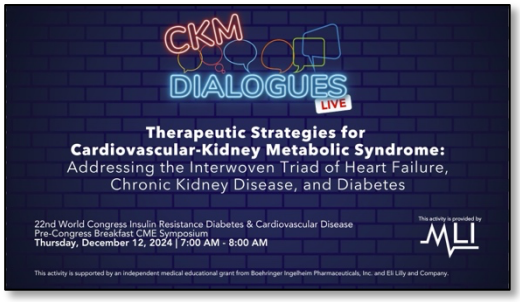
Therapeutic Strategies for Cardiovascular-Kidney Metabolic Syndrome: Addressing the Interwoven Triad of Heart Failure, Chronic Kidney Disease, and Diabetes



Jay H Shubrook, DO, FAAFP, FACOFP: On behalf of MLI, we thank you for attending this early morning program to open up the Congress. This is Therapeutic Strategies for Cardiovascular-Kidney Metabolic Syndrome: Addressing the Interwoven Triad of Heart Failure, Chronic Kidney Disease, and Diabetes.

This activity has been supported by an independent medical education grant from Boehringer Ingelheim and Eli Lilly and Company.

I'm Jay Shubrook. I'm a professor and a diabetologist at Touro University, California, just up the state near Napa, California. I am delighted to introduce a panel that you probably know very well. We'll just go down the order to introduce ourselves.

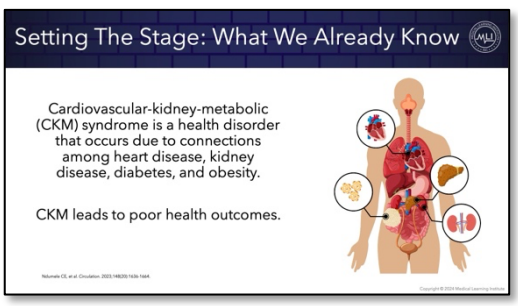
Pam R Taub, MD, FACC, FASPC: I'm Pam Taub. I'm a cardiologist and professor of medicine at UC San Diego. I want to welcome everyone to this incredible conference, which is one of my favorites.

Matthew R Weir, MD: Matt Weir from Baltimore. It's a pleasure to be here in beautiful, sunny Southern California because it's raining and then freezing now in the East Coast.

Jennifer B Green, MD: I'm Jennifer Green. I'm an endocrinologist and professor of medicine at Duke University in Durham, North Carolina. I'm also pleased to be here. Thank you so much for getting up early to come attend this session.

Dr. Shubrook: Excellent. These are educational objectives, and you have them as well. I just want to highlight; we really want this to be a conversation. We have the whole healthcare team here. We want to be able to talk about this, sort this out, and see how we can utilize our best skills for each and best practices for great care.

The things we really want to explore are looking at exploring the connections between heart failure, kidney disease, and type 2 diabetes, unveiling the epidemiologic trends and the pathophysiologic links between these, looking at emerging therapeutic strategies for CKM syndrome, and then tailoring the treatment for the syndrome based upon the patient's problems and as well as the team members.



Setting the Stage: What We Already Know

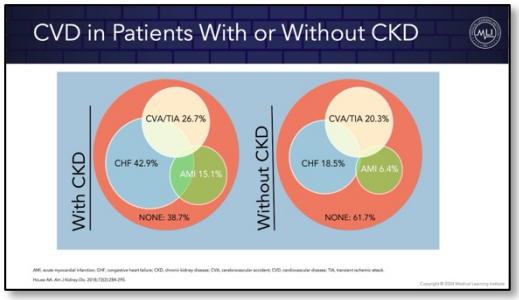
As a level-setting thing, which again, you're at this meeting so you probably are well aware of cardiovascular-kidney-metabolic syndrome. This is an increasingly common by awareness condition that looks at the connections between heart disease, kidney disease, diabetes, and obesity.

As someone in the primary care space that has historically seen them all separate, it can be really overwhelming. The idea

that we need to bring these together under a single pathophysiologic process can raise awareness, can make it simpler for us. We know that CKM increases poor outcomes and so we have a lot of work to do.

We know that also, if we think about components of that, there's a dramatically increasing awareness about chronic kidney disease being one of the fastest growing non-communicable conditions in the US and now is competing with diabetes.

We know that people with diabetes have much higher rates of heart failure, and people with heart failure also have higher rates of chronic kidney disease. Diabetes as an amplifier will increase cardiovascular disease and chronic kidney disease.

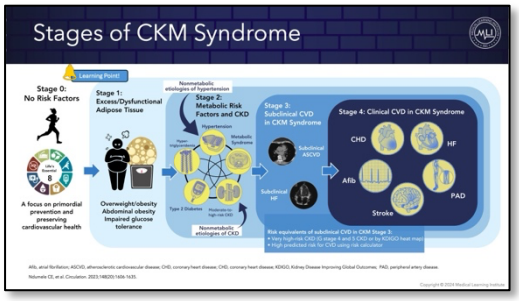


CVD in Patients with or Without CKD

Dr. Taub: I want to highlight the relationship between cardiovascular disease and kidney disease. When you look at outcomes, those that have chronic kidney disease have much higher rates of heart failure, atherosclerotic cardiovascular disease compared to those without CKD.

This is really a new paradigm for cardiologists to be thinking about kidney disease. I was just reflecting back on my fellowship, and I learned nothing about this. We were not thinking about the kidney except when we overdiuresed our patients.

This is really a new paradigm, really thinking about CKD in the context of cardiovascular disease. What all of the data highlights is that when you have even a mild decrease in eGFR, so we're talking about eGFR in the 50s, that is associated with increased cardiovascular mortality. Cardiologists have to think about kidney disease, which is really a new paradigm.



Stages of CKM Syndrome

Dr. Shubrook: For those that are not aware, the American Heart Association has come out with guidelines regarding CKM and really looking at the staging. I think we're going to discuss the staging of this, looking at those people that have no risk factors, we're trying to prevent from having the condition at all, looking at excess adiposity or visceral adiposity as a driver for CKM syndrome, and making sure that we know that that could be something as our earliest input.

