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Effect of Finerenone on the KCCQ in Patients With HFmrEF/HFpEF

A Prespecified Analysis of FINEARTS-HF

Mingming Yang, MD, PhD,[a] Alasdair D. Henderson, PhD,[a] Atefeh Talebi, PhD,[a] John J. Atherton, MBBS, PhD,[b] Chern-En Chiang, MD, PhD,[c] Vijay Chopra, MB, BS, MD,[d] Josep Comin-Colet, MD, PhD,[e] Mikhail N. Kosiborod, MD,[f] Jose F. Kerr Saraiva, MD, PhD,[g] Brian L. Claggett, PhD,[h] Akshay S. Desai, MD MPH,[h] Peter Kolkhof, PhD,[i] Prabhakar Viswanathan, MBBS PhD,[i] Andrea Lage, MD,[j] Carolyn S.P. Lam, MD, PhD,[k] Michele Senni, MD,[l] Sanjiv J. Shah, MD,[m] Katja Rohwedder, MD,[n] Adriaan A. Voors, MD, PhD,[o] Faiez Zannad, MD, PhD,[p] Bertram Pitt, MD,[q] Muthiah Vaduganathan, MD, MPH,[h] Pardeep S. Jhund, MBChB, MSc, PhD,[a] Scott D. Solomon, MD,[h] John J.V. McMurray, MD[a]

ABSTRACT

BACKGROUND Patients with heart failure (HF) are limited by symptoms and have impaired quality of life. The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a patient-reported outcome measure that enables evaluation of the effect of HF and the impact of new therapies on health status in patients with HF.

OBJECTIVES This prespecified analysis of FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) assessed the efficacy and safety of finerenone according to baseline KCCQ Total Symptom Score (TSS) and the effect of finerenone on KCCQ-TSS.

METHODS FINEARTS-HF tested the efficacy of the nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone, compared with placebo, in patients with HF with mildly reduced ejection fraction/preserved ejection fraction. The primary endpoint was the composite of cardiovascular death and total worsening HF events. The KCCQ was completed by patients at randomization and at 6, 9, and 12 months after randomization. Change in KCCQ-TSS was a key secondary endpoint. Patients were stratified by KCCQ-TSS tertiles at baseline. The association between KCCQ tertile and clinical outcomes was evaluated using semiparametric proportional-rates models for total events and Cox models for time-to-first-event data, and the effects of finerenone vs placebo on the primary endpoint were assessed across tertiles of KCCQ-TSS.

RESULTS Of the 6,001 participants in FINEARTS-HF, 5,986 (99.8%) had baseline KCCQ-TSS recorded (median score 69.8 of a possible 100; higher score = better health status). Lower (worse) KCCQ-TSS was associated with a higher risk of the primary endpoint. Finerenone, compared with placebo, reduced the risk of the primary endpoint across the range of KCCQ-TSS: tertile 1 (score 0-<57): RR: 0.82 (95% CI: 0.68-1.00); tertile 2 (57-<81): 0.88 (95% CI: 0.70-1.11); tertile 3 (81-100): 0.88 (95% CI: 0.69-1.14) ($P_{interaction} = 0.89$). Compared with placebo, finerenone significantly improved KCCQ-TSS from baseline with a mean difference at 12 months of 1.62 points (95% CI: 0.69-2.56 points) ($P < 0.001$). Numerically fewer finerenone-treated patients experienced clinically meaningful deterioration, and more had improvements in KCCQ-TSS.

CONCLUSIONS Finerenone significantly reduced HF events and improved health status in patients with HF and mildly reduced ejection fraction/preserved ejection fraction across the spectrum of KCCQ-TSS at baseline. (Study to Evaluate the Efficacy [Effect on Disease] and Safety of Finerenone on Morbidity [Events Indicating Disease Worsening] & Mortality [Death Rate] in Participants With Heart Failure and Left Ventricular Ejection Fraction [Proportion of Blood Expelled Per Heart Stroke] Greater or Equal to 40% [FINEARTS-HF], NCT04435626; Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure; EudraCT 2020-000306-29) (JACC. 2025;85:120-136) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Heart failure with mildly reduced ejection fraction (HFmrEF)/heart failure with preserved ejection fraction (HFpEF) constitutes a significant and growing component of the overall global burden of HF.[1-3] Afflicted patients experience not only a heightened risk of adverse clinical outcomes but also a profound burden of symptoms, significant physical limitations, and a markedly diminished health-related quality of life.[4-6] Thus, improving health status is a key objective of the comprehensive care of patients with HFmrEF/HFpEF, as increasingly recognized by regulatory bodies, clinical practice guidelines, and health care providers.[7-10]

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Aldosterone has a multifaceted role in the complex pathophysiology of HF, disrupting electrolyte balance, driving autonomic dysfunction, inducing myocardial and vascular fibrosis, reducing arterial compliance, as well as impairing baroreceptor sensitivity.[11-15] The novel nonsteroidal MRA finerenone was studied in the FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure) trial. When compared with placebo in 6,001 patients with heart failure (HF) and an ejection fraction ≥40%, finerenone reduced the primary outcome of total worsening HF events and cardiovascular (CV) death (RR: 0.84; 95% CI: 0.74-0.95; $P = 0.007$) over a median follow-up of 32 months.[16] In this prespecified analysis of FINEARTS-HF, we conducted a detailed evaluation of the benefits of finerenone on clinical outcomes according to baseline Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS), and of the effect of finerenone on health status (assessed by KCCQ-TSS) in these patients (a prespecified secondary outcome).

