

The Connection between Chronic Kidney Disease and Cardiovascular Disease

Andrew South:

[00:00:24] Hello, everyone, and welcome to our podcast on the connection between chronic kidney disease and cardiovascular disease. This is the first podcast in a five-part series on the relationship between CKD (chronic kidney disease) and CVD (cardiovascular disease) and the importance of urine albumin-creatinine ratio (uACR) and estimated GFR (glomerular filtration rate) testing for chronic kidney disease. The relationship is complex and bidirectional, with each condition increasing the incidence and progression of the other. Early testing and diagnosis of CKD is critical to improving health outcomes for patients, by preventing the progression of CKD and CVD.

[00:00:55] In this first episode, we will discuss the many common risk factors between CKD and CVD, prevalence and incidence of undetected CKD, prevalence and incidence of undetected CVD in known chronic kidney disease patients, and new treatments for CKD. As we get started, I want to mention this series is sponsored by Bayer, and the recommendations and opinions presented may not be representative of the official position of the American Heart Association. 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.

[00:01:30] I'm Dr. Andrew South, a pediatric nephrologist at Wake Forest University School of Medicine, and my research team, the Collaborative Researcher Coach Catalyst, investigates the development and progression of disease across the life course, with a particular emphasis on both hypertension and cardiovascular disease, as well as chronic kidney disease. And joining me today are Dr. Brian Byrd and Dr. Michael Hall.

Dr. Byrd, you want to introduce yourself? And then Dr. Hall.

Brian Byrd:
[00:02:00] Thank you, Andrew. I'm an adult cardiologist and hypertension specialist as well as researcher at the University of Michigan Medical School where I'm an assistant professor. My research group is interested in mineralocorticoid biology, including primary aldosteronism as well as other aspects of hypertension. I've learned over the years that the biology that pertains to injuries to the heart, is often rooted in the same factors that lead to injury of the kidney. In fact, I recently wrote a chapter for a forthcoming textbook of nephrocardiology. I'm sure people could debate whether it should be called cardioneurology, but there's no question that these are to be jointly considered. With that said, I'm very happy to be here with you today to think about the connection between chronic kidney disease and cardiovascular medicine. Thank you, Andrew.

Michael Hall:
[00:02:50] And I am Dr. Michael Hall. I am a cardiologist at the University of Mississippi Medical Center where I serve as chair of the Department of Medicine. Our team's research focus is on the links between obesity and cardiorenal diseases. So we'll talk a little bit about that, in this topic today. Thank you.

The Connection between Chronic Kidney Disease and Cardiovascular Disease

Andrew South: All right, well, let's get started, and to provide an overarching theme for today, our learning objective will be to identify the connection between CKD and CVD and the need to test and diagnose patients earlier, due to their cardiovascular health risk. All right, so one thing I'm really eager to hear y'all's perspective on, today, is where we are in the field with our kind of emerging understanding of this newer connection between chronic kidney disease and cardiovascular disease that really is epitomized over the past year or two by the new syndrome that's the cardiovascular kidney metabolic syndrome. In y'all's minds and your training and practice to date, how have you seen the field evolve from the more traditional siloing to between the two conditions and now that they're more integrated?

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Michael Hall: I guess I'll start. Yeah, I think it's a really exciting time. There's been a lot of evolution of the cardioneurology or nephrocardiology space, and so I think we all recognize the interplay now between the different organ systems and the complex disease processes that occur in both organs. And so I think this is a really good time. There's been a lot of recent studies published that really highlight the treatment opportunities we have, as clinicians. So I think this is a really exciting time. Really excited to talk about this topic.

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Brian Byrd: Right. I agree that it's a very exciting time. If we look at the history of evidence that the same factors can cause cardiovascular and kidney disease, I know it goes back to at least the 1940s and I think you could look back at Dr. Bright's work from the 1800s and also include that too. But more recently we've seen increasing amounts of evidence that mineralocorticoid receptor activation plays some role in injury to both the kidneys and the heart, as well as other pathways that we did not expect to play a role in both conditions or both types of organ injury. So it is really a very exciting time with a lot of new discoveries and then the culmination of decades of research into new branches and new areas where these things are going to benefit patients.

