Rossing Peter (Orcid ID: 0000-0002-1531-4294)

Agarwal Rajiv (Orcid ID: 0000-0001-8355-7100)

Fonseca Vivian (Orcid ID: 0000-0002-3381-7151)

Umpierrez Guillermo (Orcid ID: 0000-0002-3252-5026)

Bakris George L (Orcid ID: 0000-0003-1183-1267)

Finerenone in patients across the spectrum of chronic kidney disease and type 2 diabetes by GLP-1RA use

Peter Rossing MD[1,2] | Rajiv Agarwal, MD, MS[3] | Stefan D. Anker MD[4] | Gerasimos Filippatos MD[5] | Bertram Pitt MD[6] | Luis M. Ruilope MD[7-9] | Vivian Fonseca MD[10] | Guillermo E. Umpierrez MD[11] | Maria Luiza Caramori MD, MSc, PhD[12] | Amer Joseph MBBS[13] | Marc Lambelet Dipl. Math[14] | Robert Lawatscheck MD[15] | George L. Bakris MD[16] | on behalf of the FIDELIO-DKD and FIGARO-DKD Investigators

Institution(s)

[1]Steno Diabetes Center Copenhagen, Herlev, Denmark

[2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[3]Richard L. Roudebush VA Medical Center and Indiana University, Indianapolis, Indiana, USA

[4]Department of Cardiology (CVK); Berlin Institute of Health Center for Regenerative Therapies; German Centre for Cardiovascular Research partner site Berlin; Charité – Universitätsmedizin, Berlin, Germany

[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

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: 10.1111/dom.14883

[9]Faculty of Sport Sciences, European University of Madrid, Madrid, Spain

[10]Tulane University Health Sciences Center, New Orleans, LA, USA

[11]Emory University, Atlanta, GA, USA

[12]Department of Medicine and Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA

[13]Cardiology and Nephrology Clinical Development, Bayer AG, Berlin, Germany

[14]Chrestos Concept GmbH & Co. KG, Essen, Germany

[15] Clinical Research, Bayer AG, Berlin, Germany

[16]Department of Medicine, University of Chicago Medicine, Chicago, IL, USA

Contact information for corresponding author:

Name: Peter Rossing

Address: Steno Diabetes Center Copenhagen, Borgmester Ib Juuls Vej 83, DK 2730 Herlev, Denmark

Tel: +45 30 91 33 83; email: peter.rossing@regionh.dk

Journal: Diabetes, Obesity and Metabolism (DOM)

Word counts: abstract 250/250; main text: 3469/3500

Tables/figures: 5 (max total of 5 tables/figures) in main body; additional tables or figures and/or extra methodological detail can be included in a separate appendix

No. of references: 31/40

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 cardiovascular (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure) and kidney (kidney failure, sustained ≥57% eGFR decline, or renal death) composite outcomes, change in UACR, and safety were analyzed by GLP-1RA use.

Results

Of 13,026 patients, 944 (7.2%) used GLP-1RAs at baseline. Finerenone reduced the risk of the cardiovascular (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 kidney (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) composite outcomes 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 hyperkalemia 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.

Introduction

Type 2 diabetes (T2D) accounts for >90% of the global diabetes burden and is the leading cause of kidney failure in developed countries.[1-3] Chronic kidney disease (CKD) affects ~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 glycemic targets despite use of metformin and a sodium-glucose co-transporter-2 inhibitor (SGLT-2i) 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 on 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 running FLOW trial.[13]

Finerenone is a distinct, selective, non-steroidal 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 the 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.

Materials and methods

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–<300 mg/g and estimated glomerular filtration rate (eGFR) of ≥25–≤90 mL/min/1.73 m^2 or UACR ≥300–≤5000 mg/g and eGFR ≥25 mL/min/1.73 m^2.

Patients with glycated hemoglobin (HbA1c) >12% (>108 mmol/mol) 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 glycemic control. Patients were recruited from September 2015 through 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.

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–<300, ≥300 mg/g) and eGFR at screening (25–<45, 45–<60, ≥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.