METHODS

TRIAL DESIGN AND STUDY POPULATION. The design, baseline characteristics, and primary results of the FINEARTS-HF trial have been published.[17,18] Briefly, FINEARTS-HF was a prospective, randomized, double-blind, event-driven trial that examined the efficacy and safety of finerenone compared with placebo in patients with HFmrEF/HFpEF. The trial protocol was approved by the ethics committee for the 653 participating institutions in 37 countries, and all patients provided written informed consent. The trial is registered as NCT04435626 and EudraCT 2020-000306-29.

Key inclusion criteria were age ≥40 years, diagnosis of symptomatic HF in NYHA functional class II-IV, diuretic treatment for ≥30 days before randomization, LVEF ≥40% with evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy), and elevated natriuretic peptide levels (N-terminal pro-B-type natriuretic peptide [NT-proBNP] >300 pg/mL [B-type natriuretic peptide >100 pg/mL] for patients in sinus rhythm or NT-proBNP >900 pg/mL [B-type natriuretic peptide >300 pg/mL] for patients in atrial fibrillation), measured within 30 days before randomization in those without a recent worsening HF event or within 90 days in those with a recent worsening HF event. Both ambulatory and hospitalized patients were eligible for enrollment. Patients with improved ejection fraction, ie, prior LVEF <40% with subsequent improvement to ≥40%, were also

ABBREVIATIONS AND ACRONYMS

CSS = Clinical Summary Score
HFmrEF = heart failure with mildly reduced ejection fraction
HFpEF = heart failure with preserved ejection fraction
KCCQ = Kansas City Cardiomyopathy Questionnaire
OSS = Overall Summary Score
SAP = Statistical Analysis Plan
TSS = Total Symptom Score

From the [a]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [b]Cardiology Research Department, Royal Brisbane and Women's Hospital, University of Queensland, Brisbane, Queensland, Australia; [c]General Clinical Research Center and Division of Cardiology, Taipei Veterans General Hospital and National Yang Ming Chiao Tung University, Taipei, Taiwan; [d]Clinical Cardiology, Heart Failure and Research, Max Super Specialty Hospital, New Delhi, India; [e]Department of Cardiology, Bellvitge University Hospital and Bellvitge Biomedical Research Institute, CIBER-CV, University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain; [f]Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City, Kansas City, Missouri, USA; [g]Cardiovascular Division, Instituto de Pesquisa Clínica de Campinas, Campinas, Brazil; [h]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [i]Bayer, Research and Development, Pharmaceuticals, Whippany, New Jersey, USA; [j]Cardiology and Nephrology Clinical Development, Bayer SA, São Paulo, Brazil; [k]National Heart Centre Singapore and Duke-National University of Singapore, Singapore; [l]University of Milano-Bicocca, Papa Giovanni XXIII Hospital, Bergamo, Italy; [m]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [n]Bayer AG, Global Medical Affairs, Berlin, Germany; [o]University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; [p]Université de Lorraine, Inserm Clinical Investigation Centre, CHU, Nancy, France; and the [q]University of Michigan, School of Medicine, Ann Arbor, Michigan, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics According to Baseline KCCQ-TSS Category Divided by Tertile

	Tertile 1: 0 to <57 (n = 1,949; 32.6%)	Tertile 2: 57 to <81 (n = 1,984; 33.1%)	Tertile 3: 81 to 100 (n = 2,053; 34.3%)	*P* Value for Trend
Demographic characteristics				
Age, y	72.9 ± 9.3	72.6 ± 9.4	70.6 ± 10.0	<0.001
Sex				<0.001
Female	1,094 (56.1)	918 (46.3)	712 (34.7)	
Male	855 (43.9)	1,066 (53.7)	1,341 (65.3)	
Race				<0.001
White	1767 (90.7)	1646 (83.0)	1310 (63.8)	
Black or African American	29 (1.5)	26 (1.3)	32 (1.6)	
Asian	104 (5.3)	260 (13.1)	630 (30.7)	
Other	49 (2.5)	52 (2.6)	81 (3.9)	
Region				<0.001
North America	158 (8.1)	160 (8.1)	151 (7.4)	
Latin America	207 (10.6)	204 (10.3)	226 (11.0)	
Western Europe, Oceania, other	464 (23.8)	418 (21.1)	368 (17.9)	
Eastern Europe	1,020 (52.3)	947 (47.7)	682 (33.2)	
Asia	100 (5.1)	255 (12.9)	626 (30.5)	
Physiological measurements				
SBP, mm Hg	129.3 ± 15.1	129.5 ± 14.7	129.3 ± 16.1	0.87
DBP, mm Hg	75.2 ± 10.3	75.5 ± 10.3	75.7 ± 10.4	0.12
Baseline pulse, beats/min	72.5 ± 11.7	71.4 ± 11.8	70.4 ± 11.8	<0.001
BMI, kg/m^2	31.8 ± 6.4	29.9 ± 5.9	28.2 ± 5.5	<0.001
BMI category, kg/m^2				<0.001
<18.5	7 (0.4)	21 (1.1)	37 (1.8)	
18.5-<25	258 (13.3)	412 (20.8)	568 (27.7)	
25-<30	581 (29.9)	648 (32.7)	754 (36.8)	
30-<35	523 (26.9)	543 (27.4)	477 (23.3)	
≥35	575 (29.6)	355 (17.9)	214 (10.4)	
Medical history				
Hypertension	1,801 (92.4)	1,759 (88.7)	1,751 (85.3)	<0.001
Atrial fibrillation	1,121 (57.5)	1,092 (55.0)	1,053 (51.3)	<0.001
Myocardial infarction	463 (23.8)	505 (25.5)	570 (27.8)	0.004
Stroke	222 (11.4)	238 (12.0)	247 (12.0)	0.53
Type 2 diabetes mellitus	861 (44.3)	786 (39.8)	784 (38.2)	<0.001
Chronic obstructive pulmonary disease	320 (16.4)	264 (13.3)	188 (9.2)	<0.001
Sleep apnea	168 (8.6)	126 (6.4)	106 (5.2)	<0.001
Smoking status				<0.001
Never	1,270 (65.2)	1,242 (62.6)	1,178 (57.4)	
Former	523 (26.8)	594 (29.9)	670 (32.6)	
Current	156 (8.0)	148 (7.5)	205 (10.0)	

