Transcription

CMHC 2022 AHA Symposium: What You Need to Know About Optimizing Cardiorenal Outcomes with Novel Nonsteroidal MRAs

DR. GEORGE L. BAKRIS: Well, okay, we'll start a minute early. Well good evening and thank you for coming. Let's see, we have a capacity crowd. Very good, there are some housekeeping things that I have to tell you about. There is a CME pretest that we're going to do here in a second. It's going to be very brief. But then we're going to go through it at the end. And then, we're going to have a series of talks that are going to focus on the topic that you see.

And hopefully, you'll get something out of this besides dinner. So, let's just dive in. The faculty are here, and you can see them, myself, George Bakris, professor of medicine at the University of Chicago, Professor Rajiv Agarwal from Indiana University, Sylvia Rosas from the great Joslin Diabetes Center, associate professor, and the great Pam Taub, who is coming to us all the way from California, professor of medicine.

And we're going to put together a program for you that we hope you'll learn something from and at the same time is enjoyable. So, these are just things that you can look at. This is sponsored by Bayer. All CME information and faculty disclosures can be found online, for those of you who are interested in that kind of stuff. The learning of objectives are here. I'm not going to read them to you. They're pro forma.

And this is important. The iPads are available where you're sitting, and this is your communication link to submit questions or ask questions. And we will get them up here and hopefully address them. So, if we can go to the next slide – can we go to the next slide? Next slide, please. I'm not doing a song and dance, so don't even think about it. Are you ready to go? You're sure? Okay, here you go. So here are the questions that you have to go through, your first salvo.

So, the presence of chronic kidney disease, that is an eGFR less than 45 with greater than 30 mg the albuminuria associated with a high risk of kidney disease progression, is a cardiovascular risk factor, is associated with a high risk of heart failure, has no significance until eGFR is less than 30, or none of the above? So, go ahead and answer that. I love the giant font that you have. That's great. I didn't realize it was doing an eye test.

Okay, which of the following treatments should be included to reduce the risk of diabetic kidney disease, as well as heart failure risk? Maximally tolerated doses of an ACE or an ARB, SGLT2, finerenone, chlorthalidone, A through C, all of the above? Go, you've got five seconds. Okay, next question, which of the following distinguishes finerenone from steroidal MRAs? Its half-life, its lack of metabolites, the receptor specificity, the generally good tolerability, or all of the above?

Okay, next slide, which of the following pathophysiologic aspects of diabetic kidney disease progression do nonsteroidal MRAs target? Hemodynamics, glycemic control, inflammation and fibrosis, hypertension, all of the above or you don't know, you're unsure? It's an interesting category.

Okay, next, compared to steroidal MRAs, nonsteroidal MRAs are associated with which of the following? Increased risk for hyperkalemia, reduced risk for hyperkalemia, increased risk for sexual side effects, equal selectivity and potency for the MR inhibition, or you just have no clue, you're unsure?

Okay, next slide – in the results of the FIDELITY primary analysis there was a significant reduction in? CV morbidity and mortality and little or no reduction in the risk of CKD progression, there was no statistical reduction in both CV morbidity and mortality, as well as CKD progression, there was a significant reduction in both CV morbidity and mortality as well as CKD progression, or, again, you have no clue?

Okay, next, a 65-year-old female presents for follow-up for previously diagnosed diabetes and has a history of hyperlipidemia and hypertension. She is currently on metformin 500 BID, atorvastatin, and lisinopril. The exam and labs reveal a HbA1c of 7.8%, serum creatinine of 1.3 – that's in the eGFR of 45 – serum K of 4.5. Her CBC was within normal limits. Her LDL was 96.

What is the next step in the evaluation and treatment of this patient? Increase the dose of metformin, order urine albumin to creatinine ratio, order a lipid panel, or refer to a nephrologist? For the same patient, 90 days repeat labs show that the HbA1c is 7.5, the eGFR is 52 and the uACR is 58 with a BP of 128/88. She is currently also on dapagliflozin 10 mg a day. What would be the most appropriate next step? Wait and repeat labs in another 90 days, add a GLP-1 RA, add finerenone and monitor K, add a TZD?

Next, okay, thank god we're through that. All right, it's coming back. We're not done yet. Is coming back at the end, okay, so I want to talk to you and set the stage here for the next talks. I'm going to talk to you about the interrelationship between the heart and the kidney in a metabolic milieu. And this is important, especially for those of you out there that are cardiologists because I can tell you right up front, the point I'm going to make is that having kidney disease is a cardiovascular risk factor, not a marker.

These of my consulting fees. There you go. So, the interrelationship between the metabolic system, heart, and kidneys is well-recognized. And you can see here that if there's acute dysfunction of either the heart or the kidney, or there is a change in the metabolic milieu, these organs will be affected. The kidney is a regulatory organ. It's going to respond to the milieu that it's presented with and try to adjust and make accommodations to balance things out and bring things back to normal.

Metabolic dysfunction adds to cardiac risk in kidney burden and you can see this here. I'm not going to go through this with you it sets the stage that if you have insulin resistance, that if you have difference increased adipokine inflammatory markers coming out, that's going to affect not just hemodynamics, but is going to affect fluid retention and kidney responses as well as cardiac function. Cardiac dysfunction, I think is obvious.

And most cardiologists know that if the heart function – if the heart pumping ability is reduced – kidney function is reduced. And it's a pretty simple relationship. And I think it's important to understand that increasing insulin resistance and adding metabolic disturbances to that situation further increases the risk of harm. And kidney dysfunction definitely affects the heart. It's not just because of volume.

But it also has changes that result as kidney disease progresses in the gut microbiota and a whole host of other metabolic changes related to that. So, a patient with early type 2 diabetes is at increased risk of complications due to metabolic disturbances and the interconnected risk factors that you can see there, and ultimately leading to a lot of consequences that you are familiar with. CKD and heart failure are the most frequent first cardiorenal disease manifestations in patients with type 2 diabetes.

And you can see this in this analysis, heart failure is an early, highly prevalent and often asymptomatic complication in patients with type 2 diabetes. And again, you can see that 68% of patients who had type 2 diabetes for five years showed signs of asymptomatic LV dysfunction. And when you look kidney disease as an early or kidney disease is an early and highly prevalent complication in patients with type 2 diabetes.

And I want to point out to you the figure on the right looking at the prevalence of microalbuminuria and the worsening of the disease in the proportion of patients over time. So, albuminuria should not be dismissed. Albuminuria is the kidneys product to tell you how bad it sees the situation. If you ignore it, then you're at your own peril. Patient does not revolve around the heart. It revolves around the interaction of what these organs are seeing and what they tell each other.

And so when you look at the coexistence of type 2 diabetes and kidney disease, it is associated with increased mortality. I think everybody in the room knows that. I don't have to waste my time showing you this. And likewise, when you look at heart failure and kidney function decline, they are interconnected. So as heart function decreases, kidney function will decrease. And as kidney function decreases, cardiac function will decrease.

