Poster No.: SA-PO274

Cardiorenal outcomes with finerenone in Asian patients with chronic kidney disease and type 2 diabetes: *Post hoc* analysis from FIDELIO-DKD

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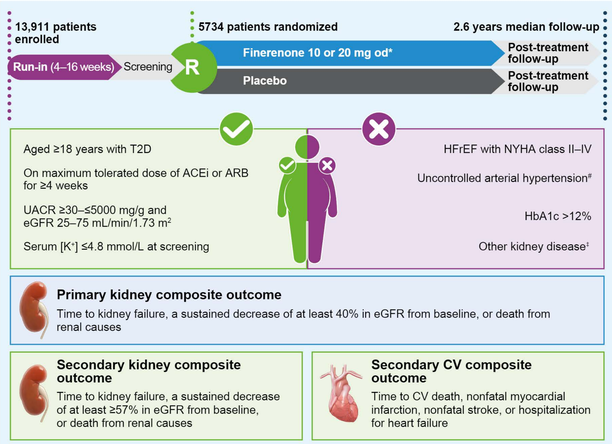
1. Background

- Chronic kidney disease (CKD) is a common complication of type 2 diabetes (T2D)[1]
- Data suggest that Asian patients with T2D have a higher prevalence of CKD than non-Asian patients[2,3] and tend to experience more rapid deterioration in their kidney function than White patients[2,4]
- In the phase III FIDELIO-DKD trial (FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease; NCT02540993), finerenone significantly improved cardiorenal outcomes in patients with CKD and T2D[5]
- This *post hoc* analysis of FIDELIO-DKD data was conducted to explore the cardiorenal effects of finerenone in patients from Asian regions

2. Study design and methods

- The FIDELIO-DKD trial randomized 5734 patients from 48 countries. Adult patients with T2D, with either urine albumin-to-creatinine ratio (UACR) ≥30–<300 mg/g, an estimated glomerular filtration rate (eGFR) ≥25–<60 mL/min/1.73 m^2, and a history of diabetic retinopathy, or UACR ≥300–≤5000 mg/g and an eGFR ≥25–<75 mL/min/1.73 m^2, were randomized (1:1) to finerenone or placebo. All patients were treated with optimized renin–angiotensin system blockade[5] (**Figure 1**)
- For this analysis, the Asian subgroup included patients randomized from sites in 10 Asian countries and territories
- The key inclusion and exclusion criteria for FIDELIO-DKD, and the primary kidney composite endpoint and secondary kidney and cardiovascular (CV) composite endpoints are described in **Figure 1**

Figure 1. FIDELIO-DKD study design, key inclusion and exclusion criteria and efficacy outcomes



*10 mg if screening eGFR <60 mL/min/1.73 m^2; 20 mg if eGFR ≥60 mL/min/1.73 m^2, up-titration was encouraged from month 1 if serum [K$^+$] ≤4.8 mmol/L and eGFR was stable; #mean sitting SBP ≥170 mmHg or mean sitting DBP ≥110 mmHg at the run-in visit, or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the screening visit; ‡known significant nondiabetic kidney disease, including clinically relevant renal artery stenosis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; [K$^+$], potassium concentration; NYHA, New York Heart Association; od, once daily; R, randomization; SBP, systolic blood pressure; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

2.1. Statistical analysis

- Efficacy analyses were performed in the full analysis set (all randomized patients without critical Good Clinical Practice violations)
- Safety analyses were performed in the safety analysis set (all randomized patients without critical Good Clinical Practice violations who took at least one dose of study drug)
- Time-to-event treatment outcomes (kidney and CV composite endpoints) were analyzed using a stratified cox proportional hazards model; results are expressed as hazard ratios (HRs) with corresponding confidence intervals (CIs) and a *p*-value for interaction
- Events were reported from randomization up to the end-of-study visit. Patients without an event were censored at the date of their last contact, with complete information on all components of their respective outcomes

3. Results

3.1. Baseline characteristics

- Of 5674 patients in full analysis set of FIDELIO-DKD, 1327 (23.4%) were from sites in 10 Asian countries and territories
  - Of the Asian subgroup, 665/1327 (50.1%) patients received finerenone
- Median follow-up was 2.7 years for patients in the Asian subgroup and 2.6 years for the patients from the rest of the world (ROW)
- The baseline clinical and demographic characteristics are shown in **Table 1**

