Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by diuretic use: A FIDELITY analysis

Dr Robert Mentz (Duke University School of Medicine, Durham, NC, USA)

on behalf of Stefan D. Anker, Bertram Pitt, Peter Rossing, Luis M. Ruilope, Martin Gebel, Peter Kolkhof, Robert Lawatscheck, Katja Rohwedder, George L. Bakris, and the FIDELIO-DKD and FIGARO-DKD investigators

28 August 2023

Hypertension and CKD are independent risk factors for CV disease[1]

~85% of patients with **CKD** suffer from **hypertension**[2]

Patients with hypertension and CKD are at **increased risk of CV morbidity and mortality**[1]

Thiazide and **loop diuretics** are **commonly** used to **treat hypertension** and **volume overload** in **patients with CKD**[1,3]

K^+

Diuretics might cause **[K^+] loss**, which is also associated with **CV outcomes**[4]

Diuretic requirement is a **marker of disease severity**,[5] with **potential** to be a **marker and mediator of adverse outcomes**

Patients with **CKD and T2D** remain at risk of **CKD disease progression and CV events** despite **blood pressure control**[1,6]

CKD, chronic kidney disease; CV, cardiovascular; [K^+], potassium concentration; T2D, type 2 diabetes

1. Pugh D, *et al. Drugs* 2019;79:365–379; 2. Mutner P, *et al. Am J Kidney Dis* 2010;55(3):441–451; 3. Sinha AD & Agarwal R. *Clin J Am Soc Nephrol* 2019;14(5):757–764; 4. Collins AJ, *et al Am J Nephrol* 2017;46:213–221; 5. Khan YH, *et al. PLoS One* 2016;11: doi: 10.1371/journal.pone.0159335; 6. Chaudhuri A, *et al. Diabetes Obes Metab* 2022;42(3):365–376

Finerenone is a selective, non-steroidal MRA that has demonstrated CV and kidney benefits in patients with CKD and T2D[1–5]

In the phase 3 finerenone trials **FIDELIO-DKD** and **FIGARO-DKD**, **finerenone significantly improved CV outcomes and slowed CKD progression** in patients with CKD and T2D[2–4]

FIDELIO-DKD[2] N=5674* + **FIGARO-DKD**[3] N=7352* = **FIDELITY** N=13,026*

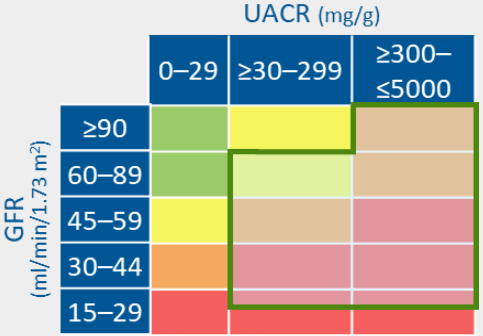
Prespecified pooled individual patient data analysis of FIDELIO-DKD and FIGARO-DKD[5]

1:1 randomisation to **finerenone** (10 mg or 20 mg) or **placebo**

Median follow-up: **3 years**

Key eligibility criteria

- ✓ CKD and T2D
- ✓ 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

*Patients analysed. eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalisation for heart failure; MI, myocardial infarction; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; UACR, urine albumin-creatinine ratio

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. Filippatos G, *et al. Circulation* 2021;143:540–552; 4. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263;
5. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

FIDELITY

In this FIDELITY post hoc analysis, the efficacy and safety of finerenone was assessed in patients with and without diuretic use at baseline

Outcomes and patient subgroups

Key composite CV outcome:

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

The composite CV outcome was analysed in the following **subgroups of interest**:

- **Diuretic use** (all, loop and thiazide diuretics)
- **Diuretic doses** (low vs high)
- **eGFR** (<60 vs ≥60 ml/min/1.73 m^2)
- **Race** (Asian vs non-Asian)

Additional outcomes:

- Treatment-emergent hypokalaemia
- Safety outcomes (including hyperkalaemia)