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Andrew South: The one thing that's been fascinating to me, but also difficult to wrap my head around, is the concept of causation. How do you conceptualize the causal relationships over time, amongst cardiovascular disease, chronic kidney disease, and then the antecedent cardiovascular risk factors like hypertension or diabetes?

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Michael Hall: Yeah, so I guess, looking at different pathophysiologies, they're really intertwined when you talk about shared risk factors between cardiovascular disease and chronic kidney disease. And namely hypertension and diabetes really affect both organ systems. And I think previously kind of focused on one organ system or the other. We are more and more recognizing that interplay between the two, and each affects the other. And it's not necessarily one or the other first. But I do think in certain diseases, you can oversimplify things and say the heart's weak and it's pumping less blood to the kidneys. However, the kidneys are responsible for long-term blood pressure control and salt and water balance,

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[00:06:29] and so you can make the case that they might precede some heart. But I think the main message is here that both organs can be affected by these problems simultaneously, but then really creates a vicious cycle where you have worse and worse cardiorenal diseases.

And I tend to link them as far as the causative pathway to, our research interest is in obesity, and if you account for the fact that overweight and obesity or excess adiposity is responsible for upwards of 75% of cases of high blood pressure and even more cases of type two diabetes. And I think you can also make the case that focusing on prevention of overweight and obesity are really important. I think some of the recent clinical trial data have underscored the importance of treating obesity to prevent not only cardiovascular disease now, but we have recent data showing that that also prevents renal decline.

Andrew South: Yeah. To jump in there, I think that's really interesting. So, we have some unpublished data we presented but we leveraged data from our superhero registry, which is the study of the epidemiology of pediatric hypertension. So, over seven sites across North America of youth referred to subspecialists such as cardiologists and nephrologists for hypertension disorders. And we've shown that, through some causal mediation analysis using observational data, that you could actually prevent or mitigate target organ injury, if you actually intervened on obesity, either preventative or treatment, instead of treating blood pressure, to lower blood pressure in those youth.

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[00:08:22] So, very early stages on those findings, but it kind of hits your point of, if we have to work on resource allocation, are we better served at preventing or treating obesity both pharmacologically and through other means, to see a bigger bang for our buck, so to speak, on reducing overall adverse cardiovascular health. So it'll be really interesting as we move forward, and in future podcasts in this series, we'll talk more about that topic to see if we might have a paradigm shift in how we approach both prevention and treatment.

Brian Byrd: I think those comments are all spot on. One other point that I would raise is there probably is an underappreciated role for primordial prevention at a very young age. And I'm sure, Andrew, that you know a lot about this. One of the things I'm thinking about is, when I was younger, there would be advertisements for fast food restaurants on Saturday morning during the cartoons I was watching and I would impose upon my parents to get me that food. And so I think some of the early dietary patterns that get set when we're very young, can have a big influence. And we look at studies like the Bogalusa study, and it shows that even at a young age, people have evidence of atherosclerotic plaques or streaks in their coronary arteries. And it concerns me greatly that that would be true of very young people. And I suspect that the kidneys can also be abnormal for a great deal of time before it's detected, for a variety of reasons I think we'll explore further, because of some imperfections in the measurement of kidney function and the reporting of it once it's above a certain threshold.

[00:9:43] So I think there's certainly a great deal of importance to this obesity issue and

nutrition, and to the extent that we can primordially prevent people from becoming obese in the first place, that's going to be incredibly powerful, I think.

