Finerenone in patients with CKD and T2D by SGLT-2i treatment: The FIDELITY prespecified pooled analysis

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FIDELITY

FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis

Disclosures: Peter Rossing

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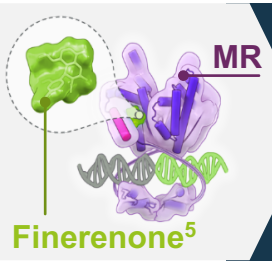
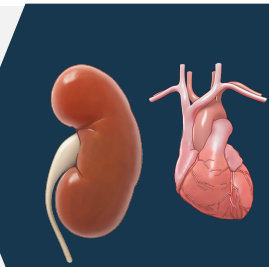
- Research grants from AstraZeneca and Novo Nordisk

The FIDELITY prespecified pooled analysis showed cardiorenal benefits of finerenone across the spectrum of CKD and T2D



Finerenone is a **novel, selective, nonsteroidal MRA** that **inhibits MR overactivation**, which is associated with **inflammation and fibrosis**[1,2]

FIDELITY was a prespecified pooled analysis of the FIDELIO-DKD and FIGARO-DKD phase III trials, which included **patients with T2D** across the **spectrum of CKD** receiving **optimized RAS inhibitor** therapy[1–3]



FIDELITY showed significant **risk reductions** of **14%** in the **CV composite** endpoint, and **23%** in the **57% kidney composite** endpoint[3]

CKD, chronic kidney disease; CV, cardiovascular; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin system; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes

1. Bakris GL, *et al. N Engl J Med* 2020;383;2219–2229; 2. Pitt B, *et al. N Engl J Med* 2021; doi: 10.1056/NEJMoa2110956; 3. Filippatos G and Agarwal R, presented at the ESC Congress 2021 Hot Line session 28 August 2021 available at: https://esc365.escardio.org/presentation/238815

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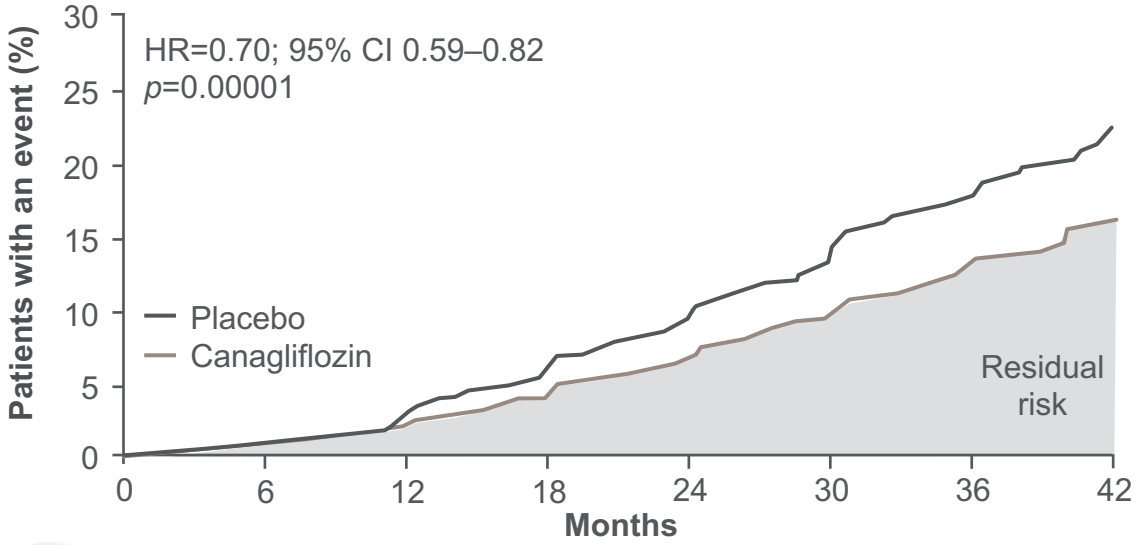
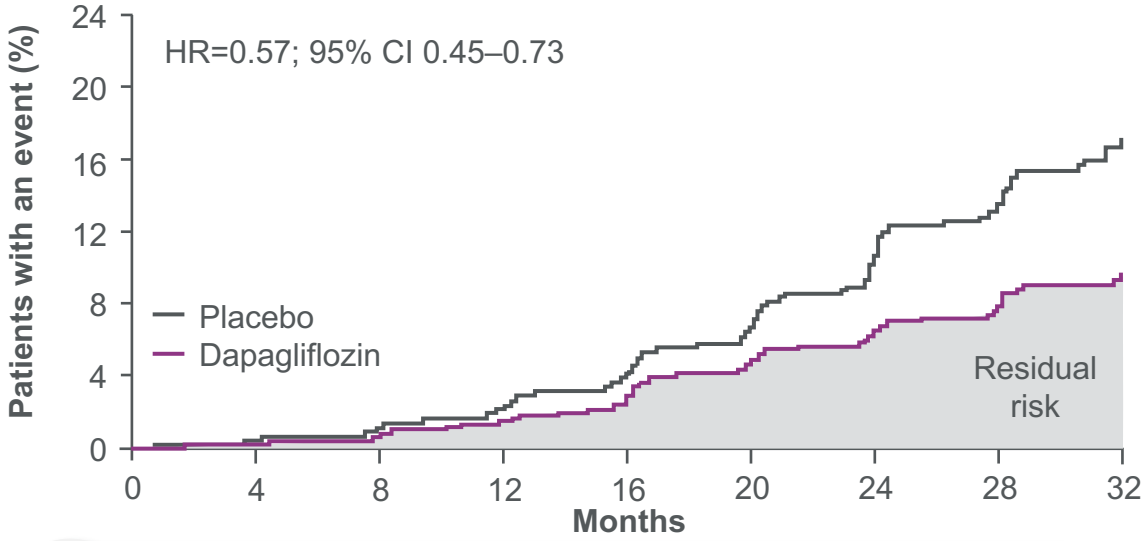
Despite SGLT-2i treatment being recommended for patients with CKD and diabetes,[1] further treatment options are needed

