189-OR

FIDELIO-DKD study – Analysis of effects of finerenone by baseline HbA1c

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On behalf of P. Rossing, R. Agarwal, S.D. Anker, G. Filippatos, B. Pitt, L.M. Ruilope, P. Gillard, A. Joseph, M. Brinker, C. Scott, G.L. Bakris, and the FIDELIO-DKD Investigators

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FIDELIO-DKD
FInerenone in reducing kiDnEy faiLure and dIsease prOgression in DKD

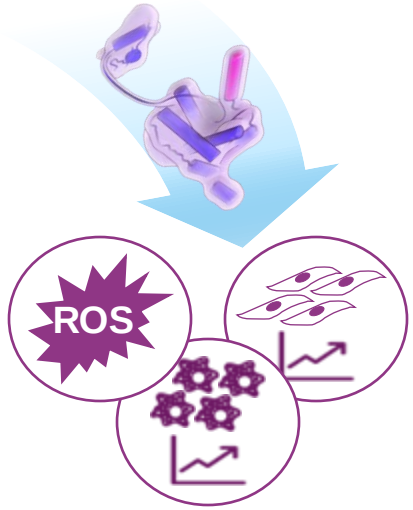
Disclosures: Ellen Burgess, MD

- Prof. Burgess is a member of the steering committee for FIDELIO-DKD

UNIVERSITY OF CALGARY

MR overactivation causes kidney and CV damage through inflammation and fibrosis

MR overactivation
through multiple mechanisms[1,2]

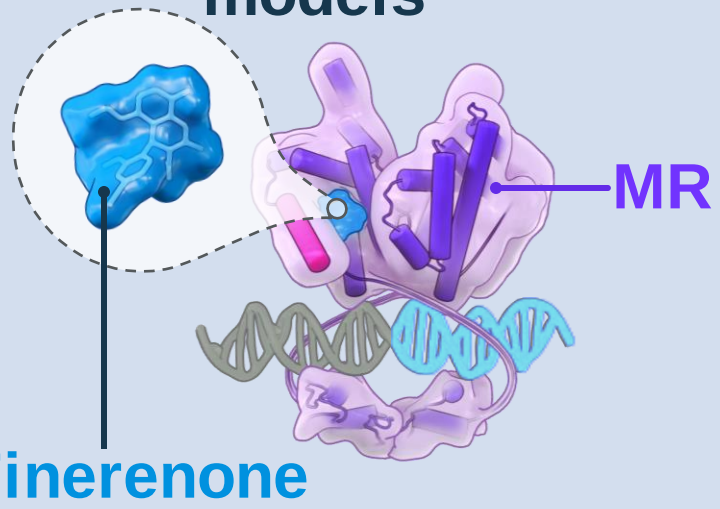


Increased gene expression of pro-inflammatory cytokines, and pro-fibrotic mediators[1–8]

Inflammation and fibrosis

- **Kidney damage**[3,7]
- **Vascular damage**[1,6]
- **Heart damage**[1,3]

Finerenone is a **novel, nonsteroidal, selective MRA** that **inhibits inflammation** and **fibrosis in preclinical models**[9]



CV, cardiovascular; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; NADPH, nicotinamide adenine dinucleotide phosphate oxidase; ROS, reactive oxygen species

1. Buonafine M, *et al. Am J Hypertension* 2018;31:1165–1174; 2. Kolkhof P, *et al. Handb Exp Pharmacol* 2017;243:271–305; 3. Bauersachs J, *et al. Hypertension* 2015;65:257–263; 4. Gomez-Sanchez E & Gomez-Sanchez CE. *Compr Physiol* 2014;4:965–994; 5. Brown NJ. *Nat Rev Nephrol* 2013;9:459–469; 6. Biwer LA, *et al. Am J Hypertension* 2019;32:123–134; 7. Barrera-Chimal J, *et al. Kidney Int* 2019;96:302–319; 8. van de Heijden CDCC, *et al. Cardiovasc Res* 2018;114:944–953; 9. Agarwal R, *et al. Eur Heart J* 2021;42:152–162

FIDELIO-DKD study design

5734 patients randomized

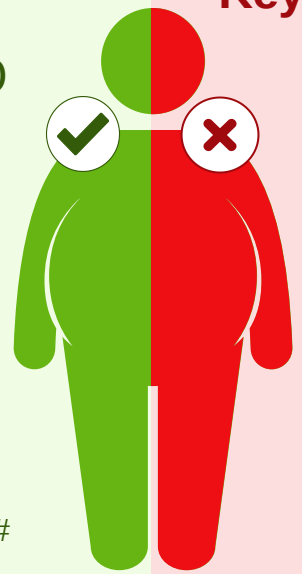
2.6 years' median follow-up

Run-in (4–16 weeks) → Screening → R

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

Key inclusion criteria

- Aged ≥18 years with T2D
- On max. tolerated dose of RASi for ≥4 weeks
- eGFR ≥25–<75 mL/min/1.73 m^2
- UACR ≥30–≤5000 mg/g*
- Serum [K^+] ≤4.8 mmol/L#



