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COMMENTARY

The FIDELIO Study Podcast

Robert Toto · George Bakris

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DIGITAL FEATURES

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R. Toto
Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, USA

G. Bakris
Department of Medicine, University of Chicago Medical Center, Chicago, IL, USA

G. Bakris (✉)
Hypertension Center, University of Chicago Medicine, 5841 S. Maryland Ave, Chicago, IL 60637, USA
e-mail: gbakris@gmail.com

PODCAST TRANSCRIPT

Robert Toto (RT): Professor of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas.
George Bakris (GB): Professor of Medicine and Director of the American Heart Association Comprehensive Hypertension Center, University of Chicago, Chicago, Illinois.

RT: Hello, everyone. Welcome to this podcast. My name is Robert Toto. I'm a Professor of Internal Medicine at the University of Texas Southwestern Medical Center in Dallas. I am joined by my friend Dr George Bakris. George, welcome.

GB: Thank you, Bob. It's a pleasure to be here. I'm a Professor of Medicine and Director of the American Heart Association Comprehensive Hypertension Center at the University of Chicago. I think we're going to have a very nice conversation today about some very new findings.

RT: So let's jump right in. George, you were a lead author on the FIDELIO study [1], and that is what we are here to talk about. What I would like to do is to begin by giving the audience some background on the design and conduct of the FIDELIO study, just so that we can have a foundation for the discussion we are going to have.

GB: FIDELIO was really part of a finerenone program. Finerenone is a novel nonsteroidal

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mineralocorticoid receptor antagonist [MRA], and we designed a program around this. We had the FIDELIO study; there was also the FIGARO study, which was a sister study; and then we had the FIDELITY single-patient analysis of both trials together. The point was that FIDELIO was a renal endpoint trial in diabetes, FIGARO was a cardiovascular endpoint trial in diabetes, and then FIDELITY integrated both of them in one analysis to look at the spectrum of the effect of this class of agents in diabetes with kidney disease and high cardiovascular risk.

So, FIDELIO involved people with average estimated glomerular filtration rates [eGFRs] around 44 mL/min/1.73 m^2, albuminuria in the range of 850 mg/day, and clearly a higher cardiovascular risk. We excluded patients with heart failure because spironolactone, the steroidal MRA, is mandated in this population and we did not want to cloud the analysis with patients treated with this drug. In total, over 5000 patients were studied, and the median follow-up was around two and a half years.

RT: We should also mention that all of the patients enrolled in the study had to be on the maximum dose of an angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]. The reason I bring that up is because I wanted you to delve briefly into the rationale for adding an MRA onto that kind of treatment background in this patient population. It is an area where we have been working for many years to try to make some progress, and you have finally succeeded.

GB: I want to thank you very much for bringing that up, and I apologize for the oversight on my part, as that is one of the distinguishing features of this study. We mandated that people be enrolled not just receiving an ACE inhibitor or an ARB, as in most if not all previous diabetes studies, but they had to be on the maximum tolerated doses. Why? Because in all previous renal outcome studies, it was people receiving maximal doses, rather than those at low doses or those who had been treated for a while and then stopped, that achieved the most benefit.

One of the major reasons for using an MRA in FIDELIO is because patients with diabetes experience a lot of inflammation, and we know from previous studies that drugs such as spironolactone have anti-inflammatory activity. Traditional agents, such as the renin–angiotensin system [RAS] blockers, even the sodium-glucose cotransporter 2 inhibitors [SGLT2is], do not do a great job of quelling inflammation; they reduce it, but they do not really make it go away. The nonsteroidal MRAs add to that benefit in terms of being anti-inflammatory, and ultimately antifibrotic if you wait long enough. And the advantage we had with finerenone was that although it was associated in some elevations in potassium like other drugs in the family, the extent was not as great as seen with steroidal MRAs.

RT: I think that is a key point, especially because of the results that you were able to demonstrate with the study. You gave us a very nice background on the design of FIDELIO. It was a randomized, double-blind, placebo-controlled study in nearly 5700 patients. What about the ranges of eGFR reported among the FIDELIO population?

GB: Patients were eligible for inclusion if they had eGFR levels as low as 25 mL/min/1.73 m^2, and on the high end we had patients with eGFR levels into the 60s [mL/min/1.73 m^2]. Baseline albuminuria in this study also varied widely among patients. People were included if they had persistent microalbuminuria (UACR [urine albumin–creatinine ratio] of $\geq$ 30 mg/g but $<$ 300 mg/g) and eGFR $\geq$ 25 but $<$ 60 mL/min/1.73 m^2 and presence of diabetic retinopathy, but those with persistent very high albuminuria (UACR of $\geq$ 300 mg/g) and eGFR $\geq$ 25 but $<$ 75 mL/min/1.73 m^2 were also eligible. There was therefore a huge range, both in terms of eGFR and albuminuria.

RT: One of the things that always comes up with these studies in diabetes is the control of other comorbidities such as glycemic control and blood pressure control. I assume that all of these factors were evenly balanced between groups with the randomization in the study.

