Poster 16-LB

Effects of Finerenone in Patients with CKD and T2D are Independent of HbA1c at Baseline, HbA1c Variability and Duration of Diabetes

Janet B. McGill,[1] Rajiv Agarwal,[2] Stefan D. Anker,[3] George L. Bakris,[4] Gerasimos Filippatos,[5] Bertram Pitt,[6] Luis M. Ruilope,[7–9] Andreas L. Birkenfeld,[10,11] M. Luiza Caramori,[12] Meike Brinker,[13] Amer Joseph,[14] Andrea Lage,[15] Robert Lawatscheck,[16] Charlie Scott,[17] Peter Rossing,[18,19]

[1]Division of Endocrinology, Metabolism and Lipid Research, Washington University School of Medicine, St. Louis, MO, USA; [2]Richard L. Roudebush VA Medical Center and Indiana University, Indianapolis, IN, USA; [3]Department of Cardiology (CVK), and Berlin Institute of Health Center for Regenerative Therapies, German Centre for Cardiovascular Research Partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany; [4]Department of Medicine, University of Chicago Medicine, Chicago, IL, USA; [5]National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Athens, Greece; [6]Department of Medicine, University of Michigan School of Medicine, Ann Arbor, MI, USA; [7]Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12, Madrid, Spain; [8]CIBER-CV, Hospital Universitario 12 de Octubre, Madrid, Spain; [9]Faculty of Sport Sciences, European University of Madrid, Madrid, Spain; [10]Department of Diabetology, Endocrinology and Nephrology, University Clinic, Tübingen, Germany; [11]Institute for Diabetes Research and Metabolic Diseases of Helmholtz Center Munich, University of Tübingen, Tübingen, Germany; [12]Department of Medicine and Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA; [13]Cardiology and Nephrology Clinical Development, Bayer AG, Wuppertal, Germany; [14]Research and Development, Clinical Development Operations, Bayer AG, Wuppertal, Germany; [15]Cardiology and Nephrology Clinical Development, Bayer SA, São Paulo, Brazil; [16]Clinical Research, Bayer AG, Berlin, Germany; [17]Data science and analytics, Bayer PLC, Reading, United Kingdom; [18]Steno Diabetes Center Copenhagen, Herlev, Denmark; [19]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

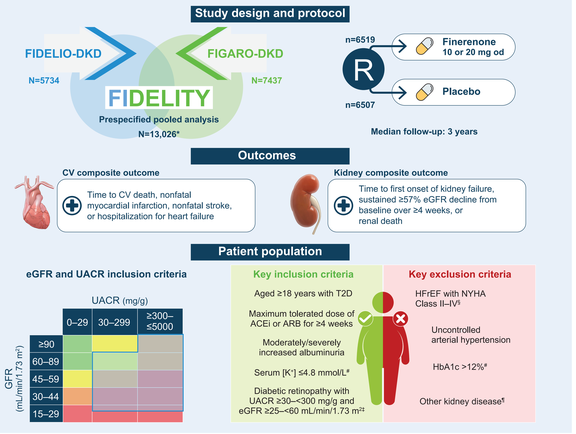
1. Introduction

- Chronic kidney disease (CKD) is a common complication of type 2 diabetes (T2D)[1]
- FIDELITY is a prespecified pooled analysis of the FIDELIO-DKD and FIGARO-DKD studies forming the largest cardiorenal outcomes program in patients with CKD and T2D to date[2]
- In the FIDELITY analysis finerenone reduced the risk of cardiovascular (CV) and kidney outcomes without affecting glycated hemoglobin (HbA1c) in patients with CKD and T2D[3,4]
- The aim of this FIDELITY post hoc analysis was to evaluate the effect of finerenone by baseline HbA1c categories, HbA1c variability (first year of treatment), and diabetes duration

2. Methods

- This analysis combines individual patient-level data from the FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) phase III clinical trials. The designs and results of these studies have been published previously[5,6]
- Study design, efficacy outcomes, and inclusion/exclusion criteria for FIDELITY are shown in (**Figure 1**)
- Cox proportional-hazards models were used to investigate the relationships between HbA1c categories, HbA1c variability (in the first year of treatment), diabetes duration, and CV/renal outcomes
  - HbA1c variability was defined as the mean absolute residual of HbA1c measurements to the line connecting index HbA1c with closing HbA1c, reflecting both increases and decreases in HbA1c to show the change from the 'expected' values between two timepoints
  - This measure therefore assesses how the magnitude of change in HbA1c over time contributes to the risk of outcomes

