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

New Horizons: Unraveling Novel Therapies for Enhanced Cardiovascular Outcomes in Patients With Heart Failure

Announcer:
Welcome to CME on ReachMD. This activity, titled “New Horizons: Unraveling Novel Therapies for Enhanced Cardiovascular Outcomes in Patients With Heart Failure” is provided by Medcon International.

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Chapter 1

Dr. Lam:
Hello and welcome to this educational series. We have 3 chapters, beginning with this first chapter where we will explore the molecular mechanisms underlying mineralocorticoid receptor-mediated cardiac and kidney dysfunction.

This is CME on ReachMD, and I'm Dr. Carolyn Lam.

Dr. Kosiborod:
And I'm Mikhail Kosiborod from Kansas City, United States.

Dr. Solomon:
And I'm Scott Solomon from Harvard Medical School, Brigham and Women's Hospital in Boston.

Dr. Lam:
That’s so great. Thanks again, both Scott and Mikhail. I'm so thrilled to be here with you. Please, let's start from the basics, mineralocorticoid receptors in the heart and kidney. What do we think they're actually doing that makes heart failure worse?

Mikhail, you want to start us off?

Dr. Kosiborod:
Sure. Well, I think, Carolyn, we have some reasonable ideas about what MRAs do in the heart, especially when it comes to patients that have heart failure, especially in heart failure with reduced to ejection fraction. We, of course, have done a lot of work in that space in the past several decades. And as the clinical trials that have been done in patients with heart failure and reduced ejection fraction with steroidal MRAs like spironolactone and eplerenone were done predicated on the notion that this type of heart failure is a neurohormonal disease, and activation of renin-angiotensin-aldosterone system is critical to the development of progression of this type of heart failure and that inhibition of mineralocorticoid receptor, or antagonism of that receptor is going to have additional benefits, because it interferes with that neurohormonal axis that we believe is really, really important in the progression of heart failure with reduced ejection fraction. And in fact, that hypothesis was proven to be correct in multiple trials, including the RALES and EMPHASIS Heart Failure, and also in EPHESUS trial with eplerenone which really was more of a post-MI heart failure prevention trial.

So the benefits were, in fact, very large and included both reductions in death, one of the most potent reductions in cardiovascular

death we've seen with any agent in heart failure with reduced EF, and also reductions, very potent reductions in heart failure hospitalization. So, and I think given the timeline, if you will, of the benefit, that neurohormonal effect, which appears to be pretty quick and probably prevents, in some ways, direct toxicity of MRA activation on the myocardium in addition to neurohormonal effects, probably plays a significant role.

Now, our understanding of MRAs and different type of MRAs have since evolved. We now have nonsteroidal MRAs that have some important differences from kind of our older steroidal MRAs like spironolactone, so finerenone being a great example of nonsteroidal MRAs that's now used in many countries for prevention of diabetes-related kidney disease progression.

And the differences between nonsteroidal and steroidal MRAs have partly to do with selectivity for mineralocorticoid receptor, which is high for a nonsteroidal MRA like finerenone and less so for steroidal MRAs. There are some differences in potency, which is higher for finerenone and spironolactone, for example, than it is eplerenone. But potentially of importance, it's also the tissue distribution of heart versus kidney, which tends to be more balanced with finerenone than it is for steroidal MRAs. And that may have also something to do with the mechanisms as well.

We can obviously talk about the evidence we now have with finerenone, both in kidney disease progression and also in heart failure, but at least, I think, one of the theories about how nonsteroidal MRAs may add to some of the potential effects we've previously observed with steroidal MRAs is through inhibition of MR receptor. At least with this mechanism, you may potentially have effects on inflammation and the fibrosis as well. I think that's at least what we think may be happening here in addition to the neurohormonal effects and potentially direct effects. These things can be somewhat more difficult to really nail down and prove, but I think, like with most medications that we use in people with kidney disease and heart failure, the true answer probably is that it's more than one mechanism that's probably responsible for the benefits that we see.

