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Effects of finerenone in people with chronic kidney disease and type 2 diabetes are independent of HbA1c at baseline, HbA1c variability, diabetes duration and insulin use at baseline

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Abstract

Aim: To evaluate the effect of finerenone by baseline HbA1c, HbA1c variability, diabetes duration and baseline insulin use on cardiorenal outcomes and diabetes progression.

Materials and Methods: Composite efficacy outcomes included cardiovascular (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or

hospitalization for heart failure), kidney (kidney failure, sustained ≥ 57% estimated glomerular filtration rate decline or renal death) and diabetes progression (new insulin initiation, increase in antidiabetic medication, 1.0% increase in HbA1c from baseline, new diabetic ketoacidosis diagnosis or uncontrolled diabetes).

Results: In 13 026 participants, risk reductions in the cardiovascular and kidney composite outcomes with finerenone versus placebo were consistent across HbA1c quartiles (*P* interaction .52 and .09, respectively), HbA1c variability (*P* interaction .48 and .10), diabetes duration (*P* interaction .12 and .75) and insulin use (*P* interaction .16 and .52). HbA1c variability in the first year of treatment was associated with a higher risk of cardiovascular and kidney events (hazard ratio [HR] 1.20; 95% confidence interval [CI] 1.07-1.35; $P = .0016$ and HR 1.36; 95% CI 1.21-1.52; $P < .0001$, respectively). There was no effect on diabetes progression with finerenone or placebo (HR 1.00; 95% CI 0.95-1.04). Finerenone was well-tolerated across subgroups; discontinuation and hospitalization because of hyperkalaemia were low.

Conclusions: Finerenone efficacy was not modified by baseline HbA1c, HbA1c variability, diabetes duration or baseline insulin use. Greater HbA1c variability appeared to be associated with an increased risk of cardiorenal outcomes.

KEYWORDS
cardiovascular disease, clinical trial, diabetes complications, diabetic nephropathy, type 2 diabetes

1 | INTRODUCTION

The prevalence of diabetes is rising. In 2021, ~537 million adults had diabetes, and this number is estimated to reach 783 million by 2045, equating to 10.5% and 12.2% of the global population, respectively.[1] Diabetes is the leading cause of chronic kidney disease (CKD)[2]; approximately two in five people with type 2 diabetes (T2D) also have CKD.[3]

A U-shaped association of HbA1c levels and health outcomes exists, where HbA1c levels of less than 6% and 9% or higher are associated with a higher risk of death in people with CKD and diabetes.[4] Higher HbA1c levels are strongly associated with increased cardiovascular (CV) events, an increased rate of estimated glomerular filtration rate (eGFR) decline and accelerated progression of CKD to end-stage kidney disease.[5-9] Not only the HbA1c level per se, but also its variability, are associated with an increased risk of cardiorenal adverse outcomes and all-cause mortality in people with T2D.[7,10-12] Evidence also suggests that T2D duration is independently associated with an increased risk of microvascular and macrovascular complications.[13-15] People with T2D may eventually require treatment with insulin if other agents fail to achieve glycaemic control,[1,16] and people with T2D on insulin treatment tend to have higher rates of CV death and hospitalization for heart failure (HHF) because of the high level of co-morbidities.[17] Given the role of HbA1c, diabetes duration and insulin use in determining the morbidity and mortality of CKD in T2D, investigating the impact of these factors on the efficacy and safety of therapies that mitigate the cardiorenal impact of CKD in T2D is crucial.

Finerenone is a distinct, selective, non-steroidal mineralocorticoid receptor antagonist (MRA), which, in a subanalysis of the FInerenone in reducing kiDnEy failure and dIsease prOgression in Diabetic Kidney Disease (FIDELIO-DKD; NCT02540993) trial, reduced the risk of cardiorenal outcomes in participants with CKD and T2D, irrespective of HbA1c levels or insulin use.[18] It is of interest to investigate these findings in a broader CKD and T2D population from the FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analysis (FIDELITY) prespecified pooled analysis of the complementary phase 3 trials, FIDELIO-DKD and FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease (FIGARO-DKD; NCT02545049).[19,20] In FIDELITY, finerenone reduced the risk of CV outcomes and kidney disease progression compared with placebo.[21] Another outcome of interest is diabetes progression; excessive aldosterone and associated mineralocorticoid receptor (MR) activation are related to impaired insulin secretion and insulin metabolic signalling, thus, development of T2D.[22] Accordingly, it can be hypothesized that MR antagonism with finerenone may decrease the development and progression of diabetes.

The objective of this post hoc analysis was to evaluate the effect of finerenone by baseline HbA1c, HbA1c variability, diabetes duration and baseline insulin use on cardiorenal outcomes and diabetes progression.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The FIDELITY prespecified pooled analysis combines individual patient-level data from the FIDELIO-DKD and FIGARO-DKD phase