Figure 1. Study design, efficacy outcomes, and patient population



*Prospective exclusion of 145 patients; #at the run-in or screening visit; ‡FIDELIO-DKD only; ¶run-in only; ¶known nondiabetic kidney disease, including clinically relevant renal artery stenosis

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

3. Results

- Among the 13,026 patients included in the analysis, mean baseline HbA1c was 7.7% and diabetes duration was 15.4 years
  - Patients were stratified by baseline HbA1c quartiles (**Table 1**) and diabetes duration quartiles (≤9.1 years, >9.1 and ≤15.1 years, >15.1 and ≤20.2 years, >20.2 years)
- Patients in higher baseline HbA1c quartiles had longer diabetes duration and more diabetes-related complications at baseline (**Table 1**)
  - The proportion of females in this group was higher than the other quartiles and they were more likely to have a higher UACR
- History of CV disease was similar across the diabetes duration quartiles

Table 1. Patient characteristics by HbA1c quartiles at baseline

Characteristic	≤6.7% (n=3471)	>6.7 and ≤7.5% (n=3245)	>7.5 and ≤8.5% (n=3118)	>8.5% (n=3170)
Age (years), mean	65.7	65.6	65.0	62.6
Sex (female), n (%)	903 (26.0)	891 (27.5)	916 (29.4)	1216 (38.4)
Duration of diabetes (years), mean ± SD	12.80 ± 8.6	15.39 ± 8.6	16.95 ± 8.7	16.68 ± 8.2
HbA1c (%), mean ± SD	6.2 ± 0.4	7.1 ± 0.2	8.0 ± 0.3	9.6 ± 0.9
BMI (kg/m²), mean ± SD	30.5 ± 6.1	30.9 ± 5.8	31.5 ± 5.8	32.4 ± 6.3
Waist-hip ratio, mean ± SD	0.99 ± 0.1	1.00 ± 0.1	1.00 ± 0.1	1.01 ± 0.1
Systolic blood pressure (mmHg), mean ± SD	135.7 ± 14.1	137.1 ± 14.6	137.1 ± 14.3	137.2 ± 13.8
History of CV disease, n (%)	1546 (44.5)	1462 (45.1)	1475 (47.3)	1443 (45.5)
History of diabetic retinopathy, n (%)	957 (27.6)	1203 (37.1)	1338 (42.9)	1446 (45.6)
eGFR (mL/min/1.73 m²), mean ± SD	55.9 ± 20.7	56.5 ± 21.0	57.0 ± 21.6	61.2 ± 23.1
UACR (mg/g), median (IQR)	479 (175–1071)	496 (184–1119)	497 (188–1124)	599 (250–1325)
Serum potassium (mmol/L), mean ± SD	4.31 ± 0.5	4.33 ± 0.4	4.36 ± 0.4	4.40 ± 0.4
Baseline medications, n (%)				
RAS inhibitors	3467 (99.9)	3237 (99.8)	3112 (99.8)	3165 (99.8)
Beta blockers	1691 (48.7)	1614 (49.7)	1597 (51.2)	1592 (50.2)
Diuretics	1713 (49.4)	1696 (52.3)	1662 (53.3)	1630 (51.4)
Statins	2407 (69.3)	2385 (73.5)	2323 (74.5)	2265 (71.5)
Potassium supplements	118 (3.4)	92 (2.8)	96 (3.1)	78 (2.5)
Potassium-lowering agents	56 (1.6)	55 (1.7)	38 (1.2)	33 (1.0)
Glucose-lowering therapies				
Insulin and analogues	1154 (33.2)	1789 (55.1)	2137 (68.5)	2537 (80.0)
Biguanides	2029 (58.5)	1909 (58.8)	1796 (57.6)	1812 (57.2)
Sulphonamides	860 (24.8)	915 (28.2)	854 (27.4)	754 (23.8)
DPP-4 inhibitors	937 (27.0)	949 (29.2)	762 (24.4)	622 (19.6)
GLP-1RAs	181 (5.2)	245 (7.6)	284 (9.1)	232 (7.3)
SGLT-2 inhibitors	127 (3.7)	257 (7.9)	244 (7.8)	249 (7.9)

BMI, body mass index; 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; RAS, renin–angiotensin system; SD, standard deviation; SGLT-2, sodium-glucose co-transporter-2; UACR, urine albumin-to-creatinine ratio