And you can see the analysis here of people with and without heart failure and incident CKD. And so, this is again epidemiologic data but it makes the point. So this is the seminal study that was done at Kaiser but it makes the point that if your eGFR is below 45, you have a dramatically increased risk of all-cause mortality of about 4.7-fold and cardiovascular events that are up over 11-fold. And it gets worse. It goes up geometrically, not linearly.

So, it's important to recognize what kidney function is in the context of cardiovascular events. And this just points out an analysis, again, and epidemiologic analysis. If you look at the left, these are people with CKD. And you can see heart failure here accounts for 43% compared to people without CKD, heart failure is about 18.5%. So, heart failure is the major issue that you have to focus on.

Now as far as kidney disease progression, we know that ACEs and ARBs need to be used and not just ACEs and ARBs five of lisinopril or lig doses of enalapril, real doses used in the trials at the dosage used in the trials. And even then, we have a tremendous amount of residual risk. Then, we had nothing for 15 years, 20 years. And then we have our friends, the SGLT2s, who allegedly were glucose-lowering agents. And low and behold, they kind of fixed everything.

You can see here a summary of the data both with kidney outcomes and cardiovascular outcomes. And you can see how sick these patients were by looking at the uACR, the far right, and where there on the KDIGO heat map. So, you can see these people have advanced kidney

disease. This is a meta-analysis looking at people with and without atherosclerotic cardiovascular disease. And you can see very clearly the kidney benefits are across-the-board.

It's irrelevant what trial you want to pick, irrelevance whether they had atherosclerotic disease or not. The kidney received a benefit. So, these are cardiorenal risk-reducing agents that happen to lower glucose if you've got good kidney function. This looks at heart failure outcomes. And you can see SGLT2s win big. GLP-1s do not. You know this, but it's summarized here.

So the ADA guidelines very clearly state that–these are the 2022 guidelines–clearly state that you should be giving you SGLT2s to people with heart failure or GLP-1s to people with atherosclerotic cardiovascular disease. And if you need glucose control, be my guest. Use metformin if kidney function is there. But that really should be your priority. Now we have a newcomer and that is a nonsteroidal MRA. We have agents that fulfil hemodynamic effects, metabolic effects.

We've reduced the residual risk, as you can see here. And now, we still have a lot of risk. So, we still have a ways to go. Guess what I'm building for you? The cardiologists in the audience are very familiar with this. I'm building pillars of therapy for you. Nephrologists don't know this concept. They should, but they don't. And so the reality is, we need to start using multiple agents, not pick one, forget this because if you do that, that's what you're going to get multiple benefits.

And so, the FIDELIO trial was the first trial that looks at this in a patient population of people with diabetic kidney disease and advanced kidney disease. And you can see that one trial. There was the FIGARO trial, which was a cardiovascular outcomes trial. Together, because the protocols were the same and inclusion criteria were different, we were able to do an individual patient analysis. And professor Agarwal was the one who led this. He's in the audience. You're going to hear from him later.

But this is the overall bottom line here. 13,000+ patients were randomized between the two trials. The prerequisite of this trial compared to all of the trials is, every patient had to be on a maximally tolerated dose of an ACE or an ARB not five of lisinopril. Whether they be on 40 of lisinopril, that's great, but that's what you needed to be on because that's what was used in the trial. So, you needed that as background. Then you came in if your eGFR was less than 60. You got 10 mg of finerenone. If it was 60 or greater, you got 20.

And we did not check potassium the first month because we knew it was not a big deal because we had data from the previous trial, the ARTS-DN that show the potassium increases were not that dramatic and we did not need to worry about them the first month. So, let's be clear this is not your mother's spiro and I'm going to show you that in a minute. Look at the heat map. Look how much work covering in terms of area. That was not what was there before. So, let's talk about the nonsteroidals.

Here's the steroidals up on top and the nonsteroidals are on the bottom and we're focused on finerenone. So, you can see chemically, they are very different, but you could care less, I'm sure. But this is an important slide that you need to pay attention to because this looks at structural properties. They're clearly different. The potency is similar to spironolactone

without all the extra garbage that spironolactone brings you.

It's highly selective, far more selective than spiro or even eplerenone. There is no CNS penetration. There are no sexual side effects and the half-life is two-to-three hours, not three weeks. And there's no active metabolite. And there is an effect on blood pressure. That paper was just published, and you need to be aware if your blood pressure is elevated, there is an effect. So again, just making the point, the primary endpoints here MACE endpoint with hospitalization for heart failure and doubling of serum creatinine, ESRD, or renal death.

Those are the renal endpoints. Dr. Agarwal is going to show you the data from that but I just wanted to point out to you there is a joint ADA/KDIGO guideline that has come together. And for the cardiologists in the audience, you need to know that the ACC reviews the cardiovascular indications from this guideline. So, it's really a triple threat in the sense of everybody's got a buy-in. But you can see here, as I said earlier, that SGLT2s have to be in the drinking water if you have heart failure.

And metformin can be used, which is fine. ACEs and ARBs need to be in there. And then, if you have significant albuminuria or do you have any kind of residual albuminuria that has been reduced but is still high given the level blood pressure, then a drug like finerenone needs to be added and, in fact, it has nothing to do with glycemic control. So I think you have to understand. If you have a patient that's coming in with an eGFR of 45-50 and he's got 400 mg of albuminuria, you put them on an SGLT2, you got here on max out doses of ACEs and ARBs, and he comes back.

And his blood pressure is 137, 136, and he's still got 150, 200 mg of albuminuria, finerenone needs to be added. And even if it doesn't, if it's lower, it still needs to be added. You need that third pillar to further slow progression. And everybody's going to say well, where's the trial that shows that? Well, I can tell you there's some meta-analysis coming out that supports the. There are good animal studies that support that.

But I will tell you cardiologists don't have a trial with all four drugs versus three drugs versus two. They give good trials and they understand the data. They're not demanding basic science-level evidence, so get a grip. I'm going to finish by basically saying that we have come to the point nephrologists should wake up, come to the point where we have pillars of therapy, RAS blockade, we've got the SGLT2s, no arguments.

And now, we have finerenone and we may soon have GLP-1s. We don't know. That will be in 2024. Stay tuned for the FLOW trial results. But that's where we are for right now. So, I hope that's been instilled in your cerebrum because we're going to move now to professor Agarwal's talk and the title is there. And I can hardly wait to see what he's going to say. Rajiv?

PROF. RAJIV AGARWAL: Thanks, George, I think you have set up the stage quite nicely to look in the MRAs. I'm just kind of going to walk you through it because to this audience, spironolactone is quite clear. It was approved by the FDA in 1960 was just a dossier that they submitted, and some animal studies and it was approved. And it wasn't until 43 years later that eplerenone was approved by the FDA for the treatment of hypertension and post-myocardial infarction in heart failure patients.