TABLE 1 Patient baseline characteristics according to HbA1c quartile at baseline

	HbA1c quartile at baseline			
	≤ 6.7% (n = 3471)	> 6.7 and ≤ 7.5% (n = 3245)	> 7.5 and ≤ 8.5% (n = 3118)	> 8.5% (n = 3170)
Age, y, mean	65.7	65.6	65.0	62.6
Sex, female, n (%)	903 (26.0)	891 (27.5)	916 (29.4)	1216 (38.4)
Follow-up, y, median (IQR)	3.1 (0.1-5.1)	3.1 (0.1-5.0)	3.0 (0.1-5.1)	2.9 (0.0-5.1)
Race, n (%)				
White	2373 (68.4)	2119 (65.3)	2165 (69.4)	2198 (69.3)
Black/African American	112 (3.2)	128 (3.9)	122 (3.9)	159 (5.0)
Asian	829 (23.9)	839 (25.9)	657 (21.1)	564 (17.8)
Systolic blood pressure, mmHg, mean ± SD	135.7 ± 14.1	137.1 ± 14.6	137.1 ± 14.3	137.2 ± 13.8
Diastolic blood pressure, mmHg, mean ± SD	75.9 ± 9.7	76.1 ± 9.8	76.1 ± 9.6	77.3 ± 9.3
Diabetes duration, y, mean ± SD	12.8 ± 8.6	15.4 ± 8.6	17.0 ± 8.7	16.7 ± 8.2
HbA1c, %, mean ± SD (mmol/mol)	6.2 ± 0.4 (44.3)	7.1 ± 0.2 (54.5)	8.0 ± 0.3 (63.9)	9.6 ± 0.9 (81.5)
HbA1c variability, mean absolute residual ± SD	0.4 ± 0.4	0.5 ± 0.4	0.6 ± 0.5	0.8 ± 0.6
Serum potassium, mmol/L, mean ± SD	4.3 ± 0.5	4.3 ± 0.4	4.4 ± 0.4	4.4 ± 0.4
BMI, kg/m^2, mean ± SD	30.5 ± 6.1	30.9 ± 5.8	31.5 ± 5.8	32.4 ± 6.3
History of CVD, n (%)	1546 (44.5)	1462 (45.1)	1475 (47.3)	1443 (45.5)
Current smoker, n (%)	613 (17.7)	534 (16.5)	492 (15.8)	451 (14.2)
eGFR, ml/min/1.73m^2, mean ± SD	55.9 ± 20.7	56.5 ± 21.0	57.0 ± 22.0	61.2 ± 23.1
eGFR, ml/min/1.73m^2, n (%)				
< 25	44 (1.3)	42 (1.3)	43 (1.4)	33 (1.0)
25-< 45	1193 (34.4)	1092 (33.7)	1038 (33.3)	901 (28.4)
45-< 60	948 (27.3)	888 (27.4)	821 (26.3)	769 (24.3)
≥ 60	1286 (37.0)	1223 (37.7)	1216 (39.0)	1467 (46.3)
UACR, mg/g, median (IQR)	479 (175-1171)	496 (184-1119)	497 (188-1124)	599 (250-1325)
UACR, mg/g, n (%)				
< 30	67 (1.9)	53 (1.6)	63 (2.0)	47 (1.5)
30- < 300	1169 (33.7)	1076 (33.2)	993 (31.8)	855 (27.0)
≥ 300	2235 (64.4)	2116 (65.2)	2061 (66.1)	2267 (71.5)
Baseline medications, n (%)				
ACE inhibitors	1330 (38.3)	1167 (36.0)	1253 (40.2)	1316 (41.5)
ARBs	2141 (61.7)	2073 (63.9)	1860 (59.7)	1854 (58.5)
Beta-blockers	1691 (48.7)	1614 (49.7)	1597 (51.2)	1592 (50.2)
Diuretics	1713 (49.4)	1696 (52.3)	1662 (53.3)	1630 (51.4)
Statins	2407 (69.3)	2385 (73.5)	2323 (74.5)	2265 (71.5)
Potassium supplements	118 (3.4)	92 (2.8)	96 (3.1)	78 (2.5)
Potassium-lowering agents	56 (1.6)	55 (1.7)	38 (1.2)	33 (1.0)
Glucose-lowering therapies, n (%)				
At least one concomitant medication of interest	3263 (94.0)	3199 (98.6)	3039 (97.5)	3149 (99.3)
Insulin and analogues	1154 (33.2)	1789 (55.1)	2137 (68.5)	2537 (80.0)
Metformin	2029 (58.5)	1909 (58.8)	1796 (57.6)	1812 (57.2)
Sulphonylureas	860 (24.8)	915 (28.2)	854 (27.4)	754 (23.8)
DPP-4 inhibitors	937 (27.0)	949 (29.2)	762 (24.4)	622 (19.6)
GLP-1RAs	181 (5.2)	245 (7.6)	284 (9.1)	232 (7.3)
SGLT-2 inhibitors	127 (3.7)	257 (7.9)	244 (7.8)	249 (7.9)
Alpha glucosidase inhibitors	175 (5.0)	191 (5.9)	151 (4.8)	139 (4.4)

TABLE 1 (Continued)

	HbA1c quartile at baseline			
	≤ 6.7% (n = 3471)	> 6.7 and ≤ 7.5% (n = 3245)	> 7.5 and ≤ 8.5% (n = 3118)	> 8.5% (n = 3170)
Meglitinides	177 (5.1)	148 (4.6)	131 (4.2)	74 (2.3)
Thiazolidinediones	145 (4.2)	146 (4.5)	122 (3.9)	104 (3.3)
Medical history findings of interest (investigator reported), n (%)				
Diabetic retinopathy	957 (27.6)	1203 (37.1)	1338 (42.9)	1446 (45.6)
Diabetic neuropathy	713 (20.5)	776 (23.9)	891 (28.6)	1116 (35.2)
CAD	1008 (29.0)	986 (30.4)	1009 (32.4)	988 (31.2)
Myocardial infarction	473 (13.6)	499 (15.4)	509 (16.3)	539 (17.0)
Heart failure	215 (6.2)	223 (6.9)	269 (8.6)	296 (9.3)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; IQR, interquartile range; SD, standard deviation; SGLT-2, sodium-glucose co-transporter-2; UACR, urine albumin-to-creatinine ratio.

