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Efficacy and Safety of Finerenone in Type 2 Diabetes: A Pooled Analysis of Trials of Heart Failure and Chronic Kidney Disease

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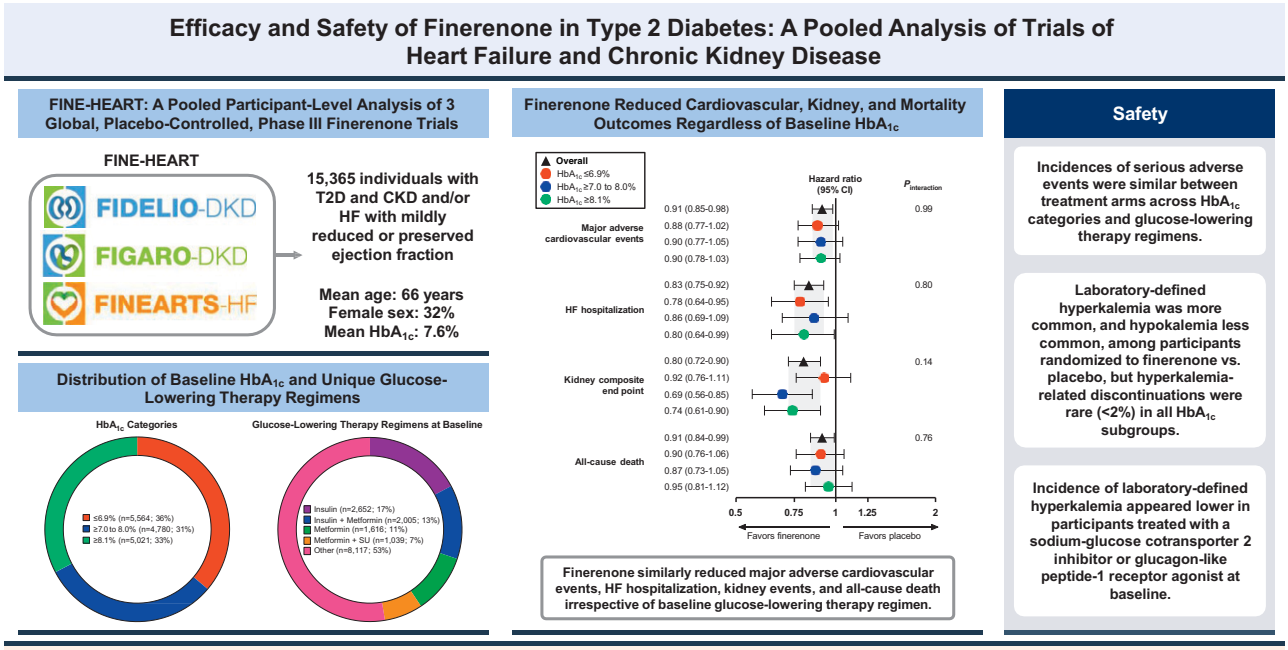

CKD, chronic kidney disease; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; FIGARO-DKD, Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease; FINEARTS-HF, FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure; HF, heart failure; T2D, type 2 diabetes;

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Whether the benefits of finerenone are generalizable to the wide clinical spectrum of type 2 diabetes (T2D) remains uncertain.
- **What is the specific question we wanted to answer?**
  This prespecified analysis of three outcomes trials explored effects of finerenone versus placebo in individuals with T2D according to baseline hemoglobin A_{1c} level and glucose-lowering therapy regimen.
- **What did we find?**
  Finerenone reduced the risk of a wide range of adverse clinical outcomes among individuals with T2D, including heart failure hospitalization, major adverse cardiovascular events, kidney events, and all-cause mortality, irrespective of baseline hemoglobin A_{1c} or glucose-lowering therapy regimen.
- **What are the implications of this finding?**
  These findings support the use of finerenone to improve clinical outcomes in persons with T2D and either kidney disease or heart failure.

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OBJECTIVE

To evaluate the efficacy and safety of finerenone, a nonsteroidal mineralocorticoid receptor antagonist, in individuals with type 2 diabetes (T2D) and either chronic kidney disease (CKD) or heart failure (HF) with mildly reduced ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF).

RESEARCH DESIGN AND METHODS

In this prespecified participant-level pooled analysis of all phase III clinical trials evaluating finerenone versus placebo conducted to date (FINE-HEART), the safety and efficacy of finerenone was evaluated among participants with a history of T2D. Treatment effects on the primary outcome of cardiovascular death and other secondary outcomes were evaluated according to baseline glycated hemoglobin (HbA_{1c}) and glucose-lowering therapy (GLT) regimen using stratified Cox proportional hazards models.

RESULTS

Of 18,991 FINE-HEART participants, 15,365 (80.9%) had T2D and available HbA_{1c} at baseline (mean age, 66 ± 10 years; 32% women; mean HbA_{1c}, 7.6 ± 1.4%). The most common GLT regimens were insulin alone (n = 2,652), insulin and metformin (n = 2,005), metformin alone (n = 1,616), metformin and sulfonylurea (n = 1,039), and "other" (n = 8,117), including sodium–glucose cotransporter 2 inhibitor (SGLT2i) and glucagon-like peptide 1 receptor agonist (GLP-1RA). Over a median follow-up of 2.9 years, treatment effects of finerenone versus placebo on cardiovascular death were consistent across baseline HbA_{1c} ($P_{interaction}$ = 0.75) and GLT regimen ($P_{interaction}$ = 0.46). Finerenone consistently reduced the kidney composite outcome, HF hospitalization, major adverse cardiovascular events, and all-cause mortality, irrespective of baseline HbA_{1c} and GLT regimen. Treatment effects of finerenone were also consistent across number of background GLTs and irrespective of concomitant treatment with a SGLT2i or GLP-1RA.

CONCLUSIONS

Finerenone consistently reduced morbidity and mortality in individuals with T2D across a broad range of glycemia and glucose-lowering regimens.

Type 2 diabetes (T2D), forecasted to impact nearly 1.3 billion individuals worldwide by 2050 (1), represents a leading risk factor for the onset and progression of cardiovascular and kidney disease (2). Between 1999 and 2020, persistently high or

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increasing burdens of cardiovascular disease (CVD) and chronic kidney disease (CKD) in the U.S. were largely attributable to expanding overlap between T2D, CVD, and/or CKD (3). These emerging trends, coupled with increasingly shared prevention and treatment opportunities, have recently driven the development of novel staging systems, risk-prediction algorithms, and collaborative care frameworks targeting cardiovascular-kidney-metabolic (CKM) health (4).

Mineralocorticoid receptor activation is a well-recognized pathophysiological pathway to systemic inflammation and fibrosis in CKM conditions (5). Finerenone, a selective and potent nonsteroidal mineralocorticoid receptor antagonist (5–7), has been shown to improve clinical outcomes in individuals with T2D and CKD and in heart failure (HF) with mildly reduced ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF) (8–10).

