Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis

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Clinical Question

Do you agree patients with diabetic kidney disease should use finerenone chronically for cardiorenal protection?

Disagree

Need more evidences

Agree

01

Background

Diabetic Kidney Disease (DKD)

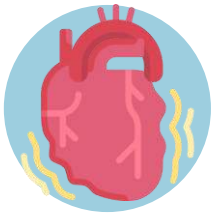
463 million in 2019

Diabetes Mellitus

20-40%

Diabetic Kidney Disease

End Stage Kidney Disease



Cardiovascular Disease

Vodosek Hojs, N., et al., *Mineralocorticoid Receptor Antagonists in Diabetic Kidney Disease*. Pharmaceuticals (Basel), 2021. **14**(6).

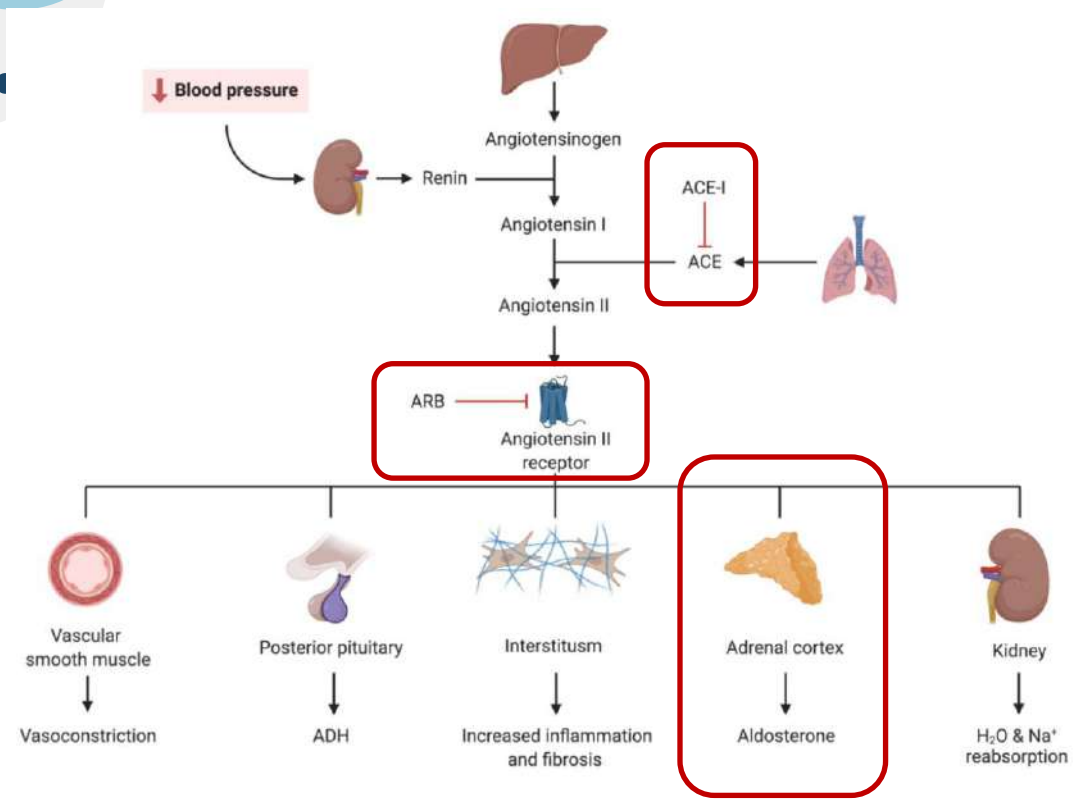
de Boer, I.H., et al., Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment. Kidney Int, 2020. 98(4): p. 839-848.

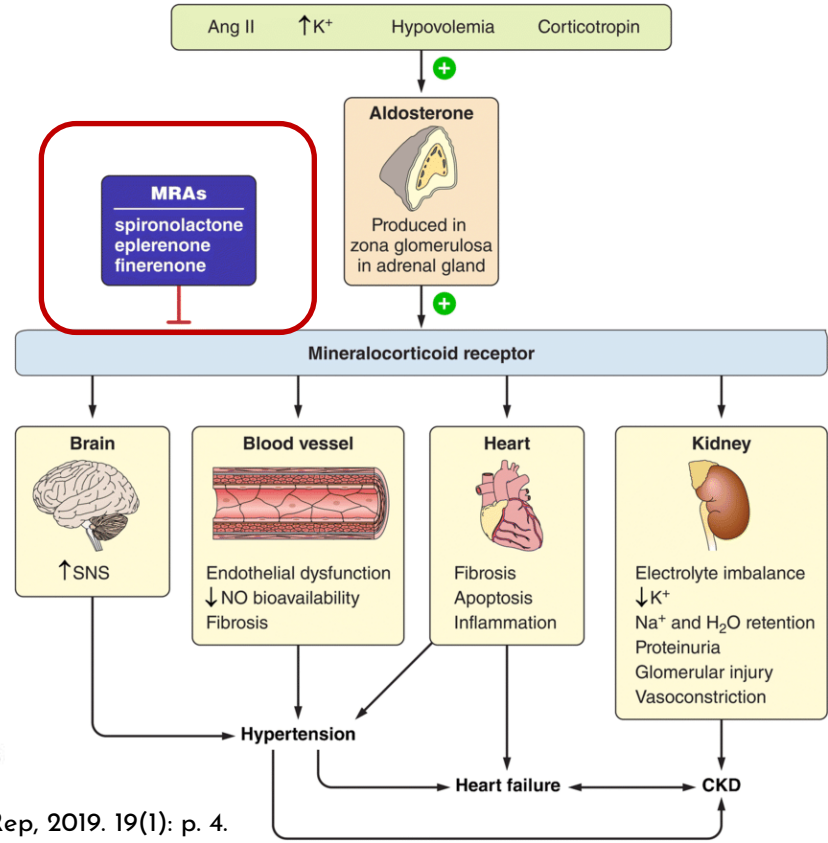
Diabetic Kidney Disease

Kidney outcomes

Drug	Trial	Kidney-related eligibility criteria	Primary outcome	Effect on primary outcome	Effect on albuminuria or albuminuria-containing composite outcome	Effect on GFR loss[a]	Adverse effects
			Primary outcome				
SGLT2 inhibitors			**MACE; CKD progression**				
Empagliflozin	EMPA-REG OUTCOME	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA
Canagliflozin	CANVAS trials	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA, amputation
	CREDENCE	ACR >300 mg/g [30 mg/mmol] and eGFR 30–90 ml/min per 1.73 m²	Progression of CKD[b]	↓↓	↓↓	↓↓	Genital mycotic infections, DKA
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥60 ml/min	Dual primary outcomes: MACE and the composite of hospitalization for heart failure or CV death[c]	↔/↓	↓	↓↓	Genital mycotic infections, DKA
GLP-1 receptor agonists							
Lixisenatide	ELIXA	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	↓	↔	None notable
Liraglutide	LEADER	eGFR ≥15 ml/min per 1.73 m²	MACE	↓	↓	↔	GI
Semaglutide[d]	SUSTAIN-6	Patients treated with dialysis excluded	MACE	↓	↓↓	NA	GI
	PIONEER 6	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	NA	NA	GI
Exenatide	EXSCEL	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	↔	↔	None notable
Albiglutide	HARMONY	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↔	NA	Injection site reactions
Dulaglutide	REWIND	eGFR ≥15 ml/min per 1.73 m²	MACE	↓	↓	↓	GI
DPP-4 inhibitors							
Saxagliptin	SAVOR-TIMI 53	eGFR ≥15 ml/min per 1.73 m²	MACE	↔	↓	↔	HF; any hypoglycemic event (minor and major) also more common

Renin-angiotensin-aldosterone system (RAAS)





Lytvyn, Y., et al., Mineralocorticoid Antagonism and Diabetic Kidney Disease. Curr Diab Rep, 2019. 19(1): p. 4.
Sawaf, H., et al., Therapeutic Advances in Diabetic Nephropathy. J Clin Med, 2022. 11(2).