3 clinical trials.[19-21] The trials were conducted in accordance with the principles of the Declaration of Helsinki, and protocols were approved by relevant regulatory authorities and ethics committees for each trial site; written informed consent was obtained from all participants. Eligible participants were adults (age ≥ 18 years) with CKD (urine albumin-to-creatinine ratio [UACR] ≥ 30-< 300 mg/g and eGFR ≥ 25-≤ 90 ml/min/1.73m^2, or UACR ≥ 300-≤ 5000 mg/g and eGFR ≥ 25 ml/min/1.73m^2) and T2D, receiving renin-angiotensin system therapy with a serum potassium level of 4.8 mmol/L or less. People with chronic symptomatic heart failure (HF) with reduced ejection fraction (New York Heart Association Class II-IV) or an HbA1c of more than 12.0% were excluded. Standard-of-care therapy, including a maximum tolerated labelled dose of a renin-angiotensin system inhibitor, was optimized during the run-in period. Participants were randomized (1:1) to receive once-daily oral treatment with finerenone (at titrated doses of 10 or 20 mg), or matching placebo. Physicians and participants were advised to follow local guidelines for the management of glycaemia. The use of oral antidiabetics was not restricted during the trials (Table 1).

2.2 | Key outcomes

Efficacy outcomes included a CV composite of CV death, non-fatal myocardial infarction, non-fatal stroke or HHF and a kidney composite of kidney failure, a sustained decrease of 57% or higher in eGFR from baseline (equivalent to a doubling of the serum creatinine level) maintained for at least 4 weeks or renal death. Kidney failure was defined as end-stage kidney disease—described as the initiation of long-term dialysis (≥ 90 days) or kidney transplantation—or a sustained decrease in eGFR to less than 15 ml/min/1.73m^2. A sustained decline in eGFR required confirmation with a second consecutive central laboratory measurement at least 4 weeks after the initial measurement.

The diabetes progression composite outcome included new insulin initiation, increase in the number of antidiabetic medication classes, an increase in HbA1c of 1.0% from baseline, a new diagnosis of diabetic ketoacidosis or uncontrolled diabetes (an investigator-reported adverse event [AE]). Safety outcomes and incidence of AEs, treatment-emergent hyperkalaemia and hypoglycaemia were also evaluated. AEs were coded using the latest version of the Medical Dictionary for Regulatory Activities.

2.3 | Statistical analysis

Efficacy outcomes were analysed in the pooled full analysis set (by intention-to-treat), comprising all participants randomized who did not have critical Good Clinical Practice violations. The included analyses were exploratory in nature. Composite outcomes were analysed by defined categorical subgroups (i.e. baseline HbA1c quartiles, baseline diabetes duration quartiles and baseline insulin use [yes/no]). Analyses were adjusted for baseline HbA1c, and stratification factors were screening UACR, screening eGFR, region and CV disease history. Because of randomization between the treatment groups, diabetes duration was similar between groups; therefore, it was not adjusted for in this analysis. Outcomes were also analysed over the range of continuous HbA1c variability in the first year of treatment. Based on a publication by Skriver et al.[23] HbA1c variability was defined as the mean absolute residual of HbA1c measurements to the interpolated months 4 and 8 values between baseline and year 1, reflecting both increases and decreases in HbA1c to show the change from the 'expected' values between two time points. This measure assesses how the magnitude of increase in HbA1c over time contributes to the risk of outcomes. The analysis included descriptive statistics, time-to-event analyses, a statistical test for interaction, subject to sufficient sample size with a given subgroup and mixed models for repeated measures. Time-to-event treatment effects were expressed as hazard ratios (HRs) with corresponding confidence intervals (CIs). HRs (95% CI) are based on the stratified Cox proportional hazards model estimated within each level of the subgroup variable. HRs with

corresponding CIs for the components of the composite outcomes were also calculated. The *P* interaction of the treatment group (finerenone or placebo) and each baseline subgroup is based on the Cox proportional hazards model, including the terms treatment group, baseline subgroup and their interaction. The relationship of the CV and kidney composite outcomes with HbA1c variability in the first year of treatment as a continuous variable was investigated post hoc by means of a Cox proportional hazards model with cubic B-splines of HbA1c with three equally spaced knots, stratified by region, albuminuria at screening and eGFR at screening, with treatment interaction as covariates. Models were fitted separately in each treatment group (i.e. finerenone and placebo) to investigate the relationship between HbA1c variability and outcomes. Furthermore, an exploratory analysis was conducted for the HHF component of the CV composite outcome (as in the FIDELITY analysis, HHF was the main driver of the cardiovascular benefit with finerenone). Events were reported from randomization up to the end-of-study visit. In the variability analyses, events that occurred in year 1 were removed to allow the estimation of effect of year 1 variability on subsequent events.

3 | RESULTS

3.1 | Study cohort

In total, 13 026 study participants were included in the FIDELITY analysis; mean baseline HbA1c was 7.7% (60.7 mmol/mol), mean diabetes duration was 15.4 years and 7630 (58.6%) participants used insulin at baseline. Median follow-up was 3.0 years (interquartile range 2.3-3.8 years). The distribution of participants by baseline HbA1c quartile was 6.7% or less (n = 3471); more than 6.7% and 7.5% or less (n = 3245); more than 7.5% and 8.5% or less (n = 3118); and more than 8.5% (n = 3170), with mean baseline HbA1c values of 6.2%, 7.1%, 8.0% and 9.6%, respectively. The distribution of participants by diabetes duration quartile was 9.1 years or less (n = 3259); more than 9.1 and 15.1 years or less (n = 3246); more than 15.1 and 20.2 years or less (n = 3251); and more than 20.2 years (n = 3252), with mean diabetes duration of 5.3, 11.8, 17.5 and 27.0 years, respectively.