Andrew South: [00:10:03] Tell us a little bit about, both from your personal experience and the research you've been a part of, and your understanding of the field to date, where we're at on outcomes in terms of those who have chronic kidney disease, developing cardiovascular disease, and as I hope we all well understand, that cardiovascular disease is the main cause of mortality in patients with chronic kidney disease, but give us a sense, especially in the adults, because I don't see adults very often as a pediatrician, where we're at in terms of outcomes on the spectrum of chronic kidney disease and cardiovascular disease. [00:10:29]

Brian Byrd: [00:11:00] Well, I would point out that we're well positioned to make progress on that. The tools exist for us to diagnose kidney disease early and to treat it early and with improvement in cardiovascular and kidney outcomes, at least in certain settings like diabetic kidney disease. So there are certainly opportunities for us to make a difference in that strong connection between chronic kidney disease and cardiovascular disease. However, whether or not people are doing what they need to do to find those cases of chronic kidney disease at an earlier stage and then determine who needs to be treated, who has high risk features of progression to more severe chronic kidney disease, well, we're not doing particularly well in that regard.

[00:11:30] So for example, although GFR is commonly estimated, the measurement of albumin-creatinine ratio is currently far too rare, including in diabetic patients, in patients with hypertension, and other patients who are at risk for chronic kidney disease. So I think we're well-tooled and well-equipped to make progress, but we need to do more, in terms of detecting problems and treating them.

[00:12:00] Michael Hall: Just to add to that, we know from multitudes of studies, epidemiologic studies, et cetera, that hypertension is the major attributable risk factor for all cardiovascular disease. It's also one of the most common causes of chronic kidney disease, and from the SPRINT (Systolic Blood Pressure Intervention Trial) study in other studies, we know that controlling blood pressure to lower levels is very effective at reducing both cardiac or cardiovascular and kidney outcomes. However, there's still a factor of clinician inertia there and I think we don't do an adequate job of treating blood pressure, again, the most common risk factor for these diseases. So I think that can't be overemphasized. So I think that there's clearly opportunity there. [00:12:22]

[00:12:43] So, I think we can do a better job there. And I do think that CKD is linked to some cardiovascular diseases more closely, namely, while the risk of all cardiovascular disease is higher in patients with chronic kidney disease, it's really more tightly linked to cardiovascular mortality, broadly speaking, but also to heart failure. So I think from some of the heart failure studies we've really seen, and you'll talk this in later podcasts, some really robust data indicating that some of the therapies that are either meant for another target organ or, say cardiac disease, are really

showing dramatic benefits in renal function preservation.

Andrew South: And what do you think is the cause of that inertia, or especially the lower uptake of urine albumin-creatinine ratio testing? What have you all been seeing or hearing from your colleagues?

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Brian Byrd: I would put forth that part of the issue may be guidelines like KDIGO (Kidney Disease: Improving Global Outcomes) that have helped to define the stages of chronic kidney disease, may not be well attended to or known to cardiologists who are so often seeing patients with hypertension. So I would be concerned that there might be a bit of a siloed approach that remains, in terms of what people read, what people think about. And I think it's really important that we have venues like this for crosstalk so that we can make sure everybody is aware that in order to properly define the stage of chronic kidney disease, you really do need albumin-creatinine ratio as well as an estimated GFR.

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Michael Hall: And I think the American Heart's done a really good job with programs like Know Your Numbers with blood pressure and diabetes. I think 90% of people with chronic kidney disease, don't know that they have it, so that's a problem. And so whether we can empower the patient more to know their numbers as it relates to if they're at risk for kidney disease and knowing, because sometimes that helps when the patients ask their doctors. But certainly we can do a better job of educating clinicians that these are important ways to screen for potentially very damaging diseases.

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Andrew South: That's great insight. And we certainly see that in pediatrics at all ages, just an under-appreciation, under-recognition of kidney disease in general, both in the community for patients and their families, but also for primary care providers. It's an exciting time in our world to see an increasing emphasis in a lot of my colleagues really driving advocacy and education both professionally and in the community. So that'll be fun to see it come through, hopefully in my lifetime.

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[00:15:24] All right, so tell us a little bit more about, how common is undetected chronic kidney disease, both in patients who have known cardiovascular disease and those at high risk, such as the patients with hypertension you treat, or the patients with obesity or diabetes, that you treat?

Michael Hall: So if you look at patients with advanced chronic kidney disease, say stage four or stage five, about 50% of them also have cardiovascular disease. And again, hypertension is a major contributor to both CKD and CAD (coronary artery disease). So, it's highly prevalent across the board, as your renal function class or as your class worsens or your CKD stage worsens, the more likely you are to have cardiovascular diseases.

