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Expert Perspectives on Nonsteroidal MRAs and Cardiorenal Protection

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Chapter 1

Dr. Vaduganathan:
Welcome, everyone. There were some very interesting data presented at this year's American College of Cardiology Conference in Chicago, and, today, we are going to discuss some perspectives on the potential clinical implications of 6 particular analyses and presentations, as well as discussing patients who may benefit the most from these modern therapies.

This is CME on PACE-CME and ReachMD, and my name is Dr. Muthu Vaduganathan from the Brigham and Women's Hospital and Harvard Medical School.

Dr. Lala-Trindade:
And I'm Anu Lala, a heart function cardiologist at Mount Sinai Fuster Heart Hospital in New York, New York.

Dr. Neuen:
And I'm Brendon Neuen. I'm a nephrologist from Sydney, Australia, at Royal North Shore Hospital and the George Institute for Global Health.

Dr. Vaduganathan:
A delight to be joined by both of you, and thank you, friends. I look forward to this discussion.

So FINEARTS-Heart Failure, as a reminder, was a large-scale global, randomized clinical trial of the nonsteroidal MRA, or mineralocorticoid receptor antagonist, finerenone compared with placebo on worsening heart failure events and cardiovascular death. And this trial specifically enrolled patients with symptomatic heart failure and a left ventricular ejection fraction equal to or greater than 40%. And, as a reminder, this encompassed both the mildly reduced and preserved ejection fraction cohorts and patients who had improved ejection fraction—previous reduced EF—who had improved over time with either medical therapy or time were also allowed to be included in this trial.

So this specific analysis, the first analysis we'll discuss, examines the mode of death patterns. This is really important because mode of death was specifically adjudicated in this randomized clinical trial, and understanding how these patients, how patients with HFpEF die, is something that we are only growing to appreciate in recent years.

So in the 6,001 individuals enrolled in the FINEARTS-Heart Failure trial, mode of death greatly varied by baseline left ventricular ejection fraction. Ejection fraction modified the risk of death such that people died at a much greater frequency at lower ejection

fractions, and there were a greater proportion of patients who died from cardiovascular causes at that lower ejection fraction range. Specific modes of death include sudden death and worsening heart failure, especially in this mildly reduced EF category. And as the EF is higher, there are greater proportions of non-cardiovascular causes of death, and this pattern of death was actually consistent even in that cohort of patients with heart failure with improved ejection fraction.

Finerenone did not modify the overall rates of death, all-cause mortality, or specific causes of death in this trial. But, as a reminder, these trials weren't specifically powered for mortality effects; they were powered for the composite of heart failure events and cardiovascular death.

So this, in my opinion, is an important advance in our understanding of how patients with HFpEF die, including some of these interesting other cohorts like mildly reduced EF and improved ejection fraction. We also learn a bit about finerenone's effect, but as a reminder, finerenone is not yet approved for this indication of HFpEF or heart failure with mildly reduced ejection fraction, and the FDA has granted it priority designation, so we should learn more in the latter half of 2025 about its approval process.

So, Dr. Lala, I'm very curious, especially from your perspective as a practicing heart failure cardiologist, what are the potential clinical implications of these data?

Dr. Lala-Trindade:
Thanks, Muthu. It's so good to be here with you. You know, I think that heart failure with preserved ejection fraction and mildly reduced ejection fraction just represents such a significant and growing burden, not only in cardiovascular medicine, but I would say across the spectrum of disease globally. But what's interesting about them, before we get into the specifics of this analysis, is that these syndromes exist in the broader context of cardio-renal-metabolic syndrome where diabetes, chronic kidney disease, and cardiovascular dysfunction or abnormalities intersect to really amplify systemic inflammation, vascular stiffness, and volume overload, just as 3 major hallmarks. But unlike heart failure with reduced ejection fraction, heart failure with preserved ejection fraction and mildly reduced ejection fraction have historically been limited with respect to therapies that are effective.

