22-OR

Finerenone in Patients Across the Spectrum of CKD and T2D by GLP-1RA Use

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On behalf of Stefan D. Anker, Gerasimos Filippatos, Bertram Pitt, Luis M. Ruilope, Vivian Fonseca, Guillermo E. Umpierrez, Luiza Caramori, Mark Lambelet, Prabhakar Viswanathan, Robert Lawatscheck, Amer Joseph, George L. Bakris and the FIDELIO-DKD and FIGARO-DKD Investigators

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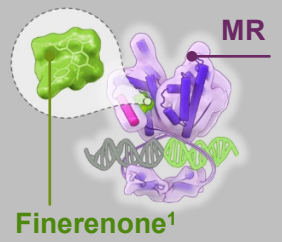
Disclosures

- Professor Rossing has received the following:

  - Personal fees from Bayer during the conduct of the study
  - Research support and personal fees from AstraZeneca and Novo Nordisk
  - Personal fees from Astellas Pharma Inc., Boehringer Ingelheim, Eli Lilly and Company, Gilead, Merck, Merck Sharp & Dohme, Mundipharma, Sanofi, and Vifor Pharma
  - All fees are given to Steno Diabetes Center Copenhagen, Herlev, Denmark

Given the current use of GLP-1RAs in patients with CKD and T2D, their combined use with finerenone is of interest



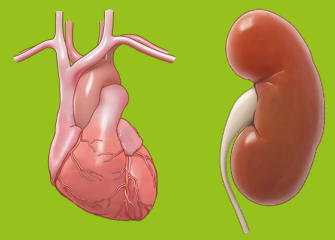
Finerenone is a **new, selective, nonsteroidal MRA** that **inhibits inflammation** and **fibrosis**. It has been shown to reduce the risk of **CV disease** and **CKD progression** in patients with **CKD** and **T2D**[1–3]

In recognition of their CV and kidney benefits, **guidelines recommend use of GLP-1RAs** in patients with T2D and CKD and/or at CV risk[4–6] with **evidence supporting kidney benefits based on secondary analyses** of CVOTs in patients with T2D[7]

CKD, chronic kidney disease; CV, cardiovascular; CVOT, cardiovascular outcome trial; GLP-1RA, glucagon-like peptide-1 receptor agonist; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor agonist; T2D, type 2 diabetes

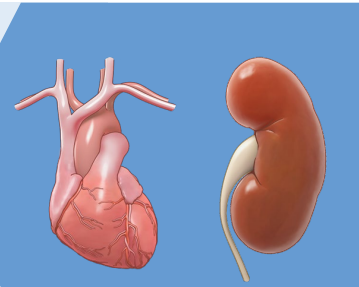
1. Agarwal R, *et al. Eur Heart J* 2021;42:152–161; 2. Bakris GL, *et al. N Engl J Med* 2020;383;2219–2229; 3. Pitt B, et al. *N Engl J Med* 2021;385:2252−2263;
4. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int* 2020;98:S1–S115; 5. American Diabetes Association. *Diabetes Care* 2022;45:S144–S174;
6. Cosentino F, *et al. Eur Heart J* 2020;41:255–323; 7. Shaman AM, *et al. Circulation* 2022;145:575–585

There is a need for robust data exploring cardiorenal outcomes of finerenone and a GLP-1RA in patients with CKD and T2D



