Andrew South: [00:00:30] Hello everybody, my name is Andrew South. I'm a pediatric nephrologist at Wake Forest, and it is my pleasure to welcome you back to our series of podcasts from the American Heart Association, discussing the increasingly important relationship between chronic kidney disease and cardiovascular disease. Today is our second podcast in our five-part series. And we'll be discussing the importance of urine albumin-creatinine ratio and estimated GFR testing for patients with CKD relative to the risk of cardiovascular disease.

[00:00:52] The relationship is complex and bidirectional, with each condition increasing the incidence and progression of the other. During this episode, we will discuss the need for early uACR and eGFR testing to diagnose patients with chronic kidney disease, and ultimately improve clinical outcomes. 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.

[00:01:15] 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. Joining us today are Dr. Joshua Barzilay and Dr. Maria Clarissa Tio. It is my pleasure to welcome you all with us today, and I'll let you both have a chance to briefly introduce yourselves as well.

Joshua Barzilay: [00:01:30] My name is Joshua Barzilay. I'm an endocrinologist with the Kaiser Permanente system in Georgia. I'm a practicing endocrinologist for the past 30 years. I'm also a clinical epidemiologist. And I've been working with the Cardiovascular Health Study for many, many years. The Cardiovascular Health Study is a large NIH-sponsored study of aging, in which I have put emphasis on the role of albuminuria. I am on the adjunct faculty of Emory University School of Medicine. [00:02:04]

Maria Clarissa Tio: [00:02:32] Hello, I am Maria Clarissa Tio. I'm an adult nephrologist here, faculty at University of Mississippi Medical Center in Jackson, Mississippi. And my research interests include the epidemiology of chronic kidney disease and the intersection of CKD and heart failure.

Andrew South: [00:03:00] Terrific. Well, I have a lot to learn from you both. All right, so let's get started. So, I'm sure you both can relate to this, but certainly in my world, we both from the provider standpoint and the patient and family standpoint, we get frustrated because of the lack of symptoms in patients with chronic kidney disease often until more advanced stages. So, I'd like to start the discussion today in terms of the needs assessment leading into the discussion about uACR and eGFR testing. Tell us a little bit about where we are now in the field with chronic kidney disease risk classification for diagnosing. And then once diagnosed, staging CKD, and how that fits into the larger framework of cardiovascular disease.

Maria Clarissa Tio: I can talk about how we currently diagnose chronic kidney disease. Most chronic

kidney disease is actually diagnosed not because of symptoms but because of laboratory abnormalities. So, the Kidney Disease: Improving Global Outcomes or KDIGO defines chronic kidney disease as abnormalities in kidney structure or function that's persistent for three months. So, the criteria includes the

[00:03:50] following. One is having a decrease in GFR or glomerular filtration rate. Or having one or more markers of kidney damage such as albuminuria, and abnormal urine sediment, persistent hematuria, electrified abnormalities due to tubule disorders, abnormal histology, or structural abnormalities detected by imaging, or a history of kidney transplantation. So currently, that's how chronic kidney disease is usually diagnosed in the clinical setting.

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Joshua Barzilay: The problem with it is that we're not doing a very good job in identifying kidney disease early on, and you cannot help to prevent the disorder or ameliorate a disorder if you did not recognize it at its earliest stages. If you wait till there is nephrosis, or the creatinine has gone above two, then there is no possibility of ameliorating the disease. It becomes self-fulfilling, and it is inexorable. The important thing is that we do today have armamentarium that can prevent further kidney function decline, so long as it is at an early stage. The other point to remember is that if you recognize early kidney disease as cardiologists, you will also be helping the patient from a cardiac point of view. We will discuss it later, but albuminuria, irrespective of GFR, is a potent risk factor for heart disease.

