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Effects of finerenone on cardiorenal outcomes in blood pressure subgroups in patients with CKD and T2D

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on behalf of R. Agarwal, S.D. Anker, G. Filippatos, B. Pitt, P. Rossing, P. Sarafidis, R.E. Schmieder, A. Joseph, N. Mentenich, C. Nowack, G.L. Bakris, and the FIDELIO-DKD investigators

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Disclosures

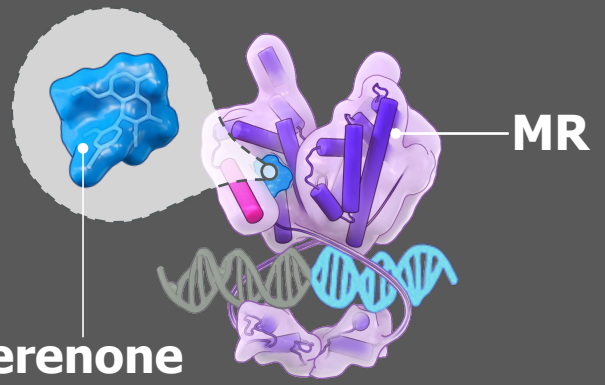
- Professor Luis M. Ruilope has received consultancy fees from Bayer

The FIDELIO-DKD trial demonstrated kidney and CV benefits with finerenone in patients with CKD and T2D

Arterial hypertension is highly prevalent in patients with **CKD** and **T2D**[1,2]

- **CKD** commonly **coexists** with **hypertension**, and **poorly controlled BP** contributes to the **progression of CKD**[1,2]

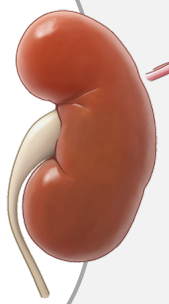
Finerenone is a **novel**, **selective**, **nonsteroidal MRA** that **inhibits inflammation** and **fibrosis** in preclinical models[3]

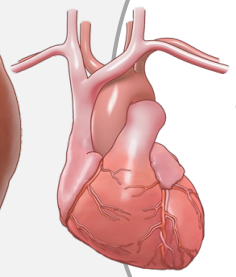


In the FIDELIO-DKD patient population with **advanced CKD in T2D**, finerenone was well tolerated and significantly reduced:[4]

CKD progression by **18%**

NNT=29*





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

NNT=42*

*NNT to prevent one event based on absolute risk reductions at 36 months

CV, cardiovascular; NNT, number needed to treat

1. Ku E, *et al. Am J Kidney Dis* 2019;74:120–131; 2. Van Buren PN, Toto R. *Adv Chronic Kidney Dis* 2011;18:28–41; 3. Agarwal R, *et al. Eur Heart J* 2021;42:152–162; 4. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229

Patients in FIDELIO-DKD were treated with optimised RASi therapy and had well-controlled BP and HbA1c

13,911 patients enrolled

48 countries

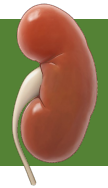
5734 patients randomised

2.6 years' median follow-up

Run-in (4–16 weeks) → Screening → R

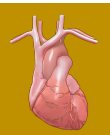
- **Finerenone 10 or 20 mg od***
- **Placebo**

Key outcomes



Kidney composite

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



CV composite

Time to CV death, nonfatal MI, nonfatal stroke or hospitalisation for HF

*10 mg if screening eGFR 25–<60 ml/min/1.73 m^2; 20 mg if ≥60 ml/min/1.73 m^2, up-titration encouraged from month 1 if serum potassium ≤4.8 mmol/l and eGFR stable
eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; MI, myocardial infarction; od, once daily; RASi, renin–angiotensin system inhibitor; SBP, systolic blood pressure
Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229

Aim of this analysis

To determine **how much** of the **treatment effect** observed for **finerenone** versus placebo on **cardiorenal outcomes** was **mediated by changes in office systolic blood pressure** using a **Cox proportional hazards model***

*The complete time course of SBP was considered by means of a stratified Cox model including a time-varying covariate for SBP

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

FIDELIO-DKD was a global trial consisting of patients with CKD and T2D on optimised standard of care