3.2 | Baseline characteristics

Participant baseline characteristics according to HbA1c quartile, diabetes duration and insulin use are shown in Tables 1, S1 and S2, respectively. Compared with participants with lower HbA1c, participants with higher HbA1c had longer diabetes duration, higher body mass index, higher median UACR and were more probable to have a history of diabetic retinopathy, diabetic neuropathy, coronary artery disease, myocardial infarction or HF. Higher insulin, glucagon-like peptide-1 receptor agonist and sodium-glucose co-transporter-2 inhibitor use were also observed among these participants. Participants with baseline insulin use had longer diabetes duration, higher HbA1c and an increased history of CV disease than participants without baseline insulin use.

3.3 | CV composite outcomes

As previously reported, the CV composite outcome was less frequent with finerenone versus placebo in the overall population of the FIDELITY analysis (HR 0.86; 95% CI 0.78-0.95).

3.3.1 | According to baseline HbA1c quartile and HbA1c variability

The incidence of CV events was highest among participants in higher baseline HbA1c quartiles: 406/3118 (13.0%) and 531/3170 (16.8%) for HbA1c of more than 7.5% and 8.5% or less and HbA1c of more than 8.5%, respectively; and was lowest for those with a baseline HbA1c of 6.7% or less or HbA1c of more than 6.7% and 7.5% or less: 429/3471 (12.4%) and 391/3245 (12.0%), respectively. Finerenone reduced the incidence of the CV composite outcome compared with placebo across baseline HbA1c quartiles, with no significant interaction observed among subgroups (*P* interaction .52; Figure 1).

Higher HbA1c variability in the first year of treatment was associated with an increased risk of CV events; each unit increase in mean absolute residual of HbA1c was associated with a 20% increased risk of a CV event (HR 1.20; 95% CI 1.07-1.35; $P = .0016$; Figure 2). Across the range of HbA1c variability in the first year as a continuous variable, overall CV outcomes were improved if HbA1c variability was minimized; that is, greater HbA1c variability was associated with a higher risk of CV outcomes (Figure 2). HbA1c variability did not modify the treatment effect of finerenone on the CV outcome (*P* interaction .49). Although no statistical interaction was observed, a numerical risk reduction for one unit increase in variability when comparing finerenone with placebo was observed (Figure 2).

3.3.2 | According to diabetes duration

The incidence of CV events was highest in participants with a longer diabetes duration compared with those with a shorter diabetes duration, at 333/3259 (10.2%) for 9.1 years or less; 403/3246 (12.4%) for more than 9.1 and 15.1 years or less; 518/3251 (15.9%) for more than 15.1 and 20.2 years or less; and 508/3252 (15.6%) for more than 20.2 years. Finerenone reduced the risk of the CV composite outcome compared with placebo across all quartiles of diabetes duration at baseline, with no interaction observed among subgroups (*P* interaction .12; Figure 1).

3.3.3 | According to baseline insulin use

Participants with baseline insulin use had increased incidence of CV composite outcomes compared with those without baseline insulin use at 1176/7630 (15.4%) versus 588/5396 (10.9%), respectively (HR 1.44; 95% CI 1.30-1.60). The reduction in relative risk of the CV composite outcome with finerenone was consistent in participants

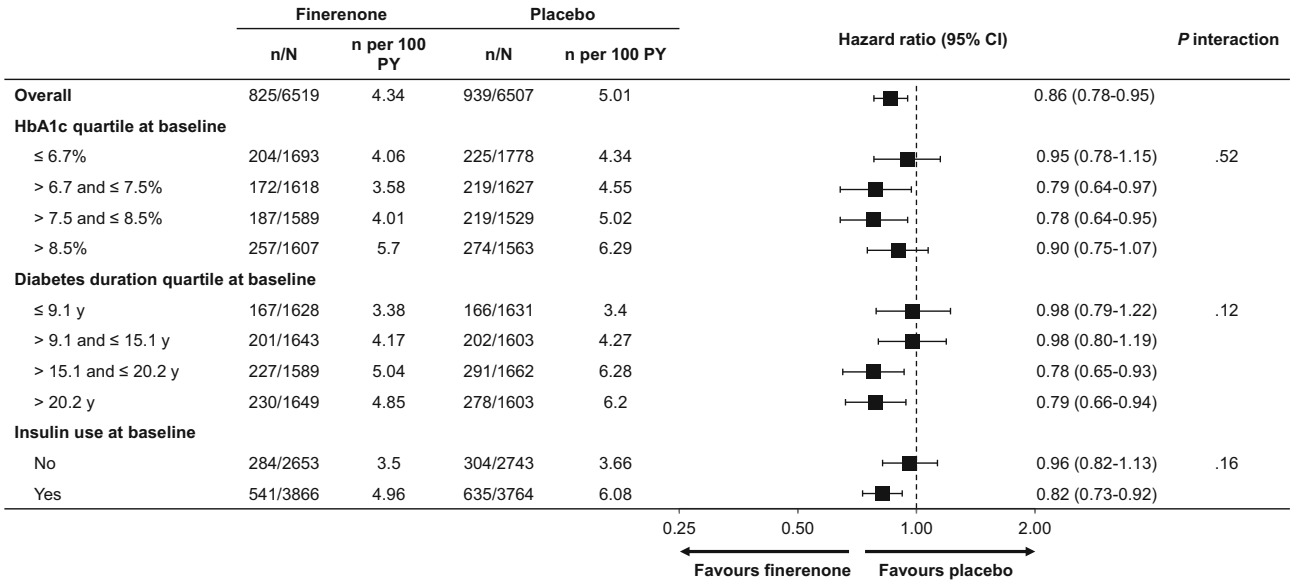


FIGURE 1 CV composite outcome according to HbA1c quartile at baseline, diabetes duration at baseline and insulin (yes/no) use at baseline. CI, confidence interval; CV, cardiovascular; PY, patient-years

