ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 996–1005
doi:10.1002/ejhf.2469

RESEARCH ARTICLE

Finerenone in patients with chronic kidney disease and type 2 diabetes with and without heart failure: a prespecified subgroup analysis of the FIDELIO-DKD trial

Gerasimos Filippatos[1]*, Bertram Pitt[2], Rajiv Agarwal[3], Dimitrios Farmakis[4], Luis M. Ruilope[5,6,7], Peter Rossing[8,9], Johann Bauersachs[10], Robert J. Mentz[11], Peter Kolkhof[12], Charlie Scott[13], Amer Joseph[14], George L. Bakris[15], and Stefan D. Anker[16], on behalf of the FIDELIO-DKD Investigators

[1]National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Athens, Greece; [2]Department of Medicine, University of Michigan School of Medicine, Ann Arbor, MI, USA; [3]Richard L. Roudebush VA Medical Center and Indiana University, Indianapolis, IN, USA; [4]University of Cyprus Medical School, Nicosia, Cyprus; [5]Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12, Madrid, Spain; [6]CIBER-CV, Hospital Universitario 12 de Octubre, Madrid, Spain; [7]Faculty of Sport Sciences, European University of Madrid, Madrid, Spain; [8]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [9]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [10]Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; [11]Department of Medicine, Duke University School of Medicine, Durham, NC, USA; [12]Research and Development, Preclinical Research Cardiovascular, Bayer AG, Wuppertal, Germany; [13]Data Science and Analytics, Bayer PLC, Reading, UK; [14]Cardiology and Nephrology Clinical Development, Bayer AG, Berlin, Germany; [15]Department of Medicine, University of Chicago Medicine, Chicago, IL, USA; and [16]Department of Cardiology (CVK) and Berlin Institute of Health Center for Regenerative Therapies, German Center for Cardiovascular Research Partner Site Berlin, Charité – Universitätsmedizin, Berlin, Germany

Received 15 November 2021; revised 7 February 2022; accepted 1 March 2022; online publish-ahead-of-print 19 May 2022

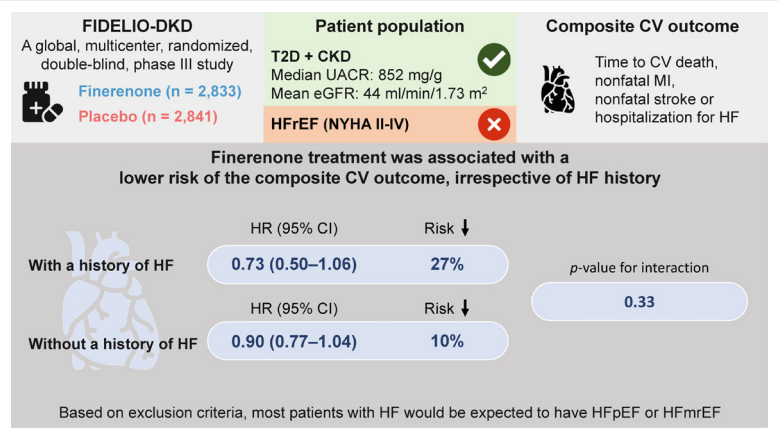
Aims This prespecified analysis of the FIDELIO-DKD trial compared the effects of finerenone, a selective non-steroidal mineralocorticoid receptor antagonist, on cardiorenal outcomes in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) by history of heart failure (HF).

Methods and results Patients with T2D and CKD (urine albumin-to-creatinine ratio ≥30–5000 mg/g and estimated glomerular filtration rate [eGFR] ≥25–<75 ml/min/1.73 m^2), without symptomatic HF with reduced ejection fraction (New York Heart Association II–IV) and treated with optimized renin–angiotensin system blockade were randomized to finerenone or placebo. The composite cardiovascular (CV) outcome (CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for HF) and composite kidney outcome (kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death) were analysed by investigator-reported medical history of HF. Of 5674 patients, 436 (7.7%) had a history of HF. Over a median follow-up of 2.6 years, the effect of finerenone compared with placebo on the composite CV outcome was consistent in patients with and without a history of HF (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.50–1.06 and HR 0.90, 95% CI 0.77–1.04, respectively; interaction $p = 0.33$). The effect of finerenone on the composite kidney outcome did not differ by history of HF (HR 0.79, 95% CI 0.52–1.20 and HR 0.83, 95% CI 0.73–0.94, respectively; interaction $p = 0.83$).

Conclusion In FIDELIO-DKD, finerenone improved cardiorenal outcome in patients with CKD and T2D irrespective of baseline HF history.

*Corresponding author. National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Rimini 1, Athens 15772, Greece. Tel: +30 21 05832352, Email: gfilippatos@gmail.com

Graphical Abstract



Cardiovascular outcomes by history of heart failure in the FIDELIO-DKD trial. CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

Keywords Chronic kidney disease • Diabetes • Heart failure • Aldosterone • Mineralocorticoid receptor antagonists • Finerenone

Introduction

Heart failure (HF), chronic kidney disease (CKD), and type 2 diabetes (T2D) often coexist, with each condition increasing the incidence and worsening the prognosis of the others.[1,2] CKD and T2D are highly prevalent among patients with HF, being present in up to 50% of patients enrolled in modern HF trials.[3,4] The prognosis of patients with HF, CKD, and T2D is unfavourable and further studies are needed to improve their outcomes.[1,2]

Steroidal mineralocorticoid receptor antagonists (MRAs), including spironolactone and the more selective and less potent eplerenone, improve prognosis in HF with reduced ejection fraction (HFrEF) and have a class IA recommendation in European and US guidelines for the treatment of these patients.[5–7] Mechanistic studies have suggested that MRAs may further improve left ventricular (LV) diastolic function, but a clear benefit in outcomes has not been demonstrated in HF with mildly reduced ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF) in randomized trials.[8–10]

Finerenone, a novel, selective, non-steroidal MRA, demonstrated clinically meaningful effects on improving kidney outcomes and reducing cardiovascular morbidity and mortality in patients with CKD and T2D without HFrEF in the Finerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease (FIDELIO-DKD) trial.[11,12] Phase II studies have demonstrated promising results with finerenone in patients with HFrEF, with T2D and/or CKD.[6,13,14] The aim of this prespecified analysis of the FIDELIO-DKD trial is to examine the effects of finerenone on cardiovascular, kidney and HF outcomes in patients with and without a history of HF (HFpEF or HFmrEF) at baseline (*Graphical Abstract*).

