Su3022

Air pollution exposure and effect of finerenone treatment in patients with chronic kidney disease and type 2 diabetes: A FIDELITY analysis

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Introduction

- Exposure to air pollution is a key environmental contributor to the global burden of cardiovascular (CV) disease[1]
- Particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$) is an important component of air pollution and is independently associated with atherosclerotic CV disease, type 2 diabetes (T2D), chronic kidney disease (CKD), and premature mortality[2–6]
- There is a complex interplay between $PM_{2.5}$ exposure and CV and kidney health,[1,4] highlighting the importance of assessing whether treatments that address cardiometabolic risk can benefit individuals similarly across different $PM_{2.5}$ exposure levels
- In FIDELITY, a prespecified pooled analysis of two phase III trials, finerenone significantly reduced the risk of adverse CV and kidney outcomes compared with placebo in patients with CKD and T2D[7]
- In this FIDELITY post hoc subanalysis, we explored the effect of finerenone on CV and kidney outcomes in participants exposed to varying levels of $PM_{2.5}$ air pollution

Methods

- FIDELITY combined individual patient-level data from the complementary FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) trials, in which patients with CKD and T2D on maximum tolerated doses of renin–angiotensin system blockade were randomized 1:1 to receive finerenone or placebo[7]
- Time-to-event efficacy outcomes in the trials included:
  - A composite CV outcome (CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure)
  - A composite kidney outcome (kidney failure, sustained ≥57% decrease in estimated glomerular filtration rate [eGFR] from baseline over at least 4 weeks, or kidney-related death)
  - A combined composite CV and kidney outcome including all components of the individual composite outcomes
- In this analysis, FIDELITY participants were assigned to annual $PM_{2.5}$ exposure levels based on treatment center location at the time of enrollment into the FIGARO-DKD or FIDELIO-DKD clinical trials; the models used provided accurate $PM_{2.5}$ concentration estimates at a spatial resolution of 1×1-km grids
- The effect of finerenone versus placebo was assessed on the composite outcomes across strata of $PM_{2.5}$ exposure, including ≤ versus > median exposure and quartiles, with patients grouped using the median $PM_{2.5}$ exposure and interquartile range as cutoffs (quartiles: ≤Q1; >Q1 and ≤Q2; >Q2 and ≤Q3; and >Q3); $PM_{2.5}$ was also assessed as a continuous variable

Statistical analysis

- Time-to-event treatment outcomes were analyzed using a stratified Cox proportional hazards model estimated within each level of the subgroup variable; results are expressed as hazard ratios with corresponding 95% confidence intervals (HR [95% CI])
- Event probabilities at 3.5 years were evaluated with $PM_{2.5}$ as a continuous variable using a Cox proportional hazards model; two-slope linear splines used knots at the 1st, 50th, and 99th percentiles of the $PM_{2.5}$ value range
- Efficacy analyses were performed in the full analysis set (FAS), which included all randomized patients without critical Good Clinical Practice violations; the safety analysis included all randomized patients who took ≥1 dose of study drug or placebo

Results

Baseline characteristics

- The FAS included 12,990 patients
- Median $PM_{2.5}$ exposure was 15.7 (interquartile range 9.8–21.2) µg/m³ in the finerenone arm and 15.4 (9.7–20.9) µg/m³ in the placebo arm, with most participants within the 5–25 µg/m³ range
- Baseline characteristics were generally balanced across the $PM_{2.5}$ exposure subgroups; however, mean eGFR and median urine albumin-to-creatinine ratio tended to be higher among patients in with $PM_{2.5}$ exposure above the median, and there were more Asian individuals in these subgroups (**Table 1**)

Table 1. Baseline demographic and clinical characteristics by $PM_{2.5}$ exposure ≤ versus > the median