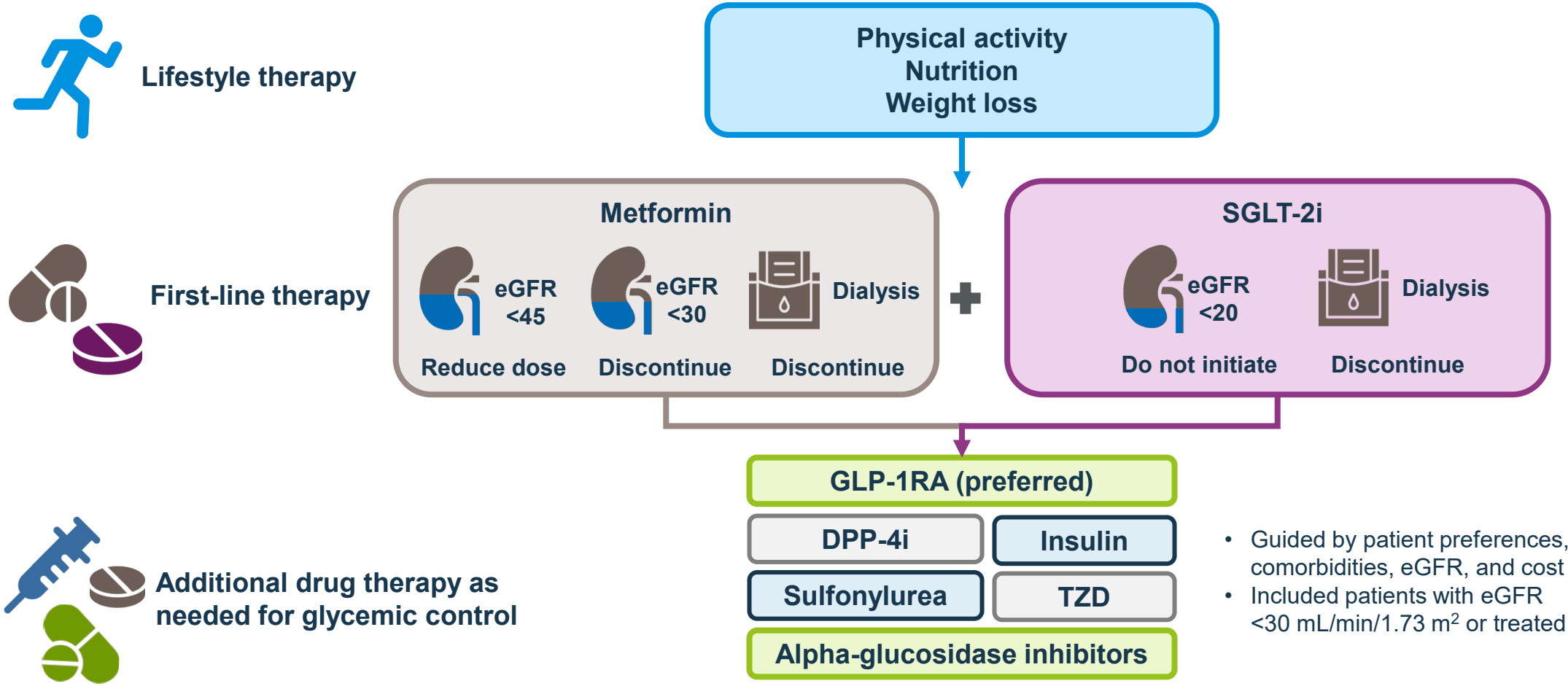
A recent analysis of data from the FIDELIO-DKD phase III trial showed that the effects of finerenone on CV and kidney outcomes compared with placebo were **consistent irrespective of GLP-1RA use at baseline or any time during study treatment**

This larger FIDELITY analysis of pooled data from two phase III trials examines whether the cardiorenal benefits of finerenone versus placebo in patients with CKD and T2D is influenced by the concomitant use of a GLP-1RA



Rossing P, *et al. Diabetes Obes Metab* 2022;24:125–134

After metformin and SGLT-2i, GLP-1RA is the preferred antihyperglycemic therapy in patients with T2D and CKD



- Guided by patient preferences, comorbidities, eGFR, and cost
- Included patients with eGFR <30 mL/min/1.73 m^2 or treated with dialysis

Figure adapted from KDIGO 2020
DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; TZD, thiazolidinedione
Kidney Disease: Improving Global Outcome (KDIGO) 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease – Public Review Draft; March 2022

FIDELITY is a large pooled trial dataset with prespecified analyses of the FIDELIO-DKD and FIGARO-DKD trials[1–3]

33,292 patients screened from 48 countries
(September 2015 to October 2018)

