

- Andrew South: 00:04 Hello everybody, and welcome back to the fifth and final podcast in this five-part series on the relationship between chronic kidney disease, CKD, and cardiovascular disease, CVD, and the importance of urine albumin-creatinine ratio or uACR and eGFR (estimated glomerular filtration rate) testing for patients with CKD. This relationship is complex and bidirectional with each condition, increasing the incidence and progression of the other. During this episode, we will discuss the importance of chronic kidney disease awareness, detection, and intervention to achieve optimal outcomes for persons with cardiovascular, kidney, metabolic, or CKM syndrome.
- 00:44 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 positions 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. Without further ado, we'll get started. I'm your host, Dr. Andrew South. I'm a pediatric nephrologist at Wake Forest University School of Medicine and Brenner Children's Hospital. I run our hypertension clinic and I do a lot of research in hypertension as well as CKM syndrome. Joining me today are Dr. Abinet Aklilu and Dr. Katherine Tuttle. Dr. Aklilu, can you tell us a little bit about yourself?
- Abinet Aklilu: 01:28 Hello, I'm Abinet Aklilu. I'm a nephrologist at Yale University School of Medicine. I do clinical research, primarily focused on cardiorenal therapeutic clinical trials and clinical decision support tools. I'm happy to be here.
- Andrew South: 01:43 Wonderful, so glad that you're joining us today. And Dr. Tuttle?
- Katherine Tuttle: 01:46 Yes, hello everyone. I'm Kathy Tuttle. I'm a nephrologist and an endocrinologist by training. I am the Executive Director for research at Providence Inland Northwest Health and I'm a Professor of Medicine at the University of Washington. I've spent most of my career studying diabetes, the kidney and its complications, including cardiovascular disease that now has a new term, CKM syndrome, so I'm really pleased to join you today to talk more about it.
- Andrew South: 02:13 Wonderful, thanks. I have to be honest, I think you're the first double nephrologist-endocrinologist I've ever met. That's very cool and very timely now.
- Katherine Tuttle: 02:23 Yes, indeed.

Andrew South: 02:26 All right. To get started, some points I've been thinking about recently that will inform a lot of our discussion today is just the fact that as both of you know I'm sure, patients with type two diabetes face a much higher risk of cardiovascular death compared to the general population or even compared to some of the other cardiovascular disease risk factors, including almost triple greater risk compared to patients without type two diabetes.

When patients with type two diabetes develop albuminuria their risk of cardiovascular mortality further increases. Compared with patients with type two diabetes alone, those with albuminuria are at four times greater risk of cardiovascular death and five times greater risk of hospitalization due to heart failure. Detection of persistent urine albumin-creatinine ratio greater than or equal to 30 is crucial to identify chronic kidney disease, which puts patients with type two diabetes at significant cardiovascular risk.

03:25 Dr. Tuttle, one of the things we want to talk about today is the fact that with the advent of the new CKM syndrome, patients with CKM conditions require a holistic patient-centered care. In your experience, how has that looked to you, and where do you think we should go with the field?

Katherine Tuttle: 03:46 Thanks, Andrew. I think it's a really important concept. Like you said, CKM syndrome includes even people without diabetes. But if we just want to take the type two diabetes population with CKD, that's an enormous slice of the CKM pie. I think we ought to really reframe what problems we're trying to solve because as you pointed out, the major risk is actually death. Most people with diabetes who develop chronic kidney disease will die on the road to kidney failure, and in fact, only 10% even reach a kidney failure outcome because of the enormous competing risk of death, not because they're getting better. The reason it matters so much is that in addition to ringing the alarm bell, there's a lot we can do about it now. We have highly effective therapies that not only reduce risks of losing kidney function and kidney failure, but most importantly, reduce all-cause mortality.

04:46 For example, in the FLOW (Evaluate Renal Function with Semaglutide Once Weekly) trials, semaglutide reduced all-cause mortality by 20%. A lot of it was cardiovascular, but also really interesting. There was a reduction in infections as well. What we need to really focus on is the totality of risks, and we now

have therapies that can improve survival and among the living, reduce rates of major cardiovascular complications, both heart failure and atherosclerotic cardiovascular events, and then kidney failure.