with and without baseline insulin use (*P* interaction .16; Figure 1). Of the components of the composite outcome, participants with baseline insulin use had an increased incidence of HHF compared with those without baseline insulin use at 405/7630 (5.3%) and 176/5396 (3.3%), respectively. Although a trend was observed towards a greater risk reduction with finerenone on the HHF component among participants with baseline insulin use versus without baseline insulin use (HR, 0.71; 95% CI 0.58-0.86 and HR, 0.98; 95% CI 0.73-1.32, respectively), this interaction was not significant (*P* interaction .09).

3.4 | Kidney composite outcomes

As previously reported, the kidney composite outcome was lower with finerenone versus placebo in the overall population of the FIDELITY analysis (HR 0.77; 95% CI 0.67-0.88; $P = .0002$).

3.4.1 | According to baseline HbA1c quartile and HbA1c variability

Participants with the lowest (≤ 6.7%) and highest (> 8.5%) baseline HbA1c had the greatest incidence of kidney events at 252/3471 (7.3%) and 198/3170 (6.2%), respectively. Incidence was lower among participants with HbA1c of more than 6.7% and 7.5% or less and HbA1c of more than 7.5% and 8.5% or less at 185/3245 (5.7%) and 189/3118 (6.1%), respectively. Finerenone reduced the relative risk of the kidney composite outcome compared with placebo across baseline HbA1c quartiles, with no interaction observed between subgroups (*P* interaction .09; Figure 3).

Higher HbA1c variability in the first year of treatment was associated with an increased risk of kidney events; each unit increase in mean absolute residual of HbA1c was associated with a 36% increased risk of a kidney event (HR 1.36; 95% CI 1.21-1.52; $P < .0001$). Across the range of HbA1c variability in the first year as a continuous variable, overall kidney outcomes were improved if HbA1c variability was minimized; that is, greater HbA1c variability was associated with a higher risk of kidney outcomes (Figure 2). HbA1c variability did not modify the treatment effect of finerenone on the kidney composite outcome (*P* interaction .10). Although no statistical interaction was observed, a numerical risk reduction for one unit increase in variability when comparing finerenone with placebo was found (Figure 2).

3.4.2 | According to diabetes duration

The incidence of kidney events was greatest in participants with a diabetes duration of more than 15.1 and 20.2 years or less, 237/3251 (7.3%), yet was lowest in participants with a diabetes duration of more than 20.2 years, 187/3252 (5.8%). Incidence was similar in participants with a diabetes duration of 9.1 years or less, and of more than 9.1 and 15.1 years or less, at 200/3259 (6.1%) and 198/3246 (6.1%), respectively. Finerenone reduced the relative risk of the kidney composite outcome compared with placebo across all quartiles of diabetes duration at baseline, with no interaction observed between subgroups (*P* interaction .75; Figure 1).

3.4.3 | According to baseline insulin use

Participants with baseline insulin use had an increased incidence of kidney composite outcomes, 537/7630 (7.0%), compared with participants without baseline insulin use, 288/5396 (5.3%) (HR 1.15; 95% CI