13,171 patients randomized

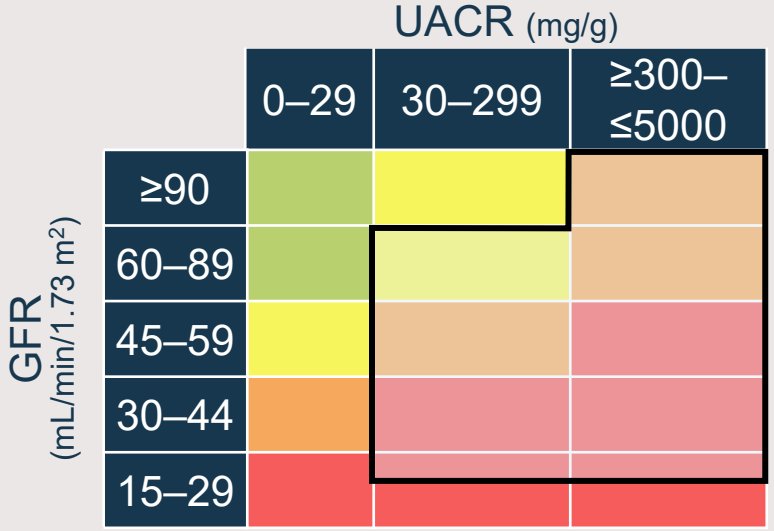
R

- **Finerenone 10 or 20 mg od***
- **Placebo**

3 years' median follow-up

Key eligibility criteria

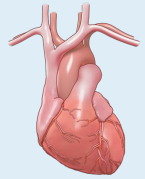
- ✓ **T2D**
- ✓ **CKD**
- ✓ On single RAASi
- ✓ Serum [K^+] ≤4.8 mmol/L
- ✗ Symptomatic HFrEF



Key outcomes

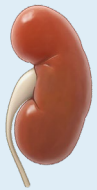
CV composite

Time to CV death, nonfatal MI, nonfatal stroke, or HHF



≥57% eGFR kidney composite

Time to kidney failure,[#] sustained ≥57% decrease in eGFR from baseline, or kidney-related death



*10 mg if screening eGFR 25–<60 mL/min/1.73 m^2; 20 mg if ≥60 mL/min/1.73 m^2, uptitration encouraged from month 1 if serum [K^+] ≤4.8 mEq/L and eGFR stable; [#]kidney failure defined as either ESKD (initiation of chronic dialysis for ≥90 days or kidney transplant) or sustained decrease in eGFR <15 mL/min/1.73 m^2

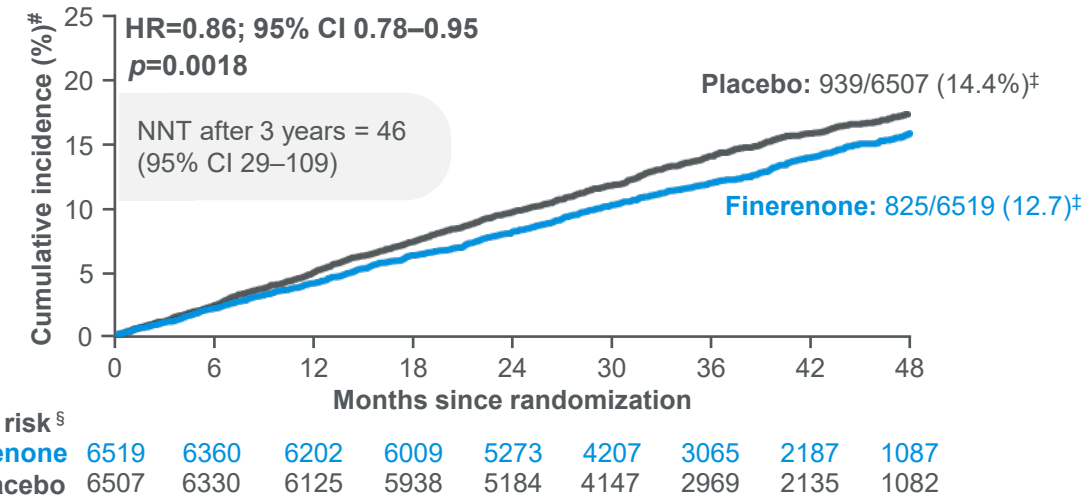
ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HHF, hospitalization for heart failure; HFrEF, heart failure with reduced ejection fraction; [K^+], potassium concentration; MI, myocardial infarction; od, once daily; RAASi, renin–angiotensin–aldosterone system inhibitor; UACR, urine albumin-to-creatinine ratio

1. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229; 2. Pitt B, *et al. N Engl J Med* 2021;385:2252−2263; 3. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