Then looking at the components of those conditions, both from a metabolic and a non-metabolic standpoint, and then looking at this as being a multidisciplinary interaction between these conditions through multiple different pathways, eventually ending up causing subclinical cardiovascular disease through one of these pathways.

Then, of course, often, or historically, we've come to these patients once they've had clinical disease. We really need to have increased awareness so we can go backwards and start finding these patients earlier, because we certainly weren't trained as well.

Now to the team. How do we approach CKD? I would like to hear from each of you in terms of, how do we diagnose this? How do you use the classification in your practice? Jennifer, maybe you could go first.

Dr. Green: Looking at the CKM syndrome, everybody who comes to see me has the M component already, right? They either have prediabetes or diabetes, and they have excess adiposity.

I am routinely, of course, screening for kidney disease. As a country, we're not really doing a very good job at doing that to the extent that we should be. We do a pretty good job at measuring creatinine's and calculating eGFRs for people with diabetes in this country. The UACR tends to fall by the wayside.

I think at best, a person with diabetes has a 40% chance overall of getting their UACR checked once a year. The traditional way of identifying and monitoring for kidney disease, it's no more complicated than that.

The cardiovascular is actually a little trickier, because the ADA, for example, does not generally recommend routine screening of asymptomatic individuals. I am vigilant for symptoms or signs that could indicate that a person has established clinically important cardiovascular disease.

I've become much more sensitive to potential signs or symptoms of heart failure in particular, because that is one of the more likely cardiovascular complications, I think, that my patients would be likely to experience.

Dr. Shubrook: Yes, thank you. Matt?

Dr. Weir: I would just say, quite honestly, you can almost identify it walking through the door into your office. These are typically people who are overweight. What I really like to focus on, obviously, besides the history and physical exam, is their blood pressure, their adequacy of glucose control, their history of glucoses, whether fasting or non-fasting, or an A1C.

As Jen mentioned, definitely a urinalysis and a spot urine albumin-to-creatinine ratio. I think with this type of information, you can get a lot of information. It's coupling the estimated GFR with the UACR, with the blood pressure, cholesterol, and glucose, which are so very important for finding people early at risk for subclinical cardiovascular disease.

Dr. Green: It doesn't have to be that complicated.

Dr. Taub: Yes, and I think this is really the golden era of cardiometabolic disease. As a preventive cardiologist, that CKM diagram is just beautiful. Let's keep it simple. It's really about recognizing the underlying substrate and drivers of end organ damage. Really focusing on hypertension, managing hyperlipidemia, and managing not just diabetes but prediabetes and metabolic syndrome.

Also looking at metabolism and looking at weight and managing all of these risk factors very early. The key is concomitantly. As a preventive cardiologist, that's what I do every day, is I look at all of these risk factors and manage all of them.

Dr. Shubrook: You all highlighted some of the phenotypical features that you would see in a patient. The UACR is something that is actually quite important. We already know that less than half of people

get that done. How do we start doing that in each of our practices? Matt, I'll assume you're doing it already.

Dr. Weir: Yes. I think it's important to remember that clinicians are going to use a test if they know how to interpret it. Many laboratories have many different ways of either a spot urine albumin-to-creatinine ratio, a spot urine protein-to-creatinine ratio, or just a pure microalbumin level.

There has to be some consistency in this regard, because you're not going to use a test you don't know how to interpret. I actually use the UACR longitudinally in my patients. Typically, with each visit, which could be anywhere, depending on their level of kidney function, from a month to a year.

I monitor it longitudinally the same way I would monitor their blood pressure, their A1C, or their LDL level. I use it as a longitudinal measure of risk, and we'll discuss response to therapy.

Dr. Shubrook: Okay. How about in cardiology?

Dr. Taub: Cardiologists aren't going to do anything unless there's something actionable. UACR is very actionable. When you have evidence of microalbuminuria, there's a lot that you can do to prevent progression to macroalbuminuria. That includes using SGLT2 inhibitors, a non-steroidal MRA, ACE inhibitors, angiotensin receptor blockers.

It's a very actionable biomarker. I see this often when you detect microalbuminuria, and you take action. It can improve very quickly, and it can also change the trajectory of that patient, because elevated UACR is associated with increased cardiovascular risk. When you improve that parameter, you decrease cardiovascular risk.

Dr. Shubrook: Jennifer, you had highlighted that, of course, cardiovascular disease is one of our challenges. Most of your patients with type 2 probably are going to have CKM syndrome. How do you introduce that concept, and when do you pull other people in?

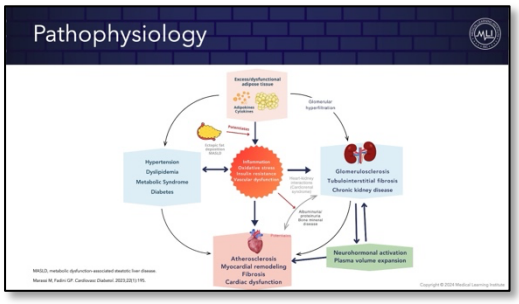
Dr. Green: I'll be honest. I don't think that I often tell the person that they have CKM syndrome. Let's be honest. I don't think the field is quite there yet. I have to say, it was interesting that Pam mentioned that she never thought about kidney disease in any major way during her training.

I think a lot of this compartmentalization has to do with the way we actually train to become various types of physicians. Now, as an endocrinologist, I'm comfortable thinking about more than one body part. This whole CKM syndrome is not new to us.

We've really embraced, at least during my career, the fact that our role is to address multiple modalities of risk, multiple risk factors, not just hyperglycemia. I think I'm living it and breathing it every day in my clinic. I don't perhaps use that descriptor when I'm talking with patients about it. Mostly it's for discussions with other providers.

Dr. Weir: No silos. Take care of the whole patient. That's why I believe primary care is so very important, because they're on the front line dealing with the whole patient. They need to, in a sense, globalize their therapeutic approaches.