And it wasn't until 61 years later that we have finerenone approved on the 9th of July 2021 by the FDA for the prevention of cardiorenal outcomes in people with type 2 diabetes and CKD. So, if you're wondering why finerenone is indicated for heart failure of HFpEF or HFrEF, so we don't have data. That's eplerenone HFrEF but you know, eplerenone is not used in people to prevent cardiorenal outcomes in type 2 diabetes and CKD where the major indication of finerenone is.

Now many people called these drugs aldosterone blockers and it's a complete mistake. These are mineralocorticoid receptor antagonists. And the reason it is an issue is because there are three key cells, cardiomyocytes - - and monocytes where cortisol is the major activator of mineralocorticoid receptors because the three cell types lack 11b-HSD2 which can worsen the cortisol to cortisone.

And cortisone can bind to the mineralocorticoid receptor. But these cells don't have it. And cortisol circulating is about 1000 times more than aldosterone. In addition, you can activate the mineralocorticoid receptor through RAC1 and other pathways. That means you can have obesity and inflammation and they can activate the mineralocorticoid receptors. If you block this pathway, you're doing much more than simply removing aldosterone.

And that's important because I don't think we should call spironolactone an aldosterone blocker. It's a mineralocorticoid receptor blocker. I don't think we should call finerenone an aldosterone antagonist. It's a mineralocorticoid receptor antagonist. And that's the purpose of this slide. As George pointed out, the finerenone is a very different structure than a steroidal structure that you're used to seeing steroidal structures like cholesterol, which is a cyclopentanoperhydrophenanthrene nucleus.

It's four rings and it's very different. This is a dihydropyridine molecule that was discovered through a high throughput screening of about a million compounds. And then they modified the molecule to fit the mineralocorticoid receptor lay selectively so it would activate the other say androgen or progesterone estrogen receptors and at the same time, it would not have off-target effects, for example, liver necrosis or skin necrosis, things like that.

So, this molecule was actually engineered in the lab before it was tested in humans, and this is what we're going to talk about. So, why not steroidal MRAs? You might wonder, says okay, finerenone is an MRA, why can't I just use spironolactone? And the question is, does finerenone lower blood pressure? George just mentioned this about blood pressure, that it does lower it, but this is something that was just published a few days ago. It says in press but it just went online.

It's a comparative post hoc analysis of finerenone and spironolactone in resistant hypertension and moderate-to-advanced CKD. We have done a trial call the AMBER trial and AMBER trial was done in patients with resistant hypertension will have an eGFR between 25 to 45. And we were looking at the same kind of a population in the FIDELITY database. And we identified 624 patients compared to 295 patients who have participated in the AMBER trial.

We kind of matched them in terms of blood pressure and antihypertensive drugs and diuretic use and potassium range and asked the question of how much blood pressure reduction would occur if we did the Fidelity analysis in an AMBER -like population and how much

potassium would go up in an indirect comparisons study. So here are the data. You can see that the placebo drops 1.3 mm and the finerenone drops about 7 mm and it's about 11 to 12 mm change with spironolactone.

Remember that spironolactone was used in the AMBER trial in everyone. Half the patients were getting patiromer, half the patients placebo. In AMBER trial at 12 weeks, you have an 11- to 12-millimeter drop in the FIDELITY or the finerenone trials. The drop in blood pressure is 17 weeks, so a little bit longer exposure. So, it's about 60% of the effect of spironolactone. Now, when you look at the potassium, they're quite remarkably different.

The definitions of hyperkalemia are the same, potassium of more than 5.5 at the central lab. And placebo has a 3.3% incidence in Fidelity. With finerenone, you have 11.6%. If you give spironolactone by itself, you have a 64% incidence of hyperkalemia within 12 weeks and even if you give it with patiromer, it's 35%, so about tripling of the incidence even when you give patiromer with finerenone. How about treatment discontinuations?

It was just one patient in the finerenone trial who discontinued compared to 6.8% in AMBER with patiromer and 23% without patiromer. So, the data are pretty stark. Yes, you get much less hyperkalemia, and the blood pressure lowering is about 60%. But this is comparing a resistant-hypertension population. So, this is what we concluded, that yes, finerenone will reduce blood pressure a little less.

But the potassium would be one-third the incidence of hyperkalemia compared to even if you give spironolactone with a binder. Now we did two trials, FIDELIO and FIGARO. FIDELIO was in to protect kidney failure outcomes and FIGARO was to protect from cardiovascular outcomes. And we say that they're complementary trials and are they twins? Are they sisters or just cousins? And that's important because we like to do megatrials and meta analysis but we also can learn by looking at the individual trials.

And I would like to show you that really looking at the individual trials makes the most sense. We can learn more than just pooling the data. So, let me just walk you through the FIDELIO and FIGARO trials. FIDELIO DKD is 5734 patients. FIGARO DKD is 7437 patients, larger trial. Primary endpoint is kidney protection and FIDELIO CV protection and FIGARO. The mean eGFR in FIDELIO is 44 compared to 68 in FIGARO. That's an important difference.

And the median uACR is 851 in FIDELIO compared to 312 in FIGARO. And that's an important difference. Let's explore this a little further. We are looking at FIDELIO. We are trying to enrich this population to have kidney failure outcomes. So, we are predominantly taking patients who have a low eGFR, between 25 and 75 and 90% of the patients have macroalbuminuria or more than 300. We capped the 60 to 75 population with just 10% of the patients. So, you can see we have enriched the population between 25 and 60 with macroalbuminuria.

You have only 10% of the patients who have a A2 albuminuria or what we call microalbuminuria. And since there was a concern that these patients might have nondiabetic kidney disease, we said let's make sure that they have diabetic retinopathy before we include them in the trial. So, that was the rationale for including the retinopathy inclusion criteria in FIDELIO. In the FIGARO trial we are looking at cardiovascular outcomes. And we included

patients with all albuminuria ranges.

And nearly half of them are microalbuminuria 10% of the patients could be between 60 and 90 eGFR who have microalbuminuria. Now 60 to as high as the eGFR can go, if they have macroalbuminuria, we could put them in FIGARO trial. So, there's a small overlap between the two studies but by and large, we are sort of looking at two separate populations of studies because the way the albuminuria and eGFR is designed.. And here's the actual data from the overall study where you can see 87% of the patients in the FIDELIO study have macroalbuminuria.

And in the FIGARO study, half the patients have micro-and have the patients have macroalbuminuria. Number two, 62% of the patients in the FIGARO study have a eGFR more than 60. So, they have well-preserved eGFR. That's only 12% of the population in FIDELIO. So, they seemed like very different studies that we are doing because one is designed to look at cardiovascular protection. If they reach dialysis, we are sort of soiling the data.

So, we want to give them a long runway where they can have cardiovascular outcomes. Now, here's a very important slide because it shows you the cardiovascular outcomes in the placebo groups. See the outcomes, 14.8% in FIDELIO and placebo, and 40.2% in FIGARO. In other words, it didn't really matter. You have an eGFR of 44 or you have an eGFR of 67. Your placebo cardiovascular event rate, which is almost identical.