Mineralocorticoid Receptor Antagonists (MRAs)

	Spironolactone	Eplerenone	Finerenone
Generation	1st	2nd	3rd
Class	Steroidal	Steroidal	Non-steroidal
Selectivity	Low	Moderate	High
Potency	High	Moderate	High
Tissue distribution	Kidney > heart	Kidney > heart	balanced kidney–heart
Indication	*NYHA Class III-IV HFrEF *HTN *Edema * Primary hyperaldosteronism	*CHF Post-MI with LVEF ≤40% *HTN	Reduce the risk of cardiorenal outcomes in adult patients with CKD associated with T2DM

Vodosek Hojs, N., et al., *Mineralocorticoid Receptor Antagonists in Diabetic Kidney Disease*. Pharmaceuticals (Basel), 2021. **14**(6).

Finerenone

- A nonsteroidal mineralocorticoid receptor antagonist (MRA)
- FDA approval: 2021/07
- Dosage: 10 mg or 20 mg orally once daily based on estimated glomerular filtration rate (eGFR) and serum potassium thresholds.

eGFR (mL/min/1.73m^2)	Starting Dose
≥ 60	20 mg once daily
≥ 25 to < 60	10 mg once daily
< 25	Not Recommended

Increase dosage after 4 weeks to the target dose of 20 mg once daily

		10 mg once daily	20 mg once daily
Current Serum Potassium (mEq/L)	≤ 4.8	Increase the dose to 20 mg once daily.*	Maintain 20 mg once daily.
	> 4.8 – 5.5	Maintain 10 mg once daily.	Maintain 20 mg once daily.
	> 5.5	Withhold Kerendia. Consider restarting at 10 mg once daily when serum potassium ≤ 5.0 mEq/L.	Withhold Kerendia. Restart at 10 mg once daily when serum potassium ≤ 5.0 mEq/L.

* If eGFR has decreased by more than 30% compared to previous measurement, maintain 10 mg dose.

FIDELIO-DKD & FIGARO-DKD

	FIDELIO-DKD (2020)	FIGARO-DKD (2021)
Study design	Phase III, randomized, double-blind, placebo-controlled, multicenter clinical trial	
Sample size	5734	7437
Inclusion criteria	• Age ≥ 18 years • T2D and **CKD*** • Maximum tolerated dose of an RAS inhibitor • Serum potassium ≤ 4.8 mmol/L	
Exclusion criteria	• Non-diabetic kidney disease • Uncontrolled hypertension • HbA1c >12% • SBP <90 mmHg	• Chronic symptomatic HFrEF • Recent CV event • Dialysis for acute kidney failure • Kidney transplant

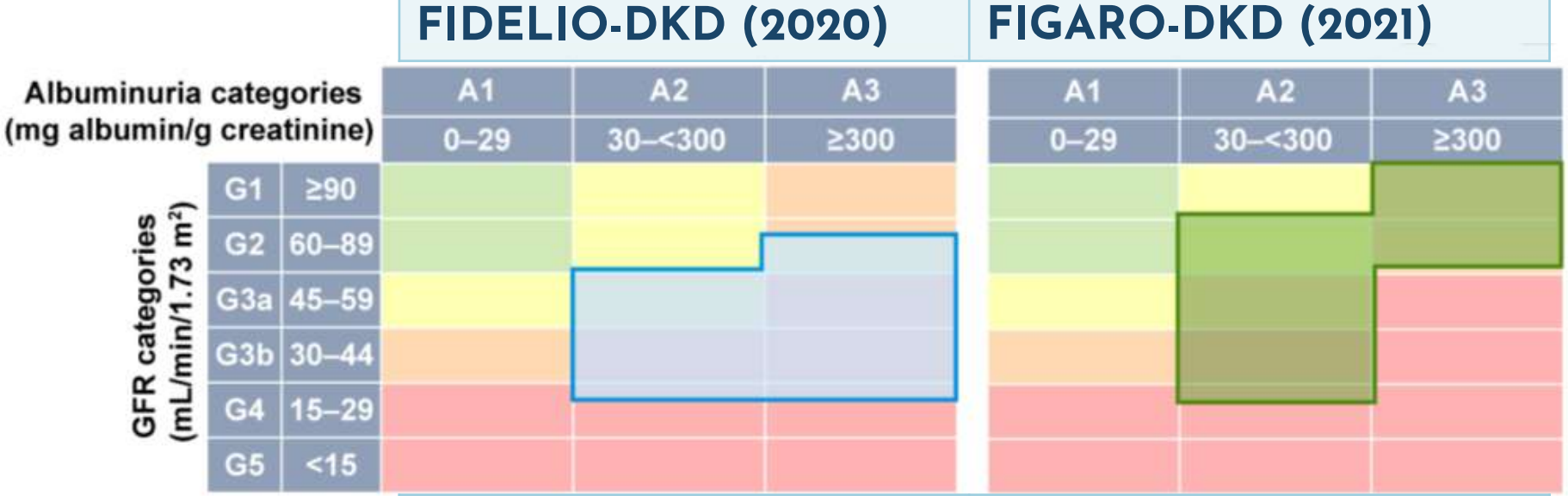
Bakris, G.L., et al., Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. N Engl J Med, 2020. 383(23): p. 2219-2229.
Pitt, B., et al., Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. N Engl J Med, 2021. 385(24): p. 2252-2263.

HFF, hospitalization for heart failure

FIDELIO-DKD & FIGARO-DKD

	FIDELIO-DKD (2020)	FIGARO-DKD (2021)
Follow-up period (median)	2.6 years	3.4 years
Primary outcome	Time to • kidney failure • sustained ≥40% decrease in eGFR from baseline • renal death	Time to • CV death • non-fatal MI • non-fatal stroke • HHF
Secondary outcome	Time to • CV death • non-fatal MI • non-fatal stroke • HHF	Time to • kidney failure • sustained ≥40% decrease in eGFR from baseline • renal death
Trial registry	NCT02540993	NCT02545049

*Definition of CKD in FIDELIO-DKD & FIGARO-DKD



UACR 30-<300 mg/g, eGFR 25-<60 mL/min/1.73 m^2, and diabetic retinopathy, or
UACR 300-5000 mg/g and eGFR 25-<75 mL/min/1.73 m^2

UACR 30-<300 mg/g, eGFR 25-90 mL/min/1.73 m^2, and diabetic retinopathy, or
UACR 300-5000 mg/g and eGFR ≥ 60 mL/min/1.73 m^2

02

Journal

ESC European Society of Cardiology

European Heart Journal (2022) **43**, 474–484
https://doi.org/10.1093/eurheartj/ehab777

FASTTRACK CLINICAL RESEARCH
Diabetes and metabolic disorders

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis

Rajiv Agarwal [1*†], Gerasimos Filippatos[2*†], Bertram Pitt [3], Stefan D. Anker[4], Peter Rossing [5,6], Amer Joseph[7], Peter Kolkhof [8], Christina Nowack[9], Martin Gebel [10], Luis M. Ruilope [11,12,13], and George L. Bakris [14]; on behalf of the FIDELIO-DKD and FIGARO-DKD investigators[‡]

Study objective

To provide more robust estimates of finerenone efficacy and safety across the spectrum of patients with CKD and type 2 diabetes, to provide reassurance regarding outcomes in a wide range of patients with a degree of precision that was not possible to obtain by considering the two trials separately

P	Patients with CKD and type 2 diabetes
I	Finerenone 10 or 20 mg
C	Placebo
O	Efficacy and safety