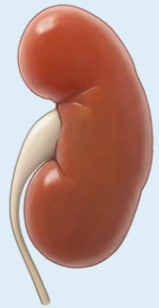
Key exclusion criteria

- HFrEF with NYHA Class II–IV
- Uncontrolled arterial hypertension‡
- HbA1c >12%
- Other kidney disease §

Key outcomes

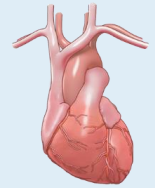
1. Kidney composite

Time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death



2. CV composite

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



*Patients with moderately elevated albuminuria (UACR 30–300 mg/g) were required to also have diabetic retinopathy; #at run-in and screening visits; ‡mean sitting SBP ≥170 mmHg or mean sitting DBP ≥110 mmHg at the run-in visit or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the screening visit; § known significant nondiabetic kidney disease, including clinically relevant renal artery stenosis

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; [K^+], potassium concentration; MI, myocardial infarction; NYHA, New York Heart Association; RASi, renin–angiotensin system inhibitor; SBP, systolic blood pressure; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

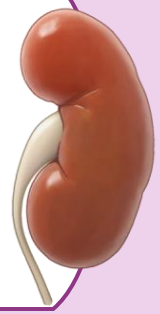
Bakris GL, *et al*. *N Engl J Med* 2020;383:2219–2229

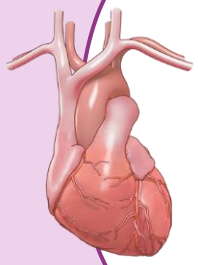
Subgroup analysis of FIDELIO-DKD was performed to evaluate whether glycemic control affects the efficacy of finerenone

In FIDELIO-DKD,
finerenone significantly reduced the risk of:[1]

CKD progression by **18%**

NNT = 29*





CV morbidity and **mortality** by **14%**

NNT = 42*

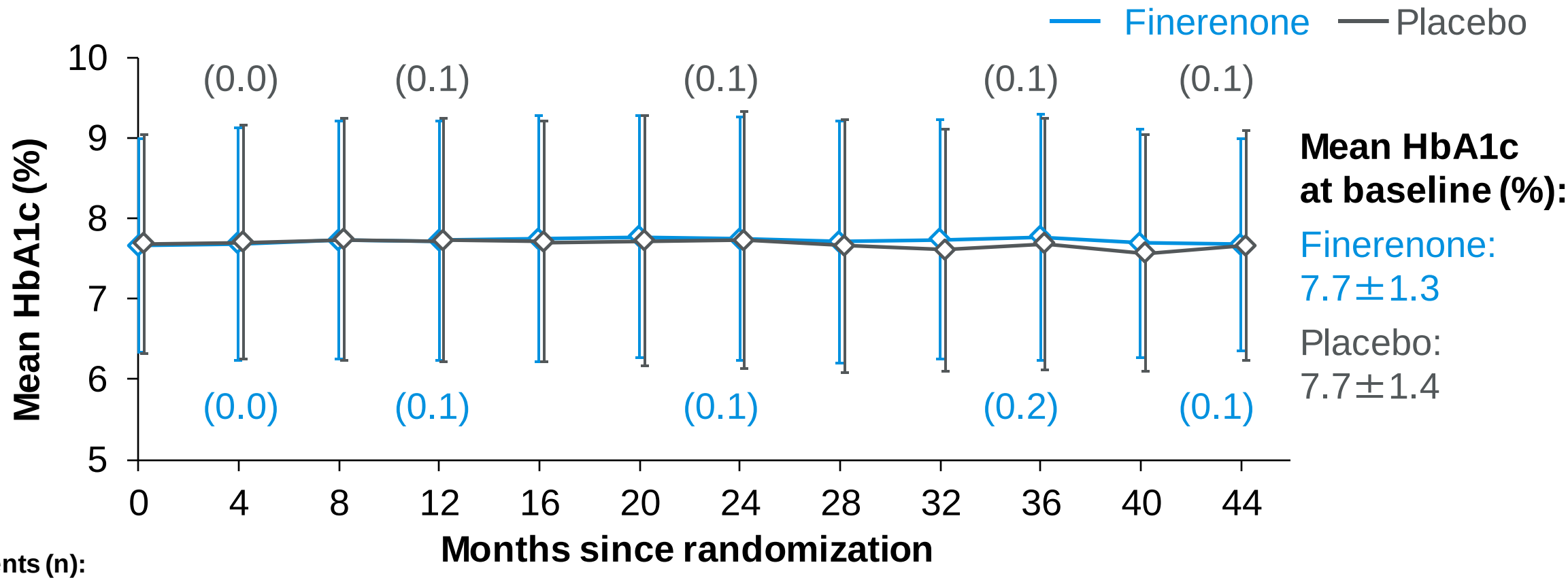
Evidence regarding the relationship between glycemic control and disease outcomes in patients with advanced CKD and T2D from large phase III trials is lacking