Table 1. Baseline characteristics and medications

Characteristic	Asian (n=1327)	ROW (n=4347)
Age, years	63 ± 10	66 ± 9
Sex, male	980 (73.9)	3003 (69.1)
Duration of diabetes, years	15.3 ± 8.4	16.9 ± 8.8
HbA1c, %, (mmol/mol) [mmol/L]	7.5 ± 1.3 (58.5) [9.4]	7.7 ± 1.4 (60.7) [9.7]
Systolic blood pressure, mmHg	134.8 ± 15.1	139.0 ± 4.0
History of CV disease	472 (35.6)	2133 (49.1)
eGFR, mL/min/1.73 m^2	43.5 ± 11.3	44.6 ± 12.9
UACR, mg/g, median (IQR)	978.6 (498.5–1853.3)	809.8 (435.4–1567.3)
[K$^+$], mmol/L	4.3 ± 0.4	4.4 ± 0.5
Baseline medications, n (%)		
ACEis	195 (14.7)	1747 (40.2)
ARBs	1130 (85.2)	2595 (59.7)
Beta blockers	434 (32.7)	2534 (58.3)
Diuretics	398 (30.0)	2816 (64.8)
Statins	897 (67.6)	3318 (76.3)
Potassium-lowering agents	51 (3.8)	85 (2.0)
Glucose-lowering therapies	2059 (98.1)	10,661 (97.6)
Insulin and analogues	766 (57.7)	2871 (66.0)
Biguanides	484 (36.5)	2006 (46.1)
Sulfonamides	392 (29.5)	935 (21.5)
DPP-4 inhibitors	557 (42.0)	965 (22.2)
GLP-1RAs	58 (4.4)	336 (7.7)
SGLT-2is	49 (3.7)	210 (4.8)

All values are either n (%) or mean ± standard deviation, unless specified otherwise.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP 1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; IQR, interquartile range; [K$^+$], potassium concentration; ROW, rest of the world; SGLT-2i, sodium glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

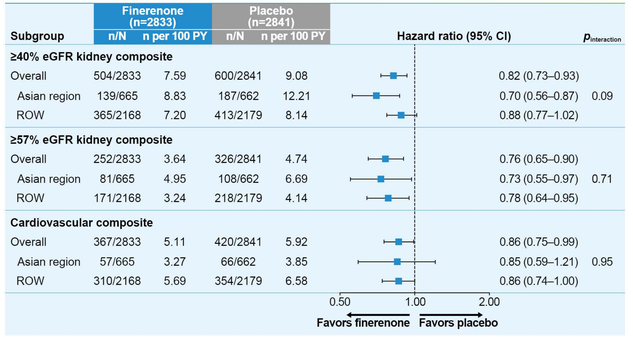
3.2. Primary outcomes

- The beneficial effect of finerenone observed for the ≥40% eGFR kidney composite outcome versus placebo was not modified in the Asian subgroup
  - Although a numerical difference can be seen in the HRs, the difference was not statistically significant (Asia: HR=0.70; 95% CI 0.56–0.87; ROW: HR=0.88; 95% CI 0.77–1.02; $p_{interaction}$=0.09) (**Figure 2**)

3.3. Secondary outcomes

- The beneficial effect of finerenone on the ≥57% eGFR kidney composite outcome versus placebo was not modified in the Asian subgroup
  - Although a numerical difference was observed in the HRs, the difference was not statistically significant (Asia: HR=0.73; 95% CI 0.55–0.97; ROW: HR=0.78; 95% CI 0.64–0.95; $p_{interaction}$=0.71) (**Figure 2**)
- Additionally, the beneficial effect of finerenone on the cardiovascular composite outcome versus placebo was not modified in the Asian subgroup
  - A numerical difference was observed in the HRs, however, this difference was not statistically significant (Asia: HR=0.85; 95% CI 0.59–1.21; ROW: HR=0.86; 95% CI 0.74–1.00; $p_{interaction}$=0.95) (**Figure 2**)

Figure 2. Kidney and cardiovascular outcomes in the Asian region versus ROW



CI, confidence interval; eGFR, estimated glomerular filtration rate; PY, patient-years; ROW, rest of the world