05:14 We really have an opportunity now to address the totality of risk, but we need to recognize that it's all of the above and it's really the lens that we look at patients through. So yes, we want to prevent kidney failure, but we also, dead people don't get kidney failure. We also need to improve survival and then improve the other outcomes that are either causes of death or terribly debilitating in the population.

Andrew South: 05:41 I agree, yes. That's what I've loved about this CKM syndrome, recontextualization of all of our fields where we move away from a siloed approach to more of integrated physiology and integrated care, which is I think really important moving forward. I love the fact that we now have more tools at our disposal that bring the nephrologist, the cardiologist, the endocrinologist to the table. For example, the PREVENT (Predicting Risk of Cardiovascular Disease Event) equation where we can now incorporate estimated GFR and urinary albumin-creatinine ratio measures in a cardiovascular risk assessment equation. That really speaks to the fact that when patients with type two diabetes for example, develop albuminuria, their cardiovascular mortality risk can go up fourfold and a five times higher, greater risk of hospitalization due to heart failure.

06:36 Finally, we're at this point where we have the evidence that can be integrated in clinical care with a prediction model. Obviously now that this has been implemented, we'll have to obviously get more data to make sure it's being used effectively as intended. Can you speak more to us about how PREVENT equation was built, how we should be using it, and any barriers that you see?

Katherine Tuttle: 07:02 Yeah, no, I think this is another extremely important contribution from the AHA CKM initiative. I was involved in the development and validation of the PREVENT equation. First off, it incorporates total cardiovascular risk too so not just risks of ASCVD (atherosclerotic cardiovascular disease) but also heart failure. That's another conceptually important change that I think a lot of people haven't appreciated. And then as you pointed out, it recognizes the extraordinary contribution of the kidney to cardiovascular risk. That's why K is in the middle of CKM.

07:37 While we recognize that albuminuria, as you pointed out, is an extremely important cardiovascular risk predictor, we recognize that unfortunately in real world practice, it's not measured nearly as often as eGFR. The base PREVENT equation requires eGFR, plus a number of demographic variables and conventional cardiovascular risk factors. But we highly encourage measurement of albuminuria, and when albuminuria is available, it can be included in the PREVENT equation. It only improves the risk prediction.

08:11 This is extremely important because historically, cardiologists have not used kidney disease as a predictor of cardiovascular risk. And then the integrated approach of two measures both GFR and albuminuria for optimal risk prediction and incorporating heart failure. This is important because we now have treatments, and as I mentioned, these treatments in this extremely high-risk population certainly reduce atherosclerotic cardiovascular disease risk, but they also reduce heart failure risk and kidney failure risk. We've now moved to a much more holistic risk assessment that includes the totality of risks with the idea that it's going to guide us to therapies that modify those risks.

09:01 And then I'll make one other comment that I was thinking about, especially with your pediatric lens, is the other thing that we've really recognized and emphasized with regard to CKM is a lifespan approach, that the origins of the risks of these serious complications occur over a lifespan. Many of the origins are in early life, and while so far we've mainly talked about drug therapy but really emphasizing prevention, primordial and primary prevention of maintaining a healthy weight, maintaining optimal levels of blood pressure, cholesterol, glucose in order to help people maintain health, but among the people who do develop CKM conditions where we welcome this major advance of these highly effective therapies now that are really poised to extend life and reduce major complications that occur commonly not only in high-income countries, but especially in low and middle-income countries where there's many fewer options for either kidney replacement therapies or cardiovascular interventions. All the more important that we also take a global approach.

Andrew South: 10:15 Yeah, that's a great point. We can't focus on just the older adult population in the United States or high-income countries. I'm really interested in how can we better integrate this across the life course. I'm glad that these equations are trending to be used in younger adults. We still have the ways to go until they're ready for adolescents or younger kids, but I think that's

really going to be important but we can't just be copy and paste because we have a lot there over time that needs to be sorted out, especially when we talk about more preventative treatment options.

10:52 All right, so let's talk, Dr. Aklilu, about the evolution in the field in terms of risk assessment for major kidney outcomes such as eGFR decline, kidney failure and initiation of dialysis, and cardiovascular death. Can you tell us about the recent advances in the field and where we are to date?