Aim of this subgroup analysis

To evaluate the impact of baseline HbA1c level (< or ≥ median at baseline) **on the composite kidney and CV outcomes and safety** in patients treated with finerenone or placebo

*NNT to prevent one event based on absolute risk reductions at 36 months
CKD, chronic kidney disease; NNT, number needed to treat
1. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229

In FIDELIO-DKD, finerenone had no effect on HbA1c



Patients (n):

Finerenone	2821	2697	2605	1889	893	346
Placebo	2828	2694	2610	1871	870	349

Data are mean ± SD. Numbers in parentheses show mean change from baseline; error bars show SD
SD, standard deviation
Bakris GL, *et al*. *N Engl J Med* 2020;383:2219–2229

Patients in both baseline HbA1c groups had advanced CKD

	HbA1c <7.5% (n=2794)	HbA1c ≥7.5% (n=2869)
Age, years	66±9	65±9
Gender, male	2073 (74)	1904 (66)
Duration of T2D, years	15±9	18±8
BMI, kg/m^2	30±6	32±6
SBP, mmHg	138±15	139±14
Serum [K$^+$], mmol/L	4.4±0.5	4.4±0.5
eGFR, mL/min/1.73 m^2	44±13	45±13
UACR, mg/g, median (IQR)	798 (445–1567)	815 (447–1693)

Values are n (%) or mean ± SD unless otherwise stated
Full analysis set. Missing data for n=7 patients (finerenone) and n=4 patients (placebo)
BMI, body mass index; IQR, interquartile range

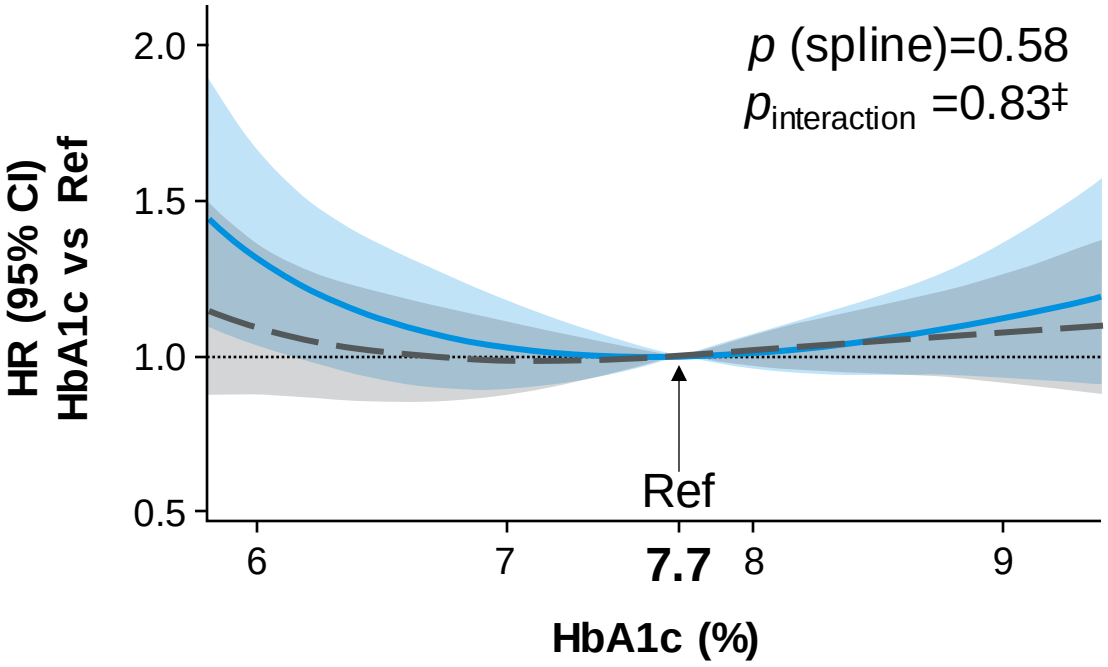
A higher proportion of patients with HbA1c ≥7.5% were receiving insulin at baseline