Dr. Shubrook: Okay. We're going to move on to epidemiologic trends and pathophysiologic links on faculty.



Pathophysiology

Dr. Green: I'm going to kick off some of the discussion about pathophysiology and what we think is going on in our patients who have the CKM syndrome.

You really could start anywhere on this slide, to be honest. I think it's most clinically appropriate to start at the top, which is really the person with the burden of excess and dysfunctional adipose tissue. Adipose tissue is a hormonally, biologically active component of the body. It can be deposited in certain very unfavorable locations, like the liver, and this in turn can contribute--

I'm just going to go down the left-hand side first, to the clinical comorbidities or complications of hypertension, dyslipidemia, the whole spectrum of metabolic syndrome, and then progression to frank diabetes.

Now that in turn is a little bit hard, I think, to make all of the arrows connect here the way that they really should. In this figure, it's really getting us directly to the cardiovascular complications through those channels.

On the right-hand side, again, the excess adipose tissue is associated with glomerular hyperfiltration. Then a lot of these other comorbidities, the hypertension, the dyslipidemia, for example, all contribute to the development and progression of kidney disease as well.

What's really new and different about the way that we think about the CKM syndrome is really right there in the middle. You see highlighted the core pathophysiology that is related to, in particular, inflammation that is probably common to the development of all of these complications. Pam, I don't know if you want to comment specifically about the cardiovascular component.

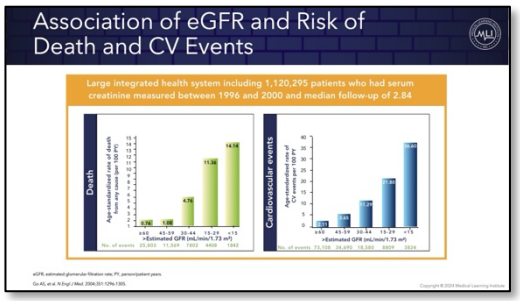
Dr. Taub: I think you've really emphasized the underlying drivers and the substrate for all of these diseases, which include inflammation, oxidative stress, insulin resistance, and endothelial dysfunction.

From a cardiac perspective, all of those are drivers of atherosclerotic cardiovascular disease, heart failure, arrhythmias. These drivers are common to all of these conditions. One organ we cannot forget about is the liver, because the liver is also an important part of CKM.

What we also know is obesity and some of these underlying pathophysiologic substrates also drive fatty liver, MASH, and MAFLD. All of these organs are interconnected. There is organ crosstalk. If we address and listen to that crosstalk early on, we can really modify the course of these diseases.

Dr. Weir: I would just briefly comment that, historically, we focused on blood pressure, cholesterol, and glucose. That's the left-hand part of the slide. We've learned that more intensive strategies to control these factors can be very important.

There is accruing information with many of the newer clinical studies that targeting inflammation is also an extremely important part. Most of the newer clinical trials actually show an incremental opportunity, on top of more intensive blood pressure, cholesterol, and glucose control, to modulate these risk factors. That's why identifying the risk early is important.



Association of eGFR and Risk of Death and CV Events
This is a very old but very important slide from Alan Go and the Kaiser Permanente Group in Northern California. What I'd really like you to focus your attention on is on the right-hand panel for cardiovascular events.

If you will notice, the risk really starts to escalate at a GFR of 45 mL/min. There are a lot of patients who are in the 45 to 60 range who really don't have kidney disease per se but may have age-related declines in kidney function.

Adding a urine albumin-to-creatinine ratio is a very powerful tool, particularly in this group, to assess risk. There is a continuous relationship between the amount of albumin in the urine and cardiovascular events. Not kidney events, cardiovascular events. That's why I think the estimated GFR and the UACR are such powerful tools for predicting risk.

Dr. Shubrook: We have a wonderful educational tool that talks about these relationships, the indicators and the amplifiers between the heart, kidney and endocrine system

Dr. Taub: Let's touch on some of the underlying pathophysiological mechanisms. One thing we did all learn about is the renin-angiotensin-aldosterone pathway. We learned about various medications that act on that pathway.

The mineralocorticoid receptor activation is a really important driver of so many diseases, including hypertension and chronic kidney disease. It represents an overactivation of the sympathetic nervous system.

From a cardiac perspective, when this pathway is overactivated, you get a lot of end organ damage. That includes left ventricular hypertrophy, myocardial stiffness, which leads to heart failure with preserved ejection fraction.

From a kidney perspective, you get interstitial fibrosis and eventual development of CKD. This is a really important pathway that we need to focus on. We need to make sure that at a very early stage that patients are on the appropriate therapies that targets this pathway.

When we talk about these pathways, there's a lot of really new therapies that are in development that we'll talk about a little bit later. Some of the therapies that are available to us that really act on this renin-angiotensin-aldosterone pathway include the ACE inhibitors, ARBs, SGLT2 inhibitors.

Matt had talked a little bit about inflammation. When you really prevent overactivation of this pathway, that is something that decreases. UACR, people think about it more as a biomarker for kidney function. As a cardiologist, I like to think about it as a marker of inflammation as well.

It's actually, in some patients, a better marker of inflammation than high sensitivity CRP. When I see that elevation in UACR, it really is a call to action to be more aggressive with all of the different therapies that are acting on, whether it's hypertension, hyperlipidemia, insulin resistance.

Dr. Weir: I agree with you, Pam. I've been saying that for years, and many people have pooh-poohed me. A spot UACR longitudinally measured can actually provide more consistency of risk as opposed to the fluctuations of a high-sensitivity CRP.

Dr. Shubrook: Yes, and I think if we want to get on this, these are not symptomatic stages. We actually have to have the awareness to know, "I need to screen," and then think about, "I want to move upstream," because otherwise we waited too long.

Dr. Green: I would just like to add, since we're talking about the role of the mineralocorticoid system, these are not people who have hyperaldosteronism. I've been asked that question multiple times recently, "Do I need to measure the aldosterone level to know if my patient will benefit from agents that address this MRA overactivation?"

