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Finerenone in patients across the spectrum of chronic kidney disease and type 2 diabetes by glucagon-like peptide-1 receptor agonist use

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Abstract

Aims: To explore the modifying effect of glucagon-like peptide-1 receptor agonist (GLP-1RA) use on outcomes with finerenone across a wide spectrum of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the pooled analysis of FIDELIO-DKD and FIGARO-DKD.

Materials and methods: Patients with T2D and CKD treated with optimized renin-angiotensin system blockade were randomized to finerenone or placebo. Effects of

finerenone on a cardiovascular composite outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) and a kidney composite outcome (kidney failure, sustained ≥57% estimated glomerular filtration rate [eGFR] decline, or renal death), change in urine albumin-to-creatinine ratio (UACR), and safety were analysed by GLP-1RA use.

Results: Of 13 026 patients, 944 (7.2%) used GLP-1RAs at baseline. Finerenone reduced the risk of the cardiovascular composite outcome (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.52–1.11 with GLP-1RA; HR 0.87, 95% CI 0.79–0.96 without GLP-1RA; *P*-interaction = 0.63) and the kidney composite outcome (HR 0.82, 95% CI 0.45–1.48 with GLP-1RA; HR 0.77, 95% CI 0.67–0.89 without GLP-1RA; *P*-interaction = 0.79) irrespective of baseline GLP-1RA use. Reduction in UACR with finerenone at Month 4 was −38% in patients with baseline GLP-1RA use compared with −31% in those without GLP-1RA use (*P*-interaction = 0.03). Overall safety and incidence of hyperkalaemia were similar, irrespective of GLP-1RA use.

Conclusions: The cardiorenal benefits of finerenone on composite cardiovascular and kidney outcomes and UACR reduction in patients with CKD and T2D appear to be maintained, regardless of GLP-1RA use. Subsequent studies are needed to investigate any potential benefit of this combination.

1 | INTRODUCTION

Type 2 diabetes (T2D) accounts for more than 90% of the global diabetes burden and is the leading cause of kidney failure in developed countries.[1-3] Chronic kidney disease (CKD) affects approximately 40% of people with T2D, and in comparison with T2D alone, comorbid CKD leads to three times greater risk of cardiovascular (CV) mortality.[4,5]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are recommended in patients with T2D, and guidelines were updated in 2020 to recommend GLP-1RAs for patients with T2D and CV disease and/or high risk for CV events to reduce the risk of CV disease progression.[6-8] GLP-1RAs are also recommended for use in patients with CKD and T2D who have not achieved individualized glycaemic targets despite use of metformin and a sodium-glucose cotransporter-2 (SGLT2) inhibitor or who are unable to use those medications.[7] Moreover, despite the use of guideline-recommended therapies, some patients with CKD and T2D still experience CKD progression or kidney failure, highlighting the need for additional therapeutic options in this patient population.[9,10] Previous CV outcome trials have indicated potential benefits with regard to kidney outcomes.[11] Thus, GLP-1RAs have been shown to reduce the risk of developing or worsening CKD mostly by reducing the development of overt albuminuria.[12] Potential protective mechanisms of GLP-1RAs include attenuation of oxidative stress, fibrosis, and cellular apoptosis in the kidney.[12] In a pooled analysis of the SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) and LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trials, semaglutide and liraglutide were suggested to have kidney-protective effects in patients with T2D, which will need to be proven by the ongoing FLOW trial.[13]

Finerenone is a distinct, selective, nonsteroidal mineralocorticoid receptor antagonist,[14,15] which is recommended in patients with CKD who are at increased risk of CV events or CKD progression.[16] Given the current use of GLP-1RAs in patients with T2D, their combined use with finerenone is of interest.[6,7]

A recent analysis of data from the FIDELIO-DKD (FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease; NCT02540993) study in patients with advanced CKD stratified by GLP-1RA use at baseline showed that the effects of finerenone on CV and kidney outcomes were consistent, irrespective of GLP-1RA use.[17] This analysis provided meaningful insights into the effect of finerenone on change in urine albumin-to-creatinine ratio (UACR) by GLP-1RA use; however, because of the low number of CV and kidney clinical endpoints, this analysis was less informative on the evaluation of the CV and kidney composite outcomes.

In this FIDELITY (The FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analysis) subgroup analysis, we expand upon previous results by examining the modifying effect of GLP-1RA use on cardiorenal outcomes in the prespecified pooled populations of the FIDELIO-DKD and FIGARO-DKD (FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease; NCT02545049) studies, which include more than twice as many patients across a wider spectrum of CKD and T2D.

