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Finerenone in Mild to Severe Chronic Kidney Disease and Type 2 Diabetes: a FIDELITY Subgroup Analysis in Patients With Heart Failure

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Introduction

- Patients with chronic kidney disease (CKD), type 2 diabetes (T2D), and heart failure (HF) have a very high cardiorenal risk.[1]
- Finerenone, a potent and selective, orally administered, non-steroidal mineralocorticoid receptor antagonist (MRA), slowed progression of CKD and reduced the risk of cardiovascular outcomes vs placebo in patients with CKD and T2D in the FIDELIO-DKD (NCT02540993, N=5674) and FIGARO-DKD (NCT02545049, N=7352) randomized phase III trials.[2,3]
  - Incidence of hyperkalemia was higher with finerenone vs placebo; however, the incidence of discontinuation due to this adverse event was low (FIDELIO-DKD 2.3%, FIGARO-DKD 1.2%).[2,3]
- The FIDELITY analysis evaluated the efficacy and safety of finerenone, across the spectrum of patients with CKD and T2D, including findings from the FIDELIO-DKD and FIGARO-DKD phase III clinical trials.
- In the overall population, the FIDELITY analysis showed that finerenone significantly reduced the risk of cardiovascular (CV) morbidity and mortality by 14% vs placebo (hazard ratio [HR]=0.86; 95% confidence interval [CI] 0.78–0.95), with a number needed to treat (NNT) of 46 at 3 years to prevent a CV outcome (95% CI 29–109).
- This analysis also found a significant reduction in the risk of CKD progression of 23% with finerenone vs placebo (HR=0.77; 95% CI 0.67–0.88), and an NNT of 60 at 3 years to prevent a kidney outcome (95% CI 38–142).
- This FIDELITY sub-study analyzed the effects of finerenone in patients with and without a history of HF at baseline.

Objectives

- To evaluate the efficacy and safety of finerenone across the spectrum of patients with CKD associated with T2D and to provide insights into the relationship between CKD stage and the effects of finerenone on composite cardiovascular- and kidney-specific endpoints.

Methods

Study Design

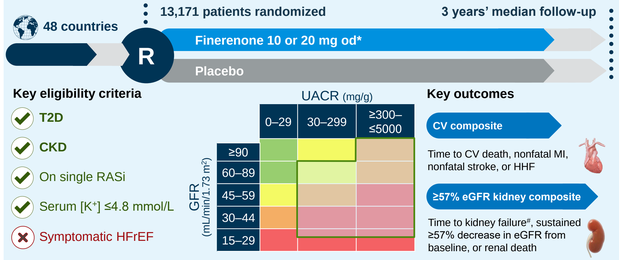
- FIDELITY is a prespecified pooled analysis of FIDELIO-DKD[2] and FIGARO-DKD.[3]
- Inclusion criteria for FIDELIO-DKD and FIGARO-DKD have been previously reported.[2–5] In brief, patients were ≥18 years of age, with CKD and T2D, and were treated with optimized renin–angiotensin system (RAS) blockade therapy.
- Key exclusion criteria included symptomatic chronic HF with reduced ejection fraction or recent HF hospitalization (HHF).
- Patients were randomized 1:1 to finerenone or placebo (**Figure 1**).
- The primary endpoint was a CV composite of time to CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. A composite kidney outcome was also reported.
- Safety was assessed by investigator-reported adverse events.

Results

Patients

- 13,171 patients were randomized to either finerenone or placebo.
- Of the 13,026 eligible patients, 5936 (46%) had a history of CV disease and 1007 (7.7%) had a history of HF at baseline (**Table 1**).
- At baseline, patients had well-controlled blood pressure and HbA1c. Most patients were using CV medications and around 7% were using GLP-1R agonists and SGLT-2 inhibitors (**Table 1**).

Figure 1. Study design



*10 mg if screening eGFR 25–<60 mL/min/1.73 m²; 20 mg if ≥60 mL/min/1.73 m², up-titration encouraged from month 1 if serum [K+] ≤4.8 mEq/L and eGFR stable; #kidney failure defined as either ESKD (initiation of chronic dialysis for ≥90 days or kidney transplant) or sustained decrease in eGFR <15 mL/min/1.73 m² eGFR, estimated GFR; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; [K+], potassium concentration; od, once daily; RASi, renin–angiotensin system inhibitor.

