Diabetes Care
American Diabetes Association

Outcomes With Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Baseline Insulin Resistance

Thomas Ebert, Stefan D. Anker, Luis M. Ruilope, Paola Fioretto, Vivian Fonseca, Guillermo E. Umpierrez, Andreas L. Birkenfeld, Robert Lawatscheck, Charlie Scott, Katja Rohwedder, and Peter Rossing, on behalf of the FIDELIO-DKD and FIGARO-DKD Investigators

Diabetes Care 2024;47(3):362–370 | https://doi.org/10.2337/dc23-1420

Outcomes With Finerenone in Patients With Chronic kidney Disease and Type 2 Diabetes by Baseline Insulin Resistance

A post hoc analysis to explore whether insulin resistance, assessed by eGDR, is associated with heart and kidney risk, and whether it modifies finerenone efficacy in the FIDELITY pooled data set

Protocol

n = 6519 / *n* = 6507 — R — Finerenone (10 or 20 mg od) / Placebo — Median follow-up: 3 years

Outcomes

CV composite: Time to CV death, non-fatal MI, non-fatal stroke, or HHF

≥57% kidney composite: Time to kidney failure, sustained ≥57% decrease in eGFR, or renal death

eGDR as an estimate of baseline insulin resistance

Calculated using waist circumference, hypertension status, and glycated hemoglobin for **12,964** patients with **CKD and T2D**

Median eGDR: 4.1 mg/kg/min

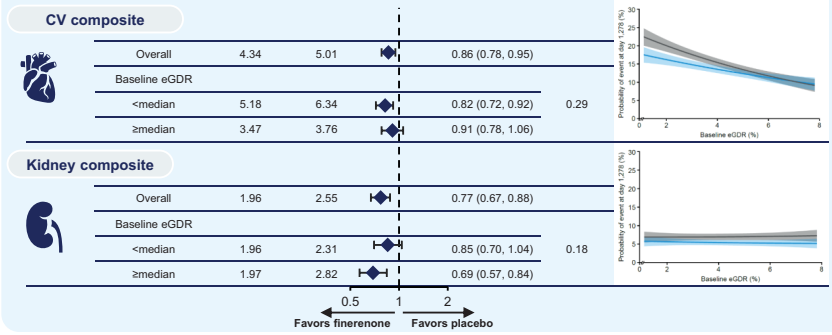
<median (insulin-resistant) — *n* = 6484 — 50 %

≥median (insulin-sensitive) — *n* = 6480 — 50 %

Finerenone reduced the risk of the CV and kidney outcomes irrespective of baseline eGDR

eGDR <median was associated with a higher incidence of cardiovascular events vs eGDR ≥median
The effect of finerenone vs placebo on CV and kidney outcomes showed no change across the range of eGDR values at baseline

	Finerenone *n* per 100 PY	Placebo *n* per 100 PY	HR (95% CI)	*P*-value for interaction
CV composite				
Overall	4.34	5.01	0.86 (0.78, 0.95)	
Baseline eGDR				
<median	5.18	6.34	0.82 (0.72, 0.92)	0.29
≥median	3.47	3.76	0.91 (0.78, 1.06)	
Kidney composite				
Overall	1.96	2.55	0.77 (0.67, 0.88)	
Baseline eGDR				
<median	1.96	2.31	0.85 (0.70, 1.04)	0.18
≥median	1.97	2.82	0.69 (0.57, 0.84)	



In FIDELITY:

- **Insulin resistance was not a predictor of CKD progression in advanced CKD**
- **Insulin resistance was associated with increased cardiovascular (but not kidney) risk, with the benefit of finerenone maintained irrespective of baseline insulin resistance**

CKD, chronic kidney disease; CV, cardiovascular; eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction; od, once daily; PY, person-year; T2D, type 2 diabetes.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Insulin resistance contributes to kidney and cardiovascular (CV) morbidity and mortality, and investigating the cardiorenal impact of existing therapies is important.

- **What is the specific question(s) we wanted to answer?**
  This analysis explored whether insulin resistance was associated with CV events and chronic kidney disease (CKD) progression, and whether it modified finerenone efficacy.

- **What did we find?**
  Insulin resistance was associated with an increased CV (but not kidney) risk. Insulin resistance was not a predictor of CKD progression in advanced CKD; however, finerenone efficacy was maintained irrespective of baseline insulin resistance.

- **What are the implications of our finding?**
  These findings suggest that finerenone slows the progression of CKD and CV disease regardless of insulin resistance; further studies are needed to further explore this association.

ORIGINAL ARTICLE

Outcomes With Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Baseline Insulin Resistance

Diabetes Care 2024;47:362–370 | https://doi.org/10.2337/dc23-1420

Thomas Ebert,[1] Stefan D. Anker,[2] Luis M. Ruilope,[3,4,5] Paola Fioretto,[6] Vivian Fonseca,[7] Guillermo E. Umpierrez,[8] Andreas L. Birkenfeld,[9,10,11] Robert Lawatscheck,[12] Charlie Scott,[13] Katja Rohwedder,[14] and Peter Rossing,[15,16] on behalf of the FIDELIO-DKD and FIGARO-DKD Investigators

[1]*Medical Department III – Endocrinology, Nephrology, Rheumatology, University of Leipzig Medical Center, Leipzig, Germany*
[2]*Department of Cardiology of German Heart Center Charité; Institute of Health Center for Regenerative Therapies, German Centre for Cardiovascular Research partner site Berlin, Charité Universitätsmedizin, Berlin, Germany*
[3]*Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12, Madrid, Spain*
[4]*CIBER-CV, Hospital Universitario 12 de Octubre, Madrid, Spain*
[5]*Faculty of Sport Sciences, European University of Madrid, Madrid, Spain*
[6]*Department of Medicine, University of Padua, Italy*
[7]*Tulane University Health Sciences Center, New Orleans, LA*
[8]*Division of Endocrinology, Emory University School of Medicine, Atlanta, GA*
[9]*Department of Diabetology, Endocrinology and Nephrology, University Clinic, Tübingen, Germany*
[10]*Institute for Diabetes Research and Metabolic Diseases, Helmholtz Center Munich, University of Tübingen, Tübingen, Germany*
[11]*German Center for Diabetes Research, Neuherberg, Germany*
[12]*Clinical Research, Bayer AG, Berlin, Germany*
[13]*Data Science and Analytics, Bayer PLC, Reading, U.K.*
[14]*Medical Affairs, Bayer AG, Berlin, Germany*
[15]*Steno Diabetes Center Copenhagen, Herlev, Denmark*
[16]*Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark*

Corresponding author: Thomas Ebert, thomas.ebert@medizin.uni-leipzig.de

Received 1 August 2023 and accepted 24 November 2023

Clinical trial reg. nos. NCT02540993 and NCT02545049, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.24697368.

OBJECTIVE

To explore whether insulin resistance, assessed by estimated glucose disposal rate (eGDR), is associated with cardiorenal risk and whether it modifies finerenone efficacy.