And finerenone cuts the rate by almost the same proportion, about 14%. The kidney outcome you can see is quite remarkably different. Placebo is 21% versus 10% in FIGARO. So, you can see that they're quite different. But notice this if we take people who are early in kidney disease, we really are talking about cardiovascular risk. The cardiovascular risk in a FIGARO patient is greater than the kidney outcome risk. And that's important to appreciate because many people feel that oh, FIGARO is a kidney trial.

It's really not a kidney trial. It's actually a cardiovascular trial because the cardiovascular event rate in FIGARO is 14% and the placebo rate of kidney outcomes is 10.8%. FIDELIO is a kidney trial, yes, but FIGARO is a cardiovascular trial. It's for the cardiologist to appreciate that these are people who have type 2 diabetes and kidney disease, early kidney disease. Those are the people we are treating

The absolute, relative risk reduction is approximately the same, about 14% in FIDELIO, 13% in FIGARO. The absolute risk reduction is also the same, 1.8%, 1.8%. The number not needed to treat works out to 47. But when you enrich the kidney failure outcome, you have a 3.3% absolute risk reduction which gives you a 29 NNT. And you have a nonsignificant risk reduction in FIGARO.

It's quite evident that you won't have that risk reduction in FIGARO because you are not enriching for the kidney failure outcome, the baseline rate is so low. The key question which was posed by the FIDELITY analysis was done finerenone, a nonsteroidal MRA added to maximize RAS inhibition and reduce cardiovascular disease and kidney disease progression or a broad range of CKD in patients with type 2 diabetes because you have now a huge range of patients that you can study.

And this is what George showed that this is people from an eGFR of 25 onwards and micro- to

macro-albuminuria, so albuminuria spanning from 30 to 5000. We excluded patients with symptomatic HFrEF because that becomes an ethical issue. You can't really include patients with symptomatic HFrEF in a clinical trial where spironolactone is indicated, so we exclude those patients. But we randomize these patients to either 10 or 20 of finerenone, 10 of the eGFRs less than 60, 20 if it's more than 60.

But we try to get everybody on 20 mg of finerenone. The median follow-up is three years. The CV composite is a 4-point MACE, your traditional MACE plus hospitalized heart failure. In the kidney outcome is a 57% decline in kidney function, which is approximately doubling of serum creatinine, which is what we typically use as an endpoint in clinical trials of diabetes, or going on dialysis, or having kidney failure or renal death.

Here's the population that we're studying, 65 years of age, and 70% are men. Everybody is on a RAS inhibitor, three quarters on statins. A1c is 7.7, blood pressure's not bad – 137/76. But prior heart failure history is kind of low compared the SGLT2 inhibitor trials in part because we excluded patients with symptomatic heart failure with reduced ejection fraction.

Now if you ask me this question, “can you improve outcomes in this group of patients by giving another drug?” That would be a pretty risky undertaking. But you know, that's what we study. Now this slide points out that 40% of the patients in the finerenone program would not be identified as having kidney disease without the measurement of uACR in the reason being because 40% don't have an eGFR of less than 60. That's usually how most people define kidney disease.

And most people kind of ignore uACR. But a third of the patients in the FIDELITY analysis had microalbuminuria and yes, two-thirds had macroalbuminuria, but those patients would not be identified without the measurement of albuminuria. Not on anybody's radar screen but uACR is a very important biomarker for cardiovascular disease, not just for the detection. But you can see now from the Fidelity analysis that you can modify the course of cardiovascular disease in the patient type 2 diabetes simply by measuring urine albumin.

I understand that you guys do blood pressure and lipids and EBCTs and coronary calcification scores. But with such a simple test, you can do a uACR and you can treat these patients and identify the increased cardiovascular risk, especially in people with type 2 diabetes. So, we have the outcomes here of kidney outcomes and you have a 23% reduction. And we have, most important that we have a fit reduction in end-stage kidney disease. We also have an improvement in cardiovascular outcomes by 14%.

And you can see here that the drug really has a more reasonable NNT for cardiovascular protection than kidney outcome protection because we have a larger study over milder patients in FIGARO compared to a smaller study of enriched patients in FIDELIO. But if you treat these patients, you realize what the cardiovascular and kidney outcome risk. So major points you already made here about a fifth reduction in heart failure, a fifth reduction in dialysis, hyperkalemia is the major issue.

And these are rates presented for 100 patient years so if you follow 100 patients for one year, less than one patient will experience hyperkalemia, even with finerenone, less than one patient in 100. That's what “100 patient years” means. So, 0.66 is the rate in the finerenone

group, 0.22 in the placebo. So you have to treat almost 200 patients to see one patient experiencing hyperkalemia within a year.

Serious hyperkalemia and discontinuations due to hyperkalemia, they're a relatively small number but that's really if you have a better kidney function, there's going to be less hyperkalemia that people will experience. So, the key finding here is that we have improvements in both CV and kidney failure outcomes and screening for albuminuria is more than an academic interest. If you understand nothing from this talk is just to recognize that uACR is an important cardiovascular risk factor. Thank you for your attention.

Oh, just one last slide, what's coming, you know, the FIDELITY program was limited to people with type 2 diabetes. And we are now doing a trial in people who don't have diabetes, which is called the FIND-CKD study. It's a Phase 3 RCT looking at eGFR slopes and finerenone. The other trial, which is very relevant to the cardiologist, is called the FINEARTS study. It's about 6000 patients with heart failure with preserved ejection fraction.

And in this trial, we are going to a finerenone dose as high as 40 mg, so much higher dose than what we have the registration for. And the endpoint they are is the number of cardiovascular death and heart failure events. So five points that you can remember to ponder when using finerenone, so it's five for finerenone. Initiate finerenone only if K is at most five. Don't use if eGFR is less than 25. Don't start finerenone unless the K gets to more than 5.5. We don't start reducing the dose at say 5.2, 5.3. And if you do this, you can expect a fifth reduction in dialysis, and a bit more than a fifth reduction in the risk hospitalized heart failure. Thank you.

DR. BAKRIS: Very good, thank you, Rajiv. Now Prof. Rosas is going to talk about synergy

PROF. SYLVIA ROSAS: Welcome, so these are my disclosures. I'm going to discuss the frequency of our patients with type 2 diabetes being on different medications for their antidiabetic affects. So, I'm going to discuss SGLT2 inhibitors and GLP-1 receptor agonists. And then, I'm going to discuss ongoing trials that are on the way.

So, as Dr. Agarwal mentioned, if one looks at the FIDELIO-DKD study, one could think that the results are very different from the SGLT2 inhibitor studies because the outcome in one was an 18% reduction in the primary outcome of kidney disease and cardiovascular disease versus the other one.