CREDENCE: Canagliflozin (+ RASi) vs placebo[2]



Primary composite outcome:
Kidney failure, doubling of SCr or death from kidney/CV causes

DAPA-CKD: Dapagliflozin (+ RASi) vs placebo (T2D subgroup)[3]



Secondary composite renal outcome:
Sustained ≥50% eGFR decline, ESKD or renal death

CREDENCE and DAPA-CKD have shown that **SGLT-2is offer kidney protection and lower the risk of CV events**; however, in these studies, **CKD progression or kidney failure still occurred in ~7% of patients and CV events in ~5–8% of patients** after a median follow-up of ~2.5 years[2,3]

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; RASi, renin–angiotensin system inhibitor; SCr, serum creatinine

1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int* 2020;98:S1–S115; 2. Perkovic V, *et al. N Engl J Med* 2019;380:2295–2306;
3. Heerspink HJL, *et al. N Engl J Med* 2020;383:1436–1446

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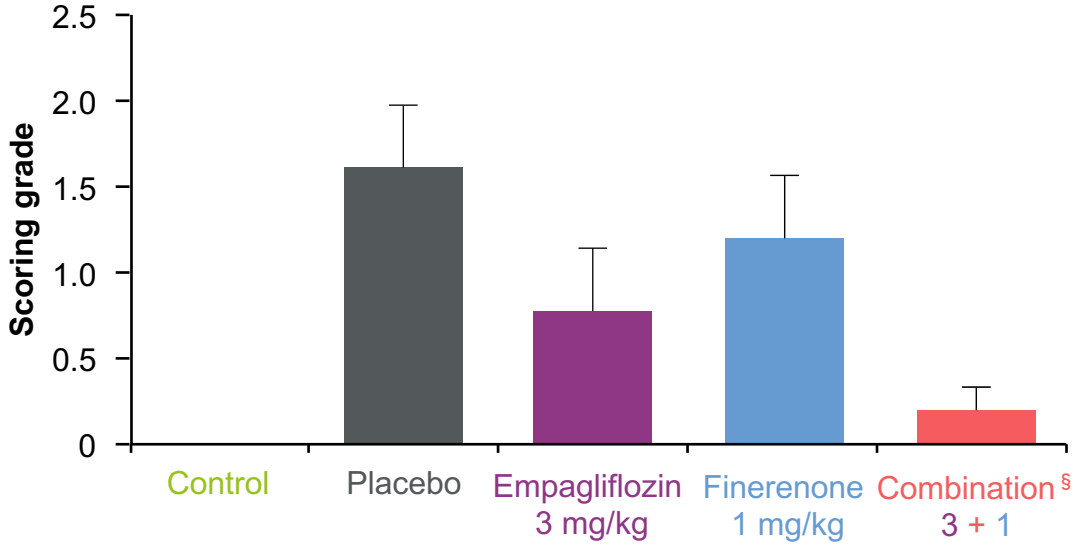
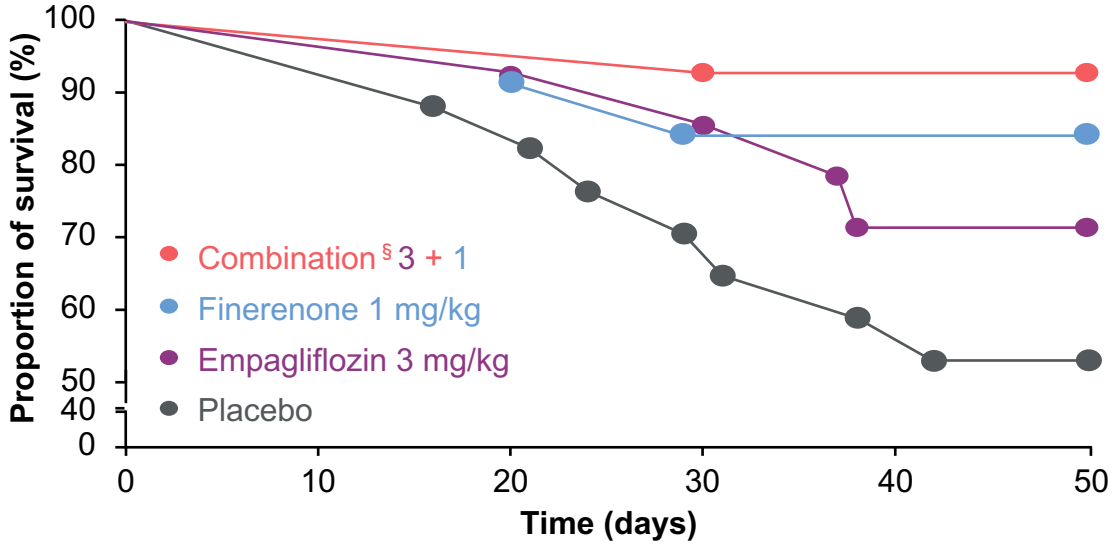
Preclinical data show that combination therapy with finerenone and an SGLT-2i has benefits over monotherapy*

Cardiac fibrosis#



Low-dose combination tended to have more anti-fibrotic effects than each low-dose monotherapy

Survival‡



Greatest survival benefit observed with combined treatment with finerenone and empagliflozin

*CV morbidity and mortality studied in hypertensive, N(ω)-nitro-L-arginine methyl ester-treated, renin-transgenic (mRen2)27 rats; *cardiac fibrosis determined by Sirius Red/Fast Green staining; ‡proportion of survival defined as the absence of mortality and severe morbidity per group over the course of the study; § combination therapy of finerenone (1 mg/kg) and empagliflozin (3 mg/kg); Data are mean ± SEM.