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Brian Byrd: That's all very well expressed. And one of the things that I've noticed is, it's still very common for me to see patients in my hypertension clinic who say, oh, I've

[00:16:40] recently been informed that I have stage 3A chronic kidney disease, and that's typically the very first notification they have of it, or maybe stage four. So it seems like even in a referral population to a hypertension clinic, very frequently, patients did not get diagnosed with chronic kidney disease at an earlier stage, but rather at an intermediate level of severity or later.

Michael Hall: [00:17:03] And that's an important point. If you look...we know that when patients are diagnosed, say with stage three CKD, the prescription rates for drugs that reduce the decline in kidney function, that blunt that, you're more likely to receive a prescription for these drugs. So it's very important on the diagnostic side, to make that diagnosis so that we can begin treatment. And I think the fact that 90% of people don't even know they have CKD and it's undiagnosed in more than 75% of patients, that's a problem everywhere.

Andrew South: [00:17:30] All right. And let's flip the logic here and talk about patients with known chronic kidney disease, are already diagnosed, they receive care from a nephrologist. I'm going to be vulnerable and ask your honest feedback about how we as nephrologists are doing. I know in the pediatric world, I don't feel confident about screening for cardiovascular disease, detecting it, and acting on it, because the vast majority of data is from adults and it's hard to extrapolate that to kids when we're talking a decades longer time duration, having hypertension for example, so that we treat it for 60 years. So how good are we as nephrologists, am I doing, shall we say, of screening for, detecting, and doing something about cardiovascular disease? [00:18:00]

Brian Byrd: [00:18:26] I would say in my hypertension clinic role, I'm probably most often seeing patients who are not also being seen by nephrologists who may handle the hypertension themselves. So I don't think I have a great window on that question. The other thing is, sometimes I see patients in my general cardiology clinic, who need to undergo kidney transplantation, and then the nephrologists are very interested to know what we think is the risk that the person will have a cardiovascular event around the time of surgery, which is a very good question. So I would say that in general, I feel like I live in a parallel lane to the nephrologists, and we may not be seeing the same patients, all that often.

Michael Hall: [00:19:22] Yeah, I think the nephrologists do a great job. The problem is if they haven't seen a nephrologist, which is the vast majority of people with this underlying problem. So I think nephrologists clearly recognize the problem more than the rest of us. And so I think it's really important that organizations really highlight this interplay and we'll all be more aware and do a better job of screening at-risk patients to prevent these long-term diseases.

Andrew South: [00:19:44] So, assuming, and we'll talk about this in a few podcasts, but assuming we have a better, more efficient and valuable way to define and diagnose early chronic kidney disease, how do y'all think we can better incorporate chronic kidney disease and meaningful measures of kidney function into cardiovascular disease risk calculators?

The Connection between Chronic Kidney Disease and Cardiovascular Disease

Michael Hall: Oh, I think there's a lot of room or a lot of opportunity there. We don't really impute kidney disease into most of the calculators of cardiovascular disease. We recognize it's a problem, and sometimes it's used as an add-on in some models, but I think if you look at prediction models, kidney diseases is certainly not reflected well. And also, another important point is that if you look at clinical trials, almost all of our clinical trials exclude patients with CKD, and so we don't know if a lot of these therapies work similarly in patients with kidney disease.

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Brian Byrd: I would agree with what Michael said. That's very well stated. I don't think I have anything too insightful to add to that.

Andrew South: Yeah, I think that's a great point, and something I hope eventually trickles down to pediatrics, because we're always waiting in the wings after the adult trials conclude, when we can ask them data in kids. So, I think especially with the advent of the SGLT2 (sodium-glucose co-transporter-2) inhibitors, that we're seeing more and more, that urgency to not exclude patients with chronic kidney disease, but more than that, specifically target that population that has both chronic kidney disease and cardiovascular disease. And so what do you think would be good incentives to make that the case, right off the bat, rather than post hoc analyses, stratified analyses and things like that? Because in my simple mind, why wouldn't industry want to investigate that population? Because it seems like there would be an indication for those types of pharmacotherapies in both populations right off the bat.