I'm sorry, that was a kidney-specific event versus in CREDENCE. It had a cardiorenal event that was both of the kidney and the study. So, when you look at the outcome, there was a 30% reduction in events. So, you're going to say oh, this one medication is better than the other medication. So what Dr. Agarwal did in this post hoc analysis was to try to make the FIDELIO-DKD population similar to the CREDENCE population.

And so initially, you can see in the first column once you made the composite outcome to be decline in eGFR less than 57. Remember the FIDELIO, the original study, the outcome was a decrease in 40% versus in CREDENCE was a decrease in 57% of the eGFR. So right there, there was a difference. So once you made that difference, you can see that the hazard ratio reduction is seen there. And then, when you for the look at the same DKD criteria, remember, in FIDELIO, you only had patients between 25 and 75.

So, once you create the right population with the right uACR, those reductions are seen. And then, when you have everything combined, you can see that the results are basically the same, one is a 28% reduction and the other one is a 30% reduction. So, differences in the trial design are quite important. So, there was before the study was ongoing, that was preclinical data that showed that combination therapy of SGLT2 inhibitor and mineralocorticoid receptor agonist was perhaps beneficial for both kidney fibrosis and cardiac fibrosis.

I'm including here cardiac fibrosis outcome and you can see that in green is the combination of both finerenone and SGLT2 inhibitor. And you can see that the survival in preclinical data was better with both, followed by finerenone, an SGLT2 inhibitor, and of course, placebo animals did worse. Here, there was the early evidence. Here, there was the early evidence. This is using only FIDELIO data. And you can see in the left half individuals that were on SGLT2 inhibitors.

Again, this was a subset. Remember when FIDELIO was done, SGLT2 inhibitors were new to the market so really, only 6 or 7% of the patients in the trial were on SGLT2 inhibitors at the time. And on the right, you see everybody else. So that's why they're about 5000, on the graph on the right. And you can see that because the confidence intervals are a lot smaller on the graph on the right than they are on the left. But you can see that the effect of albuminuria over time is basically the same with or without SGLT2 inhibitors.

So, the numbers are really small here. But it's like -30 on the left and -35 on the right. Once the studies were merged, we're calling the FIDELITY a trial, you can see that again, the 6-7% of individuals that were on SGLT2 inhibitors or perhaps a little bit different than those that were not on SGLT2 inhibitors. And some of the differences are that the eGFRs were a little bit better in those that were on SGLT2 inhibitors, and the uACR was a little bit less.

And you can see that they were perhaps aggressively treated because they were more likely to be on statins and they were more likely to be on GLP-1 receptor agonists. But having said that, you can see that those individuals that were on finerenone, whether they were on SGLT2 inhibitors are not they had a significant reduction in urine albumin uACR. And you can see that the difference is not significant. So, the outcomes are the cardiovascular and the kidney outcomes that were totally consistent, irrespective of the SGLT2 use.

Again, SGLT-2 use, they were smaller so that the range, the confidence intervals were wider. But you can see that there was no interaction between the outcomes and SGLT2 use. And this included cardiovascular outcomes, the kidney outcomes, hospitalization for heart failure, or all-cause death. One of the things as has been mentioned before that people worry a lot about is adverse events, of course. And one of the most important ones is hyperkalemia.

So you can see in the lower three lines that individuals that were on SGLT2 inhibitors had the same rate of hyperkalemia as those that were on placebo and no SGLT2 inhibitor. So, it looked like there was a potential benefit of using the combination of finerenone and SGLT2 inhibitors because those individuals had a low incidence of hyperkalemia both mild and severe, defined as zero potassium of more than 6. But adverse events were all similar between all groups.

So, now I'm going to discuss GLP-1 receptor agonists. These are what people know as the

ominence octa [phonetic]. These are the reasons why people develop hyperkalemia when they have type 2 diabetes. And in the squares, you can see all the areas where GLP-1 receptor agonists work. And initially here you can see the effect of albuminuria over time by the use of GLP-1 receptor agonists. And again, here this is FIDELIO data, so you can see there's about 5000 individuals.

Only about 300 were on GLP receptor agonists, or even less that SGLT2 inhibitors. But you can see that whether you are on a GLP-1 or not, there was no different in the effect on albuminuria and looking at the primary and secondary composite outcomes cardiovascular or kidney disease it did not matter if you are on GLP-1 receptor agonist or not. The effect of finerenone on the outcomes was similar. Looking again at safety data, here we do not see any difference between hyperkalemia or not hyperkalemia and the effects on adverse events are about the same.

So, everybody had similar events and perhaps even those on GLP-1 receptor agonists have perhaps a little bit more adverse event than those that were not on it, but no difference in hyperkalemia events. So, because we want to make sure that we understand the effects of SGLT2 inhibitors on the effects of finerenone and look to see if there are any additive effects between both medications, there's an ongoing trial. And I guess we're learning from cardiology how you make a very big title and then you call it confidence.

There are going to be about 807 participants and they're in 13 countries. It's going to be mild CKD-associated stages two and three, so about 30 to 90. And everybody would have high uACRs. And they would be randomized into three different groups. It would be finerenone and empa, finerenone or placebo, or empagliflozin and placebo. And it's basically to look if the dual therapy has a benefit compared to each individual therapy by itself. So, the next speaker is Dr. Taub.

DR. BAKRIS: So, before you go down, come up, Rajiv because Pam's going to present these cases, and then we're going to discuss them.

PROF. PAM TAUB: Okay, I get to have some fun with the nephrologists.

DR. BAKRIS: Don't get too hyper about that.

PROF. TAUB: I like being the only cardiologist. Well, I'm actually really looking forward to this because I'm using finerenone as a cardiologist and it's always nice to get insights from the nephrologists on what things we can do better. So, I have the task of taking all these wonderful lectures and putting it into a patient case. And I always like to do real patients.

So, whenever I prepare these cases, I go into the medical record of my patients and I review things and some things actually strike me, first of all, that I've been practicing for close to 15 years, and how much medications have changed.

And this was one of those patients I've seen this patient since 2014. And it was really when I went back through his record and read all of the medication changes, really parallels all the great clinical trials and advances that we've had. So, let me talk to you about this real patient of mine is now 78 and he has a history of hypertension, type 2 diabetes, and hyperlipidemia. But I first met him in 2014 when he was 70.

And I saw him after he had an episode of exertional chest pain. As part of the workup for his chest pain, I did get a stress test and echo. At that time, his BMI was 39. His blood pressure was 148/78. And these are the medications he came to me on from his primary care provider. He was on an amlodipine-benazepril combination. He was on aspirin. He was on atenolol. He was on atorvastatin, hydrochlorothiazide. And I laugh today.

He was on niacin. He was on potassium for a history of hypokalemia, and I laugh at this one, too. He was on a DPP4 sitagliptin. So, these were his medications in 2014 and his labs revealed his A1c was 6.7. His total cholesterol was 153, and triglycerides 100. His HDL was 48, LDL 83, and creatinine was 0.76. So, he did have an abnormal stress test but had a normal ejection fraction on his echocardiogram.