The FIDELITY primary analysis showed significant risk reductions in CV and kidney outcomes with finerenone

CV composite

Time to CV death, nonfatal MI, nonfatal stroke, or HHF

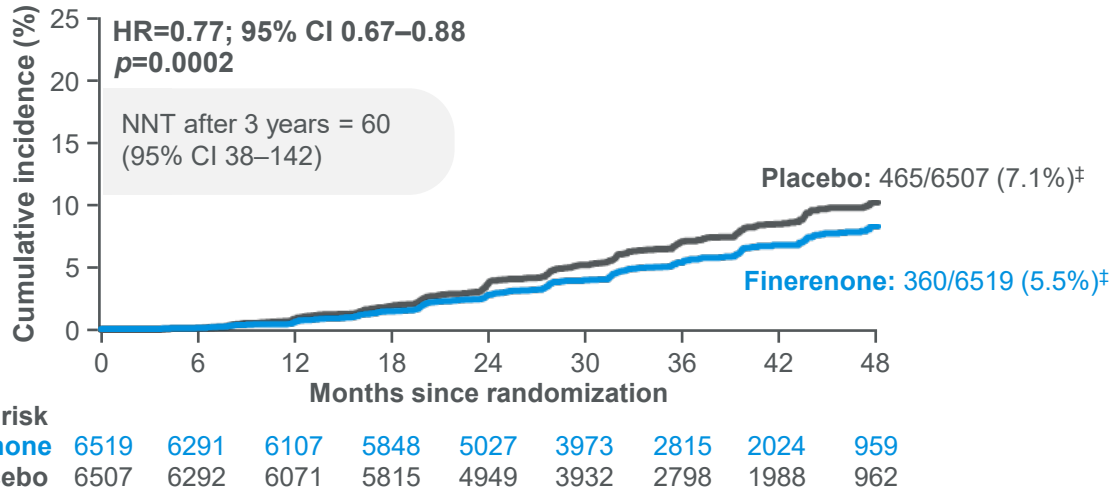


No. at risk §									
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

14% reduced **risk of CV morbidity and mortality** vs placebo (HR=0.86; 95% CI 0.78–0.95)

Kidney composite

Time to kidney failure,* sustained ≥57% decrease in eGFR from baseline, or kidney-related death



No. at risk									
Finerenone	6519	6291	6107	5848	5027	3973	2815	2024	959
Placebo	6507	6292	6071	5815	4949	3932	2798	1988	962

23% reduced **risk of CKD progression*** vs placebo (HR=0.77; 95% CI 0.67–0.88)

*ESKD or an eGFR <15 mL/min/1.73 m^2; events were classified as renal death if: (1) the patient died; (2) KRT had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death; #cumulative incidence calculated by Aalen–Johansen estimator using deaths due to other causes as competing risk; ‡number of patients with an event over a median of 3.0 years of follow-up; § at-risk subjects were calculated at start of time point. CI, confidence interval; HR hazard ratio; KRT, kidney replacement therapy; NNT, number needed to treat

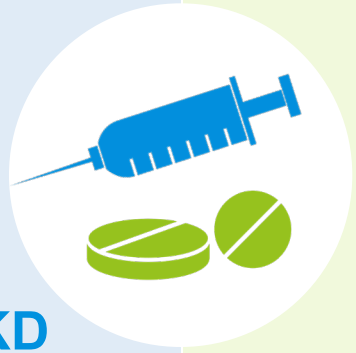
Agarwal R, *et al. Eur Heart J* 2022;43:474–484

Subgroup analyses of FIDELITY were performed according to GLP-1RA use

FIDELITY:
prespecified meta-analysis of FIDELIO-DKD + FIGARO-DKD

Subgroup analysis objective:
To evaluate whether the use of a GLP-1RA influences the cardiorenal benefits and safety of finerenone compared with placebo in patients with CKD associated with T2D

GLP-1RA use was permitted at any time during FIDELIO-DKD and FIGARO-DKD



At baseline, 7.2% of patients (n=944/13,026) were receiving a GLP-1RA

7.6% of the finerenone group (n=497/6519)

Duration of GLP-1RA use prior to randomization	• Median: 1.2 years • ≥4 months: 76.7% (n=381/497)

6.9% of the placebo group (n=447/6507)

