Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/beyond-steroidal-mras-the-nonsteroidal-mra-lens-in-hf/49198/

Released: 03/26/2026
Valid until: 03/26/2027
Time needed to complete: 15 minutes

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

Beyond Steroidal MRAs: The Nonsteroidal MRA Lens in HF

Announcer:
Welcome to CE on ReachMD. This activity, titled **"Beyond Steroidal MRAs: The Nonsteroidal MRA Lens in heart failure"** is provided by Medcon International.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Mentz:
For years, MRAs and heart failure have been synonymous with steroidal agents, but that lens is shifting. As our understanding of mineralocorticoid receptor biology evolves, so does how we think about risk, stability, and patient selection. Today, we're looking beyond steroids to explore what nonsteroidal MRAs add to modern heart failure care.

This is CE on ReachMD, and I'm Dr. Robert Mentz.

Dr. Pabon:
And I'm Dr. Maria Pabon.

Dr. Mentz:
Great. So let's jump right in. When we talk about MRAs in heart failure, many clinicians still turn to fluid and potassium first. What can you tell us about the real role of mineralocorticoid receptor blockade in heart failure today?

Dr. Pabon:
Yeah, thank you for the question. So when we talk about MRAs in heart failure, I think we need to move beyond their effects in fluid and potassium. Mineralocorticoid receptor overactivation is actually a core pathophysiologic driver in heart failure. Aldosterone and MR signaling can promote myocardial fibrosis, inflammation, endothelial dysfunction, all leading to adverse ventricular remodeling. So this isn't just about congestion; it's about blocking the biology of disease progression.

What's particularly important is that MR signaling continues to drive structural remodeling, even when patients feel clinically stable. So a patient can look euvolemic and well in clinic, but at a cellular level, fibrosis and maladaptive remodeling may still be advancing. So we should think of MRAs as disease-modifying therapies, not simply symptom-relieving medications.

The classic heart failure trials with MRAs like spironolactone and eplerenone clearly demonstrated reductions in mortality and heart failure hospitalizations. And more recently, nonsteroidal MRAs have reinforced the concept that targeting MR signaling has meaningful cardiovascular and renal benefits, specifically in the HFpEF population, not simply a decongestive signal; it's a survival signal.

Finally, it's helpful to think in terms of end-organ protection. MR overactivation affects not just the myocardium but also the kidney and the vasculature. So by blocking this pathway, we are protecting both the heart and the kidney, which is especially relevant now in the cardiovascular-kidney-metabolic spectrum we increasingly recognize in heart failure today.

Dr. Mentz:

Yeah, thanks so much. I mean, beautifully summarized. We need to get away from this mindset of heart failure being just congestion, that really the pathology is driven by MR overactivation, and now we have the nonsteroidal MRA agents that can really help with the underlying disease modification. This is not merely symptom relief targeting fluid and electrolyte management; this is changing the underlying disease. And I loved how you framed that with the CKM construct that we're now incorporating into practice.

So let's transition and really unpack the biology a little bit. At a high level, what really helps to distinguish steroidal MRAs from nonsteroidal MRAs at the receptor level? And why should clinicians care?

Dr. Pabon:
Yeah, totally. I think it's the key distinction, right? And it really comes to the receptor pharmacology and tissue behavior. And so, at a high level, as the name implies, the steroidal MRAs like spironolactone and eplerenone are basically structurally similar to endogenous steroid hormones. And because of that, they can interact with progesterone and androgen receptors to varying degrees. Spironolactone, in particular, has a broader receptor engagement, which explains some of the off-target endocrine effects we often face with our patients, like gynecomastia.

Nonsteroidal MRAs, in contrast, were designed to be highly selective for the mineralocorticoid receptor. And even though we're still learning about them, pharmacokinetic studies done in animals have shown that nonsteroidal MRAs have a more balanced distribution of the drug in the heart and the kidneys versus the steroidal MRAs, which may have higher accumulation of the drug in the kidneys compared to the hearts. So as you can imagine, this could potentially explain the effects of the steroidal MRAs on electrolyte abnormalities, particularly in hyperkalemia.

Nonsteroidal MRAs are also metabolized into inactive metabolites, and so they have a shorter half-life than, for example, spironolactone, which gets metabolized into active metabolites like canrenone, which sometimes make it difficult to use in end-stage renal disease patients.