He then underwent an angiogram and had three-vessel disease and underwent bypass surgery in June 2014. Postop after his bypass surgery, he did develop postoperative atrial fibrillation and he was started on apixaban. After his surgery, he's had kind of a tenuous course with his ejection fraction going up and down depending on how well his blood pressure control and his volume status was. So in September 2014, he had a decrease in his ejection fraction to 41% and mild pulmonary hypertension reflective of his volume overload.

So, at that time, I changed his hydrochlorothiazide to a loop diuretic, also adjusted his blood pressure medications and his ejection fraction improved to 55%. And so here is where all the clinical trial data starts coming in and I will always be an early adopter and loving all these trials, I mean I was one of the first people to read George and Rajiv's paper in the *New England Journal of Medicine* and just very excited about how I could apply their clinical trial data to my patients.

So, with this patient as soon as the data on sacubitril valsartan emerged, I thought he would be a really good patient just because he's had a decreased ejection fraction. And I didn't go through all of his echoes, but he's had kind of an up-and-down course where he can go into the 40s when his ejection fraction, that he gets better. So, I did make that switch.

And then, in 2017, I added an SGLT2 inhibitor to his medication regimen based on the data from the EMPA-REG OUTCOME trial. So, this is his medications in 2021. So this is how far we've come. He's on apixaban. I switched him from a crappy beta blocker, atenolol to a more evidence-based beta blocker carvedilol, which also has some blood pressure effect. He continues to be on amlodipine. That was one of the few things that I did continue.

He is on an SGLT2 inhibitor. He's on empagliflozin. He's on Bumex because he does have volume overload and he's also on sacubitril valsartan. I also put him on a more potent statin. I switched him from atorvastatin to rosuvastatin. He's on aspirin. He has a history of coronary disease. He needs lifelong aspirin. And he's on potassium because he does have a tendency towards hypokalemia. And so that was one of the other medications that was continued in 2021.

His A1c is 6.3 and with the switch to a more potent statin, his LDL was better. It's 55. In 2021, after reading a lot of the papers by this esteemed panel, I started to think about uACR. It wasn't that I necessarily checked it, but I looked at it in the medical record because most of these patients that have diabetes followed by primary care and endocrine. And they were

checking uACR. So, I started to look at that and incorporate that into my clinical decision-making.

So, he had a uACR of 283, normal eGFR, and a creatinine of 0.7. And his potassium always tends to be a little bit low at 3.4. He is on a pretty good dose of a diuretic and his blood pressure is now much better. He's on sacubitril valsartan. He's on amlodipine and it's 100/65, and his heart rate is 65. So, we'll ask the audience this question and will ask the panel what they recommend. What would you add and I'm going to go back because I agree with George. This is like an eye exam. I'm going to go to my slide.

Would you increase his empagliflozin to 25 mg or B, would you increase the empagliflozin to 97 mg over 102 mg twice a day? Would you add finerenone 10 mg or would you add finerenone 20 mg? And sometimes in clinical medicine, there's not exactly a black-or-white right answer. There are different things you do. But then, there's also kind of best practices. So, let me give you some time to answer that question.

DR. BAKRIS: They have 10 seconds.

PROF. TAUB: Wow, so let me ask the panel. What would you do?

DR. BAKRIS: Well, what would I do? I'd want to find out why, before I did this, I'd want to find out why this person has perennially low Ks. He's either a salt hog or he's got primary hyperaldo that you've missed. Or he's got some of the variant of that, so …

PROF. TAUB: He is a salt hog.

DR. BAKRIS: Okay.

PROF. TAUB: And we've been, I mean his BMI is, as I said, elevated. His wife is always telling me that he's eating potato chips.

DR. BAKRIS: Okay, okay. Well yes, I mean based on these choices and with the blood pressure being what it is, finerenone is not going to trust the blood pressure and give you all the other benefits. So, I would do that and he is eGFR was what? It was lower.

PROF. TAUB: It was 65.

DR. BAKRIS: Oh, it was 65? Well fine, then I'd give him 20 of finerenone.

PROF. TAUB: Okay. So, I think what's interesting is, there's a little bit of a split between the 10 and the 20 mg. So, I think that's a good point of discussion in this case. And this is an algorithm that guides you towards what you should do what it's pretty simple. He has a normal eGFR. His potassium is actually on the lower side. So for somebody like him, you can actually start finerenone at 20 mg. Any comments from the nephrologists on when you start at 10 mg?

DR. AGARWAL: Ten if you have an eGFR less than 60. But since this patient's eGFR is 65 or 67, more than 60, you can start with 20. The key would be to call the patient back in four weeks to check potassium. And if the potassium is reasonable, you can just call the patient when as you would, clinically. The only stipulation is – you should call the patient back in four weeks

to have a K check and blood pressure check.

PROF. TAUB: So, what would you do with the potassium supplement that he's taking?

DR. AGARWAL: Great question. So, I probably would stop at that time. I don't know what the serum potassium was in this patient.

DR. BAKRIS: Yeah.

PROF. TAUB: It was 3.4.

DR. AGARWAL: So, if it's 3.4, I probably would continue the K supplement until I see him four weeks later.

PROF. TAUB: And that's what I did.

DR. AGARWAL: Yeah, I wouldn't stop the supplement.

DR. BAKRIS: I think for the audience's benefit, these doses that were suggesting at eGFR, they're not arbitrary. They're in the PDR. And this is exactly what we did in the trial. So, you don't need to be scared of hyperkalemia and all this stuff. These are all validated and tested in long-term studies.

PROF. TAUB: And Dr. Rosas has already really highlighted that you can actually use finerenone and SGLT2 inhibitors together, that it's safe. There is also some early data that your incidence of hypokalemia is actually less when you use a combination. I'm actually curious. What you think the mechanism is of lower rates of hypokalemia when you use the two together? Any theories?

DR. AGARWAL: Well, you know, you could probably be having a more delivery of sodium to the distal nephron because SGLT2 inhibitors block proximal sodium reabsorption. And perhaps you will have in the presence of ambient aldosterone, you would have a K exchange in the cortical collecting duct and therefore, potassium would be maintained. And most of the epidemiological studies have suggested that when you use it in combination, you have a lesser risk of hypokalemia.

Personally, I was surprised at that finding because SGLT2 inhibitors are relatively weak diuretics. I expected that with a loop diuretic or a thiazide diuretic, but I was surprised that you find this effect with the SGLT2 inhibitors also.

PROF. TAUB: And Dr. Rosas has also talked about an ongoing study where they will look at the combination of SGLT2 inhibitors and finerenone so I'm very excited about that study. And so, what we ended up doing for this patient is, finerenone was started and potassium supplements was stopped. And then, his routine labs two months after without potassium supplement, his potassium was 3.9. His uACR had improved pretty quickly. Is that what you would expect?