Duration of GLP-1RA use prior to randomization	• Median: 1.3 years • ≥4 months: 79.2% (n=354/447)

During the trial, an additional 6.3% (410/6519) of the finerenone group and 6.6% (431/6507) of the placebo group also initiated GLP-1RA therapy

GLP-1RA use at baseline was associated with longer duration of T2D and higher BMI

Patient characteristics*	GLP-1RA use at baseline (n=944)	No GLP-1RA use at baseline (n=12,082)
Age, years	63±9.0	65±9.6
Sex, male	676 (71.6)	8412 (69.6)
SBP, mmHg	136.1±14.5	136.8±14.2
BMI, kg/m^2	34.1±6.1	31.1±5.9
Duration of diabetes, years	16.8±8.1	15.3±8.7
HbA1c, %	7.8±1.2	7.7±1.4
Serum potassium, mmol/L	4.3±0.4	4.4±0.4
eGFR, mL/min/1.73 m^2	58.7±21.6	57.5±21.7
UACR, mg/g, median (IQR)	484 (180–1052)	517 (201–1157)
History of CV disease	405 (42.9)	5530 (45.8)
History of HF	40 (4.2)	967 (8.0)

Patients with GLP-1RA use at baseline appear to have greater use of antidiabetic, antihypertensive and lipid-lowering medications

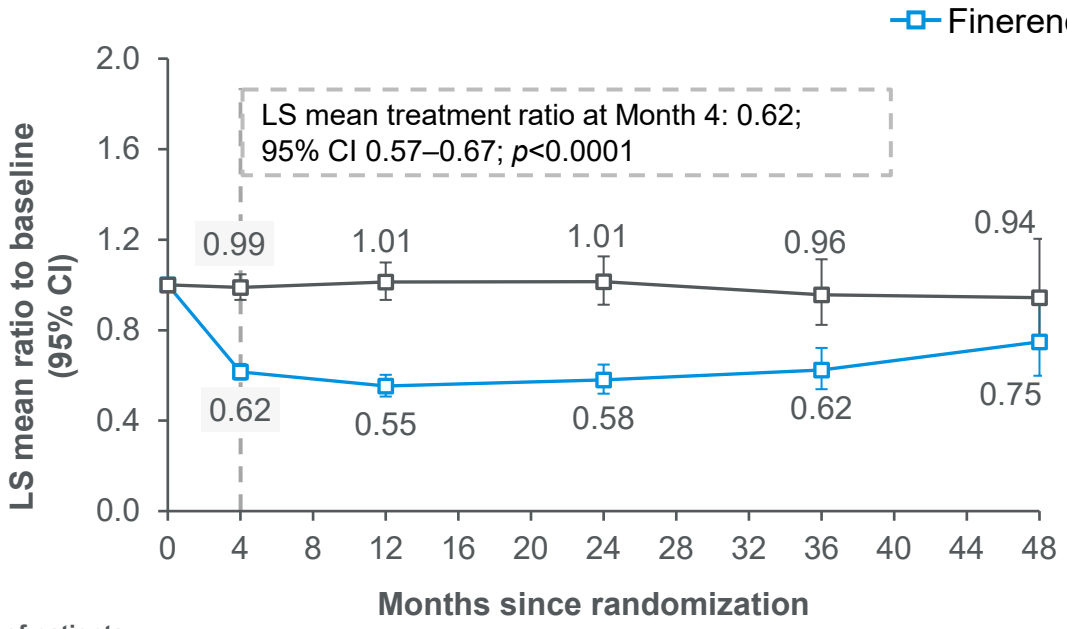
Medication use at baseline, n (%)	GLP-1RA use at baseline (n=944)	No GLP-1RA use at baseline (n=12,082)
RAS inhibitor	942 (99.8)	12,061 (99.8)
Beta blocker	512 (54.2)	5992 (49.6)
Diuretic	564 (59.7)	6146 (50.9)
Statin	782 (82.8)	8617 (71.3)
Potassium supplement	51 (5.4)	334 (2.8)
Potassium-lowering agent	9 (1.0)	173 (1.4)
Glucose-lowering therapies	944 (100)	11,776 (97.5)
Insulin and analogs	624 (66.1)	7006 (58.0)
Metformin	651 (69.0)	6906 (57.2)
Sulfonylurea	213 (22.6)	3176 (26.3)
SGLT-2 inhibitor	167 (17.7)	710 (5.9)
DPP-4 inhibitors	46 (4.9)	3232 (26.8)
Alpha-glucosidase inhibitors	30 (3.2)	626 (5.2)
Meglitinide	47 (5.0)	484 (4.0)
Thiazolidinedione	57 (6.0)	460 (3.8)