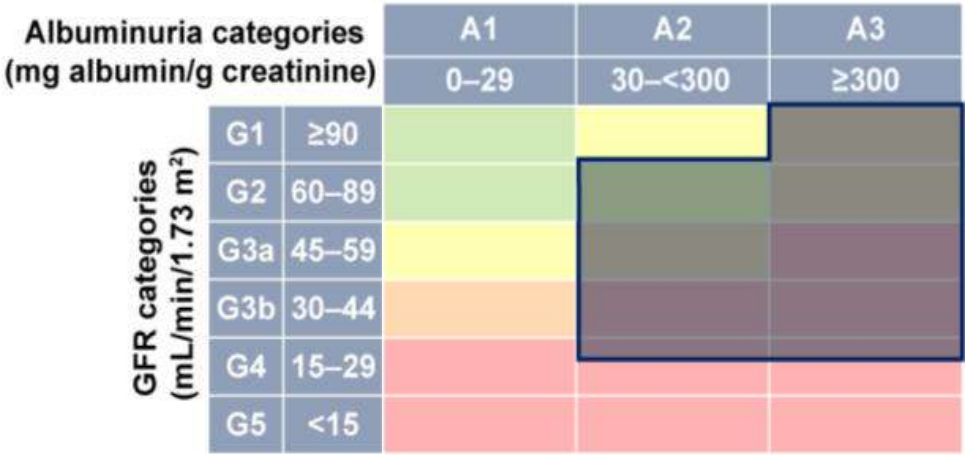
Study design

- This prespecified pooled efficacy and safety analysis, which was prespecified in a formal statistical analysis plan, combines data from FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049), two phase III, randomized, double-blind, placebo-controlled, multicenter clinical trials

Patients

Inclusion Criteria

- Adults (aged ≥ 18 years)
- Type 2 diabetes and **CKD***
- Treated with a maximum tolerated labelled dose of an ACEi or ARB



FIDELIO-DKD (2020)	FIGARO-DKD (2021)
UACR 30-<300 mg/g, eGFR 25-<60 mL/min/1.73 m^2, and diabetic retinopathy, or UACR 300-5000 mg/g and eGFR 25-<75 mL/min/1.73 m^2	UACR 30-<300 mg/g, eGFR 25-90 mL/min/1.73 m^2, and diabetic retinopathy, or UACR 300-5000 mg/g and eGFR ≥ 60 mL/min/1.73 m^2

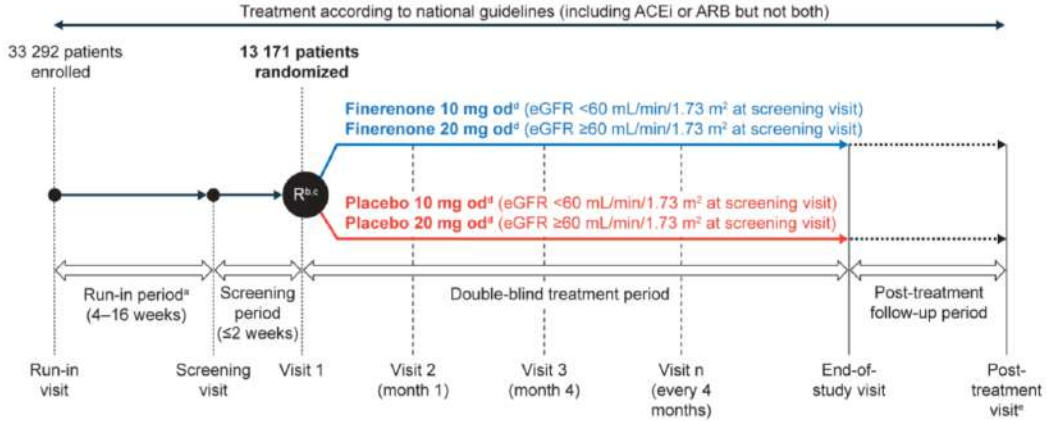
Patients

Exclusion Criteria

- Non-diabetic kidney disease
- UACR >5000 mg/g (>565 mg/mmol)
- Uncontrolled hypertension
- HbA1c >12%
- SBP <90 mmHg
- Chronic symptomatic HFrEF (NYHA class II-IV)
- Recent CV event (Stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening heart failure)
- Dialysis for acute kidney failure
- Kidney transplant
- Addison's disease
- Hepatic insufficiency classified as Child–Pugh C

Procedures

- Eligible patients were randomized 1:1 to receive oral finerenone (10 or 20 mg) or placebo.
- The run-in period required ACEi or ARB therapy to be adjusted to a maximum tolerated labelled dose that did not lead to unacceptable side effects.
- Study drug was withheld if potassium concentrations exceeded 5.5 mmol/L and restarted when potassium levels fell to ≤ 5.0 mmol/L.



Outcomes

Primary Efficacy Outcomes

- **Composite cardiovascular outcome of time to**
  - cardiovascular death
  - non-fatal MI
  - non-fatal stroke
  - hospitalization for heart failure (HHF)
- **Composite kidney outcome of time to**
  - first onset of kidney failure
  - sustained ≥ 57% decrease in eGFR from baseline over ≥ 4 weeks
  - renal death

Outcomes

Secondary Efficacy Outcomes

- **A second composite kidney outcome of time to**
  - first occurrence of kidney failure
  - sustained ≥ 40% decrease in eGFR from baseline over ≥ 4 weeks
  - renal death
- Time to all-cause mortality
- Time to all-cause hospitalization
- Change in UACR from baseline to Month 4

Outcomes

Safety Outcomes

- Treatment emergent adverse events
  - started or worsened during study drug intake or up to 3 days after any temporary or permanent interruption.

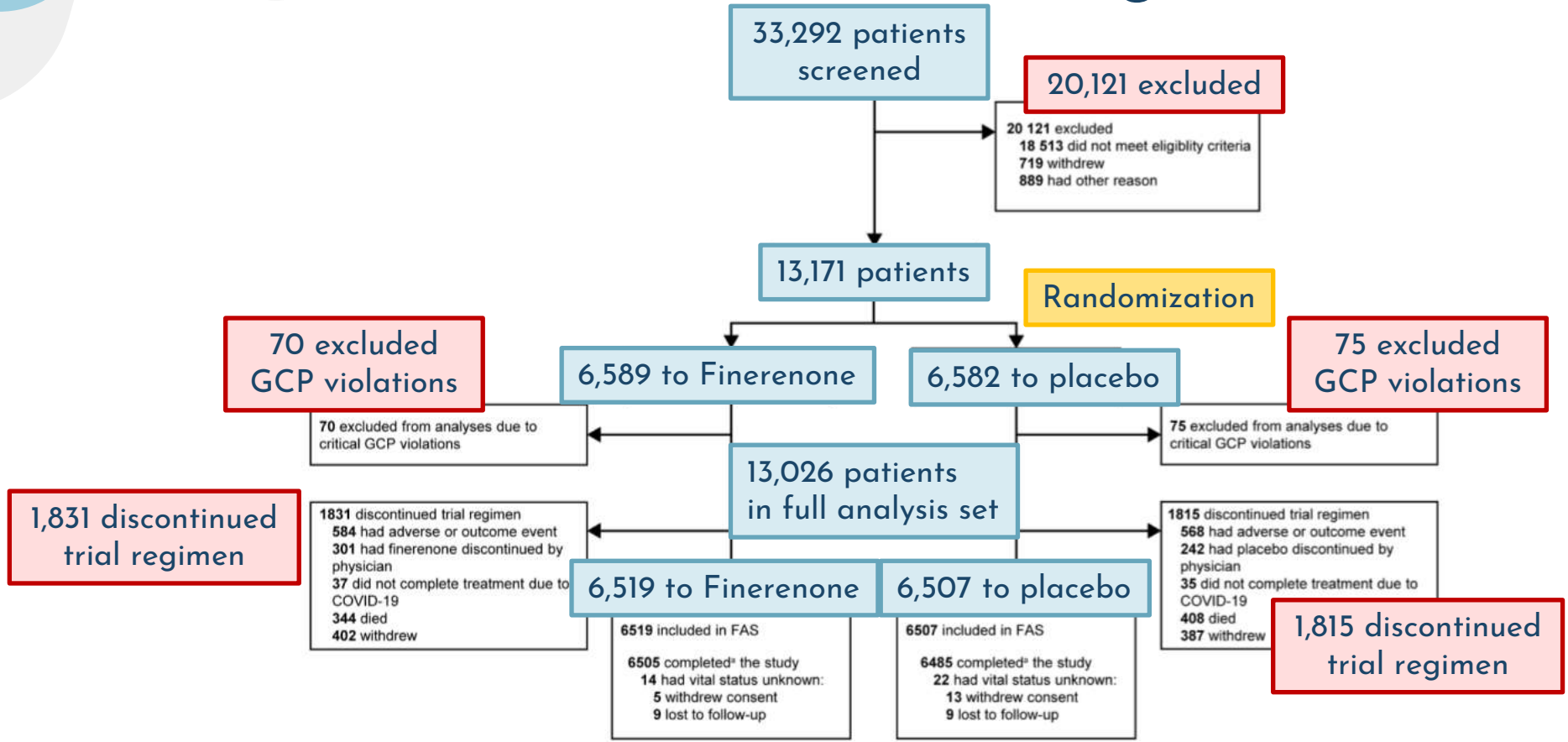
Statistic Analysis

- Statistical analyses were prespecified exploratory evaluations rather than hypothesis confirming.
- Study outcomes were analyzed using stratified Cox proportional hazards models.
- P-values for the comparison of treatment groups are presented based on a stratified log-rank test.
- Treatment effects are expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) from the stratified Cox proportional hazards models.
- The sponsor, Bayer, conducted the statistical analyses, and all authors had access to the data and participated in its interpretation.
- All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA)

Funding

- This work was supported by Bayer AG, who funded by the FIDELIO-DKD and FIGARO-DKD studies and pooled analysis.