T2D is a complex disease characterized by substantial variation in pathobiological mechanisms, glycemic control, multiorgan complications, and treatment approaches (2,11,12). As such, research efforts evaluating the safety and efficacy of novel CKM-oriented risk-reduction strategies across this heterogeneous clinical spectrum are critical to inform implementation. In this prespecified participant-level analysis of three phase III, global, multicenter, double-blind, placebo-controlled, randomized clinical trials of finerenone (FINE-HEART), we evaluated the efficacy and safety of finerenone versus placebo on cardiovascular-kidney outcomes in participants with T2D according to baseline glycemic control and the background glucose-lowering therapy (GLT) regimen.

RESEARCH DESIGN AND METHODS

The Integrated FINE-HEART Program

The rationale and design of FINE-HEART has been previously described (13). In brief, FINE-HEART is a participant-level pooled analysis (prospective PROSPERO registration: CRD42024570467) of three global, multicenter, double-blind, placebo-controlled, randomized clinical trials evaluating the safety and efficacy of finerenone. Two trials (FIDELIO-DKD [Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease] and FIGARO-DKD [Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease]) included individuals with proteinuric CKD and T2D (8,9), and one trial included individuals with HF with HFmrEF/HFpEF, with or without diabetes (FINEARTS-HF [FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure]) (10). The design, baseline characteristics, and primary results of each of the trials included in FINE-HEART are previously reported (8–10,14–17).

FINE-HEART Patient Population and Trial Characteristics

FINE-HEART included adults with CKD and T2D or HFmrEF/HFpEF with or without T2D. In brief, the FIDELIO-DKD and FIGARO-DKD trials enrolled adults (aged $\geq$18 years) with T2D and CKD across 48 countries. FIDELIO-DKD required a urine albumin-to-creatinine ratio (UACR) of 30 to $<$300 mg/g, an estimated glomerular filtration rate (eGFR) of 25 to $<$60 mL/min/1.73 m^2, and a history of diabetic retinopathy or a UACR of 300 to 5,000 mg/g and eGFR of 25 to $<$75 mL/min/1.73 m^2. FIGARO-DKD required either a UACR of 30 to $<$300 mg/g with an eGFR of 25 to 90 mL/min/1.73 m^2 or a UACR of 300 to 5,000 mg/g with an eGFR of $\geq$60 mL/min/1.73 m^2. Both trials required a serum potassium of $\leq$4.8 mmol/L for enrollment. Use of renin-angiotensin system inhibitors and dosing was optimized prior to screening during run-in phases (lasting 4 to 16 weeks) in both trials. Patients with symptomatic HF with reduced ejection fraction were excluded, but those with HF and higher left ventricular ejection fraction were eligible.

The FINEARTS-HF trial enrolled adults (aged $\geq$40 years) with symptomatic HFmrEF/HFpEF across 37 countries. Key inclusion criteria included left ventricular ejection fraction $\geq$40%, elevated natriuretic peptides (adjusted based on atrial fibrillation status and clinical setting of screening), evidence of structural heart disease, and recent diuretic use for $\geq$30 days. Patients were required to have an eGFR $\geq$25 mL/min/1.73 m^2 and a serum potassium level $\leq$5.0 mmol/L for enrollment. Participants were eligible for enrollment regardless of T2D status and clinical care setting (whether hospitalized, recently hospitalized, or ambulatory).

Trial Procedures

Participants in each of the three trials were randomly allocated to finerenone or placebo, with initial dosing determined based on kidney function. The initial dose of study medication was 10 mg once daily for participants with a baseline eGFR of $<$60 mL/min/1.73 m^2 (FIDELIO-DKD and FIGARO-DKD) or $\leq$60 mL/min/1.73 m^2 (FINEARTS-HF), titrated to a target dose of 20 mg once daily as tolerated. For participants with a baseline eGFR of $\geq$60 mL/min/1.73 m^2 (FIDELIO-DKD and FIGARO-DKD) or $>$60 mL/min/1.73 m^2 (FINEARTS-HF), study medication was initiated at a dose of 20 mg once daily, but further titration to a target dose of 40 mg once daily occurred only in FINEARTS-HF; 20 mg once daily was the target dose in FIDELIO-DKD and FIGARO-DKD, irrespective of baseline eGFR. The trial protocols were approved by ethics committees or institutional review boards at all participating sites, and all patients provided written informed consent.

Ascertainment of T2D Status and GLT

Participant T2D status was ascertained according to American Diabetes Association criteria by trial investigators during screening. Concomitant medications were additionally established at screening, randomization, and subsequent trial visits. To enable analysis of mutually exclusive participant subgroups, this analysis focused on the most common unique combinations of GLT (grouped according to medication class) at baseline. Unique GLT regimens used by $<$1,000 participants were included in an "other" category. For additional perspective, treatment effects of finerenone versus placebo on clinical outcomes were assessed in FINE-HEART participants according to baseline use of sodium–glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide 1 receptor agonists (GLP-1RA), and number of GLTs (zero to one, two, or three or more) at baseline.

FINE-HEART Pooled Analysis End Points

Individual participant-level data were accessed and pooled with harmonized data elements for baseline characteristics and clinical outcomes (13). All participants randomized in each of the three trials were considered for this pooled analysis, and only those with critical Good Clinical Practice violations were excluded (13). All efficacy outcomes were analyzed in randomized patients under intention-to-treat principles, while all safety outcomes were analyzed in randomized patients

who had taken at least one dose of the study drug.

The prespecified primary end point for FINE-HEART was time to cardiovascular death (excluding unknown deaths) (13). All deaths were adjudicated by independent clinical end point committees in each of the respective trials included in this analysis. Other prespecified end points included a kidney composite end point (defined as a sustained ≥50% decline in eGFR from baseline, sustained decrease in eGFR to <15 mL/min/1.73 m^2, end-stage kidney disease, and death due to kidney failure), HF hospitalization, composite of cardiovascular death or HF hospitalization, new-onset atrial fibrillation, major adverse cardiovascular events (a composite of nonfatal myocardial infarction, nonfatal stroke, HF hospitalization, or cardiovascular death), all-cause death, and all-cause hospitalization. Select treatment-emergent adverse events related to hyperkalemia, acute kidney injury, hypotension, and gynecomastia were also reported in the pooled population.