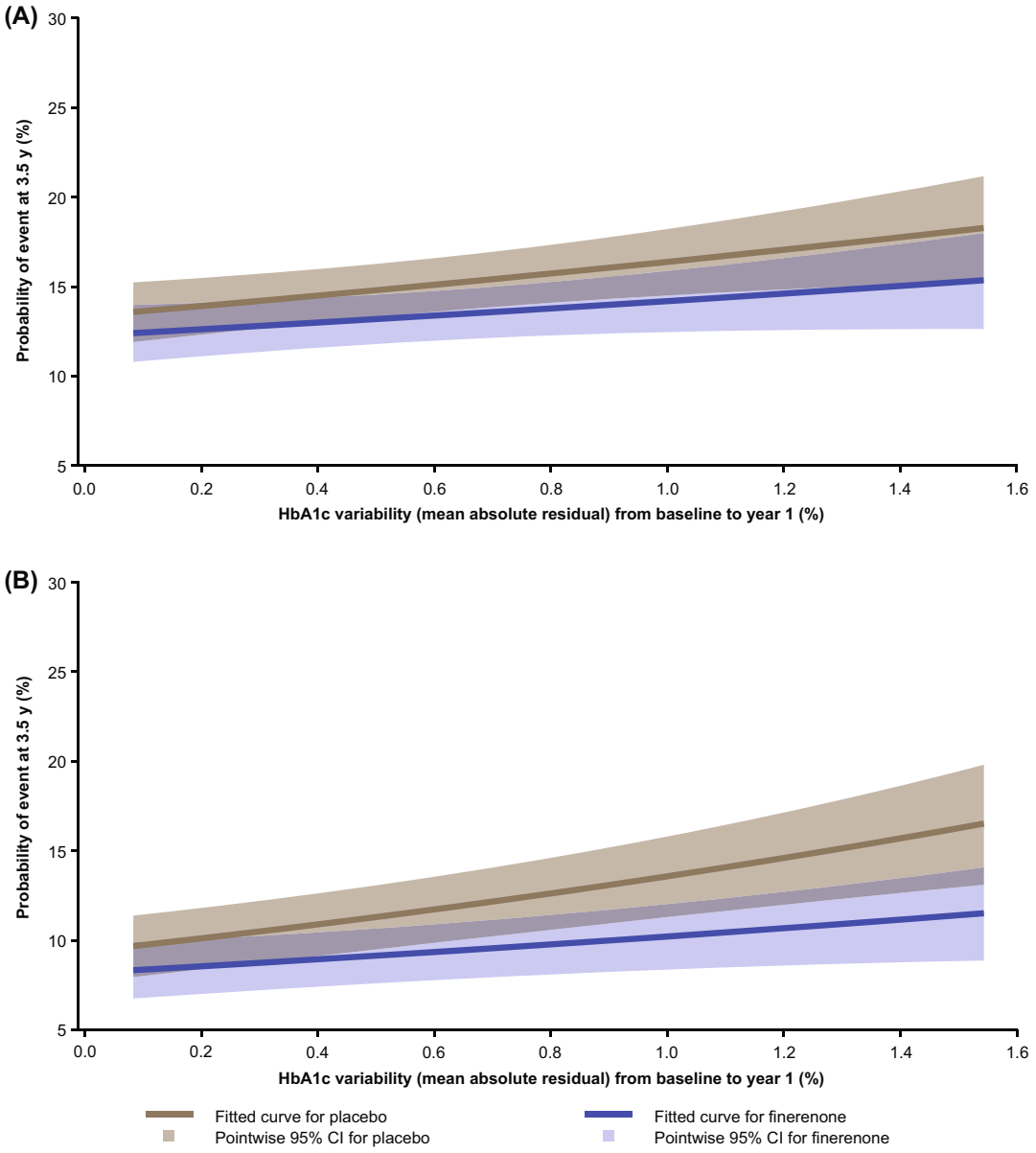


FIGURE 2 Event probability at 3.5 years for A, CV[†], and B, Kidney[‡] composite outcomes by HbA1c variability from baseline to year 1. [†]The composite of time to first onset of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure. [‡]The composite of time to first onset of kidney failure, sustained ≥ 57% decrease in eGFR from baseline over ≥ 4 weeks or renal death. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate

0.99-1.33). The kidney composite outcome occurred less frequently among finerenone-treated participants compared with placebo, irrespective of baseline insulin use (*P* interaction .52; Figure 3).

3.5 | Diabetes progression composite outcome

In the overall population of the FIDELITY analysis, the diabetes progression composite occurred in 4109/6519 (63.0%) participants randomized to finerenone and in 4113/6507 (63.2%) participants randomized to placebo (HR 1.00; 95% CI 0.95-1.04; Figure 4). Numerically fewer participants initiated new glucose-lowering therapies in the finerenone treatment group compared with the placebo treatment group; new insulin initiation was 8.1% versus 9.0%, and the increase in the number of antidiabetic medication classes was 32.1% versus 34.0% with finerenone compared with placebo, respectively. An increase in HbA1c of 1.0% from baseline was similar between participants treated with finerenone and placebo (48.8% and 48.1%, respectively), as were new diagnoses of diabetic ketoacidosis or uncontrolled diabetes (2.6% in both groups).

3.6 | Safety

Safety outcomes according to HbA1c quartile, diabetes duration and baseline insulin use are shown in Tables S3-S5, respectively. The

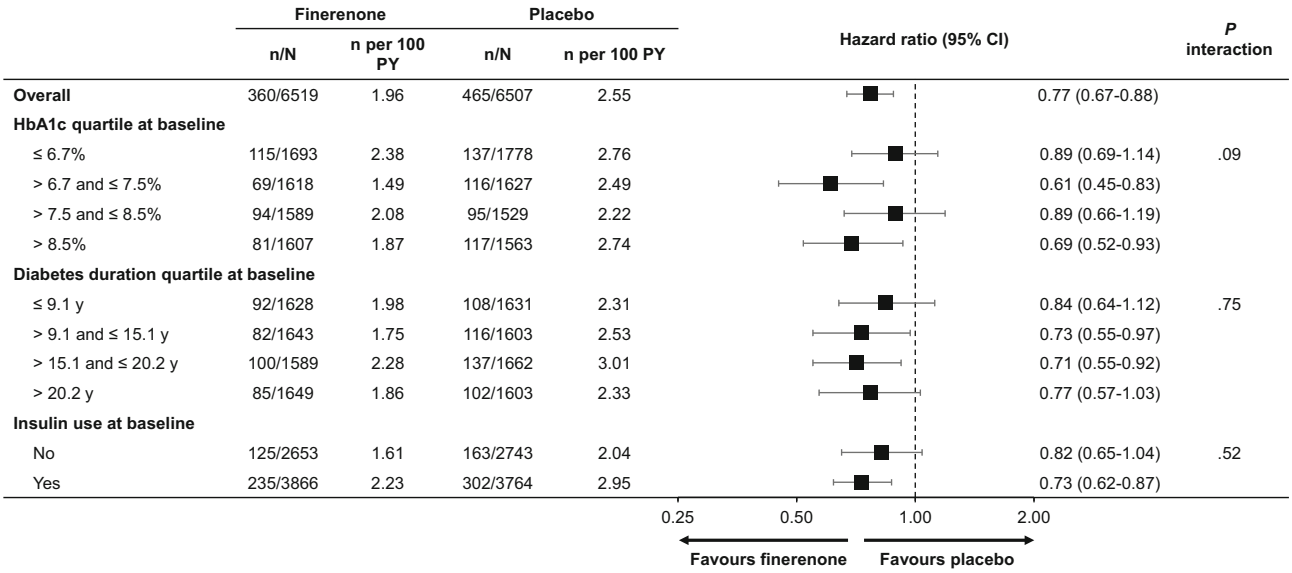
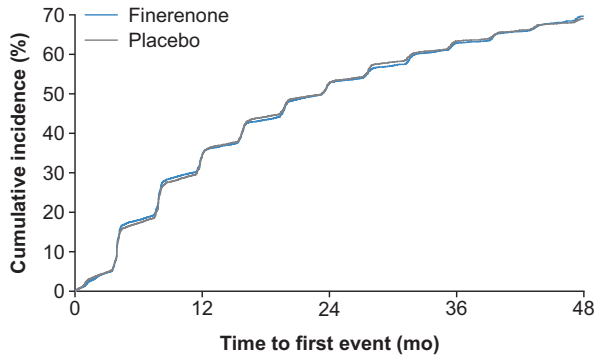