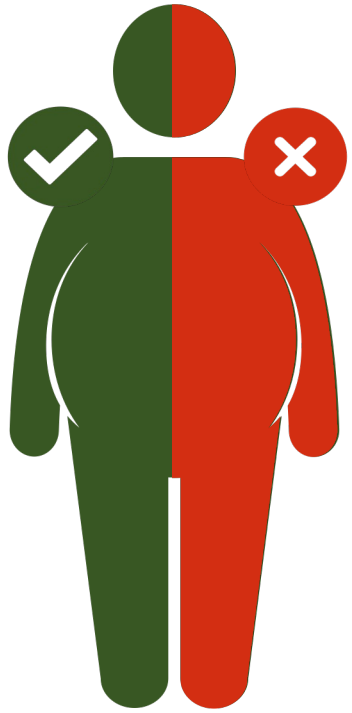
Aged ≥18 years with T2D

On maximum tolerated dose of ACEi or ARB for ≥4 weeks

eGFR of ≥25–<75 ml/min/1.73 m²

Moderately*/severely elevated albuminuria

Serum [K⁺] ≤4.8 mmol/l at run-in and screening visit



HFrEF with NYHA class II–IV

Uncontrolled arterial hypertension#

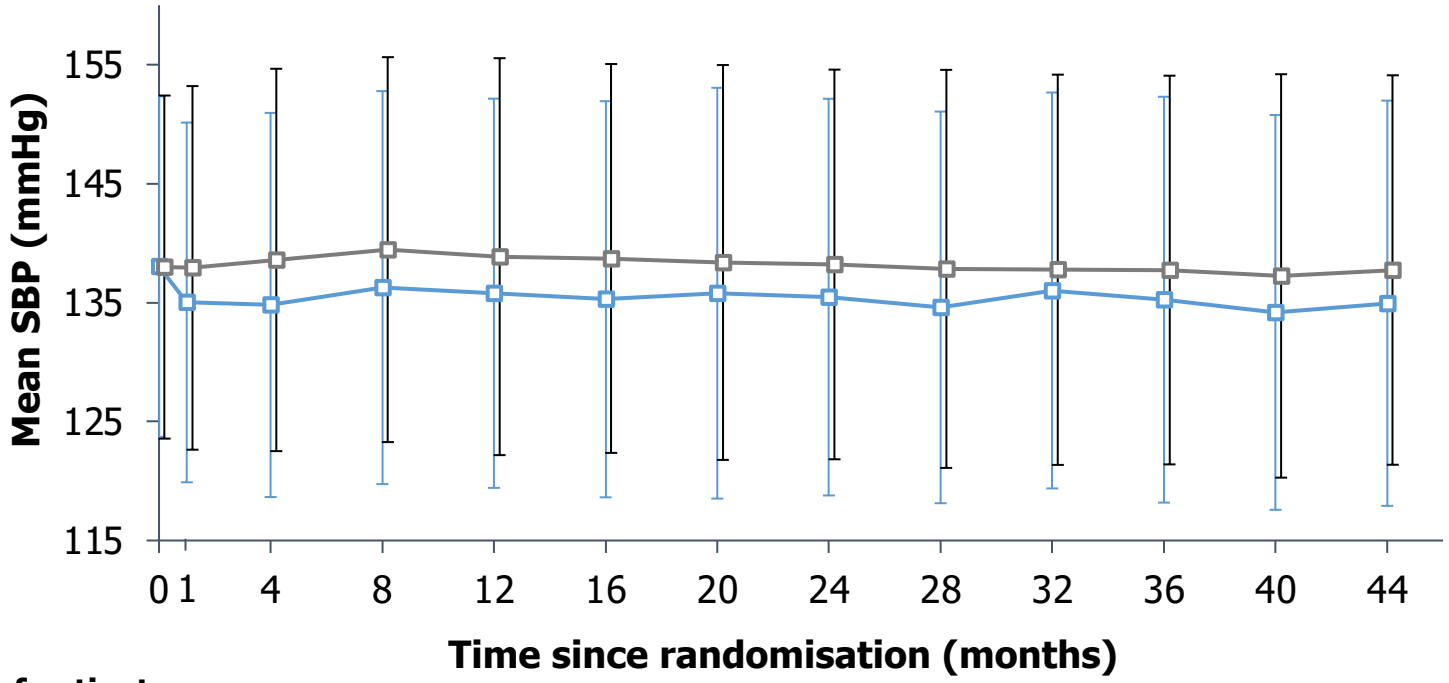
HbA1c >12%

Other kidney disease‡

A total of **5669 patients with available SBP data** were **grouped** by **quartiles of baseline SBP**