Andrew South: I'm curious for both of you, and especially in clinical practice. So, Dr. Barzilay,

[00:05:58] when you have a patient who's either at risk or does not have risk for cardiovascular disease, how do you think your field is doing in primary care, for example, so that those who are referred to subspecialty care in cardiovascular disease or kidney disease. How well are we doing with thinking about screening for chronic kidney disease, and actually doing it? And then on your side, Dr. Tio, what do you see when referrals come to you as well? And let's look at it on the lens of, how can we improve that? How can we empower our colleagues to not only do better, but make it easier for them to do better?

Joshua Barzilay: The problem we have with recognizing albuminuria is, in a sense, the American

[00:06:46] health system is quite fractured. People go see their doctor, the doctor may obtain a blood test on them, and then refer them to a heart doctor. And then the heart doctor may refer them to the nephrologist, et cetera, et cetera. One of the problems we have is that no one takes responsibility for the albuminuria

[00:07:25] results. Secondly, and perhaps much more importantly, is that the screening for albuminuria is very low. People only obtain it generally speaking when there is diabetes, and rather advanced kidney disease. In several recent United States population studies, the screening for albuminuria has only been anywhere from 45, 50%. And as I said, the follow-up for it, who takes ownership of it is low.

[00:08:08] And there are many reasons for this. I'm sure Dr. Tio can speak to this. First of all, I assume there's a lack of awareness of the role of albuminuria in the health care field itself. Many people are not minded to it, and do not know that there

[00:08:36] are tests to obtain it at an early stage. Secondly, when most doctors and cardiologists obtain a urine albumin, it is done through a routine urinalysis. And it's only when the kidney disease is advanced and there is spilling of significant amounts of albumin in the urine, does the dipstick test show proteinuria?

[00:09:08] There's also no reimbursement or no financial incentive for doing albuminuria testing. And most people do not realize that albuminuria is actually more common in people with hypertension than in people with diabetes. And cardiologists of course see lots and lots of hypertension, and yet that opportunity is missed for lack of knowledge. And there are people who develop

[00:09:38] albuminuria even in the absence of diabetes and hypertension. What to do about it? I'll speak to that in a couple of minutes, but I'll let Dr. Tio speak her part.

Maria Clarissa Tio:

[00:10:03] Thank you, Dr. Barzilay. So yeah, what we have to remember is that epidemiologically, about 60% of patients who have a diagnosis of chronic kidney disease actually have CKD based on albuminuria alone. That means their eGFR is preserved or over 60, and what defines their chronic kidney disease is the albuminuria. So, I think that highlights the importance of being able to screen for albuminuria in our patients. In addition to Dr. Barzilay's points, one other reason I could think of, of why the screening rates are very low is that there is

[00:10:31] inconsistency in society guideline recommendations on who should get CKD and/or albuminuria screening, right? I mean, if we look historically, the USPSTF (U.S. Preventive Services Task Force) in 2012 recommended against the routine screening for chronic kidney disease for adults who are asymptomatic.

[00:11:00] Later on, the ACP (American College of Physicians) in 2013 said that there was no significant benefit of albuminuria testing among asymptomatic adults with CKD risk factors. And in that year, they also recommended against the testing of albuminuria in those with or without diabetes who are already on RAS (renin-angiotensin-system). Of course, that was a different time, and right now, times have changed such that there's already a development of multiple other drug therapies of kidney preserving medical therapies that can slow down the progression of kidney disease beyond RAS blockade.

[00:11:35] Diabetes guidelines recommend routine albuminuria testing. But if we look at the hypertension guidelines, the guidelines are also quite inconsistent. The 2017 ACC and AHA, and 2020 International Society of Hypertension recommended dipstick testing, and saying that uACR or testing for albuminuria and quantifying add value to care. So, add to this point, it's why it's important that we're talking about this now is that the USPSTF is actually reviewing and updating its guidelines for CKD screening.