FIGURE 3 Kidney composite outcome according to HbA1c quartile at baseline, diabetes duration at baseline and insulin use (yes/no) at baseline. CI, confidence interval; PY, patient-years



No. at risk					
Finerenone	6519	4195	2614	1269	366
Placebo	6507	4168	2582	1238	383

FIGURE 4 Diabetes progression composite outcome. The composite refers to time to new insulin initiation, increase in the number of antidiabetic medication classes, increase in HbA1c of 1.0% from baseline, new diagnosis of diabetic ketoacidosis or uncontrolled diabetes

incidence of any AEs, including serious AEs (SAEs), was greater in participants with baseline insulin use versus those without baseline insulin use and in participants with longer versus shorter diabetes duration. The incidence of AEs was similar with finerenone and placebo, irrespective of patient subgroup. The incidence of SAEs leading to study discontinuation remained low across subgroups, ranging from 1.6% to 3.0%.

Generally, incidence of hypoglycaemia tended to be lower with finerenone compared with placebo, particularly in participants with higher baseline HbA1c, longer diabetes duration and with baseline insulin use (Tables S3-S5, respectively).

Any investigator-reported hyperkalaemia-related AEs, including SAEs, were more frequent in participants receiving finerenone than in those receiving placebo across all subgroups. Any investigator-reported hyperkalaemia-related AEs were similar among HbA1c quartiles, irrespective of treatment group, although they were notably more frequent in participants with a longer diabetes duration and in participants with baseline insulin use across both finerenone and placebo treatment groups. Nevertheless, investigator-reported hyperkalaemia-related AEs leading to discontinuation and SAEs leading to hospitalization were low across subgroups and treatment groups.

4 | DISCUSSION

These results are in line with FIDELIO-DKD subanalyses, where the cardiorenal benefits of finerenone in participants with CKD and T2D are consistent, irrespective of HbA1c level or baseline insulin use.[18] This post hoc analysis shows that the benefits of finerenone in participants with CKD and T2D are also not significantly modified by HbA1c variability or baseline diabetes duration. Additionally, there was no effect on diabetes progression with finerenone or placebo; however, a trend was observed with finerenone towards lower initiation of new insulin and new antidiabetic medication versus placebo.

Notably, HbA1c variability was associated with a greater risk of cardiorenal outcomes, consistent with prior research. A recent meta-analysis of people with T2D showed that high levels of glycaemic variability are significantly associated with an increased risk of CV events.[24] A prospective analysis found that participants who progressed to CKD had higher HbA1c variability compared with participants who maintained normal renal function.[7]

Similar to this study, participants with T2D and CKD treated with canagliflozin had similar risk reductions of CV events, regardless of baseline HbA1c.[25] Conversely, the Empagliflozin Cardiovascular

Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial showed significant heterogeneity in CV outcomes between participants with T2D at high risk of CV events with HbA1c levels of less than 8.5% versus 8.5% or higher, suggesting that empagliflozin had no observed CV benefits in participants with an HbA1c of 8.5% or higher.[26] However, comparing the results of FIDELITY with trials of other treatments is difficult because of variances in entry criteria and efficacy outcomes between trials.

Insulin use may be indicative of more advanced and a longer diabetes duration, which contribute to poorer clinical outcomes.[1,16] Additionally, the sodium-retaining effect of insulin may precipitate worsening of HF.[27,28] Accordingly, an increased incidence of HHF was observed among participants with baseline insulin use in the current analysis (although this may be related to confounders such as disease severity and longer diabetes duration). This aligns with findings from observational studies, systematic reviews and meta-analyses where insulin is associated with worse CV and HF outcomes in people with T2D compared with other therapies, even when controlling for diabetes duration.[29,30] Notably, finerenone appeared to show a trend towards a reduction in the risk of cardiorenal events in participants with baseline insulin use versus without, albeit this was not a significant difference. In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, participants with insulin-treated diabetes experienced a larger magnitude of benefit from eplerenone, a steroidal MRA, compared with those participants not treated with insulin.[17] Because of its mechanism of action, preclinical evidence shows that finerenone exerts a natriuretic effect[31]; therefore, the observed benefit of finerenone may be explained, at least in part, by a natriuretic mechanism counteracting the sodium-retaining effect of insulin.