*Values are n (%) or mean ± SD unless otherwise stated

BMI, body mass index; HbA1c, glycated hemoglobin; HF, heart failure; IQR, interquartile range; RAS, renin–angiotensin system; SBP, systolic blood pressure; SD, standard deviation

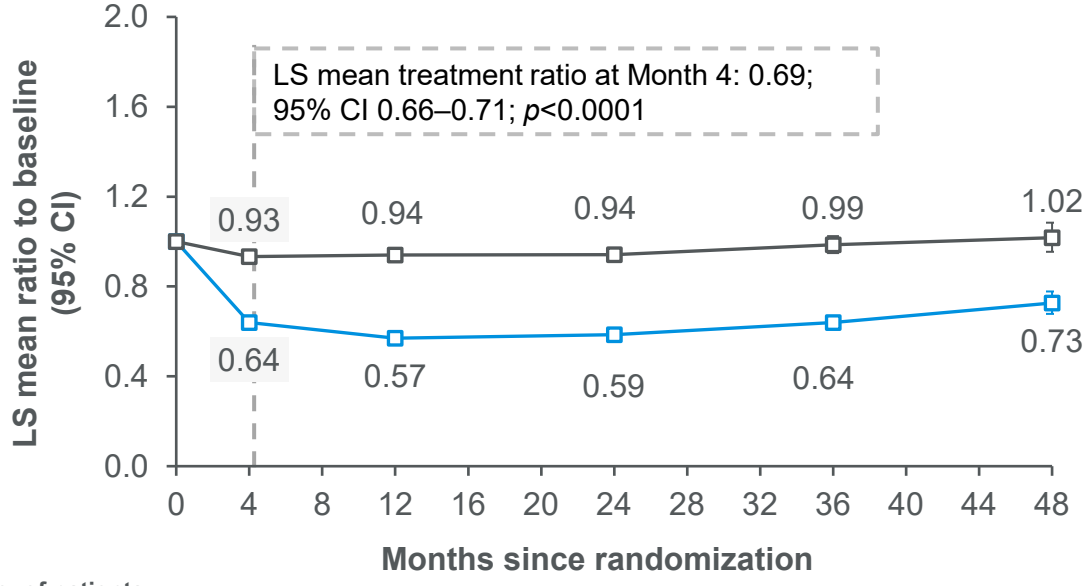
The use of a GLP-1RA at baseline was associated with a greater reduction in UACR with finerenone versus placebo

GLP-1RA use at baseline



No. of patients					
Finerenone	483	462	378	244	91
Placebo	426	414	337	201	60

No GLP-1RA use at baseline



No. of patients					
Finerenone	5790	5526	4489	2501	808
Placebo	5813	5559	4492	2505	812

The placebo-corrected reduction in UACR at 4 months was greater in patients with GLP-1RA use at baseline compared with patients without GLP-1RA use at baseline (−38% vs −31%, respectively; $p_{interaction}$=0.03*)

Mixed model with factors: treatment group, region, eGFR category at screening, type of albuminuria at screening, time, treatment time, study, study treatment, log-transformed baseline value nested within type of albuminuria at screening and log-transformed baseline value*time as covariate

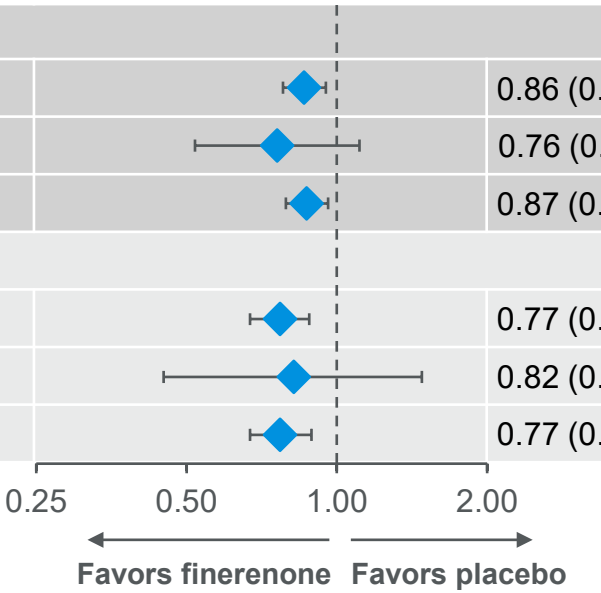
*$p_{interaction}$ at 4 months derived from ANCOVA

