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Connecting Chronic Kidney Disease and Cardiovascular Risk in Primary Care

Announcer:
You're listening to *Heart Matters* on ReachMD. Here's your host, Dr. Alexandria May.

Dr. May:
This is *Heart Matters* on ReachMD, and I'm Dr. Alexandria May. Joining me to explore why chronic kidney disease, or CKD, should be recognized as an early cardiovascular risk condition, and what that might mean for primary care is Dr. Javed Butler. He's the Maxwell A. and Gayle H. Clampitt Endowed Chair and the President of the Baylor Scott and White Research Institute in Dallas, Texas.

Dr. Butler, welcome to the program.

Dr. Butler:
Great to be here with you. Thank you.

Dr. May:
Dr. Butler, let's start by looking at the big picture. We often view CKD as just a renal diagnosis, but why should we reframe it as an early and actionable marker of cardiovascular disease?

Dr. Butler:
Yeah, so let's look at this from a historical perspective. So there was a time when hypertension was considered a renal disease, and people were looking at all sorts of secondary diagnoses, like pheochromocytoma, until we learned a lot from the Framingham Heart Study and other studies that hypertension is associated with increased risk for cardiovascular diseases.

And then we did a whole bunch of clinical trials and found that therapies and blood pressure control leads to improvement in outcome. And here it is, that you cannot possibly go to a clinician's office and not get your blood pressure checked, because it's squarely a cardiovascular risk factor.

Believe it or not, lipids, at one point, used to be an endocrine disease. But now, obviously, it's cardiovascular, because it increases cardiovascular risk. So, in that sense, CKD is the same thing. Of course, early diagnosis and treatment of CKD is good for the kidneys and, of course, we should have that vision.

But here, what we are talking about is that early forms of CKD are a risk factor for cardiovascular disease, per se. And it's not only a theoretical association. We actually have clinical trials and therapies. When we detect chronic kidney disease early and we implement effective therapies, we effectively reduce not only the progression of chronic kidney disease, but actual cardiovascular outcomes are improved.

And that's why it is really important for cardiologists, primary care physicians and clinicians, nurse practitioners, and everybody to worry about early kidney disease.

Dr. May:
Now, with that in mind, what do we know about cardiovascular morbidity and mortality in patients who have CKD—particularly those with type two diabetes?

Dr. Butler:
Yeah, so this is really interesting. If you look at the epidemiology of chronic kidney disease, you have a whole bunch of people in stage

one and then two. But then, all of the sudden, from stage three to stage four, there is a big drop off. So you have a lot of people with GFR of 45 to 60, but then very few people, relatively speaking, from say 30 to 45 GFR.

So the question is, what happened? If the kidney disease is just progressing, you should have the same number of people with stage 3A versus stage 3B CKD. But that's not the case. And the reason for that is that those patients get such higher risk of cardiovascular events that they die of cardiovascular death.

In a way, you can think about progression of CKD as somebody who has successively navigated cardiovascular disease, per se. So we actually know a lot about cardiovascular risk, whether it is vascular risk—things like myocardial infarction and stroke—or development of heart failure or arrhythmias in patients with CKD.

And there is almost a linear relationship that as your GFR falls, that risk continues to increase. And not many people with CKD progress to needing dialysis or transplantation because, unfortunately, even before they get to that point, they die of cardiovascular diseases. Hence, the importance of early detection and early effective treatment of these patients.

And I would also mention one more thing: that if you have diabetes, all of these associations, unfortunately, get multiplied. So CKD itself is a bad prognostic factor. CKD for other causes like hypertensive nephropathy: bad prognosis. But if you have diabetes, then the risk is multiplied—in part because with diabetes, kidney disease progresses more rapidly, and in part because diabetes simultaneously affects the cardiovascular system as well. So with these patients, we have to be even more careful.

Dr. May:
Now, given that primary care providers regularly see patients with CKD, where are the biggest opportunities to recognize and act on cardiovascular risk earlier?

Dr. Butler:
So one is just the recognition that early CKD is important, because most of us are trained to do something about CKD when you start getting to a point where you worry about hyperkalemia.

So you're talking about really low GFR and hyperkalemia, and you're talking about acute problems—not necessarily chronic problems. And, in part, that dynamic existed because there was really nothing to do—even if you were to diagnose people early—but to give patients ACE inhibitors. And, ACE inhibitors, most of these patients get for some other indication anyways, like hypertension.

But now that has completely changed, because we have trials with earlier forms of CKD with other therapies like SGLT2 inhibitors and nonsteroidal MRAs that significantly protect from the progression of kidney disease and simultaneously reduce the cardiovascular risk as well.

Now, what is interesting to note is that the earlier sign of development of CKD is actually albuminuria. So you have a high UACR or albuminuria that occurs before there is substantial reduction in GFR. Both UACR and GFR have additive prognostic value. So it's not that if you have one or the other, then you don't need the second—you really need both. But the earlier form, before your GFR is significantly reduced, is actually the UACR starts going up. So I think that the biggest opportunity in the primary care is to think about early CKD as a remediable disease for which we now have multiple therapies, and also, to get into the habit—just like we check blood pressure, just like we check cholesterol—to start assessing UACR on a routine basis, especially in the high-risk population.

Dr. May:
For those just tuning in, you're listening to *Heart Matters* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Javed Butler about the role of primary care providers in identifying and managing cardiovascular risk in patients with CKD.

So, Dr. Butler, recent guidelines from KDIGO and ADA emphasize routine use of both eGFR and UACR to improve early detection and risk stratification, and they highlight albuminuria as a key marker of both renal and cardiovascular risk. From your perspective, how have these recommendations reshaped the way you approach screening and risk stratification in your clinical practice?