The answer is no. There's no need to diagnose hyperaldosteronism, and in fact, this is probably a receptor problem rather than an actual aldosterone level problem. Don't even worry about having to work up whether or not someone has hyperaldosteronism. This is an intrinsic pathophysiologic process that contributes to the development and progression of the CKM syndrome.

Dr. Weir: Of course, there's interesting data suggesting that ectopic islands of visceral adipose tissue actually contain aldosterone synthase and can produce aldosterone ectopically, independent of the adrenal gland, and that this can contribute to the inflammation and fibrosis of the various vascular beds and target organs.

Dr. Shubrook: You've all hinted at this, but I think the question in the room is, are these multiple independent things going on unrelated to each other, or are they amplifying each other? How do we know?

Dr. Green: I think it's very likely that these are overlapping pathophysiologic mechanisms. What we're seeing clinically are different end results in the various organs or systems that we really think about and can assess the health of a little bit more specifically.

Dr. Weir: I suspect too, there are systemic and obviously environmental factors that come into play here. I don't think you can entirely generalize, other than to say we know that pro-inflammatory circumstances coupled with reduced kidney function are really drivers of systemic vascular disease progression.

Dr. Shubrook: I've heard that we want to find people upstream on the metabolic pathway. I've heard that we need to do UACR more actively, maybe even longitudinally. What is the advice that you would give to the larger clinical audience above and beyond that, and when do we start referring?

Dr. Weir: Personally, I think the earlier you can identify people at risk, you can provide early risk management. I'd much rather be in a primary prevention study than in a secondary prevention study.

Certainly, as Pam shared with you, probably the single overriding concern that we see is the development of heart failure, which, by far and away, I think comes as a surprise to many clinicians.

If you look at it carefully, it is all tied very much together. I'm more of a cardionephrologist than I am a nephrologist, because I am very aware that the heart is really the most important byproduct of kidney disease.

Dr. Taub: I think we've done our patients a big disservice by really having this black and white classification of primary prevention and secondary prevention. What we are moving towards as a field is this concept of high-risk primary prevention.

Those are people that have not yet had the heart attack or stroke but have a lot of these risk factors that make them very high risk for the heart attack and stroke. We need to really focus on identifying these people.

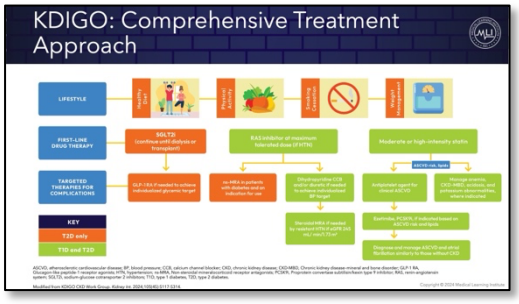
From a cardiac perspective, one of the areas that we're very interested in is subclinical atherosclerosis. This is where we use, whether it's biomarkers or imaging techniques like coronary artery calcium scoring.

It's really critical that we focus on these high-risk primary prevention patients. We're now starting to do clinical trials in these patients, including how do we prevent heart failure in these patients.

Dr. Shubrook: Yes, I love that. Thinking again about the inflammation cascade, it's using-- This is what I need to start to intervene with.

Dr. Green: Yes. I have to say, personally, the way that the guidelines are structured, there are buckets of high and low risk patients. I'll be honest, it's really hard for me to think of a person with diabetes as intrinsically being low risk at all. I tend to err on the side of assuming people are higher risk than I am aware of.

Dr. Shubrook: Sure. I want to remind everybody, if you have questions, this is your chance to start writing these questions down on the card. The runners will bring them up to us. I want to make sure that you have time to get your questions answered as well. We're going to move forward and talk about some emerging therapeutic strategies in CKM syndrome. That's you.



KDIGO: Comprehensive Treatment Approach

Dr. Weir: Many people ask, "What does KDIGO stand for?" I'll start out first, that's Kidney Disease Improving Global Outcomes. It's a large group of clinicians oriented towards nephrology, cardiology and endocrinology. We've put together many different suggestions for guidelines. I think we can all agree that lifestyle modifications are important and should be emphasized, but they don't work for everybody. We have now started to adjust our conditions and recommendations for treatment.

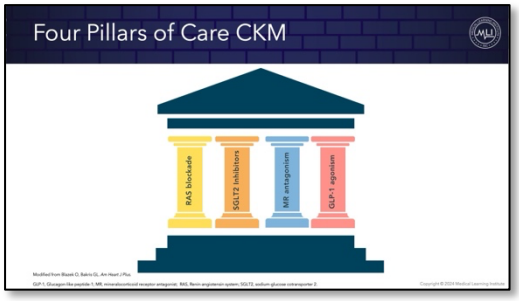
I think we can all agree that improved and more intensive control of blood pressure, cholesterol, and glucose are important. There are also some therapies as part of this intensified effort that need to be considered. Among those are obviously the renin-angiotensin system modulators, which have been

around for many decades. Then, of course, newer data supporting the use of SGLT2 inhibitors and, of course, aggressive and intensive lipid-lowering therapies.

We've also learned, too, if you look at the second line down, that GLP-1RAs can be very effective for treating diabetes, even in people with kidney disease. We've already talked a little bit about non-steroidal mineralocorticoid receptor antagonists and obviously other therapies to achieve more intensive and effective blood pressure and lipid goals. I think the key point is try to start earlier and modify risk and individualize your approach. Of course, there are many different add-on therapies that can be done to further improve blood pressure, cholesterol, glucose in your patients.

Dr. Shubrook: You highlight there that there was a time where we would screen for kidney disease and not feel like we had a lot we could do. Now we have plenty that we can do. In fact, it's just how do we choose what to do in what order. This, again, is another resource available for you.

So, about these pillars...



Four Pillars of Care CKM

Dr. Weir: Yes. every patient's different. There are now four recognized therapeutic opportunities for people, particularly with hypertension and diabetes, where there are opportunities on top of more intensive strategies to control blood pressure, cholesterol, and glucose, which may provide an incremental opportunity. Of course, the renin-angiotensin system blockers have been around for many years. Sadly, most people don't use them the way they should be, considering changes in serum potassium and GFR.