RESEARCH DESIGN AND METHODS

In FIDELITY (*N* = 13,026), patients with type 2 diabetes, either *1*) urine albumin-to-creatinine ratio (UACR) of ≥30 to <300 mg/g and estimated glomerular filtration rate (eGFR) of ≥25 to ≤90 mL/min/1.73 m^2 or *2*) UACR of ≥300 to ≤5,000 mg/g and eGFR of ≥25 mL/min/1.73 m^2, who also received optimized renin-angiotensin system blockade, were randomized to finerenone or placebo. Outcomes included cardiovascular (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) and kidney (kidney failure, sustained decrease of ≧57% in eGFR from baseline, or renal death) composites. eGDR was calculated using waist circumference, hypertension status, and glycated hemoglobin for 12,964 patients.

RESULTS

Median eGDR was 4.1 mg/kg/min. eGDR <median (insulin resistant) was associated with higher cardiovascular event incidence regardless of treatment versus ≥median (insulin sensitive) (incidence rate/100 patient-years of 5.18 and 6.34 [for finerenone and placebo] vs. 3.47 and 3.76 [for finerenone and placebo], respectively). However, eGDR was not associated with kidney outcomes. There was no significant heterogeneity for effects of finerenone by eGDR on cardiovascular (<median: hazard ratio [HR] 0.81, 95% CI 0.72–0.92; ≥median: HR = 0.92, 95% CI 0.79–1.06; *P* interaction = 0.23) or kidney outcomes (<median: HR = 0.84, 95% CI 0.68–1.02; ≥median: HR = 0.70, 95% CI 0.58–0.85; *P* interaction = 0.28). Overall, finerenone demonstrated similar safety between subgroups. Sensitivity analyses were consistent.

CONCLUSIONS

Insulin resistance was associated with increased cardiovascular (but not kidney) risk and did not modify finerenone efficacy.

Metabolic and inflammatory abnormalities associated with diabetes and chronic kidney disease (CKD), such as insulin resistance, contribute to an increased risk of cardiovascular (CV) disease and progression to end-stage kidney disease (1,2).

Insulin resistance can exist in early-stage CKD, and prevalence increases as CKD progresses (1). Although the exact mechanisms of insulin resistance are not fully

understood, resistance to the metabolic actions of insulin has been associated with heart, vasculature, and kidney dysfunction (2,3). In the kidneys, insulin acts on multiple sites along the nephron, including the glomerulus, and podocyte insulin signaling is known to play a critical role in the maintenance of glomerular function. For example, podocyte-specific insulin receptor–knockout mice develop a glomerular phenotype consistent with CKD in type 2 diabetes, including albuminuria (4).

The hyperinsulinemic-euglycemic clamp method is considered the gold standard technique to measure insulin action in vivo to precisely determine the rate of whole-body glucose disposal. However, this method is invasive and costly, meaning use is limited. Alternative, simple indices (e.g., homeostasis model assessment [HOMA], quantitative insulin sensitivity check index) have been developed and validated for clinical use (5). The estimated glucose disposal rate (eGDR) is another indicator originally developed as a validated score to measure insulin resistance in patients with type 1 diabetes based on waist circumference (WC), hypertension, and glycated hemoglobin (HbA_{1c}) (6–8). Recently, Penno et al. (9) validated eGDR as an insulin resistance index in patients with type 2 diabetes in a comparison with the hyperinsulinemic-euglycemic clamp technique. The study found that eGDR was independently associated with mortality in patients without CKD or with nonalbuminuric CKD but not in those with albuminuric CKD. Even though albuminuria is predictive of CV and kidney events, and eGDR was shown to be strongly associated with the development and progression of albuminuria in patients with type 2 diabetes, there is limited evidence on the predictive value of eGDR for kidney outcomes (9–11). A recent retrospective study reported that lower eGDR was a predictive biomarker for rapid eGFR decline in patients with type 2 diabetes. In patients with eGFR $\leq$60 mL/min/1.73 m^2, the predictive value of eGDR was superior to WC and HbA_{1c}, and similar to hypertension (11). In a different study, Zabala et al. (12) showed that changes in insulin resistance as measured by eGDR were associated with the risk of stroke and mortality in patients with type 2 diabetes.

Historically, patients with CKD have been excluded from many studies of insulin resistance (1). Given that insulin resistance contributes to CV and kidney morbidity and mortality, it is crucial to investigate the cardiorenal impact of existing therapies. Previous research has linked insulin resistance and enhanced mineralocorticoid receptor (MR) activation (13). In preclinical studies, aldosterone had deleterious effects on the CV system by promoting adipose tissue expansion via MR activation (14). In addition, a positive correlation between aldosterone and insulin resistance was reported in hypertensive patients (15). Steroidal MR antagonists have been shown to provide survival benefits in patients with heart failure (16,17). However, MR antagonist use in patients with CKD has been limited because of safety concerns (18).

Finerenone is a distinct, selective, nonsteroidal MR antagonist. Compared with steroidal MR antagonists, finerenone is thought to provide heart and kidney benefits with fewer side effects, particularly hyperkalemia (19,20). In preclinical models of obesity, data suggest finerenone may enhance insulin sensitivity by increasing interscapular brown adipose tissue recruitment (14). In clinical trials, finerenone reduced the risk of cardiorenal outcomes, compared with placebo, across a broad population of patients with CKD and type 2 diabetes (21).

This post hoc analysis aims to explore whether insulin resistance (estimated by eGDR) is associated with risk of cardiorenal outcomes and whether insulin resistance modifies the cardiorenal efficacy of finerenone in the Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial Programme Analysis (FIDELITY) pooled data set.

RESEARCH DESIGN AND METHODS

Study Design and Patients

FIDELITY, a prespecified pooled analysis, combines individual patient-level data from Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD; NCT02540993) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD; NCT02545049), two multicenter, phase 3, randomized, double-blind, placebo-controlled, parallel-group, event-driven trials (22,23). The study designs and efficacy and safety outcomes of these trials have been previously published (22–25). The trials were conducted in accordance with the principles of the Declaration of Helsinki, and the protocols were approved by relevant regulatory authorities and ethics committees for each trial site; written informed consent was obtained from all participants.

Briefly, eligible patients were adults (aged $\geq$18 years) with CKD (urine albumin-to-creatinine ratio [UACR] of $\geq$30 to $<$300 mg/g and estimated glomerular filtration rate [eGFR] of $\geq$25 to $\leq$90 mL/min/1.73 m^2, or UACR of $\geq$300 to $\leq$5,000 mg/g and eGFR of $\geq$25 mL/min/1.73 m^2) and type 2 diabetes. Patients were required to be treated with maximum-tolerated dose of renin-angiotensin system therapy, with a serum potassium level of $\leq$4.8 mmol/L at run-in and screening visits, and HbA_{1c} of $\leq$12% (108 mmol/mol) (21). The use of insulin and other oral glucose-lowering agents, including dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, biguanides, sulfonylureas, α-glucosidase inhibitors, meglitinides, and thiazolidinediones, was not restricted during the trials (21).