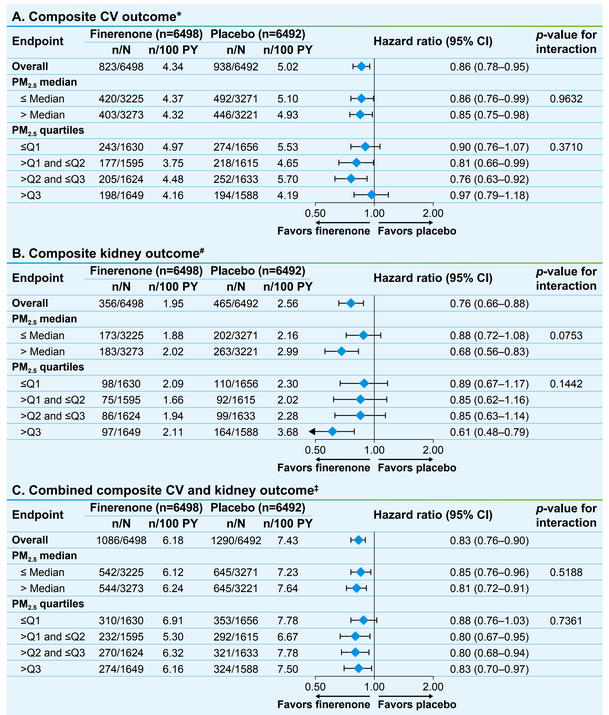
Characteristics	$PM_{2.5}$ exposure			
	≤ Median		> Median	
	Finerenone (n=3225)	Placebo (n=3271)	Finerenone (n=3273)	Placebo (n=3221)
Age, years, mean ± SD	65.8 ± 9.2	66.1 ± 9.5	63.6 ± 9.4	63.5 ± 9.6
Sex, male, n (%)	2300 (71.3)	2387 (73.0)	2163 (66.1)	2208 (68.6)
Race				
White	2404 (74.5)	2405 (73.5)	2045 (62.5)	2015 (62.6)
Black/African American	225 (7.0)	241 (7.4)	26 (0.8)	28 (0.9)
Asian	443 (13.7)	477 (14.6)	970 (29.6)	970 (30.1)
Other*	153 (4.7)	148 (4.5)	232 (7.1)	208 (6.5)
Systolic blood pressure, mmHg, mean ± SD	137.2 ± 14.7	137.3 ± 14.7	136.4 ± 13.6	136.1 ± 13.8
BMI, kg/m², mean ± SD	32.3 ± 6.4	32.0 ± 6.1	30.4 ± 5.5	30.6 ± 5.7
HbA1c, %, mean ± SD	7.7 ± 1.3	7.6 ± 1.3	7.8 ± 1.4	7.8 ± 1.4
Duration of diabetes, years, mean ± SD	16.3 ± 9.0	16.0 ± 8.9	14.7 ± 8.4	14.7 ± 8.4
Serum potassium, mmol/l, mean ± SD	4.3 ± 0.4	4.3 ± 0.4	4.4 ± 0.5	4.4 ± 0.5
eGFR, mL/min/1.73 m², mean ± SD	54.8 ± 20.6	54.97 ± 20.3	60.1 ± 22.2	60.4 ± 22.8
UACR, mg/g, median (Q1–Q3)	444.7 (156.3–1012.7)	453.9 (152.0–1050.2)	596.3 (247.5–1236.0)	588.2 (262.9–1322.7)
Current smoker, n (%)	476 (14.8)	462 (14.1)	583 (17.8)	561 (17.4)
History of CVD, n (%)	1499 (46.5)	1549 (47.4)	1474 (45.0)	1406 (43.7)

*Other includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, not reported, and multiple categories.
Patient demographics are reported for the full analysis set, which included all 12,990 randomized patients.
BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; $PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 µm; Q, quartile; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.

Time to CV and kidney events

- There were fewer composite CV events with finerenone versus placebo across $PM_{2.5}$ exposures ≤ versus > the median ($p_{interaction}$=0.96) and across $PM_{2.5}$ exposure quartiles ($p_{interaction}$=0.37) (**Figure 1A**)
- There were fewer composite kidney outcomes with finerenone compared with placebo across the strata of $PM_{2.5}$ exposure ($p_{interaction}$=0.08 for $PM_{2.5}$ ≤ vs > the exposure median and 0.14 for $PM_{2.5}$ quartiles) (**Figure 1B**)
- Time to the combined composite outcome showed a similar pattern, with finerenone providing benefit over placebo across the strata ($p_{interaction}$=0.52 for ≤ vs > the $PM_{2.5}$ exposure median and 0.74 for quartiles) (**Figure 1C**)

Figure 1. Effect of finerenone on time to composite CV and kidney outcomes by $PM_{2.5}$ subgroup (FAS)