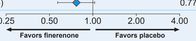
3.1. Efficacy outcomes

3.1.1 Outcomes by Hb1Ac and diabetes duration at baseline

- The effect of finerenone on CV and kidney composite outcomes was consistent across HbA1c quartiles (p-interaction=0.52 and 0.09, respectively) and diabetes duration quartiles (p-interaction=0.12 and 0.75, respectively) (**Figure 2**)

Figure 2. CV and kidney outcomes by Hb1Ac and diabetes duration quartiles

Composite endpoint	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	p-value for interaction
CV by HbA1c				0.5202
≤6.7% (≤Q1)	204/1693 (12.05)	225/1778 (12.65)	0.95 (0.78–1.15)	
>6.7% and ≤7.5% (>Q1, ≤Q2)	172/1618 (10.63)	219/1627 (13.46)	0.79 (0.64–0.97)	
>7.5% and ≤8.5% (>Q2, ≤Q3)	187/1589 (11.77)	219/1529 (14.32)	0.78 (0.64–0.95)	
>8.5% (>Q3)	257/1607 (15.99)	274/1563 (17.53)	0.90 (0.75–1.07)	
CV by diabetes duration				0.1196
≤9.1 years (≤Q1)	167/1628 (10.26)	166/1631 (10.18)	0.98 (0.79–1.22)	
>9.1 and ≤15.1 years (>Q1, ≤Q2)	201/1643 (12.23)	202/1603 (12.60)	0.98 (0.80–1.19)	
>15.1 and ≤20.2 years (>Q2, ≤Q3)	227/1589 (14.29)	291/1662 (17.51)	0.78 (0.65–0.93)	
>20.2 years (>Q3)	230/1649 (13.95)	278/1603 (17.34)	0.79 (0.66–0.94)	
Kidney by HbA1c				0.0860
≤6.7% (≤Q1)	115/1693 (6.79)	137/1778 (7.71)	0.89 (0.69–1.14)	
>6.7% and ≤7.5% (>Q1, ≤Q2)	69/1618 (4.26)	116/1627 (7.13)	0.61 (0.45–0.83)	
>7.5% and ≤8.5% (>Q2, ≤Q3)	94/1589 (5.92)	95/1529 (6.21)	0.89 (0.66–1.19)	
>8.5% (>Q3)	81/1607 (5.04)	117/1563 (7.49)	0.69 (0.52–0.93)	
Kidney by diabetes duration				0.7542
≤9.1 years (≤Q1)	92/1628 (5.65)	108/1631 (6.62)	0.84 (0.64–1.12)	
>9.1 and ≤15.1 years (>Q1, ≤Q2)	82/1643 (4.99)	116/1603 (7.24)	0.73 (0.55–0.97)	
>15.1 and ≤20.2 years (>Q2, ≤Q3)	100/1589 (6.29)	137/1662 (8.24)	0.71 (0.55–0.92)	
>20.2 years (>Q3)	85/1649 (5.15)	102/1603 (6.36)	0.77 (0.57–1.03)	

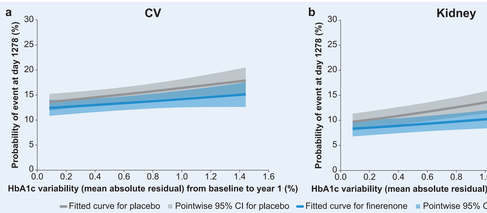


CI, confidence interval; CV, cardiovascular; HbA1c, glycated hemoglobin; HR, hazard ratio; Q, quartile

3.1.2 HbA1c variability

- In the overall population greater HbA1c variability in the first year of treatment was associated with higher cardiorenal risks
  - Each 1 unit increase in the mean absolute residual of HbA1c from baseline to year 1 was associated with a 20% increased risk of a CV event (HR=1.20; 95% CI 1.07–1.35; p=0.0016) and a 36% increased risk of a kidney event (HR=1.36; 95% CI 1.21–1.52; p<0.0001)
- HbA1c variability had no impact on the treatment effect of finerenone on CV (**Figure 3a**) or kidney (**Figure 3b**) outcomes
- Treatment with finerenone was associated with a difference in probability of events at 3.5 years for both CV and renal outcomes; however, this was found to be statistically non-significant (p-interaction=0.48 and 0.09, respectively)

Figure 3. (a) Event probability at 3.5 years for the CV outcome by HbA1c variability and **(b)** event probability at 3.5 years for the eGFR ≥57% kidney outcome by HbA1c variability