DR. BAKRIS: Well, my history with this is yes, you're going to get a response within a month but if you think this is good, keep going because I've seen – I've got one patient that went from – not combination, though, SGLT-2, finerenone 20, and max RAS blockade go from 1.4

grams down to 150 mg over nine months so, there's a healing process is going on.

PROF. TAUB: So, you think there's …

DR. AGARWAL: The mean reduction is 30% but it's a log distribution. So, you're going to have some patients you would like to have 75, 90% reduction in other people might have just 10% reduction. But regardless of the reduction in uACR, you have to continue using this drug. One more point I wanted to make is that with SGLT2 inhibitors, you don't see hypokalemia as a side effect.

So, it's not like they are hypokalemic drugs. And that's why I was surprised that by itself, SGLT2 inhibitors don't cause hypokalemia. But when you use it in combination with finerenone, it reduces the incidence of hypokalemia. Could it be that they are protecting the tubules more in the long term? They are reducing the tubular inflammation and therefore the tubules are sensitive? I don't know. I think it's perhaps more than a hemodynamic mechanism by which the improvement is happening.

PROF. TAUB: We know SGLT2 inhibitors really decrease that glomerular pressure. And then, now you have finerenone coming in and really reducing inflammation and fibrosis. So, it makes sense that they were well together and one thing that George would be really excited about, because he is involved in the SOUL study looking at the impact of GLP-1 receptor agonists semaglutide on kidney function. So this is someone that I also ended up starting a GLP-1 receptor agonist one because I really have a hard time with his diet and his salt.

And I just couldn't make a dent on his elevated BMI. And one of the things that I know is when I get that BMI down, so many of the things that I really worry about as a cardiologist get better. So, his blood pressure will get better. His atrial fibrillation and arrhythmia burden will get better. So, we did end up doing this. This patient of mine has really good insurance coverage; he was a retired superintendent for a school district and somehow, he has the Cadillac of medical insurance. Whatever, he always says get me whatever drug you want because I don't really have any co-pays. As you can see, I gave him all the great drugs but they're expensive. So, one question I have is, he's not the typical patient with incredible insurance coverage. What do you do when someone has his profile and can't afford all these medications? What do you do in your practice?

DR. BAKRIS: Well, I cheat because the University has a program that I can give them a lot of these medicines, not the GLP-1s, but everything else at 15 bucks a month. And they've got some arrangement that they've worked out. There's some government program that if you're indigent and whatever, you can get this. But most people don't have that. There is a website in the …

DR. AGARWAL: The scavendiasavingsdrug.com [phonetic] I think, you know, when you can go and get a coupon.

PROF. TAUB: But he's on Medicare.

DR. AGARWAL: Yeah, so Medicare is going to be an issue. But you know, you're asking me if a patient doesn't have good insurance, what would you do? I think that that's one option. I work at the VA they don't have Medicare but if you are at the VA and you have failed an

SGLT2 inhibitor, in other words, you still have persistent albuminuria, and you qualify for the eGFR and potassium, I can prescribe them. I can request that drug and they can get it.

I think overall is greater and greater awareness because end-stage renal disease is a lot more expensive than preventing end-stage kidney disease. And the prognosis of end-stage kidney disease is terrible.

DR. BAKRIS: I mean, you can get this at the VA in the bottom line is the patients have come to me. And I assume that they needed scripts. And they said no, we went to the VA. We're good. So even the patients that have a script, they can go to the VA, request, and they get it and Humana now has it on the formulary, so you can get it from them. So things are …

PROF. TAUB: Getting better.

DR. BAKRIS: Yeah, yeah.

PROF. TAUB: It's great to know. So, I just put this at a table because as I said, when I was going through this patient's chart, it kind of gave me some perspective on how much clinical trial data we've had in so many arenas that have really altered people's medication regimens. So, here's an example of where we got rid of his old beta blocker and put them on a more evidence-based beta blocker. We got him on a high-potency statin.

We changed his thiazide diuretic to a loop diuretic. We added empagliflozin. We were able to actually stop the potassium so, we got rid of one of medication with the finerenone. But he's really on kind of state-of-the-art medications based on the latest clinical trials. So, it's nice to see him doing well. The latest update that I got from him, I just got a MyChart message from him. He's lost about 15 pounds.

He's been on semaglutide for about four months. But he still won't stop eating the potato chips. He's from the South, tells me he just loves his salt and he'll take the medications.

DR. BAKRIS: Very nice, Pam, there you go.

PROF. TAUB: Thank you.

DR. BAKRIS: Very good, have a seat. So, we are taking questions from the audience and I'm going to throw the first one to Rajiv. Can you speak to the potential role of potassium binders in the management of hyperkalemia that may occur with finerenone? Any reason to expect a differential profile than observed with other MRAs?

DR. AGARWAL: There's absolutely, I mean these drugs are not MR. It's not like spironolactone or eplerenone. The incidence of hyperkalemia that you see, and this is why we did the head-to-head comparison and direct-comparison study, where you're taking patients with an eGFR with between 25 and 45, very high risk of hyperkalemia. And you're seeing that the risk of hyperkalemia is extremely low. Treatment discontinuation is very low.

So this is, there's no question that they're much lower risk of hyperkalemia. As far as the binders go, we did allow the use of potassium binders in the clinical trial. And there was a greater use of the binders in the finerenone group compared to placebo. But most of the binder use was transient. It happened over a couple of days or at most, a week. It wasn't like

long, persistent use of these binders.

I think that most of the time, if you get hyperkalemia, you have got to look at other things. Is the patient obstructed? Are you using nonsteroidals? Are there other reasons that there could be hyperkalemia? I don't think that I would use a long-term potassium binder just to enable finerenone use. That would be against the label.

If you can get potassium to more than 5.5 you will stop the drug. And if you have resolution of potassium goes to less than 4.8 unless, you can start the drug back at a 10 mg dose. But if you still get hyperkalemia, then finerenone is not for you. That's what we did.

DR. BAKRIS: Yeah. There's a question here asking about "Can finerenone and SGLT2 inhibitors be administered together?" In other words, can they start simultaneously? And I'll answer that. In fact, all kidney-protective drugs have an initial drop in eGFR, and that includes ACE inhibitors, ARBs, SGLT2s, and finerenone. The concept of it these people all going to be on ACEs or ARBs, the concept of starting an SGLT-2 and finerenone together, especially if you're on diuretics, you run the risk of getting an exaggerated drop in that initial eGFR.

Now that's theoretical, what I'm saying, because it hasn't really been tested. It's going to be tested in the studies that are doing but the reality is right now, what I do is, I'll start SGLT2. I'll wait two weeks, or I'll start finerenone. I'll wait two weeks, and then I'll start the other compound. And I haven't had any problems doing it that way. Could I do it together? Maybe, but at least cautionary until we know for sure. That's one way to do it. I don't know what any of you think about that.