Outcomes

Efficacy outcomes of the present analysis included a CV composite outcome of time to CV death, non-fatal myocardial infarction, non-fatal 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 analyzed.

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 (SBP). Data for these efficacy and safety outcomes are reported in patients stratified by GLP-1RA use at baseline.

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 analyzed 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 derived by no GLP-1RA and GLP-1RA at baseline based on separate Cox regression models, including treatment (finerenone vs. placebo), and stratified by prespecified stratification 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, as well as the interaction of the fixed and time-varying terms.

Changes in UACR over time were analyzed 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 a 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 ANCOVA model using adjustment factors as above by combined use of GLP-1RA and SGLT-2i use at baseline.

Analyses of safety outcomes, including treatment-emergent hyperkalemia-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).

Results

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 (**Supplementary Table S1**). Median duration of baseline GLP-1RA medication use prior to randomization was 1.2 years and 1.3 years in the finerenone and placebo groups, respectively. Among patients taking GLP-1RA 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**). Among 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 total the 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 types of GLP-1RA received at baseline and on-treatment are shown in **Supplementary Table S3**.

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 had 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 values of HbA1c, and higher body mass index and waist–hip ratio and were more likely to have a history of hyperlipidemia compared with those not receiving a GLP-1RA. The number of patients with a history of ischemic stroke was lower among patients receiving versus not receiving a GLP-1RA at baseline **(Supplementary Table S4)**. Concomitant use of SGLT-2is, insulin, metformin, beta-blockers, diuretics, and statins were 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)**.

Efficacy

Overall, the risk of the CV composite outcome of time to CV death, non-fatal myocardial infarction, non-fatal 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; HR 0.87; 95% CI 0.79–0.96 without GLP-1RA; 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; HR 0.77; 95% CI 0.67–0.89 without GLP-1RA; *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; HR 0.89; 95% CI 0.79–1.00 without GLP-1RA; *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 [LS] mean treatment ratio: 0.62; 95% CI 0.57–0.67] with GLP-1RA and –31% [LS mean treatment ratio: 0.69; 95% CI 0.66–0.71] 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 **(Figure2)**. 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 SGLT-2i use showed a consistent reduction in UACR from baseline to month 4 with finerenone vs. placebo (–40% in patients with both GLP-1RA and SGLT-2i use at baseline [LS mean treatment ratio: 0.60; 95% CI 0.50–0.72]; –38% in patients with GLP-1RA use only at baseline [LS mean treatment ratio: 0.62; 95% CI 0.57–0.68]; and 36% in patients with SGLT-2i use only at baseline [LS mean treatment ratio: 0.64; 95% CI 0.57–0.72] with no significant difference across subgroups [*p*-interaction = 0.11]; **Figure 4])**.

Safety and vital signs

Overall safety by GLP-1RA use at baseline is shown in **Supplementary Table 5**. Tolerability profiles were similar across all treatment groups (**Supplementary Table 5** and

Supplementary Table S6). There were higher rates of nausea and vomiting in patients receiving a GLP-1RA than in those not receiving a GLP-1RA (**Supplementary Table S6**). The incidence of hyperkalemia 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 5**). Moreover, the incidence of hypoglycemia was similar in the GLP-1RA and no GLP-1RA groups, and in the finerenone and placebo groups (**Supplementary Table 5**). A modest reduction in SBP was observed with finerenone versus placebo, irrespective of whether patients were receiving a GLP-1RA at baseline or not (**Supplementary Figure S2**).

Discussion

This FIDELITY subgroup analysis showed consistent CV and kidney benefits with finerenone compared with placebo, irrespective of whether a patient received a GLP-1RA 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 SGLT-2is 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 owed to differential mechanisms of action of the two classes of medication. For example, GLP-1RAs primarily target metabolic factors (poor glycemic 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 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 glycemic control similar to that achieved with

insulin glargine, but with a significantly reduced decline in eGFR [28] . However, there are limited data available for 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.