But part of the challenge, I think, lies in their heterogeneous pathophysiology. While patients may appear clinically stable, they're still at extremely high risk for progressive renal disease or decline, recurrent hospitalizations, and death. Often, or we at least we thought—and this is why this study is so informative—from sudden cardiac death or pump failure. It's in keeping with our conventional understanding that those patients with mildly reduced ejection fraction had more of that cardiovascular death, as you alluded to.

But what I think is so important, and what I'm excited about in our field more broadly, is the fact that CKM syndrome emphasizes that heart failure is not a disease of the heart alone. Metabolic derangements, renal dysfunction, neurohormonal activation, particularly of the mineralocorticoid receptor pathway, really contribute to disease progression in a way that traditional therapies have failed to fully address. And I just love the fact that we're finally recognizing the fact that these are full-body system issues that require recognition of systemic processes, which is why it's so great to be discussing these data with a nephrologist as well.

I think one thing to really bear in mind is the fact that we know that steroidal mineralocorticoid receptor antagonists, or MRAs, are very effective—spironolactone, eplerenone—in heart failure with reduced ejection fraction. Some controversial data in heart failure with preserved ejection fraction. But importantly, with these steroidal MRAs, they also engage off-target steroid receptors. And this leads to side effects like gynecomastia, and even potentially potentiating hyperkalemia.

Finerenone, on the other hand, as you already mentioned, is a nonsteroidal MRA, so it's more selective, and it also has the potential benefit of reducing inflammation and fibrosis that might be distinct. There also tends to be a lower incidence of hyperkalemia. And I think, importantly, we shouldn't see significant sex hormone-related adverse effects.

Still, I think therapeutic gaps remain. Guidelines still offer limited directed options for heart failure with preserved ejection fraction and mildly reduced ejection fraction, especially in patients with overlapping renal and metabolic disease. And so it's an exciting period of time. I think our understanding is expanding, and I look forward to hearing some of the other analyses you have for us.

Dr. Vaduganathan:
Terrific perspectives. Thank you so much. I think the data from the FINEARTS-Heart Failure trial have also informed some of the implementation of this therapy in clinical practice. You have nicely highlighted some of the guideline limitations currently in HFpEF and heart failure with mildly reduced ejection fraction, but there has been an increasing emphasis on the implementation of these therapies in patients during hospitalization or during a worsening heart failure event. And FINEARTS-Heart Failure was a pretty unique trial in that it allowed enrollment irrespective of the patient setting, whether they were hospitalized or recently hospitalized or in the outpatient setting. And so there was another analysis that was presented at or around the time of the ACC, in which finerenone was studied in those individuals who had recent worsening heart failure. They were either randomized and started on these therapies at the time of

hospitalization, or shortly thereafter. And, in fact, we found that the benefits of this therapy were not only consistent, but the safety profile was also maintained even when these therapies were initiated during hospitalization, during the high-risk period around the time of acute heart failure. This allows the broadening of this therapy, not only in chronic ambulatory care that we're used to, but also during the captured time frame of hospitalization.

There was another analysis from the FINEARTS-Heart Failure trial that examined the effect of finerenone on outpatient worsening heart failure, so the corollary among the many patients we meet in the chronic ambulatory setting. And, in fact, there was a reduction in not only worsening heart failure events, but also those more subtle changes of worsening heart failure, those that required outpatient diuretic intensification, for instance. And finerenone consistently reduced those outpatient events. So it does seem that a therapy like finerenone has operative effects in acute heart failure, in the high-risk window after hospitalization, the so-called vulnerable phase, and in the chronic heart failure setting where subtle worsening heart failure is also prevented and delayed.

So I'm very excited for Chapter 2. We'll focus on many other additional analyses, including looking at which patients may benefit more from a therapy like finerenone.

Chapter 2

Dr. Vaduganathan:
So, excellent. We'll move forward with Chapter 2, which focuses on 3 important analyses from the FINEARTS-Heart Failure trial, looking at important subgroups in this overall trial population and examining how finerenone's effects, whether efficacy or safety, vary across these subgroups.

The first was New York Heart Association classification, NYHA classification. It continues to be the way that physicians, clinicians, assess functional status among patients with heart failure. And FINEARTS-Heart Failure enrolled patients with NYHA class II, III, and IV functional class, and patients had a broad representation of functional class at baseline.