Continued on the next page

eligible for enrollment provided that ongoing HF symptoms were present. Key exclusion criteria were estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m^2 or serum/plasma potassium >5.0 mmol/L at screening or randomization; continuous (≥90 days) treatment with an MRA within 12 months, or treatment with an MRA within 30 days, before screening; systolic blood pressure ≥160 mm Hg if not on treatment with ≥3 blood pressure-lowering medications; systolic blood pressure ≥180 mm Hg irrespective of background antihypertensive therapy; or symptomatic hypotension with mean systolic blood pressure <90 mm Hg at screening or randomization. A complete list of exclusion criteria is provided in the design paper.[17] The use of drugs and devices at baseline was captured by the electronic case report form.

Eligible participants were randomized in a 1:1 ratio to finerenone or matching placebo. Participants with an eGFR ≤60 ml/min/1.73 m^2 started 10 mg once daily with a maximum maintenance dose of 20 mg once daily, whereas participants with an eGFR >60 mL/min/1.73 m^2 started 20 mg once daily with a maximum maintenance dose of 40 mg once daily.

TRIAL OUTCOMES. The primary trial outcome was the composite of CV death and total (first and recurrent) worsening HF events (ie, HF hospitalizations or urgent HF visits). Prespecified secondary outcomes

TABLE 1 Continued

	Tertile 1: 0 to <57 (n = 1,949; 32.6%)	Tertile 2: 57 to <81 (n = 1,984; 33.1%)	Tertile 3: 81 to 100 (n = 2,053; 34.3%)	*P* Value for Trend
HF characteristics and investigations				
Any prior hospitalization for HF	1,291 (66.2)	1,165 (58.7)	1,151 (56.1)	<0.001
Time since index HF event				<0.001
Randomized during/at HF event	428 (22.0)	211 (10.6)	110 (5.4)	
≤7 d	247 (12.7)	165 (8.3)	56 (2.7)	
>7 d to ≤3 mo	557 (28.6)	672 (33.9)	790 (38.5)	
>3 mo	263 (13.5)	307 (15.5)	365 (17.8)	
No index HF event	454 (23.3)	629 (31.7)	732 (35.7)	
KCCQ total symptom score	38.5 ± 13.8	69.2 ± 6.8	92.0 ± 6.4	<0.001
KCCQ clinical summary score	40.9 ± 14.5	66.5 ± 11.2	87.4 ± 9.7	<0.001
KCCQ overall summary score	39.7 ± 15.0	63.8 ± 12.7	83.8 ± 11.0	<0.001
EQ-5D VAS	58.0 ± 17.2	66.8 ± 15.2	77.3 ± 14.3	<0.001
NYHA functional class				<0.001
II	910 (46.7)	1,424 (71.8)	1,801 (87.7)	
III	1,007 (51.7)	554 (27.9)	248 (12.1)	
IV	32 (1.6)	6 (0.3)	3 (0.1)	
LVEF, %	52.9 ± 7.7	52.7 ± 7.7	52.1 ± 8.0	<0.001
Pooled LVEF groups				<0.001
<50%	640 (32.9)	693 (35.0)	833 (40.6)	
50%-<60%	908 (46.6)	898 (45.3)	860 (42.0)	
≥60%	399 (20.5)	390 (19.7)	357 (17.4)	
History of LVEF<40%	50 (2.6)	78 (3.9)	145 (7.1)	<0.001
ECG AF	806 (41.5)	767 (38.8)	714 (34.8)	<0.001
NT-proBNP, pg/mL	1,169 (497-2,312)	1,027 (442-1,946)	958 (414-1,714)	<0.001
ECG AF	1,812 (1,178-3,030)	1,786 (1,163-2,807)	1,573 (1,124-2,461)	0.002
No ECG AF	656 (335-1,566)	579 (307-1,228)	548 (300-1,141)	<0.001
HbA_{1c}, %	6.5 ± 1.3	6.4 ± 1.2	6.4 ± 1.1	<0.001
Potassium	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	0.42
UACR, mg/g	206.5 ± 698.0	143.2 ± 578.6	136.1 ± 549.2	<0.001
UACR category, mg/g				<0.001
<30	1,069 (56.6)	1,171 (61.0)	1,265 (63.9)	
30-<300	580 (30.7)	566 (29.5)	562 (28.4)	
≥300	239 (12.7)	182 (9.5)	152 (7.7)	
Creatinine, μmol/L	101.0 ± 31.7	99.5 ± 30.5	98.8 ± 34.9	0.02
eGFR, mL/min/1.73 m^2	59.8 ± 19.7	61.9 ± 19.3	64.4 ± 20.0	<0.001
eGFR <60 mL/min/1.73 m^2	1,039 (53.3)	947 (47.7)	895 (43.6)	<0.001
Medical treatment				
Diuretic agents	1,923 (98.7)	1,961 (98.8)	2,032 (99.0)	0.36
Loop diuretic	1,775 (91.1)	1,730 (87.2)	1,720 (83.8)	<0.001
Digitalis	179 (9.2)	148 (7.5)	143 (7.0)	0.009
Beta-blocker	1,661 (85.2)	1,685 (84.9)	1,739 (84.7)	0.65
ACEI	714 (36.6)	701 (35.3)	735 (35.8)	0.59
ARB	712 (36.5)	713 (35.9)	673 (32.8)	0.01
ARNI	99 (5.1)	150 (7.6)	261 (12.7)	<0.001
CCB	692 (35.5)	690 (34.8)	584 (28.4)	<0.001
SGLT2 inhibitor	257 (13.2)	255 (12.9)	305 (14.9)	0.12
Pacemaker	118 (6.1)	128 (6.5)	84 (4.1)	0.006
CRT-P or CRT-D	16 (0.8)	8 (0.4)	9 (0.4)	0.11
ICD (including CRT-D)	15 (0.8)	10 (0.5)	23 (1.1)	0.20