Results-Consort diagram



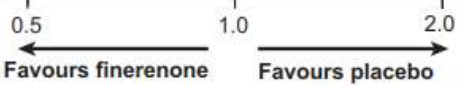
Results-Baseline Characteristics

	Finerenone (10 mg od or 20 mg od) (*n* = 6519)	Placebo (*n* = 6507)	All patients (*n* = 13 026)
Age, years	64.7 ± 9.4	64.8 ± 9.7	64.8 ± 9.5
Sex, *n* (%)			
Male	4481 (68.7)	4607 (70.8)	9088 (69.8)
Female	2038 (31.3)	1900 (29.2)	3938 (30.2)
Race or ethnic group, *n* (%)			
White	4449 (68.2)	4420 (67.9)	8869 (68.1)
Black/African American	253 (3.9)	269 (4.1)	522 (4.0)
Asian	1432 (22.0)	1462 (22.5)	2894 (22.2)
Others	385 (5.9)	356 (5.4)	741 (5.8)
Duration of diabetes, years	15.4 ± 8.7	15.4 ± 8.7	15.4 ± 8.7
HbA1c, %	7.7 ± 1.4	7.7 ± 1.4	7.7 ± 1.4
Systolic blood pressure, mmHg	136.8 ± 14.2	136.7 ± 14.3	136.7 ± 14.2
History of cardiovascular disease, *n* (%)	2979 (45.7)	2956 (45.4)	5935 (45.6)
Heart failure, *n* (%)	485 (7.4)	522 (8.0)	1007 (7.7)
eGFR, mL/min/1.73 m^2	57.5 ± 21.6	57.7 ± 21.8	57.6 ± 21.7
eGFR, mL/min/1.73 m^2, *n* (%)			
>60	2603 (39.9)	2592 (39.8)	5195 (39.9)
45–<60	1717 (26.3)	1717 (26.4)	3434 (26.4)
25–<45	2117 (32.5)	2115 (32.5)	4232 (32.5)
<25	81 (1.2)	81 (1.2)	162 (1.2)
UACR, mg/g, median (IQR)	514 (198–1129)	515 (198–1163)	515 (198–1147)
UACR, mg/g, *n* (%)			
<30	120 (1.8)	110 (1.7)	230 (1.8)
30–<300	2076 (31.8)	2023 (31.1)	4099 (31.5)

The median follow-up period was 3.0 years [IQR 2.3–3.8 years].

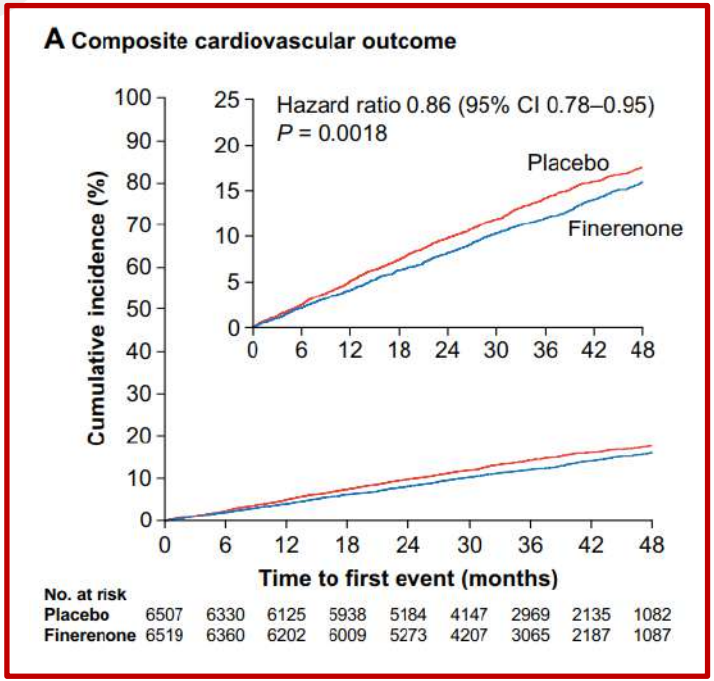
Results-Composite CV Outcome

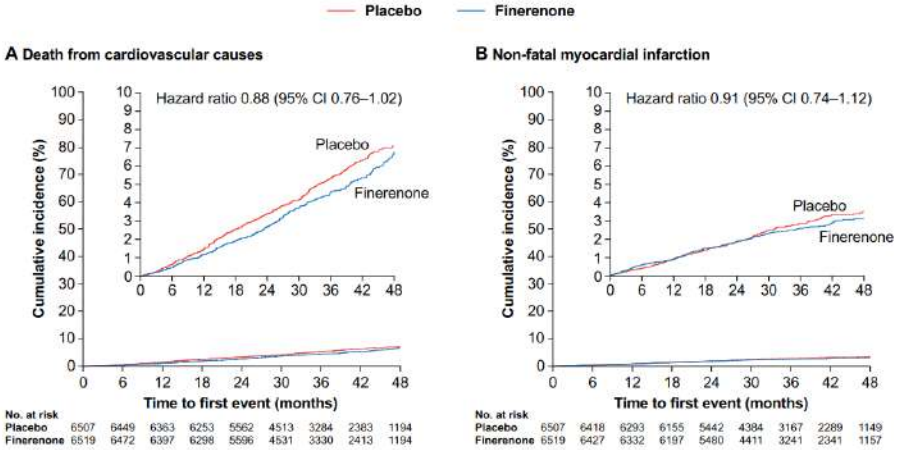
Outcome	Finerenone (n = 6519)		Placebo (n = 6507)		Hazard ratio (95% CI)	*P*-value[a]
	Number of patients with event (%)	Number of patients with event per 100 patient-years	Number of patients with event (%)	Number of patients with event per 100 patient-years		
Composite cardiovascular outcome[b]	825 (12.7)	4.34	939 (14.4)	5.01	0.86 (0.78–0.95)	0.0018
Death from cardiovascular causes	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)	0.092
Non-fatal myocardial infarction	173 (2.7)	0.88	189 (2.9)	0.97	0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	1.01	198 (3.0)	1.02	0.99 (0.82–1.21)	0.95
Hospitalization for heart failure	256 (3.9)	1.31	325 (5.0)	1.68	0.78 (0.66–0.92)	0.0030