Statistical Analysis

Participants without an investigator-reported history of T2D at baseline were excluded from this prespecified analysis. Subgroups were then defined according to baseline glycated hemoglobin (HbA_{1c}) category (≤6.9%, ≥7.0 to ≤8.0%, and ≥8.1%). Participants with missing HbA_{1c} at baseline were excluded from glycemia-focused subgroup analyses. Additional subgroups—including all participants with T2D irrespective of HbA_{1c} availability—were defined according to the most common unique GLT regimen (insulin monotherapy, insulin plus metformin, metformin monotherapy, metformin plus sulfonylurea, and "other"). Baseline characteristics were separately compared according to baseline HbA_{1c} category and GLT regimen using global tests. ANOVA or Kruskal-Wallis tests were used for comparison of continuous variables, as appropriate, and χ^2 tests were used for comparison of categorical variables.

All primary and secondary end points were analyzed as time-to-first end points using a stratified Cox proportional hazards model including the study intervention group as a fixed effect with stratification by geographic region and trial. All treatment effect estimates are presented as hazard ratios with 95% CIs. Select primary and secondary end points were additionally graphically displayed by baseline HbA_{1c} category using Kaplan-Meier methods. Treatment effects on cardiovascular death and other key secondary end points were assessed across HbA_{1c}, GLT subgroups, and number of GLTs at baseline, with interaction terms to assess potential effect modification of treatment effects of finerenone by HbA_{1c} category, GLT regimen, and number of GLTs. Treatment effects of finerenone on cardiovascular death and select secondary end points were additionally evaluated across the continuous spectrum of baseline HbA_{1c} using Poisson regression models, allowing for potentially nonlinear relationships using restricted cubic splines with 3 knots. Statistical analyses were conducted using Stata 18 software (StataCorp LLC, College Station, TX), with two-sided *P* values <0.05 considered statistically significant.

Data Resource and Availability

Data will be made available to qualified scientific and medical researchers through https://vivli.org/. All requests will be reviewed by an independent scientific review panel and data provided according to these conditions (https://vivli.org/ourmember/bayer/).

RESULTS

Patient Population

Overall, of 18,991 FINE-HEART participants, 15,429 (81.2%) had an investigator-reported history of T2D at baseline. Of these, 15,365 (99.6%) had available HbA_{1c} data (mean age, 66 ± 10 years; 32% women; 70% White) and were included in the analysis. Overall, FINE-HEART participants with T2D had a BMI of 31 ± 6 kg/m^2, HbA_{1c} of 7.6 ± 1.4%, eGFR of 58 ± 22 mL/min/1.73 m^2, and median UACR of 423 (interquartile range 114, 1,030) mg/g (Table 1). Statins were used in 73% of FINE-HEART participants with T2D, and 10% and 7% were cotreated with an SGLT2i and GLP-1RA at baseline, respectively. Further, most FINE-HEART participants with T2D were using multiple GLTs at baseline: 5,959 (39%) were using zero to one GLTs, 5,649 (37%) were using two GLTs, and 3,811 (25%) were using three or more GLTs (Supplementary Fig. 1).

Baseline Characteristics According to Baseline HbA_{1c} Category and GLT Regimen

Higher baseline HbA_{1c} in FINE-HEART participants with investigator-reported T2D was associated with younger age, Black race, higher BMI, longer diabetes duration, higher UACR, and a greater number of GLTs at baseline. However, individuals with higher baseline HbA_{1c} were less likely to have atrial fibrillation and a history of HF (Table 1). Alternatively, FINE-HEART participants with the lowest HbA_{1c} ≤6.9% had the lowest eGFR of all groups, highest prevalence of comorbid HF, and were most likely to have been enrolled in FINEARTS-HF.

Substantial between-subgroup differences in demographic and clinical characteristics were observed across GLT regimens (Supplementary Table 1). Broadly, participants using insulin alone or in combination with metformin were more likely to have self-reported Black race, higher BMI, and highter systolic blood pressure, baseline HbA_{1c}, and baseline UACR. Participants with insulin monotherapy had the lowest eGFR and highest UACR across all GLT subgroups. Alternatively, participants with metformin monotherapy were generally older, White, and had the lowest UACR across GLT subgroups.

Clinical Outcomes According to Baseline HbA_{1c} Category

Over a median follow-up of 2.9 (interquartile range 2.3, 3.7) years, significant differences in the cumulative incidence of cardiovascular death (*P* for trend < 0.001), HF hospitalization (*P* for trend = 0.002), and all-cause mortality (*P* for trend = 0.001), but not the composite kidney outcome (*P* for trend = 0.97), were observed between HbA_{1c} subgroups (Supplementary Fig. 2). Participants with baseline HbA_{1c} ≥8.1% exhibited the highest rates of cardiovascular death (incidence rate, 1.5 per 100 patient-years) and all-cause mortality (incidence rate, 3.9 per 100 patient-years). However, the incidence of HF hospitalization was highest among participants with HbA_{1c} ≤6.9%, the subgroup with the highest prevalence of comorbid HF at baseline (Table 1).

Treatment Effects of Finerenone According to Baseline HbA_{1c} Category

Treatment effects of finerenone versus placebo on the primary end point of cardiovascular death were consistent irrespective of baseline HbA_{1c} category

Table 1—Baseline characteristics of FINE-HEART participants with type 2 diabetes, by baseline HbA_{1c} category