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Michael Hall: Yeah. To me, the simple answer is just doing a better job of diagnosing the disease. So again, if we don't even diagnose the vast majority of cases with chronic kidney disease, again, 75%+ of people with chronic kidney disease don't even have a diagnosis. So it'd be really hard for therapies to be developed for a smaller population. I think the larger the population, which we know is there, is stimulus to do more studies there, but we have to be able to diagnose them to include them in these trials, and I think we're lacking there.

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Brian Byrd: Right. I think that that's a great way to look at it. If diseases are underdiagnosed, it becomes very difficult to recruit adequate sample sizes to study the disease or treatment. And we see that with conditions like primary aldosteronism, that lead to both kidney disease and heart disease. I'd like to point out, with respect to your question about risk calculation, there is this new PREVENT™ (Predicting Risk of cardiovascular disease EVENTS) Online Calculator, which does take into account the estimated GFR as well as urine albumin-creatinine ratio, if that's available. So that's something that I think is a very promising development. You can find that calculator on the American Heart Association's website.

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Andrew South: Yeah, that's a great point, Brian. I'm excited to see the data come out, now that that PREVENT Calculator is out. I personally haven't used it yet. I always play around with it with pediatrics, since it wasn't developed for kids, but I think it

shows a lot of promise, but we'll see what the data show.

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Andrew South:

So, I'm very curious, Brian, to hear more about your take in your work on primary aldosteronism, because I think that seems to me a population that can have a lot of conditions undetected, not the least of which is chronic kidney disease. And I'm curious if those patients also have a poorly defined cardiovascular health profile, generally?

Brian Byrd:

Thank you for asking this question. You're right that primary aldosteronism is a key contributor to chronic kidney disease in the patients who have that condition, who have primary aldosteronism. And it also does contribute to an increased risk of atrial fibrillation, an increased risk of cardiovascular death, and increased risk of myocardial infarction, among other adverse events. The diagnosis of the condition is woefully inadequate, currently. We published in Annals of Internal Medicine a few years back, that in a large number of veterans in the Veterans Affairs healthcare system in the United States, who had evidence of treatment-resistant hypertension, that 1.6% were tested for primary aldosteronism with an aldosterone and a renin test. And that's disappointing because one in five of those people would've had overt primary aldosteronism if they had been tested. And it has specific treatments, primary aldosteronism. Sometimes it can be surgically cured, other times it's treated with mineralocorticoid receptor antagonists. And those medications are not very commonly used outside the setting of resistant hypertension and primary aldosteronism. So, people aren't necessarily getting the treatments that they need, if they're not getting diagnosed. There are a number of different approaches that people are taking to try to increase the diagnosis of primary aldosteronism. I'm working with a group that is interested in taking computational approaches to that. And there are other approaches as well, that people are taking to try to improve the diagnosis.

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Andrew South:

Yeah, and I'm really interested to see how that field of primary aldosteronism evolves, especially in young adults. And I want to extend it to adolescents as well, because my hypothesis is we're missing some of those cases, so it'll be interesting within this context of chronic kidney disease and cardiovascular disease.

Andrew South:

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So, Michael, I want to bring it back to a point I think you raised earlier in the podcast, is what role social determinants of health, commercial determinants of health, now play in this intersectionality between cardiovascular disease and chronic kidney disease. And I think we're starting to get a lot more support

behind that thought. So that's definitely an area of emphasis with the new cardiovascular kidney metabolic syndrome. And that's an optional metric to calculate within the PREVENT Calculator as well. They ask for the zip code to estimate social deprivation index. I still think we have a long ways to go, especially for those of us like me, who are relatively new to the field of social determinants of health. And we always want to make sure we're doing the right thing and don't inadvertently make mistakes along the way. But how do you conceptualize how we can better understand and use that type of information, Michael, to better detect these conditions earlier on, and then therefore guide the full range of treatment and prevention, both from the policy standpoint and population-wide measures as well as the individual patient treatment.