SEM, standard error of the mean

Kolkhof P *et al*. *Am J Nephrol* 2021; doi: 10.1159/000516213

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FIDELITY is a prespecified pooled analysis of individual patient data sets from the FIDELIO-DKD[1] and FIGARO-DKD trials[2]

48 countries

13,171 patients randomized

3 years' median follow-up

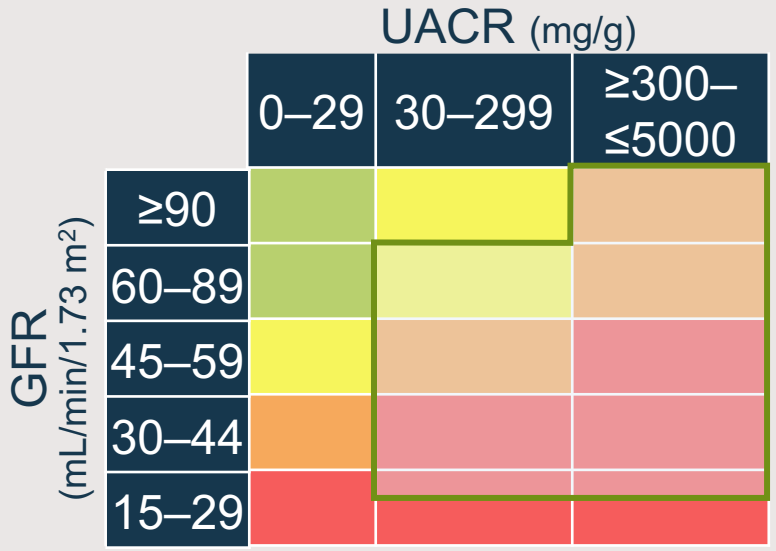
R

Finerenone 10 or 20 mg od*

Placebo

Key eligibility criteria

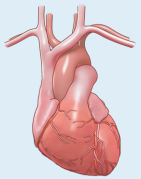
- ✓ T2D
- ✓ CKD
- ✓ On single RASi
- ✓ Serum [K^+] ≤4.8 mmol/L
- ✗ Symptomatic HFrEF



Key outcomes

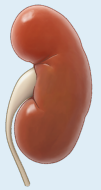
CV composite

Time to CV death, non-fatal MI, non-fatal stroke, or HHF



≥57% eGFR kidney composite

Time to kidney failure,# sustained ≥57% decrease in eGFR from baseline, or renal death



Aim of this subgroup analysis: To explore the treatment effect of finerenone in patients with and without concomitant SGLT-2i use at baseline

*10 mg if screening eGFR 25–<60 mL/min/1.73 m²; 20 mg if ≥60 mL/min/1.73 m², up-titration encouraged from month 1 if serum [K^+] ≤4.8 mmol/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 m²

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; 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; doi: 10.1056/NEJMoa2110956

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Patients treated with an SGLT-2i at baseline had a higher eGFR and lower UACR than those not receiving an SGLT-2i at baseline

Patient characteristic*	No SGLT-2i (n=12,149)	SGLT-2i (n=877)
Age, years	65	62
Male, %	69	76
Duration of diabetes, years	15.4	15.6
BMI, kg/m^2	31	33
SBP/DBP, mmHg	137/76	133/76
HbA1c, %	7.7	8.0
eGFR, mL/min/1.73 m^2 ≥60 mL/min/1.73 m^2, n (%)	**57** 4701 (39)	**66** 494 (56)
UACR, mg/g, median **≥300 mg/g, n (%)**	**521** **8114 (67)**	**448** **578 (66)**
History of CV disease, n (%)	5530 (45.5)	405 (46%)
Serum [K$^+$], mmol/L	4.4	4.3

Medication use, %	No SGLT-2i (n=12,149)	SGLT-2i (n=877)
RASis	100	100
Diuretics	52	50
Statins	**71**	**84**
Glucose-lowering therapies	98	100
Metformin	56	79
Insulin and analogs	59	59
GLP-1RA	**6**	**19**

*Values are mean unless otherwise stated
BMI, body mass index; DBP, diastolic blood pressure; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure

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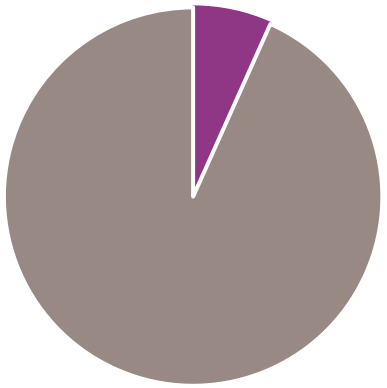
Phenomena in chronic kidney disease and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis

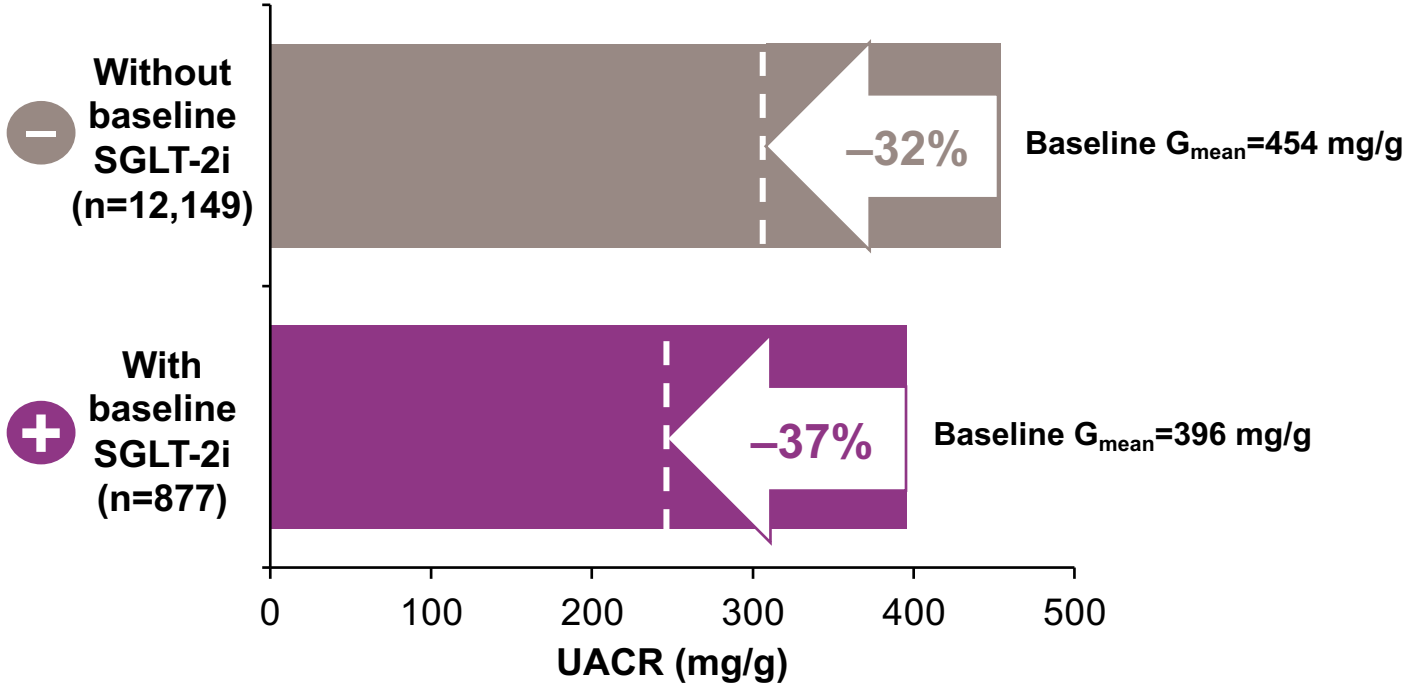
Finerenone improved UACR in patients with CKD and T2D irrespective of SGLT-2i use at baseline