		Baseline HbA_{1c} category		
	Overall (*N* = 15,365)	≤6.9% (*n* = 5,564)	≥7.0% to ≤8.0% (*n* = 4,780)	≥8.1% (*n* = 5,021)
Age, years	65.8 ± 9.8	67.4 ± 9.8	66.2 ± 9.6	63.7 ± 9.6
Female sex	4,938 (32.1)	1,662 (29.9)	1,410 (29.5)	1,866 (37.2)
Race[a]				
Asian	3,237 (21.1)	1,254 (22.5)	1,088 (22.8)	895 (17.8)
Black	559 (3.6)	163 (2.9)	179 (3.7)	217 (4.3)
Other	801 (5.2)	226 (4.1)	237 (5.0)	338 (6.7)
White	10,768 (70.1)	3,921 (70.5)	3,276 (68.5)	3,571 (71.1)
Region				
Asia	3,013 (19.6)	1,178 (21.2)	1,008 (21.1)	827 (16.5)
Eastern Europe	4,336 (28.2)	1,618 (29.1)	1,192 (24.9)	1,526 (30.4)
Latin America	1,698 (11.1)	477 (8.6)	480 (10.0)	741 (14.8)
North America	2,268 (14.8)	782 (14.1)	719 (15.0)	767 (15.3)
Western Europe, Oceania, and others	4,050 (26.4)	1,509 (27.1)	1,381 (28.9)	1,160 (23.1)
Trial enrollment				
FIDELIO-DKD	5,651 (36.8)	1,899 (34.1)	1,814 (37.9)	1,938 (38.6)
FIGARO-DKD	7,317 (47.6)	2,408 (43.3)	2,342 (49.0)	2,567 (51.1)
FINEARTS-HF	2,397 (15.6)	1,257 (22.6)	624 (13.1)	516 (10.3)
Baseline BMI, kg/m^2	31.3 ± 6.0	30.6 ± 6.0	31.1 ± 5.9	32.2 ± 6.1
Baseline systolic blood pressure, mmHg	135.8 ± 14.5	134.6 ± 14.5	136.2 ± 14.8	136.6 ± 14.2
Baseline potassium, mmol/L	4.4 ± 0.4	4.3 ± 0.4	4.4 ± 0.4	4.4 ± 0.5
Baseline HbA_{1c}, %	7.6 ± 1.4	6.3 ± 0.5	7.5 ± 0.3	9.2 ± 1.0
Duration of diabetes at baseline,[b] years				
<5	2,028 (13.2)	1,209 (21.8)	460 (9.6)	359 (7.2)
5 to <10	2,792 (18.2)	1,226 (22.1)	824 (17.3)	742 (14.8)
10 to <15	3,278 (21.4)	1,165 (21.0)	1,031 (21.6)	1,082 (21.6)
15 to <20	3,102 (20.2)	882 (15.9)	1,025 (21.5)	1,195 (23.8)
20 to <25	2,119 (13.8)	558 (10.1)	716 (15.0)	845 (16.9)
≥25	2,004 (13.1)	504 (9.1)	711 (14.9)	789 (15.7)
Baseline eGFR, mL/min/1.73 m^2	57.9 ± 21.5	56.6 ± 20.4	57.3 ± 21.2	60.0 ± 22.6
eGFR category, mL/min/1.73 m^2				
<25	183 (1.2)	60 (1.1)	66 (1.4)	57 (1.1)
25 to <45	4,844 (31.5)	1,820 (32.7)	1,552 (32.5)	1,472 (29.3)
45 to <60	4,050 (26.4)	1,530 (27.5)	1,267 (26.5)	1,253 (25.0)
≥60	6,288 (40.9)	2,154 (38.7)	1,895 (39.6)	2,239 (44.6)
Baseline UACR, mg/g	423 (114, 1,030)	340 (75, 884)	426 (125, 1,033)	515 (174, 1,176)
Baseline UACR category, mg/g				
<30	1,344 (8.8)	742 (13.4)	332 (7.0)	270 (5.4)
30 to <300	4,895 (32.0)	1,867 (33.8)	1,579 (33.1)	1,449 (29.0)
≥300	9,054 (59.2)	2,920 (52.8)	2,855 (59.9)	3,279 (65.6)
Atrial fibrillation on electrocardiogram	1,342 (8.7)	685 (12.3)	351 (7.3)	306 (6.1)
History of HF[c]	3,400 (22.1)	1,528 (27.5)	941 (19.7)	931 (18.5)
Baseline CKD[d]	14,249 (92.7)	4,991 (89.7)	4,485 (93.8)	4,773 (95.1)
Background medication use				
Diuretics	9,058 (59.0)	3,395 (61.0)	2,775 (58.1)	2,888 (57.5)
ACE inhibitor/ARB/ARNI	14,902 (97.0)	5,336 (95.9)	4,657 (97.4)	4,909 (97.8)
Aspirin	7,276 (47.4)	2,415 (43.4)	2,316 (48.5)	2,545 (50.7)
Statin	11,175 (72.7)	3,958 (71.1)	3,569 (74.7)	3,648 (72.7)
SGLT2i	1,476 (9.6)	462 (8.3)	517 (10.8)	497 (9.9)
GLP-1RA	1,101 (7.2)	292 (5.2)	399 (8.3)	410 (8.2)
Potassium-lowering therapies[e]	190 (1.2)	73 (1.3)	66 (1.4)	51 (1.0)

Continued on p. 5

Table 1—Continued

	Overall (*N* = 15,365)	Baseline HbA_{1c} category		
		≤6.9% (*n* = 5,564)	≥7.0% to ≤8.0% (*n* = 4,780)	≥8.1% (*n* = 5,021)
GLT therapies at baseline, *n*				
0 or 1	5,939 (38.7)	2,821 (50.7)	1,571 (32.9)	1,547 (30.8)
2	5,632 (36.7)	1,760 (31.6)	1,863 (39.0)	2,009 (40.0)
≥3	3,794 (24.7)	983 (17.7)	1,346 (28.2)	1,465 (29.2)

Values reported as *n* (%), mean ± SD, or median (interquartile range). *P* value reflects comparison of HbA_{1c} categories. ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor. [a]Represents self-reported race. Participants choosing not disclose race or who self-identified as multiple races are included in the "other" category for descriptive purposes. [b]Date of diabetes diagnosis collected by trial investigators at baseline. The 42 participants (0.3%) without a recorded year of diabetes diagnosis, or with a recorded date of diabetes diagnosis after randomization (but also with established diabetes at baseline), were excluded from the analysis of this variable. Otherwise, missing months were imputed as June, and missing day of the month was imputed as 15. [c]HF includes all participants in FINEARTS-HF and those with investigator-reported history of HF in the primary CKD outcomes trials (FIDELIO-DKD, FIGARO-DKD). [d]CKD includes all participants in the primary CKD outcomes trials (FIDELIO-DKD, FIGARO-DKD) and participants in FINEARTS-HF with baseline eGFR < 60 mL/min/1.73 m^2. [e]Includes patiromer, sodium polystyrene sulfonate, calcium polystyrene sulfonate.

($P_{interaction}$ = 0.75) (Fig. 1). Finerenone additionally reduced the kidney composite end point ($P_{interaction}$ = 0.14), HF hospitalization ($P_{interaction}$ = 0.80), major adverse cardiovascular events ($P_{interaction}$ = 0.99), all-cause mortality ($P_{interaction}$ = 0.76), and other key secondary end points irrespective of baseline HbA_{1c} category (Fig. 1 and Supplementary Fig. 3). Similar findings were observed when HbA_{1c} was evaluated as a continuous variable (Supplementary Fig. 4).

Treatment Effects of Finerenone According to Baseline GLT Regimen

Treatment effects of finerenone versus placebo on cardiovascular death and key secondary outcomes were additionally consistent irrespective of baseline GLT regimen (Fig. 2*A*) and number of GLTs at baseline (Supplementary Fig. 5). Moreover, finerenone compared with placebo consistently reduced the kidney composite outcome, HF hospitalization, major adverse cardiovascular events, and all-cause mortality irrespective of whether cotreated with an SGLT2i or GLP-1RA at baseline (Fig. 2*B*).

Safety of Finerenone According to Baseline HbA_{1c} Category

Irrespective of treatment assignment, the incidence of all safety events was similar across the baseline HbA_{1c} categories, with the exception of laboratory-defined hyperkalemia (>5.5 mmol/L), which increased modestly with higher baseline HbA_{1c} (Table 2).