Values are mean ± SD, n (%), or median (Q1-Q3).

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BMI = body mass index; CCB = calcium-channel blocker; CRT-D cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy-pacemaker; DBP = diastolic blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol 5-dimensional questionnaire; HbA_{1c} = glycated hemoglobin; HF = heart failure; ICD = implantable cardioverter-defibrillator; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-Total Symptom Score; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter 2; UACR = urine albumin-to-creatinine ratio; VAS = visual analogue scale.

included the total number of worsening HF events; change in the KCCQ-TSS from baseline to 6, 9, and 12 months; improvement in NYHA functional class from baseline to 12 months; a composite kidney endpoint (defined as sustained decline in eGFR ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline <15 mL/min/1.73 m^2, or initiation of dialysis or renal transplantation); and all-cause death. All deaths and potential primary outcome nonfatal events were adjudicated by an independent blinded committee. The composite kidney outcome was not explored further in the present analysis because there were few events overall, making subgroup analysis unreliable.

In this study, further analyses focusing on various KCCQ domains at 6, 9, and 12 months were prespecified in the Academic Statistical Analysis Plan (SAP), which was finalized before the database lock and unblinding. Additionally, the Regulatory and Academic SAPs prespecified responder analyses, which examined clinically significant deterioration (≥5 points) as well as small (≥5 points), moderate (≥10 points), or large (≥20 points) improvements over time.

Safety analyses were performed in patients who had undergone randomization and received at least 1 dose of either finerenone or placebo (a total of 15 randomized patients were excluded from these analyses).

TRIAL PROCEDURES AND KCCQ. Following a screening period of up to 2 weeks, eligible participants were randomized in a 1:1 ratio to receive either finerenone or a matching placebo. After randomization, patients attended 2 scheduled visits within the first 3 months and then had follow-up visits every 3 months for the first year. After 1 year, subsequent follow-up alternated between telephone and on-site visits every 4 months until the end of the trial. KCCQ was completed by patients, without assistance from site study staff (as validated), and evaluated at randomization and at 6, 9, and 12 months.