Concomitant medications, n (%)	HbA1c <7.5% (n=2794)	HbA1c ≥7.5% (n=2869)
ACEi	914 (33)	1022 (36)
ARB	1875 (67)	1845 (64)
Diuretics	1529 (55)	1681 (59)
Glucose-lowering therapies	2672 (96)	2842 (99)
Insulin and analogues	1353 (48)	2279 (79)
Metformin	1264 (45)	1219 (43)
Sulfonylureas	687 (25)	639 (22)
DPP-4 inhibitors	833 (30)	686 (24)
GLP-1RAs	158 (6)	235 (8)
SGLT-2 inhibitors	100 (4)	159 (6)

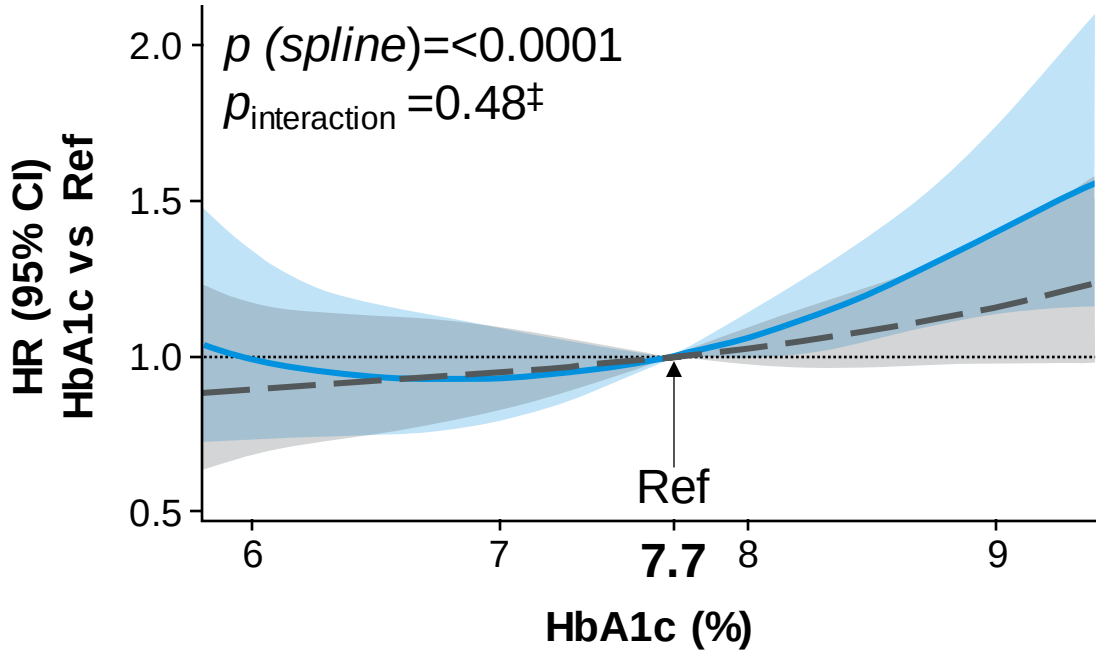
Full analysis set. Missing data for n=7 patients (finerenone) and n=4 patients (placebo)
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Relationship between baseline HbA1c and primary composite kidney and key secondary composite CV outcomes