*Patients with moderately elevated albuminuria were required to also have diabetic retinopathy; #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 non-diabetic kidney disease, including clinically relevant renal artery stenosis
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; HFrEF, heart failure with reduced ejection fraction; [K⁺], potassium concentration; NYHA, New York Heart Association

Finerenone resulted in a modest and consistent reduction in office SBP (overall LS-mean difference of –2.71)



Mean SBP at baseline (mmHg):

Placebo: 137.98±14.42

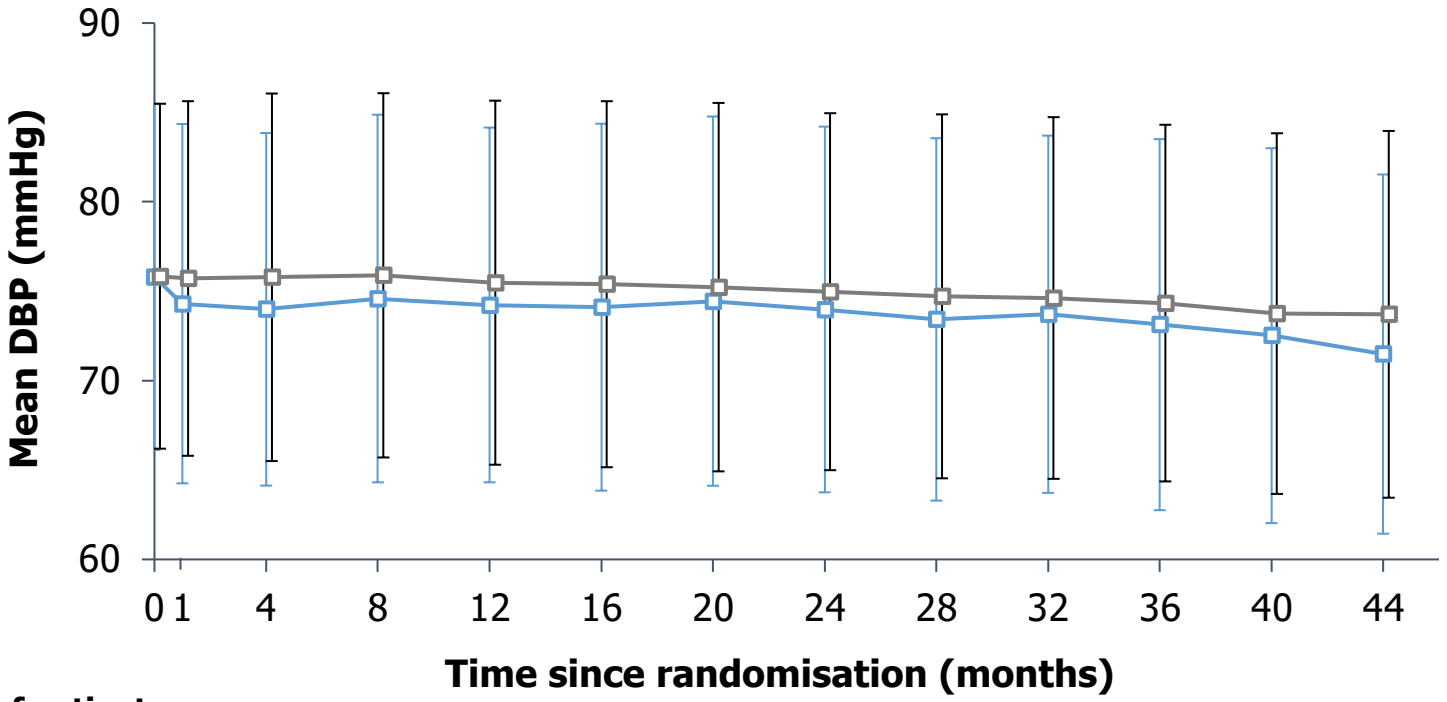
Finerenone: 138.02±14.31

Overall LS-mean difference: –2.71 (95% CI –3.29 to –2.12)

Number of patients					
Finerenone		2745	2628	1907	903	348
Placebo		2754	2640	1895	884	353
LS-mean change in SBP from baseline (mmHg)						
Finerenone	Ref	–3.20	–2.07	–1.61	–1.82	–2.01
Placebo	Ref	0.67	0.85	0.62	0.37	0.13