Methods

Study design and participants

FIDELIO-DKD was a global, multicentre, phase III, randomized, double-blind, placebo-controlled trial to determine the effect of finerenone in reducing cardiorenal morbidity and mortality in patients with CKD and T2D. The design, primary and secondary efficacy outcomes, and safety outcomes have been published.[11] Eligibility criteria included: adult patients (≥18 years of age) with a clinical diagnosis of T2D and CKD defined as (i) urine albumin-to-creatinine ratio (UACR) ≥30–<300 mg/g, estimated glomerular filtration rate (eGFR) ≥25–<60 ml/min/1.73 m^2, and a history of diabetic retinopathy, or (ii) UACR ≥300–5000 mg/g and eGFR ≥25–<75 ml/min/1.73 m^2; patients also had to be treated for at least 4 weeks with either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) at a maximum tolerated labelled dose before the screening visit, and have a serum potassium level of ≤4.8 mEq/L at the run-in and screening visits.[11] Key exclusion criteria were known HFrEF (New York Heart Association [NYHA] class II to IV); stroke, transient ischaemic cerebral attack, acute coronary syndrome, or hospitalization for worsening HF, in the 30 days prior to the screening visit; uncontrolled hypertension; non-diabetic kidney disease; a recent

history of dialysis for acute kidney failure; or a kidney transplant.[11] Exclusion of patients with HFrEF and NYHA class II to IV means that those patients with HF at baseline had either asymptomatic HFrEF, HFrEF with NYHA class I, HFpEF, or HFmrEF. The principles of the Declaration of Helsinki were followed throughout the trial and protocol approvals were obtained from local regulatory authorities and ethics committees. All participants provided written informed consent.[11] The study is registered with the EU Clinical Trials Register (EudraCT 2015-000990-11) and ClinicalTrials.gov (NCT02540993).

Procedures and outcomes

Patients were randomly assigned (1:1) to receive once daily oral treatment with finerenone (10 or 20 mg) or matching placebo.[11] For this prespecified subgroup analysis, patients were categorized by the presence or absence of HF, as reported by investigators based on a documented diagnosis in the medical history. Patients with a class IA recommendation for MRA treatment (i.e. clinical diagnosis of HFrEF with NYHA class II to IV symptoms) at the run-in visit were excluded.[11] The composite cardiovascular outcome was defined as time to first occurrence of cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for HF.[11] The composite kidney outcome was time to first occurrence of kidney failure (defined as eGFR <15 ml/min/1.73 m^2, initiation of chronic dialysis for >90 days, or kidney transplantation), a sustained decrease of at least 40% in eGFR from baseline over a period of at least 4 weeks, or death from renal causes.[11] An additional, composite cardiovascular outcome defined as the time to first occurrence of the composite endpoint of cardiovascular death or hospitalization for HF was evaluated as a prespecified exploratory endpoint. All reported outcome events were reviewed and adjudicated by an independent clinical event committee blinded to treatment assignment; definition criteria for outcome events have been published previously and, for hospitalization for HF, are included in the online Supplementary Information.[11] Safety analyses included adverse events (AEs) and central laboratory testing; AEs that initiated or exacerbated during finerenone or placebo treatment and up to 3 days after temporary or permanent treatment interruption were considered as treatment-emergent AEs.[11]

Statistical analysis

The full analysis set and safety analysis set of all randomized patients without critical Good Clinical Practice violations (which consisted of site or patient misconduct) were used for efficacy and safety analyses, respectively.[11] For the safety analysis, patients were included if they had taken at least one dose of study drug or placebo.[11] For time-to-event outcomes, assessed in the overall population, the superiority of finerenone versus placebo was evaluated via a log-rank test and stratified at screening by geographic region (North America, Latin America, Europe, Asia, and other), and category of eGFR (25–<45, 45–<60, or ≥60 ml/min/1.73 m^2) and albuminuria (UACR 30–<300 or ≥300–5000 mg/g).[11] Cox regression models were used to analyse the treatment effects, and results were expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs).[11]

For the subgroup analyses, similar Cox regression models (with an added treatment/subgroup interaction term) were used to analyse the treatment effect within the subgroup. Results are shown as HRs, CIs, and *p*-values for interaction. An interaction *p*-value of <0.05 indicated that the treatment effect was modified by the subgroup. Events were reported from randomization up to the end-of-study visit.[11] Patients were censored if there was no event at the date of their last contact; complete information on all components of their respective outcomes was recorded.[11] Tests for interaction, *p*-values for significance ($p < 0.05$), and HRs/CIs in the subgroups are reported regardless of significance given the hypothesis-generating nature of the present analysis.