Primary kidney outcome*



Key secondary CV outcome#

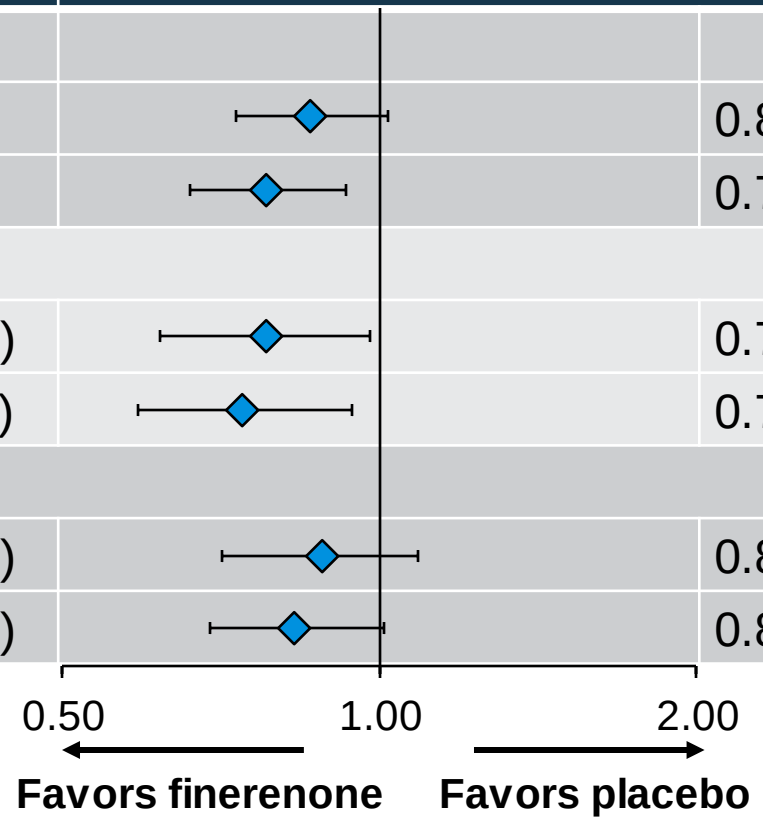


Placebo 95% CI | Finerenone 95% CI | Placebo HR | Finerenone HR | No effect

Full analysis set
Confidence interval; HR, hazard ratio
Cox proportional hazards models fitted separately, by treatment group and stratified by region, albuminuria at screening and eGFR at screening and including a cubic B-spline of HbA1c with 3 equally spaced knots
*Kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death; #a composite of time to first onset of death from CV causes, nonfatal MI, nonfatal stroke, or HHF; ‡finerenone vs placebo

Cardiorenal benefits of finerenone were consistent independent of HbA1c category at baseline

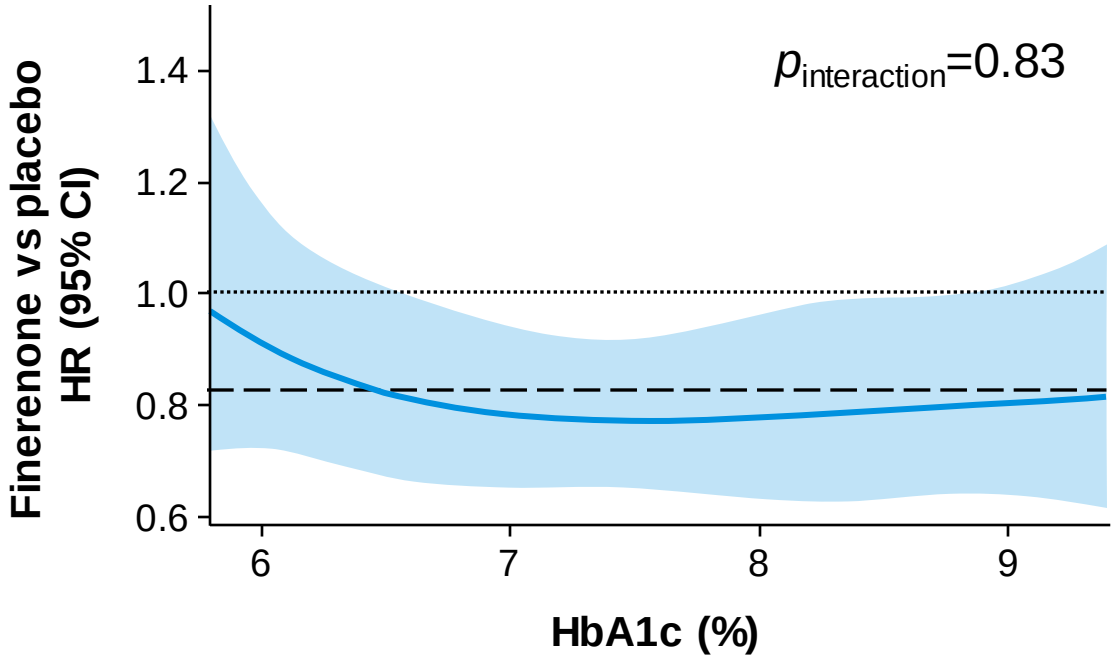
Outcome	Finerenone (n=2826)	Placebo (n=2837)	Hazard ratio (95% CI)	*p* inter-action
	n/N (%)	n/N (%)		
Primary composite kidney outcome*				
HbA1c <7.5%	260/1384 (19)	304/1410 (22)	0.86 (0.73–1.02)	0.41
HbA1c ≥7.5%	243/1442 (17)	296/1427 (21)	0.78 (0.66–0.93)	
Secondary composite kidney outcome#				
HbA1c <7.5%	129/1384 (9)	171/1410 (12)	0.78 (0.62–0.98)	0.80
HbA1c ≥7.5%	122/1442 (9)	155/1427 (11)	0.74 (0.59–0.94)	
Key secondary composite CV outcome‡				
HbA1c <7.5%	164/1384 (12)	187/1410 (13)	0.88 (0.71–1.09)	0.70
HbA1c ≥7.5%	201/1442 (14)	233/1427 (16)	0.83 (0.69–1.01)	