CI, confidence interval; CV, cardiovascular; HbA1c, glycated hemoglobin

3.2 Safety outcomes

- The overall incidence of treatment-emergent adverse events was similar between the finerenone and placebo groups across the baseline HbA1c (**Table 2a**) and diabetes duration quartiles (**Table 2b**)
  - Incidence of investigator-reported, treatment-emergent hyperkalemia was higher in patients treated with finerenone compared with placebo, with the highest incidence observed in the group with the longest diabetes duration

Table 2a. Adverse events by HbA1c quartiles at baseline

n (%)	≤6.7%		>6.7% and ≤7.5%		>7.5% and ≤8.5%		>8.5%	
	Finerenone (n=1691)	Placebo (n=1775)	Finerenone (n=1615)	Placebo (n=1625)	Finerenone (n=1587)	Placebo (n=1522)	Finerenone (n=1606)	Placebo (n=1558)
Any TEAE	1445 (85.5)	1511 (85.1)	1410 (87.3)	1430 (88.0)	1369 (86.3)	1340 (88.0)	1371 (85.4)	1319 (84.7)
Hyperkalemia	201 (11.9)	106 (6.0)	202 (12.5)	88 (5.4)	201 (12.7)	93 (6.1)	176 (11.0)	95 (6.1)
Any AE leading to study drug discontinuation	123 (7.3)	117 (6.6)	95 (5.9)	93 (5.7)	102 (6.4)	75 (4.9)	93 (5.8)	65 (4.2)
Any serious AE	510 (30.2)	549 (30.9)	484 (30.0)	554 (34.1)	526 (33.1)	519 (34.1)	535 (33.3)	561 (36.0)

AE, adverse event; HbA1c, glycated hemoglobin; TEAE, treatment-emergent adverse event

Table 2b. Adverse events by diabetes duration quartiles at baseline

n (%)	≤9.1 years		>9.1 and ≤15.1 years		>15.1 and ≤20.2 years		>20.2 years	
	Finerenone (n=1626)	Placebo (n=1627)	Finerenone (n=1639)	Placebo (n=1600)	Finerenone (n=1589)	Placebo (n=1656)	Finerenone (n=1647)	Placebo (n=1598)
Any TEAE	1356 (83.4)	1367 (84.0)	1422 (86.8)	1394 (87.1)	1380 (86.8)	1435 (86.7)	1437 (87.2)	1403 (87.8)
Hyperkalemia	156 (9.6)	64 (3.9)	184 (11.2)	111 (6.9)	201 (12.6)	109 (6.6)	239 (14.5)	98 (6.1)
Any AE leading to study drug discontinuation	82 (5.0)	74 (4.5)	100 (6.1)	77 (4.8)	104 (6.5)	103 (6.2)	127 (7.7)	97 (6.1)
Any serious AE	445 (27.4)	479 (29.4)	512 (31.2)	524 (32.8)	529 (33.3)	623 (37.6)	571 (34.7)	553 (34.6)

AE, adverse event; HbA1c, glycated hemoglobin; TEAE, treatment-emergent adverse event

4. Conclusions

- A greater variability in HbA1c, that is, the magnitude of the increase and decrease in HbA1c levels beyond 'expected' values over time (less-controlled disease), was associated with increased risks of cardiorenal outcomes
- Baseline HbA1c, HbA1c variability, or duration of diabetes did not affect the risk reductions observed for CV and kidney outcomes in patients treated with finerenone compared with placebo
- The safety of finerenone was generally consistent across HbA1c quartiles and diabetes duration quartiles

Acknowledgments

Funded by Bayer AG. FIDELIO-DKD and FIGARO-DKD clinicaltrials.gov numbers NCT02540993 and NCT02545049, respectively. Medical writing assistance was provided by Chameleon Communications International and was funded by Bayer AG.

References

1. United States Renal Data System. 2017. https://www.usrds.org/media/1652/v1_00_executive.pdf [accessed 25 May 2022].
2. Agarwal R, *et al. Eur Heart J* 2022;43:474–484.
3. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229.
4. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263.
5. Rulippe LM, *et al. Am J Nephrol* 2019;50:345–356.
6. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344.