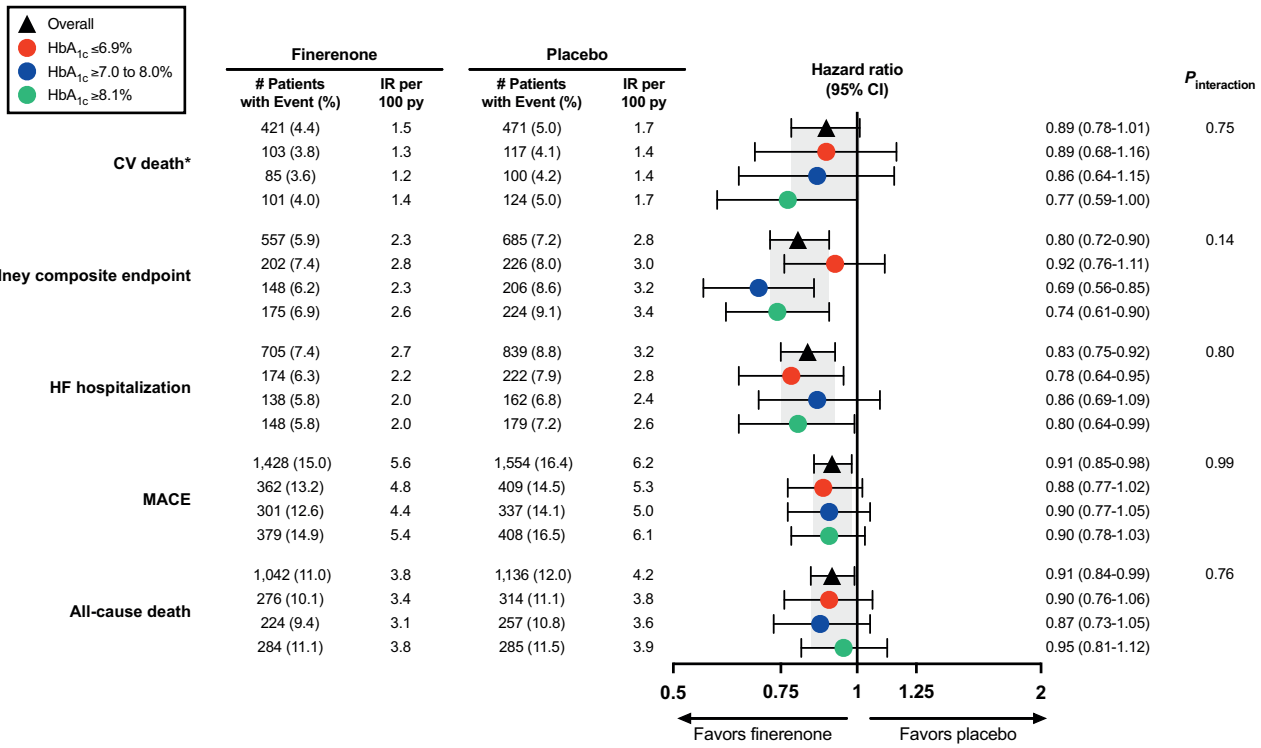

Figure 1—Treatment effects of finerenone on key efficacy outcomes by baseline HbA_{1c} category. *Reflects prespecified primary end point definition, in which undermined death was excluded. Overall treatment effects (full FINE-HEART population) for each outcome reported for contextualization. Major adverse cardiovascular events (MACE) reflect a composite of nonfatal myocardial infarction, nonfatal stroke, HF hospitalization, or cardiovascular (CV) death. IR, incidence rate; py, person-years.