Finerenone's efficacy and safety were maintained irrespective of whether they had mild, moderate, or severe limitations in their daily activities. And importantly, this showed that the absolute treatment benefits were in fact greater in that higher-risk population with greater functional limitations at baseline. Both the placebo and finerenone arms experienced improvements in NYHA classification over time during the course of the trial, through 12 months of therapy, without a difference.

The second key analysis was related to NT-proBNP. NT-proBNP continues to be the biomarker with the greatest discrimination that we have available to us in clinical practice in heart failure care and has the most prognostic significance. So understanding how a therapy behaves and the interplay of the therapy with that biomarker is of great importance. FINEARTS-Heart Failure enrolled individuals who are at high risk for disease progression. They had elevated NT-proBNPs at baseline. But finerenone's efficacy and safety were maintained irrespective of baseline NT-proBNP levels. And importantly, during the course of the trial, there was about a 10% to 15% reduction in NT-proBNP levels with the therapy, with finerenone, compared with placebo.

And then finally, the third specific analysis was related to kidney risk. Patients in the FINEARTS-Heart Failure trial were enrolled across a broad range of kidney risk, as defined by the KDIGO risk classification. And I'm going to ask our colleague Brendon Neuen to discuss that a bit further, but importantly, the benefits of finerenone were seen even in low-, moderate-, or high-risk or very-high-risk individuals for kidney disease progression. And that was, importantly, the safety. While risks like hyperkalemia were higher in those with more advanced or higher risk kidney disease, that treatment differential was actually consistent with finerenone versus placebo.

So lots of new information about functional status, biomarkers, and kidney risk as a way to risk stratify and subgroup patients with HFpEF. I'm curious. First, perhaps, Dr. Lala, you can start us off as a practicing heart failure clinician. What do you think some of the practical considerations are, especially to a pretty broad risk population like those we've managed with HFpEF in practice?

Dr. Lala-Trindade:
Yes, so interesting. Thanks so much, Muthu. I think I'll comment on the first 2 analyses and then leave the expert nephrologist amongst us to comment on the renal disease one that you mentioned. But what I think is, is the first two that you mentioned are actually kind of complementary in terms of how I interpret their clinical value in practice in that it shows us that the safety profile of finerenone was not modified by baseline functional status, which is important. And it supports overall the use of finerenone in symptomatic individuals regardless of their functional status. So why I think that's important is, typically we feel like, okay, those patients with the most severe symptoms, perhaps they're at the highest risk, and maybe there's more trepidation typically in clinical practice for initiating a new therapy because there's more fear of having an adverse event as a result of that new therapy.

But what these analyses show and support is that finerenone was effective regardless of baseline functional status, and NT-proBNP for that matter, but, in fact, seem to be more effective in those patients with a worse baseline functional status, so the NYHA class III and IV

patients, as well as those patients with higher NT-proBNP levels. But overall, I think this is just—and this is in keeping with many of the other therapies, especially along the CKM syndrome—which is that those patients who are the sickest seem to benefit the most, even though those are the patients we're most nervous about initiating new therapies in.

Dr. Vaduganathan:
For those just tuning in, you're listening to CME on PACE-CME and ReachMD. My name is Muthu Vaduganathan, and here with me are Dr. Lala and Dr. Neuen. And we're discussing some key findings that were just presented at the 2025 American College of Cardiology Conference and giving you perspectives about the potential clinical implications about who may benefit from modern therapies that affect the cardio-kidney-metabolic spectrum.

Fantastic. And we had started by sharing that finerenone was still under regulatory evaluation for the management of HFpEF, but finerenone has been in widespread use for the management of chronic kidney disease in the context of type 2 diabetes.

And so, Dr. Neuen, I'm curious. How does this come together, these new data from FINEARTS, with a kidney lens? How does that actually come together with your own clinical use and clinical experience with finerenone in patients with chronic kidney disease?