Results

Patients

Out of a total of 5674 patients analysed, 436 (7.7%) had a history of HF at baseline, including 195 patients (3.4%) in the finerenone group and 241 patients (4.2%) in the placebo group.[11] Patients with a history of HF were more likely to be White, female, and to have a history of cardiovascular disease and atrial fibrillation, as well as higher body mass index, waist circumference, and high-sensitivity C-reactive protein concentration (*Table 1* and online supplementary *Table S1*), consistent with a predominantly HFpEF population phenotype. These patients also had lower eGFR at baseline, but similar UACR compared with those without a history of HF. Details of ejection fraction and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were not routinely collected. Patients with a history of HF were more likely to be receiving loop diuretics, beta-blockers, ACE inhibitors, statins, or insulin but were less likely to be receiving ARBs or sodium–glucose cotransporter 2 inhibitors at baseline. No patients were receiving sacubitril/valsartan at baseline (*Table 2*). Relevant demographic and clinical characteristics were balanced between the finerenone and placebo groups (online supplementary *Table S1*).

Effect of finerenone on the composite cardiovascular outcome and its components in patients with or without a history of heart failure

After a median follow-up of 2.6 years (interquartile range: 2.0–3.4 years), finerenone significantly reduced the composite cardiovascular outcome of cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for HF compared with placebo in the total study population (HR 0.86; 95% CI 0.75–0.99; $p = 0.03$).[11] The composite cardiovascular outcome occurred ≥2 times more frequently in patients with a history of HF than those without, irrespective of treatment assignment (finerenone: 9.88 vs. 4.78 patients with event per 100 patient-years, respectively; placebo: 13.42 vs. 5.32 patients with event per 100 patient-years, respectively). However, the effect of finerenone compared with placebo on the composite cardiovascular outcome appeared to be consistent across patients with (HR 0.73; 95% CI 0.50–1.06) or without (HR 0.90; 95% CI 0.77–1.04) a history of HF (interaction $p = 0.33$; *Figure 1*; *Graphical Abstract*). Similarly, in the present analysis, a history of HF did not appear to modify the effect of finerenone versus placebo on the components of the composite cardiovascular outcome, including hospitalization for HF (HR 0.65; 95% CI 0.39–1.09 and HR 0.95; 95% CI 0.73–1.22 for patients

Table 1 Patient baseline characteristics by history of heart failure

Characteristic	With history of HF (n = 436)[a]	Without history of HF (n = 5238)[b]
Age, years, mean (SD)	66.30 (8.63)	65.50 (9.08)
Male sex, *n* (%)	280 (64.2)	3703 (70.7)
Race, *n* (%)		
White	343 (78.7)	3249 (62.0)
Black/African American	28 (6.4)	236 (4.5)
Asian	50 (11.5)	1390 (26.5)
Systolic blood pressure, mmHg, mean (SD)	138.02 (14.44)	138.03 (14.36)
Diastolic blood pressure, mmHg, mean (SD)	75.83 (9.57)	75.82 (9.68)
BMI, kg/m^2, mean (SD)	33.15 (6.52)	30.94 (5.94)
Duration of diabetes, years, mean (SD)	16.67 (9.02)	16.55 (8.75)
HbA1c, %, mean (SD)	7.84 (1.32)	7.66 (1.34)
Serum potassium, mmol/L, mean (SD)	4.38 (0.51)	4.37 (0.45)
eGFR, ml/min/1.73 m^2, mean (SD)	42.29 (12.66)	44.51 (12.53)
eGFR, ml/min/1.73 m^2, *n* (%)		
<25	16 (3.7)	119 (2.3)
25–<45	262 (60.1)	2719 (51.9)
45–<60	117 (26.8)	1783 (34.0)
≥60	41 (9.4)	615 (11.7)
UACR, mg/g, median (IQR)	867.01 (447.54–1613.97)	850.49 (446.03–1639.02)
UACR, mg/g, *n* (%)		
<30	3 (0.7)	20 (0.4)
30–<300	47 (10.8)	638 (12.2)
≥300	386 (88.5)	4577 (87.4)
Mean waist–hip ratio, mean (SD)	1.01 (0.12)	1.00 (0.11)
Waist circumference, cm, mean (SD)	111.44 (16.04)	106.35 (15.07)
hs-CRP, mg/L, mean (SD)	6.53 (12.50)	4.41 (8.63)
Heart rate, bpm, mean (SD)	70.13 (10.49)	72.45 (11.46)
History of cardiovascular disease, *n* (%)		
Yes	328 (75.2)	2277 (43.5)
No	108 (24.8)	2961 (56.5)
Coronary artery disease, *n* (%)	274 (62.8)	1428 (27.3)
Atrial fibrillation, *n* (%)	95 (21.8)	346 (6.6)
Hypertension, *n* (%)	427 (97.9)	5078 (96.9)
Current smoker, *n* (%)	55 (12.6)	751 (14.3)

Note: Medical history of HF was determined by the investigator.
BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.
[a]Missing data for $n \leq 2$ patients across all characteristics.
[b]Missing data for $n \leq 25$ patients across all characteristics.

with and without a history of HF, respectively; interaction $p = 0.20$; *Figure 2*; online supplementary *Figure S1*).

There was no clear difference of the effect of finerenone versus placebo on all-cause, cardiovascular, or non-cardiovascular hospitalization in patients with or without a history of HF (online supplementary *Figure S2*).

Effect of finerenone on kidney outcomes in patients with or without heart failure

In the overall patient population, there was a significant reduction in the composite kidney outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes with finerenone than with placebo (HR 0.82; 95% CI 0.73–0.93; p = 0.001).[11] The effect of finerenone compared with placebo on the composite kidney outcome appeared to be consistent across patients with (HR 0.79; 95% CI 0.52–1.20) or without (HR 0.83; 95% CI 0.73–0.94) a history of HF (interaction p = 0.83; online supplementary *Figure S3*).

Estimated glomerular filtration rate over time in patients with and without a history of HF, and the effects of finerenone and placebo on the chronic eGFR slopes by history of HF are shown in online supplementary *Figure S4*.