As we'll discuss now, the SGLT2 inhibitors, the mineralocorticoid receptor antagonists, the GLP-1 receptor agonists, are substantial and incremental opportunities to reduce risk. As a group, I think we can talk more about how best to individualize these approaches, how to add them to various patients, and, whether or not we need to use all of these medicines in our patients.

Dr. Green: Could I jump in just for a second?

Dr. Shubrook: Please.

Dr. Green: I think it is possible that these pillars, figures, sometimes can feel overwhelming. The first reaction often tends to be, "Do I really have to have all my patients on all of these things?" I would think of this as an opportunity, actually, because not every person, for example, can take an SGLT2 inhibitor or a GLP-1 receptor agonist, for example. Then we have multiple other avenues to mitigate the risk of progressive disease.

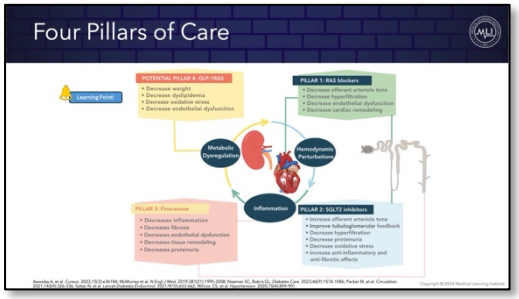
Think of it, I think, as an opportunity. Then, as I'll talk about a bit later, there's tremendous synergy in our approaches to the management of the different components of the CKM syndrome. There's quite a lot, really, with a single intervention, you can improve the outcome of multiple different conditions.

Dr. Weir: I think the medical comorbidity can also assist you in your decision-making-

Dr. Shubrook: For sure.

Dr. Weir: -in terms of which direction to go. My gut feeling in many years of using these therapies is that, on top of blood pressure, cholesterol, glucose, depression, osteoarthritis, GERD, et cetera, et cetera, that we're going to come to a limit in terms of what we can add. Again, modifying cardiovascular risk is so very important. Certainly, at least two of these, if not three, may be a key opportunity in many different types of patients.

Dr. Shubrook: As we know these pillars, I think, again, going back to put them on a RAS agent and then just watch people with kidney disease the rest of their life, now, each time you check in, if there's continued kidney disease or albuminuria, you've got other things you can do. I think for the team-based care, you should be prepared that any one of us might be adding any one of these agents. We're going to have to have a lot of awareness about this and make sure that we're talking to each other.



Four Pillars of Care

Dr. Green: Actually, I show this slide or a version of it quite a lot of the time when I give presentations about the CKM syndrome. That's because it is, I think, intuitively very useful to think about these different pillars, these different interventions, and what they might be affecting with respect to improving cardiometabolic outcomes or cardio-kidney metabolic outcomes, excuse me.

If we look at Pillar 1, for example, our old friends, the RAS inhibitors, we have long known that they decrease efferent arterial tone, they decrease hyperfiltration, decrease endothelial dysfunction, as well as cardiac remodeling. This is pointing towards the heart here, but much of this is related to the kidney as well. There may be some overlap with respect to the way that the drugs work, but they all have very different mechanisms of action and therefore are considered complementary therapies.

The SGLT2 inhibitors, again, really considered foundational care of the person with CKM syndrome. These increase efferent arterial tone; they're thought to improve tubuloglomerular feedback in the kidney. They decrease hyperfiltration. They are also felt to decrease oxidative stress and increased anti-inflammatory and anti-fibrotic effects. It helps me to think about inflammation in the organs as being a chronic process that's eventually going to result in fibrosis and frank organ dysfunction. You can see this described in the development of both cardiovascular and kidney diseases, as well as steatotic liver disease.

Now I would say the third pillar, Finerenone, probably came third in the sequence of pillars that we talk about for this condition. We think, again, because we've talked about the contribution of MRA over-activation to the development of these conditions, we think it works primarily to decrease inflammation related to over-activation of the MRA receptors, and in turn, decrease fibrosis.

Then this final pillar that's been added, it was always there in the background waiting, but we have the GLP-1 receptor agonist. Listed here is a potential pillar, but the guidelines are starting to move towards use of GLP-1 receptor agonist as a key intervention to improve outcomes in affected

individuals. These are drugs that, I'll be honest, when the flow trial results came out, I was like, "Great, already giving these drugs anyway in my clinic."

It is, I think, very, very appealing and attractive to me to know that with a single intervention, I'm altering, in a positive way, many different types of adverse outcomes. These are drugs with tremendous potential to improve not just metabolic states like dysglycemia and overweight, but they also probably decrease oxidative stress and endothelial dysfunction, and we're seeing more and more evidence that they're organ-protective.

Dr. Weir: I would add, they all lower blood pressure. Always important.

Dr. Shubrook: Yes, and see, there's complementary effects here. I think one of the things that's maybe less appreciated outside the diabetes world is that actually every GLP-1 study that included kidney outcomes showed benefit, even before we had the primary benefit of flow. This is a natural place in those pillars.

Dr. Taub: What I think is really incredible is, 15 years ago, we really didn't have these agents. We've had a lot of new drug classes emerge that have really changed the way we take care of patients. As a cardiologist, I think about when I first started my practice over a decade ago, as a preventive cardiologist, I should say, I felt pretty powerless. I would see my colleagues in interventional cardiology put in stents, my electrophysiology colleagues put in devices, and I was in the clinic really almost twiddling my thumbs.

Then all of these incredible drug classes emerged, and now I feel like I'm this powerful alchemist figuring out what's the best titration and what's the best medications to use. Now my interventional cardiologists and electrophysiologists are coming to me and say, "Well, how do I use an SGLT2 inhibitor? What's your experience with these GLP-1 receptor agonists?" We're really in a new era of medical management.