Dr. Neuen:
Well, thanks, Dr. Vaduganathan. I think it's great to be here discussing this with you. And I think this is a really important trial from a kidney perspective, from a nephrologist perspective, for 3 key reasons. The first one you've articulated, which is that finerenone is already approved for reducing kidney disease progression in people with type 2 diabetes, so we're already using this agent in practice. The second thing is that in patients with CKD, the predominant form of heart failure is heart failure with preserved ejection fraction. We see that much more frequently than heart failure with reduced ejection fraction. And the third point is that FINEARTS-HF enrolled about half of patients with a GFR less than 60 and also collected information on albuminuria. And that is really important because it gives us information about not only efficacy, but safety of this agent across the spectrum of kidney function and kidney risk.

Now, in nephrology, the way we think about risk is by using both glomerular filtration rate, or GFR, but also albuminuria, and many heart failure trials have not collected data on albuminuria. And albuminuria, as measured by the urinary albumin-to-creatinine ratio, gives you additional really important prognostic information, not only from the kidney failure perspective, but also from a heart failure perspective. And both those 2 biomarkers are multiplicative in terms of their risk.

Now, when we look at the KDIGO classification of kidney disease, it classifies people based on both GFR and albuminuria into low-, moderate-, high-, and very-high-risk categories, and FINEARTS enrolled people across the whole spectrum of risk. About a third in low-, moderate-, high-, or very-high-risk categories. And what you can see in the trial results is exactly what you would expect. People at higher KDIGO risk categories were at higher risk of heart failure events. But the effect of finerenone was consistent across all of those risk categories.

Part of our trepidation in using steroidal MRAs in patients with advanced CKD, in particular, is because there has been little evidence and we have concerns about safety, particularly from a hyperkalemia perspective. So it's very reassuring to see that safety was consistent across the whole spectrum of kidney risk. And I think that will engender a lot of confidence amongst my colleagues in using finerenone in patients with heart failure and chronic kidney disease.

Dr. Vaduganathan:
So increasingly in 2025, we're seeing that the same therapies that are indicated for one of these disease states, like chronic kidney disease, are actually going to be, or may be indicated for heart failure with preserved ejection fraction. But how do these therapies work together, and can they actually be effectively combined in an individual patient? And I think that is a question that often clinicians may wonder about and may ask.

And so, Brendon, how do you answer that?

Dr. Neuen:
I think this is a really good point that Dr. Lala initially highlighted, which is that we've known for a long time that there are pathophysiological overlaps between heart failure and kidney disease. But now we also have therapeutic overlaps with agents like finerenone improving heart failure and kidney disease outcomes, we have SGLT2 inhibitors that improve kidney and heart failure outcomes and increasing evidence with other therapeutic agents as well.

So it begs the question of how we're going to use these agents in combination. Certainly, from a kidney perspective, we realize increasingly that albuminuria is an important marker of residual risk, much in the way like the LDL cholesterol is a marker of residual risk for atherosclerotic cardiovascular disease. And using albuminuria to guide the initiation of combination therapies is going to be increasingly important.

Now, as you know, Dr. Vaduganathan, the CONFIDENCE trial will be reported, and that is evaluating in about 800 patients with type 2 diabetes and albuminuria, the initiation of empagliflozin, an SGLT2 inhibitor, finerenone, or both simultaneously. And whilst that approach of a rapid initiation of therapy and heart failure has been practiced and is recommended, we don't really have that evidence yet in kidney disease, so that's going to be a really important trial. And better understanding who is at most risk for which outcomes is going to be important so that we can really tailor who requires combination or combination therapies compared to individual agents alone.

Dr. Vaduganathan:
And a quick follow-up, Brendon, because I'm greedy and because you are here. Much of the data, at least my understanding of much of the data with the chronic kidney disease benefits are in patients with concomitant type 2 diabetes. But the world of CKD is quite a bit broader, and there are many individuals with nondiabetic drivers of kidney disease. So do we know anything about finerenone's effects in that growing population?

Dr. Neuen:
Yeah, it's a really important question because, whilst diabetic kidney disease is the single most common cause of kidney failure worldwide, in actual fact, there are more people with kidney disease who do not have diabetes than people with diabetic kidney disease. And so in the FINEARTS-HF trial, there were many patients who did not have diabetes, about half of the patients, and we see reductions in albuminuria in FINEARTS-HF, which is a promising sign for kidney protection. But what we really need is evidence from a dedicated kidney outcome trial that finerenone can reduce kidney disease progression in people with nondiabetic kidney disease.