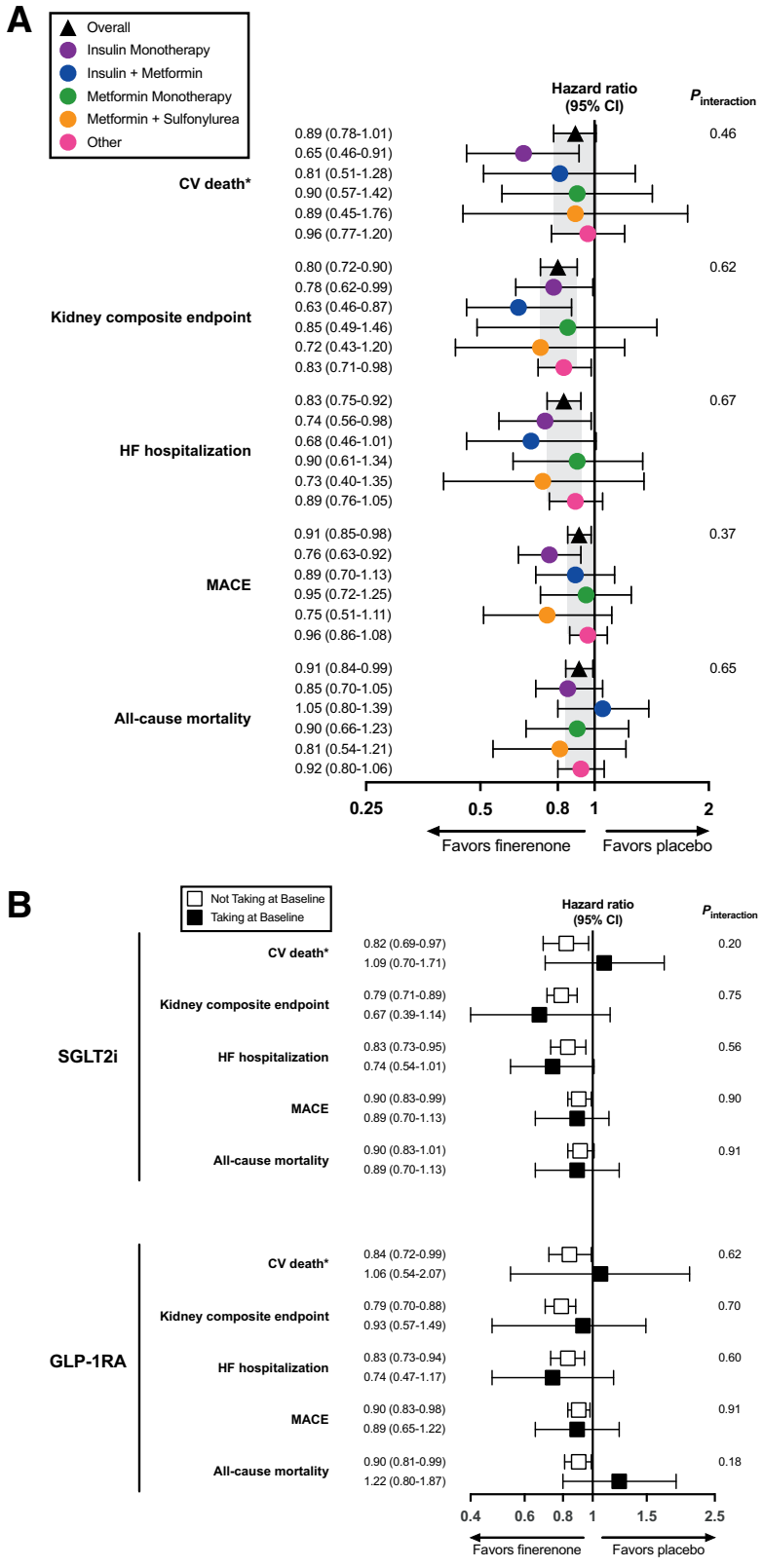

Figure 2—Treatment effects of finerenone versus placebo are shown according to subgroups defined by the most common unique GLT regimen at baseline (*A*) and baseline use of SGLT2i or GLP-1RA (*B*). *Reflects prespecified primary end point definition, in which undermined death was excluded. Overall treatment effects (full FINE-HEART population) for each outcome reported for contextualization. Major adverse cardiovascular events (MACE) reflects a composite of nonfatal myocardial infarction, nonfatal stroke, HF hospitalization, or cardiovascular (CV) death. IR, incidence rate; py, person-years.

Between treatment arms, the incidence of any serious adverse event was similar among participants randomized to finerenone compared with placebo in each of the baseline HbA_{1c} categories. The incidence of laboratory-defined hyperkalemia was higher, and the incidence of laboratory-defined hypokalemia lower, with finerenone versus placebo in each of the baseline HbA_{1c} categories. However, hyperkalemia leading to treatment discontinuation or hospitalization was uncommon with finerenone, both $<2\%$ in all HbA_{1c} categories, but occurred more frequently compared with placebo. Hypotension (systolic blood pressure <100 mmHg) was additionally more common with finerenone in each of the baseline HbA_{1c} categories. The incidence of acute kidney injury was generally similar between the treatment arms across HbA_{1c} categories.

Safety of Finerenone According to Baseline GLT Regimen

Irrespective of assigned treatment, incidences of any serious adverse event, laboratory-defined hyperkalemia, acute kidney injury, and hypotension varied across baseline GLT regimen (Supplementary Table 3). Incidences of any serious adverse event, laboratory-defined hyperkalemia, and acute kidney injury were highest among participants receiving insulin monotherapy at baseline.

Incidences of any serious adverse event and acute kidney injury were similar between treatment arms across baseline GLT regimen. The incidence of serious adverse events leading to drug discontinuation was similar with finerenone versus placebo across GLT regimen, with the exception of participants using insulin monotherapy at baseline, in whom the incidence was higher with finerenone (7.2%) versus placebo (4.4%). Laboratory-defined hyperkalemia and hypotension were more common with finerenone in all GLT regimen subgroups.

Irrespective of treatment assignment, the incidences of any serious adverse event and hypotension were higher among SGLT2i users and GLP-1RA users at baseline compared with those who were nonusers (Supplementary Tables 4 and 5). However, laboratory-defined hyperkalemia appeared less common among SGLT2i users versus nonusers (8.3% vs. 13.3%) and among GLP-1RA users versus nonusers (10.2% vs. 13.0%). Laboratory-defined hyperkalemia

Table 2—Safety outcomes of FINE-HEART participants with type 2 diabetes, by baseline HbA_{1c} category

	Baseline HbA_{1c} category								
	≤6.9%			≥7.0% to ≤8.0%			≥8.1%		
	Overall (*n* = 5,555)	Finerenone (*n* = 2,739)	Placebo (*n* = 2,816)	Overall (*n* = 4,773)	Finerenone (*n* = 2,388)	Placebo (*n* = 2,385)	Overall (*n* = 5,007)	Finerenone (*n* = 2,545)	Placebo (*n* = 2,462)
Any serious adverse event	1,930 (34.7)	926 (33.8)	1,004 (35.7)	1,654 (34.7)	796 (33.3)	858 (36.0)	1,806 (36.1)	909 (35.7)	897 (36.4)
Any adverse event leading to treatment discontinuation	331 (6.0)	168 (6.1)	163 (5.8)	260 (5.4)	140 (5.9)	120 (5.0)	253 (5.1)	148 (5.8)	105 (4.3)
Any potassium >5.5 mmol/L[a]	655 (12.0)	468 (17.3)	187 (6.7)	597 (12.7)	407 (17.3)	190 (8.1)	684 (13.8)	454 (18.1)	230 (9.5)
Any potassium >6.0 mmol/L[a]	135 (2.5)	103 (3.8)	32 (1.2)	109 (2.3)	76 (3.2)	33 (1.4)	136 (2.8)	92 (3.7)	44 (1.8)
Any potassium <3.5 mmol/L[a]	432 (7.9)	129 (4.8)	303 (10.9)	345 (7.3)	107 (4.5)	238 (10.1)	345 (7.0)	121 (4.8)	224 (9.2)
Hyperkalemia[b]	575 (10.4)	382 (13.9)	193 (6.9)	496 (10.4)	334 (14.0)	162 (6.8)	534 (10.7)	357 (14.0)	177 (7.2)
Hyperkalemia leading to									
Treatment discontinuation[b]	66 (1.2)	48 (1.8)	18 (0.6)	40 (0.8)	27 (1.1)	13 (0.5)	53 (1.1)	43 (1.7)	10 (0.4)
Hospitalization[b]	34 (0.6)	30 (1.1)	4 (0.1)	20 (0.4)	16 (0.7)	4 (0.2)	32 (0.6)	24 (0.9)	8 (0.3)
Acute kidney injury[b]	190 (3.4)	94 (3.4)	96 (3.4)	191 (4.0)	90 (3.8)	101 (4.2)	198 (4.0)	107 (4.2)	91 (3.7)
Acute kidney injury leading to									
Treatment discontinuation	10 (0.2)	5 (0.2)	5 (0.2)	7 (0.1)	4 (0.2)	3 (0.1)	9 (0.2)	5 (0.2)	4 (0.2)
Hospitalization	83 (1.5)	41 (1.5)	42 (1.5)	70 (1.5)	29 (1.2)	41 (1.7)	77 (1.5)	51 (2.0)	26 (1.1)
Any systolic blood pressure <100 mmHg	433 (7.9)	286 (10.6)	147 (5.3)	335 (7.1)	199 (8.4)	136 (5.8)	338 (6.8)	205 (8.1)	133 (5.5)
Gynecomastia	3 (0.1)	2 (0.1)	1 (0.0)	15 (0.3)	6 (0.3)	9 (0.4)	10 (0.2)	4 (0.2)	6 (0.2)

Data are presented as *n* (%). Treatment-emergent adverse events are defined as any adverse event occurring in any patient who has received at least one dose of study drug and within 3 days of permanent discontinuation. This safety table includes one patient with baseline HbA_{1c} ≥8.1% who was randomized to placebo but who actually received finerenone. There were no instances of death due to hyperkalemia. [a]Based on central laboratory measurements of potassium levels. [b]Based on investigator-reported adverse events.

was more common and hypokalemia less common with finerenone versus placebo irrespective of SGLT2i or GLP-1RA cotreatment.