Efficacy Outcomes

- Finerenone significantly reduced the risk of the first hospitalization for HF by 22% vs placebo (HR=0.78; 95% CI 0.66–0.92; **Figure 2A**).
- In this HF subanalysis, finerenone reduced the risk of the composite outcome of CV death and first hospitalization for HF by 17% vs placebo (HR 0.83; CI 95% 0.74–0.93; **Figure 2B**).
- The risk of total HHF was reduced by 21% (HR=0.79; 95% CI 0.64–0.96; **Figure 2C**).
- The risk of the composite outcome of CV death and total HHF was reduced by 18% vs placebo (HR=0.82; 95% CI 0.72–0.95; **Figure 2D**).
- The effects of finerenone on the HF outcomes were similar among the estimated glomerular filtration rate (eGFR) and urine albumin-to-creatine ratio (UACR) subgroup (**Figure 3**).
- Similarly, finerenone reduced the risk of the composite outcome of time to CV death and first hospitalization for HF vs placebo, irrespective of eGFR and UACR category (**Figure 4**).

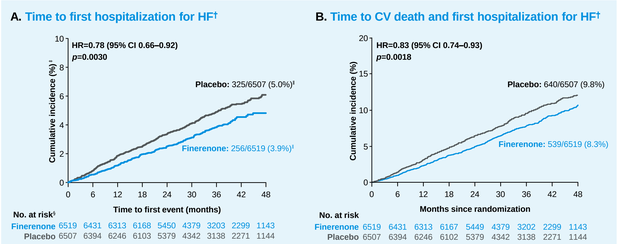
Table 1. Baseline characteristics and medication history

Characteristic	Total (n=13,026)
Age, years	65
Male, %	70
Duration of T2D, years	15.4
HbA1c, %	7.7
SBP/DBP, mmHg	**137/76**
History of CV disease, n (%)	**5935 (46)**
History of HF, n %	**1007 (7.7)**
Serum [K+], mmol/L	4.4

Medication history, n (%)	Total (n=13,026)
CV medications	
RASi	**13,003 (100)**
Statins	**9399 (72)**
Beta-blockers	6504 (50)
Calcium antagonists	7358 (57)
Diuretics	6710 (52)
Glucose-lowering therapies	12,720 (98)
Metformin	7557 (58)
Insulin	7630 (59)
GLP-1RAs	**944 (7.2)**
SGLT-2is	**877 (6.7)**

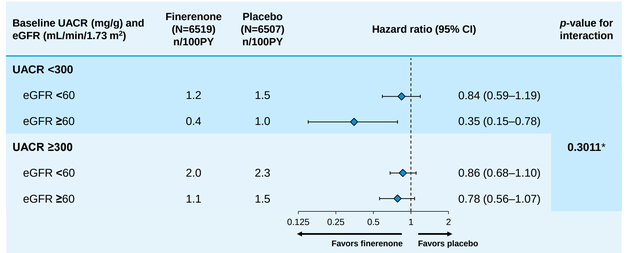
Data are mean unless otherwise stated
CV, cardiovascular; DBP, diastolic blood pressure; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HF, heart failure; RASi, renin-angiotensin system inhibitor; SBP, systolic blood pressure; SGLT-2, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes.

Figure 2. Kaplan-Meier plots showing time to first hospitalization (A), time to CV date and first hospitalization for HF (B), time to total HHF (first and recurrent; C), and time to CV death and total HHF (first and recurrent; D)



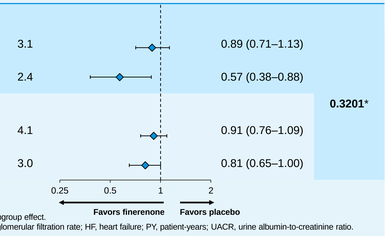
†First hospitalization for HF defined as first event after randomization; ‡cumulative incidence calculated by Aalen–Johansen estimator using deaths due to other causes as competing risk; §at-risk subjects were calculated at start of time point; ¶number of patients with an event over a median of 3.0 years of follow-up; #Cumulative incidence based on mean cumulative function.
CI, confidence interval; CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio.

Figure 3. Time to first hospitalization for HF across the eGFR and UACR spectrum



*Typically, a *p*-value <0.1 indicates a statistically significant subgroup effect
CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; PY, patient-years; UACR, urine albumin-to-creatinine ratio.

Figure 4. Time to CV death and first hospitalization for HF across the eGFR and UACR spectrum



*Typically, a *p*-value <0.1 indicates a statistically significant subgroup effect.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; PY, patient-years; UACR, urine albumin-to-creatinine ratio.

Conclusion

- In the FIDELITY prespecified pooled analysis, in patients with CKD stage 1–4 with moderate-to-severely elevated albuminuria (UACR ≥30 mg/g), well-controlled SBP and HbA1c, treated with optimized RAS blockade:
  - Finerenone reduced the risk of first hospitalization for HF by 22% (HR 0.78; 95% CI 0.66–0.92)
  - Finerenone reduced the risk of hospitalization for HF and CV death by 17% (HR 0.83; 95% CI 0.74–0.93)
  - Finerenone reduced hospitalization for HF and CV death, irrespective of eGFR and UACR category

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