Andrew South: Welcome to the fourth podcast in a five-part series on the relationship between chronic kidney disease (CKD) and cardiovascular disease (CVD), and the importance of urine albuminuria and estimated GFR (glomerular filtration rate) testing to identify chronic kidney disease. The relationship is complex and bidirectional, with [00:00:23] each condition increasing the incidence and progression of the other. During this episode, we will discuss utilizing guideline-directed medical therapy and shared decision-making on available therapies. As we get started, I want to mention this series is sponsored by Bayer, and the recommendations and opinions presented may not represent the official position of the American Heart Association (AHA). This podcast is for educational purposes only, and do not constitute an endorsement or instruction by AHA. The AHA does not endorse any product or device.

[00:00:54] Hello everyone. Welcome back to our amazing series on the intersection between CKD and CVD, specifically looking at kidney testing. I am your host, Dr. Andrew South, a pediatric nephrologist at Wake Forest University School of Medicine in Brenner Children's Hospital. Joining me today are Dr. Lourdes Gonzalez and Dr. Khaled Boubes. Dr. Gonzalez, would you please give a brief introduction to yourself?

[00:01:22]
Lourdes Gonzalez: Hi. Thank you for the kind invitation to participate in this platform. I'm a nephrologist at Mayo Clinic in Rochester, Minnesota. I'm the Director of the Chronic Kidney Disease Clinic, and I specialize in chronic kidney disease and hypertension. Thank you.

Andrew South: Welcome. So glad you could join us today. And Dr. Boubes, can you please tell us a bit about yourself?

Khaled Boubes: My name is Khaled Boubes. I'm a nephrologist here at the Ohio State University. I'm [00:01:47] the Director of Interventional Nephrology, so I see a lot of my patients towards the end of the spectrum, unfortunately, but happy to be here.

Andrew South: We are pleased you're here as well. Let's get started. So, I've been really fascinated the past few years with the evidence we have supporting our highly effective guideline-directed medical therapy (which we will abbreviate as GDMT) that's now [00:02:14] available for all of these proven therapies that holistically reduce risks of kidney disease, cardiovascular disease, and the associated mortality. Dr. Boubes, can you tell us more about your experience and how you've seen the field evolve to date now that we have more of a consolidation of the kidney and cardiovascular spaces?

Khaled Boubes: Over the last seven to eight years, I would say, we've had tremendous changes in [00:02:41] both the fields of cardiology and nephrology, I think, and a huge body of evidence has emerged regarding the new therapies that are available now, and how they can affect kidney function and cardiac function and obviously overall mortality and morbidity. I think we are definitely at this time in medical history, I would say, that [00:03:03] things are definitely changing in a tremendous way. Obviously we all know about gliflozins, mineralocorticoid receptor antagonists and the GLP-1 (glucagon-like

peptide-1) antagonists. So, a lot of new therapies that are emerging, their effects are definitely synergistic. So, as we all learned in medical school, we learned in math that one plus one equals two, but sometimes in medicine one plus one equals
[00:03:30] five. So very exciting time to witness these changes.

Andrew South: I agree. I love practicing medicine in exciting times. It keeps me young. Dr. Gonzalez, can you speak to something that I've been noticing more and more. As we've had the introduction of the new kidney cardiovascular metabolic syndrome,
[00:03:42] or CKM syndrome, it seems to be putting a glaring spotlight on the fact that despite this GDMT, we're having pretty significant underutilization of the best practice medications in this population. Can you speak to that for us?

Lourdes Gonzalez: Yes, certainly. So, the guideline-directed therapy for cardiovascular kidney
[00:04:16] metabolic syndrome has been underutilized for several different reasons. So there are several challenges associated with that. One of those was a significant lack of awareness and familiarity among the health care providers regarding the cardiovascular and renal benefits of agents such as SGLT-2 inhibitors and GLP-1 receptor agonists. These medications were initially approved for glucose reduction,
[00:04:47] and they were not very well appreciated, perhaps in the beginning, despite the proven benefits in reducing the cardiovascular and kidney disease risks. Now thankfully, this barrier is being lifted as more and more health care providers are using these medications. For example, I'll say probably like five years ago or so, there were only very few patients that will come to my practice with the use of
[00:05:15] SGLT-2 inhibitors already on board. But nowadays, I can see that pretty much 70 to 80% of them are using them. Nowadays, the primary care providers are feeling more comfortable with prescribing these medications than before.

So, it's not only just the specialists that are using these medications, but we see it now more days in the primary care practice, which is great. But there are also some
[00:05:43] other barriers for the underutilization, such as the systemic barriers, such as if there is poor communication in between the different health care providers or the areas, fragmented care in between different specialties of very complex patients, meaning who's going to be prescribing the medications, should it be cardiologists or nephrologists, or if it is something that can be done from the primary care
[00:06:07] office? And the introduction of a more multidisciplinary approach for these patients is great in order to reduce that gap of the utilization of these medications.

