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Finerenone and left ventricular hypertrophy in chronic kidney disease and type 2 diabetes

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ehf2.14962

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Short title: Finerenone in patients with LVH in FIDELITY

Journal: *ESC-HF Journal* (Short Communication)

Word count: 1420 of 1500 (excludes references and figure legend)

No. of suggested tables and/or figures: 1 of 1

No. of references: 4 of 10

Keywords: left ventricular hypertrophy, chronic kidney disease, type 2 diabetes, finerenone, hospitalization for heart failure, cardiorenal outcomes

Trial registration number:

FIDELIO-DKD: NCT02540993

FIGARO-DKD: NCT02545049

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Abstract

Aims

Left ventricular hypertrophy (LVH) has been associated with an increased risk of cardiovascular (CV) disease and linked to increased morbidity and mortality. In patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) hypertension is common and patients with these comorbidities additionally have a high prevalence of LVH. This analysis of the prespecified pooled FIDELITY analysis comprising the randomized, double-blind, placebo-controlled, multicentre FIDELIO-DKD and FIGARO-DKD phase III studies, aimed to explore the CV and kidney effects of finerenone, a nonsteroidal mineralocorticoid receptor antagonist, in patients with CKD and T2D stratified by a diagnosis of LVH at baseline.

Methods

A diagnosis of LVH in the FIDELITY patient population was determined at baseline using investigator-reported electrocardiogram (ECG) findings. The two efficacy outcomes, assessed by baseline LVH, were the composite CV outcome of time to CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure (HHF), and a composite kidney outcome of time to onset of kidney failure, a sustained decrease in estimated glomerular filtration rate (eGFR) ≥57% from baseline over ≥4 weeks, or kidney-related death. Safety outcomes by baseline LVH were reported as treatment-emergent adverse events.

Results

At baseline out of 13,026 patients in FIDELITY, 96.5% had hypertension and 9.6% had investigator-reported LVH. The relative risk reduction for the composite CV and kidney outcomes with finerenone versus placebo was lower in the LVH subgroup; however, the

treatment effect of finerenone was not modified by baseline LVH for either outcome ($P_{interaction}$ =0.1075 for composite CV outcome, $P_{interaction}$=0.1782 for composite kidney outcome). Analysis of the composite CV outcome components showed a greater reduction in the risk of HHF versus placebo for patients with baseline LVH compared with those without ($P_{interaction}$=0.0024). Overall safety events were comparable between the LVH subgroups and treatment arms. Treatment-emergent hyperkalaemia was observed more frequently with finerenone versus placebo, but discontinuation rates were low in both treatment arms and between LVH subgroups.

Conclusions

In conclusion, the overall CV and kidney benefits of finerenone versus placebo were not modified by the presence of LVH at baseline, with overall safety findings being similar between LVH subgroups. A greater benefit was observed for HHF in patients with versus without LVH suggesting that LVH may be a predictor of the treatment effect of finerenone on HHF.

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Background

Cardiovascular disease (CVD) and its related morbidity and mortality is associated with left ventricular hypertrophy (LVH).[1-3] Hypertension is common in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D); patients with these comorbidities have a high prevalence of left ventricular (LV) hypertrophy.[1-3] Finerenone is a selective, nonsteroidal mineralocorticoid receptor antagonist (MRA). In FIDELITY, a prespecified pooled analysis of the randomized, double-blind, placebo-controlled, multicentre FIDELIO-DKD and FIGARO-DKD phase III studies, finerenone demonstrated cardiovascular (CV) and kidney benefits across the spectrum of CKD severity in patients with T2D.[4] The relative risk reduction with finerenone versus placebo for a composite CV outcome of time to CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for heart failure (HHF) was shown to be a 14%. For HHF, a 22% relative risk reduction was observed with finerenone compared with placebo.[4]

Aims

The aim of this exploratory FIDELITY subgroup analysis was to explore the CV and kidney effects of finerenone in patients stratified by a diagnosis of LVH at baseline, allowing hypothesis development for further research into the effects of finerenone on modifying LVH risk.