Dr. Lam:
Right. Wow, Mikhail, so thank you. You've covered a lot from talking about mineralocorticoid receptor antagonists in general, the data that convinced us they're definitely doing something worthwhile in HFrEF at least, and then covering sort of moving from steroidal to nonsteroidal MRAs.

Scott, though, can I have your thoughts? We tend to associate their mechanisms of action, how are they working, with fibrosis, inflammation. Do you think that's the main action? And where do you think the gaps are?

Dr. Solomon:
No, as Mikhail said, we clearly don't know all the answers here. We're learning still about why these drugs are effective, but let's think about all the different things that they do. First and foremost, they block aldosterone receptor, and that, I think, happens very quickly when you give these drugs, and the hemodynamic effects happen quite quickly. And we can tell, because when we look at the trials, we can see changes that occur very, very quickly, way too fast for fibrosis and inflammation, which we know are affected by MRAs. It was 50 years ago about when Hans Selye showed that aldosterone caused fibrosis in the heart and the kidney. But that happens over a relatively long period of time. In the short term, this is blocking the effects of renin-angiotensin system activation, which, as Mikhail just mentioned, is happening in patients with heart failure as a compensatory mechanism.

Now it's interesting, though, because these drugs have other things that they do. I mean, one of the things that we know MRAs do is raise potassium, and we worry about that sometimes, maybe too much, and hopefully we'll talk a little bit about that. But possibly the elevation of potassium also accounts for some of the benefits that we've seen, certainly in HFrEF where we know that, for example, sudden death is a big problem, and patients with low potassium are at increased risk in sudden death. So we've always wondered to what extent that mechanism may be playing a role in the benefit that we've seen.

So I think that over time, probably, we are having an effect on inflammation and fibrosis, but the immediate effect is relatively hemodynamic and it's occurring – we have data now from the FINEARTS trial that the benefit occurs within the first month. We are really seeing evidence of benefit within a first month, and that's too early for fibrosis.

Dr. Lam:
Well, Scott, you are preempting the following chapters. And so I think that's a great hook to leave us on. You've heard about the MRAs, the anti-inflammatory, the anti-fibrotic effects. We were reminded today not to forget about the hemodynamic effects. I mean, I'm reminded of med school where we learned it as a potassium-sparing diuretic, and we know that we can use it in blood pressure control, at least spironolactone. So there are a myriad of effects going on here. We've covered it really nicely today.

And in Chapter 2, as we hinted, we'll be discussing key findings of new and ongoing clinical trials. Stay tuned.

Chapter 2

Dr. Lam:
Welcome back. In the first chapter of this educational series, we discussed the role of mineralocorticoid receptor antagonists in mitigating fibrosis inflammation, as well as having hemodynamic effects. In the current chapter, we're going to look at exciting new data and upcoming data with a focus on cardiovascular outcomes. I'm here with two of the world's best experts and best friends, Scott Solomon and Mikhail Kosiborod, and I'm Dr. Carolyn Lam.

Scott, if I could start with you, please tell us about the FINEARTS-HF trial.

Dr. Solomon:
Thanks, Carolyn.

Now, if you think about heart failure with mildly reduced or preserved ejection fraction, there's been one study with a mineralocorticoid receptor antagonist, and that was, of course, the TOPCAT trial which studied spironolactone. And that was a trial which was sponsored by the NIH and failed to meet its primary endpoint. But when we dissected that trial after it was over, we saw that there were two different populations of patients who were in it, the Americas and patients who were in Russia and the Republic of Georgia, and the patients in Russia and the Republic of Georgia look very different in terms of event rates, thinking that they probably didn't actually have heart failure. This made many people think that in TOPCAT there would have been a benefit had it been done in the right patients. Now that was, of course, spironolactone, a steroidal MRA, compared to placebo. We felt that there was no definitive data in this population, so we went ahead and designed the FINEARTS trial with finerenone, which you've already heard is a nonsteroidal MRA and distinct in a number of ways from steroidal MRAs.