Abinet Aklilu: 11:11 Yes, absolutely. Just to follow on what Dr. Tuttle has just mentioned about the PREVENT risk score as well, having both eGFR and urinary albumin-creatinine ratio is useful to adequately assess a patient's risk of major adverse kidney outcomes, which include a major decline in eGFR, which could be by 25 or 40% depending on which trial we're looking at, kidney failure requiring dialysis as well as kidney and cardiovascular death. Knowing about the eGFR and the degree of albuminuria helps us to be able to utilize the KDIGO heat map as well as the kidney failure risk equation tool. When seeing a patient with known CKD or risk factor for CKD such as hypertension, diabetes, or other cardiometabolic diseases, it's important to look at both their eGFR and their urine albumin-creatinine ratio, and not only for CKD diagnosis but also for prognosis and management.

12:12 Having these two markers of kidney function and injury allows us to properly utilize, like Dr. Tuttle mentioned, that PREVENT score for CKD or cardiovascular risk, but it also helps clinicians properly use the KDIGO (Kidney Disease: Improving Global Outcomes) heat map and the kidney failure risk equation tool, which are designed to provide more kidney specific prognostic and therapeutic guidance at the point of care. The KDIGO CKD prognosis heat map is a useful guide for CKD staging as well as risk stratification. It can provide guidance on how frequently to monitor eGFR and uACR, and also when to refer to a kidney specialist.

12:52 The KFRE or the kidney failure risk equation, is a risk estimation tool that has now been validated in more than 30 countries worldwide. It takes in four variables: age, sex, eGFR, and uACR. And specifically, it provides future risk of kidney failure specifically, two and five year risk estimates for kidney failure. It also provides modified risk estimates if we were to start the patient on guideline directed medical therapy and also guidance as to when to refer to nephrology based on their estimated risk of kidney failure in two and five years and having both the eGFR

and uACR if the patient is essential to properly use these widely available tools which can assist in shared decision making.

Andrew South: 13:42

Can you tell us a little bit more, Dr. Aklilu, about how we can use these risk assessments to inform the implementations of the guideline directed medical therapy (GDMT)?

Abinet Aklilu: 13:55

Now, if we're seeing a patient in clinic for example, and we have their eGFR and their urine albumin-creatinine ratio, we can use the KDIGO heat map and we can find where they fall within that heat map, what risk group they fall under. It can tell us what CKD the stage they're at as well, as how often if we need to monitor their urine albumin-creatinine ratio or eGFR more frequently based on their risk of progressing to a higher stage of kidney dysfunction or risk of kidney failure.

Andrew South: 14:30

We're all human, as much as I forget that sometimes, both us as providers and our patients and their families. What are your thoughts on how we can, like always happens with new therapeutic options or new guidelines, new tools, or toys as we like to call them in pediatrics, how can we avoid and overcome therapeutic inertia, both as providers at whatever level, and at the patient level for our patients and their families?

Abinet Aklilu: 15:02

Absolutely. So therapeutic inertia is a known barrier to optimal implementation of GDMT. Also, to just go back and provide more answer to your previous question, so incorporating these risk-based tools into our CKD care is essential for implementation of highly efficacious GDMT to prevent these major kidney outcomes, and also cardiovascular outcomes and cardiovascular mortality and all-cause mortality as Dr. Tuttle mentioned earlier, we now over the past decade have multiple therapeutics that slow CKD progression and also have other cardiometabolic benefits through multiple mechanisms including lowering proteinuria or targeting inflammation and fibrosis.

15:47

These include the RAS (renin-angiotensin system) inhibitors that have been around for a while, but also SGLT2 (sodium-glucose cotransporter) inhibitors, which now have indications for both patients with and without diabetes. GLP-1 (glucagon-like peptide-1) receptor agonists, and non-steroidal mineralocorticoid receptor antagonists like finerenone, which have been associated with significant benefits in terms of markedly slowing kidney function decline, improving their KDIGO (Kidney Disease: Improving Global Outcomes) risk strategy category and lowering cardiovascular complications,

ultimately improving mortality as well as also lowering risk of AKI as we've seen in some meta-analyses.