Table 2 Medication use at baseline

Medication use at baseline, *n* (%)	With history of HF		Without history of HF	
	Finerenone (*n* = 195)	Placebo (*n* = 241)	Finerenone (*n* = 2638)	Placebo (*n* = 2600)
Angiotensin-converting enzyme inhibitors	73 (37.4)	122 (50.6)	877 (33.2)	870 (33.5)
Angiotensin receptor blockers	123 (63.1)	120 (49.8)	1756 (66.6)	1726 (66.4)
Beta-blockers	142 (72.8)	188 (78.0)	1320 (50.0)	1318 (50.7)
Diuretics	139 (71.3)	173 (71.8)	1438 (54.5)	1464 (56.3)
Loop diuretics	114 (58.5)	129 (53.5)	672 (25.5)	704 (27.1)
Thiazide diuretics	17 (8.7)	26 (10.8)	683 (25.9)	629 (24.2)
Statins	152 (77.9)	197 (81.7)	1953 (74.0)	1913 (73.6)
Potassium supplements	15 (7.7)	16 (6.6)	70 (2.7)	69 (2.7)
Potassium-lowering agents	4 (2.1)	8 (3.3)	66 (2.5)	58 (2.2)
Glucose-lowering therapies	190 (97.4)	239 (99.2)	2557 (96.9)	2538 (97.6)
Insulin and analogues	135 (69.2)	176 (73.0)	1708 (64.7)	1618 (62.2)
Metformin	74 (37.9)	86 (35.7)	1177 (44.6)	1153 (44.3)
Sulfonylureas	50 (25.6)	52 (21.6)	604 (22.9)	621 (23.9)
DPP-4 inhibitors	48 (24.6)	50 (20.7)	716 (27.1)	708 (27.2)
GLP-1RAs	9 (4.6)	7 (2.9)	180 (6.8)	198 (7.6)
SGLT2 inhibitors	7 (3.6)	7 (2.9)	117 (4.4)	128 (4.9)
Alpha glucosidase inhibitors	9 (4.6)	9 (3.7)	154 (5.8)	152 (5.8)

DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2, sodium–glucose cotransporter 2.

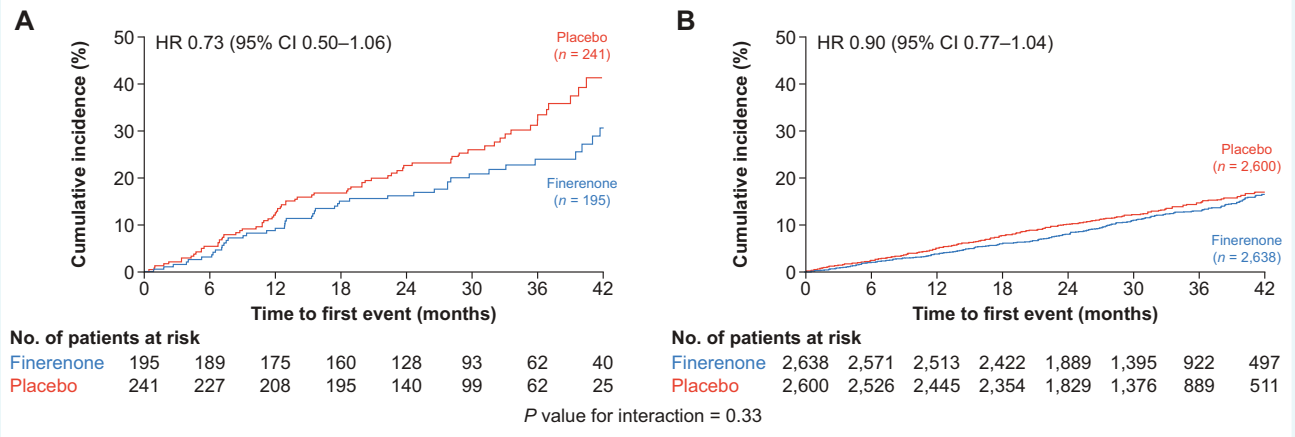


Figure 1 Composite cardiovascular outcome by history of heart failure at baseline. Incidence of the composite cardiovascular outcome was assessed in a time-to-event analysis. The Kaplan–Meier curves show the cumulative incidence of cardiovascular events tended to be lower with finerenone versus placebo in patients with (*A*) and without (*B*) a history of heart failure at baseline. CI, confidence interval; HR, hazard ratio.

Effect of finerenone on heart failure outcomes

In the total study population, the incidence of the prespecified cardiovascular composite outcome of cardiovascular death or hospitalization for HF was numerically lower in finerenone-treated patients than in the placebo group (HR 0.86; 95% CI 0.73–1.02; $p = 0.08$; *Figures 2* and *3*). The effect of finerenone compared with placebo on the composite of cardiovascular death or hospitalization for HF appeared consistent across patients with (HR 0.80; 95% CI 0.53–1.20) or without (HR 0.89; 95% CI 0.74–1.07) a history of HF (interaction $p = 0.63$; *Figure 2*).