Joshua Barzilay:

[00:12:00] What can be done about the low screening grades, and the lack of effort put into doing something about this, about the CKD? There are several developments that have come in the last few years. The first one is HEDIS. HEDIS is the (Healthcare Effectiveness Data and Information Set). It's part of the National Committee for Quality Assurance, and it's used by employers to see how health

[00:12:40] plans or HMOs (Health Maintenance Organization) and large medical systems are doing in terms of caring for their patients. It's kind of a benchmark or a bellwether of the kind of care that people are receiving through that health care system, about two or three years ago in response to the high rates of CKD. And
[00:13:09] today, it's estimated about one in seven Americans has CKD. In response to this emergency, HEDIS has now required health insurers and health plans to include at least once a year, an estimated glomerular filtration rate (eGFR) and a urine albumin-creatinine ratio (uACR) level.

[00:13:36] So, this doesn't so much apply to private practice, shall we say, but there are many health care systems in the country, and many different HMOs. And this will, with time, increase the degree of urine albumin screening. Also, from a cardiology point of view. The second thing that has now happened is that both
[00:14:11] the PREVENT™ (Predicting Risk of cardiovascular disease EVENTs) cardiovascular calculator and the SCORE (Systematic Coronary Risk Evaluation) calculator for CVD in Europe, have in the last year or two included GFR (glomerular filtration rate) and albuminuria in their calculators. The calculators are now becoming
[00:14:36] more, quote, unquote, "holistic" or looking at the risk of cardiovascular disease from a broader point of view. Now, these estimates are going into the calculators. They have not made very big impacts on area under the curve or disease discrimination. But the point is, the AHA and the European Society of Cardiology (ESC) now acknowledge that kidney disease is a risk factor for heart disease and cardiovascular illness. And it is slowly integrating these values and biomarkers into its risk calculators.

[00:15:28] Now the last thing that I can suggest is not for everyone. I work in an HMO, and an HMO has a captured or captive population. And we are able to do automatic screening for albuminuria in all our participants. Which means, if somebody... We did this in people with diabetes, we will most likely expand it later to people with hypertension. Among the 20 to 25,000 people in our HMO who had
[00:16:18] diabetes, they had an automatic request in the computer system for a urine albumin-creatinine ratio. So, if Mr. Smith came to the office because he had a headache, or Mrs. Jones stubbed her toe and she was sent to the laboratory to do some blood tests. If she had not had a urine albumin level done, it was
[00:16:52] automatically ordered. And we found that using this approach, we had an 80% urine albumin screening rate.

And the people who did have urine albumin screening had lower systolic blood pressure and lower A1C levels than the people who did not have the screening.
[00:17:27] In other words, the screening served as a bellwether for proper diabetes management. We did publish this information. And in addition, the African Americans and the older people had the highest rates of screening. This is
[00:17:48] significant because the people with the highest risk for kidney disease and cardiovascular disease are African Americans and the elderly.

So, we felt that an automated system works well. Our findings have been
[00:18:12] duplicated in Denmark and in South Korea. Both are small countries, and both countries have centralized laboratory systems. So, if you are able to set up

automated systems in closed populations, you can achieve very high levels of screening. And this is something that I'm sure health insurers will be looking at
[00:18:47] via the HEDIS mandate now.

Andrew South: It's all well and good for us to say that we should do increased screening, or having guidelines say we should do increased screening. But how do you all kind of sell on the actual data behind it? So, if you could talk on the data we have to
[00:19:10] show that early CKD screening improves clinical outcomes. The data that CKD screening is cost-effective. And that CKD screening is something that patients and advocates want. Because I think all three of those can be really powerful selling points if we're trying to get our individual colleagues involved, as well as to your point, Dr. Barzilay, getting health systems involved to change clinical practice as well. Could you all speak to that?