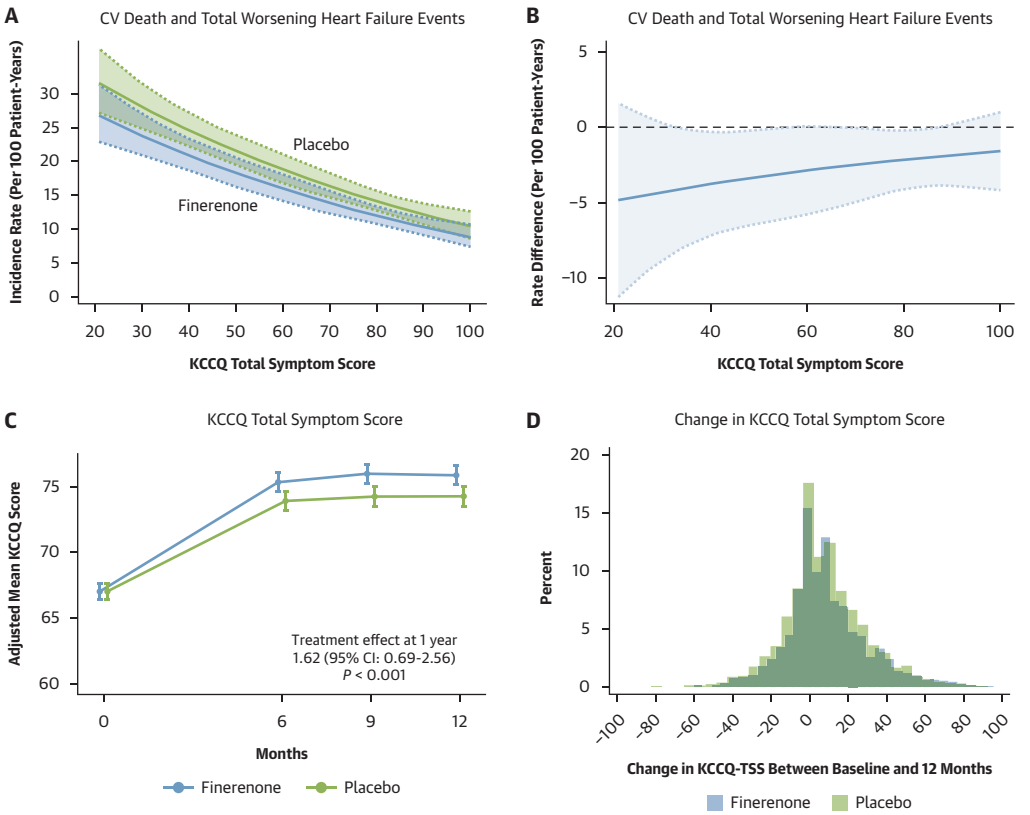
The KCCQ is a 23-item, self-administered HF-specific instrument that quantifies symptoms (frequency, severity, and recent change), physical function, quality of life, and social function over the preceding 2 weeks.[19,20] The TSS quantifies the symptom frequency and severity, while the Physical Limitation score assesses the physical function. Together, these 2 can be combined to create the Clinical Summary Score (CSS). The Overall Summary Score summarizes all key domains including TSS, physical function, social function, and quality of life. The validity, reproducibility, responsiveness, and interpretability of these scores have been independently established. Each score is scaled with a range of 0 to 100, with higher scores indicating better health status.[19,20]

STATISTICAL ANALYSIS. Patients were categorized into 3 subgroups based on tertiles of baseline KCCQ-TSS (the prespecified secondary endpoint): 1) <57 points: (0-<57); 2) 57 to <81 points: (57-<81); and 3) ≥81 points: (81-100). Baseline characteristics for each category are presented as mean ± SD, median (Q1-Q3), and frequencies with proportions, as appropriate. The Jonckheere-Terpstra test was used to test for trends across groups for continuous variables, and the Cochran-Armitage test was used to assess the binary variables.

Incidence rates for each outcome of interest are presented per 100 person-years of follow-up. The event rates of clinical outcomes as a function of KCCQ-TSS as a continuous variable were estimated using Poisson using restricted cubic splines with 3 knots, placed at the 10th, 50th, and 90th percentiles of the data. The cumulative incidence of events was estimated using the Nelson-Aalen method and Kaplan-Meier method for total (first and recurrent) events and time-to-first-event outcomes and presented graphically. The association between KCCQ-TSS tertiles and clinical outcomes was evaluated using semiparametric proportional-rates models for total (first and recurrent) events and Cox proportional-hazards models for time-to-first-event data, stratified according to geographic region and baseline LVEF (<60%, ≥60%).[21] Further adjustment was performed for age, sex, heart rate, systolic blood pressure, body mass index, prior hospitalization for HF, NYHA functional class III/IV, LVEF, eGFR, NT-proBNP (log-transformed), atrial fibrillation, myocardial infarction, and type 2 diabetes mellitus.

The effect of finerenone compared with placebo was calculated as a rate ratio (RR) and 95% CI derived from semiparametric proportional-rates models for total (first and recurrent) events or as an HR and 95% CI from Cox proportional hazards models for time-to-first events.[21] All models were stratified by geographic region and baseline LVEF (<60%, ≥60%) as prespecified in the statistical analysis plan for the main trial. The effect of finerenone on clinical outcomes according to KCCQ-TSS (analyzed as a continuous variable) was examined using restricted cubic splines with 3 knots, placed at the 10th, 50th, and 90th percentiles of the data. The proportion of patients with improvement in NYHA functional class from baseline to 12 months was analyzed using a logistic regression model, adjusted for geographic

CENTRAL ILLUSTRATION **Finerenone and Health Status in Patients With Heart Failure With Mildly Reduced/Preserved Ejection Fraction**



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(A) Lower (worse) baseline KCCQ-TSS was associated with higher risk of subsequent clinical outcomes. Placebo: green (upper line); finerenone: blue (lower line). (B) The benefit of finerenone on clinical outcomes was maintained across baseline KCCQ-TSS. (C) Treatment with finerenone improved KCCQ-TSS between baseline and 12 months compared with placebo. (D) Distribution of change in KCCQ-TSS between baseline and 12 months by treatment assignment. CV = cardiovascular; KCCQ = Kansas City Cardiomyopathy Questionnaire; TSS = Total Symptom Score.

region and baseline LVEF. The changes in KCCQ-TSS (and other domain scores) from baseline to 6, 9, and 12 months were analyzed using mixed-effect models for repeated measurements, adjusted for baseline value, visit, treatment-group assignment, baseline value-by-visit interaction, treatment-by-visit interaction, geographic region, and baseline LVEF. Responder analyses were performed to compare the proportions of patients experiencing a deterioration (defined as a worsening of ≥5 points) and those showing clinically significant improvements defined as small change (≥5 points); moderate change (≥10 points); or a large change, (≥20 points) in KCCQ total scores at 1 year. The definition of the groups accounted for a maximal score of 100 that can be achieved in the KCCQ score. In patients with a baseline score of >95 (who cannot gain 5 points because of the ceiling score of 100), a score of >95 at month 12 without decline from baseline was counted as a responder. Similarly, for a ≥10-point increase, maintaining a score of >90 from baseline to month 12 without a decrease from baseline was counted as a responder, and for a ≥20-point increase maintaining a score of >80 without a decrease from baseline was counted as a responder. These comparisons were assessed using logistic regression models, with the outcome variable consisting of a binary variable of responder vs nonresponder or deterioration vs no deterioration, adjusted for baseline KCCQ score, stratification factors region, and LVEF (<60%, ≥60%).