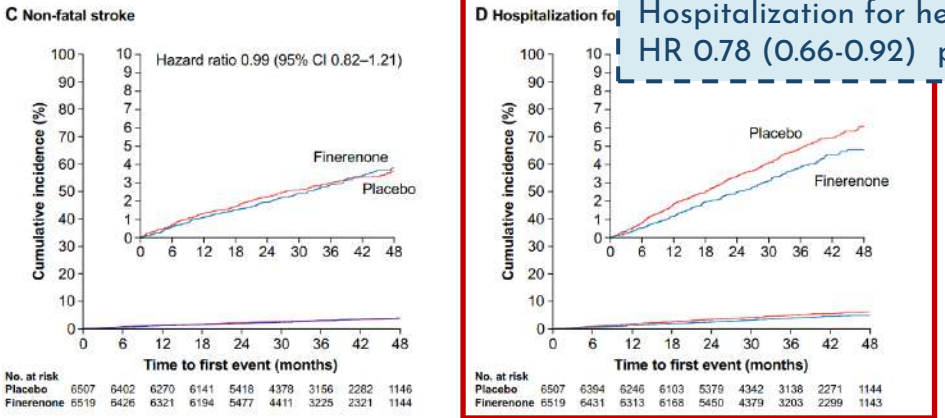


NNT: 46 (95% CI, 29-109) at 3 years

Results-Composite CV Outcome



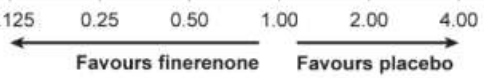




Hospitalization for heart failure
HR 0.78 (0.66-0.92) p=0.0030

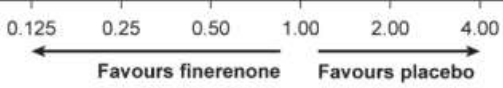
Results-Composite CV Outcome(subgroup)

Subgroup	Finerenone	Placebo	Finerenone	Placebo	Hazard ratio (95% CI)	*P*-interaction
	Number of patients with event/total number		Number of patients with events per 100 patient-years			
All patients	**825/6519**	**939/6507**	**4.34**	**5.01**	**0.86 (0.78–0.95)**	
Age at run-in visit						0.20
<65 years	323/2958	337/2931	3.74	3.93	0.94 (0.81–1.10)	
≥65 years	502/3561	602/3576	4.83	5.92	0.82 (0.73–0.93)	
Sex						0.92
Male	579/4481	675/4607	4.39	5.08	0.86 (0.77–0.96)	
Female	246/2038	264/1900	4.21	4.83	0.87 (0.73–1.04)	
Region						0.46
Western Europe	184/1344	207/1392	4.48	4.94	0.91 (0.75–1.11)	
Eastern Europe	221/1592	235/1534	4.85	5.38	0.89 (0.74–1.06)	
North America	154/1026	185/1025	5.08	6.15	0.84 (0.68–1.04)	
Asia	157/1600	187/1604	3.25	3.94	0.80 (0.65–0.99)	
Latin America	69/719	93/715	3.78	5.25	0.72 (0.53–0.99)	
Other[a]	40/238	32/237	5.99	4.79	1.22 (0.76–1.94)	
Race						0.91
White	621/4449	699/4420	4.78	5.50	0.86 (0.78–0.96)	
Black	39/253	53/269	5.68	7.40	0.79 (0.51–1.24)	
Asian	122/1432	139/1462	2.82	3.16	0.90 (0.70–1.15)	
Other	43/385	48/356	4.29	5.21	0.79 (0.51–1.22)	
Baseline eGFR						0.14
<25 mL/min/1.73 m²	11/81	23/81	5.24	12.21	0.48 (0.22–1.03)	
25–<45 mL/min/1.73 m²	321/2117	331/2115	5.66	5.84	0.94 (0.81–1.10)	
45–<60 mL/min/1.73 m²	197/1717	247/1717	4.01	5.11	0.80 (0.66–0.97)	
≥60 mL/min/1.73 m²	295/2603	337/2592	3.59	4.18	0.87 (0.74–1.01)	



Results-Composite CV Outcome(subgroup)

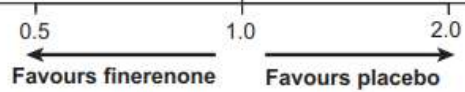
Subgroup	Finerenone	Placebo	Finerenone	Placebo	Hazard ratio (95% CI)	*P*-interaction
	Number of patients with event/total number		Number of patients with events per 100 patient-years			
Baseline UACR						0.41
<30 mg/g	10/120	15/110	2.43	4.27	0.59 (0.24–1.45)	
30–<300 mg/g	260/2076	292/2023	3.79	4.40	0.86 (0.73–1.02)	
≥300 mg/g	554/4321	631/4371	4.71	5.37	0.89 (0.79–<1.00)	
History of CV disease						0.35
Yes	551/2979	595/2956	6.26	7.56	0.83 (0.74–0.94)	
No	314/3540	344/3551	2.89	3.16	0.91 (0.78–1.06)	
Baseline potassium						0.85
≤4.3 mmol/L	461/3318	470/3284	4.25	4.88	0.85 (0.75–0.98)	
>4.3 mmol/L	408/3200	468/3220	4.42	5.13	0.87 (0.76–0.99)	
Baseline SBP						0.60
≤137.0 mmHg (median)	375/3304	410/3290	3.84	4.25	0.88 (0.76–1.01)	
>137.0 mmHg (median)	448/3212	528/3215	4.85	5.80	0.84 (0.74–0.95)	
Baseline BMI						0.44
<30 kg/m²	334/2948	380/2991	3.99	4.40	0.89 (0.77–1.03)	
≥30 kg/m²	476/3548	557/3504	4.60	5.53	0.82 (0.73–0.93)	
Baseline HbA1c						0.74
≤7.5%	376/3311	444/3405	3.83	4.44	0.88 (0.76–1.01)	
>7.5%	444/3196	493/3092	4.84	5.65	0.84 (0.74–0.96)	
SGLT-2i at baseline						0.41
No	786/6081	887/6068	4.44	5.08	0.87 (0.79–0.96)	
Yes	39/438	52/439	2.95	4.08	0.63 (0.40–<1.00)	
GLP-1RA at baseline						0.63
No	767/6022	875/6060	4.38	5.02	0.87 (0.79–0.96)	
Yes	58/497	64/447	3.79	4.90	0.79 (0.52–1.11)	



Cardiovascular outcomes across subgroups by baseline demographics and clinical characteristics were generally consistent.

Results-Composite Kidney Outcome

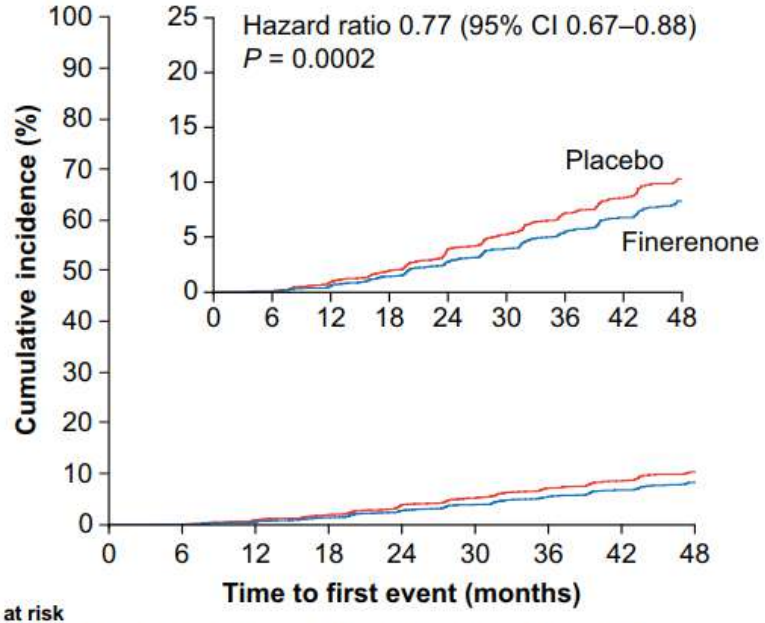
Outcome	Finerenone (n = 6519)		Placebo (n = 6507)		Hazard ratio (95% CI)	*P*-value[a]
	Number of patients with event (%)	Number of patients with event per 100 patient-years	Number of patients with event (%)	Number of patients with event per 100 patient-years		
eGFR ≥57% composite kidney outcome[c]	360 (5.5)	1.96	465 (7.1)	2.55	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	1.38	297 (4.6)	1.62	0.84 (0.71–0.99)	0.039
End-stage kidney disease[d]	151 (2.3)	0.76	188 (2.9)	0.96	0.80 (0.64–0.99)	0.040[e]
Sustained decrease in eGFR to <15 mL/min/1.73 m^2	195 (3.0)	1.06	237 (3.6)	1.29	0.81 (0.67–0.98)	0.026[e]
Sustained ≥57% decrease in eGFR from baseline	257 (3.9)	1.40	361 (5.5)	4.03	0.70 (0.60–0.83)	< 0.0001
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02	0.53 (0.10–2.91)	0.46[e]
eGFR ≥40% composite kidney outcome[f]	854 (13.1)	4.81	995 (15.3)	5.64	0.85 (0.77–0.93)	0.0004
Sustained ≥40% decrease in eGFR from baseline	817 (12.5)	4.60	962 (14.8)	5.45	0.84 (0.76–0.92)	0.0002