There is also of course the socioeconomic factors that will be playing a significant role. Unfortunately, many of these medications have very high cost, and if there is limited insurance coverage of these newer therapies, that can delay the widespread use of these medications. There are disparities in the health care
[00:06:38] access. There are prescription patterns that may be different among providers, some feeling more comfortable of prescribing these medications than others. But trying to close those gaps will be important, especially as we know that this problem with the CKM syndrome, so the cardiovascular kidney metabolic syndrome, is approaching unfortunately very young populations and those adult
[00:07:02] populations that is widespread, and different patterns causing a lot of problems, and the use of this medication will be very beneficial for all of us.

Andrew South: Dr. Boubes, have you experienced that underutilization, and if so, what solutions have either worked for you, or what do you think we should be doing to improve health care access to those medications in that GDMT?

[00:07:30]
Khaled Boubes: So, we've definitely experienced that, and I think, as Dr. Gonzalez mentioned, it's definitely much less right now compared to five years ago. I joke and it's like prescribing the gliflozins was like a hot potato. I'm afraid of the side effects, I'm afraid of this, I'm afraid of that, so each different specialty was pushing it to the
[00:07:56] next. And obviously the fear of prior authorization and all that kind of paperwork that comes with it also was part of it. But I think the biggest thing was, these were new drugs with certain side effects that people were not used to, and change is always difficult. So, there was this notion that this needs to be prescribed by
[00:08:21] specialists.

I think the best approach is basically, number one, taking responsibility; number two, direct communication between the specialists and the primary care. For example, here we reached this agreement between nephrology, endocrine, and the primary care doctors. Kind of like if the patient is being already followed by
[00:08:44] endocrine, then it's the endocrine's responsibility to prescribe these drugs. If not, then it's either the nephrologist or the primary care, or obviously the cardiologist. As Dr. Gonzalez said, I've been seeing a lot more patients coming to me on these medications already, compared to five years ago.

[00:09:04]
Andrew South: Great. Dr. Boubes, can you tell us a bit of an overview of what is the current goal-directed medical therapy for patients with chronic kidney disease?

Khaled Boubes: Yeah, definitely. So, I think you break it into two main categories, and then maybe one into two more. So basically, diabetic versus non-diabetic kidney disease. And
[00:09:29] the diabetic kidney disease is type one or type two. Obviously, we all know that RAS (renal artery stenosis) blockade with ACE (angiotensin-converting enzyme) or ARBs (angiotensin receptor blocker) is the main state of treatment of chronic kidney disease. SGLT-2 (sodium-glucose co-transporter 2) inhibitors were added
[00:09:43] initially for type two diabetics, and then more and more evidence has been coming out that they're also beneficial in non-diabetic kidney disease. So obviously regardless of their effect on diabetes and blood sugars, they've shown significant decrease in the progression of CKD. And then more and more evidence is also showing that there's also benefit in type one diabetics. I think right now the
[00:10:10] guidelines include type two diabetics and non-diabetic kidney disease as indications for SGLT-2 inhibitors, but I think in the near future I would imagine that type one diabetics will be also included. The benefits of SGLT-2 inhibitors for chronic kidney disease are numerous.

[00:10:28] They reduce the intraglomerular pressure, decrease proteinuria, improve the
Khaled Boubes: energy metabolism on a cellular level, and they have anti-inflammatory and anti-

fibrotic effects. So, all of these combined lead to better chronic kidney disease health and better cardiovascular benefits. And as I said, this is where in medicine you see one plus one equals five rather than one plus one equals two. And then the benefits are irrespective of their control of diabetes.

[00:11:06]
Andrew South: Great, thank you. It's fascinating to see that possible multiplicative role, that synergistic role. So, it will be interesting to see how that advances moving forward. So, Dr. Gonzalez, I'm interested: despite all our best efforts, if we do GDMT in patients with CKD and type 2 diabetes, there's still a population that we can't quite control and reduce their cardiovascular disease risk. So, what are the next steps
[00:11:35] within GDMT for those patients who are not yet controlled on RAS blockade and an SGLT-2 inhibitor?

Lourdes Gonzalez: So, we usually will try other therapies as well. Now we use the combination of non-steroidal mineralocorticoid receptor agonists, the MRAs, along with the prior
[00:11:58] therapies of phase inhibitors, ARB and SGLT- 2 inhibitors. There are two main trials, the FIGARO and FIDELIO trials that have shown that finerenone can reduce the risk of cardiovascular composite outcomes and kidney composite outcomes, that includes renal failure and significantly declines in the estimated glomerular filtration rate. So, they have now recommended for the use of finerenone in
[00:12:28] patients with type 2 diabetes and chronic kidney disease to reduce the risk of CKD progression.