Furthermore, when considering the subgroup of patients with both SGLT-2i 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 SGLT-2i or GLP-1RA, 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 reduce the effect of finerenone, rather the contrary. However, given the small number of patients in the subgroup with both SGLT-2i 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. There were key differences 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 on 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 centers that are more thorough in their care, which was also reflected by a greater concomitant use of beta-blockers, statins, SGLT-2is, and diuretics at baseline among patients receiving a GLP-1RA. Additionally, there may be further inequalities in quality of care dependent on the socio-economic 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 unlikely 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, kidney composite, and mortality events, the confidence intervals are wide, which therefore limits the interpretation of these data. Given the limited sample size, we were also 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 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 glycemic control. Additional randomized trials are required to further assess if the combination of a selective, non-steroidal mineralocorticoid receptor antagonist with GLP-1RAs, in addition to renin–angiotensin system inhibition, would provide incremental cardiorenal benefits for patients.

Acknowledgements

Medical writing assistance was provided by Camille Bautista of Chameleon Communications International and was funded by Bayer AG.

Contributors

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.

Role of the funding source

The FIDELIO-DKD and FIGARO-DKD trials were conducted and sponsored by Bayer AG. The sponsor participated in the analysis design, data collection, data analysis, data interpretation, and approval of the manuscript. Analyses were conducted by the sponsor, and

all authors had access to and participated in the interpretation of the data. The authors made the decision to submit for publication.

Data-sharing statement

- Data not currently available
- Will data be available: Yes
- Where: Electronic repository
- When will data availability begin: Date to be confirmed by Bayer

Funding

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

Conflict of Interest

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 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.

RA reported personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals Inc. during the conduct of the study; he also reported personal fees and non-financial 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, Opko Pharmaceuticals, and Otsuka America Pharmaceutical; he is a member of data safety monitoring committees for Amgen, AstraZeneca, and Celgene; 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 an 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 U.S. Veterans Administration and the National Institutes of Health.

SDA 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.

GF 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 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 Pharmaceuticals, scPharmaceuticals, SQ Innovation, Tricida, and Vifor Pharma/Relypsa Inc.; he 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.; 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).

LMR has received consultancy fees from Bayer.

VF has served as a paid consultant for Abbott, Asahi, AstraZeneca, Bayer, Novo Nordisk, and Sanofi. He has patent and ownership interests in BRAVO4Health.

GEU has received research support (to Emory University) from AstraZeneca, Bayer, and Dexcom Inc.

MLC reports grants and personal fees from Bayer, personal fees from AstraZeneca and Boehringer-Ingelheim and grants from Novartis. Grants are paid to Institution.

AJ was a full-time employee of Bayer AG, Division Pharmaceuticals, Germany, at the time of the studies and analysis; he is now a full-time employee of Chiesi Farmaceuitici S.p.A, Parma, Italy.

ML is an external employee of Bayer AG.

RL is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany.

FFGB 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 for and received personal fees from Alnylam, Merck, and Relypsa, Inc.; he is an editor of the *American Journal of Nephrology*, *Nephrology*, and *Hypertension*, and section editor of UpToDate; and he is an associate editor of *Diabetes Care* and *Hypertension Research.*

References

1. United States Renal Data System *Chapter 1: Incidence, prevalence, patient characteristics, and treatment modalities*. USRDS Annual Data Report Volume 2: ESRD in the United States, 2020.
2. United States Renal Data System *Chapter 11: International comparisons*. USRDS Annual Data Report Volume 2: ESRD in the United States, 2020.
3. International Diabetes Federation, *IDF Diabetes Atlas*. 10th ed. 2021, Brussels, Belgium: International Diabetes Federation.
4. Afkarian, M., et al., *Kidney disease and increased mortality risk in type 2 diabetes.* J Am Soc Nephrol, 2013. **24**(2): p. 302–8.
5. Wu, B., et al., *Understanding CKD among patients with T2DM: prevalence, temporal trends, and treatment patterns-NHANES 2007-2012.* BMJ Open Diabetes Res Care, 2016. **4**(1): p. e000154.
6. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group, *KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease.* Kidney Int, 2020. **98**(45): p. S1–S115.
7. American Diabetes Association, *10. Cardiovascular disease and risk management: standards of medical care in diabetes-2021.* Diabetes Care, 2021. **44**(Suppl 1): p. S125–S150.
8. Cosentino, F., et al., *2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD.* Eur Heart J, 2020. **41**(2): p. 255–323.
9. Perkovic, V., et al., *Canagliflozin and renal outcomes in type 2 diabetes and nephropathy.* N Engl J Med, 2019. **380**(24): p. 2295–306.
10. Wheeler, D.C., et al., *Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney*

disease: a prespecified analysis from the DAPA-CKD trial. Lancet Diabet Endocrinol, 2021. **9**(1): p. 22–31.