NNT: 60 (95% CI, 38-142) at 3 years

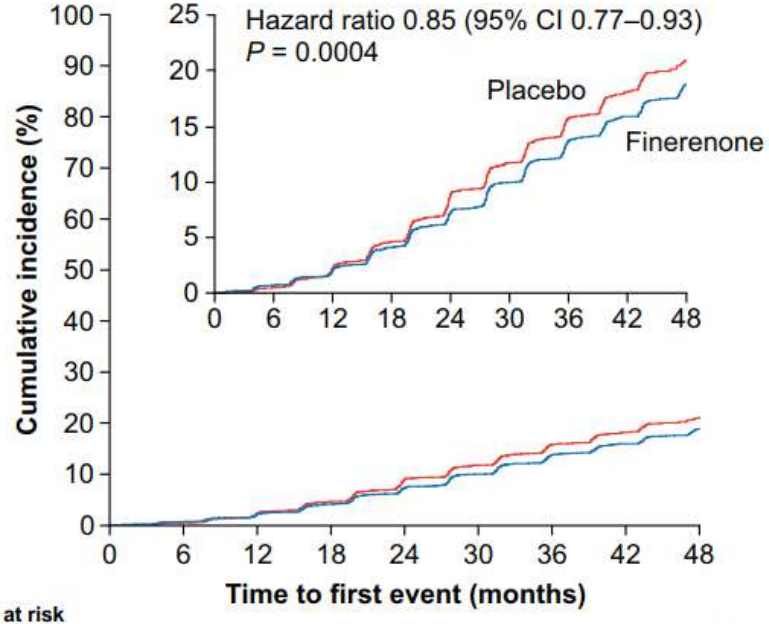
Results-Composite Kidney Outcome

B eGFR ≥57% composite kidney outcome



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

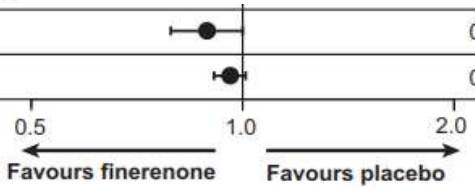
C eGFR ≥40% composite kidney outcome



No. at risk									
Placebo	6507	6270	5994	5661	4710	3709	2603	1850	891
Finerenone	6519	6255	6020	5698	4811	3764	2603	1868	882

Results-Mortality, Hospitalization

Outcome	Finerenone (n = 6519)		Placebo (n = 6507)		Hazard ratio (95% CI)	*P*-value[a]
	Number of patients with event (%)	Number of patients with event per 100 patient-years	Number of patients with event (%)	Number of patients with event per 100 patient-years		
Death from any cause	552 (8.5)	2.76	614 (9.4)	3.10	0.89 (0.79–>1.00[g])	0.051[e]
Hospitalization for any cause	2836 (43.5)	19.04	2926 (45.0)	19.91	0.96 (0.91–1.01)	0.087[e]

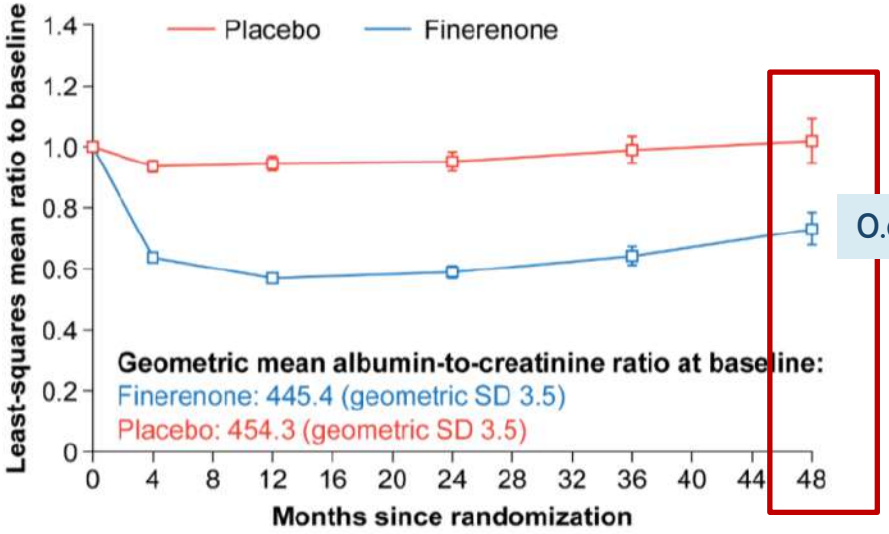


Incidences of all cause mortality and hospitalization for any cause with finerenone were not significantly different from placebo (P = 0.051 and P = 0.087, respectively).

Results-UACR Change

A Urine albumin-to-creatinine ratio

32% lower with finerenone vs. placebo

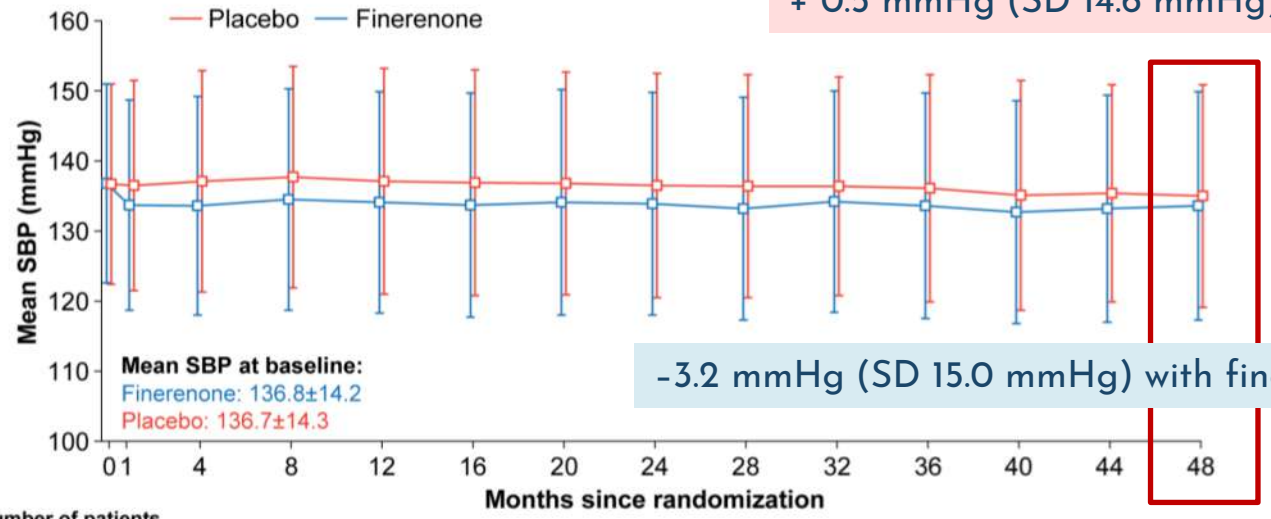


0.68 (95% CI, 0.66–0.70)

Number of patients						
Finerenone	6517	6273	5988	4867	2745	899
Placebo	6504	6239	5973	4829	2706	872
Mean change in UACR from baseline (%)						
Finerenone	Ref	–36%	–43%	–41%	–36%	–27%
Placebo	Ref	–6%	–6%	–5%	–1%	+2%

Results-Mean systolic blood pressure

+ 0.5 mmHg (SD 14.6 mmHg) with placebo



-3.2 mmHg (SD 15.0 mmHg) with finerenone

Number of patients						
Finerenone	6509	6324	6070	5001	2842	926
Placebo	6489	6310	6057	4968	2814	901
Mean change in SBP from baseline (mmHg)						
Finerenone	Ref	−3.2	−2.5	−2.4	−2.9	−1.8
Placebo	Ref	0.5	0.5	0.0	−0.1	−1.1

The effects of finerenone and placebo on mean systolic blood pressure (safety analysis set). Data are shown as mean ± standard deviation.
SBP, systolic blood pressure.