2 | MATERIALS AND METHODS

2.1 | Study design

This analysis combines individual patient-level data from the FIDELIO-DKD and FIGARO-DKD Phase III clinical trials; the designs and results of these studies have been published previously.[14,18] Briefly, adults (aged ≥18 years) with CKD and T2D who were receiving maximum tolerated labelled renin-angiotensin system inhibitor therapy were eligible to participate if they had a serum potassium level ≤4.8 mmol/L at screening. Patients had either a UACR of ≥30 to <300 mg/g and an estimated glomerular filtration rate (eGFR) of ≥25 to ≤90 mL/min/1.73 m^2 or a UACR of ≥300 to ≤5000 mg/g and an eGFR of ≥25 mL/min/1.73 m^2.

Patients with glycated haemoglobin (HbA1c) >108 mmol/mol (>12%) at screening were not eligible to participate. There were no restrictions on the use of antidiabetic treatment, and the use of GLP-1RAs was permitted at baseline and throughout the trial, as was the initiation of GLP-1RA treatment during the trial.

During the study, healthcare providers were advised to follow local guidelines for the management of T2D, including recommendations for glycaemic control. Patients were recruited from September 2015 to October 2018, a period when guidelines and recommendations for GLP-1RA use in patients with T2D at risk of CV events were being updated. The trial protocol was approved by the institutional review board at each study site, and all patients provided written informed consent.

2.2 | Randomization and masking

In both studies, patients were randomized 1:1 to receive double-blind therapy with either oral finerenone (at titrated doses of 10 or 20 mg) or matching placebo once daily. Randomization was stratified by region (North America, Europe, Asia, Latin America, other), albuminuria at screening (UACR 30 to <300 mg/g, ≥300 mg/g) and eGFR at screening (25 to <45 mL/min/1.73 m^2, 45 to <60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2). Patients were also stratified by history of CV disease in FIGARO-DKD.[19] All patients and study personnel (except for the independent data monitoring committee) were masked to treatment allocation.

2.3 | Outcomes

Efficacy outcomes of the present analysis included a CV composite outcome of time to CV death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure, and a kidney composite outcome of time to kidney failure, sustained ≥57% eGFR decline from baseline (equivalent to a doubling of the serum creatinine level) maintained for at least 4 weeks or renal death. Change in UACR from baseline to end of study and all-cause mortality were also analysed.

Potential endpoint events were prospectively adjudicated by an independent committee blinded to treatment assignment and considered from randomization until the end-of-study visit. Safety outcomes of the current analysis included treatment-emergent adverse events and change in systolic blood pressure. Data for these efficacy and safety outcomes are reported in patients stratified by GLP-1RA use at baseline.

2.4 | Statistical analysis

Statistical analysis methods for the efficacy outcomes in the FIDELIO-DKD and FIGARO-DKD studies have been described previously.[18,19] In this analysis, efficacy outcomes were analysed in the pooled full analysis set, comprising all patients randomized who did not have critical Good Clinical Practice violations. The included analyses were exploratory. Treatment effect for time-to-event outcomes in patients with no GLP-1RA use and patients with GLP-1RA use at baseline based on separate Cox regression models including treatment (finerenone vs. placebo), and stratified by prespecified factors (albuminuria and eGFR at screening, CV disease history, region, and study) were expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). *P*-values for the subgroup-by-treatment interaction were derived from a stratified Cox proportional hazards model, which included terms for treatment, subgroup, and a subgroup-by-treatment interaction. To consider on-treatment GLP-1RA use, outcome HRs and associated 95% CIs were based on a stratified Cox model, including finerenone treatment as a fixed covariate, co-medication with GLP-1RA use as a time-varying covariate, and the interaction of the fixed and time-varying terms.

Changes in UACR over time were analysed by GLP-1RA use at baseline. Separate mixed-model repeated-measures analyses were conducted for change in UACR, assuming an unstructured covariance matrix and adjusting for treatment group, stratification factors, study, log-transformed baseline value nested within type of albuminuria at screening, visit and the interactions of treatment-by-visit, baseline value-by-visit, and treatment-by-study. Changes in UACR at Month 4 were additionally evaluated with an analysis of covariance (ANCOVA) model using adjustment factors as above by combined use of GLP-1RA and SGLT2 inhibitor use at baseline.

Analyses of safety outcomes, including treatment-emergent hyperkalaemia-related adverse events, were carried out in all randomized patients who received ≥1 dose of study drug (by treatment received) and by GLP-1RA use at baseline (yes/no).