11. Novo Nordisk A/S. *A research study to see how semaglutide works compared to placebo in people with type 2 diabetes and chronic kidney disease (FLOW)*. 2021; Available from: https://clinicaltrials.gov/ct2/show/NCT03819153.
12. Alicic, R.Z., et al., *Incretin drugs in diabetic kidney disease: biological mechanisms and clinical evidence.* Nat Rev Nephrol, 2021. **17**(4): p. 227–44.
13. Shaman, A.M., et al., *Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: pooled analysis of SUSTAIN 6 and LEADER.* Circulation, 2022. **145**(8): p. 575–85.
14. Bakris, G., et al., *Effects of canagliflozin in patients with baseline eGFR <30 ml/min per 1.73 m^2: Subgroup analysis of the randomized CREDENCE trial.* Clin J Am Soc Nephrol, 2020. **15**(12): p. 1705–14.
15. Agarwal, R., et al., *Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine.* Eur Heart J, 2021. **42**(2): p. 152–61.
16. American Diabetes Association Professional Practice Committee, *11. Chronic kidney disease and risk management: Standards of medical care in diabetes—2022.* Diabetes Care, 2022. **45**(Supplement_1): p. S175–S184.
17. Rossing, P., et al., *Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by GLP-1RA treatment: a subgroup analysis from the FIDELIO-DKD trial.* Diabetes Obes Metab., 2022. **24**(1): p. 125–134.
18. Pitt, B., et al., *Cardiovascular events with finerenone in kidney disease and type 2 diabetes.* N Engl J Med, 2021. **385**(24): p. 2252–63.
19. Bakris, G., *Finerenone and kidney outcomes in patients with chronic kidney disease and type 2 diabetes: Results from FIGARO-DKD*, in *American Society of Nephrology*. 2021, Virtual.

20. Buse, J.B., et al., *2019 update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).* Diabetologia, 2020. **63**(2): p. 221–8.

21. Muskiet, M.H.A., et al., *Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial.* Lancet Diabetes Endocrinol, 2018. **6**(11): p. 859–869.

22. Agarwal, R., et al., *Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: The FIDELITY pooled analysis.* Eur Heart J, 2022. **43**(6): p. 474–84.

23. Kolkhof, P., et al., *Steroidal and novel non-steroidal mineralocorticoid receptor antagonists in heart failure and cardiorenal diseases: comparison at bench and bedside.* Handb Exp Pharmacol, 2017. **243**: p. 271–305.

24. American Diabetes Association, *6. Glycemic targets: standards of medical care in diabetes–2021.* Diabetes Care, 2021. **44 Suppl 1**: p. S73–S84.

25. von Scholten, B.J., et al., *The potential of GLP-1 receptor agonists in type 2 diabetes and chronic kidney disease: from randomised trials to clinical practice.* Ther Adv Endocrinol Metab, 2022. **13**: p. 20420188221112490.

26. Htike, Z.Z., et al., *Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis.* Diabetes Obes Metab, 2017. **19**(4): p. 524–36.

27. Mann, J.F.E., et al., *Effects of once-weekly subcutaneous semaglutide on kidney function and safety in patients with type 2 diabetes: a post-hoc analysis of the SUSTAIN 1-7 randomised controlled trials.* Lancet Diabetes Endocrinol, 2020. **8**(11): p. 880–93.

28. Tuttle, K.R., et al., *Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial.* Lancet Diabetes Endocrinol, 2018. **6**(8): p. 605–17.

29. American Diabetes Association, *Standards of medical care in diabetes-2015.* Diabetes Care, 2015. **38 Suppl**: p. S1–S94.