Key methods

- **Efficacy analyses** were performed using a **stratified cox proportional hazards model***
- An **on-treatment sensitivity analysis** was conducted to assess any **fluctuations in diuretic use** during the trial
- **Safety outcomes** were assessed by **TEAEs**, defined as any AE that started or worsened during treatment with the study drug#

*Stratification factors: Geographic region (North America, Latin America, Europe, Asia and others), eGFR category at screening (25–<45, 45–<60, and ≥60 ml/min/1.73 m^2), albuminuria category at screening (moderately increased and severely increased), history of CV disease, and study (FIDELIO-DKD and FIGARO-DKD); #including up to 3 days after any temporary or permanent discontinuation

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

Overall, 51.5% of patients were treated with diuretics at baseline

Baseline characteristics	With diuretics n=6710 (51.5%)	Without diuretics n=6316 (48.5%)
Age, years, mean	65.71	63.73
Gender, male, %	70.1	69.4
SBP, mmHg, mean	137.80	135.63
DBP, mmHg, mean	75.83	76.92
BMI, kg/m^2, mean	32.55	29.96
Duration of diabetes, years, mean	16.09	14.66
eGFR, ml/min/1.73 m^2, mean	54.01	61.38
UACR, mg/g, median	493	547
Medical history (%)		
CV disease	49.2	41.7
Heart failure	10.1	5.3
Atrial fibrillation or flutter	11.1	5.7

Baseline medication use (%)	With diuretics n=6710 (51.5%)	Without diuretics n=6316 (48.5%)
CV medications		
ACEi	38.3	39.8
ARB	61.8	60.0
Statins	76.5	67.5
Potassium supplements	5.0	0.8
Diuretics		
Loop diuretics	41.8	0
Thiazide diuretics	47.0	0
Glucose-lowering agents		
Insulin and analogues	62.8	54.1
DPP-4i	23.6	26.8
GLP-1RA	8.4	6.0
SGLT-2i	6.5	6.9
Alpha glucosidase inhibitors	3.0	7.2

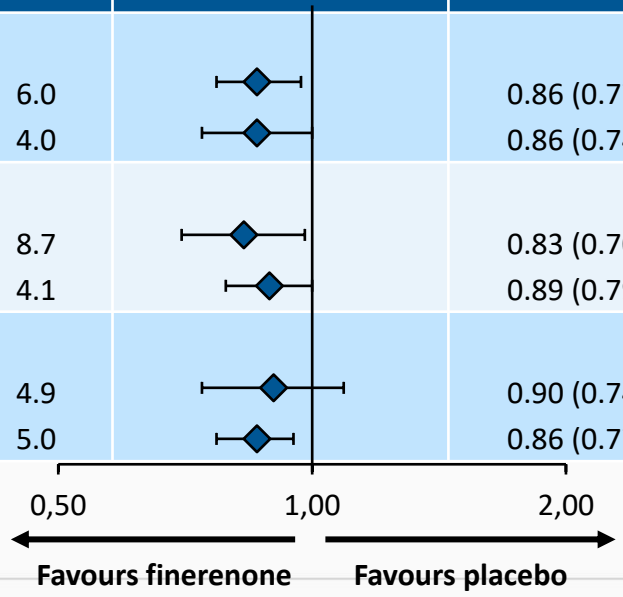
On-treatment analysis showed concomitant diuretic use with study treatment to be mainly constant throughout the study

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SBP, systolic blood pressure; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Finerenone reduced the risk of the composite CV outcome in patients treated with and without diuretics

Composite CV outcome (time to CV death, nonfatal MI, nonfatal stroke, or HHF)

	Finerenone		Placebo			Hazard ratio (95% CI)	*p*-value for interaction
	n (%)	n/100 PY	n (%)	n/100 PY			
Diuretics							
Yes	493 (14.8)	5.2	576 (17.0)	6.0		0.86 (0.77–0.97)	0.95
No	332 (10.4)	3.5	363 (11.6)	4.0		0.86 (0.74–1.00)	
Loop diuretics							
Yes	262 (19.0)	7.0	321 (22.6)	8.7		0.83 (0.70–0.98)	0.43
No	563 (11.0)	3.7	618 (12.2)	4.1		0.89 (0.79–1.00)	
Thiazide diuretics							
Yes	203 (12.6)	4.3	224 (14.5)	4.9		0.90 (0.74–1.09)	0.82
No	622 (12.7)	4.4	715 (14.4)	5.0		0.86 (0.77–0.95)	

