Transcript: The Cardiorenal Connection: Diagnosis & Treatment of CKD Associated with T2D

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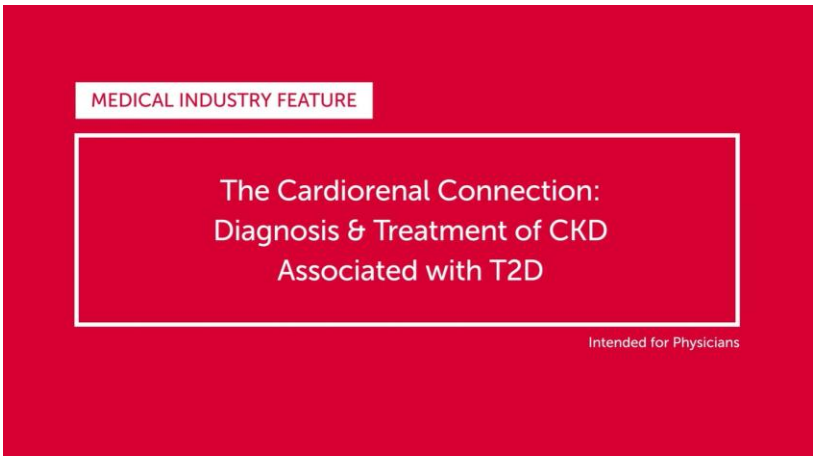


Here's your host, Dr. Norman Lepor.

Dr. Lepor:
Type 2 diabetes is the #1 cause of kidney failure, which can lead to dialysis or kidney transplant. Chronic kidney disease, or CKD, impacts approximately 40% of adults with type 2 diabetes. Further, patients with type 2 diabetes and CKD have a 3 times greater risk of cardiovascular-related death compared to patients with type 2 diabetes alone.

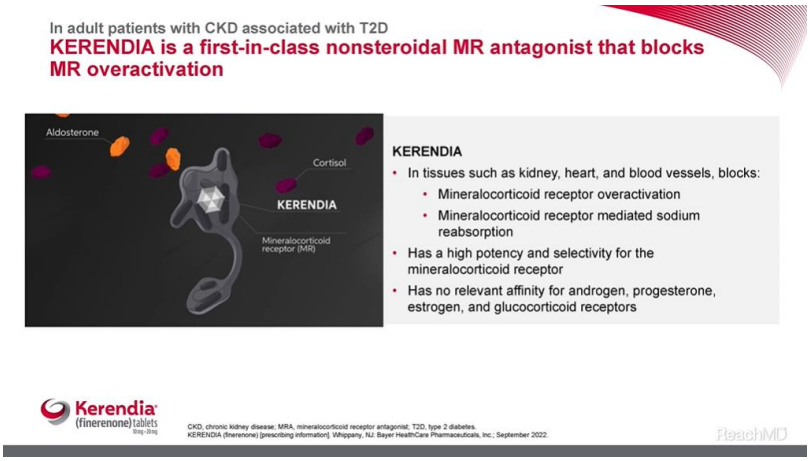
Hello, my name is Dr. Norman Lepor, and I'm a Clinical Professor at the Geffen School of Medicine at the University of California in Los Angeles. I'm also Attending Cardiologist, Smidt Cedars-Sinai Heart Institute and Director of the National Heart Institute in Beverly Hills, California.
Joining me to discuss a treatment option for patients with CKD associated with type 2 diabetes is Dr. Holly Kramer. Dr. Kramer is a Professor of Public Health Sciences and Medicine in the Division of Nephrology and Hypertension at Loyola University Chicago. Welcome to the program!

Dr. Kramer:
Thank you, Dr. Lepor.

Dr. Lepor:
Now let's dive into our discussion, Dr. Kramer, what can you tell us about KEREDNIA?