3 | RESULTS

3.1 | Patients

Of 13 026 patients included in the analysis, 944 (7.2%) received a GLP-1RA at baseline, comprising a similar proportion in the finerenone (497/6519 [7.6%]) and placebo (447/6507 [6.9%]) groups

TABLE 1 Baseline characteristics in patients receiving/not receiving glucagon-like peptide-1 receptor agonists at baseline

	GLP-1RA use at baseline (n = 944)	No GLP-1RA use at baseline (n = 12 082)
Mean age (SD), years	63 (9.0)	65 (9.6)
Male sex, n (%)	676 (71.6)	8412 (69.6)
Race, n (%)		
White	720 (76.3)	8149 (67.4)
Asian	151 (16.0)	2743 (22.7)
Black/African American	43 (4.6)	479 (4.0)
Mean systolic blood pressure (SD), mmHg	136.1 (14.5)	136.8 (14.2)
BMI, kg/m^2, mean (SD)	34.1 (6.1)	31.1 (5.94)
Mean duration of diabetes (SD), years	16.8 (8.1)	15.3 (8.7)
Mean HbA1c (SD), mmol/mol [%]	61.8 (13.3) [7.8]	60.6 (15.0) [7.7]
Mean serum potassium (SD), mmol/L	4.3 (0.4)	4.4 (0.4)
History of CVD, n (%)	405 (42.9)	5530 (45.8)
History of HF, n (%)	40 (4.2)	967 (8.0)
eGFR		
Mean (SD), mL/min/1.73 m^2	58.7 (21.6)	57.5 (21.7)
Distribution, n (%)		
<25 mL/min/1.73 m^2	7 (0.7)	155 (1.3)
25 to <45 mL/min/1.73 m^2	295 (31.3)	3937 (32.6)
45 to <60 mL/min/1.73 m^2	250 (26.5)	3184 (26.4)
≥60 mL/min/1.73 m^2	392 (41.5)	4803 (39.8)
UACR		
Median (IQR), mg/g	483.5 (180–1052)	517.2 (201–1157)
Distribution, n (%)		
<30 mg/g	17 (1.8)	213 (1.8)
30 to <300 mg/g	313 (33.2)	3786 (31.3)
≥300 mg/g	614 (65.0)	8078 (66.9)
Medication use at baseline, n (%)		
RAS inhibitors	942 (99.8)	12 061 (99.8)
Beta-blockers	512 (54.2)	5992 (49.6)
Diuretics	564 (59.7)	6146 (50.9)
Statins	782 (82.8)	8617 (71.3)
Potassium supplements	51 (5.4)	334 (2.8)
Potassium-lowering agents	9 (1.0)	173 (1.4)
Glucose-lowering therapies	944 (100.0)	11 776 (97.5)
Insulin and analogues	624 (66.1)	7006 (58.0)
Metformin	651 (69.0)	6906 (57.2)
Sulphonylureas	213 (22.6)	3176 (26.3)
SGLT2 inhibitors	167 (17.7)	710 (5.9)
DPP-4 inhibitors	46 (4.9)	3232 (26.8)
Alpha glucosidase inhibitors	30 (3.2)	626 (5.2)
Meglitinides	47 (5.0)	484 (4.0)
Thiazolidinediones	57 (6.0)	460 (3.8)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; IQR, interquartile range; RAS, renin-angiotensin system; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2; UACR, urine albumin-to-creatinine ratio.

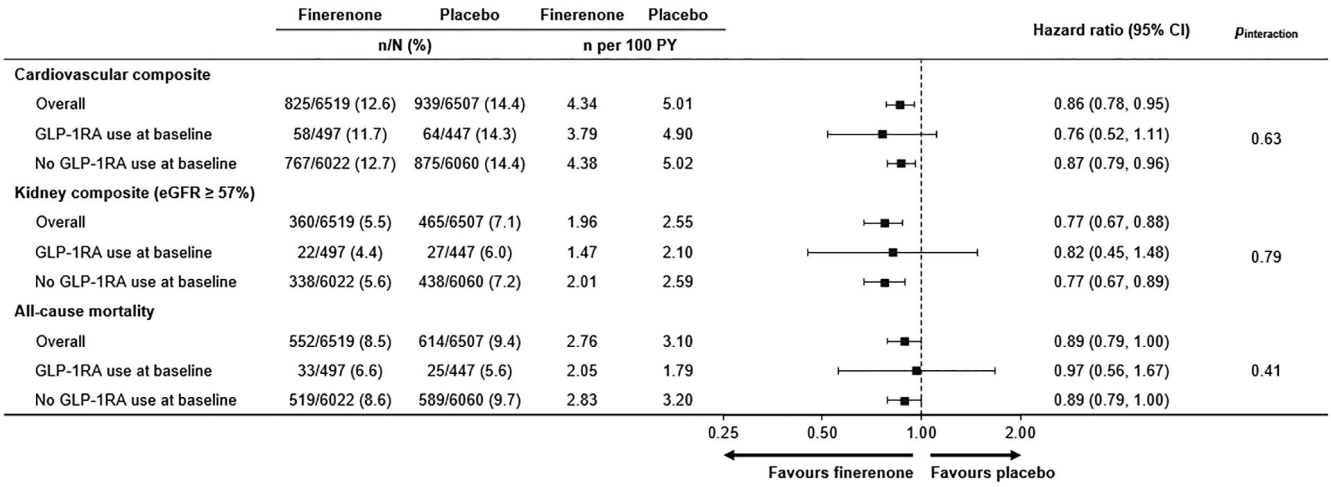

FIGURE 1 Analysis of efficacy outcomes in patients receiving/not receiving a glucagon-like peptide-1 receptor agonist (GLP-1RA). The cardiovascular composite outcome included time to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The kidney composite outcome included time to kidney failure, sustained ≥57% estimated glomerular filtration rate (eGFR) decline from baseline, or renal death. CI, confidence interval; PY, patient-years