Dr. Weir: I would say, Pam, it's not even 15 years it was really with the EMPA-REG outcome trial in 2015 that we first suddenly and serendipitously noticed that, oh my God, these drugs are not only safe, they're better to be utilized in our patients with cardiovascular risk. Really this is new information, and it seems like every day, as you can see on this screen here, it seems like there's another newer study coming out indicating an opportunity to improve upon what we've done in the past.

Dr. Shubrook: For those that want more details, we highlight some of the more recent studies relevant to this condition. Certainly not an exhaustive list, but just again for your reference.

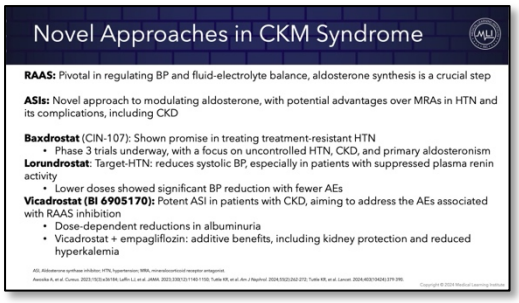
Dr. Green: I just want to make a plug for traditional modalities of risk reduction, though. These are all therapies that are superimposed upon our traditional risk reduction strategies. Which really have been very effective. For example, if you look at the incorporation of use of RAS inhibitors and statins into the care of people with diabetes, it really has significantly reduced the risk of certain outcomes, like in particular myocardial infarction. We're not replacing those traditional risk reduction modalities with these newer agents. We are layering them on top.

Dr. Weir: Blood pressure below 130 over 80. A1C below seven or possibly lower depending. For all of my patients with diabetes and or CKD, I aim for LDL targets below 55. I think these are all some of the newer opportunities on top of more intensified traditional goals.

Dr. Green: They can help make it easier to reach those targets in many cases.

Dr. Weir: Absolutely.

Dr. Taub: Let's not forget some of the basics, which is lifestyle therapy is still the cornerstone of how we should be managing patients. These medications are synergistic with lifestyle therapy. The best results are achieved when we combine lifestyle therapy with some of these medications.



Novel Approaches in CKM Syndrome

We talked about some of the existing drugs that are available to us including GLP-1 receptor and the SGLT2 inhibitors. There is a new class of drugs that are in late-stage clinical trials, the aldosterone synthase inhibitors, also called ASIs. Again, this is really just incredible drug development and elegant drug development because what the ASIs are doing is they are acting on that renin- angiotensin aldosterone pathway, but just at a different place and so you're targeting aldosterone synthesis in multiple ways. You can work on RAS inhibition, but now you can also impact aldosterone synthesis.

Matt had mentioned earlier that now we're learning a lot more about where aldosterone is synthesized, and in many people it's outside of the kidneys in places like ectopic fat. Having just ACE inhibitors and ARVs isn't enough to really knock out this pathway, and this is where having another drug class, such as the ASIs, can be very helpful.

We have multiple ASIs now in clinical trials. One of them is Baxdrostat, and there is actually now a study that is just started where they're looking at the combination of baxdrostat with an SGLT2 to prevent heart failure. It's called the Prevent Heart Failure Trial. These drugs are also being studied for refractory hypertension, so lorundrostat is another one. Then another drug that's also being looked at, and Jennifer is involved in this trial, and that's with the Vicadrostat in combination with SGLT2 inhibitors for kidney protection.

Dr. Weir: I think it's interesting, Pam, because whether or not targeting aldosterone synthase may incrementally target aldosterone made not only in the adrenal gland, but in ectopic, nasty, visceral adipose tissue is, I think, a very interesting question. Of course, the other intriguing area is potentially having better tolerability without any endocrine side effects, and also less of a change in the serum potassium. I think all of these are potential opportunities that are being gauged.

I've been using traditional MRAs for more than 20 years to suppress proteinuria in my patients with diabetes and chronic kidney disease, and we even have data that we just published a couple of months ago in circulation showing in humans that you can prevent progression of atheroma in humans with MR blockade over just a period of one year compared to placebo. I think there are some interesting opportunities here, and to be able to expand this into clinical practice, I think, is going to be very important.

Dr. Shubrook: We have not only multiple treatments available today, but newer and easier-to-use treatments potentially coming. Let's just start with SGLT2. Who's going to start them? Where does it fit best? When do we start them?

Dr. Taub: I said this very early on after EMPA-REG outcome trial results came out. It's whoever sees the patient first. It's whether it's the primary care provider, whether it's our nurse practitioners, PAs, whether it's the cardiologist, the endocrinologist, because for a lot of these indications, timing is essential, especially in our patients with heart failure. We've seen, especially in EMPA-REG outcome, that very early separation of the curves. The earlier you start these agents, the more impact you're going to have in preventing, for instance, a future heart failure readmission.

Dr. Weir: I think, quite honestly, as a nephrologist or nephrocardiologist, I was very entranced by the early observations, which was later confirmed in many large-scale clinical trials. Pam, I think the biggest issue is the fact that many people felt uncomfortable in starting these therapies.

There were a number of reports about your appendages falling off, diabetic ketoacidosis, bone fracture, all this stuff, which was very minor. UTI, minor stuff, and then suddenly all of these impacts on heart failure, kidney disease progression. I think it slowed the uptake quite a bit. I know that Jennifer, as an endocrinologist, you've been using these drugs ahead of the curve, so to speak. In large part now, I think it's going to have to start to change in order to expand the opportunity for many people to receive these drugs.

Dr. Green: I think that's true. I think the optimal use would be to use them early and often. When I'm reviewing my patients' medication lists, I think of the SGLT2 inhibitors in the same way that I think about statin therapy at this point. It's like, if those drugs are not a component of the regimen that I'm prescribing for them, there needs to be a very clear explanation in the medical record why the person is not taking it. I know that that is not the usual approach that most people taking care of patients with diabetes take, that they may not be thinking about it as such an effective and meaningful intervention. We're going to get there. We need to get there.

Dr. Shubrook: There was a day, a few days ago, where ACE inhibitors were kidney drugs, and now they're just medications we all use. Are we at the point where these four pillars are medications that we would all use and we shouldn't call them diabetes-related agents or kidney-related agents?