That evidence is forthcoming in the FIND-CKD trial. That trial is enrolling approximately 1,600 individuals with proteinuric CKD, a large proportion of whom have glomerular diseases, like IgA nephropathy, FSGS, and other kidney diseases. And the primary outcome of that study is change in kidney function over 3 years, or total GFR slope over 3 years. That trial, we are awaiting the results of with great anticipation. And if the results are as we hope them to be, then the potential indications for finerenone may expand from diabetic kidney disease to nondiabetic kidney disea

Chapter 3

Dr. Vaduganathan:
In Chapter 3, we explore 2 final presentations from the American College of Cardiology meeting that focus on atrial fibrillation. And these are very complementary analyses. The first was examining baseline atrial fibrillation status in the FINEARTS-Heart Failure trial and showed that the efficacy and safety of finerenone were consistent irrespective of the type of atrial fibrillation, whether patients had paroxysmal, persistent, or permanent forms of atrial fibrillation, and importantly, atrial fibrillation was again demonstrated to be really a dominant comorbidity in this patient population of HFpEF.

The second key analysis related to atrial fibrillation was examining the new-onset atrial fibrillation. So, amongst the about 60% of individuals who don't have atrial fibrillation in these trials, examining does a therapy like finerenone actually modify the incidence of atrial fibrillation in trial follow-up.

To explore this in an in-depth setting across the cardio-kidney-metabolic, or CKM, spectrum, this particular analysis pooled data from the FINEARTS-Heart Failure trial, which we've been discussing, with the 2 preceding chronic kidney disease trials. That's the FIDELIO-DKD and FIGARO-DKD trials. So in total, this encompassed a large spectrum of the disease population and found that finerenone reduced the risk of new-onset atrial fibrillation or atrial flutter by about 18%, and this was durable throughout the duration of follow-up.

So these analyses, I think, explore a key dimension of CKM health, and that's atrial fibrillation. Something, at least that I'm aware of, we've had few tools to actually prevent the new onset of this important comorbidity.

And so, Dr. Lala, I'm very, very curious about your perspectives and specifically about do patients actually think about atrial fibrillation? Do they talk about atrial fibrillation when they're trying to manage their own heart failure status?

Dr. Lala-Trindade:
Yeah, Muthu, I think that these are very exciting analyses for a number of reasons. One might initially look at them and say, okay, well, finerenone seemed to work across the spectrum of whether one had AF, paroxysmal AF, or persistent AF. And maybe that's not necessarily as exciting up front, but what we actually see is, again, a consistent message across all these analyses, which is that there seem to be consistent benefit across various subgroups.

Now, what I like so much about what you presented, particularly in the second analysis, which was pooled across the studies of finerenone, which is really this focus on prevention, right? We know that up to 40% of patients with heart failure with preserved ejection fraction have concomitant atrial fibrillation. It underscores the importance of preventing downstream effects and downstream consequences of cardio-kidney-metabolic syndrome. And so while I can't say this definitively of course—these are sub-analyses—I think

what we see as a result of these is the fact that finerenone seems to hold promise with respect to reducing new-onset atrial fibrillation. So really kind of moving things back a few steps and talking about prevention as opposed to only treating disease once it's already present.

And so, this is again, I'm super excited about this space because not only are we recognizing the systemic nature of heart failure with preserved ejection fraction and mildly reduced ejection fraction broadly, but we're also moving upstream to try and prevent consequences of advanced CKM syndrome. So I think that these data are quite promising, and it certainly lends additional evidence and confidence in using them in clinical practice.

Dr. Vaduganathan:
I share those perspectives. And, Dr. Neuen, atrial fibrillation is probably one of the most common if not the most common reason that cardiologists are consulted and streams of referral in current clinical care. Do nephrologists think about atrial fibrillation? Is this an important entity?