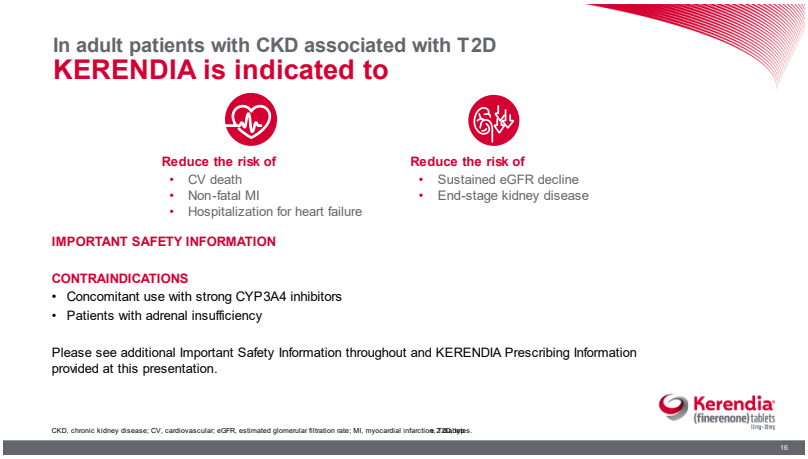
Dr. Kramer:
KERENDIA is a first in class selective mineralocorticoid receptor antagonist, or MRA, with a nonsteroidal structure, and it's been approved in the United States. KERENDIA blocks mineralocorticoid receptor overactivation, which is thought to lead to inflammation and fibrosis, which can contribute to permanent structural damage in the kidneys and the heart. It has a high

potency and selectivity for the mineralocorticoid receptor, and it has no relevant affinity for androgen, progesterone, estrogen, and glucocorticoid receptors.



Dr. Lepor:
And can you tell us more about the indication for KERENDIA?

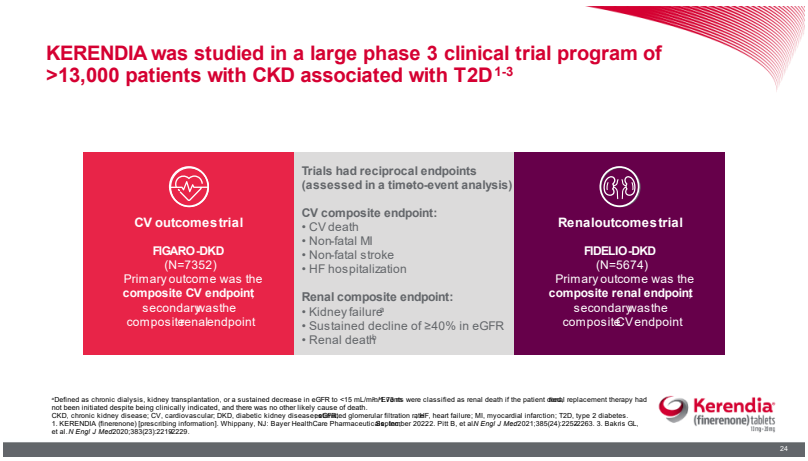
Dr. Kramer:
Sure. So KERENDIA is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with Chronic Kidney Disease associated with type 2 diabetes. Contraindications for KERENDIA include concomitant use with strong CYP3A4 inhibitors and patients with adrenal insufficiency.



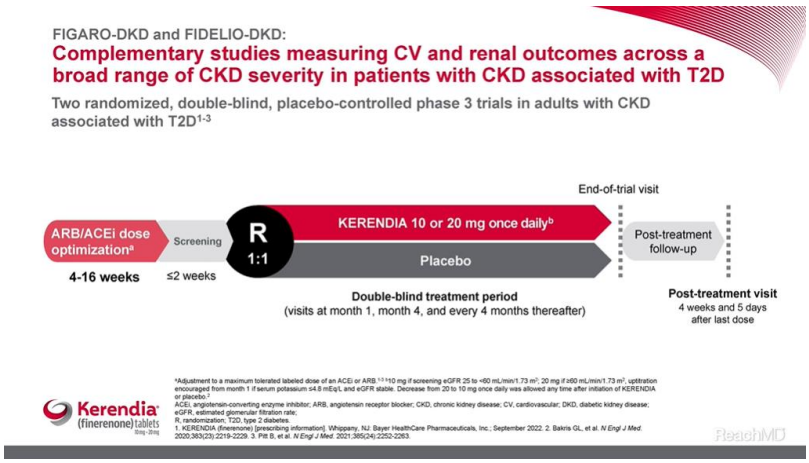
Dr. Lepor:
Now, Dr. Kramer, what were the trials that led to the FDA approved indications for KERENDIA?