Along with that, we are also looking at the use of GLP-1 receptor agonists for the use of those medications to reduce proteinuria. And by doing so, they also have
[00:12:50] some renal protective effects. We see the use of semaglutide in a trial called SUSTAIN-6, and the use of liraglutide in the trial called LEADER trial, both of them showing a significant reduction of albuminuria in decline in the GFR of patients with type 2 diabetes. So, with the use of these newer agents, we can see added effects
[00:13:17] on the reduction in proteinuria and hopefully protection towards the increased progression of the chronic kidney disease. Now you may ask whether there is a combined or added effect to use a combination of the two, the MRAs and the GLP-1 receptor agonists. They did a full analysis on the FIDELIO-CKD and FIGARO-DKD
[00:13:43] trials, and they showed that the cardio renal benefits were maintained with the use of the finerenone on those patients that were already on GLP-1 receptor agonists at the beginning of the study.

For me, they did not see, at least on this specific subgroup analysis, reduction on
[00:14:08] the progression of chronic kidney disease for example. But they do see that by month four there is a decrease on the albuminuria on those patients that were already on the GLP-1 receptor agonists and were receiving finerenone. They found that there was around 7.2% of the patients that were initially on the GLP-1 receptor agonists when they were enrolled on these studies. And that reduction of
[00:14:35] albuminuria looks promising to see whether the combination of these two therapies added to the usual directed medical therapy for this population will be something beneficial for sure. And of course, we'll need more studies to ask that specific question of combination of several different drugs trying to improve the

[00:15:05] outcomes and decrease the progression of chronic kidney disease and of course decrease the cardiovascular disease outcomes.

Andrew South: Thank you. So, Dr. Boubes, compare and contrast guideline-directed medical therapy for patients with CKD who have type 1 diabetes compared to what we do for type 2 diabetes.

[00:15:25]

Khaled Boubes: So, for type 2 diabetes, obviously patients should be on an ACE or an ARB. This is for both type 1 and type 2. SGLT-2 inhibitors have been definitely recommended to be started in type 2 diabetes. In type 1 diabetes, this hasn't been completely

[00:15:46] recommended yet, I would say. The biggest fear, I think, is the different mechanisms obviously in the diabetes, but then the risk of euglycemic DKA (diabetic ketoacidosis). Obviously in type 1 diabetes, they're at a higher risk of DKAs. Apart from that, I think we are seeing slightly more and more evidence that SGLT-2 inhibitors are beneficial in type 1 diabetes. There's the DEPICT-1 and the

[00:16:12] DEPICT- 2 trials that showed some improvement in proteinuria in these patients.

So, I think we're seeing more and more evidence that SGLT-2 inhibitors are beneficial in type 1 diabetes. So, I think in the future we'll probably see some

[00:16:28] recommendations regarding using them in these patients. Apart from that, I think finerenone is also being used in type 2 diabetes; I don't think it's recommended yet to be used in type 1 diabetes. But as you can see with many of these drugs and recommendations, it's like you take the biggest pool of patients first and then you go down the line. So, I wouldn't be surprised if we see more and more

[00:16:56] recommendations coming up for the type 1 diabetic patients.

Andrew South: Dr. Gonzalez, another really interesting development in the field has been our newer risk equations that have incorporated measures of kidney health such as urine albumin-creatinine ratio and eGFR. Can you review for us some of these

[00:17:18] newer equations and how they may or may not help us assess overall CKM syndrome risk in our patients?

Lourdes Gonzalez: Yeah, certainly. So, we have newer risk prediction tools that we use on a regular basis in the practice. One that I use very frequently, I'll say probably every day when I'm visiting with our patients with chronic kidney disease, is the kidney failure

[00:17:47] risk equation. And that is very helpful. The patients want to know what is their risk to progress on their chronic kidney disease, what are their risks of ending up needing dialysis or a kidney transplant? So that helps us have that conversation with them so they can understand what their risks are, and they can more confidently follow the recommendations regarding blood pressure and

[00:18:16] management and of course a low-salt diet and other things that we discuss in our chronic kidney disease clinic. So, the kidney failure risk equation is very helpful for that. It will use variables such as age, sex, the estimated GFR, the albumin to creatinine ratio, and will help us predict the risk of those patients end up needing dialysis or transplant.