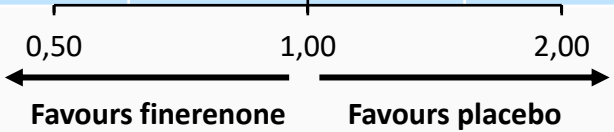


CI, confidence interval; PY, patient year

Finerenone reduced the risk of the composite CV outcome, irrespective of diuretic use or dose

Composite CV outcome (time to CV death, nonfatal MI, nonfatal stroke, or HHF)

	Finerenone		Placebo			Hazard ratio (95% CI)	*p*-value for interaction
	n (%)	n/100 PY	n (%)	n/100 PY			
No diuretics	332 (10.4)	3.5	363 (11.6)	4.0		0.86 (0.74–1.00)	0.88
Low-dose* diuretics	286 (14.1)	4.9	333 (16.2)	5.8		0.84 (0.72–0.99)	
High-dose# diuretics	207 (16.0)	5.7	243 (18.2)	6.4		0.90 (0.74–1.09)	

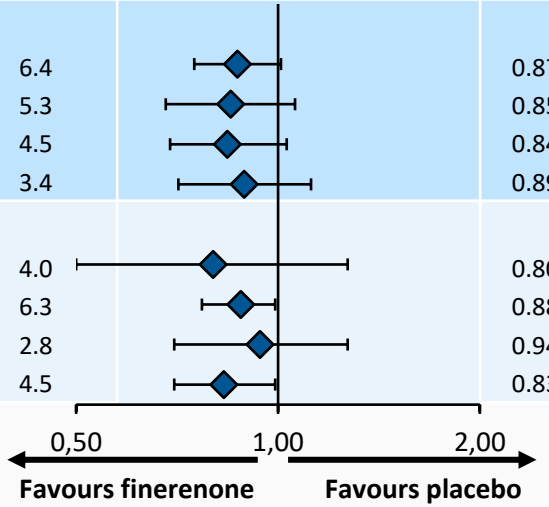


*Low dose: hydrochlorothiazide ≤12.5 mg , furosemide ≤40 mg, indapamide <2.5 mg, torasemide ≤10 mg, bendroflumethiazide ≤2.5 mg, chlortalidone ≤25 mg, metolazone ≤2.5 mg, trichlormethiazide ≤1 mg, azosemide ≤30 mg, bumetanide ≤1 mg. Diuretics not listed were considered low dose, irrespective of actual dosage; #high dose: hydrochlorothiazide >12.5 mg , furosemide >40 mg, indapamide ≥2.5 mg, torasemide >10 mg, bendroflumethiazide >2.5 mg, chlortalidone >25 mg, metolazone >2.5 mg, trichlormethiazide >1 mg, azosemide >30 mg, bumetanide >1 mg

Finerenone reduced the risk of the composite CV outcome*in patients, irrespective of diuretic use and baseline eGFR or race

Composite CV outcome (time to CV death, nonfatal MI, nonfatal stroke, or HHF)

Patient subgroup	Finerenone		Placebo		Hazard ratio (95% CI)	*p*-value for interaction
	n (%)	n/100 PY	n (%)	n/100 PY		
Diuretic use and eGFR*						
Diuretic and eGFR <60	340 (15.5)	5.7	397 (17.5)	6.4	0.87 (0.75–1.01)	1.00
Diuretic and eGFR ≥60	153 (13.6)	4.3	179 (16.1)	5.3	0.85 (0.68–1.06)	
No diuretic and eGFR <60	189 (11.0)	3.9	204 (12.5)	4.5	0.84 (0.69–1.03)	
No diuretic and eGFR ≥60	142 (9.6)	3.0	158 (10.7)	3.4	0.89 (0.71–1.12)	
Diuretic use and race						
Diuretic and Asian	33 (9.2)	3.1	49 (11.7)	4.0	0.80 (0.50–1.27)	0.83
Diuretic and non-Asian	460 (15.5)	5.5	527 (17.8)	6.3	0.88 (0.77–0.99)	
No diuretic and Asian	89 (8.3)	2.7	90 (8.6)	2.8	0.94 (0.70–1.27)	
No diuretic and non-Asian	243 (11.5)	3.9	273 (13.1)	4.5	0.83 (0.70–0.99)	