CONCLUSIONS

In this prespecified pooled analysis of the integrated FINE-HEART trials including participants with investigator-reported T2D and either CKD or HFmrEF/HFpEF, treatment effects of finerenone on cardiovascular death and all key secondary outcomes were consistent across multiple clinically relevant T2D subgroups. Namely, finerenone consistently reduced kidney disease progression, HF hospitalization, major adverse cardiovascular events, and all-cause mortality, among other secondary outcomes, compared with placebo, regardless of baseline HbA_{1c}, number of GLTs, and major unique GLT regimen, including among SGLT2i and GLP-1RA users. The safety profile of finerenone was broadly consistent with prior analyses, with an expected modestly higher incidence of hyperkalemia, but without excess serious adverse events, observed in all HbA_{1c} and GLT subgroups. Taken together, these findings highlight the potential of finerenone to reduce cardiovascular, kidney, and overall morbidity and mortality across a wide clinical spectrum of T2D.

Glycemic control is a foundational priority of T2D management efforts and a well-established determinant of microvascular outcomes (e.g., CKD) and macrovascular outcomes (e.g., CVD). In a population-level observational study using data from the Swedish National Diabetes Register, an HbA_{1c} level $\geq$7.0% was the most powerful predictor of stroke and myocardial infarction in individuals with T2D (18). Similarly, higher HbA_{1c} values have been shown to be steeply associated with risk of CKD onset and progression (19,20). Despite potential for higher absolute benefits owing to greater baseline risk, clinicians may be reticent to prioritize risk-reducing therapies that do not impact glycemic control, such as finerenone, alongside conventional GLT in individuals with higher baseline HbA_{1c}. Alternatively, lower HbA_{1c} values may be misinterpreted as signifying absence of residual cardiovascular-kidney risk (21), leading to deferral of critical opportunities to prevent or delay downstream events. However, the consistent benefits of finerenone on morbidity and mortality irrespective of HbA_{1c} emphasizes the potential of transitioning from glucocentric to more holistic and multifaceted strategies making use of the benefits of combination therapies targeting complementary and nonoverlapping mechanisms of disease. The favorable safety profile of finerenone across the spectrum of glycemia, namely rare hyperkalemia-related hospitalization ($\sim$1% in all HbA_{1c} subgroups) and no excess risk of acute kidney injury, despite high (97%) baseline use of renin-angiotensin system inhibitors, may further support this approach.

Further, owing to considerable phenotypic heterogeneity, increasingly individualized approaches to GLT selection, and expanding recognition of the unique benefits of SGLT2i and GLP-1RA, the therapeutic landscape in T2D is progressively diverse. In a prior secondary analysis of FIDELIO-DKD and FIGARO-DKD, treatment benefits of finerenone in individuals with T2D and CKD were shown to be consistent irrespective of insulin use at baseline (22). Findings from FINE-HEART support and extend this analysis, demonstrating the consistent benefits and safety profile of finerenone across multiple major GLT regimens beyond insulin alone and in individuals with T2D and HFmrEF/HFpEF. Moreover, rapid advancements in pharmacotherapy have renewed focus on polypharmacy among individuals with T2D, which has been associated with drug-drug interactions, excess out-of-pocket costs, and increased health care utilization (23). As T2D is a chronic and progressive disease, many individuals, especially those with longer-duration T2D, may require multiple GLTs to achieve T2D-related health goals. Indeed, most of the FINE-HEART participants with T2D were taking two or more GLTs at baseline. However, the consistent benefits and safety profile of finerenone irrespective of the number of background GLTs provides important reassurance for clinicians engaged in the care of individuals with T2D and either CKD or HFmrEF/HFpEF. Findings from the prospective observational FINE-REAL (a non-interventional study providing insights into the use of finerenone in a routine clinical setting) study may further inform understanding of the safety of finerenone in routine clinical practice (24).

The consistent benefits of finerenone irrespective of background SGLT2i and GLP-1RA treatment have important implications for clinical care. Namely, owing to their established benefits on CKM risk factors and disease progression, SGLT2i and GLP-1RA are firmly established in international guidelines for CVD (e.g., SGLT2i in heart failure or atherosclerotic CVD plus T2D; GLP-1RA in atherosclerotic CVD plus T2D) (25–27), CKD (28), and T2D (29). Finerenone is also presently recommended in international guidelines to reduce CKD progression and improve cardiovascular risk among individuals with CKD and T2D (27,28,30). Critically, this convergence of therapies on sizeable and expanding patient populations with CKM multimorbidity fosters substantial opportunity for risk reduction. In a recent collaborative meta-analysis of clinical trials, benefits of SGLT2i on cardiovascular and kidney outcomes were consistent irrespective of background GLP-1RA use (31). This pooled FINE-HEART analysis supports and extends prior observations from FIDELIO-DKD and FIGARO-DKD (32,33), showing consistent benefits of finerenone irrespective of background SGLT2i or GLP-1RA use. However, the within-subgroup estimates had wide CIs and should be interpreted with caution. While a combination "pillar"-based approach making use of the potentially complementary and nonoverlapping effects of these therapies is appealing to maximize CKM risk reduction (26,27), further trials, such as CONFIDENCE (COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with CKD and type 2 diabetes using a UACR Endpoint; NCT05254002) and CONFIRMATION-HF (A Study to Determine the Efficacy and Safety of Finerenone and SGLT2i in Combination in Hospitalized Patients With Heart Failure; NCT06024746), are underway to inform the safety and efficacy of combination therapy strategies inclusive of finerenone (34).

In FINE-HEART, the incidence of hyperkalemia was lower in participants treated with both SGLT2i and GLP-1RA, but finerenone modestly increased hyperkalemia irrespective of cotreatment with SGLT2i or GLP-1RA. Previous trials and observational analyses have suggested that SGLT2i and, possibly, GLP-1RA could attenuate hyperkalemia risks (35,36), which may be attributable to the kaliuretic and/or kidney-protective effects of both agents (37,38). While the rate of hyperkalemia-related treatment discontinuations was low in FINE-HEART (13), these findings may signify

the potential of SGLT2i or GLP-1RA to enhance maintenance of finerenone and other key therapies (e.g., renin-angiotensin system inhibitors) known to modestly increase risk of hyperkalemia. Indeed, SGLT2i and sacubitril/valsartan have demonstrated similar benefits in HF populations (39).