Joshua Barzilay: Okay. That's a very good question. Put differently, if you detect albuminuria, and
[00:19:36] you make efforts to lower albuminuria, do you get any bang for the buck? The answer is yes. In 2015, Heerspink is a researcher in the Netherlands, did a meta-analysis of about 13 randomized clinical trials. And those trials in those days
[00:20:09] were basically using Aldactone, low-protein diet, and RAS blockade. That was a little before the period of SGLTs (sodium-glucose cotransporters) and GLPs (glucagon-like peptides) and so forth. What Heerspink found, and this is in the
[00:20:27] Journal of the American Society of Nephrology 2015, that if you had a 30% reduction in the albuminuria, there was a 23% decrease or decline in the incidence of end-stage renal disease. Now we all know how expensive dialysis is. If you cut it by 25%, that's an enormous monetary savings, let alone the quality of life for the patient and so forth.

[00:21:02] There was a study called FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease), in which there were people already with established kidney disease, the mean urine albumin-creatinine was about 500. What they found there was that if you decreased the protein in the
[00:21:28] urine with finerenone and approximately 80% of the decrease in these outcomes was due to lowering of the urine albumin.

There is something called mediation analysis, and they found that albuminuria lowering mediated the vast amount of cardiovascular disease decline with all
[00:22:04] these medications. But again, you have to recognize the disorder in order to treat the disorder. And by the way, they found that a 30% reduction in albuminuria could be achieved in more than half the patients. And these are not
[00:22:28] patients with teeny, little doses of protein in the urine. These are patients with 500 milligrams of protein in the urine, what we call macro proteinuria or macroalbuminuria, and that's already semi-advanced kidney disease. So, imagine decreasing risk of cardiovascular outcomes in 50% of your patients, if you are aware of the problem.

Andrew South: Okay, so tell us a little bit more, Dr. Tio, about how right now we classify CKD risk once diagnosed, and so do the KDIGO Heat Maps. And then I want to get your thoughts on how we can evolve where we are now and be more in line with
[00:23:21] cardiovascular disease risk, like the new PREVENT risk calculator, which I think has a lot of potential, and I'm eager to see the data that comes out of that.

And as an aside to that, what I would love to see is how can we better incorporate the fact that as CKD progresses, you don't have a linear increase in
[00:23:42] cardiovascular disease necessarily. It may be a multiplicative increase, right? And so how can we ensure our risk calculators and how we as clinicians stratify that risk for our patients, accounts for that fact. Like the point we made earlier, if you target blunting CKD progression, you'll have an additional benefit to cardiovascular disease risk prevention as well.

Maria Clarissa Tio: Let me start off by talking about how we currently classify or stage chronic
[00:24:12] kidney disease. So, we use the KDIGO Heat Maps. And basically, in this Heat Map, patients can be categorized based on eGFR or estimated glomerular filtration rate categories and albuminuria categories based on their uACR. So, for example, the albuminuria categories are A1-A3, depending on the uACR of <30,
[00:24:38] 30 to 300, and >300 milligrams per gram. And the eGFR categories that would make someone stage G1-G5. So, the way that the KDIGO Heat Map is constructed, it's constructed that way is because it depicts the increase in relative risks of adverse events with worsening eGFR and albuminuria categories.

So, I want to emphasize here the words relative risks because the data of which were obtained in a recent meta-analysis published by the CKD Prognosis
[00:25:10] Consortium showed that as you go through the worsening of eGFR categories and ACR categories, you get an increase in relative risk of adverse outcomes. So, for example, if we look at the KDIGO Heat Maps, for the outcome of kidney failure needing kidney replacement therapy, those who belong to the eGFR
[00:25:31] category of 60 to 89 or stage 2, and uACR category of 30 to 300, that's A2 stage, have a tenfold increase in risk compared to those in the reference group. Which is those who belong to an eGFR category of 90 to 104 and uACR category of less than 10. So that's how the KDIGO Heat Maps show us the different CKD stages.

