The effect of finerenone on the incidence of hypokalemia in patients with type 2 diabetes and chronic kidney disease – A FIDELITY analysis

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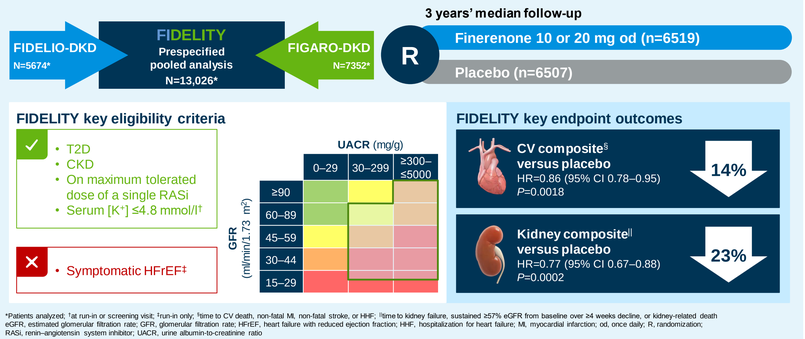
Introduction

- Hypokalemia (serum potassium concentration [K^+] <3.5 mmol/l) is a risk factor for increased adverse cardiovascular (CV) and kidney events[1–5]
- Occurrence of hypokalemia (12–18%) has been shown to be at a similar rate to hyperkalemia (14–20%) in patients with chronic kidney disease (CKD)[1]
  - In patients with CKD, the adverse CV and mortality outcomes are higher in those with serum [K^+] <4.0 mmol/l[2–4,6–9]
  - However, much attention is focused on hyperkalemia in CKD, with hypokalemia less recognized or effectively treated[1–6]
- Mineralocorticoid receptor antagonists (MRAs), in combination with renin–angiotensin system inhibitors (RASi), have demonstrated cardiorenal benefits in patients with CKD,[10–13] and a reduced rate of hypokalemia events was reported in patients with heart failure (HF)[14,15]
  - Finerenone, a nonsteroidal MRA, has shown a lower risk of treatment-emergent hyperkalemia than steroidal MRAs in patients with HF and CKD[16]
  - Therefore, potassium management with MRAs may benefit some patients with CKD who are at risk of lower serum [K^+] levels
- This FIDELITY exploratory analysis examined the incidence and effect of hypokalemia in patients with type 2 diabetes (T2D) and CKD treated with finerenone, a nonsteroidal MRA, versus placebo

Methods

- In FIDELITY,[12] a pooled analysis of the FIDELIO-DKD[10] (NCT02540993) and FIGARO-DKD[11] trials (NCT02545049), patients with CKD and T2D who were optimally treated with RASi were randomized to finerenone or placebo (Figure 1)
- Key outcomes in this analysis included serum potassium levels <4.0 or <3.5 mmol/l, a CV composite outcome (CV death, non-fatal myocardial infarction [MI], non-fatal stroke, or hospitalization for HF), and an arrhythmia composite outcome (new diagnosis of atrial fibrillation/atrial flutter, hospitalization due to arrhythmia, or sudden cardiac death)

Figure 1. FIDELITY pooled analysis study design

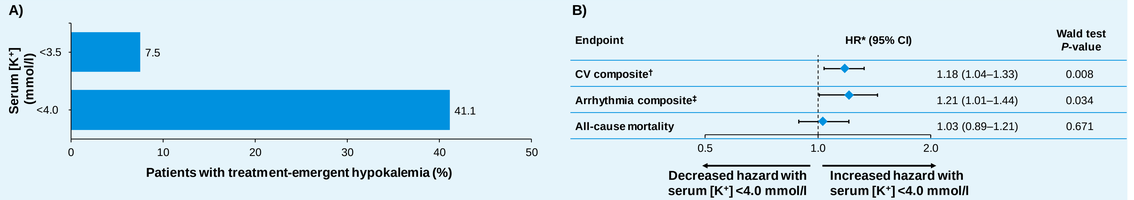


*Patients analyzed; †at run-in or screening visit; ‡run-in only; §time to CV death, non-fatal MI, non-fatal stroke, or HHF; ‖time to kidney failure, sustained ≥57% eGFR from baseline over ≥4 weeks decline, or kidney-related death
eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MI, myocardial infarction; od, once daily; R, randomization; RASi, renin–angiotensin system inhibitor; UACR, urine albumin-to-creatinine ratio