Methods

The design and results of FIDELITY have been previously published.[4] In summary, patients with CKD and T2D on optimized renin–angiotensin system inhibitor (RASi) therapy were randomized 1:1 to finerenone or placebo. Patients with heart failure (HF) with reduced ejection fraction were excluded. Patients were required to have serum potassium levels ≤4.8 mmol/L at the run-in and screening visits. A diagnosis of LVH at baseline was

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determined based on investigator-reported electrocardiogram (ECG) findings (as per local practice from either manual ECG evaluation or machine-reported results) identified from the run-in visit to randomization; no central adjudication of ECGs was performed, and no assessment criteria were applied. Any patients with LVH identified by ECG in the period from run-in to randomization were included in the LVH patient subgroup. The use of ECG is known to be less sensitive and may limit the interpretation of the results. To mitigate this, baseline LVH was defined as a diagnosis of LVH using all ECG readings from the run-in visit to randomization to ensure improved identification of patients with a finding of LVH, while reducing the possibility of misclassifying patients as without LVH.

The efficacy outcomes, assessed in the full analysis set and by LVH subgroups, were a composite CV outcome of time to CV death, non-fatal MI, non-fatal stroke, or HHF, and a composite kidney outcome of time to onset of kidney failure, a sustained decrease in estimated glomerular filtration rate (eGFR) ≥57% from baseline over ≥4 weeks, or kidney-related death. The interaction between treatment and LVH status at baseline was assessed via a stratified Cox proportional hazards model, including treatment, subgroup, and treatment by subgroup interaction terms. Chi-square tests were used to report the *P*-values of interaction terms. Safety outcomes were reported as treatment-emergent events and determined in the safety analysis set by baseline LVH.

Results

Of the 13,026 patients in the full analysis set of FIDELITY, 96.5% had hypertension, 9.6% had investigator-reported LVH, and 7.7% had HF at baseline. The median treatment duration for patients with and without LVH was 29.9 and 31.9 months, respectively, with finerenone, and 28.7 and 32.1 months, respectively, with placebo. In FIDELITY, finerenone significantly reduced the risk of the composite CV and kidney outcomes versus placebo.[4] In this analysis, the relative risk reduction for the composite CV and kidney outcomes was

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lower in the LVH patient subgroup compared with the subgroup without LVH (composite CV outcome: hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.55–0.95 versus HR 0.89; 95% CI 0.81–0.98, respectively; composite kidney outcome: HR 0.56; 95% CI 0.38–0.84 versus HR 0.80; 95% CI 0.69–0.93, respectively). The treatment effect of finerenone was not modified by baseline LVH for either the composite CV ($P_{interaction}$ = 0.1075) or kidney ($P_{interaction}$ = 0.1782) outcomes. A significant reduction in the risk of HHF was observed versus placebo for patients with baseline LVH compared with those without (HR 0.34, 95% CI 0.19–0.61 and HR 0.86, 95% CI 0.72–1.03, respectively; $P_{interaction}$ = 0.0024; **Figure**). No significant differences were seen in the other components of the CV or kidney composite outcomes.

Treatment-emergent (TE) adverse events were comparable across the LVH subgroups and treatment arms (with LVH: finerenone 85.2% versus placebo 86.4%; without LVH: finerenone 86.1% versus placebo 86.4%). TE hyperkalaemia was reported more frequently in the finerenone group versus placebo (with LVH: finerenone 12.3% versus placebo 5.7%; without LVH: finerenone 14.2% versus placebo 7.0%) but the incidence that led to treatment discontinuation was low in both treatment arms and LVH subgroups (with LVH: finerenone 1.5% versus placebo 0.5%; without LVH: finerenone 1.7% versus placebo 0.6%).

Conclusions

In patients with CKD and T2D alongside hypertension, impaired LV diastolic function is largely explained by increased LV wall thickness and concentric LVH development.[1,3] This analysis indicates that LVH was predictive of the treatment effect of finerenone for HHF and suggests its potential role in modifying risks associated with LVH risk in patients optimally treated with RASi. Further investigation is required to assess how finerenone modifies CV risk in these patients, and whether LVH is merely a marker of increased risk or an indicator

of heightened mineralocorticoid receptor activation that is responsive specifically to MRAs rather than other treatments.