30. Eberly, L.A., et al., *Association of race/ethnicity, gender, and socioeconomic status with sodium-glucose cotransporter 2 inhibitor use among patients with diabetes in the US.* JAMA Netw Open, 2021. **4**(4): p. e216139.

31. Li, H., et al., *Changing epidemiology of chronic kidney disease as a result of type 2 diabetes mellitus from 1990 to 2017: Estimates from Global Burden of Disease 2017.* J Diabetes Investig, 2021. **12**(3): p. 346–56.

Figure legends

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

Figure 2. Change in UACR over time in patients receiving/not receiving a GLP-1RA at baseline. *p*-interaction at 4 months derived from analysis of covariance = 0.0305.
Mixed model with factors treatment group, region, eGFR 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; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; LS, least-squares; UACR, urine albumin-to-creatinine ratio.

Figure 3. Efficacy outcomes considering the effect of GLP-1RA use at any time on-treatment. The cardiovascular composite outcome included time to cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. The kidney composite outcome included time to kidney failure, sustained ≥57% 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; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Figure 4. Forest plot of analysis of covariance for ratio to baseline at month 4 of UACR by GLP-1RA and SGLT-2i 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, CVD 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; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; LS, least-squares; SGLT-2i, sodium glucose transport 2 inhibitor; UACR, urine albumin-to-creatinine ratio.

Tables

Table 1. Baseline characteristics in patients receiving/not receiving GLP-1RAs at baseline

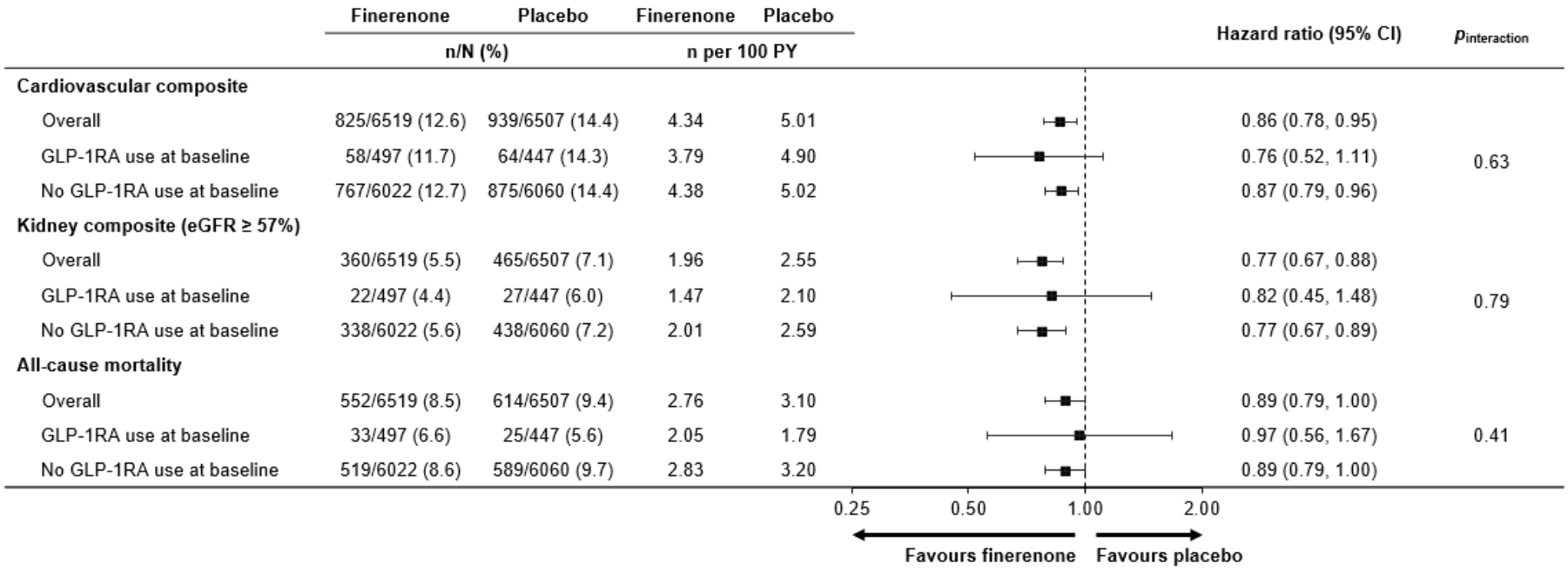
	GLP-1RA use at baseline (n = 944)	No GLP-1RA use at baseline (n = 12,082)
Mean age (SD), years	63 (9.0)	65 (9.6)
Male sex, n (%)	676 (71.6)	8412 (69.6)
Race, n (%)		
White	720 (76.3)	8149 (67.4)
Asian	151 (16.0)	2743 (22.7)
Black/African American	43 (4.6)	479 (4.0)
Mean systolic blood pressure (SD), 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]	7.8 (1.2) [62]	7.7 (1.4) [61]
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, mL/min/1.73 m^2		
Mean (SD)	58.7 (21.6)	57.5 (21.7)

