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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

A Multi-Pillar Approach to Cardio-Renal Risk Reduction

Dr. McDonough:
You're listening to *Heart Matters* on ReachMD, and I'm Dr. Brian McDonough. Today, I am joined by Drs. Anu Lala and Martha Gulati to discuss multi-pillar strategies for reducing cardiovascular and renal risk in patients with chronic kidney disease, or CKD, and type 2 diabetes.

Dr. Lala is a Professor of Medicine in Cardiology at the Icahn School of Medicine at Mount Sinai in New York. Dr. Lala, welcome to the program.

Dr. Lala:
Thanks so much for having me. Excited to be here.

Dr. McDonough:
And Dr. Gulati is a Professor of Cardiology at Houston Methodist in Houston. Dr. Gulati, thank you for being here today.

Dr. Gulati:
Oh, I'm really happy to be here today.

Dr. McDonough:
Let's start with you, Dr. Lala. When you're managing patients with both CKD and type 2 diabetes, how do you think about residual cardiovascular and renal risk even when traditional targets are met?

Dr. Lala:
When I think about patients who have both CKD and type 2 diabetes, the first thing I tell trainees, patients, et cetera, about is that meeting your targets is not the same as removing all of your risk. And that distinction really matters in how we manage these patients. I think the data from trials like ACCORD and ADVANCE show us that definitively getting an A1c down to target, even when we're aggressive, didn't translate into meaningful reductions in cardiovascular events.

What we've come to understand is that CKD and type 2 diabetes are not just additive in their risk—they actually amplify each other. A patient with both conditions is facing two to even potentially three times the cardiovascular risk for mortality as compared with someone with type 2 diabetes alone. Their risk of reaching end-stage kidney disease is also dramatically higher.

And so this key clinical insight is what drives a multi-pillar approach, which I think we're going to get more into. The residual risk persists even after you've addressed glycemia, after you've addressed blood pressure, and—this is oftentimes forgotten—after you've addressed proteinuria through traditional means.

Dr. McDonough:
Given that complexity, Dr. Gulati, what's driving the shift toward a multi-pillar treatment approach, and what does it look like in practice?

Dr. Gulati:
When we're thinking about chronic kidney disease in patients with type 2 diabetes, there are so many different things going on. There is certainly RAAS activation, inflammation, hyperfiltration, and fibrosis going on. Do we have one drug that specifically targets all of this? Not really. It's not just one pathway and it's not one drug—it's really a layered approach. And that's why I think that we've kind of stolen this idea stolen from heart failure, to be honest, this idea of talking about the pillars of treatment, meaning all the treatments are important and necessary to try to reduce risk.

So when we're thinking, we're not thinking just one thing. We're not thinking of them at separate times. Once you identify somebody at risk, you're thinking about all of them in that moment, and saying, "Well, we need all these different medications to start reducing the risk."

Dr. McDonough:
With that being said, let's walk through those pillars. Dr. Lala, can you explain how RAAS inhibitors, SGLT2 inhibitors, and non-steroidal MRAs each contribute differently to cardio-renal protection?

Dr. Lala:
These three classes are not doing the same job, and yet, they work almost synergistically to allow for better outcomes. So let's talk about the different targets that they're hitting and what makes their combination so logical.

RAAS inhibition, or inhibition of the renin angiotensin aldosterone system, is the foundation. And this has been true since the renal study—the IDNT study—in 2001. We are reducing proteinuria. We are slowing CKD progression. We are reducing blood pressure. We're leading to roughly a 20 to 30 percent reduction in end-stage kidney disease risk, and this translates all the way out to individuals who are living with heart failure as well. So reduction of the renin angiotensin aldosterone system, which is ramped up in many of these disease states, is critically important.

Then we have the SGLT2 inhibitors, which work completely differently. They are reducing intraglomerular pressure through sodium handling at the level of the renal tubules. And we've seen key insights from trials like CREDENCE, DAPA-CKD, and EMPA-KIDNEY that this benefit really doesn't have much to do with how well the glucose is controlled. Rather, it confers a hemodynamic benefit, and it, to my mind, at least, represents the first of these cardio-kidney-metabolic-improving drugs. And we're using SGLT2 inhibitors down to an eGFR of 20 now, for this purpose. So not only is it indicated in CKD regardless of diabetes, but also heart failure, regardless of the ejection fraction.

And lastly, we have the nonsteroidal mineralocorticoid receptor antagonist finerenone, and others that are actively being investigated. We know aldosterone excess is driving cardiac and renal inflammation and fibrosis independent of blood pressure or glucose, so mitigating that excess is so important.

Dr. McDonough:
For those just tuning in, you're listening to *Heart Matters* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Drs. Anu Lala and Martha Gulati about a multi-pronged approach to cardiorenal care in patients with CKD and type 2 diabetes.

If we zero in on some data now, the CONFIDENCE trials explored whether initiating finerenone and an SGLT2 inhibitor together rather than sequentially can enhance cardiorenal benefit. In light of this, Dr. Gulati, how should clinicians approach the timing and use of combination therapy in CKD and type 2 diabetes?

Dr. Gulati:
I think the CONFIDENCE trial was a really important trial. Just to give people a quick background, they took patients with chronic kidney disease who also had albuminuria and, of course, type two diabetes. And patients were already taking a RAAS inhibitor, but then they randomized them in three different ways.

So they either received finerenone, or they received an SGLT2 inhibitor—in this particular study, it was empa. And then the other group was a combination of the two.

