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FIGARO-DKD and FIDELITY Analysis: Key Takeaways

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Dr. Bakris:
Thank you for joining us today. This is CME on ReachMD, and I'm Dr. George Bakris. Today I'm joined by Drs. Agarwal and Pitt. Dr. Pitt, why don't you start us off with a top-line overview of the FIGARO-DKD findings reported at the ESC.

Dr. Pitt:
Well, before I give you the findings, I'd just like to briefly review the FIGARO trial. I think most of the audience knows about the previous trial, where you, in fact, showed that finerenone in people with more severe renal disease reduced renal outcomes as well as cardiovascular outcomes. Now the FIGARO is sort of a companion trial with overlap in the populations, and it's much milder. Overall, a higher GFR than was in the prior trial of finerenone, and included patients who had microalbuminuria, diabetes, and some of them had a reduced eGFR, from 25 up, but some of them had a normal eGFR and albuminuria. And these people were randomized to finerenone, which is the nonsteroidal, mineralocorticoid receptor antagonist, at a dose of 10-20 milligrams. And before they were randomized, they had a run-in period where a baseline therapy was optimized. And I must emphasize that we excluded people who had known heart failure and reduced ejection fraction because the MRAs are a Class I indication for people with heart failure and reduced ejection fraction. So this was a primary diabetic and renal population over a wide spectrum of renal disease, and the primary outcome was a cardiovascular outcome, which is cardiovascular death, stroke, MI [myocardial infarction], and heart failure hospitalization. And there were secondary outcomes, renal outcomes, looking at 40% reduction in eGFR, looking at 57%, looking at ESRD, and we looked at other things – changes in slope, changes in albuminuria, but the primary outcome was cardiovascular. And there was a significant 13% reduction in the primary outcome. And this was driven primarily by reduction in heart failure. So there was a 30% reduction in heart failure in these people with diabetic nephropathy, many of them who had a normal GFR and microalbuminuria. And I think that is really important, because I know that many diabetologists really pay attention to people with diabetes and albuminuria, but many of us in cardiology, when we see a normal GFR, we've not been prone to look at albuminuria. And I think the results here, showing that over the spectrum of renal disease is – including these people who have a normal eGFR and microalbuminuria – that we had a reduction in cardiovascular outcomes. Now the primary renal outcome was a 40% reduction in eGFR, but this wasn't significant. But the more robust outcome that has been used in most prior trials, and in all the SGLT2 trials and many prior trials, the 57% reduction was significant, and most importantly, there is reduction in end-stage renal disease.

And I must say that this was accomplished with relatively few episodes of hyperkalemia. There was an excess of hyperkalemia, but the number of people who dropped out because of hyperkalemia compared to placebo was less than 1%. It was, I think, 0.4% in placebo, one-point-something percent in the finerenone group. So we have a drug that was given to a large number of patients – over 7,000 patients – and followed for several years, and we've shown cardiovascular benefits and we have clues of renal benefits, and importantly,

this was very well tolerated. So I think that is the main message that I take from this trial.

So, Dr. Bakris, I've told you what the top-line results are. How do you think this will influence practice or what we already know about the MRAs?

Dr. Bakris:
Well, I think this is a major breakthrough, because historically, MRAs have been known to be beneficial, especially in heart failure, but that's with reduced ejection fraction. We now have data in preserved ejection fraction, and we not only have data on heart failure, but we have data on kidney disease. And so I think for the first time, people have been scared to use these agents because of hyperkalemia, and as you correctly pointed out, these drugs are very well tolerated. Hyperkalemia did occur, but far, far less than one would have expected when used in other situations similar to this, and so I think it is a major breakthrough to use with the armamentarium that we already have.

Dr. Agarwal, what are your thoughts on this?

Dr. Agarwal:
So, George, I completely agree with you. I think that, as you pointed out, this trial excluded people with heart failure with reduced ejection fraction, but MRA is a Class I indication, and we are not talking about heart failure patients in this trial. We are talking about people with type 2 diabetes and CKD, and this is a population that typically is not in the radar screen of physicians who take care of them, such as cardiologists or primary care, because they think, "Oh, you've got kidney disease, and you ought to be seeing a nephrologist." Now this trial is practice changing because 62% of the patients in this trial had a GFR more than 60, which is a creatinine-silent zone. These are people who won't be identified by your eGFR. And yet, they have kidney disease. So how do we pick them up? Well, we have to look at albuminuria. If they have albuminuria, then you ought to be on finerenone because it will reduce your cardiovascular risk and kidney failure risk, and that's really the major message. So the cardiologists might think, "Okay, what's new here? MRAs are indicated for heart failure." Well, this is a trial that excluded patients with heart failure, and we are simply identifying these patients to be at high risk because they have chronic kidney disease and type 2 diabetes. And chronic kidney disease is not based on eGFR; it's mostly based on albuminuria. So that's the practice-changing part of the trial, in my opinion.