Dr. Green: That is certainly what the KDIGO guidelines would indicate, yes.

Dr. Weir: I would say this, though. if you look at, again, the medical comorbidity-driving decision-making, we do know that ACE inhibitors and MRA do not treat diabetes, but we know SGLT2 inhibitors, if you have decent kidney function, and certainly the GLP-1 RA regardless of the amount of kidney function are very effective for diabetes. I think all of them, as part of a better blood pressure, cholesterol, glucose-lowering approach can obviously modify a lot of the risk. I think what impresses me most clinically is the modification of heart failure risk with the SGLT2 inhibitors.

Dr. Shubrook: Absolutely. All right, so we're going to move to the fourth section.

[VIDEO]

Nephrology: We had a minor disagreement.

Dr. Glaucomflecken: A minor disagreement? The cardiologist is covered in saline.

Nephrology: How do you know it was me? Could have been anybody.

Dr. Glaucomflecken: Nephrology, witnesses heard you shout, "diuresis this," before entering an entire liter of hypertonic saline on his head.

Cardiology: It was completely immature.

Dr. Glaucomflecken: Cardiology, how did you respond?

Cardiology: Well, I--

Dr. Glaucomflecken: You held him down and drew a QRS complex on his forehead. Nephrology, remove your hat. This is more than just a minor disagreement.

Cardiology: Well, I made it low amplitude.

Dr. Glaucomflecken: This is a pattern of immature behavior between the two of you.

Nephrology: Come on, Doc. It's not that serious.

Dr. Glaucomflecken: Oh, really? Last week, you had an argument about cardiorenal syndrome that nearly went to fisticuffs.

Cardiology Oh, you mean renal cardiac syndrome.

Nephrology: It was the heart's fault, and you know it.

Cardiology: No way. It's always the kidneys.

Nephrology: The kidneys are perfect.

Cardiology: Oh, is that why you need a backup kidney? Because the first one's so good.

Nephrology: Maybe evolution loved the kidneys so much, it made another one.

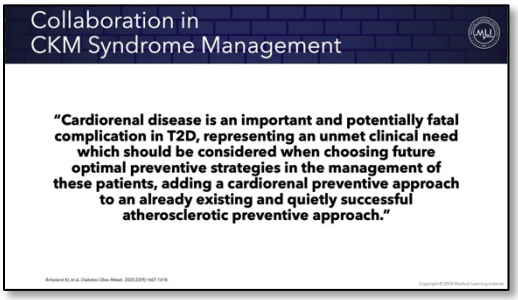
Cardiology: Evolution doesn't work that way.

Nephrology: Darwin was a nephrologist, and you know it.

Dr. Shubrook: All right.

Dr. Taub: If I drew an EKG on your forehead, I would do it with a peaked T-wave. See, so we can get along.

Dr. Weir: Absolutely, Pam.



Collaboration in CKM Syndrome Management

Dr. Shubrook: It really highlights the need that we're going to have to work as a team. I think this is more important than ever. As we think about this, what are some actions we can take? I think that's Jennifer.

Dr. Green: Well, I would say we need to move away from this traditional concept that we all have participated in. Treating risk management is kind of a hot potato that gets tossed around to the next doctor because maybe there's not enough time to talk about it at that day's visit. Risk reduction is a shared responsibility. None of us can avoid or should avoid thinking about and intervening appropriately to improve outcomes in our patients.

Dr. Weir: I think what I like to explain to my patients is that you get one spin in life, and you want to be ahead of the curve, so to speak. You want to be proactive in preventing vascular disease progression, heart failure, things like that. I'll be honest with you. I love lifestyle modifications. I preach them myself to every patient. It's often hard to change, in your 40s, and 50s, and 60s, and 70s, which is now I define as middle youth. Often what we need are incremental opportunities.

I have so many patients that tell me, "No, I'm going to readopt and I'm going to be good, and I'll be healthy, and I won't eat bad food anymore." That's not realistic. I think we really need to educate, educate. Most people don't know if they have reduced kidney function. Most people don't know if they have microalbuminuria, they can measure blood pressure. I think education is going to be the most important part moving forward as we look to expand our armamentarium in preventing disease progression.

Dr. Green: Absolutely. It's just not practical to assume that everyone with the CKM syndrome is going to be able to see, in particular, a nephrologist. Nephrologists are so overworked in this country that they traditionally have focused a bit more on patients towards the end-stage kidney disease side of the spectrum. We've made a personal decision in our clinic that we're going to implement these medications for patients with kidney disease.

It does no one any good to defer to a different type of specialist to take these steps that are very, very clearly spelled out. Get comfortable adding, perhaps, these pillars that you've not been prescribing very often before. I think the field has moved very, very far ahead, and we need to be part of it.

Dr. Taub: The one thing that is really common to these pillars is that there's pleiotropic mechanisms with many of these agents. We really need to harness the pleiotropic mechanisms of these agents to give our patients a broad benefit in the management of CKM syndrome.

Dr. Green: Yes, and one of the ways to think about this, and I'm sorry to interrupt again, but it is that with, again, with the introduction of a single intervention, there's tremendous economy or efficiency, for example, of prescribing, which I know is very, very attractive, particularly in the primary care arena, to be able to touch or address multiple issues with the single intervention.

Dr. Weir: I think, again, given the fact, and let's be honest, we still don't know how all these drugs work. Yes, blood pressure, cholesterol, glucose, we can measure that. We can measure albuminuria going down. Since we still don't know, I still think we have to educate the patients as to why we're

doing what we're doing, why you need one more drug, what it might be able to do. This is what we're going to look at. The data is very supportive because patients need the education to understand the complexity of much of the medications that they require to prevent disease progression.

Dr. Shubrook: I love it. As we think about this, we do want to make sure that you give us your thoughts. We're going to ask you to scan one more time. This is an interactive thing. We want to hear from you what are the key components, the most critical considerations when working with patients with CKM. Please scan and give us your thoughts.