Safety outcomes and vital signs in patients with or without heart failure

The incidence of treatment-emergent AEs was similar in the two treatment groups in the overall study population.[11] However, there

Time-to-event outcome	Finerenone		Placebo		Hazard ratio (95% CI)	Interaction *P* value
	n/*N* (%)	*n* per 100 PY	*n*/*N* (%)	*n* per 100 PY		
CV composite	**367/2,833 (13.0)**	**5.11**	**420/2,841 (14.8)**	**5.92**	**0.86 (0.75–0.99)**	
With HF	46/195 (23.6)	9.88	71/241 (29.5)	13.42	0.72 (0.49–1.05)	0.33
Without HF	321/2,638 (12.2)	4.78	349/2,600 (13.4)	5.32	0.90 (0.77–1.04)	
Kidney composite	**208/2,833 (7.3)**	**2.99**	**235/2,841 (8.3)**	**3.39**	**0.82 (0.73–0.93)**	
With HF	37/195 (19.0)	8.65	55/241 (22.8)	10.49	0.79 (0.52–1.20)	0.83
Without HF	467/2,638 (17.7)	7.52	545/2,600	8.96	0.83 (0.73–0.94)	
CV death or HHF	**249/2,833 (8.8)**	**3.38**	**289/2,841 (10.2)**	**3.95**	**0.86 (0.73–1.02)**	
With HF	39/195 (20.0)	8.24	57/241 (23.7)	10.33	0.80 (0.53–1.20)	0.63
Without HF	210/2,638 (8.0)	3.05	2.32/2,600 (8.9)	3.43	0.89 (0.74–1.07)	
First HHF	**139/2,833 (4.9)**	**1.89**	**162/2,841 (5.7)**	**2.21**	**0.86 (0.68–1.08)**	
With HF	23/195 (11.8)	4.86	41/241	7.43	0.65 (0.39–1.09)	0.20
Without HF	116/2,638 (4.4)	1.68	121/2,600 (4.7)	1.79	0.95 (0.73–1.22)	

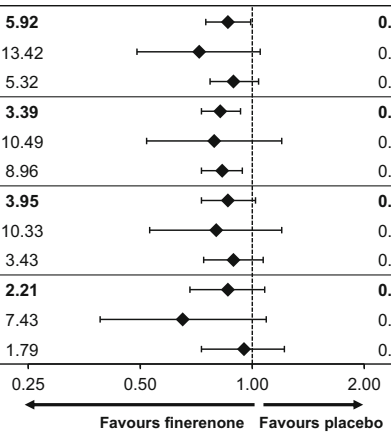


Figure 2 Summary of CV, kidney, and HF outcomes in the total study population and by history of HF at baseline. Stratified Cox proportional hazards models were used to analyse the effects of finerenone versus placebo on CV, kidney and HF outcomes, and the forest plot shows that the effects of finerenone were not modified by history of HF at baseline. CI, confidence interval; CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; PY, patient-years.

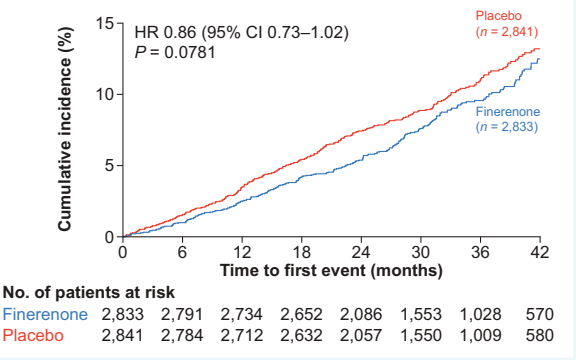


Figure 3 Time to cardiovascular death or hospitalization for heart failure in the total study population. Incidence of cardiovascular death or hospitalization for heart failure was assessed in a time-to-event analysis. The Kaplan–Meier curves show that the cumulative incidence of cardiovascular death or hospitalization for heart failure as first event. CI, confidence interval; HR, hazard ratio.

were fewer serious AEs in patients receiving finerenone compared with placebo, most notably in patients with a history of HF (31.8% vs. 40.2%; online supplementary *Table S2*).

There was a greater incidence of hyperkalaemia with finerenone than with placebo, which was consistent in patients with (19.5% vs. 7.9%) or without (18.2% vs. 9.1%) a history of HF (online supplementary *Table S3*).[11] The incidence of hyperkalaemia >5.5 mmol/L was greater in patients treated with finerenone than in those treated with placebo (20.7% vs. 12.6% in patients with a history of HF; 21.5% vs. 8.9% in patients without a history of HF). There was also an increased incidence of potassium values >6.0 mmol/L with finerenone compared with placebo, both in patients with a history of HF (3.6% vs. 2.1%, respectively) and without a history of HF (4.6% vs. 1.3%, respectively).[11] The magnitude of the change in serum potassium concentration is shown in online supplementary *Figure S5*.

The incidences of the respiratory-related AEs peripheral oedema, bronchitis, and pneumonia were lower in patients treated with finerenone versus placebo in those with a history of HF (online supplementary *Table S4*).

No difference in body weight was observed between treatment groups in patients with and without a history of HF, and systolic blood pressure changes were similar between the subgroups (online supplementary *Figures S6* and *S7*, respectively).

Discussion

In this secondary analysis of the FIDELIO-DKD trial, there was no evidence that a history of HF at baseline modified the response of patients with CKD and T2D to finerenone in terms of cardiovascular and kidney outcomes (*Graphical Abstract*).[11] Both the cardiovascular composite outcome (cardiovascular death, hospitalization for HF, non-fatal MI, and non-fatal stroke) and the kidney composite outcome (kidney failure, a sustained decrease of at least 40% in eGFR from baseline over a period of at least 4 weeks, or renal death) were improved with finerenone compared with placebo in patients with and without a history of HF in the presence of optimized renin–angiotensin system (RAS) blockade. Additionally, finerenone was well tolerated compared with placebo both in patients with and without a history of HF. This is an important finding, because patients with HF, CKD, and T2D represent a challenging population with increased morbidity and mortality, and difficulties in drug prescription and tolerance.[15,16]

The close interdependence of cardiac and kidney function and the significant interference of T2D in this complex relationship is well established.[15,16] CKD and T2D are associated with increased risk of atrial fibrillation and atrial fibrillation has been found to increase the risk of HF.[17] A recent analysis of FIDELIO-DKD found that finerenone reduced the risk of new-onset atrial fibrillation or flutter and the risk of kidney or cardiovascular events irrespective of history of atrial fibrillation or flutter at baseline.[18] Similarly, in a recent analysis of FIGARO-DKD in patients with T2D and CKD without a history of symptomatic HFrEF, finerenone led to a significant reduction in the risk of clinically important time-to-event HF outcomes and reduced the risk of new-onset hospitalization for HF by 32% versus placebo.[19]