Patients were randomly assigned (1:1) to receive once-daily oral treatment with finerenone (at titrated doses of 10 mg or 20 mg), or matching placebo (21). In this analysis, patients from the FIDELITY prespecified pooled analysis were stratified according to baseline insulin resistance, estimated by eGDR.

Procedures and Outcomes

Efficacy outcomes included a CV composite outcome (defined as time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) and a kidney composite outcome (defined as time to kidney failure, a sustained decrease of $\geq$57% 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 (initiation of long-term dialysis for $\geq$90 days, kidney transplantation, or a sustained decrease in eGFR to $<$15 mL/min/1.73 m^2). Safety outcomes and vital signs were also evaluated and included assessment of adverse events and central laboratory testing. Adverse events that occurred during the treatment period were defined as those that started or worsened during study drug intake or up to 3 days after any temporary or permanent interruption. All outcomes were adjudicated by independent clinical event committees blinded to

treatment assignment. Data for the CV composite and kidney composite outcomes were prospectively collected for all patients in the combined FIDELITY data set.

Statistical Analysis

Exploratory subgroup efficacy analyses were performed in the full analysis set, consisting of all randomized patients without any critical Good Clinical Practice violations. Post hoc laboratory parameter and safety analyses were performed in the safety analysis set, which included all randomized patients who had taken at least one dose of the study drug and were without any critical Good Clinical Practice violations. Analysis included descriptive statistics, time-to-event analyses, statistical test for interaction (subject to sufficient sample size within a given subgroup), and mixed models for repeated measures. Continuous population characteristics and demographics were summarized by mean and SD or median and interquartile range, depending on the distribution of the variable. Categorical characteristics and demographics were summarized by counts and percentages.

Insulin resistance was evaluated using eGDR (Supplementary Table 1) (7). Hypertension was considered present if a patient received more than one antihypertensive medication (renin-angiotensin system inhibitors, β-blockers, α-blockers, calcium antagonists, loop diuretics, or thiazide diuretics), or systolic blood pressure (SBP) of >140 mmHg or diastolic blood pressure of >90 mmHg. Composite outcomes were analyzed by defined categorical subgroups: <median eGDR and ≥median eGDR. The median eGDR value was selected for reference to use a simple, unbiased approach to categorizing the eGDR variable. Time-to-event treatment effects were analyzed using stratified Cox proportional hazards regression models and expressed as hazard ratios (HRs) with corresponding CIs. HRs (95% CI) were based on the stratified Cox proportional hazards model estimated within each level of the subgroup variable. The *P* interaction of the treatment assignment (finerenone or placebo) and each subgroup category was based on the Cox proportional hazards model, including the terms treatment group, the subgroup, and their interaction. Time-to-event analyses were stratified by region, UACR category at screening, eGFR category at screening, study, and CV disease history. The correlation between eGDR and log(UACR)/eGFR baseline values and their effect on outcomes were analyzed by Pearson correlation analysis.

The relationship of the CV and kidney composite outcomes with eGDR as a continuous variable was investigated using a similar stratified Cox proportional hazards model with cubic B-splines with three equally spaced knots across the range of eGDR. All Cox proportional hazards models were adjusted for blood pressure (systolic), sex, HbA_{1c} at baseline, and diabetes duration. Models were fitted separately in each treatment group (i.e., finerenone and placebo). Events were reported from randomization up to the end-of-study (EOS) visit. Patients without an event were censored at the date of their last contact, and complete information on all components of their respective outcomes was recorded. UACR over time was analyzed with a mixed model for repeated measures, adjusting for treatment group, stratification factors, baseline UACR value, and time of visit. Interaction terms for treatment group and visit, and baseline value and visit, were also included in the model.

As a sensitivity analysis, other known estimates of insulin resistance were calculated and analyzed. These included triglyceride (TG)/high-density lipoprotein (HDL)–cholesterol ratio, visceral adiposity index (VAI), and lipid accumulation product (LAP) index at baseline. Similar to eGDR, the medians of TG/HDL ratio, VAI, and LAP index were used to split the population (<median and ≥median), and the analyses described above were conducted. The correlations between eGDR and VAI, LAP and TG/HDL–cholesterol ratio baseline values, respectively, were analyzed by Pearson correlation analysis.

We conducted an additional sensitivity analysis with time-updated eGDR calculated based on the average of all of SBP measurements throughout the trial for each individual patient.

Data and Resource Availability

The data sets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request. Availability of the data underlying this publication will be determined according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations/Pharmaceutical Research and Manufacturers of America "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 U.S. and European Union as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the European Union and U.S. regulatory agencies on or after 1 January 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.

RESULTS

Patients

The FIDELITY analysis included 13,026 patients in the full analysis set, over a median follow-up of 3.0 years (interquartile range 2.3–3.8 years). Full patient demographics and baseline characteristics for the FIDELITY study population have been previously published (21). In this post hoc analysis, median eGDR was 4.1 mg/kg/min; 6,484 (50%) patients had an eGDR of <median (considered as insulin resistant) and 6,480 (50%) had an eGDR of ≥median (considered as insulin sensitive) (Supplementary Fig. 1).

Baseline Characteristics

The baseline clinical and demographic characteristics of patients with an eGDR of ≥median and <median were generally comparable, with some key differences (Table 1). Compared with patients with an eGDR of ≥median, patients with an eGDR of <median had a longer mean duration of diabetes (16.1 vs. 14.7 years), and higher median UACR (535 vs. 493 mg/g),

Table 1—Patient baseline characteristics according to insulin resistance at baseline