Results

- Of 13,026 patients enrolled in the study, data was available for 12,859 patients
- Of 12,859 patients, 41.1% and 7.5% experienced a treatment-emergent potassium level of <4.0 and <3.5 mmol/l, respectively (Figure 2A)
- Hazard ratios (HR) for the CV and arrhythmia composite outcomes in patients with baseline serum [K^+] <4.0 mmol/L were increased versus patients with baseline serum [K^+] ≥4.0 mmol/L (Figure 2B). Compared with placebo, finerenone reduced the incidence of potassium levels <4.0 mmol/l (33.9% versus 48.4%) and <3.5 mmol/l (4.8% versus 10.2% [Figure 3])
- Risk of the CV and arrhythmia composite outcomes was reduced with finerenone by 14% (HR=0.86; 95% confidence interval [CI] =0.78–0.95) and 13% (HR=0.87; 95% CI=0.76–1.00), respectively, versus placebo (Figure 4)

Figure 2. Incidence of treatment-emergent hypokalemia (A) and safety outcomes (baseline serum [K^+] <4.0 mmol/L versus ≥4.0 mmol/L) (B)



*HRs are based on stratified cox models including treatment and baseline serum [K^+] category; †time to CV death, non-fatal MI, non-fatal stroke, or HHF; ‡new diagnosis of AF, hospitalization due to arrhythmia, or sudden cardiac death
AF, atrial fibrillation/atrial flutter; CI, confidence intervals; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction

Figure 3. Incidence of treatment-emergent hypokalemia by serum [K^+] level

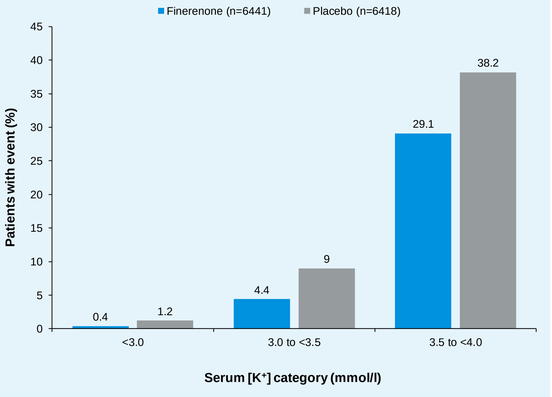
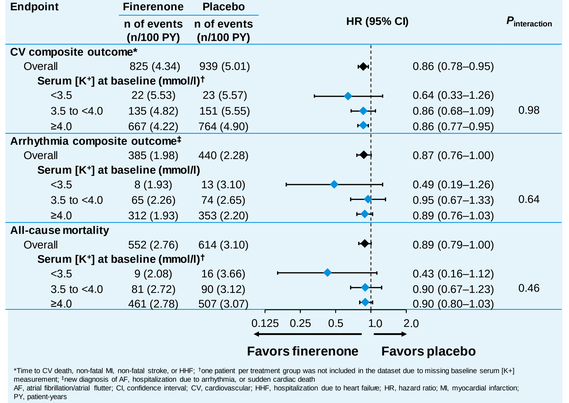


Figure 4. Outcomes by baseline serum [K^+]



*Time to CV death, non-fatal MI, non-fatal stroke, or HHF; †one patient per treatment group was not included in the dataset due to missing baseline serum [K+] measurement; ‡new diagnosis of AF, hospitalization due to arrhythmia, or sudden cardiac death
AF, atrial fibrillation/atrial flutter; CI, confidence interval; CV, cardiovascular; HHF, hospitalization due to heart failure; HR, hazard ratio; MI, myocardial infarction; PY, patient-years

Discussion

- In patients with T2D across a broad spectrum of CKD stages and severity, with well-controlled blood pressure, and treated with a RASi at the maximum tolerated dose:
  - Finerenone reduced the incidence of treatment-emergent hypokalemia and lowered the risk of CV and arrhythmia outcomes versus placebo irrespective of baseline serum [K^+]
  - Finerenone offered protection against CV outcomes and a consistent positive trend for arrhythmia outcomes and all-cause mortality across baseline serum [K^+] subgroups

Summary

- The FIDELITY prespecified pooled analysis of FIDELIO-DKD and FIGARO-DKD showed significant risk reductions in CV and kidney outcomes with finerenone
- Patients with CKD and T2D experienced treatment-emergent hypokalemia (defined as serum [K^+] <3.5 and <4.0 mmol/l) despite optimal RASi treatment
- Patients with baseline serum [K^+] <4.0 mmol/l were at increased risk for adverse CV outcomes compared to >4.0 mmol/l

Conclusions

- Low serum potassium levels are common in patients with CKD and T2D despite treatment with RASi
- Finerenone was associated with protection from hypokalemia and reduction in the risk of CV and arrhythmia outcomes

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