Finerenone has previously been studied in patients with HFrEF. In the phase II ARTS (Mineralocorticoid Receptor Antagonist Tolerability Study) trial, finerenone was at least as effective as spironolactone in reducing natriuretic peptides and albuminuria in 392 patients with HFrEF and moderate CKD but led to significantly smaller increases in serum potassium compared with spironolactone.[13] In the subsequent phase IIb ARTS-HF trial in 1066 patients with worsening HFrEF and T2D and/or CKD, finerenone was well tolerated and induced a 30% or greater decrease in plasma NT-proBNP over 3 months in a similar proportion of patients to eplerenone.[14] The study further demonstrated a nominally significant reduction in the exploratory composite endpoint of all-cause death, cardiovascular hospitalizations, or emergency presentation for worsening HF with finerenone compared with eplerenone.[14]

Patients with symptomatic HFrEF, who have a class IA indication for MRA therapy, were excluded from the FIDELIO-DKD trial.[11] As a result, patients with a history of HF at baseline studied in this analysis were likely to have asymptomatic HFrEF (LV ejection fraction [LVEF] <40%) or HFrEF with NYHA class I, HFpEF (LVEF ≥50%), or HFmrEF (LVEF 40%–49%). This is consistent with the observation that these patients were more likely to be women and had higher body mass index and prevalence of comorbidities such as atrial fibrillation, which are known features of HFpEF.[20] Both CKD and T2D are highly prevalent among patients with HFpEF.[3] In the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) trial of empagliflozin in patients with HF with LVEF >40%, NYHA class II to IV symptoms, and elevated levels of natriuretic peptides, CKD and T2D were prevalent in 50% and 49% of patients, respectively.[3] Similarly, in the PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) trial of sacubitril/valsartan in HFpEF (LVEF ≥45%), CKD and T2D were present in 47% and 43% of patients, respectively.[4]

Animal studies have demonstrated that MRAs improve LV diastolic function and reduce LV hypertrophy and myocardial fibrosis.[9,21] Several studies have evaluated the efficacy and safety of MRAs in patients with a variety of conditions associated with LV diastolic dysfunction, with or without HFpEF. In a meta-analysis of 11 randomized trials, MRA treatment was associated with improved diastolic function, as per echocardiograph results, along with reduction in circulating biomarkers of fibrosis without a change in LV dimensions or mass.[9] Among these trials, the Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) study in 422 patients with HFpEF showed that spironolactone improved diastolic function, as assessed by E/e' ratio over a 12-month period, although it failed to improve the co-primary endpoint of exercise capacity (peak oxygen consumption).[22] In the large, randomized phase III TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial in 3445 patients with HFpEF, spironolactone did not significantly reduce the incidence of the primary composite outcome of cardiovascular death, aborted cardiac arrest, or hospitalization compared with placebo.[10] However, a secondary analysis of the study suggested a possible benefit with spironolactone in the Americas subpopulation of the trial, where the diagnosis of HFpEF had been more often objectively based on natriuretic peptide elevation rather than clinical criteria.[8]

The use of steroidal MRAs, including spironolactone and the more selective and less potent eplerenone, is limited by the increased risk of hyperkalaemia and worsening kidney function, and these drugs are often prescribed sub-optimally in HFrEF despite being a class IA recommendation.[23–25] Tolerance of MRAs may be even worse in patients with CKD and T2D who are also treated with RAS inhibitors,[26] such as those studied in the FIDELIO-DKD trial.[11] Compared with steroidal MRAs, finerenone may have a better overall benefit–risk ratio.[6]

Finerenone combines the potency of spironolactone with the selectivity of eplerenone for the mineralocorticoid receptor.[26] Finerenone blocks the mineralocorticoid receptor as a bulky, passive antagonist; this mechanism is distinct from steroidal MRAs.[6] Finerenone has a unique binding mode that determines potency, selectivity, and nuclear cofactor recruitment, while its physicochemical properties (including lipophilicity and polarity) determine tissue penetration and distribution. In combination, these offer a novel MRA pharmacology with pronounced anti-fibrotic efficacy in preclinical models.[6] In animals, finerenone has a more balanced distribution between the heart and kidneys compared with spironolactone and eplerenone, which are preferentially distributed in the kidneys.[27] Finerenone has also been shown to exert more potent anti-inflammatory and antifibrotic effects on the kidney compared with equinatriuretic doses of eplerenone.[28] In the aforementioned ARTS trial, finerenone was associated with lower incidences of hyperkalaemia and worsening kidney function compared with spironolactone.[13] We observed a higher incidence of hyperkalaemia with finerenone compared with placebo in patients with CKD and T2D also receiving RAS inhibition.[11] However, the coexistence of HF did not affect the risk of hyperkalaemia. In addition, the overall risk of serious AEs was lower with finerenone compared with placebo and this risk was even lower in patients with a history of HF.[11] As a result, and in accordance with previous studies,[13,14,29] finerenone represents a new therapeutic option for these patients with an acceptable safety profile.