So FINEARTS was designed to test the hypothesis that finerenone would reduce cardiovascular death and total worsening heart failure events in patients with heart failure and mildly reduced or preserved ejection fraction. We enrolled people with an EF of 40% or over. They could either be hospitalized or recently hospitalized or ambulatory. They had to have elevation in natriuretic peptides, structural heart disease, they couldn't have potassiums greater than 5. And we randomized them to either finerenone at a target dose of 20 or 40 mg, depending on their GFR, or placebo.

And it turned out that finerenone resulted in a 16% statistically significant reduction in cardiovascular death and total heart failure events, so with a *P* value of 0.007. And there was also an 18% reduction in total heart failure events. We saw directionally, the right direction for cardiovascular death and all-cause mortality, but neither of these were significant, 7% nonsignificant reduction in each cardiovascular death and all-cause mortality. And we saw consistency of the results across every single one of the prespecified subgroups, including based on ejection fraction and including based on whether patients were on SGLT2 inhibitors at baseline. Now we didn't have that many patients on SGLT2 inhibitors at baseline, but the point estimates were identical.

We saw improvement in a measure of quality of life, the Kansas City Cardiomyopathy Questionnaire total symptom score, by 1.6 points, a magnitude that is similar to what we've seen in other large international outcomes trials in heart failure. We didn't see improvement in New York Heart Association class or a composite renal outcome.

And then, with respect to safety, Carolyn, we saw that finerenone was well tolerated. There was, as we have seen with other MRAs, more hyperkalemia, about twofold increased hyperkalemia, depending no matter whether you look at it as a laboratory value or investigator reported. But we also saw less hypokalemia in patients receiving finerenone, and there were no instances of hyperkalemia leading to death and very, very few leading to hospitalization, 16 in the finerenone group and 6 in the placebo group.

So overall, a positive study suggesting that finerenone can benefit patients with heart failure with mildly reduced or preserved ejection fraction.

Dr. Lam:
Oh, wow, Scott. First, let me say hooray for a positive, a strongly, robustly positive trial of an MRA in HFpEF. Let's not forget how important that milestone is. But a few questions. First, let's be clear: did we see the kind of differential benefit with regards to sex and ejection fraction as we saw in PARAGON?

Dr. Solomon:
John McMurray actually just presented at the Heart Failure Society of America a more detailed look at ejection fraction. And when you look at this as a continuous variable across the spectrum, it really looks like it is consistent across the spectrum of ejection fraction. So not like what we saw with PARAGON, not like what we saw with CHARM. It does look like there's benefit as you go into the higher EFs, and no difference with respect to sex.

Dr. Lam:
That's amazing. And then the next thing, there is hyperkalemia and everyone's asking, how does this compare with other trials and

steroidal MRAs?

Dr. Solomon:
Yeah, so, about a twofold increase in potassium compared to placebo. In TOPCAT, by the way, in the patients we believe got the drug in the Americas, there's about a threefold increase in potassium. The actual potassium elevation, which was maximal in this study at about 3 months, was about 0.19 to 0.20 mmol/L. Again, in TOPCAT, it was between 0.25 and 0.28 mmol/L with spironolactone. In RALES, it was even higher at about 0.30 mmol/L. So there seems to be some advantage with respect to potassium here.

Dr. Lam:
Thank you. And Mikhail, I mean, there's just been so much buzz, but just could you give us just a sneak peek. What's ongoing now with more trials?

Dr. Kosiborod:
Right. So, as Scott mentioned, FINEARTS is incredibly important because it's the first trial ever to show benefit of any MRA in this patient population with mildly reduced or preserved ejection fraction heart failure. But as important as FINEARTS is, there are still some knowledge gaps that remain. Again, frankly, like any really good clinical trial, it answers a lot of questions but it also opens the door for additional questions that we need to still address, right?