Similar trends were observed when the analysed patient cohort was split into loop diuretic and thiazide diuretic use subgroups

*Expressed in ml/min/1.73 m²

On-treatment sensitivity analysis: Incidence rate* of the composite CV outcome by diuretic use during the study was generally lower with finerenone vs placebo

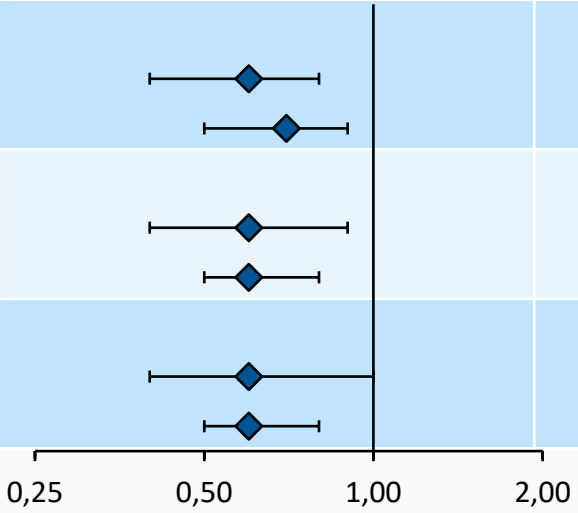
Composite CV outcome (time to CV death, nonfatal MI, nonfatal stroke, or HHF)

Diuretic type	Planned treatment group	Concomitant diuretic use	n	Number of events	PY at risk	Estimated event rate per 100 PY (95% CI)
All diuretics	**Finerenone**	With	4128	432	8415.3	5.13 (4.66–5.64)
		Without	3766	188	8403.5	2.24 (1.93–2.58)
	Placebo	With	4264	553	8981.7	6.16 (5.65–6.69)
		Without	3577	205	7773.0	2.64 (2.29–3.02)

*Restricted to the on-treatment period

Finerenone reduced the risk of treatment-emergent hypokalaemia* in patients treated with and without diuretics

Treatment-emergent hypokalaemia	Finerenone n (%)	Placebo n (%)	Relative risk (95% CI)
Diuretics			
Yes	64 (1.9)	111 (3.3)	0.6 (0.4–0.8)
No	50 (1.6)	74 (2.4)	0.7 (0.5–0.9)
Loop diuretics			
Yes	31 (2.2)	56 (4.0)	0.6 (0.4–0.9)
No	83 (1.6)	129 (2.5)	0.6 (0.5–0.8)
Thiazide diuretics			
Yes	32 (2.0)	49 (3.2)	0.6 (0.4–1.0)
No	82 (1.7)	136 (2.7)	0.6 (0.5–0.8)



*AEs were classified as hypokalaemia based on the following SMQ terms: alkalosis hypokalaemic, blood potassium abnormal, blood potassium decreased, electrocardiogram U-wave prominent, hypokalaemia, hypokalaemic syndrome, hypomagnesaemia
SMQ, standardised MedDRA queries

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

Overall TEAEs were similar between treatment arms and between patients treated with and without diuretics