Limitations

This is a secondary analysis of a randomized controlled trial and, although our findings are in broad agreement with those of the main FIDELIO-DKD study, they should be interpreted with

caution. There were a limited number of patients with a history of HF (n = 436, 7.7%) and the distribution of these patients was somewhat uneven (195 [3.4%] in the finerenone group vs. 241 [4.2%] in the placebo group). Given the limited number of patients with a history of HF, and the number of events, the CIs of the HRs are wide. Although the findings reported here, as well as from an additional adjusted Cox proportional hazard model analysis that included variables of age, sex, UACR, and eGFR at baseline (data not shown), do not show a significant interaction effect of a history of HF on the cardiovascular composite outcome, it does not appear that a history of HF mitigates the effect of finerenone on cardiovascular protection. Patients with HFrEF with an indication for MRA treatment were excluded from the trial; therefore, our results are not applicable to this particular population. There is a lack of uniform definition of HF at baseline in this study because the definition of HF was based only on investigators' reports (LVEF was not collected and echocardiography was not used to confirm LVEF at enrolment); therefore, there was a potential for misclassification. However, given the exclusion of HFrEF, patients with a history of HF studied in this analysis likely had asymptomatic HFrEF or HFrEF with NYHA class I, HFpEF, or HFmrEF; further insight may be provided by future analyses of data from the FIDELIO-DKD and FIGARO-DKD echocardiography substudies.[11] The number of events reported for each outcome was limited in patients with a history of HF, which may preclude observing significant interactions in this subgroup analysis. Patients with mainly advanced CKD were included whereas those with non-albuminuric CKD and CKD unrelated to diabetes were excluded. Only a small proportion of patients in the analysis identified as Black.

Conclusions

In FIDELIO-DKD, finerenone was well tolerated and improved cardiovascular and kidney outcomes in patients with CKD and T2D, with no difference observed between patients with and without a history of HF. The current analysis is hypothesis-generating; however, further evidence on the efficacy and safety of finerenone compared with placebo in HF is expected from the ongoing FINEARTS-HF (Finerenone Trial to Investigate Efficacy And Safety Superior to Placebo in Patients With Heart Failure) study, which is currently recruiting patients with HF and LVEF of 40% or greater.[30]

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

We are indebted to the patients, investigators, and centres who supported FIDELIO-DKD. The Executive Committee designed the study in conjunction with the sponsor. Prof. Filippatos wrote the first draft of the report and assumes responsibility for the integrity and accuracy of the data. All authors had access to study results and were involved in data analysis, interpretation, drafting and revising the report. All authors reviewed and approved the final version. Additional statistical review/assistance was provided by Christoph Tasto and Luke Roberts (Bayer AG). Medical writing assistance was provided by Richard Starke, of Chameleon Communications International, and was funded by Bayer AG.

Funding

This work, and the FIDELIO-DKD study was conducted and funded by Bayer AG. The funder participated in study design, data collection, data analysis, data interpretation, and approval of the manuscript. Analyses were conducted by the sponsor, and all authors had access to and participated in the interpretation of the data.

Conflict of interest: G.F. reports lectures fees and/or that he is a committee member of trials and registries sponsored by Amgen, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Servier, and Vifor Pharma; he is a Senior Consulting Editor for *JACC Heart Failure* and has received research support from the European Union. B.P. reports consultant fees for Ardelyx, AstraZeneca, Bayer, Boehringer Ingelheim, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, PhaseBio, Sanofi/Lexicon, Sarfez, scPharmaceuticals, SQ Innovation, Tricida, and Vifor/Relypsa; he has stock options for Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, Sarfez, scPharmaceuticals, SQ Innovation, Tricida, and Vifor/Relypsa; he also holds a patent for site-specific delivery of eplerenone to the myocardium (US patent #9931412) and a provisional patent for histone-acetylation-modulating agents for the treatment and prevention of organ injury (provisional patent US 63/045784). R.A. reports personal fees and non-financial support from Bayer Healthcare Pharmaceuticals Inc. during the conduct of the study; he also reports personal fees and non-financial support from Akebia Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Fresenius Kabi, Janssen, Relypsa, Sanofi, and Vifor Pharma; he has received personal fees from Ironwood Pharmaceuticals, Lexicon Pharmaceuticals, Merck & Co., and Reata, and non-financial support from E. R. Squibb & Sons, Opko Health, and Otsuka Pharmaceuticals America; he is a member of data safety monitoring committees for Amgen, AstraZeneca, and Celgene, a member of steering committees of randomized trials for Akebia Therapeutics, Bayer, Janssen, and Relypsa and a member of adjudication committees for AbbVie, Bayer, Boehringer Ingelheim, and Janssen; he has served as Associate Editor of the *American Journal of Nephrology* and *Nephrology Dialysis and Transplantation* and has been an author for UpToDate, and he has received research grants from the U.S. Veterans Administration and the National Institutes of Health. D.F. has received personal fees for lectures and/or consultation from Abbott Laboratories, Bayer, Boehringer Ingelheim, Leo, Novartis, Orion, and Roche Diagnostics outside the submitted work. L.M.R. reports receipt of consultancy fees from Bayer. P.R. reports personal fees from Bayer during the conduct of the study; he has received research support and personal fees from AstraZeneca and Novo Nordisk, and personal fees from Astellas Pharma, Boehringer Ingelheim, Eli Lilly, Gilead