And the good news is we have additional trials ongoing that will address those really important knowledge gaps. And one of them is, of course, while one trial is clearly critical to establish efficacy, we usually require or would like to see additional confirmation of that benefit, perhaps in several different patient populations. Scott mentions that there were patients in FINEARTS that were randomized in the hospital. And actually just over 1,200 of 6,000 patients that were enrolled in FINEARTS were randomized in the hospital or within a few days of discharge, and in that patient population, the results looked really good, both in terms of efficacy and safety. And actually, Desai just presented that data a few days ago at the Heart Failure Society.

Buta relatively small proportion of the patients enrolled in FINEARTS were on SGLT2 inhibitors, and even though there was no evidence of treatment effect heterogeneity, it would be really great to have another large outcome trial to show benefit in hospitalized patients who are at higher absolute risk of those events. And of course, we know that if we start medication in the hospital, it tends to be continued in the outpatient setting. That's how we actually encourage and drive both guideline adoption, clinical adoption, and sometimes even payer adoption in patients that really have very high absolute risk and would have great potential benefit in absolute terms, provided to the relative risk reduction is at least as good or better.

And so we have a trial specifically addressing those knowledge gaps, which is REDEFINE-HF. It's in people who have heart failure with mildly reduced or preserved EF, but all of whom are in the hospital or within 10 days of discharge. And we are anticipating that a much larger proportion, because it's a trial that got started much later, a much larger proportion will be on SGLT2 inhibitors at baseline.

We also need to understand whether, in high-risk people who are in the hospital with heart failure regardless of ejection fraction, near simultaneous initiation early in the course of that disease process with a combination therapy of nonsteroidal MRAs and SGLT2 inhibitors is an efficacious and safe strategy. And so we have a strategy trial called CONFIRMATION-HF, which is assigning patients randomly to either a simultaneous initiation at the same time, as well as the comparator group, which is open-label standard of care. So it's much more of a strategy trial. It's very different from your typical placebo-controlled kind of a tightly structured RCT, but I think it's going to address a very, very important question, which is kind of similar to what we saw in STRONG-HF, even though it's a different population and different drugs that we're looking at, but is going aggressively early on in high-risk patients the right way to go, and is it efficacious and safe?

And then finally, there is a large group of people that have heart failure with reduced EF that, despite all of the evidence that we already reviewed, the RALES trial, the EMPHASIS-HR trial, are not getting steroidal MRAs, sometimes that's clinical inertia, but frequently it's because they didn't previously tolerate them or have a contraindication. And right now, those patients have no other option as far as an MRA is concerned, and we know these drugs can be lifesaving in that patient population. So the idea in the FINALITY-HF trial, which is a randomized controlled trial of finerenone versus placebo in patients with HFrEF, heart failure with reduced EF, is to look at that population who is not on an MRA due to either a contraindication or if they had problems tolerating these medicines in the past and therefore not receiving them, and see if finerenone could be a treatment option that could potentially improve outcomes in that group.

So I think when all said and done, we'll have between FINEARTS, REDEFINE, CONFIRMATION and FINALITY, one of the largest heart failure programs ever put together that's really going to span a spectrum of ejection fraction, spectrum of clinical setting, spectrum of all kinds of different patient characteristics, and will be really incredibly inclusive for the types of patients we treat in practice.

Dr. Lam:

Wow, that's amazing. And of course, that's the MOONRAKER Heart Failure program. Everyone, you heard it right here. You're seeing the leaders right in front of you, and this is just so exciting. Thank you so much, Mikhail and Scott.

Now in Chapter 3, we will be putting all this information into clinical application, and so join us for the next chapter. Thank you.

Chapter 3

Dr. Lam:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Carolyn Lam, and here with me today are Dr. Mikhail Kosiborod and Dr. Scott Solomon. We are discussing the latest evidence on the use of nonsteroidal MRAs in patients with symptomatic heart failure.