Dr. Kramer:
So there were two trials that make up the FDA approved label for KERENDIA. There's the cardiovascular outcomes trial called FIGARO-DKD and then the renal outcomes trial called

FIDELIO-DKD. These complementary studies represent the largest clinical trial program of over 13,000 patients with Chronic Kidney Disease associated with type 2 diabetes.



FIGARO-DKD and FIDELIO-DKD were randomized, double-blind, placebo-controlled phase 3 trials in adults with Chronic Kidney Disease associated with Type 2 Diabetes. During the dose-optimization period, all patients received standard of care background therapy, including a maximum tolerated labeled dose of an angiotensin-converting enzyme inhibitor or ACE Inhibitors or angiotensin receptor blocker or ARB.

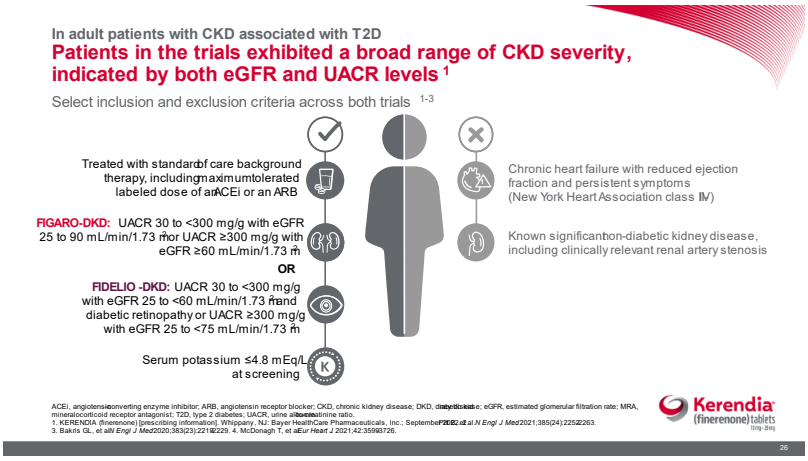


Dr. Lepor:
And as I understand it, all of the patients in these trials were already optimized on an ACE inhibitor or ARB, is that correct?

Dr. Kramer:
Yes, that's exactly right. After the optimization period, patients were randomized to receive either KERENDIA or placebo. In the KERENDIA arm, patients received 10 mg once daily if their eGFR was between 25 and 60 mL/min/1.73 m^2 and 20 mg once daily if their eGFR was greater than 60 mL/min/1.73 m^2.

Dr. Lepor:
Dr. Kramer, can you tell us a little bit about the patients who were included in these trials?

Dr. Kramer:
Sure. So, FIGARO-DKD and FIDELIO-DKD included an adult population with CKD associated with Type 2 Diabetes. Together, these trials covered a broad range of CKD severity. The FIGARO-DKD trial enrolled participants with a UACR of 30 to <300 mg/g with eGFR 25 to ≤90 mL/min/ OR UACR 300 to ≤5000 mg/g with eGFR ≥60 mL/min/. The FIDELIO-DKD trial enrolled participants with[3] UACR of 30 to <300 mg/g with eGFR 25 to <60 mL/min/ and history of diabetic retinopathy OR UACR 300 to ≤5000 mg/g with eGFR 25 to <75 mL/min/. Patients were required to have a serum potassium level of ≤4.8 mEq/L at screening.