And as I mentioned, the recent meta-analysis by the CKD-PC (Chronic Kidney Disease Prognosis Consortium) group showed that these relative risks of bad
[00:26:03] outcomes include adverse outcomes such as all-cause death, CV (cardiovascular) mortality, kidney failure, acute kidney injury, hospitalizations, MI (myocardial infarction), stroke, heart failure, AFib (atrial fibrillation) and peripheral artery disease. So that's how CKD is classified as currently. But in the past 10 or so
[00:26:23] years, we have the development of individualized calculators that calculate an individual level risk of kidney disease progression. In fact, with the recent publication of the KDIGO-CKD guidelines this year, they recommended using these risk calculators, specifically the kidney failure risk equation as something to use for our patients that can guide how we manage patients.

So, the kidney failure risk equation is an equation that uses laboratory values to

[00:27:01] calculate an individual's risk of two and five-year risk of kidney failure, needing either dialysis or kidney transplantations. So, the four variable equation uses age, sex, and eGFR, and uACR. And the eight variable equation uses those four factors, and includes calcium, bicarbonate, phosphorus, and albumin. So, at present, the kidney failure risk equation is already being used not just in clinical practice but also in guidelines.

[00:27:32] At present, the UK NICE (United Kingdom National Institute for Health and Care Excellence) guidelines uses certain cutoffs in the kidney failure risk that can determine if one should be referred to a nephrologist, for example. And the most recent KDIGO recommendations actually recommended certain thresholds and cutoffs for the kidney failure risk to determine say if when we should send patients for multidisciplinary management, when we should refer patients for transplantation or access referrals and such. So, as you can imagine, using the KFRE (Kidney Failure Risk Equation) is an incredible tool that we can use in clinical practice to guide our management of our kidney disease patients. And the only way that we can calculate their kidney failure risk is by having albuminuria.

Joshua Barzilay: [00:28:15] I would like to put out a certain hypothesis for people to consider. We are focused on albuminuria, and somebody would ask himself, why is the excretions of protein into the urine so strongly associated with cardiovascular disease? I mean, what's the real connection? How do we understand that? And what I would like to make people aware of is that albuminuria may be the first

[00:28:42] detection actually of a multisystem disease of the vasculature. It's not primarily a disease of the kidney, it is a disease of all blood vessels. It's just easier to do a urinalysis or a urine dipstick to detect microvascular disease in the kidney, than it

[00:29:09] is to start doing fundus exams, or vascular reactivity to ischemia, et cetera.

[00:29:35] And from a cardiovascular point of view, we know that albuminuria is associated with myocardial capillary disease. In other words, there's less flow of blood into the myocardium in people with albuminuria. We also know that the blood vessels, the major larger blood vessels are stiffer and have less resilience in them when albuminuria is present. And if you have stiff blood vessels and you have

[00:30:01] decreased capillary flow to the myocardium, you then get heart failure, which is also associated with albuminuria. And I'm not talking about heart failure when there is nephrotic syndrome. I'm talking about heart failure when the urine albumin is 100 to 200, not enough to give you nephrosis.

[00:30:] So, there are also associations of albuminuria with eye disease. We know that people with diabetes or kidney disease have retinopathy. We know that people with albuminuria have decreased cognition. And if you do an MRI (magnetic resonance imaging) of the brain, you will find increased white matter, abnormal

[00:30:52] white matter disease in the brain. So, in other words, you may find that albuminuria is far more pervasive than just being a kidney test. Now, that's new

[00:31:25] think, so to speak, but it would help people understand why this a little bit of protein in the urine can do so much damage to the body. We even know that microalbuminuria can be associated with hip fractures. Is osteoporosis related to microvascular disease? So on and so forth. So, this is food for thought, but again, people should take a broader look at microalbuminuria beyond the kidney. It is a systemic disorder.

Andrew South: [00:31:57] That's a great point. I think as we re-conceptualize things such as with the new cardiovascular kidney metabolic syndrome, I think that's going to help all of us reframe how do these conditions and biomarkers interrelate and how can we better use them for our patients? So, as we wrap up, I wanted to get your thoughts on how do we use our newer and emerging risk screening tools to better triage the management for our patients? The interventions we use when to refer and who to refer to the subspecialists?