Baseline characteristic	eGDR at baseline			
	eGDR <median		eGDR ≥median	
	Finerenone (*N* = 3,247)	Placebo (*N* = 3,237)	Finerenone (*N* = 3,238)	Placebo (*N* = 3,242)
Age, years, mean ± SD	64.5 ± 9.0	64.6 ± 9.2	64.9 ± 9.8	65.0 ± 10.1
Sex, *n* (%)				
Female	926 (28.5)	897 (27.7)	1,096 (33.8)	992 (30.6)
Male	2,321 (71.5)	2,340 (72.3)	2,142 (66.2)	2,250 (69.4)
Race and ethnicity, *n* (%)				
White	2,611 (80.4)	2,600 (80.3)	1,810 (55.9)	1,801 (55.6)
Black/African American	149 (4.6)	175 (5.4)	102 (3.2)	93 (2.9)
Asian	298 (9.2)	309 (9.5)	1,133 (35.0)	1,147 (35.4)
American Indian or Alaska Native	67 (2.1)	51 (1.6)	82 (2.5)	94 (2.9)
Native Hawaiian or other Pacific Islander	19 (0.6)	13 (0.4)	9 (0.3)	8 (0.2)
Multiple races	92 (2.8)	78 (2.4)	95 (2.9)	93 (2.9)
SBP, mmHg, mean ± SD	138.5 ± 14.0	138.1 ± 13.9	135.1 ± 14.1	135.3 ± 14.5
DBP, mmHg, mean ± SD	77.0 ± 9.6	77.0 ± 9.6	75.7 ± 9.6	75.8 ± 9.6
HbA_{1c}, % (mmol/mol), mean ± SD	8.2 (66) ± 1.4	8.2 (66) ± 1.4	7.2 (55) ± 1.1	7.2 (55) ± 1.1
Duration of diabetes, years, mean ± SD	16.2 ± 8.6	16.1 ± 8.5	14.7 ± 8.8	14.7 ± 8.8
Serum potassium, mmol/L, mean ± SD	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.5
eGFR, mL/min/1.73 m^2, mean ± SD	57.7 ± 21.9	57.5 ± 21.9	57.4 ± 21.3	57.8 ± 21.6
eGFR, mL/min/1.73 m^2, *n* (%)				
<25	44 (1.4)	44 (1.4)	36 (1.1)	36 (1.1)
25 to <45	1,056 (32.5)	1,084 (33.5)	1,048 (32.4)	1,021 (31.5)
45 to <60	837 (25.8)	813 (25.1)	868 (26.8)	895 (27.6)
≥60	1,310 (40.3)	1,296 (40.0)	1,286 (39.7)	1,290 (39.8)
UACR, mg/g, median	530	543	494	492
UACR, mg/g, *n* (%)				
<30	69 (2.1)	48 (1.5)	51 (1.6)	62 (1.9)
30 to <300	1,005 (31.0)	981 (30.3)	1,062 (32.8)	1,034 (31.9)
≥300	2,172 (66.9)	2,208 (68.2)	2,125 (65.6)	2,145 (66.2)
History of CV disease, *n* (%)	1,565 (48.2)	1,615 (49.9)	1,396 (43.1)	1,331 (41.1)
Current smoker, *n* (%)	463 (14.3)	456 (14.1)	592 (18.3)	568 (17.5)
Serum TGs, mg/dL, median	200.1	196.6	158.0	158.5
Serum HDL cholesterol baseline, mg/dL, median	41.0	41.0	46.0	46.0
BMI, kg/m^2, mean ± SD	34.6 ± 5.7	34.6 ± 5.6	28.1 ± 4.4	28.0 ± 4.3
Weight, kg, mean ± SD	99.1 ± 18.7	99.3 ± 18.7	76.9 ± 14.8	77.0 ± 14.1
Waist-hip ratio, cm, mean ± SD	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1
WC, cm, mean ± SD	116.9 ± 12.4	117.2 ± 12.2	97.0 ± 10.4	97.1 ± 10.2
Heart rate, bpm, mean ± SD	73.1 ± 11.5	73.1 ± 11.5	73.2 ± 11.3	72.9 ± 11.5
Baseline medications, *n* (%)				
ACEis	1,483 (45.7)	1,516 (46.8)	1,290 (39.8)	1,315 (40.6)
ARBs	2,015 (62.1)	2,045 (63.2)	2,173 (67.1)	2,179 (67.2)
Beta-blockers	2,226 (68.6)	2,241 (69.2)	1,584 (48.9)	1,665 (51.4)
Diuretics	2,446 (75.3)	2,495 (77.1)	1,809 (55.9)	1,873 (57.8)
Statins	2,672 (82.3)	2,681 (82.8)	2,448 (75.6)	2,498 (77.1)
Potassium supplements	337 (10.4)	376 (11.6)	230 (7.1)	289 (8.9)
Potassium-lowering agents	245 (7.5)	142 (4.4)	281 (8.7)	197 (6.1)
Glucose-lowering therapies, *n* (%)				
Insulin and analogs	2,298 (70.8)	2,229 (68.9)	1,551 (47.9)	1,519 (46.9)
Metformin	1,949 (60.0)	1,871 (57.8)	1,840 (56.8)	1,860 (57.4)
Sulfonylureas	769 (23.7)	760 (23.5)	914 (28.2)	933 (28.8)
DPP-4 inhibitors	704 (21.7)	698 (21.6)	951 (29.4)	909 (28.0)

Continued on p. 366

Table 1—Continued

Baseline characteristic	eGDR at baseline: eGDR <median, Finerenone (*N* = 3,247)	eGDR <median, Placebo (*N* = 3,237)	eGDR ≥median, Finerenone (*N* = 3,238)	eGDR ≥median, Placebo (*N* = 3,242)
GLP-1RAs	356 (11.0)	300 (9.3)	137 (4.2)	144 (4.4)
SGLT-2 inhibitors	275 (8.5)	268 (8.3)	162 (5.0)	170 (5.2)
α-Glucosidase inhibitors	95 (2.9)	88 (2.7)	228 (7.0)	245 (7.6)
Meglitinides	104 (3.2)	91 (2.8)	168 (5.2)	166 (5.1)
Thiazolidinediones	118 (3.6)	118 (3.6)	149 (4.6)	130 (4.0)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2, sodium-glucose cotransporter-2.

mean weight (99 vs. 77 kg), and mean WC (117 vs. 97 cm) at baseline. A greater proportion of patients in the eGDR <median subgroup identified as White compared with the eGDR ≥median subgroup (80% vs. 56%), while a substantially lower proportion identified as Asian (9% vs. 35%). At baseline, eGDR was significantly positively correlated with eGFR (r = 0.04 [95% CI 0.02–0.06; $P < 0.0001$]) and significantly negatively correlated with log(UACR) (r = –0.03 [95% CI –0.04 to –0.01; P = 0.004]). Significant negative correlations between eGDR and baseline VAI, LAP index, and TG/HDL ratio, respectively ($P < 0.0001$) were calculated (Supplementary Table 2).

CV Composite Outcome

As previously reported in the overall population of the FIDELITY analysis, the CV composite outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure was observed in 825 of 6,519 (12.7%) patients receiving finerenone and in 939 of 6,507 (14.4%) patients receiving placebo (HR = 0.86; 95% CI 0.78–0.95) (21). In the overall population, irrespective of finerenone or placebo treatment, an increase in eGDR from baseline was significantly associated with a decreased risk of the CV composite outcome (HR = 0.88, 95% CI 0.86–0.91; $P < 0.0001$). Baseline eGDR <median was associated with a higher incidence rate (IR) of the CV composite outcome in both the finerenone and placebo groups versus eGDR ≥median (eGDR <median: IR per 100 patient-years [PY] 5.18, 95% CI 4.73–5.65 [for finerenone] and IR per 100 PY 6.34, 95% CI 5.83–6.86 [for placebo]; eGDR ≥median: IR per 100 PY 3.47, 95% CI 3.11–3.86 [for finerenone] and IR per 100 PY 3.76, 95% CI 3.38–4.15 [for placebo]) (Fig. 1). There was no significant heterogeneity for the effect of finerenone on the CV composite outcome by baseline eGDR (eGDR <median: HR = 0.81, 95% CI 0.72–0.92; eGDR ≥median: HR = 0.92, 95% CI 0.79–1.06; P interaction = 0.23). Calculations using time-updated eGDR yielded results similar to the analyses based on eGDR at baseline (Supplementary Fig. 2).

Similarly, there was not a statistically significant change in the effect of finerenone versus placebo on the CV composite outcome across the range of eGDR values at baseline (Wald test P = 0.063) (Fig. 2*A*).