Michael Hall: Yeah, I think the saying that when it comes to health, zip codes more important than your genetic code, and determining outcomes is true, as you alluded to, there are several measures you can use now with EHR (electronic health record) data that will demonstrate higher risk categories. And I think, whether it's related to access to healthcare, so I'm in Mississippi, but we have the worst health outcomes, in most cases, in the country and very high prevalence of disease, but particularly chronic kidney disease and cardiovascular disease. So we have a smaller number of physicians in the state. So, access to health care, particularly specialty care, is a big problem. There are issues like food insecurity that we're working on right now. We know that in some of these places within our state, people just don't have access to healthy foods. And so there are many factors that we're becoming more aware of. And if you look in epidemiologic studies, this is very evident. And I think any of us that practice in these environments, can easily tell you that certain factors are associated with harder-to-treat conditions or worse outcomes. So I think it's great that we're bringing more awareness to this, we can target these deficiencies in our care process to take better care of our patients. And so, I think the CKM scientific statement from the American Heart Association really addressed that well.

Brian Byrd: I totally agree. And it's important to note that underlying some of the social determinants of health is a concept that the WHO (World Health Organization) put forward recently, called Commercial Determinants of Health, and this refers to the impact of decisions that commercial entities make, on people's health. And that's really quite pervasive, if you think about it. So, decisions about developing foods that are either healthier or unhealthier, where to advertise them, where to sell them, that has an impact on how people do decisions to develop certain medications that can have a very beneficial impact on people's health. As I mentioned earlier, there's fast food advertising to young people, and that can cause problems in terms of adverse health consequences down the road. But then companies may do things like reformulate foods to make them healthier, which could be beneficial. So in the end, these types of decisions that companies make, can have a big influence on how people do in a society or in regions of a society, and I think we should probably be discussing these factors a little bit more often than we are.

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Brian Byrd: Excellent point, Brian. It'll be really interesting to see how and to what extent our culture, broadly speaking, may or may not shift our priorities. Do we want to shift towards being more healthy and more equitable, or not? So, much to come.

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Andrew South: All right, so as we wrap up our conversation together, I'd like to ask either of you if there's anything else on your mind about this really important topic. Michael?

Michael Hall:

Yeah, I guess just in a broader sense, we talked about diagnosis and the challenges there. We're still using pretty simplistic measures to measure kidney outcomes, and so I think the measures we're talking about, urinary, I'm sorry, urinary albumin and serum creatinine, have been around for quite a while. So I think there's a lot of opportunity there for development of biomarkers, whether that be blood or urine or imaging techniques that can help us identify people, take the people who are at risk, and help us identify which ones would benefit from therapies upstream before they get progressive disease and more fibrosis that's less likely to show significant improvement. So I think this is evolving. It's great that everyone's bringing attention to this topic, and the interplay between these two very important systems, or multiple systems. So I think we'll see a lot of progress in the years to come.

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Brian Byrd: Those are great comments, Michael. I would mention that my experience as a clinician treating hypertension and as a researcher interested in hypertension, has been a growing awareness that hypertension is a disease at the interface of the cardiac and renal systems, it highlights that these are not discrete systems, one over here and another over there, but rather aspects of a whole organism, and they're in very direct interplay with one another, and factors that injure one may injure the other. I'm so glad to see that there's a growing appreciation of this fact, and that some of those factors that cause both chronic kidney disease and cardiovascular disease, are getting treatment. And I think that's extremely exciting.

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Andrew South: Well, thank you so much, Brian and Michael. This has been a terrific conversation. I've certainly learned a bunch from you all. I'm excited to move forward in this field and hopefully with you as well. And we really appreciate y'all's time, putting this together with us.

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Andrew South: And for our audience, thank you so much for joining us. We are thrilled to have you for this series. Please definitely join us for the next podcast. Stay tuned in our series on the connection between chronic kidney disease and cardiovascular disease, specifically focused on driving awareness of urine albumin-creatinine ratio and estimated GFR testing. Thank you.