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## Comprehensive Management of Individuals with CKM Syndrome

### Dr. Vaduganathan:

I have the easy task of summarizing the management of this relatively nascent concept of cardio-kidney-metabolism.

Here are my disclosures.

I'd like to start by reframing some of our language. We often have discussed pillars of management, of heart failure, of kidney disease, of metabolic diseases, and that is a useful construct, especially in our high-risk patients that are at very high risk of near-term clinical events or death. However, in the broader population, we often think of this pyramid-type approach, where the foundation of our approach to clinical care really still relies on the same principles that we have known are important for cardiovascular and kidney health for decades, that is, diet, exercise, smoking cessation, weight management. Really, that foundation of lifestyle and self-management is always going to be our foundation when discussing this CKM syndrome.

On the other end of the spectrum are patients with overt disease manifestations. Those are people with already manifest cardiovascular disease, already manifest kidney diseases, or maybe even those with intersecting disease populations. In those patients, we may embrace a combination-type strategy in which we're trying to target multiple pathways. So what is the rationale for combination medical therapy? Each of these conditions that we just described are complex chronic conditions. They have disease pathways that are systemic. They rely on different mechanistic pathways for disease progression. As such, it's in keeping with that that individual therapies would be difficult to fully take care of the large amount of risk borne by this population. So combination therapies, simultaneously targeting these distinct pathways of disease progression, is likely our best approach to provide best patient outcomes.

This approach has been widely embraced in other therapeutic areas. For instance, in HIV or after acute myocardial infarction, even recently in chronic obstructive pulmonary disease, there's combination forms of inhalers. So this approach is common to our own medical practices, and I think our goal here is to share that in select high-risk patients, this combination of medical therapy approach should also be extended.

So what is the management of CKM? I want to freely admit CKM was a recently coined term introduced by the American Heart Association statement, and so we are, as a community, still understanding how to best manage this cohort of patients. As Professor Lam shared, CKM is really a cohort of disease entities that all of us see commonly in practice. We identify they have shared pathways, shared epidemiology, but until now, one person may be treated by a cardiologist, another by a nephrologist, another by an endocrinologist, and the vast majority by primary care physicians. And so we don't have a shared terminology, shared framework for how we should be approaching these patients.

So when looking at this progression of stage 0 to stage 4, I would argue that it's similar; we move up that pyramid as we move down with progression of stages. So stage 0 is really people free from CKM risk factors, especially when an individual is free from CKM risk factors later in life, that portends freedom from overt cardiovascular kidney events for a long, long duration of time, even their lifetime. So we must promote, as a central foundation, the maintenance of these cardiovascular health measures, especially early in life. There have been data here at this meeting, as well as prior, that even as early as childhood interventions in schools, for instance, can help promote cardiovascular health at an earlier stage and time point.

As we move down here to stage 1/2, here are going to be patients with perhaps one of these risk conditions earlier on, they're newly developing type 2 diabetes, they are overweight or obese, but without otherwise overt cardiovascular and kidney diseases. There, we are going to selectively use therapies that have been proven to be effective in these populations. Those include each of the elements that we're going to talk about as we move down, so renin-angiotensin system inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and the nonsteroidal MRA finerenone.

These are all individually shown in individual populations to be helpful to avert cardiovascular and kidney events.

And then finally, as we move down to patients with stage 3 and 4, these are patients with either clinically overt or subclinical disease. Here is where we're embracing that combination therapy approach. So let's take you through some of those foundational pillars, as we've discussed before. First is the renin-angiotensin system inhibitors. These, of course, are background therapies that are commonly used in many of these patients for various indications, often in the management of hypertension. But I'll remind you that these are foundational classes in the management of heart failure, for instance, a strong reduction in mortality in many trials. Furthermore, these were the foundational trials in diabetic kidney disease, now over 2 decades ago. So this should form a central pillar in CKM management in those especially with overt cardiovascular kidney disease.

SGLT2 inhibitors perhaps have the broadest range of evidence studied in the last decade and have been studied across these entities, including at various levels of intersection, whether individual dyads of conditions or all 3 of these conditions. And consistently, SGLT2 inhibitors have been proven to delay disease progression and avert deaths. So SGLT2 inhibitors today are indicated in people with type 2 diabetes for glycemic control, so that's earlier-stage CKM syndrome; patients with type 2 diabetes with cardiovascular disease or cardiovascular risk; patients with chronic kidney disease irrespective of their diabetes status, especially those with evidence of albuminuria, and identifying albuminuria at an earlier stage as an opportunity to treat; and then patients with heart failure across the spectrum of ejection fraction, including whether patients are presenting in the hospital setting or in the outpatient setting.

The GLP-1 receptor agonists are not new to medicine. They've been around for, now, 2 decades, and they're indicated in various populations. Of course, they have a foundational role in obesity management and weight reduction. They too are now indicated in a number of disease populations. They're indicated for the management of type 2 diabetes, again, with established cardiovascular disease, have also been studied in those with cardiovascular risk. They are indicated for the management of obesity, especially those with preexisting cardiovascular diseases. And they're indicated in the management of chronic kidney disease to delay disease progression when in the presence of concomitant type 2 diabetes.

The nonsteroidal MRA finerenone is the final pillar. This was studied in 2 large-scale trials of chronic kidney disease and concomitant type 2 diabetes under the umbrella called the FIDELITY program. These 2 trials showed that there was a reduction in both cardiovascular events and kidney events, and now finerenone is strongly recommended to join these other therapeutic options in those with high-risk kidney disease.

So I'd started by saying that some patients, those at highest risk for disease progression, are likely to benefit from combination therapeutic approaches. Unfortunately, today we don't have a single randomized clinical trial saying that 4 is better than 3 is better than 2 is better than 1. But what I can share with you is that these therapies have entirely distinct mechanisms of action. What I can share with you is that each of the individual trials that contributed the evidence for these pillars never showed attenuation of benefit based on what patients were already taking. And so, as such, in this forecasting study, we estimated what would be the effects if all these pillars in CKM management were combined. And in fact, you can see that there are large clinically relevant and truly disease-modifying effects across domains of cardiovascular events, kidney outcomes, and even mortality. So from the earliest stages of CKM where our focus should be on CV and kidney prevention, to those in the middle stages where we're introducing individual therapies based on selected indications, and finally, those with overt disease where their risk of progression is so high that we up front make the decision to start combination medical therapies, CKM is a syndrome across stages, and there are appropriate managed steps that we can institute in our own clinical practices, even today.

So thank you very much.