Insulin is a major determinant of hypoglycaemia; ~25% of people with T2D receiving insulin for more than 5 years experience at least one severe hypoglycaemic event.[32] Here, the incidence of hypoglycaemia tended to be lower with finerenone compared with placebo in participants with baseline insulin use, consistent with the FIDELIO-DKD subanalysis.[18] Finerenone appears to have no effect on HbA1c levels in people with CKD in T2D, as shown in the FIDELIO-DKD and FIGARO-DKD trials,[19,20] thus an explanation for these findings warrants further investigation. Nevertheless, these results favour the safety profile of finerenone in people with CKD and T2D.

Given that excessive aldosterone and associated MR activation give rise to the development of T2D,[22,33] the current analysis investigated the effect of finerenone on diabetes progression. In animal studies, MRAs have shown beneficial effects on glucose tolerance and metabolic variables. Eplerenone significantly reduced insulin resistance in obese ob/ob (obese) and db/db (diabetic) mice and improved insulin sensitivity in insulin-resistant rats.[34,35] In the current study, although a trend was observed in which finerenone reduced the initiation of new glucose-lowering therapies compared with placebo, finerenone did not appear to reduce the overall risk of diabetes progression. More studies are warranted to understand the role of MRAs, including finerenone, in the prevention or improvement of insulin resistance.[22]

Limitations of the current analysis exist. The accuracy and precision, and therefore reliability, of HbA1c measurement decline with advanced CKD, particularly among participants on dialysis.[36] However, participants in the current analysis with an eGFR of less than 25 ml/min/1.73 m^2 and receiving dialysis for acute kidney failure within 12 weeks of the run-in visit were excluded; therefore, the impact of this limitation may be minimal. Additionally, 8.5% of participants initiated insulin as a new medication during the study, although these participants were analysed as participants without baseline insulin use. Finally, regarding the diabetes progression composite component of an increase in HbA1c of 1.0% from baseline, it should be noted that people with progressive CKD may have worsening anaemia that can cause a decrease in HbA1c, despite 'progressive' diabetes. However, these participants would most probably be captured in another component of the diabetes progression composite endpoint.

This FIDELITY post hoc analysis shows that the overall cardiorenal benefits and safety profile of finerenone in FIDELITY are also observed in participants with CKD and T2D regardless of HbA1c variability, baseline HbA1c, diabetes duration or baseline insulin use. Furthermore, this analysis also provides evidence that greater HbA1c variability appears to be associated with increased risks of cardiorenal outcomes.

AUTHOR 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. JBM 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 assumes 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 STATEMENT

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Nordisk, Provention Bio and Thermo Fisher; she reports research funding paid to Washington University from NIH, Beta Bionics, Dexcom and Novo Nordisk. She is a member of steering committees for Bayer and the Jaeb Center and data safety monitoring committees for NIH and the Jaeb Center and is an associate editor of the *Journal of the Endocrine Society* and *British Medical Journal Diabetes Research and Care*. RA reported personal fees and non-financial support from Bayer Healthcare Pharmaceuticals Inc. during the conduct of the study; he also reported personal fees and non-financial support from Akebia Therapeutics, Boehringer Ingelheim, Eli Lilly and Vifor Pharma; he is a member of data safety monitoring committees for Vertex and Chinook, a member of steering committees of randomized trials for Akebia Therapeutics, Bayer and Relypsa, and a member of adjudication committees for Bayer; he has served as associate editor of the *American Journal of Nephrology* and *Nephrology Dialysis and Transplantation* and has been an author for UpToDate; and he has received research grants from the U.S. Veterans Administration and the National Institutes of Health. SDA has received research support from Abbott Vascular and Vifor International and personal fees from Abbott Vascular, Bayer, Boehringer Ingelheim, BRAHMS, Cardiac Dimensions, Impulse Dynamics, Novartis, Servier and Vifor Pharma. GLB reported research funding, paid to the University of Chicago Medicine, from Bayer during the conduct of the study; he also reported 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 the *American Journal of Nephrology*, *Nephrology* and *Hypertension*, section editor of UpToDate, and is an associate editor of *Diabetes Care and Hypertension Research*. GF reported 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. BP reported consultant fees for AstraZeneca, Bayer, Boehringer Ingelheim, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, PhaseBio, Proton Intel, Sanofi/Lexicon, Sarfez, scPharmaceuticals, SQ Innovation, Tricida and Vifor/Relypsa; he has stock options for KBP Biosciences, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, Proton Intel, Sarfez, scPharmaceuticals, SQ Innovation, Tricida and Vifor/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). LMR reported receipt of consultancy fees from Bayer. ALB reported research support from Boehringer Ingelheim and personal fees from Boehringer Ingelheim, AstraZeneca and Novo Nordisk. All fees are given to the Tübingen University. MLC reports grants and personal fees from Bayer and grants from Novartis, all these paid to her institution. She has received personal fees from Boehringer Ingelheim and AstraZeneca. MB is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany. 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 Farmaceutici S.p.A, Parma, Italy. AL is a full-time employee of Bayer SA, Division Pharmaceuticals, Brazil. RL is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany. CS is a full-time employee of Bayer PLC, Division Pharmaceuticals, UK. PR reported personal fees from Bayer during the conduct of the study; he has received research support and personal fees from AstraZeneca and Novo Nordisk and personal fees from Astellas, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, Sanofi and Vifor; all fees are given to Steno Diabetes Center Copenhagen.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14999.

DATA AVAILABILITY STATEMENT

Data and Resource Availability; Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, timepoint and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014. Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal. Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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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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