(Supplementary Table S1). The median durations of baseline GLP-1RA medication use prior to randomization were 1.2 years and 1.3 years in the finerenone and placebo groups, respectively. Among patients taking GLP-1RAs at baseline, 381/497 (76.7%) in the finerenone group and 354/447 (79.2%) in the placebo group were receiving GLP-1RA therapy for a duration of 4 months or more prior to randomization (Supplementary Table S2).

Following randomization, 907 (13.9%) study patients in the finerenone group and 878 (13.5%) participants in the placebo group received treatment with a GLP-1RA at any time concomitant with study treatment (Supplementary Table S1). For finerenone- and placebo-treated study participants, 429/907 (47.3%) and 405/878 (46.1%), respectively, received co-medication with a GLP-1RA for ≥90% of the treatment period; 607/907 (66.9%) and 556/878 (63.3%), respectively, received a GLP-1RA ≥50% of the time (Supplementary Figure S1). Of the 944 patients receiving a GLP-1RA at baseline, 64% (604/944) were prescribed liraglutide (4.6% of the total population), 16% (153/944) were prescribed dulaglutide (1.2% of the total population), and 15% (145/944) received exenatide (1.1% of the total population); semaglutide was prescribed to <0.1% of patients in the total population. Data showing type of GLP-1RA received at baseline and on-treatment are shown in Supplementary Table S3.

Comparison of the baseline demographics and patient characteristics between the finerenone and placebo groups and between those who did not and those who did receive a GLP-1RA at baseline showed some key differences (Table 1 and Supplementary Table S4). GLP-1RA use was more prevalent in Western versus Eastern European populations. Patients receiving a GLP-1RA at baseline tended to have a longer duration of T2D, marginally greater HbA1c values, and higher body mass index and waist-to-hip ratio and were more likely to have a history of hyperlipidaemia compared with those not receiving a GLP-1RA. The number of patients with a history of ischaemic stroke was lower among patients receiving versus not receiving a GLP-1RA at baseline (Supplementary Table S4). Concomitant use of SGLT2 inhibitors, insulin, metformin, beta-blockers, diuretics, and statins was higher, whereas use of dipeptidyl peptidase-4 inhibitors, as expected, was lower in patients receiving a GLP-1RA at baseline versus those not receiving a GLP-1RA at baseline (Table 1 and Supplementary Table S4).

3.2 | Efficacy

Overall, the risk of the CV composite outcome of time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure was reduced with finerenone compared with placebo (HR 0.86, 95% CI 0.78–0.95; $P = 0.0018$), which was observed irrespective of GLP-1RA use at baseline (HR 0.76, 95% CI 0.52–1.11 with GLP-1RA use; HR 0.87, 95% CI 0.79–0.96 without GLP-1RA use; P-interaction = 0.63 [Figure 1]). Finerenone also reduced the risk of the kidney composite outcome of time to kidney failure, sustained ≥57% eGFR decline, or renal death compared with placebo, irrespective of GLP-1RA use at baseline (HR 0.77, 95% CI 0.67–0.88 overall; $P = 0.0002$; HR 0.82, 95% CI 0.45–1.48 with GLP-1RA use; HR 0.77, 95% CI 0.67–0.89 without GLP-1RA use; P-interaction = 0.79 [Figure 1]). The incidence rate of all-cause mortality was lower in finerenone-treated patients overall, although there was no statistical difference between groups (HR 0.89, 95% CI 0.79–>1.00; $P = 0.051$), and no interaction was observed with GLP-1RA use at baseline (HR 0.97, 95% CI 0.56–1.67 with GLP-1RA use; HR 0.89, 95% CI 0.79–1.00 without GLP-1RA use; P-interaction = 0.41). The effect of finerenone versus placebo on change in UACR from baseline to Month 4 was greater in patients with GLP-1RA use at baseline compared with those without GLP-1RA use at baseline (–38% [least squares mean treatment ratio 0.62, 95% CI 0.57–0.67] with GLP-1RA use and –31% [least squares mean treatment ratio 0.69, 95% CI 0.66–