GB: They were absolutely evened out. Average hemoglobin A1C and systolic blood pressure levels were well controlled and similar

between groups. We also looked at lipid management, and I recall approximately three-quarters of patients were on lipid-lowering therapy, so this was a very well-controlled population.

RT: Due to concern for the potential for hyperkalemia, I believe that you also had a cutoff potassium level in order to be able to enter the trial.

GB: When screened, patients were required to have a serum potassium level below 4.8 mmol/L. However, there was a subset of individuals that had a potassium level of 5.0 mmol/L when measured at baseline, despite being below 4.8 mmol/L at screening, and those patients were allowed to continue in the study. It is for this reason that the FDA [US Food and Drug Administration], when labelling the finerenone, allowed patients with a potassium level up to 5.0 mmol/L to be prescribed the drug.

RT: What are the key findings from FIDELIO that you wanted to discuss today?

GB: Treatment with finerenone reduced progression of kidney disease in a statistically significant way. Cardiovascular events were also significantly reduced. There was an 18% risk reduction in the composite kidney outcome and a 14% reduction in the composite cardiovascular outcome in favor of finerenone, and both were significant. Cardiovascular events were a prespecified secondary endpoint, and so the study was statistically powered to detect a difference in this outcome.

RT: Safety-wise, things looked pretty similar between groups. The main difference from my recollection was hyperkalemia. Do you want to comment on that, because I think it is important for the listeners to know about the magnitude of hyperkalemia in each treatment group.

GB: To our amazement there was no acute kidney injury reported in FIDELIO, and there were no increases in other conditions such as urinary tract infections. Hyperkalemia was the major issue; however, it was not out of control. In fact, based on phase 2 data, we did not check potassium for 1 month after patients started on the trial. Now, if you are really worried about potassium levels, then you are not going to wait a month to check it, so clearly that was a plus.

There were about twice as many discontinuations in the finerenone group as in the placebo group, but even then we are talking about rates of 2% with finerenone versus 1% with placebo, so it was not anything egregious. The use of potassium binders during the study was left up to the discretion of the investigators. I cannot remember exactly how many patients were given these drugs, but it was much less than 100, and as a proportion of 5700 people that is not too many. Most of these patients were prescribed kayexalate, a drug that cannot be tolerated for more than a few days, so it is not anything that was used chronically and for long periods of time.

Another important finding observed in a subgroup analysis of FIDELIO was that patients receiving an SGLT2i had less risk of hyperkalemia. This represents a "double plus" with the benefits of SGLT2is together with additional protection against hyperkalemia.

RT: FIDELIO reported out on the heels of the DAPA-CKD study, and the CREDENCE study was published a year or so before that. I am not sure that you can directly compare FIDELIO to DAPA-CKD or CREDENCE, but maybe you can. How would you put FIDELIO in perspective in comparison to these SGLT2i studies [DAPA-CKD and CREDENCE]?

GB: This is an interesting question, because we were told by a number of people that because the percent risk reduction in the primary endpoint in FIDELIO was lower than that observed in CREDENCE, the treatment was not as effective. However, from a pure clinical trial standpoint, direct comparisons between these studies can be problematic. So, what we did, with the help of Dr Rajiv Agarwal, who really led this, was to conduct a proper head-to-head analysis comparing FIDELIO to CREDENCE, the results of which are published in *Nephrology, Dialysis and Transplantation*. We conducted a propensity match analysis to examine people that had similar levels of heart disease, similar levels of kidney disease, and similar interventions. When patient groups were matched and analyzed, a 30% risk reduction was observed in CREDENCE compared to a 28% risk reduction

in FIDELIO. So, the bottom line is that there is no meaningful difference between the results of the two studies.

The question often asked is do you treat with a SGLT2i or do you treat with finerenone. Obviously, there are more data on treatment with SGLT2is, and their use is covered in current guidelines, but the forthcoming ADA [American Diabetes Association] 2022 guidelines will also include finerenone. Therefore, I believe that nephrologists and diabetologists will have to think about this in a totally different mindset: not choosing one drug versus another drug, but adopting, as my friend John McMurray says, a "pillars of therapy" approach, where RAS-blocking drugs, SGLT2is, and the nonsteroidal MRA finerenone can be used in parallel. We may also in a couple of years have more evidence for the effectiveness of the glucagon-like peptide 1 [GLP-1] receptor agonists, so we are in an expansive phase in nephrology, something we have waited 20 years for.

RT: Do you also want to talk a little bit more about FIGARO and FIDELITY since the results of these studies will potentially expand our horizons in terms of where FIDELIO fits into the armamentarium across the spectrum of people with diabetic kidney disease?

GB: FIGARO was a larger trial of over 7000 people with cardiovascular disease. The mean eGFR among patients entering the study was in the low 60s [mL/min/1.73 m^2], higher than in the renal study. The majority of these people had microalbuminuria, and so did not have heavy proteinuria. The primary endpoint in FIGARO was cardiovascular outcomes, although the study was also powered to compare renal outcomes. Finerenone was shown to significantly reduce the risk of cardiovascular outcomes, a difference predominantly due to the lower rate of heart failure hospitalizations with finerenone. Of interest to nephrologists is that the difference between groups in patients having a 40% reduction in eGFR just missed significance. However, the proportion of patients experiencing a doubling of serum creatinine levels (that approximately corresponds to a 57% decline in eGFR) was highly significant in favor of finerenone.