Distribution, n (%)		
<25	7 (0.7)	155 (1.3)
25–<45	295 (31.3)	3937 (32.6)
45–<60	250 (26.5)	3184 (26.4)
≥60	392 (41.5)	4803 (39.8)
UACR, mg/g		
Median (IQR)	483.5 (180–1052)	517.2 (201–1157)
Distribution, n (%)		
<30	17 (1.8)	213 (1.8)
30–<300	313 (33.2)	3786 (31.3)
≥300	614 (65.0)	8078 (66.9)
Medication use at baseline, n (%)		
RAS inhibitor	942 (99.8)	12,061 (99.8)
Beta-blocker	512 (54.2)	5992 (49.6)
Diuretic	564 (59.7)	6146 (50.9)
Statin	782 (82.8)	8617 (71.3)
Potassium supplement	51 (5.4)	334 (2.8)
Potassium-lowering agent	9 (1.0)	173 (1.4)
Glucose-lowering therapies	944 (100.0)	11776 (97.5)
Insulin and analogues	624 (66.1)	7006 (58.0)

Metformin	651 (69.0)	6906 (57.2)
Sulphonylurea	213 (22.6)	3176 (26.3)
SGLT-2 inhibitor	167 (17.7)	710 (5.9)
DPP-4 inhibitor	46 (4.9)	3232 (26.8)
Alpha glucosidase inhibitor	30 (3.2)	626 (5.2)
Meglitinide	47 (5.0)	484 (4.0)
Thiazolidinedione	57 (6.0)	460 (3.8)