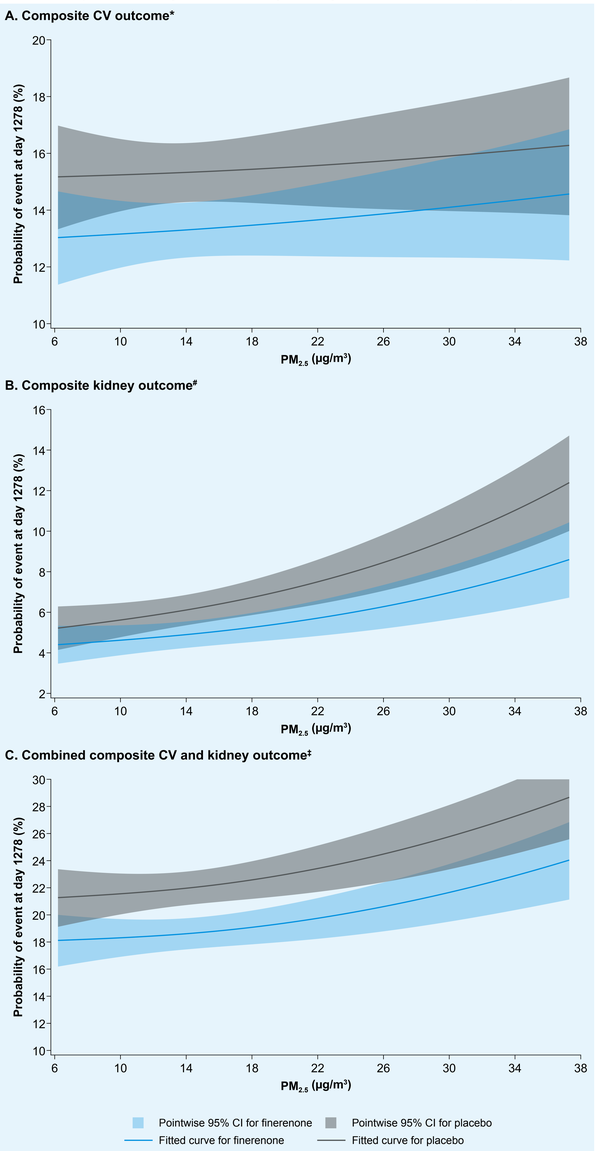


Events considered from randomization to end-of-study visit and adjudicated by an independent adjudication committee. Interaction *p* values are based on a stratified Cox proportional hazards model including treatment, subgroup, and treatment-by-subgroup interaction
*CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF; †kidney failure, sustained ≥57% decrease in eGFR from baseline over at least 4 weeks, or kidney-related death; ‡CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF; kidney failure, sustained ≥57% decrease in eGFR from baseline over at least 4 weeks, or kidney-related death.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HHF, hospitalization for heart failure; $PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 µm; PY, patient-years; Q, quartile.

Probability of CV and kidney events over 3.5 years

- When considered as a continuous variable, $PM_{2.5}$ exposure was associated with increasing CV event rates over 3.5 years in both the placebo and finerenone arms; however, event probability was consistently lower in the finerenone arm than in the placebo arm (**Figure 2A**)
- Similar patterns of increasing events in both treatment arms and finerenone benefit were seen with the composite kidney outcome (**Figure 2B**) and the combined composite outcome (**Figure 2C**)

Figure 2. Effect of finerenone on the predicted probability of a composite CV and/or composite kidney event at 3.5 years by continuous $PM_{2.5}$ (FAS)