[00:32:33] How can we better serve our patients to give them more agency and autonomy on their own care? And how can we better partner with primary care providers and other subspecialists to provide more optimal and higher quality care to ultimately improve outcomes? And with true health equity?

[00:32:42]

Maria Clarissa Tio: [00:33:04] I can talk about referrals, and I'll talk about it from the lens of a nephrologist. Usually what we always say is that there are some patients whereby the time that you refer to a nephrologist, the kidney disease is quite advanced already, right? And in this day and age where we have several kidney-preserving medical therapies, I think this is something that we need to change. Because the earlier that we get our patients who need these kidney-preserving medical therapies on them, the earlier that we can slow down the progression of kidney disease. So, as I mentioned earlier, the KDIGO guidelines for 2024 recommended using the kidney failure risk equation as one of the thresholds, for example, for a nephrology referral. So, I think there's importance in being able to educate or to [00:33:34] inform, rather, our primary care provider partners to know about the kidney failure risk equation.

[00:34:00] For example, per KDIGO, having a five-year kidney failure risk of 3 to 5% may be used as one criteria of referring a patient to a nephrologist. But aside from that though, we have to understand the limitation of this kidney failure risk equation, because this equation was developed and validated in patients who have a reduced eGFR, of less than 60. But then remember that 60% of patients with CKD are actually defined as having CKD because of albuminuria alone. Then what about those patients with albuminuria and preserved eGFR? So, in 2022, the CKD-PC or the Chronic Kidney Disease Prognosis Consortium group developed another equation called the three-year risk equation. And this equation was [00:34:27] developed and validated in both diabetics and non-diabetics, in those with preserved and reduced eGFR. So, this equation is applicable to all patients. And using this equation which not only includes age, sex, eGFR and uACR, but also includes other risk factors for this chronic kidney disease progression such as cardiovascular disease, having atrial fibrillation, diabetic control, hypertension,

BMI (body mass index), et cetera.

[00:34:58] We did a study on this and looked at the three-year risk. We termed it as a three-year risk of the entire US population. And what we found was actually very interesting. We divided our cohort into three big groups. We found that those who have chronic kidney disease with preserved eGFR, that means CKD defined
[00:35:17] by albuminuria alone. About 24% of them actually have a CKD progression risk of greater than 5% in three years, right? And so that tells you how important knowing their albuminuria or quantifying their albuminuria is.

And in fact, among them, only 59% of them had diabetes. So only 59% of them
[00:35:41] have guidelines that tell their providers that albuminuria should be measured. So that means that 41% of that high risk group would not be covered by required albuminuria testing. We also found that those who have CKD because of reduced eGFR or an eGFR of less than 60, 65% of them actually had a lower CKD progression risk of less than 5%. And a lot of these are adults who belong to the
[00:36:09] CKD stage 3a A1 category. So that just emphasizes how important it is to have individualized calculation or quantification of their risk of kidney disease progression.

And the interesting part is, is that there's about one million US adults in our study who did not meet any laboratory criteria for CKD, who actually had a CKD progression risk of greater than 5% in three years, based on their other risk factors. So that tells us how we think about CKD should be beyond just staging
[00:36:42] them of what their eGFR stage is, or what their albuminuria stage is. We should understand their individual level risk of CKD progression.

Joshua Barzilay:
[00:36:58] I second all of that. One of the biggest problems we have with kidney disease is a total lack of awareness. If the public is made aware of it, and the doctors have their guidelines you will have greater attention being paid to the management and recognition of early kidney disease.

[00:37:18]
Andrew South: Well, thank you all very much, Dr. Barzilay and Dr. Tio. It was wonderful to have you on. Thank you for taking the time to be with us today and thank you to everyone listening. We really hope that you join us for the next one. Take care, y'all.