TABLE 2 Effect of Randomized Treatment on Outcomes According to Baseline KCCQ-TSS Category Divided by Tertile

	Tertile 1: 0 to <57		Tertile 2: 57 to <81		Tertile 3: 81 to 100		
	Finerenone (n = 954)	Placebo (n = 995)	Finerenone (n = 962)	Placebo (n = 1,022)	Finerenone (n = 1,079)	Placebo (n = 974)	Interaction *P* Value
CV death and total worsening HF events							
Events	459 (250, 26.2)	572 (318, 32.0)	351 (200, 20.8)	435 (241, 23.6)	266 (171, 15.8)	274 (158, 16.2)	
Rate per 100 patient-y (95% CI)	20.6 (17.6-24.0)	24.9 (21.9-28.2)	15.0 (12.7-17.8)	17.5 (15.0-20.5)	9.9 (8.3-11.7)	11.2 (9.3-13.5)	
RR (95% CI)[a]	0.82 (0.68-1.00)		0.88 (0.70-1.11)		0.88 (0.69-1.14)		0.89
Adjusted RR (95% CI)[b]	0.81 (0.67-0.98)		0.85 (0.68-1.07)		0.86 (0.67-1.10)		0.97
Total worsening HF events							
Events	356 (194, 20.3)	449 (252, 25.3)	283 (156, 16.2)	356 (196, 19.2)	197 (126, 11.7)	217 (123, 12.6)	
Rate per 100 patient-y (95% CI)	16.0 (13.4-19.1)	19.5 (16.9-22.6)	12.1 (10.0-14.6)	14.4 (12.1-17.1)	7.3 (6.0-8.9)	8.8 (7.1-11.0)	
RR (95% CI)[a]	0.82 (0.66-1.02)		0.87 (0.67-1.12)		0.82 (0.62-1.10)		0.96
Adjusted RR (95% CI)[b]	0.80 (0.65-0.99)		0.86 (0.67-1.10)		0.78 (0.59-1.04)		0.91
Total HF hospitalizations							
Events	319 (189, 19.8)	393 (229, 23.0)	249 (146, 15.2)	296 (176, 17.2)	170 (112, 10.4)	186 (107, 11.0)	
Rate per 100 patient-y (95% CI)	14.3 (12.1-16.9)	17.1 (14.7-19.9)	10.6 (8.8-12.9)	11.9 (9.9-14.3)	6.3 (5.1-7.8)	7.6 (6.0-9.6)	
RR (95% CI)[a]	0.84 (0.67-1.04)		0.91 (0.70-1.19)		0.83 (0.61-1.13)		0.90
Adjusted RR (95% CI)[b]	0.83 (0.67-1.03)		0.89 (0.69-1.15)		0.81 (0.59-1.09)		0.88
Total urgent HF visits							
Events	37 (26, 2.7)	56 (44, 4.4)	34 (24, 2.5)	60 (43, 4.2)	27 (23, 2.1)	31 (26, 2.7)	
Rate per 100 patient-y (95% CI)	1.7 (1.0-2.6)	2.4 (1.8-3.3)	1.5 (0.9-2.3)	2.4 (1.7, 3.4)	1.0 (0.7, 1.5)	1.3 (0.8, 1.9)	
RR (95% CI)[a]	0.67 (0.39-1.15)		0.64 (0.37-1.12)		0.80 (0.44-1.44)		0.86
Adjusted RR (95% CI)[b]	0.58 (0.34-1.00)		0.65 (0.38-1.11)		0.69 (0.39-1.25)		0.87
CV death or worsening HF							
Events, N (n, %)	250 (250, 26.2)	318 (318, 32.0)	200 (200, 20.8)	241 (241, 23.6)	171 (171, 15.8)	158 (158, 16.2)	
Rate per 100 patient-y (95% CI)	12.6 (11.1-14.3)	16.2 (14.4-18.1)	9.3 (8.1-10.7)	10.7 (9.4, 12.2)	6.7 (5.8, 7.8)	6.9 (5.9, 8.0)	
RR (95% CI)[a]	0.78 (0.66-0.92)		0.88 (0.73-1.07)		0.98 (0.79-1.22)		0.27
Adjusted RR (95% CI)[b]	0.76 (0.64-0.90)		0.85 (0.70-1.03)		0.93 (0.75-1.17)		0.45
Worsening HF							
Events, N (n, %)	194 (194, 20.3)	252 (252, 25.3)	156 (156, 16.2)	196 (196, 19.2)	126 (126, 11.7)	123 (123, 12.6)	
Rate per 100 patient-y (95% CI)	9.8 (8.4-11.3)	12.8 (11.3-14.6)	7.2 (6.2-8.5)	8.7 (7.6, 10.1)	5.0 (4.2, 5.9)	5.3 (4.5, 6.4)	
RR (95% CI)[a]	0.77 (0.64-0.93)		0.85 (0.68-1.05)		0.92 (0.72-1.18)		0.50
Adjusted RR (95% CI)[b]	0.75 (0.62-0.90)		0.84 (0.68-1.05)		0.86 (0.67-1.11)		0.67
CV death							
Events, N (n, %)	103 (103, 10.8)	123 (123, 12.4)	68 (68, 7.1)	79 (79, 7.7)	70 (70, 6.5)	58 (58, 6.0)	
Rate per 100 patient-y (95% CI)	4.6 (3.8-5.6)	5.3 (4.5-6.4)	2.9 (2.3-3.7)	3.2 (2.6, 4.0)	2.6 (2.1, 3.3)	2.4 (1.8, 3.1)	
RR (95% CI)[a]	0.85 (0.65-1.10)		0.96 (0.69-1.33)		1.12 (0.79-1.58)		0.51
Adjusted RR (95% CI)[b]	0.84 (0.64-1.09)		0.85 (0.61-1.20)		1.11 (0.78-1.59)		0.56
CV death or first HF hospitalization							
Events, N (n, %)	245 (245, 25.7)	296 (296, 29.7)	191 (191, 19.9)	224 (224, 21.9)	160 (160, 14.8)	142 (142, 14.6)	
Rate per 100 patient-y (95% CI)	12.2 (10.8-13.9)	14.7 (13.1-16.6)	8.8 (7.6-10.1)	9.8 (8.6, 11.2)	6.2 (5.3, 7.3)	6.1 (5.2, 7.2)	
RR (95% CI)[a]	0.83 (0.70-0.98)		0.92 (0.75-1.12)		1.03 (0.82-1.29)		0.35
Adjusted RR (95% CI)[b]	0.82 (0.69-0.97)		0.88 (0.72-1.07)		0.99 (0.78-1.24)		0.58
First HF hospitalization							
Events, N (n, %)	189 (189, 19.8)	229 (229, 23.0)	146 (146, 15.2)	176 (176, 17.2)	112 (112, 10.4)	107 (107, 11.0)	
Rate per 100 patient-y (95% CI)	9.4 (8.2-10.9)	11.4 (10.0-13.0)	6.7 (5.7-7.9)	7.7 (6.6, 9.0)	4.4 (3.6, 5.3)	4.6 (3.8, 5.6)	
RR (95% CI)[a]	0.83 (0.69-1.01)		0.89 (0.71-1.11)		0.94 (0.72-1.23)		0.73
Adjusted RR (95% CI)[b]	0.82 (0.67-1.00)		0.88 (0.70-1.11)		0.89 (0.67-1.17)		0.89
All-cause death							
Events, N (n, %)	210 (210, 22)	234 (234, 23.5)	152 (152, 15.8)	172 (172, 16.8)	127 (127, 11.8)	114 (114, 11.7)	
Rate per 100 patient-y (95% CI)	9.4 (8.2-10.7)	10.1 (8.9-11.5)	6.5 (5.5-7.6)	6.9 (5.9, 8.0)	4.7 (4.0, 5.6)	4.6 (3.9, 5.6)	
RR (95% CI)[a]	0.91 (0.76-1.10)		0.96 (0.77-1.20)		1.02 (0.79-1.32)		0.81
Adjusted RR (95% CI)[b]	0.90 (0.74-1.09)		0.93 (0.74-1.16)		1.00 (0.78-1.30)		0.89