DR. AGARWAL: Well, that's why we are doing the Confidence trial. We are treating patients with either finerenone alone or empagliflozin alone. Or starting both the drugs simultaneously. And we will be able to address this question in probably 18 months or so once the trial was complete.

DR. BAKRIS: Pam?

PROF. TAUB: I mean, I'm excited for the results of that. But I'll say just from a practical standpoint, I never start to medications at the same time just because I don't know like when they had a side effect what the drug is. So I always do it in a staggered fashion. What I will do is at the same clinic visit, I'll give both prescriptions and I'll say start this drug first. Give it a week and then start the next one, to be efficient.

DR. BAKRIS: Okay, very good.

DR. AGARWAL: And I probably would weight maybe 4 to 8 weeks before I start the second one. I completely agree with you. I think it's safer to stagger with them than to start simultaneously.

DR. BAKRIS: There's a question for you here, Pam. While the patient presented have a very high BNP despite improvement in the cardiac status?

PROF. TAUB: So, the BNP was in the 1100 range. And if you think about it, it's actually NT-proBNP. So, if you're on sacubitril valsartan, the regular B type natriuretic peptide is just not as accurate. So, you always want to check an NT-proBNP. But from an age-adjusted cutpoint,

he's actually, it's not significantly elevated. And so remember, BNP and NT-proBNP are on a different scale. So, if you have a BNP of 100, it's an NT-pro of around 1000.

So his was about 1100, so that's equal to a BNP in the 100s, which for a 74-year-old, isn't significantly elevated. But it's not going to be the same as a 74-year-old with no comorbidities because there is going to be a little bit of an elevation because he does have some baseline hemodynamics stress. He's obese. He has type 2 diabetes. And so you would expect his BNP, even when he's euvolemic to be in this range.

DR. BAKRIS: Okay, now we have about 12 minutes left. I'm going to give you one final chance. If you have a question ask it now or forever hold your peace because you're about to get quizzed again. Just a warning but it's coming to follow through with it. so I'm just asking. Yes, you can.

DR. AGARWAL: Yeah, we have. The relative risk reduction or heart failure hospitalization is the primary driver of the outcomes, the total outcomes. And it's about 22% relative risk reduction in the Fidelity program. For strokes, there's absolutely no change. There's about a 10% improvement in myocardial infarction which is nonsignificant. And there's again, about a 15% or so improvement in cardiovascular death, again nonsignificant so if you read the label, it will exclude stroke from these four components.

PROF. TAUB: Just to follow up on that question, one thing that's very intriguing from a cardiology perspective is the decrease in new-onset atrial fibrillation. What do you think is the mechanism of that?

DR. AGARWAL: It's perhaps a reduction in the left atrial size because we do know that there is an improvement in blood pressure when you use ambulatory blood pressure monitoring. There is actually a fairly nice reduction in blood pressure. And we know from prior trials, for example the LIFE trial, where they compared losartan versus atenolol there was a reduction in new-onset atrial fibrillation, so much so that it actually reduced stroke risk.

And they showed in that study that there was a reduction in left atrial size there. We didn't have any measurement of the left atrial size. Another hypothesis is maybe that's improving inflammation and fibrosis in the heart. There are some animal data to show that, so potential mechanism.

DR. BAKRIS: Right, so here's the final question and Sylvi gets this because she's been sleeping here. And this pertains to Pam's patient. When you check his visceral fat post-semaglutide initiation?

DR. ROSAS: I don't know that we do that clinically. We do that for research. We know that visceral, even renal fat associated with progression of chronic kidney disease. So, I would say that we are learning more how to use it. I think we're measuring visceral fat and doing more studies. I don't think that it's ready for clinical use.

DR. BAKRIS: Right, there it is, not ready for primetime.

DR. AGARWAL: Not ready for primetime but actually there are clinical research data of using these GLP-1 Ras, even the dual-incretin agonists which show improvement in liver fat as well

as visceral fat using MRIs. So, if you look at the New England Journal paper on tirzepatide, there are some images of MRI that show pretty remarkable improvements in the liver fat as well as the visceral fat, and including subcutaneous fat, 30-, 40-pound reduction in body weight in some of these patients.

DR. BAKRIS: Yeah, we're never gonna cure Nash [phonetic] yet, so relax.

PROF. TAUB: I have to add this in because I'm very excited about the results of the SOUL trial. I think in the future, we're going to be talking about not just SGLT2s and finerenone but the GLP-1.

DR. BAKRIS: Did you not notice a fourth pillar on my thing that was empty? Okay, so let's start off here with the post-test questions. I know you're dying for them, so let's get them up. There we go, there's the results from before. So now, presence of chronic kidney disease, eGFR less than 45, greater than 30, albuminuria is associated with a high risk of kidney disease progression, cardiovascular risk factor associated with a high risk of heart failure, has no significance until the eGFR gets less than 30, and none of the above? Go ahead and answer that.

All right, times up. Okay, so we taught you something but give ourselves a C. Okay, which of the following treatments should be included to do reduce the risk of diabetic kidney disease as well as heart failure risk, maximum tolerated dose of ACE or ARB, SGLT2, finerenone, chlorthalidone, A through C, all the above? Go ahead. Okay, will give ourselves an A for that one, all right?

Which of the following distinguishes finerenone from steroidal MRAs? Don't get this wrong. It has a half-life its half-life, lack of metabolites, its receptor specificity, its generally good tolerability, all of the above? Okay, good answer, good answer. Which of the following pathophysiologic aspects of DKD progression do nonsteroidal MRAs target, hemodynamics, glycemic control, inflammation and fibrosis, hypertension, all of the above, you're not sure? Okay, interesting.

PROF. TAUB: Yeah, we did worse.

DR. AGARWAL: Get a D on this one.

DR. BAKRIS: All right, because we cover all that. Compared to steroidal MRAs, nonsteroidal MRAs are associated with which of the following, increased risk for hyperkalemia, reduce risk for hyperkalemia increased risk for sexual side effects, equal selectivity, and potency to the MR inhibition, unsure? Okay, good answer. According to the results of the FIDELITY primary analysis, there was a significant reduction in CV morbidity and mortality and little or no reduction in CKD progression. There was no significant CV or CKD effects. There was a significant reduction in both CV morbidity and mortality and CKD progression. You don't know. All right, there you go. Still got some outliers there. The case you can read for yourself. I'm not going to read it to you and then make a choice. Okay.

PROF. TAUB: A hundred percent.

DR. BAKRIS: Good answer, good answer. Okay. For the same patient, 90-day repeated labs,

HbA1c 7.5, eGFR is 52, uACR is 58, BP looks okay, a little high. She's currently also on dapa 10. What's the most appropriate next step, wait and repeat it in 90 days, add a GLP-1, add finerenone and monitor K, add a TZD? Okay, is that it? That's it, so this is the most important thing for all of you, how you can get your CME. So, take a look at that, read that. Thank you very much for coming, very much appreciate you sticking around, and hope you got something out of it. On behalf of us, thank you. You did an excellent job. You passed the audition.