Hello and welcome back to this educational series. In Chapter 2, we discussed the FINEARTS trial and others in the MOONRAKER program. And now in Chapter 3, we're going to apply all of this in a real case scenario. And I'm, of course, really, really thrilled to be with beloved colleagues, Dr. Scott Solomon and Dr. Mikhail Kosiborod. And I'm Dr. Carolyn Lam. Mikhail, do you have a case that you could start off our discussion with?

Dr. Kosiborod:
Well, I do, in fact, Carolyn, thank you for asking. And this impacts the patients that we saw in the cardiometabolic center where I practice some time ago. And I think, a great illustration, if you will, of somebody with heart failure and mildly reduced or preserved ejection fraction who potentially could be a candidate for a variety of different treatments. And would be a good discussion about how do we prioritize now that we went from having no treatments for HFpEF as of 2021 to now having potential multiple options, efficacious options, and that patient population.

So it's a 50-year-old woman who has had a long-standing history of type 2 diabetes and also had premature coronary artery disease actually at the age of 40, ended up having bypass surgery, CABG due to being diagnosed with multivessel coronary disease after a non-ST elevation MI. And she is not experiencing angina anymore now 10 years after that event, but she's presenting with progressive symptoms of shortness of breath with physical activity and lower extremity edema and has really developed profound exertional intolerance. And physical exam is relatively unremarkable. Her lungs are clear at baseline. She does have some lower extremity edema and somewhat elevated jugular veins. And as of right now, the only treatment that she's receiving other than losartan for hypertension and low-dose aspirin and high-intensity statin is a thiazide diuretic partially for that lower extremity edema and shortness of breath that she's experiencing, and so she doesn't have a formal diagnosis of heart failure. And she's also on metformin and basal-bolus insulin for her type 2 diabetes. And on subsequent evaluation, what we see is that she has substantially elevated NT-proBNP, which is 300 µg/mL, but this is in the setting of a BMI of 39. As we all know, there is a relationship between higher BMI and lower NT-proBNP, and certainly for somebody with that degree of obesity, it's a very high NT-proBNP. And she has an echocardiogram that shows preserved ejection fraction of 60% but multiple structural abnormalities, including moderate diastolic dysfunction and large left atrium as well as left ventricular hypertrophy. And so I think, arguably, with that kind of a clinical scenario and risk factors and the natriuretic peptides and echo findings, hopefully most of us will agree that her symptoms of progressive dyspnea on exertion and lower extremity edema, and given the physical exam, probably represent a diagnosis of heart failure with preserved ejection fraction.

So this patient really, again, the only treatment that she's getting for heart failure, if you will, if you consider it efficacious treatment for heart failure, is a thiazide diuretic. So the field is wide open here in terms of what we can do. And we have several potential options, right? We have SGLT2 inhibitors, which now are highly recommended, certainly on the European side of the Atlantic, and hopefully soon to be on the American side as well as proven treatments. We have finerenone as nonsteroidal MRA with which we have kind of data hot off the press, as Scott just described from FINEARTS. And also, let's not forget that this is somebody with type 2 diabetes who has a BMI of 39, who has atherosclerotic cardiovascular disease, and also likely, at least in part, appears to be early HFpEF. And we have data, of course, from the STEP-HFpEF programs that we can substantially improve symptoms and physical limitations with semaglutide in this population, in addition to ASCVD benefits and type 2 diabetes benefits we already know that we can get with GLP-1 agonists.

So I guess the question is, what do we use in this patient, and how do we sequence it? And maybe, Scott, I will direct that to you to get your opinion on that. And I know there are different ways of slicing and dicing this. There is no right or wrong answer, but we do have the situation where we now have more than one treatment option, which is great.

Dr. Solomon:
Sure. Well, that's a very interesting case, Mikhail. And of course, this woman is on only a little bit of thiazide diuretic. It sounds like she certainly probably would benefit from being on a little more diuretic therapy, particularly loop diuretic, I think would be necessary in her for decongestion, which is obviously the mainstay of therapy in patients with heart failure.