Sciences, Mundipharma, Sanofi, and Vifor Pharma; all fees are given to Steno Diabetes Center, Copenhagen; he has an equity interest in Novo Nordisk. J.B. received honoraria for lectures/consulting from Abiomed, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cardior, CVRx, Daiichi-Sankyo, Medtronic, MSD, Novartis, Orion, Pfizer, Servier, and Vifor Pharma; and research support from Abiomed, CVRx, Vifor Pharma, and Zoll unrelated to this paper. R.J.M. has received research support and honoraria from Abbott, American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim/Eli Lilly, Boston Scientific, Cytokinetics, Fast BioMedical, Gilead, Innolife, Medtronic, Merck, Novartis, Relypsa, Respicardia, Roche, Sanofi, Vifor Pharma, and Windtree Therapeutics. P.K. is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany. He is the co-inventor of finerenone and holds US and European patents relating to finerenone (US8436180B2 and EP2132206B1). C.S. is a full-time employee of Bayer PLC, Division Pharmaceuticals, United Kingdom. A.J. is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany. G.L.B. reports research funding paid to the University of Chicago Medicine from Bayer, during the conduct of the study; he also reports research funding paid to the University of Chicago Medicine from Novo Nordisk and Vascular Dynamics; he acted as a consultant for and received personal fees from Merck, Relypsa, and Alnylam Pharmaceuticals; he is an Editor of the *American Journal of Nephrology*, *Nephrology* and *Hypertension*, and Section Editor of UpToDate, he is also an Associate Editor of *Diabetes Care* and *Hypertension Research*. S.D.A. has received research support from Abbott Vascular and Vifor Pharma, and personal fees from Abbott Vascular, Boehringer Ingelheim, Bayer, BRAHMS, Novartis, Servier, Vifor Pharma, Impulse Dynamics, and Cardiac Dimensions.

References

1. Seferovic PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;**20**:853–72.
2. Filippatos G, Farmakis D, Parissis J. Renal dysfunction and heart failure: things are seldom what they seem. *Eur Heart J*. 2014;**35**:416–8.
3. Anker SD, Butler J, Filippatos G, Shahzeb Khan M, Ferreira JP, Bocchi E, et al.; EMPEROR-Preserved Trial Committees and Investigators. Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial. *Eur J Heart Fail*. 2020;**22**:2383–92.
4. Solomon SD, Rizkala AR, Lefkowitz MP, Shi VC, Gong J, Anavekar N, et al. Baseline characteristics of patients with heart failure and preserved ejection fraction in the PARAGON-HF trial. *Circ Heart Fail*. 2018; **11**:e004962.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;**37**:2129–200.
6. Agarwal R, Kolkhof P, Bakris G, Bauersachs J, Haller H, Wada T, et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J*. 2021;**42**:152–61.
7. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, et al. 2021 Update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution set Oversight Committee. *J Am Coll Cardiol*. 2021;**77**: 772–810.
8. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;**131**:34–42.
9. Pandey A, Garg S, Matulevicius SA, Shah AM, Garg J, Drazner MH, et al. Effect of mineralocorticoid receptor antagonists on cardiac structure and function in patients with diastolic dysfunction and heart failure with preserved ejection fraction: a meta-analysis and systematic review. *J Am Heart Assoc*. 2015; **4**:e002137.
10. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al.; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;**370**:1383–92.
11. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope L, Rossing P, et al.; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med*. 2020;**383**:2219–29.
12. Filippatos G, Anker SD, Agarwal R, Pitt B, Ruilope LM, Rossing P, et al.; FIDELIO-DKD Investigators. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. *Circulation*. 2021;**143**: 540–52.
13. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur Heart J*. 2013;**34**: 2453–63.
14. Filippatos G, Anker SD, Bohm M, Gheorghiade M, Kober L, Krum H, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J*. 2016;**37**:2105–14.
15. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. *Nat Rev Nephrol*. 2016;**12**:610–23.
16. Aguilar D. Heart failure, diabetes mellitus, and chronic kidney disease: a clinical conundrum. *Circ Heart Fail*. 2016;**9**:e003316.
17. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;**42**:373–498.
18. Filippatos G, Bakris GL, Pitt B, Agarwal R, Rossing P, Ruilope LM, et al.; FIDELIO-DKD Investigators. Finerenone reduces new-onset atrial fibrillation in patients with chronic kidney disease and type 2 diabetes. *J Am Coll Cardiol*. 2021;**78**:142–52.
19. Filippatos G, Anker SD, Agarwal R, Ruilope LM, Rossing P, Bakris GL, et al.; FIGARO-DKD Investigators. 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**:437–47.
20. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;**19**: 1574–85.
21. Pfeffer MA, Braunwald E. Treatment of heart failure with preserved ejection fraction: reflections on its treatment with an aldosterone antagonist. *JAMA Cardiol*. 2016;**1**:7–8.
22. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, et al.; Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA*. 2013;**309**:781–91.
23. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;**351**:543–51.
24. Eschalier R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, et al.; EMPHASIS-HF Investigators. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). *J Am Coll Cardiol*. 2013;**62**: 1585–93.
25. Patel RB, Fonarow GC, Greene SJ, Zhang S, Alhanti B, DeVore AD, et al. Kidney function and outcomes in patients hospitalized with heart failure. *J Am Coll Cardiol*. 2021;**78**:330–43.
26. Pitt B, Anker SD, Bohm M, Gheorghiade M, Kober L, Krum H, et al. Rationale and design of MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF): a randomized study of finerenone vs. eplerenone in patients who have worsening chronic heart failure with diabetes and/or chronic kidney disease. *Eur J Heart Fail*. 2015;**17**:224–32.

27. Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Barfacker L, et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. *J Cardiovasc Pharmacol*. 2014;**64**:69–78.
28. Grune J, Beyhoff N, Smeir E, Chudek R, Blumrich A, Ban Z, et al. Selective mineralocorticoid receptor cofactor modulation as molecular basis for finerenone's antifibrotic activity. *Hypertension*. 2018;**71**:599–608.
29. Dojki FK, Bakris G. Nonsteroidal mineralocorticoid antagonists in diabetic kidney disease. *Curr Opin Nephrol Hypertens*. 2017;**26**:368–74.
30. ClinicalTrials.gov. Study to Evaluate the Efficacy (Effect on Disease) and Safety of Finerenone on morbidity (Events Indicating Disease Worsening) and 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). https://clinicaltrials.gov/ct2/show/NCT04435626. (Accessed 20 April 2021).