Dr. Neuen:
Yeah, we do, Dr. Vaduganathan, you won't be surprised to hear. And this is a really tricky problem for us, and it's tricky for a couple of reasons. First, it's common. We see so much subclinical cardiovascular disease, heart failure; atrial fibrillation goes hand-in-hand with that.

The other reason that some might not appreciate why this is such a wicked problem for us is because rates of thrombosis but also bleeding increase as kidney function declines. And you get to advanced CKD and we have very little to no evidence with the direct oral anticoagulants, and we don't even know whether anticoagulation is beneficial in end-stage kidney disease or harmful. So this is a problem with not a lot of clear solutions for us, particularly in advanced CKD. And therapies that can reduce the incidence of atrial fibrillation, preserve kidney function, and reduce heart failure events, that's kind of what everyone wants to see in nephrology. A therapy that can target all of these aspects speaks to something that addresses underlying, common, shared pathophysiological mechanisms that we keep talking about. And I think that's the real attraction for patients and clinicians here. This is a very, very difficult problem for us in day-to-day practice.

Dr. Vaduganathan:
Thank you. Thank you, Brendon.

Dr. Lala, do you think patients are amenable to broader prevention, prevention of heart failure, prevention of atrial fibrillation, with therapies like finerenone?

Dr. Lala-Trindade:
I think there's certainly a desire to shift our framework within which we are talking to patients. Not only from patients, but I would also say potentially from referring physicians and our colleagues who oftentimes only refer to heart failure cardiologists when it's “too late,” or patients are too far along the spectrum of CKM disease. And so the more we can think about doing things earlier on, the better we all will be for it.

Dr. Vaduganathan:
Fantastic. This has been such a delightful conversation with friends on a topic that I think we all have shared interests in. And I'd like to just quickly go around and ask for any final perspectives, maybe take-home messages, from these data.

To me, this brings exactly what we have here, together. I think it brings our fields together. And data from FINEARTS-Heart Failure not only teaches us about the epidemiology of diseases that have been difficult to treat, difficult to manage, like HFpEF, but also remind us that many of these therapies that we're studying are not to be siloed in specific disease states but may have broader effects on the system as a whole, on patients, and might actually help multisystem effects that can be embraced not only by cardiologists but by people across the aisle at nephrology, endocrinology, primary care. And hopefully, we move from heart failure to heart function to prevention as we move and shift these disease processes forward.

So I'd love both of your perspectives, as well. Maybe, Dr. Lala, we could start with you?

Dr. Lala-Trindade:
Sure. We are speaking the same language, for sure. I think, just to reiterate the two, perhaps, take-home points for me are the fact that CKM syndrome emphasizes the fact that heart failure is not just a disease of the heart. We've forgotten the systemic nature of diseases like HFpEF, whereby there is tremendous systemic inflammation, vascular stiffness, volume overload, all the things that we've spoken about. That's number one, is recognizing that this is a whole-body issue.

And number two, I think we've already talked a little bit about, is the fact that we're now moving beyond just treatment of end-stage

disease, rather to think about how we can prevent some downstream effects of CKM syndrome, not just on the heart or cardiovascular system, but also on the kidneys and otherwise. So I think it's a very exciting time for us in general and I think FINEARTS was a really exciting move in the right direction for us to further understand this issue.

Dr. Vaduganathan:
Excellent. Dr. Neuen?

Dr. Neuen:
Thanks, Dr. Vaduganathan. So I think in many ways, CKD and HFpEF are very similar. Very few therapeutic options for a long time and now tremendous therapeutic progress in the last few years. And now with multiple therapies emerging, the key thing that we'll need to do now is to align care with risk. Who are those high-risk individuals who benefit from combination therapy? Can we implement combination therapy faster for those high-risk individuals and focus on high-value prescribing so that we address simultaneously issues like polypharmacy and quality of life?

Implementation of these data are going to be the next challenge, and this is really something that we need to work on as communities: nephrology, cardiology, primary care.

Dr. Vaduganathan:
Thank you for those closing remarks, and that's all the time we have today. So I'd like to thank our audience for listening, and of course, I'd like to thank my distinguished colleagues, Dr. Lala, Dr. Neuen, for joining me and sharing their valuable insights and expertise. It was great to speak with you today.

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