Limitations to be considered for the interpretation of the data here include the lack of standardized LVH criteria for the diagnosis of LVH using ECG implied possible variation in the definition; LVH regression with finerenone was not fully assessed due to missing ECG data at later timepoints and lack of corroborating echocardiography; and identification of LVH by ECG interpretation was via machine or physician evaluation, without any central adjudication.

In this post hoc analysis, finerenone and optimized RASi reduced the risk of composite CV and kidney outcomes versus placebo in patients with CKD and T2D, irrespective of baseline LVH. Findings suggest that LVH may be a predictor of the treatment effect of finerenone on HHF, with a greater risk reduction seen for HHF in patients with baseline LVH. An increased incidence of TE hyperkalaemia was observed with finerenone versus placebo,[4] but the discontinuation rate was low for both treatment arms and LVH subgroups and the overall safety findings were similar between LVH subgroups.

Funding

This work was supported by Bayer AG, who funded the FIDELIO-DKD and FIGARO-DKD studies and FIDELITY pooled analysis.

Acknowledgements

This FIDELIO-DKD and FIGARO-DKD studies and the FIDELITY pooled analysis were sponsored by Bayer AG, the manufacturer of finerenone. Medical writing services were provided by Irena Frelichova from Chameleon Communications International and funded by Bayer AG.

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Declaration of interest

G.F. reports lecture fees and/or that he is a committee member of trials and registries sponsored by Amgen, Bayer, Boehringer Ingelheim, Cardior, Impulse Dynamics, Medtronic, Novartis, Novo Nordisk, Servier, and Vifor Pharma and has received research support from the European Union.

S.D.A. has received research support from Abbott Vascular and Vifor Pharma, and personal fees from Abbott Vascular, Bayer, BRAHMS, Boehringer Ingelheim, Cardiac Dimensions, Impulse Dynamics, Novartis, Servier, and Vifor Pharma.

G.L.B. 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 Alnylam, Merck, and Relypsa. He is an editor of *American Journal of Nephrology*, *Nephrology*, and *Hypertension.*

P.R. 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 Pharma, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, Sanofi, and Vifor Pharma. All fees are given to Steno Diabetes Center Copenhagen.

L.M.R. reported receipt of consultancy fees from Bayer.

A.J.S.C. reported honoraria and/or lecture fees from: Abbott, Actimed Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiac Dimensions, Corvia Medical, CVRx, Edwards Lifesciences, Eli Lilly, Enopace Biomedical, ESN Cleer, Faraday, Impulse Dynamics, Menarini, Novartis, Novo Nordisk, Respicardia, Servier Laboratories, Viatris, and Vifor.

S.v.H. has received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Pharmacosmos, IMI and the German Center for Cardiovascular Research (DZHK), and is a

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paid consultant for and/or received honoraria payments from AstraZeneca, Bayer, Boehringer Ingelheim, BRAHMS, Chugai, Grünenthal, Helsinn, Hexal, Novartis, Novo Nordisk, Pharmacosmos, Respicardia, Roche, Servier, Sorin, and Vifor Pharma.

P.P. reports research grants, consulting fees, speaker's bureau for AstraZeneca, Berlin-Chemie, Bayer, BMS, Boehringer Ingelheim, MSD, Novartis, Respicardia, Servier, and Vifor Pharma

G.M.C.R. has received meeting and travel support from AstraZeneca, Boehringer Ingelheim, Servier, and Vifor Pharma.

M.B. is a full-time employee of Bayer AG, Wuppertal, Germany.

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L.R. is a full-time employee of Bayer PLC, Reading, United Kingdom.

B.P. reports consultant fees for Ardelyx, AstraZeneca, Bayer, Boehringer Ingelheim, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP BioSciences, PhaseBio, Sanofi/Lexicon, Sarfez Pharmaceuticals, scPharmaceuticals, SQ Innovation, Tricida, and Vifor Pharma/Relypsa. He has stock options for Ardelyx, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP BioSciences, Sarfez Pharmaceuticals, scPharmaceuticals, SQ Innovation, Tricida, and Vifor Pharma/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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Figure legend

Figure: Efficacy outcomes by LVH* and eGFR at baseline

*LVH diagnosis determined at baseline by investigator-reported ECG findings.