Dr. Butler:
I would broaden that question to how should it reshape, because, unfortunately, when these guidelines and this evidence comes out, it takes some time for general practice to change. I again want to highlight that we need to check both eGFR and UACR. If both of them are going in the wrong direction—high UACR, low eGFR—that's even more of a perilous condition, and you need to worry about that. But before your eGFR falls to less than 60, if you have a high UACR, you're still at a high risk. And you have therapies to give to those patients to improve their clinical situation.

UACR is actually a systemic marker of vascular and endothelial dysfunction. Now, in the kidney, it manifests as proteinuria, and this early albuminuria gives you this hint about the early kidney disease. But it's actually telling you about systemic vascular dysfunction,

and hence, it's a marker, directly, of systemic cardiovascular risk as well.

Based on all of this, now, there are recommendations in people with hypertension and people with diabetes to get their UACR assessed. There are still somewhat inappropriate myths about UACR testing, that you have to go and check 24-hour urine collection and all that kind of stuff.

That is absolutely not the case. It is a simple urine test. You just pee in a cup. So when you see a patient and you send them for their blood test, at the same time, in laboratory, they can give a urine sample. It doesn't have to be fasting or anything like that. Just give a urine sample.

Now, there may be some conditions, like you shouldn't have just exercised or a female patient should not be in the middle of their period or something like that. But those things can be managed. By and large, it's a really simple test. It gives a tremendous amount of information. It gives information additive to GFR and earlier than GFR, so I think that we should be testing it much more commonly, especially in the primary care setting.

Dr. May:
And emerging evidence from studies like CONFIDENCE suggests additive benefit from targeting multiple disease pathways. In that context, when early CKD or albuminuria is identified, how do you approach treatment selection and sequencing to address both kidney disease progression and cardiovascular risk?

Dr. Butler:
So we have learned a lot of lessons on this in the heart failure arena. So, in heart failure with reduced ejection fraction, we have four foundational therapies. And the question is, do you give one or two and see how the patient does? And the community, generally, based on the empirical data that we have, achieved, a little bit of a cancer mindset. If somebody has cancer and a particular combination chemotherapy is known to improve the outcomes, you don't give half of the therapy and say, let's see what happens—whether the cancer progresses or not. You just go full in to see if you can improve the patient's outcome.

So, in the heart failure world, we have done the same. Now, human biology is complex and overlapping. Nothing is truly independent. But what you look for is the mechanism of action of different therapies shown to improve outcomes largely overlapping or not. If they are largely overlapping—say, for instance, ACE inhibitors and angiotensin receptor blockers—and you give both of them, all you get is, basically, side effects, and there's not much additive effect, because these are largely overlapping mechanisms of action.

But if they are distinct enough, we basically get additive benefit. So, in the heart failure world, we have all come to the conclusion that it doesn't really matter which one you start first and which one you start second, you really got to—irrespective of how the patient is doing or if patient is feeling better or whatever—you really need to use combination therapy. And I think, now, CKD, is going in that direction as well. One is that we have data for early CKD being a risk marker and therapies improving outcomes, even if the CKD is diagnosed at an earlier stage. So this is an evidence-based recommendation.

And then you mentioned the CONFIDENCE trials. And if you look at the data, again, for UACR reduction, there is additive benefit of adding an SGLT2 inhibitor and nonsteroidal MRAs together.

So I think that CKD is evolving in the same way—that for patients with CKD, both for CKD progression and prevention, and for cardiovascular outcomes in patients with CKD, to use the combination therapy of RAAS inhibitor, SGLT2 inhibitor, and non-steroidal MRAs in these patients.

We have a couple of trials with steroidal MRAs like spironolactone in patients with CKD, and they were actually not positive trials. So the positive trials we have are with this non-steroidal MRA finerenone. So we need to make that, distinction a little bit.

And finally, very recently, even in non-diabetic kidney disease, non-steroidal MRAs have shown some benefit. So, this field is very robust and is evolving, and we should not forget the FLOW trial with a GLP-1 receptor agonist, also in CKD patients, showing benefit.

Dr. May:
Before we wrap up, Dr. Butler, could you share some practical steps that our audience can take to better integrate albuminuria testing and earlier cardiovascular risk management into everyday primary care workflows?

Dr. Butler:
A couple of things. In the past, we used to have paper records, and we pulled them on Monday morning to see who is going to be coming to the clinic all week long, and we had all these stickies and all that kind of stuff.

We live in a different world. With electronic health records, population screening and management becomes very easy. So if you have the means to look at the population that you are treating and see how many people that you're following that have diabetes, some

changes in the GFR. or uncontrolled hypertension. For all of those patients, just remember to check UACR.

We will not see a patient in any clinical setting—whether it's primary care or specialty care, whether it's a doctor, nurse practitioner, or clinical pharmacist, it doesn't matter—you are never going to forget checking blood pressure. You're never going to forget to check cholesterol. And I think we should just get to that point of remembering to do a UACR in our patients with these chronic comorbidities. So that's my first thing.

And then the second thing is to try to get combination therapy for these patients. But get it early. Don't wait for things to progress. And, at least, my recommendation would be to use the combination therapy early and not sequentially. Now, when I say not sequentially, I don't mean that on Thursday afternoon at 2:30, start three drugs at the same time. What I mean is don't wait for six months and then start another one, and they admit another six months. In a matter of, safely, over a few weeks, just start the combination therapy.

Dr. May:
Those are some great takeaways for us to think on as we come to the end of today's program. I want to thank my guest, Dr. Butler, for joining me to discuss how primary care providers can help address cardiovascular risk in chronic kidney disease. Dr. Butler, it was great having you on the program.

Dr. Butler:
Thank you, Dr. May. Great talking to you.

Announcer:
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