CI, confidence interval; LS, least-squares

Finerenone resulted in a slight reduction in office DBP throughout the trial (overall LS-mean difference of –1.03)



Mean DBP at baseline (mmHg):

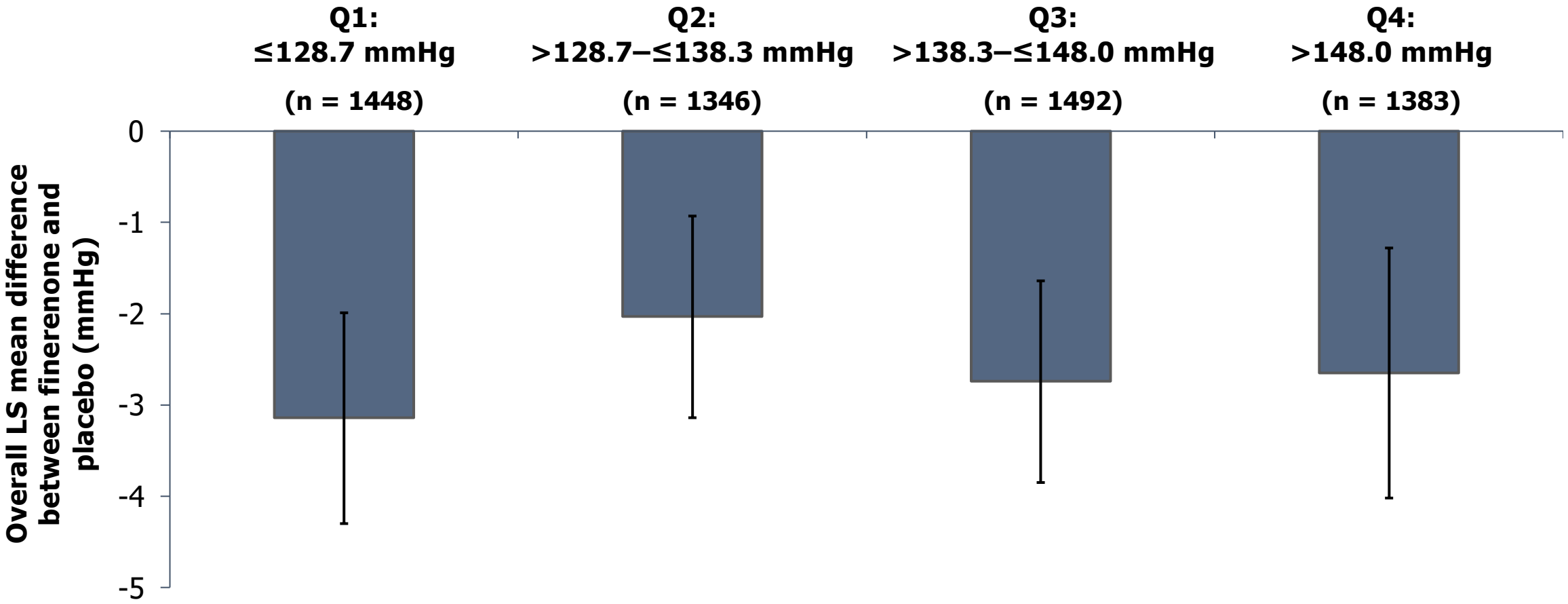
Placebo: 75.84±9.65

Finerenone: 75.80±9.68

Overall LS-mean difference: –1.03 (95% CI –1.37 to –0.69)

Number of patients						
Finerenone		2745	2628	1907	903	348
Placebo		2754	2640	1895	884	353
LS-mean change in DBP from baseline (mmHg)						
Finerenone	Ref	–1.77	–1.46	–1.44	–1.51	–2.30
Placebo	Ref	–0.06	–0.42	–0.70	–1.35	–1.37