3.4. Safety outcomes

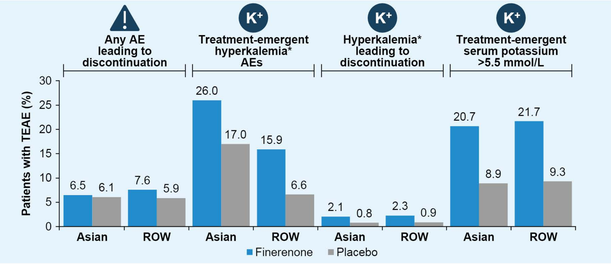
- Overall, the safety profile of finerenone was generally similar in patients from the Asian region and in patients from ROW (**Table 2**)
  - Adverse events (AEs) leading to discontinuation of study drug were low across the finerenone and placebo subgroups (**Figure 3**)
  - The incidence of investigator-reported treatment-emergent hyperkalemia AEs was higher in patients treated with finerenone compared with placebo (**Figure 3**)
  - The incidence of investigator-reported treatment-emergent hyperkalemia AEs was higher in the Asian subgroup (26.0% and 17.0% for finerenone and placebo, respectively) compared with patients from ROW (15.9% vs 6.6%, respectively) (**Figure 3**)
  - However, rates of hyperkalemia leading to study drug discontinuation remained low in patients in the Asian subgroup (2.1% vs 0.8% for finerenone and placebo, respectively) and in patients from ROW (2.3% and 0.9%, respectively) (**Figure 3**)
  - In the Asian subgroup, 20.7% of finerenone-treated and 8.9% of placebo recipients had a treatment-emergent serum potassium >5.5 mmol/L, and in patients from ROW, 21.7% and 9.3% had a treatment-emergent serum potassium >5.5 mmol/L for finerenone and placebo, respectively (**Figure 3**)

Table 2. Overall treatment-emergent AEs

Characteristic	Asian region		ROW	
	Finerenone (n=665)	Placebo (n=660)	Finerenone (n=2162)	Placebo (n=2171)
Any AE	621 (93.4)	615 (93.2)	1847 (85.4)	1863 (85.8)
Related to study drug	166 (25.0)	125 (18.9)	480 (22.2)	324 (14.9)
Leading to discontinuation of study drug	43 (6.5)	40 (6.1)	164 (7.6)	128 (5.9)
Acute kidney injury	14 (2.1)	18 (2.7)	115 (5.3)	118 (5.4)
Any SAE	233 (35.0)	259 (39.2)	669 (30.9)	712 (32.8)
AE with outcome of death	6 (0.9)	11 (1.7)	25 (1.2)	40 (1.8)

AE, adverse event; ROW, rest of the world, SAE, serious adverse event

Figure 3. Safety outcomes



*Investigator-reported AEs using MedDRA-preferred terms 'blood potassium increased' and 'hyperkalemia'

AE, adverse event; ROW, rest of the world; TEAE, treatment-emergent adverse event

4. Conclusions

- The beneficial effect of finerenone on cardiorenal outcomes in patients from the Asian region are comparable with the results observed in the overall population of FIDELIO-DKD
- These data provide support for the use of finerenone in Asian patients with T2D and CKD to reduce the risk of kidney disease progression and CV events

Acknowledgments

The FIDELIO-DKD trial was funded by Bayer AG. Medical writing assistance was provided by Lauren Wainwright, MSc, of Chameleon Communications International, with funding from Bayer AG.

Disclosures

DK has received personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals Inc. during the conduct of the study; he has received research funding, paid to the Kanazawa Medical University, from Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Ono Pharmaceutical Co., Ltd., and Taisho Pharmaceutical Holdings Co., Ltd. **SDA** has received research support from Abbott Vascular and Vifor International, and personal fees from Abbott Vascular, Bayer, Boehringer Ingelheim, BRAHMS, Cardiac Dimensions, Impulse Dynamics, Novartis, Servier, and Vifor International. **LR** reports receipt of consultancy fees from Bayer. **PR** 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, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, Sanofi, and Vifor. All fees are given to Steno Diabetes Center Copenhagen. **ZHL** reports nothing to disclose. **BWL** reports personal fees and nonfinancial support from Bayer during the conduct of the study; he has received research funding, paid to the Severance Hospital, from Boryung Pharmaceutical Co, Daewoong Pharmaceutical Co, Dong-A ST, Eli Lilly, LG Chem, Novo Nordisk, Sanofi, Handok, and Yuhan Pharma. **CTL** reports nothing to disclose. **CS** is a full-time employee of Bayer PLC, UK. **PK** 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). **RL** and **LW** are full-time employees of Bayer AG, Division Pharmaceuticals, Germany. **AJ** is a full-time employee of Bayer AG, Germany. **BP** reports consultancy fees from 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 Ardelyx, 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 63/045,784).

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Abstract SA-PO274 presented at the American Society of Nephrology 2022, 3–6 November 2022