As we do that, and we'll want you to be scanning, how do we have that discussion with each other? I think one of the challenges is we all could have our discussion. We could be passionate, telling our patient, but how do we work in sync? I'll just go down the line.

Dr. Taub: I think communication is really important. This is where I think healthcare systems can play a really important role through things like the electronic medical record. I know that that's my primary way that I'm communicating with all the other specialists that are involved in a patient's care. In real-time, they're able to see some of the adjustments that I'm making. I think that's a really great tool to leverage so that we can all communicate well and do things in real-time.

Dr. Weir: I think, Jay, the critical issue of communication continues to be a problem despite the EMR, because not every hospital system, and there are systems now, there's not one hospital, talk to each other. I can tell you in Baltimore, Hopkins and Maryland speak with each other but Kaiser's separate, Lifebridge is separate, Ascension is separate. There has to be another way that we can do it without obviously breaking HIPAA, to be able to review laboratories, to respond to abnormalities, and to provide the necessary communication between the various care providers for different patients. It's not easy, but I think we have to make the effort to make it happen.

Dr. Green: I'm going to give a very concrete example. I work both at Duke and in the VA health system. Our hospital is right across the street. A number of years ago, as the guidelines started to change, I instituted an option that it's called a diabetes management quick consult. I'll be honest, most of the questions that I get are not about glucose management. They're about what interventions can I include in this patient's care that would be appropriate and indicated to improve their outcomes.

One of the things that I've really very much enjoyed from having been involved in this process from the outset is there used to be sort of a cohort of providers who would reach out to me with similar questions about, let's say, starting SGLT2 inhibitors. Over time, I don't get those same questions from that same cohort of doctors. They've learned, and by the time they're reaching out to me, their patient's care has progressed far further. We may want to think about reasonably efficient ways to communicate this information, because we all like to teach, and this is an opportunity to really distribute the information that we have in our heads a bit more widely into our health system or network.

Dr. Shubrook: It's going to take all of us to do this and to communicate and reach out, and I certainly love it in my clinic. It's 4:00 to 5:00 PM. I get this text from everybody. We're texting back and forth between specialists saying, "Hey, can we do this? Can we do this? Do you want to do that?" I think it really does require us, however that is in your system, to find a way to optimize that. You do see just a plethora of ideas here, and I think, again, this is an exciting time, and there's a lot we can do. It does

require us to, though, work as a team and recognize patients upstream. I can't advance to the next slide.

Okay, so I do want to take just a couple questions. You all did a great job. You did exactly what we asked for. We will be available afterwards, because we do want to make sure we stay on task for today. There was a comment about, I'd love to hear your opinions about steroidal versus non-steroidal MRAs, particularly with patients with CKM, given the price issues, where do we go?

Dr. Weir: I'll comment, because I've been an MRA user for many decades. I think the newer finerenone has hit the sweet spot in terms of providing risk reduction with only a modest change in serum potassium. I think that's probably the most important factor and advantage of it if you have a decent prescription plan. Clearly, targeting MRA is important for reducing blood pressure and albuminuria, and now we have the evidence for atherosclerotic outcomes and heart failure outcomes. I think that, to me, I don't know about the chemical stories and the binding and the duration. I just look at the actual data, which is far more important for me.

Dr. Green: I have a somewhat different perspective as an endocrinologist and an endocrinologist in the health care system that cares for primarily men. Traditionally in my practice, I've used spironolactone for the treatment of people with frank hyperaldosteronism and sometimes for resistant hypertension. I would tell you that the sexual or the steroidal side effects are real and a very significant barrier to use of that medication in a not trivial proportion of patients to whom I give the drug.

Dr. Shubrook: To stay on that theme, and we will get these answers, so come up to us afterwards, the newer agents that help the CKM syndrome for diabetes as well, GLP-1s and GLT-2s, are all so expensive. How do you help your patients get those? Anyone?

Dr. Weir: I torture my assistant to try to do as many PAs as she can after she finishes all my work.

Dr. Green: Well, the VA, I have to say, is very sensible in approving the use of these medications for higher-risk patients. That doesn't mean we're doing a good job at prescribing it, though. There was a study that looked at the proportion of patients receiving care at each VA in the United States receiving an SGLT2 inhibitor who had type 2 diabetes and established atherosclerotic cardiovascular disease.

In 2020, where SGLT2 inhibitors had been available for that indication readily for five years, only 19% of such patients were prescribed an SGLT2 inhibitor throughout the entire VA system. In some hospitals, essentially nobody was being prescribed them. Access is part of the problem, but if we don't think about it, then access becomes irrelevant.

Dr. Taub: I think this is where we really need to collaborate with our pharmacy colleagues. When I'm on the inpatient service, our pharmacists do an incredible job. For instance, there's multiple SGLT2 inhibitors, and there's a different price point depending on what insurance-- They'll identify for us, for this particular patient, this is going to be the cheapest option. They work on things such as copay cards and other resources to make these drugs as affordable as possible.

The GLP-1 receptor agonists are a different story. Most of the patients that I see as a cardiologist tend to have diabetes. Because I'm able to get it under that diabetes indication, even for the Medicare patients, I can get them. Apparently, there's going to be some incredible changes to Medicare starting

in 2025, where patients are going to be capped around $2,000 in terms of their max copay. That's going to make things a little bit better.

Dr. Shubrook: Just one hack, please put your diagnosis code in your SIG. In California, that has really helped me to get all of these medications covered, because they know what you're treating.

Dr. Green: That's what I was going to say.

Dr. Weir: I also have to explain to my patients why they have all these diseases so I can get their coverage and tests paid for. That's part of the education process.

Dr. Green: Absolutely. As an endocrinologist, I need to code for the fact that person has heart failure and has kidney disease. That's part of the big picture, and we need to communicate that when we're making requests for therapies.

Dr. Shubrook: Well, thank you all very much. This does bring us to the end of the series, Therapeutic Strategies for CKM syndrome. thank you very much for joining us today.