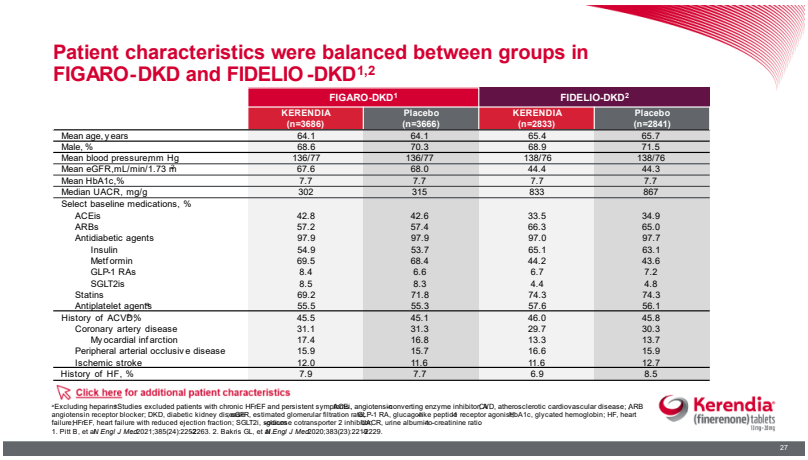


Dr. Lepor:
Sorry to interrupt but I think it's important to note that there were no protocol recommendations to restrict dietary potassium or potassium supplements. Potassium-lowering therapies (such as sodium polystyrene sulfonate, calcium polystyrene sulfonate, and potassium-binding agents) were allowed.

Dr. Kramer:
Thanks for breaking that down for us, Dr. Lepor. And now let's take a look at the patients who were excluded from these trials. Patients were excluded if they had a clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms, according to the New York Heart Association class II-IV. They were also excluded if they had known significant non-diabetic kidney disease.

Dr. Lepor:
I often get the question from my colleagues regarding why patients with heart failure with reduced ejection fraction were excluded from these trials and I think it is another important point to clarify. Due to the class IA recommendation of steroidal MRA treatment for patients with heart failure with reduced ejection fraction, these patients cannot be ethically randomized to placebo or KERENDIA.

Dr. Kramer:
I'm so glad you brought that up because I also get that same question! But before we dive into this data a little further, I want to mention the baseline characteristics of these trials. For FIGARO-DKD and FIDELIO-DKD, patient characteristics at baseline were well balanced between the treatment groups.



Patient characteristics were balanced between groups in FIGARO-DKD and FIDELIO-DKD[1,2]

	FIGARO-DKD[1]		FIDELIO-DKD[2]	
	KERENDIA (n=3686)	Placebo (n=3666)	KERENDIA (n=2833)	Placebo (n=2841)
Mean age, years	64.1	64.1	65.4	65.7
Male, %	68.6	70.3	68.9	71.5
Mean blood pressure/mm Hg	136/77	136/77	138/76	138/76
Mean eGFR, mL/min/1.73 m²	67.6	68.0	44.4	44.3
Mean HbA1c, %	7.7	7.7	7.7	7.7
Median UACR, mg/g	302	315	833	867
Select baseline medications, %				
ACEis	42.8	42.6	33.5	34.9
ARBs	57.2	57.4	66.3	65.0
Antidiabetic agents	97.9	97.9	97.0	97.7
Insulin	54.9	53.7	65.1	63.1
Metformin	69.5	68.4	44.2	43.6
GLP-1 RAs	8.4	6.6	6.7	7.2
SGLT2is	8.5	8.3	4.4	4.8
Statins	69.2	71.8	74.3	74.3
Antiplatelet agents	55.5	55.3	57.6	56.1
History of ACVD, %	45.5	45.1	46.0	45.8
Coronary artery disease	31.1	31.3	29.7	30.3
Myocardial infarction	17.4	16.8	13.3	13.7
Peripheral arterial occlusive disease	15.9	15.7	16.6	15.9
Ischemic stroke	12.0	11.6	11.6	12.7
History of HF, %	7.9	7.7	6.9	8.5

Click here for additional patient characteristics

•Excluding heparins‡Studies excluded patients with chronic HFrEF and persistent symptoms. ACEis, angiotensin-converting enzyme inhibitor; CVD, atherosclerotic cardiovascular disease; ARB angiotensin receptor blocker; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio

1. Pitt B, *et al*. *N Engl J Med*. 2021;385(24):2252-2263. 2. Bakris GL, *et al*. *N Engl J Med*. 2020;383(23):2219-2229.