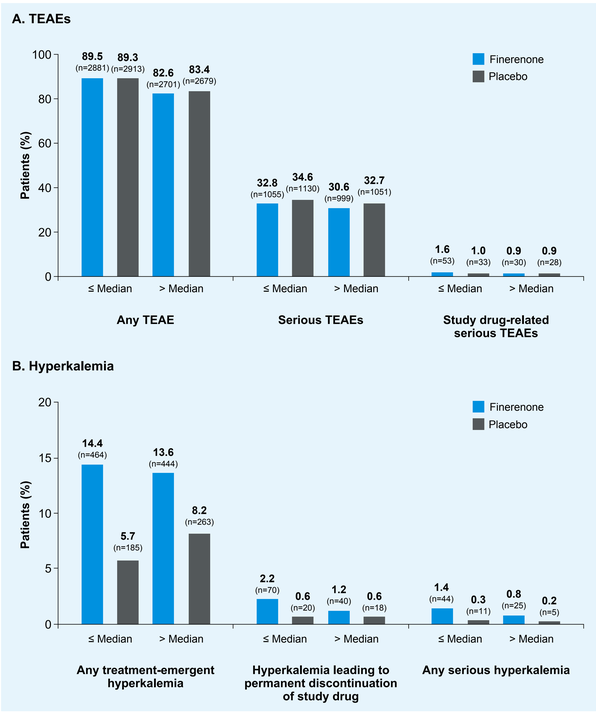


Cox proportional hazards model fitted with covariates treatment, $PM_{2.5}$, study, region, albuminuria and eGFR at screening, and CVD history. Splines used knots at 1st, 50th, and 99th percentiles of $PM_{2.5}$ value. Values of $PM_{2.5}$ were truncated between the 5th and 95th percentiles.
*CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF; †kidney failure, sustained ≥57% decrease in eGFR from baseline over at least 4 weeks, or kidney-related death; ‡CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF; kidney failure, sustained ≥57% decrease in eGFR from baseline over at least 4 weeks, or kidney-related death.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HHF, hospitalization for heart failure; $PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 µm.

Safety

- The finerenone safety profile was generally similar between treatment arms and comparable across $PM_{2.5}$ quartiles and across $PM_{2.5}$ exposures ≤ versus > the median (**Figure 3A**)
- The incidence of serious hyperkalemia leading to hospitalization was low in the finerenone and placebo arms, irrespective of $PM_{2.5}$ exposure (**Figure 3B**)

Figure 3. Incidence of TEAEs and hyperkalemia for finerenone and placebo by $PM_{2.5}$ exposure ≤ versus > the median



$PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 µm; TEAE, treatment-emergent adverse event.

Conclusions

- Increasing $PM_{2.5}$ exposure levels were associated with greater risks of CV and kidney events in the FIDELITY population
- Finerenone lowered these risks irrespective of $PM_{2.5}$ exposure levels and may be particularly beneficial in individuals exposed to higher air pollution levels

Acknowledgments

The FIDELIO-DKD and FIGARO-DKD studies and prespecified pooled FIDELITY analysis were funded by Bayer AG. The authors and study sponsor are indebted to the study participants and their families, as well as the investigators and sites participating in the studies. Medical writing and editorial assistance were provided by Alison McTavish, MSc (HCG), with funding from Bayer AG. Finally, our esteemed steering committee member George Bakris passed away in June 2024 and will be remembered for his passion for science and patient care.

References

1. Rajagopalan S, Landrigan PJ. *N Engl J Med* 2021;385:1881–1892.
2. Visseren FLJ, *et al. Rev Esp Cardiol* (*Engl Ed*) 2022;75:429.
3. Brook RD, *et al. Circulation* 2010;121:2331–2378.
4. Al-Kindi SG, *et al. Nat Rev Cardiol* 2020;17:656–672.
5. Rajagopalan S, *et al. J Am Coll Cardiol* 2018;72:2054–2070.
6. Rajagopalan S, *et al. Lancet Diabetes Endocrinol* 2024;12:196–208.
7. Agarwal R, *et al. Eur Heart J* 2022;43:474–484.

Disclosures

SAK has nothing to disclose. **ZC** has no relevant financial or nonfinancial relationships, interests, or affiliations to disclose in relation to this publication. **JED** has nothing to disclose. **YMKF** was a full-time employee at Bayer U.S. LLC at the time of data analysis. He is now a full-time employee of Alexion AstraZeneca Rare Disease Unit. **GF** reports lecture 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. **PR** reports personal fees from Bayer during the conduct of the study. He has received research support and personal fees from AstraZeneca, Bayer, and Novo Nordisk, and personal fees from Astellas Pharma, Abbott, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, Novartis, Sanofi, and Vifor Pharma; all fees are given to Steno Diabetes Center Copenhagen. **KR** is a full-time employee of Bayer AG. **PRVOS** has nothing to disclose. **CS** is a full-time employee of Bayer. **ZZ** is employed by Bayer US LLC. SR reports consultancy and scientific advisory board participation with Bayer and Novo Nordisk.

Poster Su3022 presented at the American Heart Association Scientific Sessions 2024; November 16–18, 2024; Chicago, IL, USA