Sensitivity analyses also showed there was no significant heterogeneity for the effect of finerenone on the CV composite outcome by baseline TG/HDL ratio (TG/HDL ratio <median: HR = 0.83, 95% CI 0.73–0.95; TG/HDL ratio ≥median: HR = 0.88, 95% CI 0.77–1.01; P interaction = 0.52), VAI (VAI <median: HR = 0.85, 95% CI 0.74–0.97; VAI ≥median: HR =

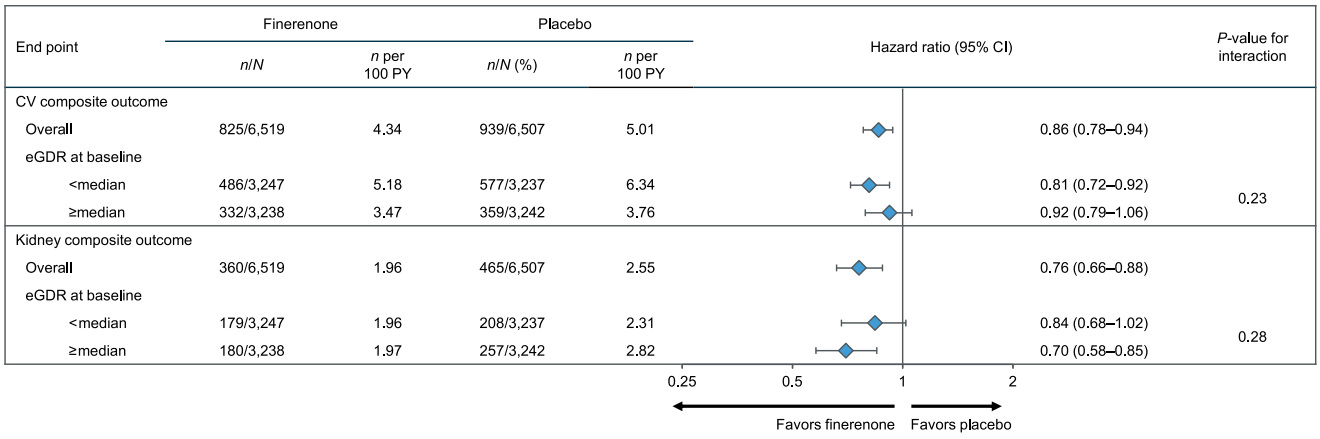


Figure 1—CV and kidney composite outcomes by eGDR subgroups (<median and ≥median). Events were adjudicated by an independent adjudication committee. A stratified Cox proportional hazards model including treatment was calculated by subgroup. The interaction P value was based on a stratified Cox proportional hazards model including treatment, subgroup, and treatment by subgroup interaction. All Cox proportional hazards models were adjusted for blood pressure (systolic), sex, HbA_{1c} at baseline, and diabetes duration. CV composite outcome denotes the of time to first onset of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure; kidney composite outcome denotes the of time to first onset of kidney failure, sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death.

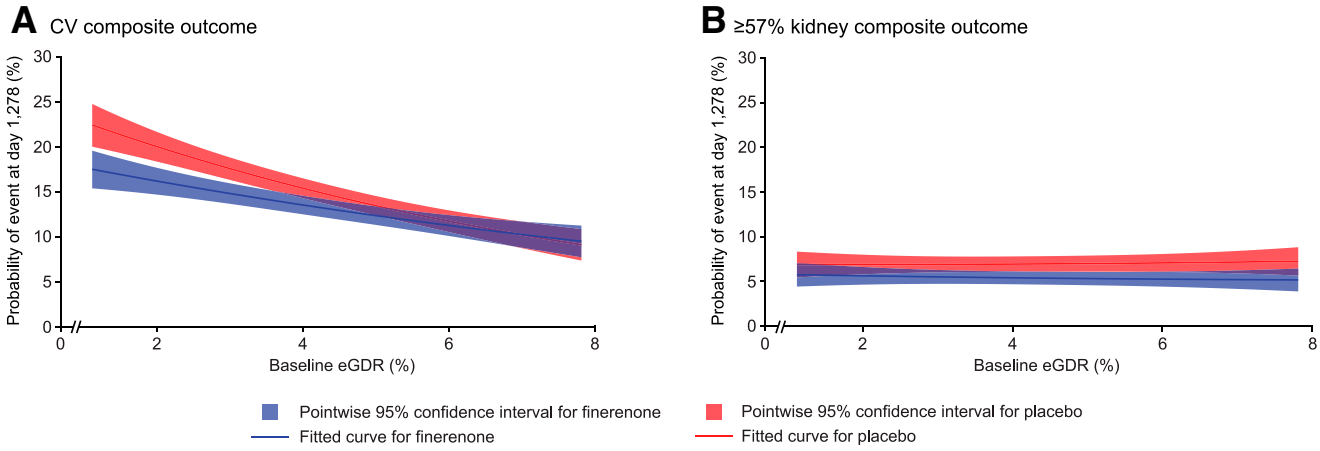


Figure 2—CV (*A*) and ≥57% kidney composite (*B*) outcomes by continuous variable eGDR.

0.85, 95% CI 0.75–0.98; *P* interaction = 0.91), or LAP index (LAP index <median: HR = 0.86, 95% CI 0.75–0.99; LAP index ≥median: HR = 0.85, 95% CI 0.74–0.97; *P* interaction = 0.84).

Kidney Outcomes

Kidney Composite Outcome

As previously reported, the kidney composite outcome of kidney failure, a sustained ≥57% decrease in eGFR from baseline, or renal death was lower with finerenone versus placebo in the overall population of the FIDELITY analysis (HR = 0.77; 95% CI 0.67–0.88; *P* = 0.0002) (21). In the overall population, irrespective of finerenone or placebo, baseline eGDR was not associated with risk of the kidney composite outcome (HR = 1.00, 95% CI 0.96–1.04; *P* = 0.93). The IR of the kidney composite outcome was similar across eGDR subgroups in the finerenone and placebo groups (eGDR <median: IR per 100 PY 1.96, 95% CI 1.68–2.26 and IR per 100 PY 2.31, 95% CI 2.00–2.63, respectively; eGDR ≥median: IR per 100 PY 1.97, 95% CI 1.70–2.27 and IR per 100 PY 2.82, 95% CI 2.49–3.18, respectively) (Fig. 1). There was no significant heterogeneity for the effect of finerenone on the kidney composite outcome by baseline eGDR subgroups (eGDR <median: HR = 0.84, 95% CI 0.68–1.02; eGDR ≥median: HR = 0.70, 95% CI 0.58–0.85; *P* interaction = 0.28). Similarly, there was no statistically significant change in the effect of finerenone versus placebo on the kidney composite outcome across the range of eGDR values (Wald test *P* value = 0.51) (Fig. 2*B*).