Results-Treatment Emergent AEs

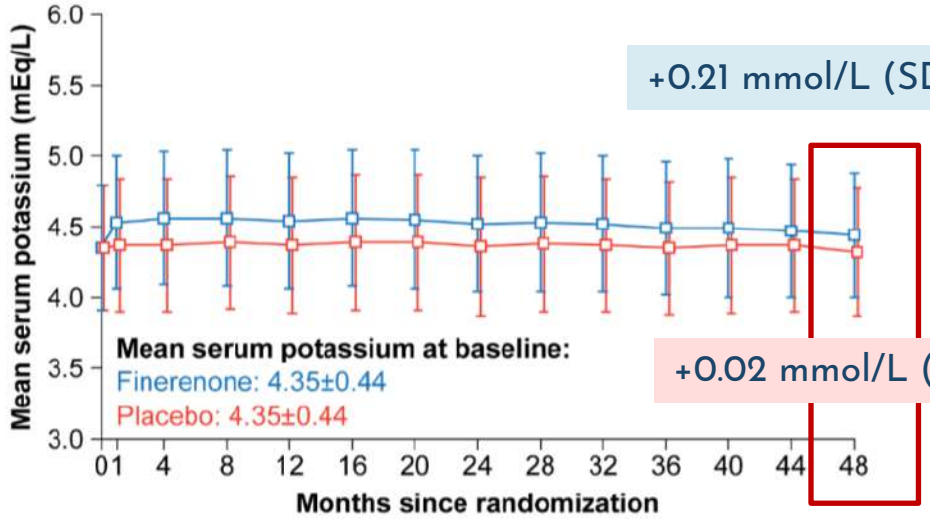
Treatment-emergent AEs[a]	Number of patients with event (%)	
	Finerenone (n = 6510)	Placebo (n = 6489)
Any AE	5602 (86.1)	5607 (86.4)
AE related to study drug	1206 (18.5)	862 (13.3)
AE leading to treatment discontinuation	414 (6.4)	351 (5.4)
Any serious AE[b]	2060 (31.6)	2186 (33.7)
Serious AE[b] related to study drug	83 (1.3)	61 (0.9)
Serious AE[b] leading to treatment discontinuation	145 (2.2)	154 (2.4)
Investigator-reported hyperkalaemia[c]	912 (14.0)	448 (6.9)
Hyperkalaemia related to study drug	573 (8.8)	249 (3.8)
Permanent discontinuation due to hyperkalaemia	110 (1.7)	38 (0.6)
Serious hyperkalaemia[b]	69 (1.1)	16 (0.2)
Hospitalization due to serious hyperkalaemia	61 (0.9)	10 (0.2)
Fatal hyperkalaemia	0 (0.0)	0 (0.0)
Investigator-reported hypokalaemia	70 (1.1)	149 (2.3)
Investigator-reported renal-related AEs		
Acute kidney injury[d]	220 (3.4)	234 (3.6)
Hospitalization due to acute kidney injury[d]	85 (1.3)	86 (1.3)
Treatment discontinuation due to acute kidney injury[d]	14 (0.2)	10 (0.2)

Incidence rate 0.66 per 100 patient-years

Incidence rate 0.22 per 100 patient-years

Results-Serum Potassium level

B Mean serum potassium



+0.21 mmol/L (SD 0.47 mmol/L) with finerenone

+0.02 mmol/L (SD 0.43 mmol/L) with placebo

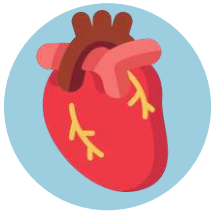
Number of patients						
Finerenone	6510	6234	5990	4916	2781	912
Placebo	6487	6229	5965	4878	2759	887
Mean change in serum potassium from baseline (mEq/L)						
Finerenone	Ref	0.21	0.20	0.18	0.17	0.13
Placebo	Ref	0.02	0.02	0.02	0.03	0.03

03

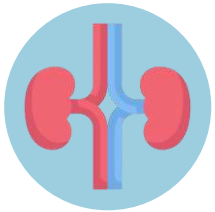
Discussion

Efficacy

Across the FIDELITY population…



Finerenone vs. Placebo



Relative risk reduction 14%

HHF was the main driver with a relative risk reduction of **22%** with finerenone vs. placebo (P = 0.0030) in), in a population that excluded patients with chronic symptomatic HFrEF

Relative risk reduction 23%

- A **30%** reduction in the risk of a **sustained ≥ 57% decrease in eGFR** on top of optimized ACEi or ARB therapy
- A relative risk reduction of **20%** in **ESKD** with finerenone vs. placebo

Efficacy

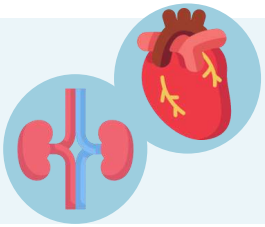
Combination with GLP-1 RAs or SGLT2 inhibitors in FIDELITY…

6.7%

SGLT2 inhibitors

7.2%

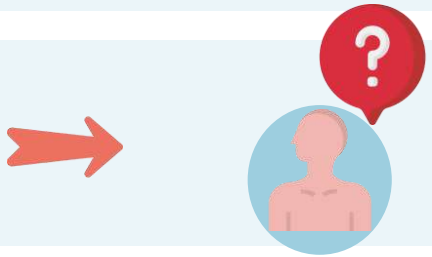
GLP-1 RAs



Benefits of finerenone are at least as large in patients on SGLT-2 inhibitors or GLP-1RAs as in those without

Finerenone + Empagliflozin (Preclinical)

hypertension-induced end-organ damage
→ protective effect across various cardiorenal outcomes



Safety

Hyperkalemia…

- More frequent with finerenone than placebo
- Hyperkalaemia-related permanent treatment discontinuation in only 1.7% of patients receiving finerenone vs. 0.6% with placebo over a median follow-up of 3.0 years (IQR 2.3–3.8 years).

Hypokalemia…

- less frequently occurred in finerenone-treated patients

Limitations

Patient population…

Most patients had advanced CKD, we excluded patients with nonalbuminuric CKD and CKD not due to type 2 diabetes

Race…

only small proportion of Black patients

Generalizability may be restricted.

Therefore, finerenone reduced the risk of clinically important cardiovascular and kidney outcomes vs. placebo across the spectrum of CKD in patients with type 2 diabetes with a manageable hyperkalemia risk and a reduction in hypokalemia.

Post-hoc Analysis

Across the FIDELIO-DKD population…

- In patients with CKD and T2D, finerenone reduced the risk of new-onset AFF
    - 82/2593 (3.2%) patients on finerenone and 117/2620 (4.5%) patients on placebo (HR: 0.71; 95% CI: 0.53–0.94; p =0.016)

Across the FIGARO-DKD population…

- In patients with CKD and T2D, finerenone reduced the risk of new-onset HF
    - 65/3396 (1.9%) patients on finerenone and 95/3385 (2.8%) patients on placebo (HR: 0.68; 95% CI: 0.50–0.93; p =0.016)

Filippatos, G., et al., *Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial*. Circulation, 2022. **145**(6): p. 437-447.
Filippatos, G., et al., Finerenone Reduces New-Onset Atrial Fibrillation in Patients With Chronic Kidney Disease and Type 2 Diabetes. J Am Coll Cardiol, 2021. 78(2): p. 142-152.