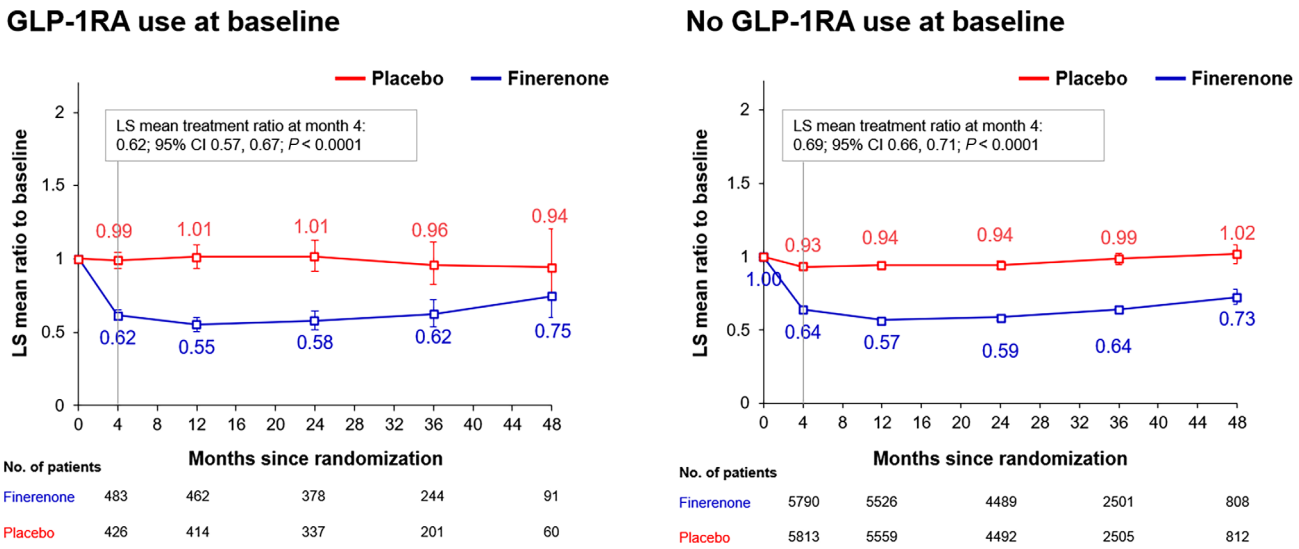

FIGURE 2 Change in urine albumin-to-creatinine ratio over time in patients receiving/not receiving a glucagon-like peptide-1 receptor agonist (GLP-1RA) at baseline. *P*-interaction at 4 months derived from analysis of covariance = 0.0305. Mixed model with factors treatment group, region, estimated glomerular filtration rate category at screening, type of albuminuria at screening, time, treatment*time, study, study*treatment, log-transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value*time as covariate. CI, confidence interval; LS, least squares

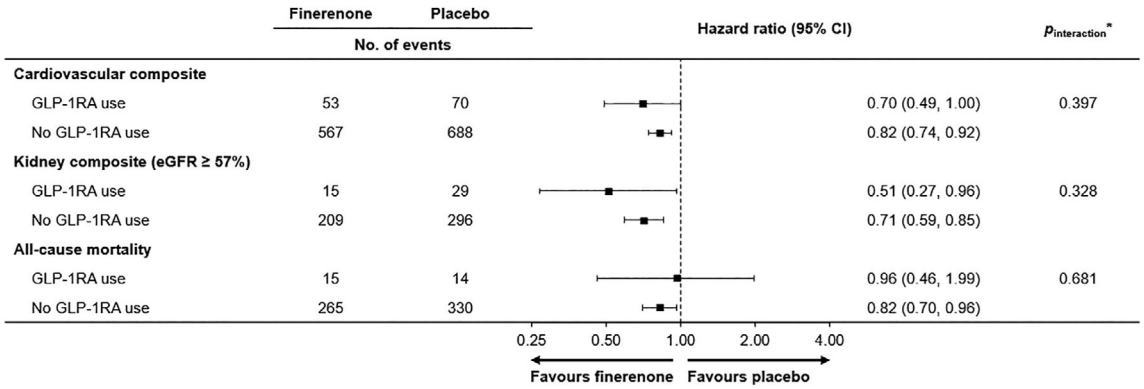

FIGURE 3 Efficacy outcomes considering the effect of glucagon-like peptide-1 receptor agonist (GLP-1RA) use at any time on-treatment. The cardiovascular composite outcome included time to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The kidney composite outcome included time to kidney failure, sustained ≥57% estimated glomerular filtration rate (eGFR) decline from baseline, or renal death. *Interaction *P*-value for adjusted hazard ratio is based on a two-sided Wald test. CI, confidence interval

0.71] without GLP-1RA use [*P*-interaction = 0.03]). The reduction in UACR with finerenone was persistent throughout the duration of the trial in both subgroups (Figure 2).

Time-varying analyses considering GLP-1RA use concomitant with study treatment confirmed that there were no clear differences in the response to finerenone based on GLP-1RA use (Figure 3): CV composite outcome (*P*-interaction = 0.40), kidney composite outcome (*P*-interaction = 0.33), and all-cause mortality (*P*-interaction = 0.68).