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TABLE 2 Continued

	Tertile 1: 0 to <57		Tertile 2: 57 to <81		Tertile 3: 81 to 100		
	Finerenone (n = 954)	Placebo (n = 995)	Finerenone (n = 962)	Placebo (n = 1,022)	Finerenone (n = 1,079)	Placebo (n = 974)	Interaction *P* Value
Improvement in NYHA functional class[c]							
Events	213 (22.3)	227 (22.8)	160 (16.6)	167 (16.3)	183 (17.0)	159 (16.3)	
OR (95% CI)[a]	0.97 (0.78-1.21)		1.02 (0.80-1.29)		1.05 (0.83-1.33)		0.90
Adjusted OR (95% CI)[b]	0.93 (0.73-1.19)		1.01 (0.77-1.32)		1.09 (0.84-1.40)		0.72

Values are N (n, %) or n (%), unless otherwise indicated. [a]Stratified by/adjusted for geographic region and baseline LVEF (<60%, ≥60%). [b]Adjusted for age, sex, heart rate, systolic blood pressure, body mass index, prior hospitalization for HF, NYHA functional class III/IV, left ventricular ejection fraction, estimated glomerular filtration rate, NT-proBNP (log-transformed), atrial fibrillation, myocardial infarction, and diabetes mellitus. [c]Improvement in NYHA functional class from baseline to month 12.

Abbreviations as in Table 1.

All observed values were included irrespective of any permanent treatment discontinuation. In case of missing data, a patient's last available postbaseline score before the time point under study (6, 9, or 12 months) was used. Patients who died before a specific time point measurement were imputed as a nonresponder at that time point and at any subsequent time point. In a further sensitivity analysis of the responder analyses, we constructed groups of deterioration/improvement that were bound by intervals of change so that the following categories were constructed: worsening (≤−5-point decrease), no change (>−5 to <5-point change), small improvement (≥5 to <10-point increase), moderate improvement (≥10 to <15-point increase), large improvement (≥15 to <20-point increase), and very large improvement (≥20-point increase). Ceiling scores were not accounted for in these analyses.