Ongoing Study

U.S. National Library of Medicine
ClinicalTrials.gov

ClinicalTrials.gov Identifier: NCT04435626

Recruitment Status : Recruiting
First Posted : June 17, 2020
Last Update Posted : February 25, 2022

Study to Evaluate the Efficacy (Effect on Disease) and Safety of Finerenone on Morbidity (Events Indicating Disease Worsening) & Mortality (Death Rate) in Participants With Heart Failure and Left Ventricular Ejection Fraction (Proportion of Blood Expelled Per Heart Stroke) Greater or Equal to 40% (FINEARTS-HF)

Study design: A Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Study

Key inclusion criteria:
- Aged ≥ 40 years
- Heart Failure (NYHA II-IV)
- Left Ventricular Ejection Fraction ≥ 40%

Key exclusion criteria:
- eGFR <25 mL/min/1.73 m²
- Serum potassium >5.0 mmol/L
- Acute inflammatory heart disease, MI, stroke, TIA within 90 days prior to randomization
- CABG in the 90 days prior to randomization
- PCI in the 30 days prior to randomization

Primary outcome:
- Number of cardiovascular deaths and heart failure events

Secondary outcome:
- Change in Total Symptom Score (TSS) from KCCQ
- Time to first occurrence of composite renal endpoint
- Time to death from any cause

04

Appraisal

A. Is the basic study design valid for a randomized controlled trial?

Q1. Did the study address a clearly focused research question?

☑ Yes ☐ No ☐ Can't tell

P	Patients with CKD and type 2 diabetes
I	Finerenone 10 or 20 mg
C	Placebo
O	Efficacy and safety

Q2. Was the assignment of participants to interventions randomized?

☑ Yes ☐ No ☐ Can't tell

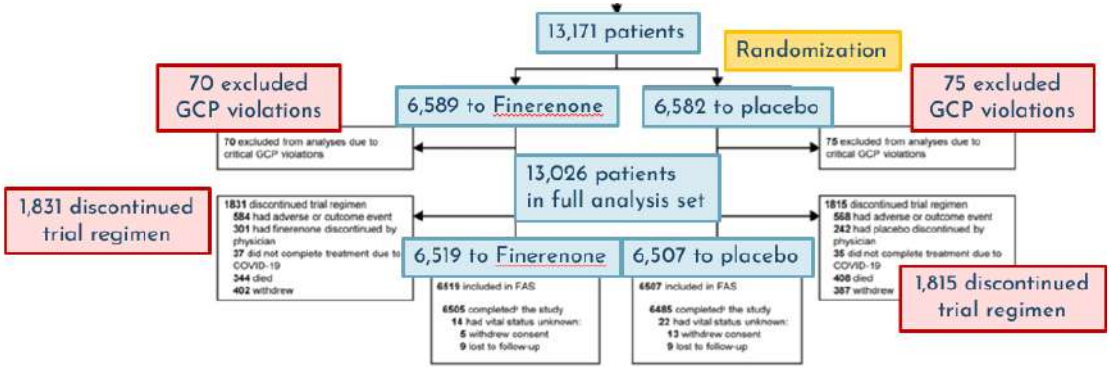
- Eligible patients were randomized 1:1 to receive oral finerenone (10 or 20 mg) or placebo.
- A clinical event committee whose members were unaware of the trial-group assignments independently reviewed and adjudicated all reported outcome events

Q3. Were all participants who entered the study accounted for at its conclusion?

☑ Yes ☐ No ☐ Can't tell

- The full analysis set comprised all randomized patients [except those with critical Good Clinical Practice (GCP) violations, who were prospectively excluded from all analyses].

Intention-to-treat analysis



B. Was the study methodologically sound?

Q4.

- **Were the participants 'blind' to intervention they were given?**

☑ Yes ☐ No ☐ Can't tell

- **Were the investigators 'blind' to the intervention they were giving to participants?**

☑ Yes ☐ No ☐ Can't tell

Finerenone IR tablets (10 mg and 20 mg) and placebo tablets will be identical in appearance (size, shape, color). The packaging and labeling will be designed to maintain the blinding of the investigator's team and the subjects.

- **Were the people assessing/analyzing outcome/s 'blinded'?**

☑ Yes ☐ No ☐ Can't tell

The study data will remain blinded until database lock and authorization of data release according to standard operating procedures. Appropriate measures will be taken to maintain blinding while bioanalysis is ongoing.

Q5. Were the study groups similar at the start of the randomized controlled trial?

☑ Yes ☐ No ☐ Can't tell

Patient characteristics, medications, and demographics at baseline were balanced between patients randomized to finerenone and placebo.

Q6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?

☑ Yes ☐ No ☐ Can't tell

Table S2. Concomitant medications initiated after start of study drug

Medication, n (%)	Finerenone (*n* = 6519)	Placebo (*n* = 6507)
Renin–angiotensin system inhibitors	2341 (35.9)	2432 (37.4)
Angiotensin-converting enzyme inhibitors	959 (14.7)	997 (15.3)
Angiotensin receptor blockers	1597 (24.5)	1711 (26.3)
Alpha-blocking agents	1702 (26.1)	1807 (27.8)
β-blockers	1662 (25.5)	1775 (27.3)
Calcium antagonists	2014 (30.9)	2310 (35.5)
Diuretics	2456 (37.7)	2613 (40.2)
Loop diuretics	1704 (26.1)	1855 (28.5)
Thiazide diuretics	659 (10.1)	747 (11.5)
Statins	1891 (29.0)	1872 (28.8)
Potassium-binders[a]	474 (7.3)	285 (4.4)
Platelet aggregation inhibitors	1528 (23.4)	1539 (23.7)
Glucose-lowering therapies	4051 (62.1)	4143 (63.7)
Insulin	2862 (43.9)	2893 (44.5)
Metformin	1485 (22.8)	1439 (22.1)
Sulfonylurea	780 (12.0)	814 (12.5)
Alpha-glucosidase inhibitor	256 (3.9)	239 (3.7)
DPP-4 inhibitors	1075 (16.5)	1044 (16.0)
GLP-1RAs	679 (10.4)	677 (10.4)
SGLT-2 inhibitors	766 (11.8)	794 (12.2)

C. What are the results?

Q7. Were the effects of intervention reported comprehensively?

☑ Yes ☐ No ☐ Can't tell

Power calculation

FIDELIO-DKD

This event-driven trial was designed to have 90% power to detect a 20% lower risk of a primary outcome event with finerenone than with placebo, on the basis of 1068 patients with a primary outcome event.

FIGARO-DKD

This event-driven trial was designed to have 90% power to detect a 20% lower risk of a primary outcome event with finerenone than with placebo, on the basis of 976 patients with an event.

Clearly specified outcomes measured, and statistical analysis

stratified Cox proportional hazards models
time-to-event analyses

Comprehensively reported results, and p value

Q8. Was the precision of the estimate of the intervention or treatment effect reported?

☑ Yes ☐ No ☐ Can't tell

Treatment effects are expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) from the stratified Cox proportional hazards models.

Q9. Do the benefits of the experimental intervention outweigh the harms and costs?

☑ Yes ☐ No ☐ Can't tell

Benefits	Harms	Costs
Finerenone improves cardiorenal outcomes in patients with CKD and type 2 diabetes	• No hyperkalemia-related adverse events were fatal • Only small proportion led to permanent treatment discontinuation	FINE-CKD model : cost-effectiveness

D. Will the results help locally?

Q10. Can the results be applied to your local population/in your context?

☑ Yes ☐ No ☐ Can't tell

	Finerenone (10 mg od or 20 mg od) (*n* = 6519)	Placebo (*n* = 6507)	All patients (*n* = 13 026)
Race or ethnic group, *n* (%)			
White	4449 (68.2)	4420 (67.9)	8869 (68.1)
Black/African American	253 (3.9)	269 (4.1)	522 (4.0)
Asian	1432 (22.0)	1462 (22.5)	2894 (22.2)
Others	385 (5.9)	356 (5.4)	741 (5.8)

Q11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

☐ Yes ☐ No ☑ Can't tell

Head-to-head comparison between MRAs in patients with DKD for cardiorenal outcomes is lacking.

Clinical Question

Do you agree patients with diabetic kidney disease should use finerenone chronically for cardiorenal protection?

Disagree

Need more evidences

Agree

THANKS

Q & A