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ns-MRAs: The Cardiovascular-Kidney-Metabolic Connection

Announcer:
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Dr. Kovesdy:
Hello, this is CME on Pace-CME on ReachMD, and I'm Dr. Csaba Kovesdy. Here with me today is Dr. Finnian McCausland.

Let's dive right in with a case presentation of a patient with heart failure who also has type 2 diabetes and worsening kidney function.

Our patient is 65, has a long history of type 2 diabetes, 20 years with retinopathy, also heart failure with mildly reduced ejection fraction, ex-smoker, and has complex medication regimen including sacubitril/valsartan, empagliflozin, a beta-blocker, a loop diuretic, furosemide, and otherwise negative review of systems: well-controlled blood pressure and normal physical exam. Main labs include a potassium of 4.5 mmol/L, an eGFR of 25, 2+ protein on UA, and when you measure the UACR, it is 1500 mg/g.

Dr. Mc Causland:
This is a very common case presentation of a patient with heart failure with a mildly reduced or preserved ejection fraction. I think they have a couple of very important risk factors in terms of their long history of type 2 diabetes and their history of hypertension. They've got significant proteinuria in the macroalbuminuria range, which, as we know, is a very potent predictor of adverse outcomes.

Their medication regimen is actually pretty decent in terms of somebody who's got heart failure with mildly reduced ejection fraction.

I think in terms of the recent evidence that's come out, though, the important additional therapeutic regimen that should be considered in a patient like this would be the addition of finerenone, which is a nonsteroidal mineralocorticoid receptor antagonist. And the recent data from the FINEARTS Heart Failure trial, and was very convincing, is they looked at their composite outcome of total heart failure events and cardiovascular death were at a very significant 16% risk reduction in addition to standard therapy.

Dr. Kovesdy:
So this patient clearly is at cardiovascular risk, and as you indicated, the FINEARTS-HF trial tells us that finerenone addition would be helpful. But this patient is also at an increased renal risk, right? Kidney output says very significant albuminuria and the low eFGRs. So how would his kidney risk be impacted by the addition of finerenone?

Dr. Mc Causland:
FINEARTS was enriched for patients who had a diagnosis of heart failure with mildly reduced or preserved ejection fraction. And the median albuminuria in patients in FINEARTS-HF was around 18 mg/g. That's in stark contrast to the other trials, for example, FIDELIO-DKD, which enrolled patients with chronic kidney disease, type 2 diabetes, and significant albuminuria, at least 200 mg/g. So overall, the risk of future kidney advance in patients with FINEARTS-HF was markedly lower than the patients from FIDELIO and the other DKD studies.

That said, we looked at this in a lot of detail, and the kidney composite outcome in FINEARTS-HF, which was one of the key prespecified secondary outcomes and was a composite of kidney failure, so that was adjudicated to dialysis or kidney transplantation, a sustained eGFR decline of 50% or greater or a sustained eGFR decline below 15 mL/min. The overall number of events was actually pretty modest in FINEARTS-HF, again, reflective of the overall low kidney risk of this population, and so there was a non-significant difference in terms of finerenone versus placebo in terms of reducing kidney events.

What was probably a little bit more intriguing, though, was when we looked at the eGFR slope difference. And, again, finerenone, not unexpected; its mechanism of action, there's an acute expected initial decline in eGFR. And for finerenone, relative to placebo, that was about 2.9 mL/min over the first 3 months of the study.

The other data, then, looking at the longer-term eGFR slope and the median follow-up in FINEARTS-HF, was about 2.6 years. So from 3 months to the end of study, we actually saw pretty parallel curves in terms of eGFR decline.

Two important notes there: the placebo rate of decline was actually very modest as well; it was about 1 mL/min/year and with no significant difference between the finerenone arm and the placebo arm. So certainly no evidence of any worsening kidney function over the duration of the rest of the study.

Second big point was even though this was a relatively low albuminuria target, we still had a significant number of patients with more moderate albuminuria, and when we examined the UACR curves, we saw a very significant 30% reduction in UACR relative to placebo over the first 6 months of the study, and, very importantly, that was sustained throughout the course of the rest of the trial.

We also examined the risk of new-onset micro- and macroalbuminuria, which were, again, significantly reduced for finerenone versus placebo. As we all know, as we said before, albuminuria is a very potent risk predictor of adverse kidney and cardiovascular outcomes in these patients.

Dr. Kovesdy:
So as we know, an additional concern with MRAs in general, including finerenone, is hyperkalemia risk. How did that work out in the FINEARTS-HF?

Dr. Mc Causland:
Yeah. So finerenone as, again, is a nonsteroidal MRA and does have actions in terms of potassium, as one might expect. And we did see across the FINEARTS Heart Failure study itself, and extended studies with finerenone, an increased risk of hyperkalemia compared to those who were on placebo.

I think the important takeaway in this matter, in my opinion, you know hyperkalemia is now a very manageable condition as long as you're paying attention to it. And so I think in that respect, we didn't see a large number of events of hyperkalemia causing hospitalizations, and we didn't see any deaths, which is a very clinically important and relevant point.

So, again, I think hyperkalemia, pay attention to it; it's manageable. And I think the important other caveat is there was an agent that increases potassium; we also saw a lower risk of hypokalemia, which is a very important consideration for patients with heart failure.

Dr. Kovesdy:
Especially in this population.

Dr. Mc Causland:
Especially in patients with heart failure for sure.

Dr. Kovesdy:
Well, this has certainly been a fascinating conversation, but before we wrap up, Finnian, what's your final take-home message?

Dr. Mc Causland:
I think, again, the case presentation was a very common clinical presentation of a patient with heart failure with mildly reduced or preserved ejection fraction with a host of other metabolic abnormalities. I think the overall message from FINEARTS-HF is that we see a significant risk reduction in terms of heart failure, hospitalizations, and cardiovascular death, and the primary results of FINEARTS-HF. And our additional data that we just presented gives additional information for both clinicians and patients themselves in terms of the expected changes, one might see in both creatinine, eGFR, and potassium in terms of these patients who will be treated with this medication.

Dr. Kovesdy:
Excellent. Well, this has been a great bite-sized discussion, but our time is up. Thanks for listening.

Dr. Mc Causland:
Thanks very much.

Announcer:
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