SGLT-2i use at baseline

877 (6.7%) patients on an SGLT-2i



Reduction in UACR (%) with finerenone vs placebo



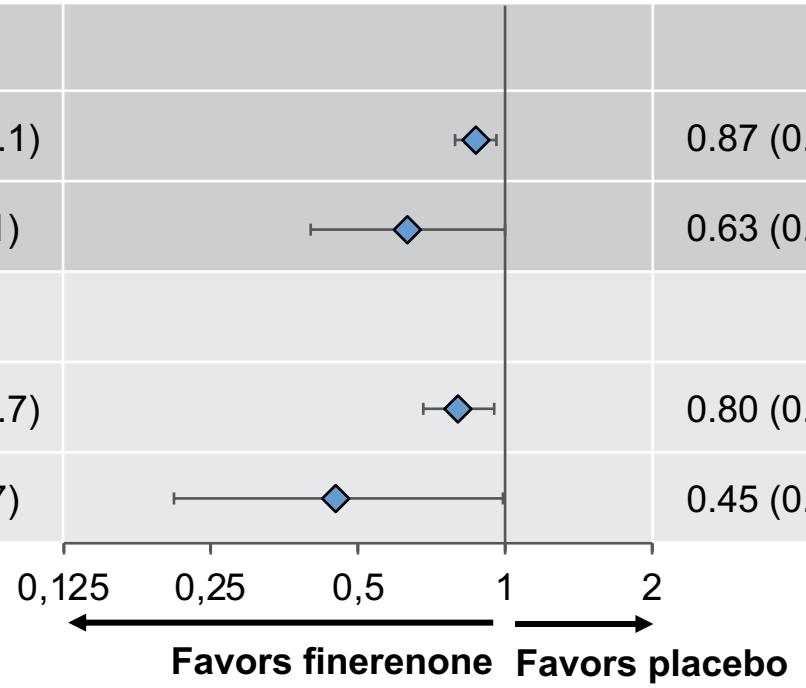
Full analysis set. Mixed model with factors for treatment group, region, eGFR category at screening, type of albuminuria at screening, CV disease history; time, treatment*time, log-transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value*time as covariates

G_{mean}, geometric mean

Rossing P, *et al. ADA* 2021; poster 14-LB

The CV benefit of finerenone was consistent irrespective of SGLT-2i use at baseline

Endpoint	Finerenone n/N (n/100 PY)	Placebo n/N (n/100 PY)	Hazard ratio (95% CI)	Adjusted HR (95% CI)*	*p*-value for interaction
CV composite#					0.41
No SGLT-2i	786/6081 (4.4)	887/6068 (5.1)		0.87 (0.79–0.96)	
SGLT-2i	39/438 (3.0)	52/439 (4.1)		0.63 (0.40–1.00)	
HHF					0.16
No SGLT-2i	246/6081 (1.4)	303/6068 (1.7)		0.80 (0.68–0.95)	
SGLT-2i	10/438 (0.7)	22/439 (1.7)		0.45 (0.21–0.99)	



*Adjusted HR for HbA1c, SBP, UACR at baseline (log-transformed), eGFR at baseline; #composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure
PY, patient-years

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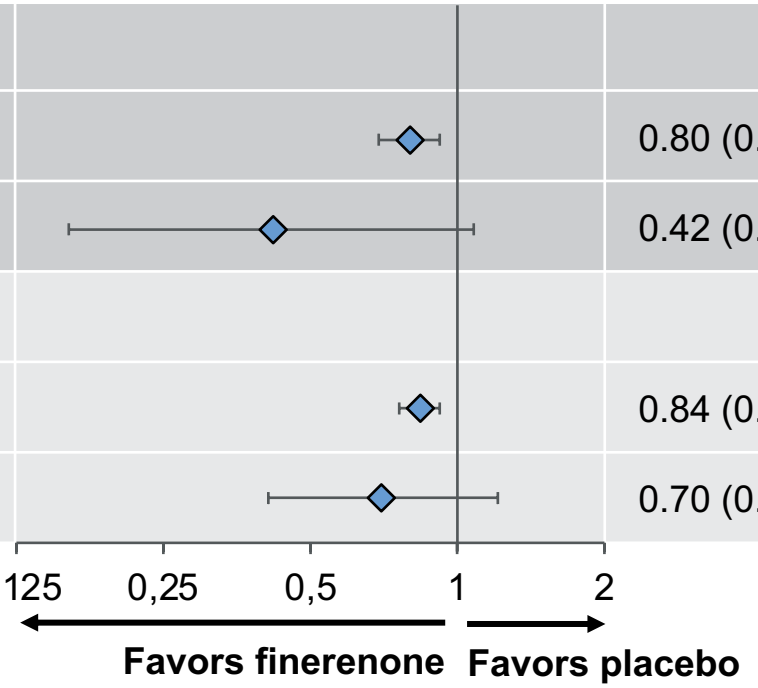
Kidney benefit was consistent irrespective of SGLT-2i use at baseline