16:24 Now, we are also learning that these drugs have additive benefits and therefore, we need to ensure patients are on the appropriate maximally tolerated GDMT based on their risk. Unless there's a strong contraindication such as low blood pressure, we should aim to use the patient visit as an opportunity to maximize GDMT. We now have multiple drugs to effectively manage hyperkalemia, which is a barrier to RAS maximization, but we should ensure that by using these drugs that hyperkalemia is not a barrier to RAS inhibitor use or up-titration. We know that proteinuria is a well-known risk factor for adverse kidney outcomes such as significant eGFR decline in kidney failure and we need to regularly assess urine albumin-creatinine ratio and to monitor response to therapy as well. If albuminuria persists despite maximally tolerated RAS inhibitor use and SGLT2 inhibitor use, should consider adding non-steroidal MRAs.

17:29 Each visit we do not ensure a patient is on the appropriate therapy is a missed opportunity to mitigate GFR progression and downstream poor outcomes. It's difficult to always remember up-titrating and ensuring a patient is on all of the appropriate GDMT, but we can now with the use of the EHR for example, we can utilize tools such as disease and visit-specific smart phrases, pathways and reminders and other clinical decision-support tools to assist clinicians in this regard. I mean, this is challenging, but the benefit is too great to miss this opportunity to improve our patient's mortality and kidney disease progression.

Andrew South: 18:15 I'm curious your thoughts. I think of healthcare almost like a life course perspective. We have downstream and upstream inputs on the care we can provide any given patient. Much of which is way out of our control, but it's not necessarily a linear process. When we talk about policymakers, whether nationally or statewide or per country, and then payers at least in the United States and how that integrates with all the different health care systems and then the trickle down to us as clinicians and then the patients that we see, what are some ideas you have on any ways to adjust barriers and promote facilitators to better implement not only GDMT but uACR testing for example? Because as Dr. Tuttle alluded to earlier, we still have a ways go to more adequately and equitably use urine albumin-creatinine ratio as a tool in our toolbox.

Abinet Aklilu: 19:17 Yes, we're still pretty far behind on this on both the diagnosis and also the management. Widespread education as we're

doing right now is key. It's very important. But also just making sure that clinicians have access to the current guideline and evidence and that it's easier to access at the time of patient evaluation is important. A major barrier to these medications are not just also prior to the patient, meaning the clinician not prescribing it, but also when we try to prescribe it as well, cost is a barrier to access to these drugs.

19:59 There are some ways that could improve this. Having a multidisciplinary CKM clinic that also has a social worker, a pharmacist available for example, could help identify cost concerns early at the point of care and provide timely assistance filling out prior authorization and access support forms to patients who could have cost as a barrier. Ultimately, it would take continued efforts by multiple stakeholders including hospitals, clinical providers, social workers, pharmacists, policymakers, and insurance companies to minimize out-of-pocket costs and ensure cost does not continue to be a barrier and accessing these medications. From our end as clinicians, we also need to always review patient's medications, not just initiation, but also making sure if they were discontinued for any reason that they need to be, that reason for discontinuation or holding these medications is not still active. We need to revisit reasons for discontinuation regularly and try to mitigate these as well so that our patients do not lose the long-term benefits due to interruptions of these life-saving medications.

Andrew South: 21:20 Dr. Tuttle, I'm curious. I increasingly think about learning health systems, specifically academic learning health systems where there's a little bit more on average rigor in terms of the data acquisition and the data utilization within any given health care system. What do you think are ways we can have a better focus effort on implementation and dissemination to optimize the usage of GDMT to really make CKM care better?

Katherine Tuttle: 21:50 I think Dr. Aklilu summarized a lot of approaches. I think what I would add is it needs to be intentional and it needs to be prioritized and there may be different models depending on the system and setting. We heard some approaches. I think another consideration is the partners, particularly in pharmacy, pharmacy-based medication management programs that can assist with monitoring dose adjustments. These have been very successful in other areas.