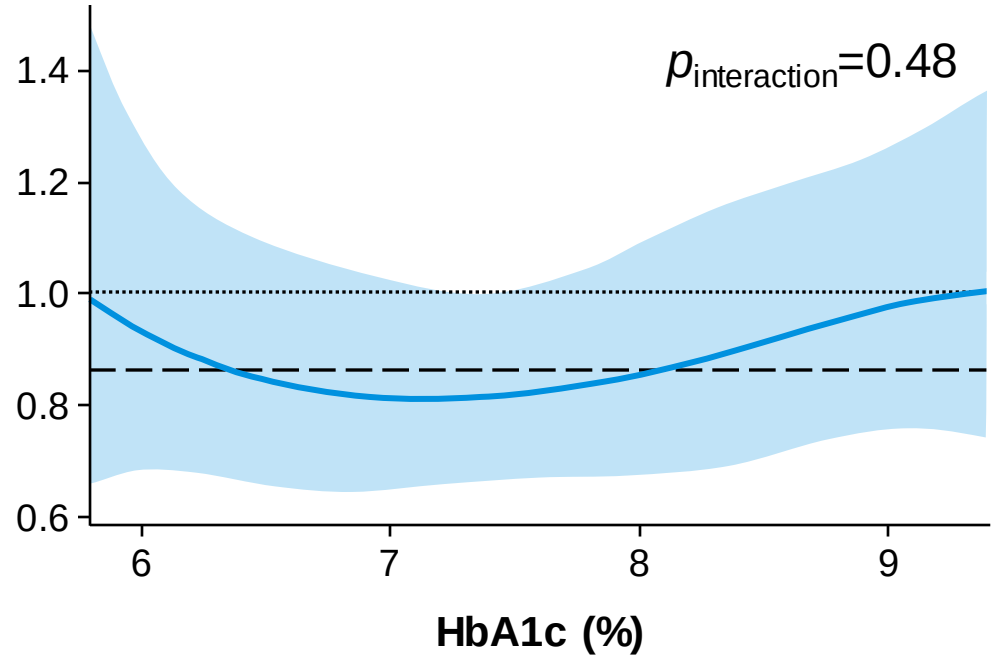
Full analysis set
*Kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death; #kidney failure, sustained ≥57% decrease in eGFR from baseline, or renal death; ‡a composite of time to first onset of death from CV causes, nonfatal MI, nonfatal stroke, or HHF

Cardiorenal benefits of finerenone were consistent independent of HbA1c at baseline modelled as a continuous variable