Sensitivity analyses also showed that there was no significant heterogeneity for the effect of finerenone on the ≥57% kidney composite outcome by baseline TG/HDL (TG/HDL ratio <median: HR = 0.82, 95% CI 0.67–0.99; TG/HDL ratio ≥median: HR = 0.71, 95% CI 0.59–0.87; *P* interaction = 0.33), VAI (VAI <median: HR = 0.77, 95% CI 0.63–0.94; VAI ≥median: HR = 0.75, 95% CI 0.61–0.91; *P* interaction = 0.75), or LAP index (LAP index <median: HR = 0.74, 95% CI 0.61–0.90; LAP index ≥median: HR = 0.81, 95% CI 0.66–0.98; *P* interaction = 0.64).

Other Kidney Outcomes

Finerenone reduced UACR regardless of eGDR category (eGDR <median: ratio of least-squares [LS] mean 0.69 (95% CI 0.66–0.72; $P < 0.0001$; eGDR ≥median: ratio of LS mean 0.67 (95% CI 0.65–0.70; $P < 0.0001$) (Supplementary Fig. 3). Finerenone also slowed eGFR decline regardless of eGDR category (Supplementary Fig. 4). In patients with eGDR <median, LS mean change in chronic eGFR slope from month 4 to EOS visit was –2.7 mL/min/1.73 m^2 per year with finerenone and –3.7 mL/min/1.73 m^2 with placebo (between-group difference: 1.0 mL/min/1.73 m^2, 95% CI 0.76–1.25; $P < 0.0001$). In patients with an eGDR ≥median, LS mean change in chronic eGFR slope from month 4 to EOS visit was –2.8 mL/min/1.73 m^2 per year with finerenone and –3.9 mL/min/1.73 m^2 with placebo (between-group difference: 1.1 mL/min/1.73 m^2, 95% CI 0.83–1.29; $P < 0.0001$).

Safety

Overall, the incidences of treatment-emergent adverse events and severe adverse events were balanced between the finerenone and placebo groups and between eGDR subgroups (Table 2). The incidence of investigator-reported, treatment-emergent hyperkalemia was higher in patients treated with finerenone versus placebo in both eGDR subgroups (eGDR <median: 14.2% vs. 6.0%, respectively; eGDR ≥median: 13.9% vs. 7.8%, respectively). However, hyperkalemia leading to discontinuation was low in the finerenone treatment group, with no notable differences between eGDR subgroups (eGDR <median: 1.9%; eGDR ≥median: 1.5%).

CONCLUSIONS

To date, insulin resistance has been poorly defined in patients with CKD and type 2 diabetes, and its independent role in CKD progression risk is unclear. Although initially developed for patients with type 1 diabetes, studies have shown that eGDR is well correlated with the gold standard hyperinsulinemic-euglycemic clamp method in patients with type 2 diabetes (12). Our analysis included patients with CKD, both those with insulin resistance and those with insulin sensitivity, as measured by eGDR at baseline. eGFR at baseline was similar between patients who were insulin resistant and patients who were insulin sensitive. This finding provides indirect support to the growing body of evidence that insulin resistance is not significantly associated with the development of CKD-related outcomes (1). When compared with the gold standard hyperinsulinemic-euglycemic clamp method, several other surrogate parameters of insulin resistance, such as HOMA, fasting insulin resistance index, Matsuda index, and Stumvoll index, did not appear to be dysregulated in patients with

Table 2—Key safety outcomes by insulin resistance at baseline

	eGDR at baseline			
	eGDR <median		eGDR ≥median	
	Finerenone (*N* = 3,242)	Placebo (*N* = 3,228)	Finerenone (*N* = 3,235)	Placebo (*N* = 3,234)
Treatment-emergent AEs, *n* (%)				
Any AE	2,823 (87.1)	2,801 (86.8)	2,751 (85.0)	2,781 (86.0)
Study drug–related AE	640 (19.7)	457 (14.2)	560 (17.3)	402 (12.4)
AE leading to discontinuation	236 (7.3)	170 (5.3)	176 (5.4)	180 (5.6)
Any SAE	1,107 (34.1)	1,181 (36.6)	937 (29.0)	999 (30.9)
Study drug–related SAE	46 (1.4)	32 (1.0)	36 (1.1)	29 (0.9)
SAE leading to discontinuation	84 (2.6)	72 (2.2)	59 (1.8)	82 (2.5)
Fatal AE	55 (1.7)	83 (2.6)	54 (1.7)	68 (2.1)
Treatment-emergent hyperkalemia events, *n* (%)				
Any AE	460 (14.2)	195 (6.0)	449 (13.9)	252 (7.8)
Study drug–related AE	286 (8.8)	107 (3.3)	285 (8.8)	142 (4.4)
AE leading to discontinuation	63 (1.9)	19 (0.6)	47 (1.5)	19 (0.6)
Any SAE	36 (1.1)	11 (0.3)	32 (1.0)	5 (0.2)
Study drug–related SAE	22 (0.7)	6 (0.2)	20 (0.6)	2 (<0.1)
SAE leading to discontinuation	8 (0.2)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Fatal AE	0	0	0	0

AE, adverse event; SAE, serious adverse event.

versus without CKD (26). In this analysis of the FIDELITY population, the median eGDR (4.1 mg/kg/min) was substantially lower than previous studies of the general population and of patients with type 1 diabetes. For context, the 2022 China Health and Retirement Longitudinal Study, (*N* = 8,267; general population), reported a median eGDR of 10.4 mg/kg/min (27), and two studies of patients with type 1 diabetes ($N \approx 200$ per study) reported mean eGDR of 6.5–10.1 mg/kg/min (28,29). In these studies, low eGDR (high insulin resistance) was defined as those with eGDR <5.39 mg/kg/min in patients with type 1 diabetes (28) and <8.92 mg/kg/min in the general population (27). In patients with type 1 diabetes, mean eGDR in patients with CKD was significantly lower than in patients without (6.4 vs. 15.9 mg/kg/min; $P < 0.001$) (29), which aligns with our results, suggesting a widespread burden of insulin resistance in patients with CKD.

Marked differences in duration of diabetes, mean weight, WC, and ethnicity between patients with insulin resistance (eGDR <median) and patients who were insulin sensitive (eGDR ≥median) were observed. Simpler clinical indicators such as WC could be of substantial utility in clinical practice to offer guidance on the risk of CKD progression. An association between WC (or BMI) and CV and kidney outcomes in FIDELITY patients has been reported (30). Patients with low-risk WC (or BMI) experienced a higher kidney outcome event rate (and the opposite for CV outcome) compared with those with high and very high risk (30). Even though BMI is the most commonly used measure of obesity, growing evidence suggests WC is moderately superior to BMI for predicting cardiometabolic risk (30,31).

We note that our results suggest greater insulin resistance, as assessed by eGDR, in patients of White ethnicity. This appears to contradict the fact that diabetes disproportionately burdens certain racial and ethnic groups, such as Black and South East Asian (32,33). Previously, epidemiological studies have reported insulin resistance in these populations; however, more recent and direct methods of measurement have provided evidence that insulin sensitivity is not significantly different between ethnic groups.

