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

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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 m²), 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.
Finerenone in patients with CKD and T2D with and without HF in FIDELIO-DKD

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; HFrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFmrEF, 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 damage (FIDELIO-DKD) trial.11,12 Phase II studies have demonstrated promising results with finerenone in patients with HFpEF, 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 cardio-renal 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 m², and a history of diabetic retinopathy, or (ii) UACR ≥ 300–5000 mg/g and eGFR ≥ 25–<75 ml/min/1.73 m²; 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
procedures and outcomes

Patients were randomly assigned (1:1) to receive once daily oral treatment with finerenone (10 or 20 mg) or matching placebo. 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 the 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 defined as the 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 7; 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/m², 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 m², mean (SD)             | 42.29 (12.66)                | 44.51 (12.53)                    |
| eGFR, ml/min/1.73 m², 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, cm, 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.

aMissing data for n ≤ 2 patients across all characteristics.
bMissing data for n ≤ 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.

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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 = 2,638) | Placebo (n = 2,600) |
| 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. However, there
Table S2

| Time-to-event outcome | Finerenone 2,833 (%) | Placebo 2,841 (%) | Hazard ratio (95% CI) |
|-----------------------|----------------------|------------------|----------------------|
| CV composite          | 367/2,833 (13.0)     | 420/2,841 (14.8) | 0.86 (0.75–0.99)     |
| With HF               | 46/195 (23.6)        | 9.88             | 13.42                |
| Without HF            | 321/2,638 (12.2)     | 4.78             | 5.32                 |
| Kidney composite      | 208/2,833 (7.3)      | 2.99             | 3.39                 |
| With HF               | 37/195 (19.0)        | 8.65             | 10.49                |
| Without HF            | 467/2,638 (17.7)     | 7.52             | 8.96                 |
| CV death or HHF       | 249/2,833 (8.8)      | 3.38             | 3.95                 |
| With HF               | 39/195 (20.0)        | 8.24             | 10.33                |
| Without HF            | 210/2,638 (8.0)      | 3.05             | 3.43                 |
| First HHF             | 139/2,833 (4.9)      | 1.89             | 2.21                 |
| With HF               | 23/195 (11.8)        | 4.86             | 7.43                 |
| Without HF            | 116/2,638 (4.4)      | 1.68             | 1.79                 |

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). 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). 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).

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.
The close interdependence of cardiac and kidney function and the significant interference of T2D in this complex relationship is well established.\(^5,6\) CKD and T2D are associated with increased risk of atrial fibrillation and atrial fibrillation has been found to increase the risk of HF.\(^7\) 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.\(^8\) 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.\(^9\)

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.\(^1\) 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.\(^1\) 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.\(^1\)

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] \(\geq 50\%\)) or HFrEF with NYHA class I, HFrEF (LVEF \(\geq 50\%\)) or HFrEF (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 HFrEF.\(^10\) Both CKD and T2D are highly prevalent among patients with HFrEF.\(^1\) In the EMPEROR-Preserved (Emaprilolzol Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) trial of emaprilolzol 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.\(^1\) Similarly, in the PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) trial of sacubitril/valsartan in HFrEF (LVEF \(\geq 45\%\)), 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.\(^9,12\) 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 HFrEF. 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 HFrEF 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).\(^20\) 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.\(^18\) 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.\(^1\) 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.\(^6\) 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...
Finerenone in patients with CKD and T2D with and without HF in FIDELIO-DKD

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 enrollment); 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, HFrEF, or HFrEF, further insight may be provided by future analyses of data from the FIDELIO-DKD and FIGARO-DKD echocardiography substudies. 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 FINEARHTS-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.

Supplementary Information

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

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