So, the primary outcome was quite simple; they looked at the urine albumin-to-creatinine ratio over 180 days, and what they found is that by giving an MRA and an SGLT2 inhibitor, they were able to see a marked improvement in the urine albumin-to-creatinine ratio. They saw that really quickly, actually, within the first four weeks. And it was about 30 percent better than either drug alone, and that is pretty remarkable to see.

And what it tells us is what I think, again, what we've been trying to emphasize in other disease states, including things like heart failure: that we don't have to do things sequentially. And the reason that I like it is because, when they prove that it's more effective—and very quickly we get patients to have an improvement in the outcome—if we don't start things, I think there becomes clinical inertia to adding in drugs. I always worry that a patient gets diagnosed, and then we start one thing, and if we forget the other drugs, people think that there's a reason that we're withholding therapies. This study I thought was very important in that sense, because they were being very intentional. What if we do this in clinical practice? What is going to happen?

The most important thing is, I don't think we need to sequence drugs. If we're really thinking about these interventions that improve the function of patients living with this and their kidney function, we shouldn't be doing things as stepwise unless there's an intentional

reason. I really think that getting people started on the medications and closely monitoring them, of course, should be our clinical approach.

Dr. McDonough:
Additionally, data from FINEARTS-HF suggests that finerenone may provide cardiovascular benefit in patients with heart failure, extending its relevance beyond traditional CKD populations. With that in mind, Dr. Lala, how can clinicians incorporate these findings alongside existing guideline recommendations?

Dr. Lala:
FINEARTS-HF is really an important trial for us to sit with, because it takes finerenone outside of the CKD/type 2 diabetes bucket. In those patients with an ejection fraction of 40 and above—so mildly reduced ejection fraction heart failure—as well as heart failure with preserved ejection fraction, finerenone, this nonsteroidal MRA, had a 16 percent reduction in total heart failure events and cardiovascular death.

What's important about this study is that a good chunk of those patients had no significant CKD or diabetes, but the biology still worked. And so I thought that these data were so interesting, because, again, it points us towards this broader understanding of cardio-kidney-metabolic health.

From a guideline standpoint, the path is actually, I think, pretty clear for us to see updates. The ADA and KDIGO are well aligned. SGLT2 inhibitor plus RAAS is your base, and you add finerenone in the CKD patient who still has residual albuminuria on a RAAS inhibitor. Of course, we await the data from ongoing trials with other non-steroidal MRAs, as well.

The patient I keep coming back to is the one with type 2 diabetes, CKD, and heart failure with preserved ejection fraction. And honestly, that's a lot of who I see in clinic. I think this patient now has solid evidence supporting all three pillars at once. And what I find compelling is that this isn't just a coincidence of trials; it's really pointing to the fact that there's similar upstream pathology, which is inflammation-based, fibrosis-based, hemodynamic stress-based, and it runs through all three diagnoses.

So these therapies then converge because of a shared pathophysiology, and I believe that this more holistic framework is a really good one for us to adopt, which hopefully will then translate into implementation, where we all recognize that it's all of our jobs as cardiologists, nephrologists, and endocrinologists to treat shared pathophysiology.

Dr. McDonough:
Before we wrap up, Dr. Gulati, what are the key challenges of applying this multi-pillar strategy in practice, and what can we do to overcome them?

Dr. Gulati:
Certainly, when we're using more medications, there is potential for greater risk of side effects. And the thing I think we all should be monitoring for is elevations in potassium. If somebody's already on RAAS inhibition and you're starting an MRA, there is definitely a greater likelihood that the potassium may rise. So you're monitoring the potassium level regularly and making adjustments to the medications patients are on. I think that you do have to work with patients and advise them about keeping a low potassium diet, because of the way these medications work.

We do have to spend time with our patients really improving their health literacy on this issue, and helping them understand the consequence of having chronic kidney disease. I know a lot of people—even in the medical community—still think about chronic kidney disease, and the first thing that they associate it with is dialysis, rather than thinking, "Oh, these people are at high risk for cardiovascular disease." And that's, I think, something even in our health community that we need to do a better job of: educating physicians, let alone our patients.

I think some of the other challenges, though, come from clinical inertia. And that's really why I like this thought of pillars of treatment, because hopefully, it's mentally a checklist to all of us of: did I start all these medications that this person needs to have better cardiovascular outcomes? So we should be screening for it, not waiting for something to go on to start that screening. But that is something that is required on a regular basis, for our patients.

And lastly, I'd say that sometimes the hardest part for us getting our patients on these newer therapies, is just the financial part of it. One of the barriers is just getting authorization to use these drugs, and then the coverage for them.

So we need to be thinking about all of that when we're taking care of these patients. I know that's a lot of work on the clinician's side, but it's necessary work, I think. And hopefully, if people have teams, our teams can help us with some of those operational challenges.

Dr. McDonough:

Those are great takeaways for us to think on as we come to the end of today's program. I want to thank my guests, Drs. Anu Lala and Martha Gulati, for joining me to discuss how we can support heart and kidney health in individuals living with CKD and type 2 diabetes. Dr. Lala, Dr. Gulati, it was great having both of you on the program.

Dr. Lala:
Thanks so much for having us.

Dr. Gulati:
Thanks for having us. We really had a fun discussion.

Dr. McDonough:
For ReachMD, I'm Dr. Brian McDonough. To access this and other episodes in our series, visit *Heart Matters* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.