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Steroidal vs Nonsteroidal MRAs: Implications for Heart Failure Care

Announcer:
You're listening to *Heart Matters* on ReachMD. Here's your host, Dr. Steve Jackson.

Dr. Jackson:
Welcome to *Heart Matters* on ReachMD. I'm Dr. Steve Jackson, and today, I'm joined by Dr. Robert Mentz to examine the clinical and pharmacologic distinctions between steroidal and non-steroidal mineralocorticoid receptor antagonists, also known as MRAs, and why they matter in heart failure care. Dr. Mentz is an Associate Professor of Medicine and Population Health Sciences at Duke University in Durham, North Carolina. He's also a member of the Duke Clinical Research Institute.

Dr. Mentz, it's great to have you here today.

Dr. Mentz:
Thanks so much. Looking forward to our conversation.

Dr. Jackson:
To begin, Dr. Mentz, how has our understanding of MRAs evolved in recent years, particularly with respect to whether they should be considered a uniform class?

Dr. Mentz:
I'm coming to this conversation as a heart failure clinician, where MRAs have historically been approached as a class effect. So we think about spironolactone and eplerenone with a robust evidence base around cardio-kidney benefits, specifically in patients with heart failure.

Now, there's growing evidence of meaningful differences across MRAs. So we can think about distinctions in pharmacology, receptor selectivity, and downstream effects. And, increasingly, the evolving trial data and guideline recommendations are altering our emphasis in helping us better understand how we can individualize these treatment decisions.

Dr. Jackson:
So then let's dig into that a little more. What are the key pharmacologic differences between steroidal MRAs like spironolactone and eplerenone and newer nonsteroidal agents such as finerenone?

Dr. Mentz:
Beginning with spironolactone, we know that this steroidal MRA has a broad receptor binding profile, so it does have more off-target hormonal effects. And historically, in my practice, when I had a patient with heart failure or I was otherwise initiating an MRA, I'd start with spironolactone.

If they had a side effect like gynecomastia, then I would switch them to eplerenone, with this idea that eplerenone has improved selectivity, but retains that steroidal structure. And I describe it as a cousin of spironolactone.

But now, distinct from those steroidal MRAs, we have important trial data with the nonsteroidal MRA finerenone. It has distinct binding characteristics and downstream signaling effects, and, importantly, has been shown in multiple robust trials—from diabetic kidney disease to heart failure with mildly reduced and preserved ejection fraction—to have important cardio-kidney benefits. And this has felt related in part to differences in tissue distribution and anti-inflammatory and anti-fibrotic effects. So it's been this evolution over time, beginning with the steroidal MRAs, most notably in HFrEF and peri MI, but now we have newer data with finerenone in diabetic kidney disease, as well as heart failure populations.

Dr. Jackson:
And as a follow up to that, how do these pharmacologic differences translate into clinical outcomes, specifically in terms of cardiovascular events and heart failure progression?

Dr. Mentz:
Thank you for this important question. So we're anchoring this in the trial data, and now we're seeing the improved clinical outcomes likely related to differences in receptor binding and downstream signaling that can influence the degree of cardiovascular protection.

So we think how there can be variation in tissue distribution and how that can affect both the heart and the kidneys, as well as the blood vessels, and this may lead to some of the observed differences.

With non-steroidal MRAs, we have observed benefits across patient populations—in particular, those with overlapping comorbidities. And this translates so commonly in clinical practice, where you're seeing a patient who doesn't just have kidney disease. It's not just heart failure or underlying diabetes. It's all of these Venn diagrams overlapping. And what's nice here is to have the safety and tolerability of these therapies as shown in robust clinical trials.

And then there are the clinical benefits that we saw as well. So we're thinking of non-steroidal MRAs as another tool in our toolkit, adding onto ACE/ARB as appropriate in different populations, or SGLT2 inhibitors as appropriate and tolerated and then adding on MRA therapies such as the non-steroidal MRA finerenone.

Dr. Jackson:
For those just tuning in, you're listening to *Heart Matters* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Robert Mentz about the key differences between steroidal and non-steroidal mineralocorticoid receptor antagonists for treating heart failure.

So, Dr. Mentz, I'd like to now zero in on hyperkalemia for a moment, which remains a common concern with MRAs. Can you tell us about the different risk profiles for steroidal and nonsteroidal agents and how that influences your prescribing?

Dr. Mentz:
Of course. So, with steroidal MRAs—spironolactone, eplerenone—we do see that there is this well-established hyperkalemia. And, in fact, when the early HFrEF trials came out with spironolactone, following that, in routine practice, we saw more, clinically relevant hyperkalemia. So it created this fear around MRAs and hyperkalemia, particularly in those with more advanced kidney disease, as well as on a background of other RAAS inhibitors.

But now, fast forward many years, and we have, on a bedrock of foundational therapies—including ACE and ARB—newer data with non-steroidal MRAs that have shown a lower rate of severe hyperkalemia in trials. I'd underscore that those trials did have close monitoring, so we know that we can get clinical benefits both on the cardio and the kidney axis with nonsteroidal MRAs, but we have to monitor patients.

So, typically, what I'll do in practice is I'll check their labs in clinic. I'll check a BMP and a UACR. I'll understand what therapies they're on. I'll start a non-steroidal MRA. And then I'll repeat labs in a week and adjust that follow-up pattern based on where their potassium is and where their trajectory's been over time.

I think this helps better balance the risk-benefit relationship. And again, just to underscore: monitor the labs and make sure patients have routine follow-up so that we can make sure that we're not only understanding their change over time but understanding what's happening with their heart and their kidneys.'

Dr. Jackson:
Finally, if we think about these medications and where they're indicated, the steroidal MRAs are a foundational pillar of quad therapy in heart failure with reduced ejection fraction, or HFrEF, whereas the nonsteroidal MRAs have been historically indicated for chronic kidney disease associated with type 2 diabetes. However, we now have emerging data supporting the use of non-steroidal MRAs in a new patient population: patients with heart failure and mildly reduced or preserved ejection fractions, specifically those with ejection fractions above 40 percent. So, Dr. Mentz, with that in mind, as new data continues to emerge, how do you see the role of MRAs evolving within the broader heart failure treatment paradigm?

Dr. Mentz:
Yeah, thanks so much. So it's an exciting time in cardio-kidney-metabolic care, with a number of recent positive trials, as well as, now, follow-up studies with the nonsteroidal MRA finerenone that will help better identify the role and the continued benefits, including on a background of SGLT2 inhibitors. We're thinking about different timing of initiation, and if it's in hospital or out of hospital.

And I think there really will be a shift from interchangeable use across, broadly, the MRA class, to a differentiated role based on pharmacology and the evolving evidence. So with greater emphasis on cardiometabolic outcomes and the heart-kidney interplay, I think that it will involve changing of guidelines, changing of consensus pathways, and changing of routine clinical practice.

And future decisions will be guided by more granular patient-specific risk stratification. We'll be thinking about creatinine, GFR, UACR, underlying patient phenotype, and their comorbidities to see how we can best initiate and titrate these therapies to optimize patient outcomes.

Dr. Jackson:
That's a great perspective for us to think on as we come to the end of today's program. And I want to thank my guest, Dr. Robert Mentz, for joining me to discuss how differences among steroidal and non-steroidal mineralocorticoid receptor antagonists may influence treatment decisions in heart failure.

Dr. Mentz, we appreciate you being here today.

Dr. Mentz:
Thank you so much, Steve. I enjoyed the conversation.

Announcer:
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