So why is this important to clinicians? I think first and foremost is tolerability. Off-target effects and hyperkalemia concerns have historically limited the uptake and continuation of steroidal MRAs, even though we know they improve survival. And studies have shown that steroidal MRAs have more than double the rates of hyperkalemia compared to nonsteroidal MRAs. So this is a good potential alternative for patients that are just unable to tolerate steroidal MRAs.

So in summary, I think the key thing to remember is that steroidal and nonsteroidal MRAs, even though they modulate the same receptor, are pharmacologically distinct tools. And those differences can potentially influence tolerability and ultimately whether the patient can stay on therapy long enough to drive full disease-modifying benefit.

Dr. Mentz:
Thanks so much for going through that to help think about how we incorporate these into clinical practice as we understand the differences between some of the historic agents. The nonsteroidal MRAs are not just the next generation; it's really a distinct mechanism here in contrast to the older agents that you noted. So this helps, just as you highlighted, around tolerability.

And now we have important data from the FINEARTS program with finerenone in HFpEF. So it'll be really wonderful to go through this as we talk about new opportunities for medical management in HFpEF.

Well, let's transition there a little bit. So in patients with HFpEF or mildly reduced ejection fraction heart failure, how do these mechanistic differences, particularly the antifibrotic and anti-inflammatory signaling, how do those translate into clinical outcomes?

Dr. Pabon:
Yeah, great question. In HFpEF, the substrate is thought to be inflammatory and fibrotic, leading to adverse remodeling. And so mineralocorticoid receptor overactivation amplifies that biology. So MR blockade is about dampening this profibrotic and proinflammatory signaling that sort of drives the stiff heart phenotype we see in HFpEF.

And I think that's why the outcomes that we most expect to change with these therapies are worsening heart failure events. And that's exactly what FINEARTS-HF showed, right? Finerenone reduced the composite outcome of total worsening heart failure events and cardiovascular death, with a clear reduction in total worsening heart failure events of almost 20%.

In FINEARTS, finerenone also showed modest but statistically significant improvements in KCCQ total symptom score, suggesting that interrupting this profibrotic and proinflammatory pathway may influence both structural disease, but also patient-reported health status.

And finally, another thing to highlight in terms of this profibrotic biologic pathway in HFpEF is that finerenone has also been shown to decrease the risk of atrial fibrillation in the broader cardiovascular–kidney–metabolic syndrome population, again, just supporting this potential antifibrotic role and potentially antiarrhythmic role as well.

Dr. Mentz:
For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Robert Mentz, and here with me today is Dr. Pabon. We're focusing on how differences in mineralocorticoid receptor biology can inform patient selection and ongoing risk.

Thanks so much for linking the underlying mechanisms to the benefits we're seeing in clinical trials and, importantly, both the reduction in clinical events as well as improvements in health-related quality of life for our patients as well.

Dr. Pabon:
Yeah, my pleasure. But now, Dr. Mentz, I'd love to ask you, since you're an expert in the field, many patients with heart failure seem stable on the surface, and how do you think about underlying risk in those patients that seem stable, but you also want to avoid therapeutic inertia?

Dr. Mentz:
Yeah, thanks so much. I mean, this is such an important question. And I'll actually draw the listeners to a nice paper that one of my colleagues, Steve Greene, wrote in *JAMA* in 2021. And it was really trying to break down this idea that there is no such thing as a stable heart failure patient.

And if you just look across cardiovascular disease, as we think of atherosclerotic cardiovascular disease, that we label these patients high risk or very high risk. But if you actually contextualize that risk, in heart failure, there is no such thing as a stable patient. The risk for cardiovascular events, including death as well as worsening heart failure events as you just noted, are so high that even in those patients that are walking into our clinic, we know that their risk for worse outcomes really puts them at a poor trajectory if we don't intervene upon that.

So Steve and colleagues nicely laid out several years ago, let's rethink this. We can't think of any patient with heart failure as stable but need to better understand that residual risk even on the background of therapies they may be receiving.

So as I think about this in my clinic, I've tried to really envision that the only way to get over this therapeutic inertia, the lack of initiating evidence-based therapies, is to have frank conversations with our patients, understand their symptoms and how they've evolved over time. And it can be helpful to really try to tease out their trajectory, because as patients' symptoms worsen, they tend to do less. So that

can mask some of the underlying disease course, where, if we're not teasing out their story, better understanding what they're doing now compared to 2 weeks ago, 2 months ago, we may miss some of that clinical trajectory that's worsening.