But with respect to targeted guideline-directed therapy, there's no question in my mind that she would benefit from an SGLT2 inhibitor. We now have, as you know, very ample evidence that SGLT2 inhibitors work across the full spectrum of ejection fraction, and they would certainly reduce her likelihood of heart failure events, and although there was not a significant benefit in terms of mortality or cardiovascular mortality with SGLT2 inhibitors, we think if we did trials that were large enough, we might see it. So I think that that is a class 1 indication now; she should be on that.

With respect to the other therapies, we did talk a little bit about finerenone today. Finerenone is not yet approved, so we can't give that for this indication as of yet. I don't remember if you said what her GFR was. But if it were under 60, she actually would be indicated for finerenone based on the FIDELIO and FIGARO trials. And then would she be eligible for sacubitril/valsartan? Her ejection fraction is reasonably high, although we did see benefit in women to a higher ejection fraction than men. If her EF was a little bit lower, I would think about using sacubitril/valsartan in the places where we can use it, and the US being one of them.

And then finally, you bring up the very intriguing possibility of treating her obesity with a GLP-1 and you, of course, have shown in the STEP-HFpEF trials and STEP- HFpEF Diabetes, how you can actually improve quality of life, you can demonstrate weight loss. You can actually reduce NT-proBNP, which is pretty fascinating with this type of drug.

We still don't have dedicated outcomes data in this population, but a lot of circumstantial evidence now from other trials and other populations that these drugs ultimately will be beneficial in people with her phenotype.

Dr. Kosiborod:
Yeah. No. Thanks, Scott. Just briefly, glad you asked about the kidney function. So it's interesting you mentioned that, and I should have brought it up up front, but I kind of wanted to see what you think before I even mentioned what her kidney function is. But her GFR happens to be 50, and her urine albumin creatinine ratio happens to be 550.

Dr. Lam:
So exactly, Mikhail. I was going to ask, as a cardiologist, ask what about the uACR?

Dr. Solomon:
In that case, I think this woman is actually indicated for finerenone. And finerenone is so far the only MRA that has proven beneficial in diabetic kidney disease.

Dr. Kosiborod:
Yeah. What's fascinating is essentially any of the options we just talked about, and that's, I think, the fascinating part of this. And maybe, Carolyn, you can address this to an extent in a bit more detail, but this kind of a cardiometabolic phenotype of HFpEF, of course, many of these patients have overweight, obesity, many of them are living with type 2 diabetes and kidney disease. And any of these treatments we mentioned, SGLT2 inhibitors, finerenone, and GLP-1 receptor agonists, also now have evidence of kidney disease progression benefits as well. So really any or maybe even a combination of all of these could be incredibly beneficial for a patient like that because they'll address multiple issues that are going on with the patient, not just heart failure per se, even though that's really important, of course, especially to us as cardiologists, but also other problems that this patient is experiencing.

Dr. Lam:
Exactly. I was going to just remind everyone, with the GLP-1 receptor agonist, we may not have outcomes data in heart failure, but we do have outcomes data in diabetes. And we now also have outcomes data in obesity and for kidney dysfunction. And so with all of that, I would start that.

And then I also want to remind everyone that we used to give MRAs for potassium-sparing effect when you add a loop diuretic. I mean, it's a perfect – I would be very, very comfortable with starting a loop diuretic and finerenone and an SGLT2 inhibitor at the same time. Of course, we watch her fluid status very closely.

This would also be a patient that we mustn't forget the basics. Ensure that her symptoms are not being precipitated by ongoing ischemia. I've been caught so many times, that we get all involved in the weeds of treating everything else and forget that. And interestingly, the GLP-1 receptor agonist can also help in the atherosclerotic disease aspect.

So I thank you, Mikhail, for just such an excellent, excellent case. We all have to figure out in guidelines what we're going to say to start and when and so on in these patients, but it's so nice, as you just said, to have these options.

So thank you very much once again, Mikhail and Scott, for these wonderful, wonderful discussions in this educational series. Wish we had more time, but that's all the time we have today. Thank you, audience, for listening in. Thank you for joining us today.

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