I do that exercise with all of our patients that come to our clinic when they come

[00:18:42] asking about a specific risk that they may have, and of course the albuminuria to creatinine ratio will play a major role on that risk prediction, and being able to tailor their therapies to try to reduce that proteinuria becomes very important. We have other tools as well, such as the KDIGO (Kidney Disease: Improving Global
[00:19:05] Outcomes) Heat Map. This tool I would think is very useful for health care practitioners to be able to visualize. It's a very visual tool that will help us determine which patients are a higher risk of progression and which of those patients should be referred to nephrologist for evaluation. It follows the same KDIGO Map of CKD stages by colors, the green, yellow, and red; and those that are in red are usually patients with very high albuminuria. So usually, an A3 or
[00:19:40] advanced chronic kidney disease between the end of CKD-3b, stages 4 or 5, that will be colored red. And those are patients that will definitely benefit from referral to see a kidney specialist.

We have a newer formula, a newer tool, which is the PREVENT (Predicting Risk of Cardiovascular Disease Events) equation that was developed by the American Heart
[00:20:03] Association. And this one uses risk factors for patients that have cardiovascular kidney metabolic syndrome in order to predict the risk of cardiovascular disease events. And it is especially useful for patients that have chronic kidney disease as well. It will incorporate age, total cholesterol, HDL, blood pressure readings, their BMI, the estimated GFR, whether they have diabetes or smokers, if they're on
[00:20:30] antihypertensive medications, if they're on lipid lowering medications. So, this will narrow down a risk assessment specifically for these patients, and it will give us two risk models. One is a ten-year risk estimate for patients that are between ages 30 and 79 years old and can also provide a 30-year risk estimate, which I found very
[00:20:55] interesting, to be able to see in those younger populations that are between 30 and 59 years old.

And by knowing this risk, patients can truly see where they should be committing to their therapies and how important it is to be able to control their blood pressure, lower the lipid levels in order to have better outcomes in the years to
[00:21:20] come. Interestingly, this PREVENT tool has been validated in a very large population. More than 6 million individuals have participated for the validation of this tool, so it is a very good tool to use in order to estimate the risk of cardiovascular disease.

Andrew South: [00:21:49] Hi, Dr. Boubes, can you paint a picture for us of where we stand right now and how these wonderful CKM risk assessment tools inform the need for and decisions we make for guideline-directed medical therapy, not just for medications, but anticipating and prepping our patients for heart and or kidney failure, and those specific treatments like dialysis or transplantation?

Khaled Boubes: [00:22:21] Yeah, definitely. So, more information is always helpful. So, as you get more and more information, you increase your ability to predict when these patients are going to need further help and further resources and further treatments. It helps you and it helps the patients plan ahead and obviously make that decision at the
[00:22:38] right time. So, one of the big examples in CKD and dialysis is obviously getting a vascular access placed or deciding whether the patient wants to do hemodialysis

[00:23:03] versus peritoneal dialysis. And if you can know the rate of the progression and predict that a certain patient will progress to renal failure earlier than others, then you can plan ahead accordingly. Obviously, also helping placing these patients on the transplant lists earlier, planning ahead whether it's a living donor or not. So all of these tools help us plan better and help the patient help the patients plan ahead much better.

[00:23:26] I think as we unravel these connected relationships between the heart and the kidneys, and the endocrine system and the kidneys, I think a huge important future step is to emphasize the need for collaboration between the different specialties,
[00:23:46] and again, looking at the patient as a whole instead of small pockets here and there. I'm just looking at the kidneys, the cardiologist is just looking at the heart. One of my dreams would be a multidisciplinary clinic where the patient would come and just get seen by a cardiologist, a nephrologist, and endocrinologist, and
[00:24:12] make a shared decision on the treatment. That way all aspects of the patient's care are covered and there's no duplication of work, but at the same time you're not missing stuff. And it's not like, "Oh, let me see if your cardiologist would think that we need to put you on this," and the next time he sees the cardiologist is like six months later. So, I think these are things that are important to keep in mind. The
[00:24:38] communication between the different teams is essential and the multidisciplinary approach is definitely the way to go in the future.

Andrew South: I agree. We need more collaboration and improved communication, and I think this new framework of CKM syndrome, CKM health, will go a long way towards doing
[00:24:58] that. So that is an exciting advancement, and we shall see where we move. Any other thoughts, any ideas, any comments from the group?

Khaled Boubes: I think this was a very helpful discussion. Thanks for the opportunity.

Lourdes Gonzalez: Yes, thank you for the invitation.

Andrew South: Well, thank you to our panelists, Dr. Lourdes Gonzalez and Dr. Khaled Boubes. And
[00:25:23] thank you so much for our listeners. We're very grateful that you spent time to join us today. Please stay tuned for our next podcast. We hope you join us then. Thank you all and take care.