†Time to CV death, non-fatal MI, non-fatal stroke, or HHF.

‡Time to onset of kidney failure, a sustained decrease in eGFR ≥57% from baseline over ≥4 weeks, or kidney-related death.

§As assessed via a stratified Cox proportional hazards model, including treatment, subgroup, and treatment by subgroup interaction terms.

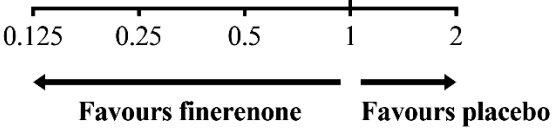
CI, confidence interval; CV, cardiovascular; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; LVH, left ventricular hypertrophy; MI, myocardial infarction; PY, patient-years.

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Figure

Figure: Efficacy outcomes by LVH* and eGFR at baseline

Endpoint	Finerenone		Placebo		Hazard ratio (95% CI)§	$P_{interaction}$§
	n/N (%)	n per 100 PY	n/N (%)	n per 100 PY		
Composite CV outcome†						
Overall	**825/6519 (12.7)**	**4.34**	**939/6507 (14.4)**	**5.01**	**0.86 (0.78–0.95)**	
With LVH	92/596 (15.4)	5.58	137/654 (20.9)	8.03	0.72 (0.55–0.95)	0.1075
Without LVH	733/5923 (12.4)	4.22	802/5853 (13.7)	4.71	0.89 (0.81–0.98)	
HHF						
Overall	**256/6519 (3.9)**	**1.31**	**325/6507 (5.0)**	**1.68**	**0.78 (0.66–0.92)**	
With LVH	17/596 (2.9)	1.00	52/654 (8.0)	2.94	0.34 (0.19–0.61)	0.0024
Without LVH	239/5923 (4.0)	1.34	273/5853 (4.7)	1.55	0.86 (0.72–1.03)	
Composite kidney outcome‡						
Overall	**360/6519 (5.5)**	**1.96**	**465/6507 (7.1)**	**2.55**	**0.77 (0.67–0.88)**	
With LVH	42/596 (7.0)	2.69	72/654 (11.0)	4.33	0.56 (0.38–0.84)	0.1782
Without LVH	318/5923 (5.4)	1.90	393/5853 (6.7)	2.38	0.80 (0.69–0.93)	



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*LVH diagnosis determined at baseline by investigator-reported ECG findings.

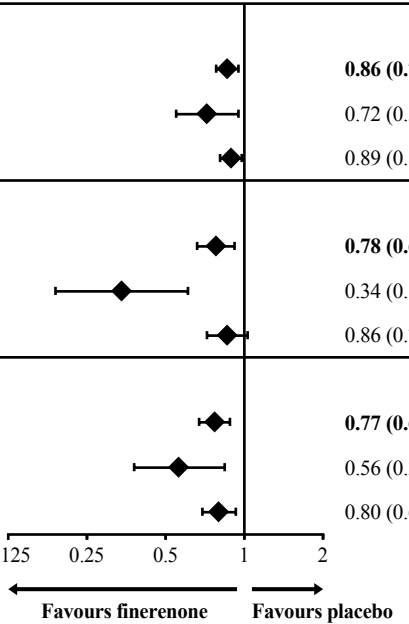
†Time to CV death, non-fatal MI, non-fatal stroke, or HHF.

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§As assessed via a stratified Cox proportional hazards model, including treatment, subgroup, and treatment by subgroup interaction terms.

CI, confidence interval; CV, cardiovascular; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; LVH, left ventricular hypertrophy; MI, myocardial infarction; PY, patient-years.

Endpoint	Finerenone		Placebo		Hazard ratio (95% CI)[§]	$P_{interaction}$[§]
	n/N (%)	n per 100 PY	n/N (%)	n per 100 PY		
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