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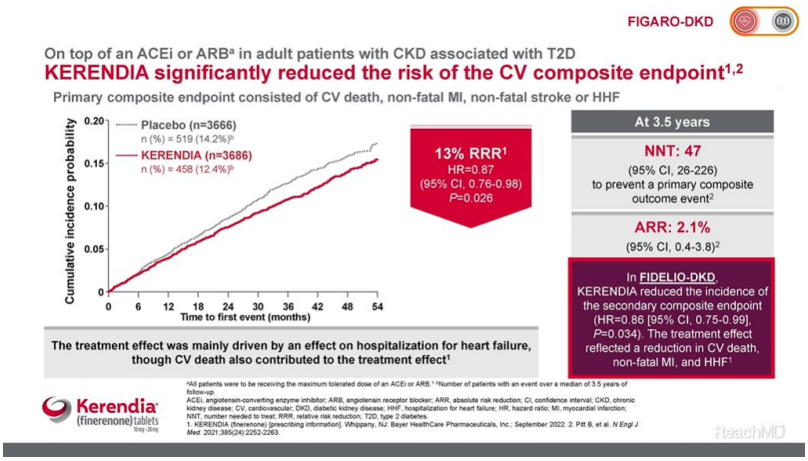
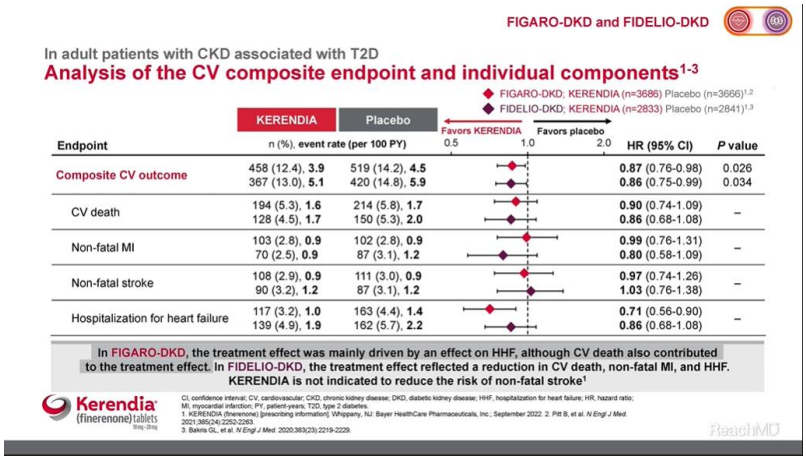
Dr. Lepor:
So, these are very much like the patients that you and I see in our practices every day!

Dr. Kramer:
Yes, exactly! I suspect that most physicians watching this will recognize a patient or two in their practice that resemble the baseline characteristics here, as well. Now Dr. Lepor, I'd like to turn to you for the cardiovascular data for KERENDIA. What were some of the cardiovascular endpoints?

Dr. Lepor:
The results of FIGARO-DKD's primary composite cardiovascular endpoint found that on top of standard of care, KERENDIA significantly reduced the risk of the cardiovascular composite endpoint by 13 percent as compared to placebo. I want to reemphasize that these results are on top of standard of care! I should also note that about 71 percent of the patient population in the FIGARO-DKD study were on a statin at baseline. The treatment effect was generally consistent across subgroups, including region, eGFR, UACR, systolic blood pressure, and HbA1c at baseline. In FIDELIO-DKD, KERENDIA significantly reduced the risk of key secondary cardiovascular composite endpoint by 14 percent.

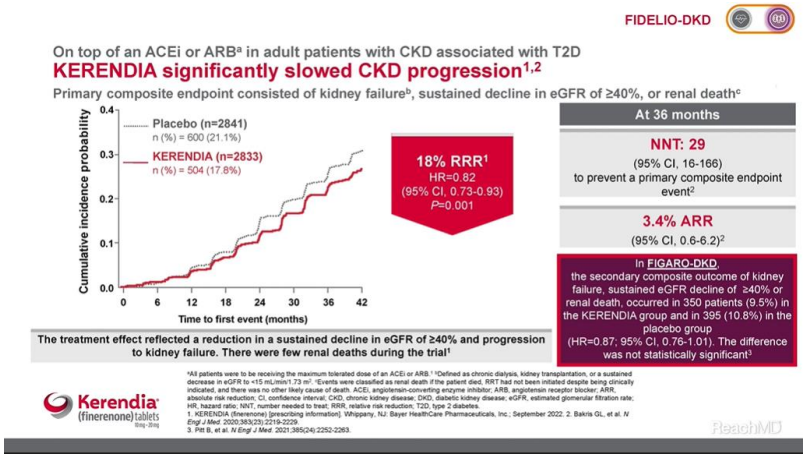


If we look at the individual components of the Cardiovascular composite time-to-event endpoint, the treatment was mainly driven by an effect on hospitalization for heart failure, though CV death also contributed, in FIGARO-DKD, and a reduction in CV death, non-fatal MI, and hospitalization for heart failure, in FIDELIO-DKD. KERENDIA is not indicated to reduce the risk of non-fatal stroke.