An additional analysis of change in UACR from baseline to Month 4 by GLP-1RA and/or SGLT2 inhibitor use showed a consistent reduction in UACR from baseline to Month 4 with finerenone versus placebo (−40% in patients with both GLP-1RA and SGLT2 inhibitor use at baseline [least squares mean treatment ratio 0.60, 95% CI 0.50–0.72]; −38% in patients with GLP-1RA use only at baseline [least squares mean treatment ratio 0.62, 95% CI 0.57–0.68]; and 36% in patients with SGLT2 inhibitor use only at baseline [least squares mean treatment ratio 0.64, 95% CI 0.57–0.72] with no significant difference across subgroups [*P*-interaction = 0.11]; Figure 4).

3.3 | Safety and vital signs

Overall safety by GLP-1RA use at baseline is shown in Supplementary Table S5. Tolerability profiles were similar across all treatment groups (Supplementary Tables S5 and S6). There were higher rates of nausea and vomiting in patients receiving a GLP-1RA than in those not

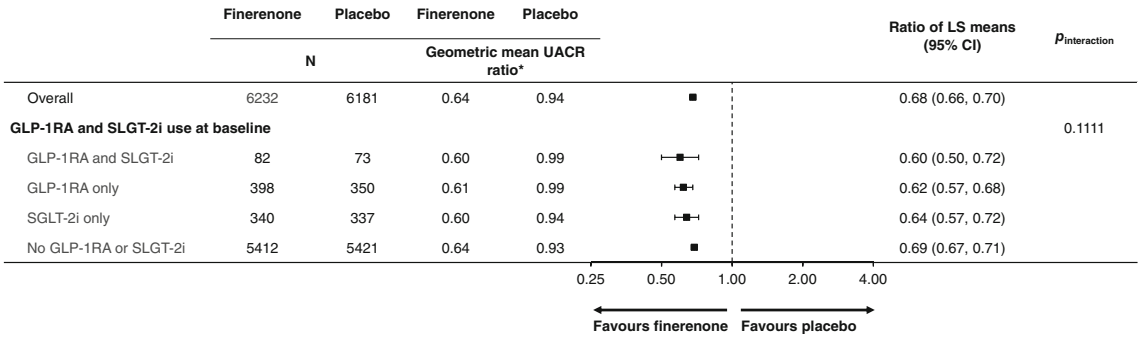

FIGURE 4 Forest plot of analysis of covariance for ratio to baseline at Month 4 of urine albumin-to-creatinine ratio (UACR) by glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium-glucose cotransporter-2 (SGLT2) inhibitor use at baseline (full analysis set). Per subgroup category an ANCOVA with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, cardiovascular disease history, study, log-transformed baseline value nested within type of albuminuria and the interaction between study and treatment was applied. For Month 4, the closest observation to Day 120 within a time window of 120 ± 30 days after randomization was used. Patients with no measurements within this time window were excluded from the analysis. *Geometric mean of the ratio of UACR at Month 4 to baseline. CI, confidence interval; LS, least squares

receiving a GLP-1RA (Supplementary Table S6). The incidence of hyperkalaemia events leading to permanent discontinuation was low with finerenone and placebo and similar between the patient subgroups (with GLP-1RA: 1.8% vs. 0.9%, respectively, and without GLP-1RA: 1.7% vs. 0.6%, respectively). The incidence of acute kidney injury was similar in finerenone versus placebo, irrespective of GLP-1RA use at baseline (Supplementary Table S5). Moreover, the incidence of hypoglycaemia was similar in the GLP-1RA and no GLP-1RA groups, and in the finerenone and placebo groups (Supplementary Table S5). A modest reduction in systolic blood pressure was observed with finerenone versus placebo, irrespective of whether patients were receiving a GLP-1RA at baseline or not (Supplementary Figure S2).

4 | DISCUSSION

This FIDELITY subgroup analysis showed consistent CV and kidney benefits with finerenone compared with placebo, irrespective of whether a patient was receiving GLP-1RA treatment at baseline or at any time concomitant with study treatment. In addition, a significantly greater reduction in UACR was observed with finerenone in patients taking a GLP-1RA at baseline compared with those without GLP-1RA use at baseline. These findings build on the observation from the FIDELIO-DKD trial that suggested finerenone was associated with consistent reduction in UACR, irrespective of GLP-1RA use at baseline.[17] The current data add to the body of information regarding the effects of finerenone and GLP-1RA co-administration on CV and kidney outcomes.