Primary kidney outcome



Key secondary CV outcome

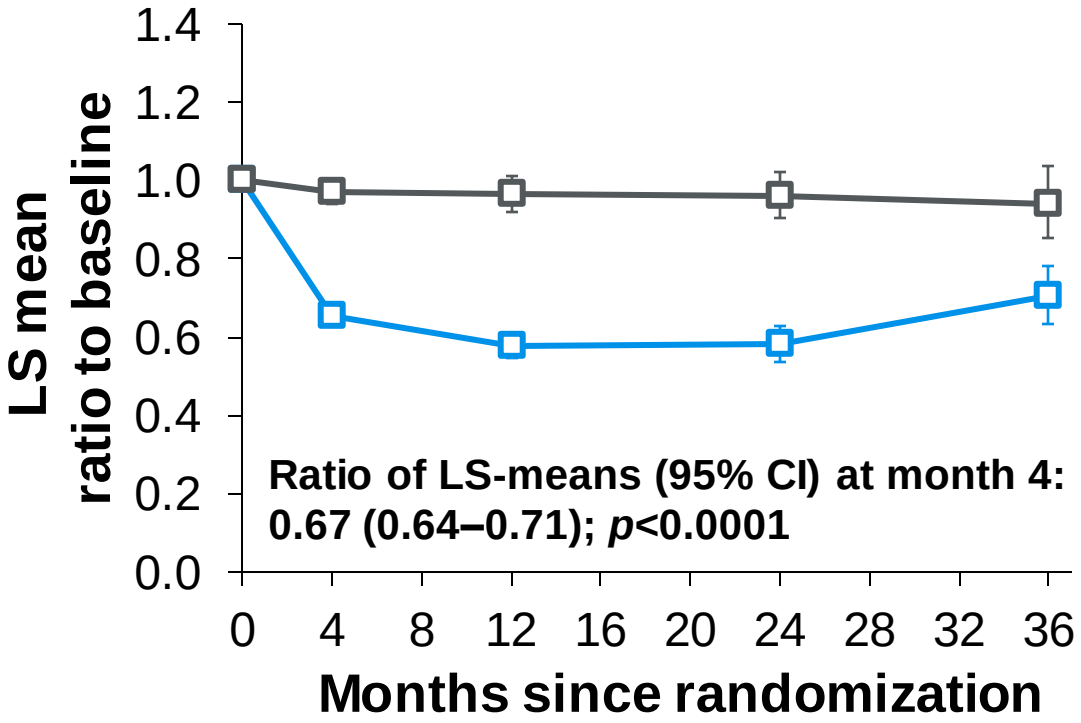


Pointwise 95% CI — Fitted curve ····· No effect – – Overall effect

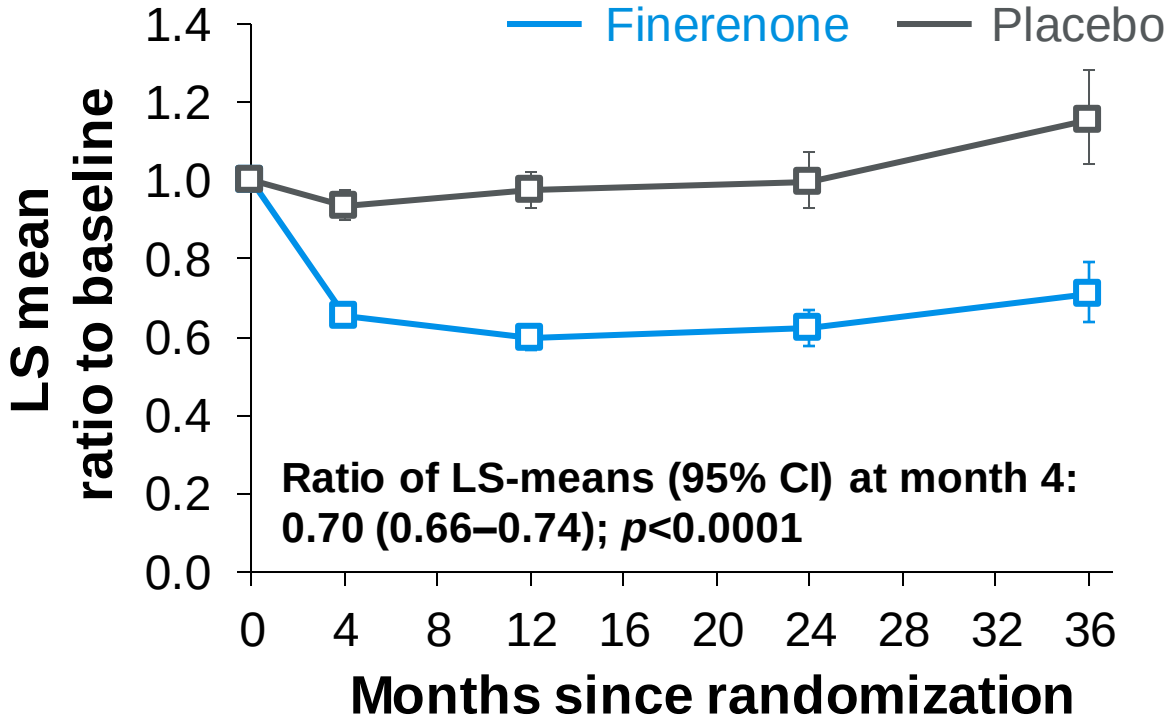
Full analysis set
A Cox proportional hazards model is fitted stratified by region, albuminuria at screening and eGFR at screening, including treatment, a cubic B-spline of HbA1c with 3 equally spaced knots and its interaction with treatment as covariates

The change in UACR from baseline to month 4 was consistent irrespective of HbA1c at baseline

HbA1c <7.5%



HbA1c ≥7.5%



No. of patients								
Finerenone	1337	1268	925	428	1382	1308	914	428
Placebo	1360	1292	927	432	1363	1303	895	401

Full analysis set. Mixed model including covariates: treatment group, stratification factors (region, eGFR category and type of albuminuria at screening), time, treatment over time, log-transformed baseline value nested within type of albuminuria at screening and log-transformed baseline value over time
LS, least-squares