In this post hoc analysis, finerenone provided consistent CV and kidney protection in patients with CKD and type 2 diabetes, irrespective of baseline insulin resistance. However, patients with insulin resistance (eGDR <median) were at greater risk of CV events compared with those without (eGDR ≥median). This aligns with previous studies, supporting the hypothesis that eGDR is an important predictor of CV disease. For example, in a cohort study of 104,697 patients with type 2 diabetes from the Swedish National Diabetes Register (2004–2016), low eGDR (<4 mg/kg/min), versus higher eGDR (4 to <8 mg/kg/min), was associated with an increased risk of stroke and CV mortality (12). Additionally, in the retrospective, population-based China Health and Retirement Longitudinal Study (*N* = 8,276), low eGDR was found to be positively correlated with risk of CV disease, stroke, and cardiac events (27). More recently, Peng et al. (11) reported that low eGDR (<6.34 mg/kg/min) at baseline was an independent risk factor for kidney outcomes in a retrospective cohort study of 956 Chinese patients.

In the present FIDELITY analysis, which used data from the largest clinical trial cohort of 13,026 patients with CKD and type 2 diabetes to date, the incidence of the kidney composite outcome was similar between eGDR subgroups (21). Even though data reported by Peng et al. (11) support an association between low eGDR and kidney function decline in patients with diabetes, our results suggest that changes in insulin kinetics in patients with diabetes with established CKD (assessed by UACR and eGFR) may no longer be predictive of CKD progression.

Furthermore, insulin signaling differs within the kidney in a cell type–specific manner (34). Because insulin resistance is often associated with podocyte dysfunction (35), it is possible to speculate that when CKD and glomerular filtration barrier dysfunction already exist, insulin resistance, assessed by eGDR, cannot

further impair kidney outcomes. These findings support our preclinical hypothesis that finerenone may increase insulin sensitivity; even though it was not possible to evaluate the effect of finerenone on insulin resistance, by eGDR over time, because of a lack of follow-up data for WC, no changes in other algorithm components (i.e., weight and HbA_{1c}) from baseline to the EOS visit were observed. Moreover, results of the sensitivity analysis using baseline eGDR were similar to those based on the time-updated eGDR calculation. These findings suggest that changes in eGDR were not associated with temporal fluctuations in SBP and provide further validation for eGDR categories as a measure of changes in insulin resistance.

Multiple studies have demonstrated that insulin resistance is implicated in CV disease in patients with CKD, but its role in CKD progression is less clear (36). Few clinical studies have explored the role of insulin resistance in predicting the deterioration of kidney function in patients with CKD with or without type 2 diabetes. In a previous study in patients with CKD without diabetes, progression of kidney disease was slower in those patients with low insulin resistance, as measured by HOMA (37). Insulin resistance as measured by HOMA was shown to be a significant risk factor for CKD progression in hypertensive patients without diabetes (38).

Thus, further studies are required to examine whether the hemodynamic effects of insulin resistance in the kidneys differ between individuals with diabetes versus patients with advanced CKD with or without diabetes.

Furthermore, these exploratory analyses suggest that insulin resistance, as measured by eGDR, is associated with higher CV events regardless of treatment, but it is not associated with kidney outcomes. Compared with placebo, the effect of finerenone on the CV composite outcomes across the range of baseline eGDR values reached near statistical significance. Given that our analyses were hypothesis generating and not adequately powered to evaluate the statistical significance of any associations between eGDR with CV and kidney outcomes, this needs to be investigated in further studies, including randomized clinical trials.

In this post hoc analysis of the FIDELITY prespecified pooled analysis, the efficacy and safety of finerenone were not modified by baseline insulin resistance. A higher risk of CV—but not kidney—outcomes was observed in patients with CKD and type 2 diabetes with greater insulin resistance.

Acknowledgments. The authors are indebted to the participants, as well as the investigators and study sites. Medical writing assistance was provided by Emilie Topley of Chameleon Communications International Ltd and was funded by Bayer AG.

Funding. 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.

Duality of Interest. T.E. has served as a paid consultant for Bayer, Lilly Deutschland, and Sanofi and reports personal fees from Bayer, Fresenius Medical Care Deutschland, Lilly Deutschland, Novo Nordisk, Sanofi, and Santis Pharmaceuticals. He has received research support from the European Foundation for the Study of Diabetes (EFSD Mentorship Programme supported by AstraZeneca) and Otsuka Pharma. S.D.A. reports grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work, and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Bioventrix, Boehringer Ingelheim, B R A H M S, Cardiac Dimensions, Cardior, Cordio, CVRx, Edwards, Faraday, Impulse Dynamics, Janssen, Novartis, Occlutech, Pfizer, Respicardia, Servier, Vectorious, and V-Wave. He is named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 and DE 102007022367), but he does not benefit personally from the related issued patents. L.M.R. reports receipt of consultancy fees from Bayer. P.F. reports consultation fees from AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Mundipharma, and Novo Nordisk. V.F. has served as a paid consultant for Abbott, Asahi, AstraZeneca, Bayer, Novo Nordisk, and Sanofi. He has patent and ownership interests in BRAVO4Health. G.E.U. has received research support (to Emory University) from Abbott, Bayer, and Dexcom Inc. A.L.B. reported research support from Boehringer Ingelheim and personal fees from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. All fees are given to Tübingen University. R.L. is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany. C.S. is a full-time employee of Bayer PLC, Division Pharmaceuticals, U.K. K.R. is a full-time employee of Bayer AG. P.R. reported personal fees from Bayer during the conduct of the study. He has received research support and personal fees from AstraZeneca, Bayer, and Novo Nordisk and personal fees from Abbott, Astellas, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, and Sanofi, and all fees are given to Steno Diabetes Center Copenhagen. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. The Executive Committee designed the study in conjunction with the sponsor. T.E. wrote the first draft of the report. T.E., S.D.A., L.M.R., P.F., V.F., G.E.U., A.L.B., R.L., C.S., K.R., and P.R. had access to the study results, were involved in data analysis and interpretation, and in drafting and critically revising the report, and reviewed and approved the final submitted version of the report. T.E. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors made the decision to submit the manuscript for publication.

Prior Presentation. Parts of this study were presented at the 83rd Scientific Sessions of the American Diabetes Association, San Diego, CA, 23–26 June 2023.

