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

Shifting Treatment Paradigm in HFmrEF/HFpEF: Steroidal and Nonsteroidal MRAs

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Dr. McMurray:
So last year, the outcomes of the FINEARTS-HF trial were presented and published, describing the effects of the nonsteroidal mineralocorticoid receptor antagonist, or MRA, finerenone in patients with mildly reduced and preserved ejection fraction heart failure. And today we want to discuss these findings and, in particular, discuss them in the context of previous data that we have with the older steroidal MRAs.

This is CME on PACE-CME and ReachMD. I'm John McMurray, and I'm delighted today to be talking to my colleague and friend, Faiez Zannad, who really is one of the grandfathers of MRA therapy for patients with heart failure.

Faiez, thank you for taking part.

Dr. Zannad:
Thank you. And thank you for having me.

Dr. McMurray:
I want to step back a bit and maybe ask you, because you're the best person in the world, really, to answer this question: What do we know about the older type of MRAs, the so-called steroidal MRAs, in patients with heart failure and reduced ejection fraction, but also the one trial that we had before FINEARTS in patients with mildly reduced and preserved ejection fraction heart failure?

Dr. Zannad:
Well, thank you so much for your kind words, but it is indeed important to look back where we were in the late ‘90s. Spironolactone, the single treatment with the steroidal MRA, was on the market and used for hypertension, mainly. Since then, it’s still used in hypertension. Certainly, after the PATHWAY trial, it is now in the guidelines as a treatment for resistant hypertension. But at that time, spironolactone was used at very high doses, 75 to 150 mg, also as a diuretic. Then we have actually, with Bert Pitt, hypothesized that a much lower dose may be effective in heart failure with reduced ejection fraction, and we did the RALES trial, which has, in severe heart failure patients, has shown that spironolactone 25 to 50 mg once a day can indeed improve outcomes, including survival. All-cause death was decreased 30%. So this opened up the door to the indication of low-dose spironolactone in heart failure. And since then, there have been many more trials in post MI.

And of course, this laid the ground for the treatment of HFpEF, and especially that we had all elements and mechanistic plausibility from the RALES trial.

Dr. McMurray:
What did TOPCAT show? Because I think we were all a little bit disappointed, perhaps. Do tell us a bit more about that specific trial.

Dr. Zannad:
Absolutely. So TOPCAT, it has shown nothing conclusive. That's my own take of the understanding of TOPCAT. It was designed at low dose, 15 mg in patients with HFpEF. And the conclusion was, overall, that the drug, spironolactone, was not effective and didn't decrease the outcome, which was the combined outcome of CV death and heart failure hospitalization. So that's the single conclusion.

But then there have been look into subgroups, and there was a large disparity of centers, centers in the Eastern Europe compared to in Americas. And the trial subgroup analysis, of course, this was not anticipated, and the conclusion much weaker, showed that in the Americas, the trial is positive, and the trial has shown that spironolactone can improve the outcomes CV death and heart failure hospitalization, but it's by no way definitive.

Dr. McMurray:
So we were left at the end of TOPCAT with this rather frustrating situation where the trial overall did not show a significant benefit. There was the tantalizing suggestion that maybe, in the right patients, an MRA might be beneficial. But we were left without a clear answer.

But as you know, Faiez, fortunately, both of us had the opportunity with other colleagues to address this question a second time, and that was because of the availability of a newer type of MRA, a so-called nonsteroidal MRA, and the lead compound in this class, finerenone, had already been shown to be of benefit in patients with type 2 diabetes and chronic kidney disease. And we were lucky enough to be able to go on to study this again in patients with heart failure and mildly reduced or preserved ejection fraction.

So again, I'll just give a very quick summary of the FINEARTS-HF trial. But as you well know, we enrolled patients with an ejection fraction of 40% or above. They were required to have a modest elevation in natriuretic peptides and to have structural heart disease. They were randomized to receive finerenone or placebo. What was different in FINEARTS-HF than in the earlier 2 trials in patients with chronic kidney disease was that some of our patients, so patients who had an eGFR of 60 or above, had a dose of finerenone of up to 40 mg daily, whereas finerenone had been used in the previous CKD trials up to a maximum dose of 20 mg daily. The primary outcome was the composite of total heart failure events, so first and recurrent heart failure events, and cardiovascular death.

And when we completed the trial, we found that finerenone had reduced the risk of this primary composite endpoint by 16%. So the rate ratio was 0.84, and that was a highly statistically significant benefit driven predominantly by reduction in heart failure hospitalization. And in addition to that, we saw an improvement in a patient-reported outcome, the Kansas City Cardiomyopathy Questionnaire, which was better in patients who received finerenone than in patients who received placebo. And overall, finerenone was well tolerated. We did see a little bit more hyperkalemia, so potassium concentration of above 6 mmol/L was identified in 3% of patients in the finerenone group compared to 1.4% patients in the placebo group. On the other hand, hypokalemia, potassium less than 3.5 mmol/L, occurred in 9.7% of the placebo group, but only 4.4% of the finerenone group.

For those just tuning in, you're listening to CME on PACE CME and ReachMD. I'm Dr. John McMurray, and here with me today is Dr. Faiez Zannad. We're discussing steroidal and nonsteroidal mineralocorticoid receptor antagonists, MRAs, shifting treatment paradigm in heart failure with mildly reduced and preserved ejection fraction.