22:24 For example, in anticoagulation clinics, I remember the day as an adult clinical practitioner where the Coumadin orders would drive us nuts, and then the DOACs (Direct Oral Anticoagulants) came, and it was such a great opportunity when our pharmacy-

based medication management programs rose up and have really greatly probably exceeded our abilities to deliver optimal anticoagulation management.

22:51 And so I think that's another use case too, is to think about our partners particularly in pharmacy because the GDMTs we're talking about, SGLT2s, MRAs (Mineralocorticoid Receptor Antagonists), GLP-1s are not fire and forget therapies like statins, at least in the old term fire and forget. But these do require dosage monitoring. They may require monitoring, for example, for potassium, GFR, and so forth. It does require some attention. That's where I think that the electronic tools are wonderful, but it is going to require some human interventions and interactions as well.

23:26 I know a lot of different groups are looking at different strategies and we need different strategies. We need to test different ones and it may end up being an amalgamation of different approaches, but remember that before we had therapies there was nothing to implement. This opens up a whole new area of inquiry and thinking about strategies that can be adapted in different settings.

23:49 I think the American Heart Association initiative working towards CKM centers of excellence will help facilitate development of some of those very intentional programs with certainly our advanced tools in electronic health records and data science but coupled with intentional people developing programs to deliver the care. I think that's part of making it holistic and personal too so I welcome the challenge. I don't think any of us have all the answers, but especially for people who are earlier career and excited about the direction we're going, this is another very important area where we need to, we need scientific inquiry to help us develop the best approaches, but we shouldn't wait for that in the meantime, we should do the best we can with what we have.

Andrew South: 24:36 That's a great point and a great spot to start wrapping up. I think that's a great call for building and sustaining multidisciplinary teams where we can really lean on and leverage each other's expertise and hopefully mitigate burnout. I think the last thing we want to do is put more and more roles and more and more pressure on each individual provider. So I love that idea of hey, it's people, but technology is great and we should have that too, but we need the right people in a sustainable model in any given system and with clear roles. I think that will be really beneficial to our patients. This is just going to get a little more complicated over the years, right.

We're just getting started, so that's wonderful. Well, thank you both. Any other thoughts or suggestions during our conversation today?

Katherine Tuttle: 25:29 Well, I guess I would add, I think we really are in a golden era. I view these as opportunities. I remember when, particularly for the CKD population of people with CKM syndrome, it was rather hopeless. We had very few therapies that worked, and all we could do was just control risk factors and say good luck. And we're now in an era where, one, we recognize the totality of risks and we have highly effective therapies. I think this should galvanize us toward everything you said, Andrew, and particularly recognizing the mortality risk, right? That is the urgency. And then to know that among the living among the survivors, they can be healthy.

26:18 I'm going to be a little bit provocative as a nephrologist, but I'm promoting that we get rid of the term progression of CKD. That's not a very hopeful term. It just says you're crawling to the cliff more slowly, but you're still going off someday. But we have therapies now that I think regression and remission are in sight. In some of the papers I've written, we've sanitized that term out of it because we want people to know that they can live well, they can live with functioning kidneys and hearts. And so I would challenge us to consider our messaging and we really do have an opportunity now to deliver hope, and I think that's our charge too, is you can stay alive and you can stay healthy.

Andrew South: 27:05 Dr. Aklilu, any other thoughts for us today?

Abinet Aklilu: 27:09 Absolutely. This was great for me to listen to Dr. Tuttle as well, who's had a lot of experience. But just to be able to not just say that the patient and not to just tell a patient that they have chronic kidney disease but also provide their risk of mortality. Not to take us to more negative words, but their risk of progression, and also solutions. To have solutions along with that, or to have these efficacious interventions or medications, to be able to offer that for patients is amazing and it's very exciting. We should all take the opportunity to that involve the patient and all collaborate and target cardiometabolic disease as using this holistic approach.

Andrew South: 27:56 Well, thank you both so much for joining us today. It's a pleasure and I've really enjoyed learning a lot from you, and I can't wait for a lot of this to trickle down to pediatric patients as well. To our audience, thank you so much for joining us. If you haven't already, please be sure to listen to our other podcasts in this series. We really appreciate your taking the time to join us.

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