This is important because the FDA, along with a large group of us back in 2012, looked at the issue of change in eGFR, and if you have an initial decline in GFR—as you do with finerenone, as you do with SGLT2is, as you do with RAS blockers—doubling of creatinine or a 57% reduction in eGFR is really the only thing that is acceptable. Everything else is interesting, but you really want that doubling of creatinine, and that was achieved in FIGARO.

The last thing I want to tell you about FIGARO is that the people that got the greatest benefit were those with high cardiovascular risk and microalbuminuria; in this subgroup, the reduction in end-stage kidney disease [ESKD] was over 30%.

RT: In studies in diabetic kidney disease, regardless of the intervention, I think that people want to know whether the results had anything to do with better glucose control and/or better blood pressure control. I think it is important to comment on that.

GB: In both FIDELIO and FIGARO, there were no differences between treatment groups in glycemic control, blood pressure, or any of the classic risk factors that you would imagine could influence this. In fact, the conclusion of Bertram Pitt, a cardiologist and lead author of FIGARO, was that cardiologists will have to start measuring albuminuria now, because that is really the key.

In FIDELITY, over 13,000 patients from the FIDELITY and FIGARO trials were analyzed, and results showed a significant reduction in composite kidney and cardiovascular outcomes. Significant decreases in heart failure hospitalizations (22% risk reduction) and ESKD (20% risk reduction) were also observed. I do not think there is any question that these drugs provide cardiorenal protection, and not at a big premium. I forgot to mention that in FIGARO, although hyperkalemia was twice as high in the finerenone group compared with placebo, the rates were 1.2% versus 0.6% in 7200 people—nothing that I am going to get excited about.

RT: It looks to me, when I look at FIDELIO and FIGARO taken together, that finerenone can benefit a broad spectrum of people, not just those with ESKD. So, when the question of who is likely to benefit from finerenone comes up,

you can include a lot of patients with DKD [diabetic kidney disease]. It is not such a narrow range of patients as when you and I were involved in the RENAAL and IDNT studies back in the late 1990s and early 2000s.

GB: I think that you raise a very important point here: that you do not need to have advanced kidney disease to benefit from treatment with finerenone. There were people in these studies with eGFR levels in the high 70s [mL/min/1.73 m^2] that saw benefit. We have had people ask how we know that patients had diabetic disease, and the answer is because we checked retinopathy. If a patient had microalbuminuria and did not have retinopathy, they were excluded from the study. These are important little "by the ways" that I think reinforce the quality of the data.

RT: You previously mentioned the "pillars of therapy" approach. It seems clear that finerenone can be used in combination with SGLT2is, and, as you pointed out, in both FIGARO and FIDELIO a subgroup of patients did receive treatment with a SGLT2i. You also stated that in the future, GLP-1 RAs could potentially be considered as another pillar of therapy. Can you foresee finerenone being used in combination with a GLP-1 RA?

GB: In total, there were over 800 people out of 13,000 in FIDELITY that were receiving SGLT2is—not a huge number, but enough for a small subgroup analysis.

Small subgroup studies in FIDELITY have analyzed outcomes in patients also receiving SGLT2is (not yet approved when these studies started) or GLP-1 RAs. There was a trend that both drug types improved outcomes, but not significantly so.

GLP-1 RAs have been shown to provide cardiovascular risk reduction, including for stroke. Neither SGLT2is nor finerenone provides benefit in reducing stroke. Could you derive stroke benefit by combining the two? Well, we do not have enough data from enough people to make that statement, but it would be interesting to look at.

RT: I think that the fact that finerenone has clearly shown benefits in improving both kidney and cardiovascular outcomes makes it a valuable addition to ACE inhibitors, ARBs, and SGLT2is in our armamentarium for the treatment of DKD.

George, thanks very much for reviewing these data and helping our audience to get your perspective on it. Before we wrap up, are there any other points you would like to address?

GB: Bob, thank you very much for having me. I think we did an excellent job of covering all of the major issues. Finerenone is effective, although it is not a great blood pressure-lowering drug, and distinctly different from spironolactone and eplerenone pharmacologically and in many other ways, and far better tolerated. So, I think that we are in a new era, and we need to grasp the opportunity and move forward with it.

RT: I agree. I am glad you mentioned that, because I think that finerenone is clearly an advance on existing MRAs because of the nature of the molecule, and other reasons that we do not have time to go into. These differentiate it from spironolactone, and clearly, we do not have any studies like FIDELIO and FIGARO with spironolactone, so the success of being able to add an MRA to other drug treatments in this patient population and get a really important result for patients I think is really setting it apart.

I think that concludes our podcast. Thank you, George, for your time and insights today. We hope that this has been of interest to our listeners.

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