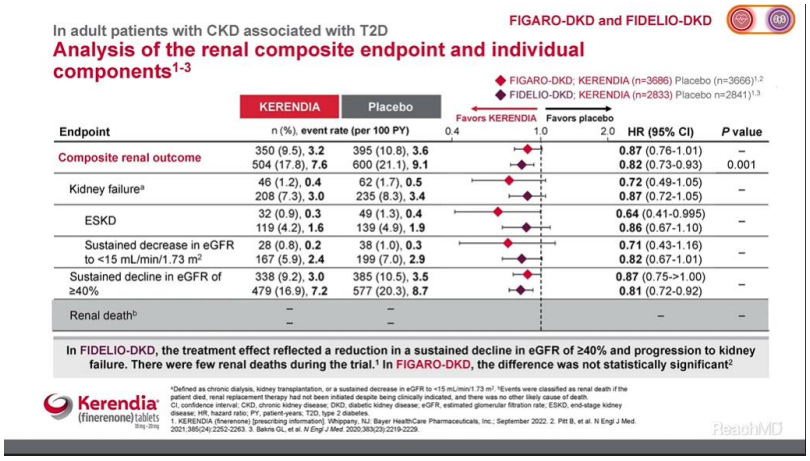


Now from your vantage point as a nephrologist, Dr. Kramer, could you take us through the renal endpoints for KERENDIA?

Dr. Kramer:
Well, Dr. Lepor, the results of the FIDELIO-DKD primary renal composite endpoint found that on top of standard of care, KERENDIA significantly reduced the risk of Chronic Kidney Disease progression by 18 percent as compared to placebo. Similar to the cardiovascular endpoints, the treatment effect was generally consistent across subgroups, including region, eGFR, UACR, systolic blood pressure, and HbA1c at baseline. In FIGARO-DKD, the secondary composite outcome of kidney failure, sustained eGFR decline of 40% or more or renal death occurred in 350 patients or 9.5%, in the finerenone group, and in 395 or 10.8% in the placebo group. The difference was not statistically significant.

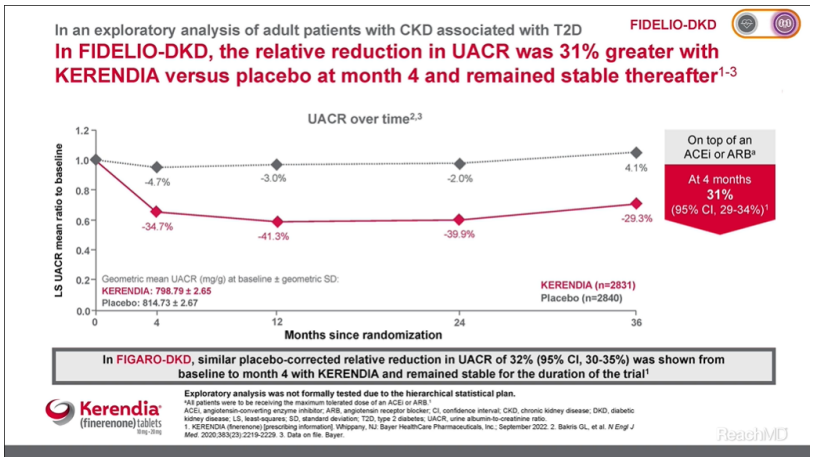


The renal composite endpoint was a composite outcome of time to first occurrence of kidney failure, a sustained decrease in eGFR of >40 percent, or renal death. In FIDELIO-DKD the treatment effect reflected a reduction in a sustained decline in eGFR of >40 percent and progression to kidney failure. The results also showed that there were few renal deaths during the trial.