Conversely, participants using insulin monotherapy at baseline experienced the highest incidence of laboratory-defined and investigator-reported hyperkalemia, irrespective of treatment assignment. While this may relate, in part, to the clinical profile of this subgroup (e.g., lower baseline kidney function), diabetes is an established driver of hyperkalemia through multifaceted pathways, such as insulin resistance, hyporeninemic hypoaldosteronism, and enhanced insulin-mediated sodium reabsorption via the proximal tubule (leading to reduced distal sodium delivery and subsequently reduced potassium excretion) (40). While hyperkalemia-related treatment discontinuations (2.3%) and hospitalizations (1.5%) were rare with finerenone even in this subgroup, this observation suggests efforts to improve insulin sensitivity (e.g., obesity management) and glycemic control may enhance longitudinal tolerance (and, therein, maximize benefits) with finerenone.

This analysis has some limitations. First, owing to sample size limitations, we were unable to rigorously evaluate the efficacy and safety of all unique GLT regimens at baseline. However, insulin, metformin, and sulfonylureas have previously been identified as the most common contemporary GLTs among individuals with T2D and CKD, as well as other forms of CKM multimorbidity inclusive of T2D, in the general population (3). Moreover, given their expanding use in many global regions and important CKM benefits, SGLT2i and GLP-1RA received dedicated attention in this analysis. However, background use of these therapies was modest even in this pooled analysis.

Second, while a key strength of this analysis lies in pooling participant-level data from all completed phase III trials evaluating finerenone to date, some subgroups may have been underpowered.

Third, the primary end point of cardiovascular death (exclusive of undetermined death) was narrowly missed in the overall FINE-HEART analysis (13), and further subgroup analysis should be interpreted in this context.

Finally, further research efforts are needed to ascertain whether these findings apply to younger individuals, to community settings, and to populations with more diverse racial and ethnic backgrounds.

Conclusion

In this prespecified analysis of FINE-HEART, encompassing participant-level pooled data from all phase III clinical trials evaluating finerenone conducted to date, treatment effects of finerenone among individuals with T2D and either CKD or HFmrEF/HFpEF were consistent irrespective of baseline HbA_{1c}, GLT regimen, and number of GLTs. These findings provide important reassurance concerning the potential of finerenone to reduce morbidity and mortality across a diverse clinical spectrum of T2D.

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Duality of Interest. B.L.C. has received personal consulting fees from Alnylam, Bristol-Myers Squibb, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, and Rocket, and has served on a Data and Safety Monitoring Board for Novo Nordisk. G.F. reports lecture fees from Bayer, Boehringer Ingelheim, Servier, and Novartis; trial committee membership fees from Bayer, Boehringer Ingelheim, Servier, Impulse Dynamics, Vifor, and Medtronic; and consulting fees from Cardior and Novo Nordisk. A.S.D. has received institutional research grants (to Brigham and Women's Hospital) from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, and Pfizer, as well as personal consulting fees from Abbott, Alnylam, AstraZeneca, Bayer, Biofourmis, Boston Scientific, Medpace, Medtronic, Merck, Novartis, Parexel, Porter Health, Regeneron, River2Renal, Roche, Veristat, Verily, and Zydus. P.S.J. reports speakers' fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, and Sun Pharmaceuticals; advisory board fees from AstraZeneca, Boehringer Ingelheim, and Novartis; and research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc, and Roche Diagnostics. P.S.J. is employed by the University of Glasgow, which has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis, and Novo Nordisk, and is a director at GCTP Ltd. M.B. is a full-time employee of Bayer AG. P.S. is an employee of Bayer AG. P.V. is an employee of Bayer AG. C.S.P.L. has received research support from NovoNordisk and Roche Diagnostics; has received consulting fees from Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, CardioRenal, CPC Clinical Research, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd., Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics, and Us2.ai; and is a cofounder and nonexecutive director of Us2.ai. M.S. has served on advisory boards, consultancy and honoraria for Novartis, Abbott, Merck, MSD, Vifor, AstraZeneca, Cardurion, Novonordisk, Bayer, and Boehringer Ingelheim. S.J.S. has received research grants from AstraZeneca, Corvia, and Pfizer and consulting fees from Abbott, Alleviant, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Imara, Impulse Dynamics, Intellia, Ionis, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sardocor, Shifamed, Tenax, Tenaya, and Ultromics. A.A.V.'s employer received consultancy fees and/or research support from Adrenomed, Anacardio, AstraZeneca, Bayer AG, BMS, Boehringer Ingelheim, Corteria, Eli Lilly, Merck, Moderna, Novartis, Novo Nordisk, Roche Diagnostics, and SalubrisBio. F.Z. reports personal fees from 89Bio, Abbott, Acceleron, Applied Therapeutics, Bayer, Betagenon, Boehringer, BMS, CVRx, Cambrian, Cardior, Cereno Pharmaceutical, Cellprothera, CEVA, Inventiva, KBP, Merck, Novo Nordisk, Owkin, Otsuka, Roche Diagnostics, Northsea, and Us2.ai, has stock options at G3Pharmaceutical and equities at Cereno, Cardiorenal, and Eshmoun Clinical Research, and is the founder of Cardiovascular Clinical Trialists. P.R.reports grants and payment of honoraria for lectures, educational events, and steering group participation from AstraZeneca, Bayer, and Novo Nordisk (all to the Steno Diabetes Center Copenhagen); honoraria for lectures and participation in advisory boards from Boehringer Ingelheim, Sanofi, Gilead, and Astellas (all to the Steno Diabetes Center Copenhagen), and has received study drugs for free for investigator-initiated studies from Bayer, Novo Nordisk and Lexicon. S.D.A reports grants from Vifor Int, Abbott; consulting fees from CVRx, AstraZeneca, Bioventrix, Repairon, Novo Nordisk, Brahms, Novartis, Actimed Therapeutics, Faraday Pharmaceuticals, Cytokinetics, HeartKinetics, GSK, Vectorious, Scirent, Sensible Medical, Edwards, Relaxera, Repairon, Regeneron Pharmaceuticals, and Cordio; steering or advisory committee work for Vifor Int, Bayer AG, Boehringer Ingelheim, Medtronic, Abbott, Impulse Dynamics, Cardior, V-Wave, Pfizer, Cardiac Dimensions, and Occlutech; and is

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Author Contributions. S.D.S. and M.V. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J.W.O., S.D.S., and M.V. designed the study. J.W.O. performed statistical analyses and drafted the manuscript. B.L.C. provided supervision and performed statistical analyses. Z.M.M. performed statistical analyses. All authors helped to interpret the data and critically revised the manuscript for important intellectual content. S.D.S. and M.V. controlled the decision to publish and attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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