Currently, GLP-1RAs are recommended in the European Society of Cardiology/European Association for the Study of Diabetes, American Diabetes Association, and Kidney Disease Improving Global Outcomes guidelines for patients with T2D and a history of CV disease,[8,16,20] in patients with an eGFR >30 mL/min/1.73 m^2, and for the management of glucose as the preferred drug after metformin and SGLT2 inhibitors because of their CV benefit.[6,8,16]

Moreover, results from GLP-1RA clinical studies demonstrate that GLP-1RA use leads to a reduction of albuminuria.[13,21] The observations from the current analysis suggest that concomitant use of finerenone and GLP-1RAs may provide additional protection in patients with CKD and T2D (although limitations of this analysis should be considered, including differences in baseline characteristics). Any potential additive effect could be attributable to differential mechanisms of action of the two classes of medication. For example, GLP-1RAs primarily target metabolic factors (poor glycaemic control) while finerenone appears to exert its anti-inflammatory and antifibrotic effects through the blockade of mineralocorticoid receptor overactivation (based on evidence from preclinical models).[12,13,15,22-25] Albeit in a limited subgroup, there were no safety signals or concern with concomitant use of finerenone and GLP-1RAs. The higher incidence of nausea and vomiting observed in patients receiving a GLP-1RA is in line with expectations for the GLP-1RA class.[26] Therefore, there is a need for additional studies on the concomitant use of finerenone and GLP-1RAs to further explore any potential additive or synergistic effect of the two treatments, and any association this may have with the amelioration of long-term risks (which was not observed in this analysis).

The results of recent analyses of pooled data from the SUSTAIN 6 and LEADER trials (N = 12 637) and from the SUSTAIN 1–7 trials (N = 8416) suggest that the GLP-1RAs semaglutide and liraglutide may be efficacious in patients with CKD and T2D.[13,27] Semaglutide or liraglutide therapy reduced albuminuria from baseline to 2 years by 24% compared with placebo, and effects appeared more pronounced in patients with pre-existing CKD, however, this was not significant.[13] It should be noted that the SUSTAIN 6 and LEADER trials were not originally powered to evaluate kidney outcomes and included patients with a relatively low kidney risk at baseline. In the AWARD-7 trial, use of dulaglutide in patients with T2D and moderate-to-severe CKD resulted in glycaemic control similar to that achieved with insulin glargine, but with a significantly reduced decline in eGFR.[28] However,

there are limited data available on the use of dulaglutide (eGFR >15 mL/min/1.73 m^2) and several other GLP-1RAs in patients with severe CKD.[6] This highlights the need for additional efficacy and safety data on the effect of GLP-1RA monotherapy in patients with CKD and T2D. The prospective FLOW Phase III trial, investigating once-weekly injectable semaglutide in patients with CKD and T2D, may confirm the use of an additional therapeutic option for patients with CKD and T2D; this trial is currently ongoing.[11] Although FLOW will not be able to evaluate the combination of semaglutide in randomized patients receiving finerenone at baseline, analysis of patients who start finerenone during the trial may provide insights to inform future research.[16] As previously highlighted, future studies are required to investigate whether the addition of a GLP-1RA to finerenone has additive or synergistic effects for patients with CKD and T2D.

When considering the subgroup of patients with both SGLT2 inhibitor and GLP-1RA use at baseline in the current analysis, the greatest reduction in UACR from baseline to Month 4 was observed in this group compared with the subgroups using either SGLT2 inhibitors or GLP-1RAs, or neither, at baseline (however, this was not found to be significantly different across the subgroups). These observations demonstrate a consistent reduction in UACR with finerenone use regardless of concomitant use of baseline antidiabetic medications, and give no indication that an increasing number of albuminuria-reducing agents at baseline reduces the effect of finerenone, rather the contrary. However, given the small number of patients in the subgroup with both SGLT2 inhibitor and GLP-1RA use at baseline, these data should be interpreted with caution; meaningful conclusions are limited and additional studies are required.

There are further limitations to this exploratory subgroup analysis. Key differences were observed in baseline characteristics across the study population. The higher body mass index and obesity-related measures might suggest that some patients receiving a GLP-1RA were being treated with these agents because of their known benefits with regard to weight loss.[29] This was a post hoc analysis with limited statistical power to fully determine additive effects from the combination of finerenone with a GLP-1RA; therefore, the results should be interpreted with caution. This analysis of GLP-1RA use at baseline should be considered, at any time, a sensitivity analysis, as patients included in this analysis were not randomized by GLP-1RA baseline use at study initiation. We cannot exclude the possibility that patients receiving a GLP-1RA at baseline were recruited from centres that are more thorough in their care, which was also reflected by a greater concomitant use of beta-blockers, statins, SGLT2 inhibitors, and diuretics at baseline among patients receiving a GLP-1RA. Additionally, there may be further inequalities in quality of care dependent on the socioeconomic status of patients who received a GLP-1RA versus those who did not, which has shown a negative correlation with burden of CKD in T2D.[30,31] Patients included in the analyses determining the effect of post-baseline use of GLP-1RAs were not randomized; therefore, these can only be considered as sensitivity analyses. Nevertheless, these limitations are unlikely to impact the observed treatment effect for comparisons of finerenone versus placebo because these were comparing randomized groups. Given the limited number of patients using GLP-1RAs and the subsequent low number of CV composite outcomes, kidney composite outcomes, and mortality events, the CIs are wide, which therefore limits the interpretation of these data. Also, given the limited sample size, we were unable to evaluate if the dose or type of GLP-1RA modified the reported outcomes. Further studies are required to elucidate the additional clinical benefits with combined finerenone and GLP-1RA therapies in this patient population.