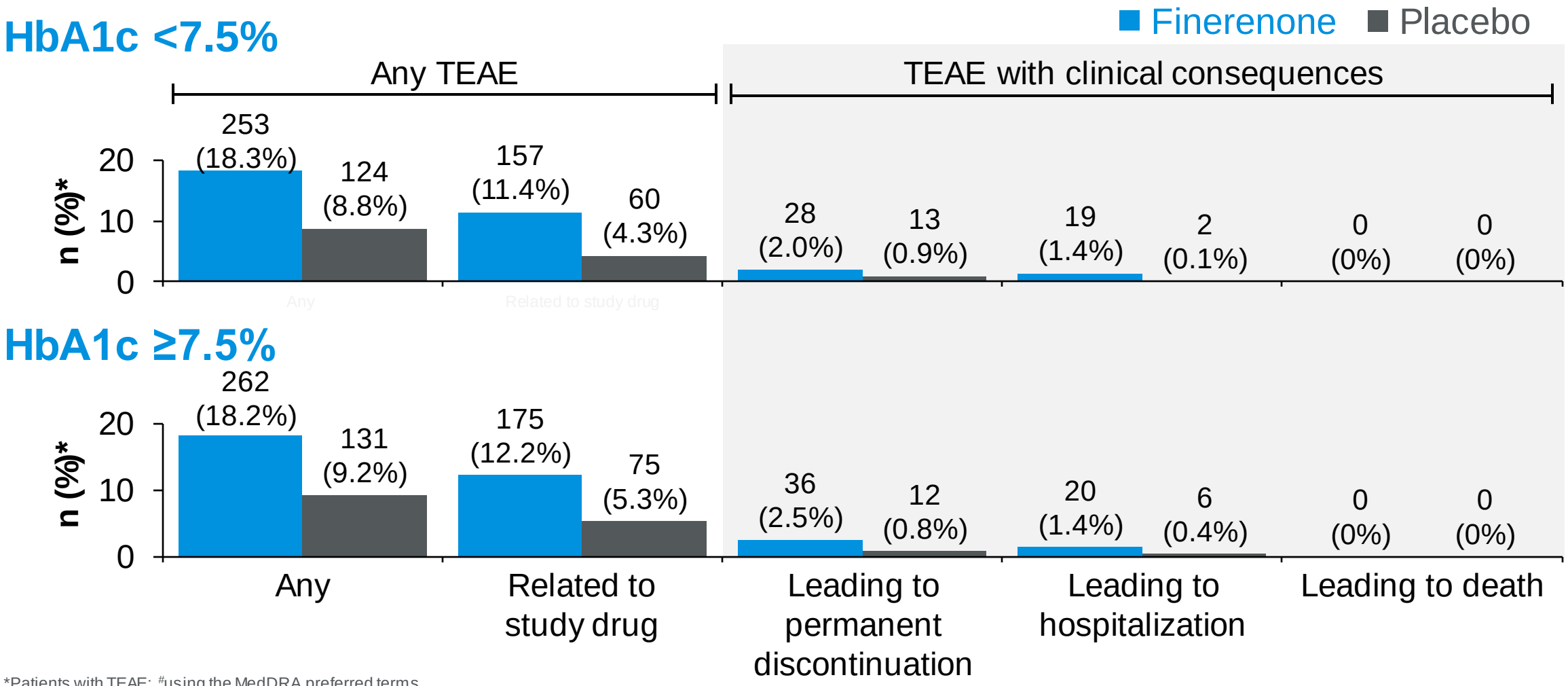
The safety profile of finerenone was consistent regardless of HbA1c at baseline

General safety outcomes

n (%)	HbA1c <7.5%		HbA1c ≥7.5%	
	Finerenone (n=1382)	Placebo (n=1407)	Finerenone (n=1439)	Placebo (n=1421)
Any AE	1206 (87)	1229 (87)	1258 (87)	1246 (88)
AE related to study drug	312 (23)	221 (16)	333 (23)	228 (16)
AE leading to permanent discontinuation	98 (7)	92 (7)	108 (8)	75 (5)
Any serious AE	415 (30)	448 (32)	485 (34)	523 (37)
Serious AE related to study drug	23 (2)	16 (1)	24 (2)	18 (1)
Serious AE leading to permanent discontinuation	36 (3)	39 (3)	38 (3)	39 (3)

Safety analysis set. Missing data for n=6 patients (finerenone) and n=3 patients (placebo)
AE, adverse event

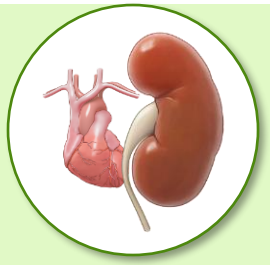
Independent of HbA1c at baseline, finerenone increased the incidence of hyperkalemia, but the clinical impact was minimal



*Patients with TEAE; #using the MedDRA preferred terms 'hyperkalemia' and 'blood potassium increased'
TEAE, treatment-emergent adverse event

Investigator-reported hyperkalemia#

Summary



The kidney and CV benefits of finerenone vs placebo were consistent, irrespective of HbA1c at baseline

Overall, AEs were similar with finerenone and placebo, independent of HbA1c at baseline

Risk of hyperkalemia was increased with finerenone, but its clinical impact was minimal

Limitations

- Secondary subgroup analysis – patients not recruited according to baseline HbA1c
- Post-baseline changes in HbA1c were not considered

Conclusion

- **Finerenone is a novel, nonsteroidal, selective MRA that inhibits inflammation and fibrosis associated with MR overactivation in preclinical models**
- **In FIDELIO-DKD:**
  - Finerenone reduced the incidence of kidney and CV outcomes in patients with CKD and T2D, despite differences in baseline glycemic control
  - Treatment with finerenone was well-tolerated

Thank you

FIDELIO-DKD
FInerenone in reducing kiDnEy faiLure and dIsease prOgression in DKD

The FIDELIO-DKD team would like to thank all participating investigators, the centers, the patients, and their families

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48 countries, 913 sites, 13,911* participants

*Number of patients who provided informed consent