Dr. Lepor:
Thank you for taking us through the renal endpoints for KERENDIA! I think it would be great to look at the Exploratory pharmacodynamic analysis that was done to look at the relative reduction in UACR from baseline.

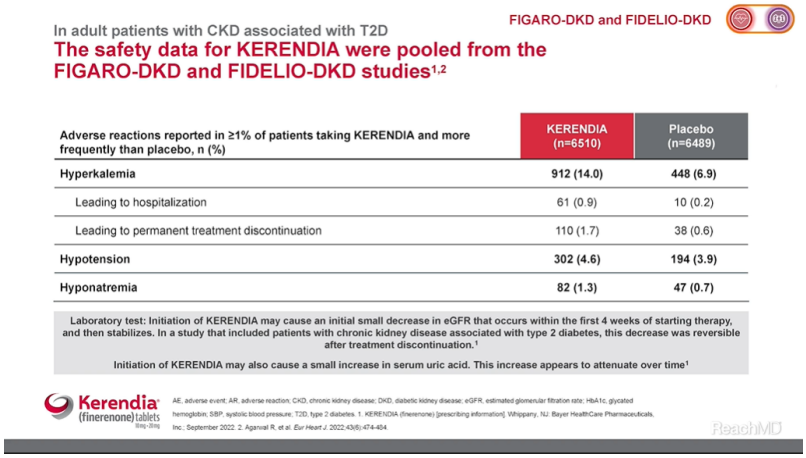
Dr. Kramer:
Great idea! You can see here that an exploratory analysis of the pharmacodynamic marker of change in UACR from baseline to month 4 found that the relative reduction in UACR in patients randomized to KERENDIA was 31% greater at Month 4 compared to placebo and remained stable for the duration of the FIDELIO-DKD trial. Similar results were seen in FIGARO-DKD, with a relative reduction in UACR from baseline to 4 months that was 32% greater with KERENDIA than placebo and remained stable throughout the trial.



Dr. Lepor:
You know, this is a really great analysis as our friends over at the American Diabetes Association recently updated their guidelines with a recommendation for a reduction of greater than or equal to 30% in milligram per kilogram urinary albumin to slow CKD progression in patients with CKD who have ≥300 mg/g urinary albumin.

Dr. Kramer:
That is right! The guidelines also recommend treatment with nonsteroidal MRA, KERENDIA, to reduce Chronic Kidney Disease progression and Cardiovascular events in patients with Chronic Kidney Disease associated with Type 2 Diabetes who are: at increased risk for Cardiovascular events or at increased risk for Chronic Kidney Disease progression or are unable to use an SGLT2i.

Dr. Lepor:
Now that we have discussed the efficacy of KERENDIA, let's take a look at the safety profile. Here we have the pooled FIDELIO-DKD and FIGARO-DKD safety data. Rates of serious adverse events related to study drug and adverse events leading to treatment discontinuation were similar between both treatment arms. The most common adverse reactions reported in at least 1 percent of patients treated with KERENDIA and more frequently than placebo are shown here. Of the participants treated with KERENDIA, 14 percent had hyperkalemia, 4.6 percent had hypotension, and 1.3 percent had hyponatremia.



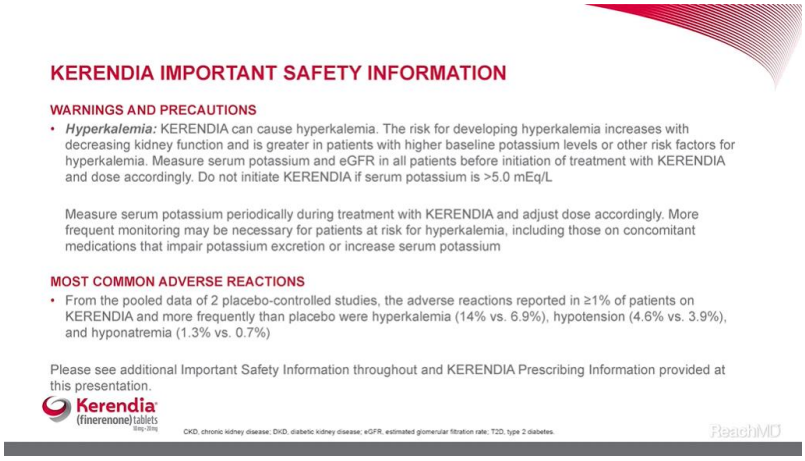
Before we wrap things up, let's review some additional Important Safety Information.

