at high risk of kidney and cardiovascular disease. They usually need multiple drugs to lower that risk. And, in fact, even with combined therapy, which is excellent, by the way—we haven't talked about that specifically, but there's no reason not to combine or RAS inhibitor, an SGLT2 inhibitor, GLP-1 receptor agonist, and even a nonsteroidal mineralocorticoid receptor antagonist; they all go together quite wonderfully—there still can be residual risk, and there's still a need for research in additional classes of drugs or precision medicine approach to better advance therapy for this population. That's down the road. Right now, we have great options, so we need to find people, and we need to treat them.

Dr. Cheeley:
Well, Dr. de Boer, anything that you want to leave us with?

Dr. de Boer:
Well, I'm excited, as are you. We've really had a revolution in diabetic kidney disease care, and it's due to the effectiveness of these new drugs. And it is potentially a devastating disease. I think there is a chance to really change that for individuals and for populations, and the way to do that is pretty simple. We have simple diagnostic tests. Pee in a cup. Get your blood tested. Check your albuminuria and your eGFR. And when you have abnormalities, there are clear proven treatments that you can use for those abnormalities that are going to make improvements for patient outcomes. So it is a very exciting time. We also have more drugs coming down the road and more options coming and more tools for our toolkit, but for right now, we have a very robust toolkit, and it's time to use it.

Dr. Cheeley:
This has been such a wonderful discussion. I love talking about diabetes management. Thank you so much to my guest, Dr. Ian de Boer, for being here and sharing his insights. This was fun. It was a pleasure.

Dr. de Boer:
I agree. Thanks so much.

Dr. Cheeley:
For ReachMD, I'm Dr. Mary Katherine Cheeley. To access this and other episodes in our series, visit *Diabetes Discourse* on Reachmd.com, where you can Be Part of the Knowledge. Thanks for listening.