ANCOVA, analysis of covariance; LS, least-squares

Finerenone reduced the risk of the CV and kidney composite outcomes compared with placebo, irrespective of GLP-1RA use

Composite efficacy outcomes by GLP-1RA use at baseline

Endpoint	n/N (%)		n events per 100 PY		Hazard ratio (95% CI)	$p_{interaction}$
	Finerenone	Placebo	Finerenone	Placebo		
Composite CV outcome*						
Overall	825/6519 (12.6)	939/6507 (14.4)	4.34	5.01	0.86 (0.78–0.95)	0.63
GLP-1RA use at baseline	58/497 (11.7)	64/447 (14.3)	3.79	4.90	0.76 (0.52–1.11)	
No GLP-1RA use at baseline	767/6022 (12.7)	875/6060 (14.4)	4.38	5.02	0.87 (0.79–0.96)	
Kidney composite outcome#						
Overall	360/6519 (5.5)	465/6507 (7.1)	1.96	2.55	0.77 (0.67–0.88)	0.79
GLP-1RA use at baseline	22/497 (4.4)	27/447 (6.0)	1.47	2.10	0.82 (0.45–1.48)	
No GLP-1RA use at baseline	338/6022 (5.6)	438/6060 (7.2)	2.01	2.59	0.77 (0.67–0.89)	



Time-varying analyses showed that finerenone reduced the risk of the composite CV outcome and kidney composite outcome versus placebo regardless of GLP-1RA use at any time during study treatment and not just at baseline ($p_{interaction}$=0.40 and $p_{interaction}$=0.33, respectively)

*Included time to CV death, nonfatal MI, nonfatal stroke, or HHF; #included time to kidney failure, sustained ≥57% eGFR decline from baseline, or renal death
PY, patient-years

The safety profile of finerenone was similar in patients with CKD and T2D irrespective of GLP-1RA use at baseline

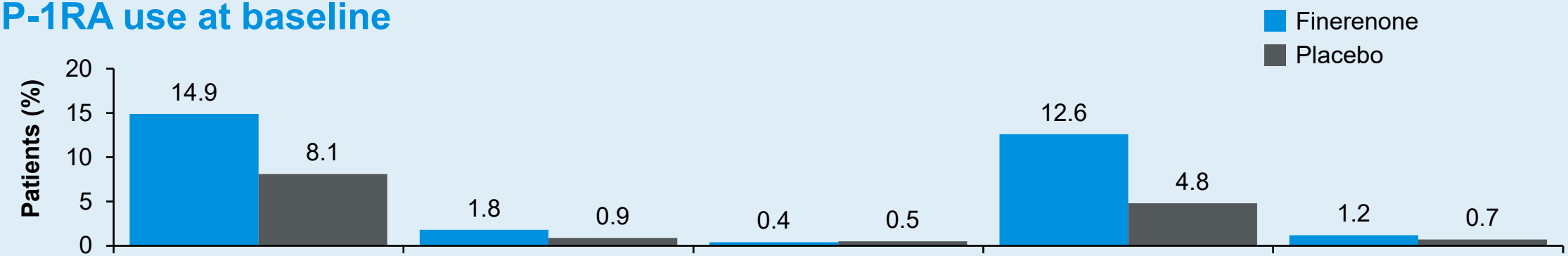
General safety outcomes and selected TEAEs of interest