Endpoint	Finerenone n/N (n/100 PY)	Placebo n/N (n/100 PY)	Hazard ratio (95% CI)	Adjusted HR (95% CI)*	*p*-value for interaction
eGFR 57% kidney composite#					
No SGLT-2i	351/6081 (2.1)	448/6068 (2.6)		0.80 (0.69–0.92)	0.29
SGLT-2i	9/438 (0.7)	17/439 (1.4)		0.42 (0.16–1.08)	
eGFR 40% kidney composite‡					
No SGLT-2i	818/6081 (5.0)	961/6068 (5.9)		0.84 (0.76–0.92)	0.59
SGLT-2i	36/438 (2.9)	34/439 (2.8)		0.70 (0.41–1.21)	



*Adjusted HR for HbA1c, SBP, UACR at baseline (log-transformed), eGFR at baseline; #eGFR 57% kidney composite outcome defined as kidney failure (end-stage kidney disease or eGFR <15 mL/min/1.73 m^2), a sustained ≥57% decrease in eGFR from baseline (equivalent to a doubling of serum creatinine) for ≥4 weeks, or renal death; ‡ eGFR 40% kidney composite outcome defined as kidney failure (end-stage kidney disease or eGFR <15 mL/min/1.73 m^2), a sustained ≥40% decrease in eGFR from baseline maintained for ≥4 weeks, or renal death

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Overall safety outcomes were consistent in patients with and without baseline SGLT-2i use

Treatment-emergent AE, n (%)	No SGLT-2i		SGLT-2i	
	Finerenone (n=6072)	Placebo (n=6050)	Finerenone (n=438)	Placebo (n=439)
Any AE	**5204 (85.7)**	**5223 (86.3)**	**398 (90.9)**	**384 (87.5)**
Leading to discontinuation	396 (6.5)	328 (5.4)	18 (4.1)	23 (5.2)
Any SAE	**1914 (31.5)**	**2045 (33.8)**	**146 (33.3)**	**141 (32.1)**
Leading to discontinuation	138 (2.3)	146 (2.4)	7 (1.6)	8 (1.8)
AE with outcome death	**108 (1.8)**	**142 (2.3)**	**2 (0.5)**	**9 (2.1)**
Hyperkalemia, n (%)				
Any AE	**867 (14.3)**	**436 (7.2)**	**45 (10.3)**	**12 (2.7)**
Leading to discontinuation	105 (1.7)	35 (0.6)	5 (1.1)	3 (0.7)

AE, adverse event; SAE, serious adverse event

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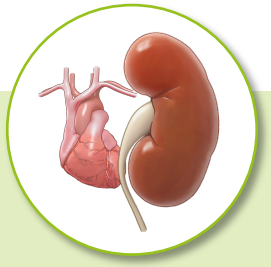
Summary and conclusion

Patients treated with an SGLT-2i at baseline had higher mean eGFR, lower UACR and higher statin and GLP-1RA use



Consistent kidney and CV benefits of finerenone vs placebo were observed, irrespective of SGLT-2i use at baseline

Finerenone improved albuminuria in patients treated with and without SGLT-2is at baseline

Safety outcomes were consistent irrespective of SGLT-2i use at baseline

Further studies are required to clarify any additional clinical benefits with combined finerenone and SGLT-2i therapies in this patient population

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Finerenone in chronic kidney disease and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analysis

Thank you

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

Executive committee
George L. Bakris; Gerasimos Filippatos; Rajiv Agarwal; Stefan D. Anker; Luis M. Ruilope; Bertram Pitt

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Clinical event committee
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FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis

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