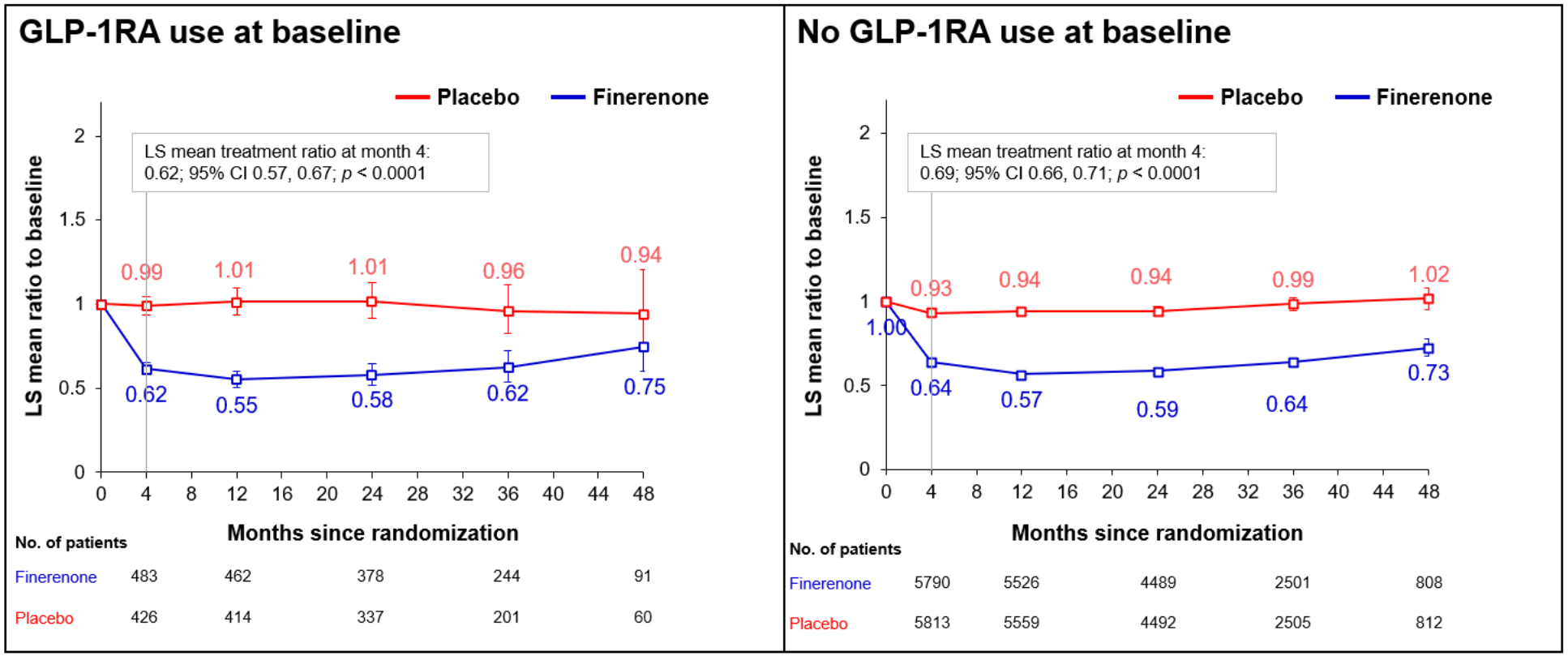
BMI, body mass index; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HF, heart failure; IQR, interquartile range; RAS, renin–angiotensin system; SD, standard deviation;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

Figure 1. Analysis of efficacy outcomes in patients receiving/not receiving a GLP-1RA



The cardiovascular composite outcome included time to cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. The kidney composite outcome included time to kidney failure, sustained ≥57% eGFR decline from baseline, or renal death. CI, confidence interval; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; PY, patient-years.

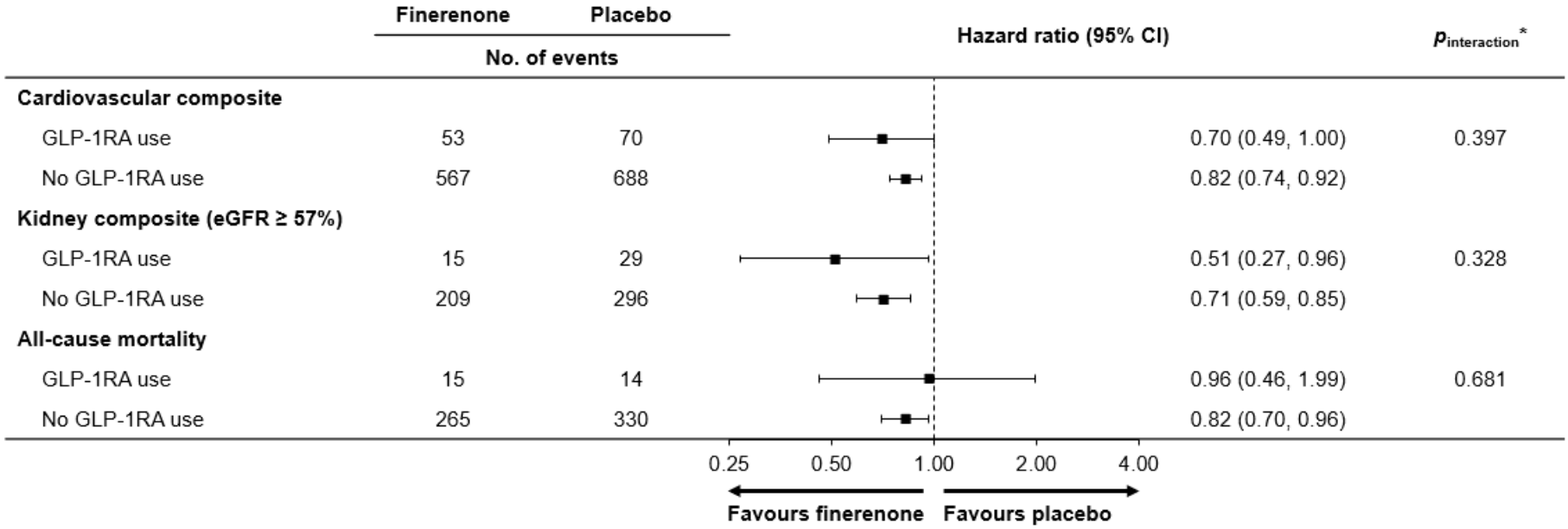
Figure 2. Change in UACR over time in patients receiving/not receiving a GLP-1RA at baseline.