Adverse event, n (%)	GLP-1RA use at baseline		No GLP-1RA use at baseline	
	Finerenone (n=496)	Placebo (n=443)	Finerenone (n=6014)	Placebo (n=6046)
Any AE	460 (92.7)	411 (92.8)	5142 (85.5)	5196 (85.9)
Leading to discontinuation	35 (7.1)	26 (5.9)	379 (6.3)	325 (5.4)
Any SAE	187 (37.7)	162 (36.6)	1873 (31.1)	2024 (33.5)
Leading to discontinuation	10 (2.0)	7 (1.6)	135 (2.2)	147 (2.4)
Any AE resulting in death	5 (1.0)	5 (1.1)	105 (1.7)	146 (2.4)
Renal AEs				
Acute kidney injury	27 (5.4)	22 (5.0)	193 (3.2)	212 (3.5)
Worsening renal function leading to discontinuation	5 (1.0)	4 (0.9)	47 (0.8)	38 (0.6)
Hypertension	32 (6.5)	37 (8.4)	387 (6.4)	544 (9.0)
Hypotension	37 (7.5)	18 (4.1)	245 (4.1)	159 (2.6)
Hypoglycemia	25 (5.0)	14 (3.2)	315 (5.2)	361 (6.0)

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

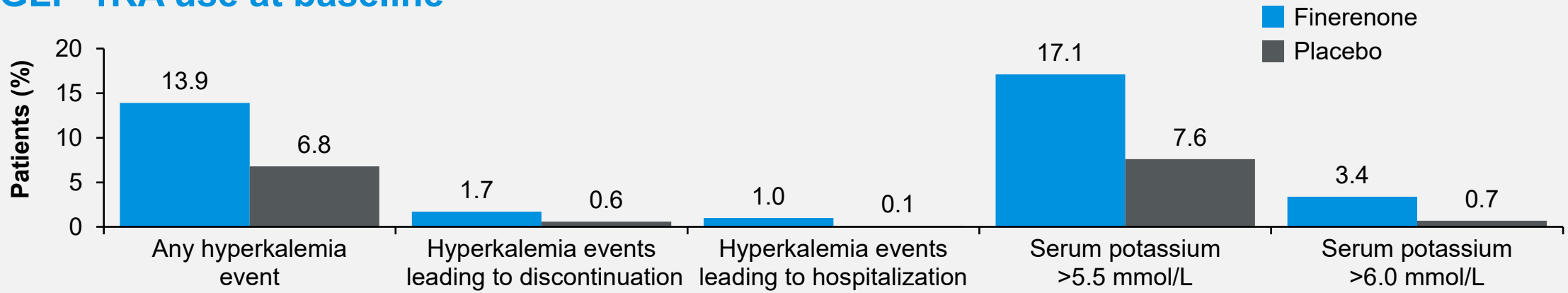
Hyperkalemia was more common with finerenone than placebo regardless of baseline GLP-1RA use, but its clinical impact was minimal

GLP-1RA use at baseline



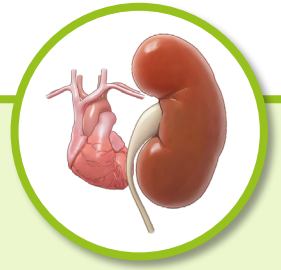
Patients, n/N	74/496	36/443	9/496	4/443	2/496	2/443	62/491	21/435	6/492	3/437

No GLP-1RA use at baseline

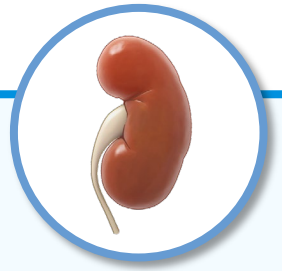


Patients, n/N	838/6014	412/6046	101/6014	34/6046	59/6014	8/6046	1013/5911	449/5935	205/5947	77/5976

Summary and limitations



The CV and kidney benefits of finerenone versus placebo could be observed in patients with T2D and CKD regardless of concomitant use of a GLP-1RA



The use of a GLP-1RA at baseline was associated with a greater reduction in UACR with finerenone compared with placebo

The safety profile of finerenone and the incidence of hyperkalemia was not influenced by use of a GLP-1RA at baseline

Limitations

- Patients included in this analysis were not randomized by GLP-1RA baseline use at study initiation
- There was a potential inequality, as expressed by baseline medication use, in quality of care between patients receiving GLP-1RA and those not receiving GLP-1RA

Thank you

48 countries, 33,292 patients enrolled, 13,171 patients randomized

Executive committee
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