Announcer:

WARNINGS AND PRECAUTIONS
KERENDIA can cause hyperkalemia. The risk for developing hyperkalemia increases with decreasing kidney function and is greater in patients with higher baseline potassium levels or other risk factors for hyperkalemia. Measure serum potassium and eGFR in all patients before initiation of treatment with KERENDIA and dose accordingly. Do not initiate KERENDIA if serum potassium is >5.0 mEq/L

Measure serum potassium periodically during treatment with KERENDIA and adjust dose accordingly. More frequent monitoring may be necessary for patients at risk for hyperkalemia, including those on concomitant medications that impair potassium excretion or increase serum potassium.

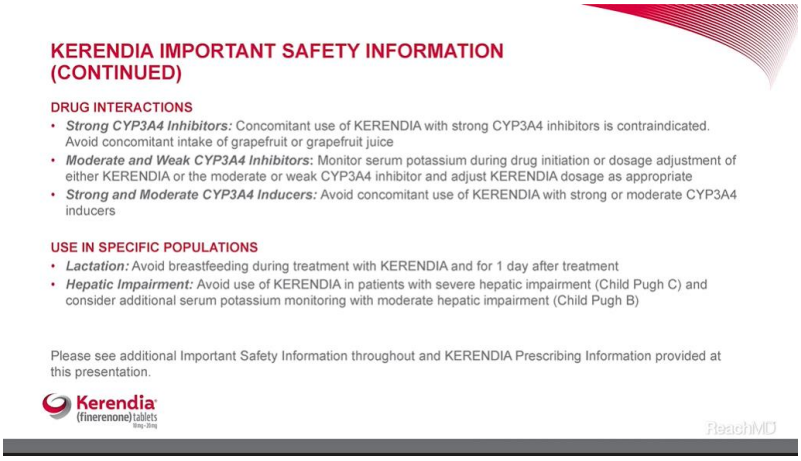
From the pooled data of two placebo-controlled studies, the Adverse reactions reported in ≥1% of patients on KERENDIA and more frequently than placebo were: hyperkalemia (14.0% vs. 6.9%), hypotension (4.6% vs. 3.9%), and hyponatremia (1.3% vs. 0.7%)



Concomitant use of KERENDIA with strong CYP3A4 inhibitors is contraindicated. Avoid concomitant intake of grapefruit or grapefruit juice

Monitor serum potassium during drug initiation or dosage adjustment of either KERENDIA or the moderate or weak CYP3A4 inhibitor and adjust KERENDIA dosage as appropriate
Avoid concomitant use of KERENDIA with strong or moderate CYP3A4 inducers

Avoid breastfeeding during treatment with KERENDIA and for 1 day after treatment
Avoid use of KERENDIA in patients with severe hepatic impairment (Child Pugh C) and consider additional serum potassium monitoring with moderate hepatic impairment (Child Pugh B)



Dr. Lepor:
And with that I will turn it to Dr. Kramer for any final thoughts.

Dr. Kramer:
Yes. So with over 35 million adults in the US with type 2 diabetes and 40 percent also with CKD, there's a huge need for early screening, diagnosis, and treatment in these patients to reduce the risk of cardiovascular events and slow the progression of kidney disease. KERENDIA offers patients a different path forward in the treatment of their CKD associated with type 2 diabetes. I also think it's important to keep in mind the ADA guidelines recommending a 30 percent or greater reduction in UACR to slow CKD progression in patients with CKD who have macroalbuminuria.

Dr. Lepor:
Well said Dr. Kramer. I'd like to reiterate the importance of the heart and kidney connection as we manage our patients with CKD associated with type 2 diabetes. We need to utilize all the tools in our belt for cardiorenal risk reduction including a non-steroidal MRA like KERENDIA. And that brings us to the end of today's program. I would like to thank Dr. Kramer for being here today and sharing her perspective on this important treatment option for patients with CKD associated with type 2 diabetes.

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