Disclosures

JBM reported personal fees and non-financial support from Bayer, personal fees from Boehringer Ingelheim, Dexcom, Mannkind, Novo Nordisk, and Provention Bio; she reports research funding paid to Washington University from NIH, Beta Bionics, Dexcom, and Novo Nordisk. She is a member of steering committees for Bayer and the Jaeb Center, data safety monitoring committees for NIH and the Jaeb Center and is an associate editor of the *Journal of the Endocrine Society* and *British Medical Journal Diabetes Research and Care*. **RA** reports personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals Inc. during the conduct of the study; he also reports personal fees and nonfinancial support from Akebia Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Fresenius, Janssen, Relypsa, Sanofi, and Vifor Pharma; he has received personal fees from Ironwood Pharmaceuticals, Lexicon, Merck & Co. and Reata and nonfinancial support from E. R. Squibb & Sons, Otpko Pharmaceuticals, and Otsuka America Pharmaceutical; he is a member of data safety monitoring committees for AstraZeneca and Ironwood Pharmaceuticals, a member of steering committees of randomized trials for Akebia Therapeutics, Bayer, Janssen, and Relypsa, a member of adjudication committees for AbbVie, Bayer, Boehringer Ingelheim, and Janssen; he has served as associate editor of the *American Journal of Nephrology* and *Nephrology Dialysis and Transplantation* and has been an author for UpToDate, and he has received research grants from the National Institutes of Health and the U.S. Veterans Administration. **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. **GLB** reports research funding, paid to the University of Chicago Medicine, from Bayer, during the conduct of the study; he also reports research funding, paid to the University of Chicago Medicine, from Novo Nordisk and Vascular Dynamics; he acted as a consultant and received personal fees from for Alnylam, Merck, and Relypsa; is an editor of the *American Journal of Nephrology*, *Nephrology*, and *Hypertension*, and section editor of UpToDate; and is an associate editor of *Diabetes Care and Hypertension Research*. **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. He is a Senior Consulting Editor for *JACC Heart Failure*, and he has received research support from the European Union. **BP** reports consultant fees for Ardelyx, AstraZeneca, Bayer, Boehringer Ingelheim, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, Phasebio, Sanofi/Lexicon, Sarfez, scPharmaceuticals, SQ Innovation, Tricida and ViforRelypsa; he has stock options for Ardelyx, Brainstorm Medical, Cereno Scientific G3 Pharmaceuticals, KBP Biosciences, Sarfez, scPharmaceuticals, SQ Innovation, Tricida and ViforRelypsa; he has stock options for Ardelyx, AstraZeneca, Bayer, Boehringer Ingelheim, Brainstorm Medical, Cereno Scientific G3 Pharmaceuticals, KBP Biosciences, Sarfez, scPharmaceuticals, SQ Innovation, Tricida and ViforRelypsa; he has also received personal fees from Alnylam, Merck, and Relypsa; is an editor of the *American Journal of Nephrology*, *Nephrology*, and *Hypertension*, and section editor of UpToDate; and is an associate editor of *Diabetes Care and Hypertension Research*. **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. He is a Senior Consulting Editor for *JACC Heart Failure*, and he has received research support from the European Union. **BP** reports consultant fees for Ardelyx, AstraZeneca, Bayer, Boehringer Ingelheim, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, Phasebio, Sanofi/Lexicon, Sarfez, scPharmaceuticals, SQ Innovation, Tricida and ViforRelypsa; he has stock options for Ardelyx, Brainstorm Medical, Cereno Scientific G3 Pharmaceuticals, KBP Biosciences, Sarfez, scPharmaceuticals, SQ Innovation, Tricida and ViforRelypsa; he also holds a patent for site-specific delivery of eplerenone to the myocardium (US patent #9031412) and a provisional patent for histone-acetylation-modulating agents for the treatment and prevention of organ injury (provisional patent US 63/045,764). **LMR** has reports receipt of consultancy fees from Bayer. **ALB** reported research support from Boehringer Ingelheim and personal fees from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. All fees are given to the Tübingen University. **MLC** reports research funding, paid to the University of Minnesota, from Bayer, during the conduct of the studies; she has received research funding, paid to the University of Minnesota, from Novartis and Novo Nordisk; personal fees from AstraZeneca and Boehringer Ingelheim. **MB** is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany. **AJ** is a full-time employee of Bayer SA, Division Pharmaceuticals, Brazil. **RL** is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany. **CS** is a full-time employee of Bayer PLC, United Kingdom. **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, Merck, Merck Sharp & Dohme, Mundipharma, Sanofi, and Vifor. All fees given to Steno Diabetes Center Copenhagen.

Abstract #2022-LB-5958-Diabetes presented at the American Diabetes Association (ADA) 2022 (June 3–7, 2022, New Orleans, LA, USA)