Dr. Bakris:
Okay, very good. Rajiv, why don't you tell us about the FIDELITY Analysis, which really incorporates the FIGARO and the FIDELIO trials?

Dr. Agarwal:
So, yes, George, FIDELITY is an analysis, not a trial. And the reason that it is an analysis is because it's looking at individual-level data in a broad spectrum of patients with Type 2 diabetes and chronic kidney disease. So the chronic kidney disease is defined as eGFR more than 25 in these analyses, so – and that's where finerenone is indicated – eGFR needs to be more than 25. We didn't have too many patients less than 25. There were some, but not too many. And it would be indicated in people where potassium is less than 5. So 5 or less, so you can have upper limit as 5. So this is the broad population of patients. More than 13,000 patients who are followed for more than 2 1/2 years median. And we are looking at the cardiovascular outcome, which is a 4-point MACE, which is cardiovascular death, stroke, MI, and hospitalized heart failure. And then we are looking at kidney failure outcome, and in the FIDELIO, we prespecified a 57% reduction in eGFR. That's a strange number, and it's roughly doubling of serum creatinine or patients getting on dialysis or dying of kidney failure – death. So these are very few people. So those are the two components of the analysis – more than 13,000 patients – and we find that taken together, finerenone significantly improves the primary outcome which is the cardiovascular outcome.

The second important finding is you have about a 20% relative risk reduction for going on dialysis. That's the most dreaded complication of kidney disease, and using finerenone in this broad population reduces that risk. The risk of discontinuations due to hyperkalemia were relatively small. In part, it's because we specified that people with the high potassiums wouldn't get into the trial, and we managed the potassium fairly well. And so we have had not very much hyperkalemia. And there were no off-target side effects of finerenone, so it's a fairly clean drug, except for some hyperkalemia. Those are top-line results of FIDELITY.

Dr. Bakris:
So, Bert, what excites you about the FIDELITY Analysis, which is really kind of a best of both the studies?

Dr. Pitt:
Well, it really convinces me that finerenone is really effective in reducing cardiovascular outcomes and renal outcomes across, really, the spectrum of renal disease in people with diabetes. And, of course, I think everyone has been focused in diabetes on the SGLT2 inhibitors and the GLP-1 receptor antagonists. And the numbers in our trial were not overwhelming, but there's enough to say, I believe,

that finerenone works on top of a SGLT2 inhibitor and on top of a GLP-1 receptor antagonist. We seem to have the same benefit. In fact, there is some preclinical data that suggests when you put finerenone and an SGLT2 inhibitor together, you have added effects, but we can't really say that from our trials because the numbers are kind of small and that really needs further work. But we are pretty confident, from the data we have, that it works on top of a SGLT2 inhibitor or a GLP-1 receptor antagonist.

Dr. Bakris:
I mean I have to agree with you. There are basic science data that actually support what you said. The clinical data, as you correctly point out, are limited, but certainly trend in that direction. So we've come to a close here. I want you all to give me kind of the top impression you want to leave with the audience. And, Bert, I'll start with you.

Dr. Pitt:
Well, I think in people who have renal disease and diabetes, first of all, as a cardiologist, it's made me more aware that I should be looking for albuminuria, even with a normal eGFR. And I should be starting an MRA, and the only MRA I know that I can really start at the moment and have it tolerated to get the effects is finerenone, and that gives me tremendous cardiovascular benefit and eventually protects my kidney diseases from progressing as well.

Dr. Agarwal:
So, George, my single message to people who take care of people with type 2 diabetes is that, yes, I know you order a blood test, but if you want to protect the heart, you got to look at the urine. And you might say not CRP. I said, no, forget about CRP; look at UACR. So what's UACR? It's urine albumin-to-creatinine ratio. And that you can order in anybody who is coming to your office. Only 1 in 5 people in the United States have that test done, and that's dismal. This is not of academic interest anymore, because if you have a UACR that is more than 30, which is the threshold for microalbuminuria, you have a treatment option now that can reduce kidney failure and heart failure, and that's a big deal for our patients.

Dr. Bakris:
I couldn't agree more. I want to remind the audience to extend what you said, and that is you really don't know what stage of kidney disease the patient is in unless you measure albuminuria. The recommendations and the guidelines are to measure albuminuria. And so I think it's very clear that albuminuria, with all due respect for cardiologists, is probably more powerful than CRP to predict cardiovascular outcomes as well as renal outcomes.

Thank you very much to both of you for joining me today. This has been a great discussion, hot information coming out that's going to change clinical practice. So I'm George Bakris for ReachMD. Thank you for joining us and have a good day. Goodbye.

Dr. Pitt:
Thank you.

Dr. Agarwal:
Thank you, George. Great to be here.

Announcer:
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