AEs, n (%)	With diuretics		Without diuretics	
	Finerenone (n=3320)	Placebo (n=3375)	Finerenone (n=3190)	Placebo (n=3114)
Any AE	2882 (86.8)	2939 (87.1)	2720 (85.3)	2668 (85.7)
Any study drug-related AE	653 (19.7)	460 (13.6)	553 (17.3)	402 (12.9)
Any AE leading to discontinuation	225 (6.8)	185 (5.5)	189 (5.9)	166 (5.3)
Any SAE	1082 (32.6)	1203 (35.6)	978 (30.7)	983 (31.6)
Any study drug-related SAE	49 (1.5)	33 (1.0)	34 (1.1)	28 (0.9)
Any SAE leading to discontinuation	82 (2.5)	75 (2.2)	63 (2.0)	79 (2.5)

AEs, n (%)	With diuretics		Without diuretics	
	Finerenone (n=3320)	Placebo (n=3375)	Finerenone (n=3190)	Placebo (n=3114)
Any hyperkalaemia	457 (13.8)	191 (5.7)	455 (14.3)	257 (8.3)
Any hyperkalaemia leading to hospitalisation	36 (1.1)	6 (0.2)	25 (0.8)	4 (0.1)
Any hyperkalaemia leading to permanent discontinuation	54 (1.6)	20 (0.6)	56 (1.8)	18 (0.6)

Incidence of hyperkalaemia was higher with finerenone versus placebo, irrespective of diuretic use; however, the incidence of hyperkalaemia leading to hospitalisation or permanent discontinuation was low

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

FIDELITY

Summary

In a patient population with CKD and T2D treated with a maximum tolerated dose of RASi:

Finerenone was associated with a **decreased risk** of the **composite CV outcome** versus placebo, **irrespective of diuretic use**

Baseline **diuretic dose**, **eGFR** and **race** generally did not modify the composite CV outcome

Finerenone consistently reduced the risk of treatment-emergent **hypokalaemia** versus placebo in patients treated **with** and **without diuretics**

The incidence of **TEAEs** was **consistent, regardless of diuretic use**

Although the incidence of **hyperkalaemia** was **higher with finerenone** versus placebo, irrespective of diuretic use, the incidence of associated **hospitalisation** or **permanent discontinuation** was **low**

A **key limitation** of the current results is that they are **based on a post hoc analysis** thus, any **reported findings are exploratory**

Thank you

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

Executive committee

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

Independent data monitoring committee

Glenn Chertow; Gerald DiBona; Murray Epstein; Tim Friede; Jose Lopez-Sendon; Aldo Maggioni; Jean Rouleau

Clinical event committee

Rajiv Agarwal; Stefan Anker; Phyllis August; Andrew Coats; Hans Diener; Wolfram Döhner; Barry Greenberg; Stephan von Haehling; James Januzzi; Alan Jardine; Carlos Kase; Sankar Navaneethan; Lauren Phillips; Piotr Ponikowski; Pantelis Sarafidis; Titte Srinivas; Turgut Tatlisumak; John Teerlink

National lead investigators

Sharon Adler; Aslam Amod; Andrés Ángelo Cadena Bonfanti; Ellen Burgess; Michel Burnier; Eugenia F. Canziani; Juliana Chan; Chien-Te Lee; Froilan De Leon; Alexander Dreval; Fernando Teixeira e Costa; Joseph Eustace; Trine Finnes; Linda Fried; Ron Gansevoort; Pieter Gillard; Ehud Grossman; Fernando González; Janusz Gumprecht; Carlos Francisco Jaramillo; Tran Quang Khanh; Sin Gon Kim; Adriaan Kooy; Daisuke Koya; Byung Wan Lee; Zhi-Hong Liu; Richard MacIsaac; Borys Mankovsky; Michel Marre; Kieran McCafferty; Martin Prazny; Giuseppe Remuzzi; László Rosivall; Peter Rossing; Luis Alejandro Nevarez Ruiz; Julio Pascual Santos; Pantelis A. Sarafidis; Ramazan Sari; Guntram Schernthaner; Roland Schmieder; Jorma Strand; Bengt-Olov Tengmark; Maria Theodora Temelkova-Kurktschiev; Sheldon Tobe; Robert Toto; Augusto Vallejos; Anantharaman Vathsala; Takashi Wada; Christoph Wanner; Mark Williams; Yoram Yagil; Sukit Yamwong

FIDELITY

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

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