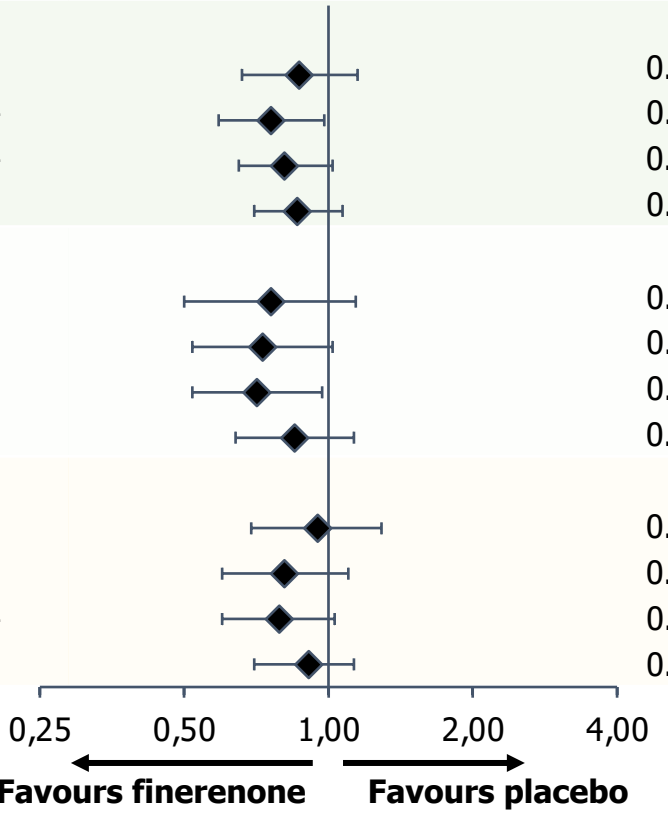
Modest reduction in office SBP with finerenone vs placebo was consistent across baseline SBP quartiles



Data presented as overall LS mean difference (95% CI) for month 1 to month 44 of visit
Q, quartile

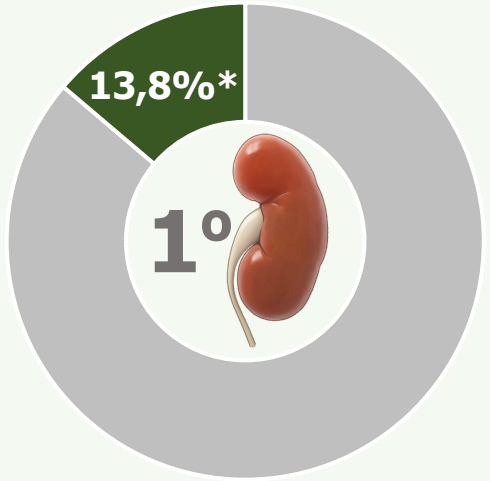
Finerenone consistently lowered the risk of kidney and CV composite outcomes across the baseline SBP quartiles

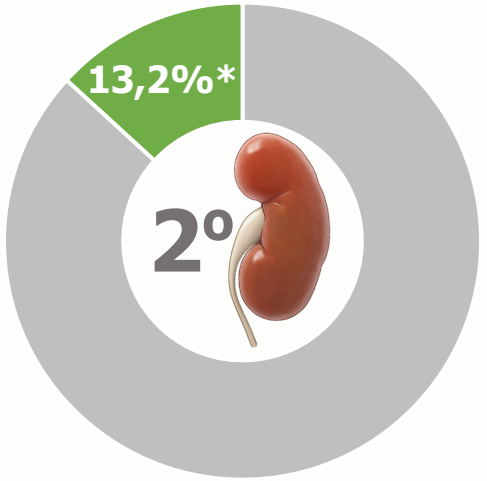
Outcome	Finerenone n/N	Placebo n/N	HR (95% CI)	*p*-value for interaction
Primary kidney composite outcome*				0.87
SBP Q1 (≤128.7 mmHg)	94/726	106/722	0.87 (0.66–1.15)	
SBP Q2 (>128.7–≤138.3 mmHg)	107/662	143/684	0.76 (0.59–0.98)	
SBP Q3 (>138.3–≤148.0 mmHg)	143/778	157/714	0.81 (0.65–1.02)	
SBP Q4 (>148.0 mmHg)	159/664	194/719	0.86 (0.70–1.07)	
Secondary kidney composite outcome#				0.85
SBP Q1 (≤128.7 mmHg)	41/726	53/722	0.76 (0.50–1.14)	
SBP Q2 (>128.7–≤138.3 mmHg)	56/662	79/684	0.73 (0.52–1.02)	
SBP Q3 (>138.3–≤148.0 mmHg)	69/778	87/714	0.71 (0.52–0.97)	
SBP Q4 (>148.0 mmHg)	85/664	107/719	0.85 (0.64–1.13)	
Key secondary CV composite outcome‡				0.78
SBP Q1 (≤128.7 mmHg)	79/726	82/722	0.95 (0.69–1.29)	
SBP Q2 (>128.7–≤138.3 mmHg)	79/662	97/684	0.81 (0.60–1.10)	
SBP Q3 (>138.3–≤148.0 mmHg)	103/778	115/714	0.79 (0.60–1.03)	
SBP Q4 (>148.0 mmHg)	104/664	125/719	0.91 (0.70–1.18)	