So, Faiez, I think you would agree, at long last, we have now strong evidence that a mineralocorticoid receptor antagonist is beneficial in patients with this heart failure phenotype. Obviously adding to the evidence that the older MRAs are beneficial in patients with heart failure and reduced ejection fraction. And I think you would probably be the first person to agree that that represents a significant clinical breakthrough and one that we've been waiting for for a long time in this neglected group of patients for heart failure.

But have I left anything out? Is there something else I should have said about FINEARTS-HF as the most recent data in this area?

Dr. Zannad:

No, you very nicely summarized the evidence. And I am particularly interested by you highlighting the effect on potassium and reciprocating hyperkalemia and hypokalemia. Most people just forget or omit the positive part of this potassium channel, which is less hypokalemia, and this is instrumental in the efficacy of the drug altogether.

Dr. McMurray:
And, Faiez, we always look at subgroups, and you know, again, better than almost anybody, all the difficulties and problems with looking at subgroups, but we like to do that. Are there any subgroups that stood out to you? Are there any questions that people have clinically about different groups of patients and whether finerenone would be beneficial in them?

Dr. Zannad:
There have been multiple subgroup analyses and across the board, actually, it is very reassuring, which is kind of what we call internal validity, giving a robustness to the trial when the results are very consistent, no matter what is the subgroup. One subgroup of interest is, of course, the recency of heart failure hospitalization. The earlier patients were enrolled after discharge from heart failure hospitalization, the higher the benefit. But this is common across all trials, because the event rate is front-loaded after a heart failure event, and therefore the absolute risk is higher and the absolute risk reduction is higher. But otherwise, it's very reassuring to see that the benefit is extremely consistent, and so is the safety as well.

Dr. McMurray:
Yeah. I mean, I think the 2 that probably stood out to me, I don't know what you think, but the people who were on an SGLT2 inhibitor at baseline, they got exactly the same size of benefit as people not taking an SGLT2 inhibitor. The reason I think that's important is because obviously SGLT2 inhibitors are beneficial in this type of heart failure. So showing benefit on top of an SGLT2 inhibitor, to me, is important because, really, I think, tells us that we should be using both of these treatments; they're not in competition. It's not one or the other. Really, our patients should be getting both.

And then this was the other subgroup that stood out to me was ejection fraction. I'm not sure what you expected. I wasn't sure whether we would see benefit in people with a completely normal ejection fraction. But in fact, it seems as though the benefit of finerenone was quite consistent across the spectrum of ejection fraction in FINEARTS-HF. Again, I don't know what you think about those 2 subgroups?

Dr. Zannad:
Yeah, the subgroup with SGLT2 inhibitors is very interesting. It actually echoes the data we have seen in SGLT2 inhibitor HFpEF trial, where the few patients received an MRA, at that time it was spironolactone, but still, the results were cumulative, and therefore there is a benefit of combining both drugs. So that's a very important group of interest.

According to the HFpEF and the normal ejection fraction, we know that there is still the controversy, where is normal and what is HFpEF, and the extreme distribution of the highest HFpEF. But it was very reassuring to see that across all ejection fraction, the benefit was very consistent.

Dr. McMurray:
So let's come to maybe the million-dollar question and one that I'm sure you've been asked many times, I've been asked, and that is, are there differences between nonsteroidal MRAs, finerenone being the one example in clinical practice, and the older steroidal MRAs, spironolactone and eplerenone?

So, Faiez, what do you think about that?

Dr. Zannad:
Yeah, I agree this is the million-dollar question. But short of direct comparison, we only have speculative answers which are related to basic science and animal studies on the one hand. And on the other, indirect comparison across trials and mechanistic plausibility. Well, indeed, nonsteroidal, at least finerenone, appears to be distributed equally in the heart and the kidney, which may actually make it more kidney friendly. And by the way, in FINEARTS, the patients were enrolled with much lower eGFR than any other steroidal MRA. So safety across kidney and efficacy in CKD with diabetes also shows that there may be some, not only kidney friendliness, but certainly protection of the kidney altogether. So that may be one major difference.

And when it comes to potassium, it's really hard to compare because, short of direct comparison but then also in basic science and some clinical data, there is a suggestion that the excess hyperkalemia may be less, but hyperkalemia is here, so the signal is there, and it is important not to believe that the drug is free from hyperkalemia, because we may be disappointed and not monitor potassium. We need to keep an eye on potassium with finerenone as well.

Dr. McMurray:
Yeah. I mean, again, you made another really good point, is that we went down to a much lower eGFR. And given how closely related kidney function and potassium levels are, then it is really not possible to compare like with like. The older trials were more cautious, more careful in enrolling patients with better kidney function than we did in FINEARTS.

And yeah, I mean, again, I agree with you, Faiez. A lot of the comparisons, by necessity, have to be indirect. I suppose the only other one that I would probably highlight is that we saw a reduction in new-onset diabetes in FINEARTS-HF. That's perhaps a little surprising in the light of, I would say, pretty consistent evidence that spironolactone causes an increase in hemoglobin A1c, dysglycemia, possibly because it displaces cortisol from its receptor.

But yes, I think the million-dollar question still remains unanswered. But I think the good news for our patients, really, to summarize, is that we've now got evidence with this broader family of agents in patients with heart failure. The strongest evidence we have in mildly reduced and preserved ejection fraction heart failure, of course, is with finerenone. The stronger evidence in people with reduced ejection fraction is with spironolactone and eplerenone. But I think that's probably the most important takeaway message.

So thank you very much, Faiez, for taking part in this conversation. I very much enjoyed it. I hope it's been of interest to our listeners. Thank you very much.

Dr. Zannad:
My pleasure.

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