References

1. Schrauben SJ, Jepson C, Hsu JY, et al. Insulin resistance and chronic kidney disease progression, cardiovascular events, and death: findings from the chronic renal insufficiency cohort study. BMC Nephrol 2019;20:60
2. Whaley-Connell A, Sowers JR. Insulin resistance in kidney disease: is there a distinct role separate from that of diabetes or obesity? Cardiorenal Med 2017;8:41–49
3. Lee SH, Park SY, Choi CS. Insulin resistance: from mechanisms to therapeutic strategies. Diabetes Metab J 2022;46:15–37
4. Lay AC, Coward RJM. The evolving importance of insulin signaling in podocyte health and disease. Front Endocrinol (Lausanne) 2018;9:693
5. Borai A, Livingstone C, Kaddam I, Ferns G. Selection of the appropriate method for the assessment of insulin resistance. BMC Med Res Methodol 2011;11:158
6. Nyström T, Holzmann MJ, Eliasson B, Svensson AM, Sartipy U. Estimated glucose disposal rate predicts mortality in adults with type 1 diabetes. Diabetes Obes Metab 2018;20:556–563
7. Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ. Can clinical factors estimate insulin resistance in type 1 diabetes? Diabetes 2000;49:626–632
8. Lu Z, Xiong Y, Feng X, et al. Insulin resistance estimated by estimated glucose disposal rate predicts outcomes in acute ischemic stroke patients. Cardiovasc Diabetol 2023;22:225
9. Penno G, Solini A, Orsi E, et al.; Renal Insufficiency And Cardiovascular Events (RIACE) Study Group. Insulin resistance, diabetic kidney disease, and all-cause mortality in individuals with type 2 diabetes: a prospective cohort study. BMC Med 2021;19:66
10. de Jong PE, Gansevoort RT, Bakker SJ. Macroalbuminuria and microalbuminuria: do both predict renal and cardiovascular events with similar strength? J Nephrol 2007;20:375–380
11. Peng J, Li A, Yin L, Yang Q, Pan J, Yi B. Estimated glucose disposal rate predicts renal progression in type 2 diabetes mellitus: a retrospective cohort study. J Endocr Soc 2023;7:bvad069.
12. Zabala A, Darsalia V, Lind M, et al. Estimated glucose disposal rate and risk of stroke and mortality in type 2 diabetes: a nationwide cohort study. Cardiovasc Diabetol 2021;20:202

13. Jia G, Lockette W, Sowers JR. Mineralocorticoid receptors in the pathogenesis of insulin resistance and related disorders: from basic studies to clinical disease. Am J Physiol Regul Integr Comp Physiol 2021;320:R276–R286
14. Marzolla V, Feraco A, Limana F, Kolkhof P, Armani A, Caprio M. Class-specific responses of brown adipose tissue to steroidal and nonsteroidal mineralocorticoid receptor antagonists. J Endocrinol Invest 2022;45:215–220
15. Colussi G, Catena C, Lapenna R, Nadalini E, Chiuch A, Sechi LA. Insulin resistance and hyperinsulinemia are related to plasma aldosterone levels in hypertensive patients. Diabetes Care 2007; 30:2349–2354
16. Lin DS, Lin FJ, Lin YS, Lee JK, Lin YH. The effects of mineralocorticoid receptor antagonists on cardiovascular outcomes in patients with end-stage renal disease and heart failure. Eur J Heart Fail 2023;25:98–107
17. Vizzardi E, Regazzoni V, Caretta G, et al. Mineralocorticoid receptor antagonist in heart failure: past, present and future perspectives. Int J Cardiol Heart Vessels 2014;3:6–14
18. Garg R, Hurwitz S, Williams GH, Hopkins PN, Adler GK. Aldosterone production and insulin resistance in healthy adults. J Clin Endocrinol Metab 2010;95:1986–1990
19. Zhang MZ, Bao W, Zheng QY, Wang YH, Sun LY. Efficacy and safety of finerenone in chronic kidney disease: a systematic review and meta-analysis of randomized clinical trials. Front Pharmacol 2022; 13:819327
20. Rico-Mesa JS, White A, Ahmadian-Tehrani A, Anderson AS. Mineralocorticoid receptor antagonists: a comprehensive review of finerenone. Curr Cardiol Rep 2020;22:140
21. Agarwal R, Filippatos G, Pitt B, et al.; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J 2022;43:474–484
22. Pitt B, Filippatos G, Agarwal R, et al.; FIGARO-DKD investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med 2021;385:2252–2263
23. Bakris GL, Agarwal R, Anker SD, et al.; FIDELIO-DKD investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020;383:2219–2229
24. Ruilope LM, Agarwal R, Anker SD, et al.; FIGARO-DKD study investigators. Design and baseline characteristics of the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease Trial. Am J Nephrol 2019;50:345–356
25. Bakris GL, Agarwal R, Anker SD, et al.; on behalf of the FIDELIO-DKD study investigators and FIDELIO-DKD study investigators. Design and baseline characteristics of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease Trial. Am J Nephrol 2019;50:333–344
26. Jia T, Huang X, Qureshi AR, et al. Validation of insulin sensitivity surrogate indices and prediction of clinical outcomes in individuals with and without impaired renal function. Kidney Int 2014;86:383–391
27. Ren X, Jiang M, Han L, Zheng X. Estimated glucose disposal rate and risk of cardiovascular disease: evidence from the China Health and Retirement Longitudinal Study. BMC Geriatr 2022; 22:968
28. Epstein EJ, Osman JL, Cohen HW, Rajpathak SN, Lewis O, Crandall JP. Use of the estimated glucose disposal rate as a measure of insulin resistance in an urban multiethnic population with type 1 diabetes. Diabetes Care 2013;36:2280–2285
29. Vladu M, Clenciu D, Efrem IC, et al. Insulin resistance and chronic kidney disease in patients with type 1 diabetes mellitus. J Nutr Metab 2017;2017:6425359
30. Rossing P, Anker SD, Filippatos G, et al. The impact of obesity on cardiovascular and kidney outcomes in patients with chronic kidney disease and type 2 diabetes treated with finerenone: post hoc analysis of the FIDELITY study. Diabetes Obes Metab 2023;25:2989–2998
31. Czernichow S, Kengne AP, Huxley RR, et al.; ADVANCE Collaborative Group. Comparison of waist-to-hip ratio and other obesity indices as predictors of cardiovascular disease risk in people with type-2 diabetes: a prospective cohort study from ADVANCE. Eur J Cardiovasc Prev Rehabil 2011;18:312–319
32. Goff LM, Ladwa M, Hakim O, Bello O. Ethnic distinctions in the pathophysiology of type 2 diabetes: a focus on black African-Caribbean populations. Proc Nutr Soc 2020;79:184–193
33. Vasishta S, Ganesh K, Umakanth S, Joshi MB. Ethnic disparities attributed to the manifestation in and response to type 2 diabetes: insights from metabolomics. Metabolomics 2022;18:45
34. Artunc F, Schleicher E, Weigert C, Fritsche A, Stefan N, Häring HU. The impact of insulin resistance on the kidney and vasculature. Nat Rev Nephrol 2016;12:721–737
35. Welsh GI, Hale LJ, Eremina V, et al. Insulin signaling to the glomerular podocyte is critical for normal kidney function. Cell Metab 2010;12: 329–340
36. Spoto B, Pisano A, Zoccali C. Insulin resistance in chronic kidney disease: a systematic review. Am J Physiol Renal Physiol 2016;311: F1087–F1108
37. Caravaca F, Cerezo I, Macías R, et al. Insulin resistance in chronic kidney disease: its clinical characteristics and prognosis significance. Nefrologia 2010;30:661–668
38. Kobayashi H, Tokudome G, Hara Y, et al. Insulin resistance is a risk factor for the progression of chronic kidney disease. Clin Nephrol 2009;71: 643–651