So it's really foundational to know that heart failure is inherently progressive, even when we may have historically thought of some of these patients as, quote/unquote, stable. And that even in the context of managing their comorbidities, optimizing their volume status, they're at high risk for coming back into the hospital with worsening heart failure symptoms. So we need to think about initiating evidence-based therapies, ongoing reassessments, and not falling into the trap of inertia.

And importantly, I draw your attention to that group of patients with heart failure with improved ejection fraction, or maybe they had a history of HFrEF with ejection fraction less than or equal to 40% and now with therapies, they're now in that mildly reduced or preserved ejection fraction group. We know that that group, as well, has high risk for worsening heart failure events, with some exciting recent data just published in *JACC* from the Kaiser group, characterizing that population that I'll draw our listeners to.

Dr. Pabon:
Yeah, I love that in that particular population, I think the fact that we're now calling them improved just signals exactly what you said, Dr. Mentz, that before we used to call it heart failure with recovered ejection fraction. And there's no such thing as recovery in heart failure, right? It's now we talk about patients with HFrEF being maybe like in remission rather than recovered. And so again, just highlighting, as you said, and as Steve Greene says, there's no stable heart failure patient.

All right, I will ask you one more question. In your clinic, which specific heart failure phenotypes or clinical profiles would prompt you to consider a nonsteroidal MRA? And what signals push you toward that decision?

Dr. Mentz:
Yeah, really great question. So thankfully, here we have the nicely designed FINEARTS trial where we know the eligibility criteria, we're at ejection fraction 40% or higher, symptomatic heart failure, treated with other evidence-based therapies is appropriate. So you can think, if you've got mildly reduced or preserved ejection fraction heart failure, those are the patients we need to think about nonsteroidal MRA, finerenone. And we know, as we just spoke through that high residual risk, these patients should be on an SGLT2 inhibitor. And now we need to think about initiation of finerenone.

Importantly, we also have data in FINEARTS on that heart failure with improved ejection fraction, so they were previously HFrEF and

they're in that mildly reduced or preserved group with symptomatic heart failure. That's another population where we uniquely have those data as one of the few trials that actually included those patients.

And then finally, you say, well, maybe my patient's already on spironolactone. They've got underlying diabetes. They've got kidney disease. That is a key case where we can think about switching that patient to finerenone. So just as we began our conversation around cardio-kidney-metabolic overlap, that's an excellent opportunity to think about evidence-based therapies where we know that finerenone reduces events in patients with diabetic kidney disease, and we have the data from FINEARTS in heart failure with mildly reduced and preserved ejection fraction. That Venn diagram there really has a very high-risk group of patients that we know we have strong data around.

And I'm encouraging our trainees to now think about incorporation of albuminuria into their assessment as well.

So this has been such a rich conversation, but I would underscore this idea that stability is no longer the case in patients with heart failure, and we need to be thinking about nonsteroidal MRAs.

So our timeline is short here today, and it's been such a wonderful conversation with you. But before we conclude, what message do you want to make sure really stays with our audience today?

Dr. Pabon:
Yeah, I think if there's one message I'd like people to walk away with is that mineralocorticoid receptor signaling is not a side pathway for heart failure; it's really central biology, and their benefits in their heart failure population cannot be understated. MR blockade is one of the ways we can interrupt the process upstream and hopefully prevent the next decompensation, right, and end up protecting both the heart and the kidney over time.

What about you, Dr. Mentz?

Dr. Mentz:
I would underscore that as we look at MRA agents in HFpEF, the only positive trial data we have is with nonsteroidal agents. None of the prior steroidal MRAs have a positive trial in heart failure with preserved ejection fraction. So we need to use evidence-based therapies.

And that's all the time we have for today. So I want to thank our audience for listening, and thank you, Dr. Pabon, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Pabon:
It was a great conversation. Thank you for inviting me and looking forward to the next step.

Announcer:
You have been listening to CE on ReachMD. This activity is provided by **Medcon International.**

To receive your free CE credit, or to download this activity, go to ReachMD.com/**CME**. Thank you for listening.