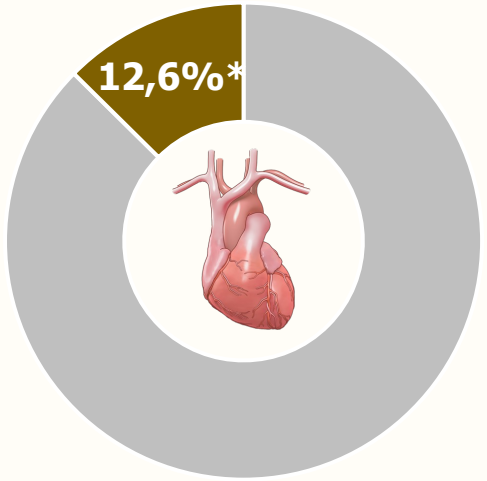


*Time to kidney failure, sustained ≥40% decrease in eGFR from baseline or renal death; #Time to kidney failure, sustained ≥57% decrease in eGFR from baseline or renal death;
‡Time to CV death, nonfatal MI, nonfatal stroke or hospitalisation for HF
HR, hazard ratio

A small proportion of the treatment effect of finerenone on cardiorenal outcomes can be attributed to effects on office SBP





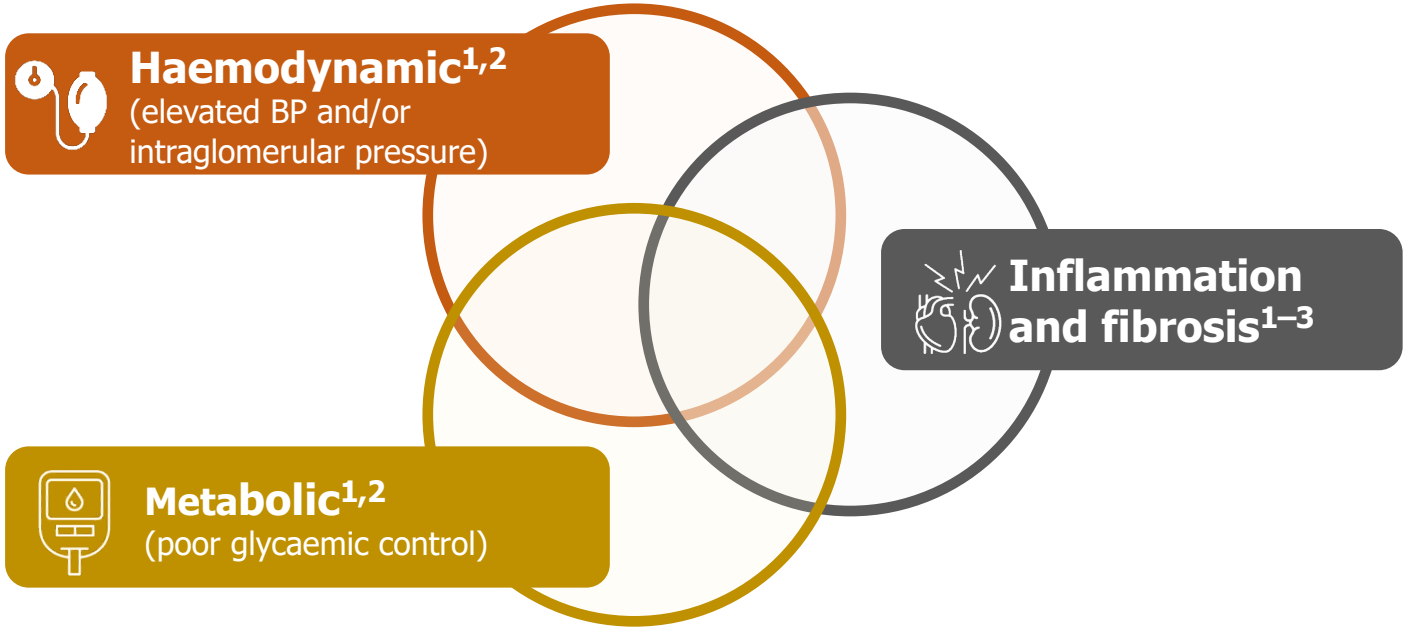


HR (95% CI)	Time to kidney failure, sustained ≥40% ↓ in eGFR from baseline or renal death	Time to kidney failure, sustained ≥57% ↓ in eGFR from baseline or renal death	Time to CV death, nonfatal MI, nonfatal stroke or hospitalisation for HF
Primary analysis	0.82 (0.73–0.93)	0.76 (0.65–0.90)	0.86 (0.75–0.99)
Adjusted analysis#	0.85 (0.75–0.96)	0.79 (0.67–0.94)	0.88 (0.76–1.01)
***p*-value for interaction‡**	0.56	0.45	0.50

*Proportion of treatment effect explained by SBP changes = 100%×([HR_0–HR_1]/[HR_0–1]), where HR_0 is the hazard ratio from the primary analysis model (unadjusted by SBP changes) and HR_1 is the hazard ratio for the adjusted analysis model (adjusted for time-varying SBP); #Hazard ratio for treatment from stratified Cox proportional hazards model and adjusted for time-varying SBP; ‡*p*-value of interaction between treatment and time-varying SBP from model as in # additionally including this interaction term

Kidney and CV benefits of finerenone may be associated with its anti-inflammatory and anti-fibrotic effects

Drivers of CKD in T2D progression[1–3]



FIDELIO-DKD[4]

A small proportion of the cardiorenal benefit of finerenone may be driven by short-term haemodynamic effects

No difference in HbA1c was observed between finerenone and placebo

Therefore, a reduction in inflammation and fibrosis may underlie the long-term kidney and CV protection with finerenone

1. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Mora-Fernández C, *et al. J Physiol* 2014;18:3997; 3. Bauersachs J, *et al. Hypertension* 2015;65:257–263;
4. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229

Incidence of any TEAE was similar between treatment arms across the SBP quartile groups

Patients with TEAEs n (%)	Baseline SBP							
	Q1 (≤128.7 mmHg)		Q2 (>128.7–≤138.3 mmHg)		Q3 (>138.3–≤148.0 mmHg)		Q4 (>148.0 mmHg)	
	Finerenone (n=726)	Placebo (n=721)	Finerenone (n=662)	Placebo (n=683)	Finerenone (n=777)	Placebo (n=712)	Finerenone (n=661)	Placebo (n=715)
Any AE	630 (86.8)	636 (88.2)	566 (85.5)	582 (85.2)	675 (86.9)	607 (85.3)	597 (90.3)	653 (91.3)
Any AE leading to discontinuation of study drug	48 (6.6)	47 (6.5)	46 (6.9)	30 (4.4)	63 (8.1)	46 (6.5)	50 (7.6)	45 (6.3)
Any SAE	237 (32.6)	254 (35.2)	215 (32.5)	189 (27.7)	236 (30.4)	263 (36.9)	214 (32.4)	265 (37.1)
Any hyperkalaemia	132 (18.2)	77 (10.7)	112 (16.9)	62 (9.1)	145 (18.7)	56 (7.9)	127 (19.2)	60 (8.4)
Hyperkalaemia leading to permanent discontinuation	18 (2.5)	4 (0.6)	12 (1.8)	8 (1.2)	17 (2.2)	7 (1.0)	17 (2.6)	6 (0.8)
Any acute kidney injury	24 (3.3)	35 (4.9)	40 (6.0)	23 (3.4)	34 (4.4)	36 (5.1)	31 (4.7)	42 (5.9)

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

Summary

Finerenone had a modest effect on office BP in patients with CKD and T2D

The modest reduction observed in office SBP was consistent across baseline SBP quartiles

The benefit of finerenone on kidney and CV outcomes was similar across quartiles of baseline SBP

Incidence of any TEAE or hyperkalaemia was similar between treatment groups across SBP quartiles

Serious AEs were generally less common with finerenone than placebo across all SBP quartiles

Most of the finerenone treatment effect on cardiorenal outcomes in FIDELIO-DKD appears to be via BP-independent mechanisms, with only a small proportion attributed to office SBP

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

Thank you

58TH ERA-EDTA CONGRESS FULLY VIRTUAL JUNE 5-8, 2021

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

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48 countries, 913 sites, 13,911* participants

*Number of patients who provided informed consent