p-interaction at 4 months derived from analysis of covariance = 0.0305.

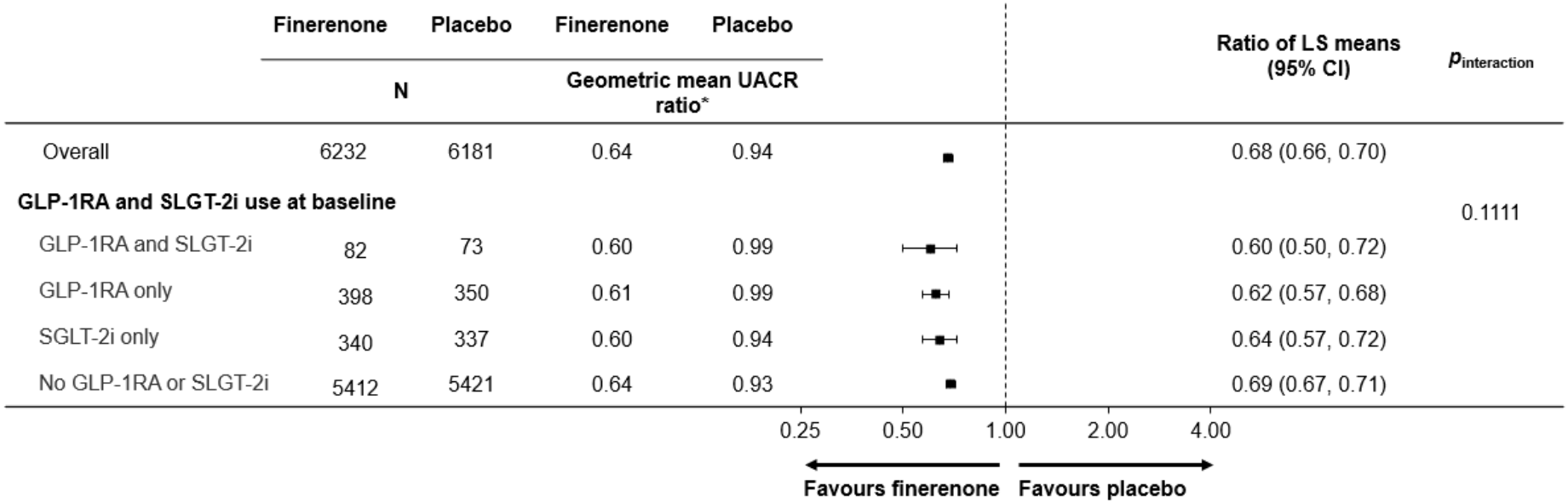
Mixed model with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, time, treatment*time, study, study*treatment, log-transformed baseline value nested within type of albuminuria at screening and log-transformed baseline value*time as covariate. CI, confidence interval; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; LS, least-squares; UACR, urine albumin-to-creatinine ratio.

Figure 3. Efficacy outcomes considering the effect of GLP-1RA use at any time on-treatment.



The cardiovascular composite outcome included time to cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. The kidney composite outcome included time to kidney failure, sustained ≥57% 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; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Figure 4. Forest plot of analysis of covariance for ratio to baseline at month 4 of UACR by GLP-1RA and SGLT-2i 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, CVD 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; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; LS, least squares; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.