In conclusion, this exploratory FIDELITY subgroup analysis supports the hypothesis that the kidney and CV outcome benefits in patients with CKD and T2D are maintained with finerenone treatment, irrespective of treatment with a GLP-1RA, with no apparent safety signals observed with the concomitant use of finerenone and a GLP-1RA. Interpretation of the potential beneficial effect of this combination is somewhat limited by the small sample size and number of events in this analysis. However, given that guidelines recommend the use of finerenone as a goal-directed treatment in patients with T2D who are at risk for CV events or CKD progression,[16] and who may already be receiving a GLP-1RA for glycaemic control, additional randomized trials are required to further assess if the combination of a selective, nonsteroidal mineralocorticoid receptor antagonist with GLP-1RAs, in addition to renin-angiotensin system inhibition, would provide incremental cardiorenal benefits for patients.

AUTHOR CONTRIBUTIONS

The Executive Committee designed the studies in conjunction with Bayer AG. Bayer AG participated in data collection, data analysis, data interpretation, and approval of the manuscript. Peter Rossing wrote the first draft of the report. All authors were involved in data analysis and interpretation and in drafting and critically revising the report. All authors had access to study results, and the first and corresponding author assume responsibility for the integrity and accuracy of the data reported. All authors reviewed and approved the final submitted version of the report.

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CONFLICT OF INTEREST

Peter Rossing reports personal fees from Bayer during the conduct of the study, and has received research support and personal fees from AstraZeneca and Novo Nordisk, and personal fees from Astellas Pharma Inc., Boehringer Ingelheim, Eli Lilly and Company, Gilead, Merck, Merck Sharp & Dohme, Mundipharma, Sanofi, and Vifor Pharma. All fees are given to Steno Diabetes Center Copenhagen. Rajiv Agarwal reports personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals Inc. during the conduct of the study, personal fees and nonfinancial support from Akebia Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Fresenius, Janssen, Relypsa, Sanofi, and Vifor Pharma, personal fees from Ironwood Pharmaceuticals, Lexicon, Merck & Co., and Reata, and nonfinancial support from E. R. Squibb & Sons, Opko Pharmaceuticals, and Otsuka

America Pharmaceutical. He is also a member of data safety monitoring committees for Amgen, AstraZeneca, and Celgene, steering committees of randomized trials for Akebia Therapeutics, Bayer, Janssen, and Relypsa, adjudication committees for AbbVie, Bayer, Boehringer Ingelheim, and Janssen, has served as an associate editor of the *American Journal of Nephrology* and *Nephrology Dialysis and Transplantation* and has been an author for UpToDate, and has received research grants from the US Veterans Administration and the National Institutes of Health. Stefan D. Anker has received research support from Abbott Vascular and Vifor Pharma, and personal fees from Abbott Vascular, Bayer, Boehringer Ingelheim, BRAHMS, Cardiac Dimensions, Impulse Dynamics, Novartis, Servier, and Vifor Pharma. Gerasimos Filippatos reports lectures 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.

Bertram Pitt 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 Inc., has stock options for Ardelyx, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, Sarfez Pharmaceutical Inc., scPharmaceuticals, SQ Innovation, Tricida, and Vifor Pharma/Relypsa Inc., and 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 63/045784). Luis M. Ruilope has received consultancy fees from Bayer. Vivian Fonseca has served as a paid consultant for Abbott, Asahi, AstraZeneca, Bayer, Novo Nordisk, and Sanofi, and has patent and ownership interests in BRAVO4Health. Guillermo E. Umpierrez has received research support (to Emory University) from AstraZeneca, Bayer, and Dexcom Inc. Maria Luiza Caramori reports grants and personal fees from Bayer, personal fees from AstraZeneca and Boehringer-Ingelheim and grants from Novartis. Grants are paid to her institution. Amer Joseph was a full-time employee of Bayer AG, Division Pharmaceuticals, Germany, at the time of the studies and analysis, and is now a full-time employee of Chiesi Farmaceuitici S.p.A, Parma, Italy. Marc Lambelet is an external employee of Bayer AG. Robert Lawatscheck is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany. George L. Bakris reports research funding, paid to the University of Chicago Medicine, from Bayer, during the conduct of the study, and research funding, paid to the University of Chicago Medicine, from Novo Nordisk and Vascular Dynamics, has acted as a consultant for and received personal fees from Alnylam, Merck, and Relypsa, Inc., and is an editor of the *American Journal of Nephrology*, *Nephrology*, and *Hypertension*, a section editor of UpToDate, and an associate editor of *Diabetes Care* and *Hypertension Research*.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are not currently available in a public repository

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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