The effects of finerenone vs placebo on KCCQ-TSS at 1 year were assessed across relevant subgroups using a linear regression model fitting the 1-year TSS value as the outcome, baseline TSS value, geographic region, and baseline LVEF (<60%, ≥60%) as covariates, as well as the treatment indicator. Interaction *P* values were reported from a likelihood-ratio test of the treatment-subgroup interaction terms.

Safety outcomes are reported as counts and percentages according to randomized treatment, and the treatment effect was analyzed with logistic regression with randomized treatment as the dependent variable and stratification factors (region and baseline LVEF [<60%, ≥60%]) as independent variables.

All analyses were performed using Stata version 18 (Stata Corp). A *P* value <0.05 was considered statistically significant.

RESULTS

Among the 6,001 participants analyzed, 5,986 (99.8%) patients completed the KCCQ-TSS at baseline. The number of patients who had other KCCQ scores and domain scores available at baseline and during follow-up can be found in Supplemental Table 1. The distribution of KCCQ-TSS is presented in Supplemental Figure 1. The median and mean values for baseline KCCQ-TSS were 69.8 (Q1-Q3: 50.0-87.5) and 67.0 ± 23.9, respectively.

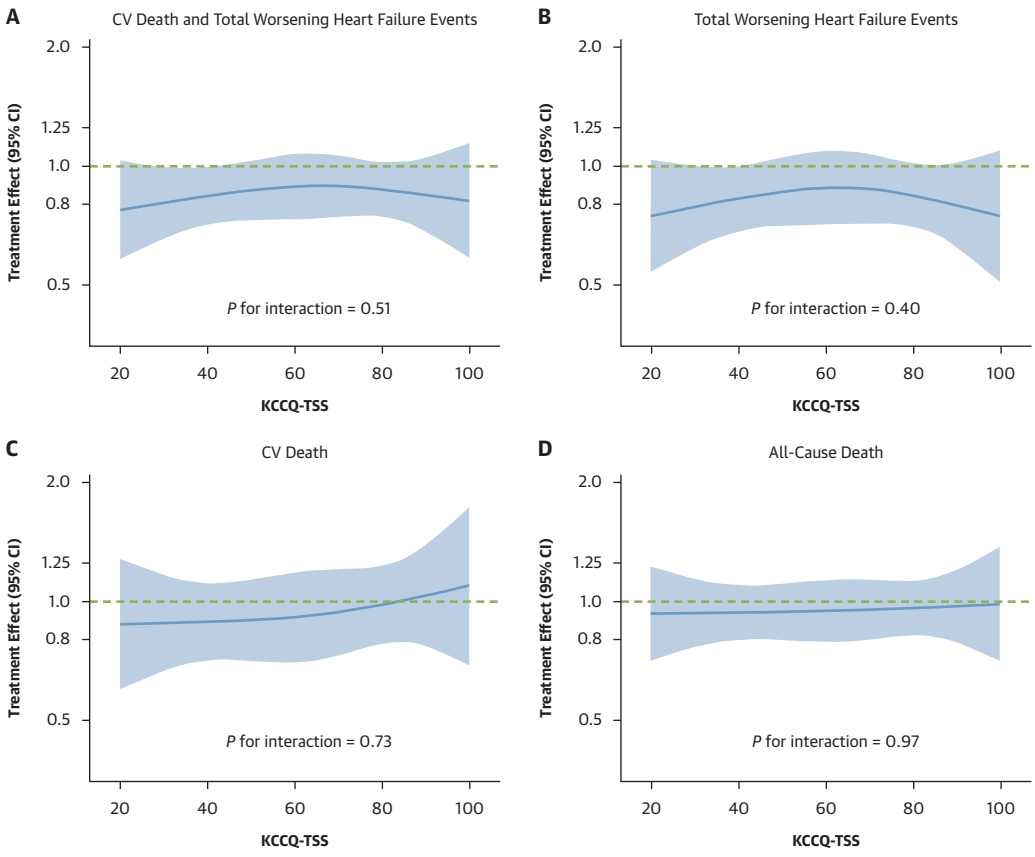
BASELINE CHARACTERISTICS OF PATIENTS ACCORDING TO TERTILE OF KCCQ-TSS. The baseline characteristics of patients according to KCCQ-TSS divided by tertile are presented in Table 1.

Demographics, physiologic measures, and medical history. Compared with participants who had higher (better) KCCQ-TSS scores at baseline, those with lower (worse) scores were more often women and White. Participants with lower baseline KCCQ-TSS also had a higher prevalence of several comorbidities, including hypertension, atrial fibrillation, and type 2 diabetes. They also had higher body mass index (BMI) and lower estimated glomerular filtration rate (eGFR) compared with those who had higher scores (Table 1).

HF history, characteristics, and treatment. Compared with participants with higher KCCQ-TSS scores at baseline, those with lower scores were more likely to be hospitalized for HF in the recent past, and were much more likely to be in NYHA functional class III/IV than in class II and to have higher NT-proBNP and urine albumin-to-creatinine ratio.

CLINICAL OUTCOMES ASSOCIATED WITH BASELINE KCCQ-TSS. Patients reporting lower KCCQ-TSS generally had worse clinical outcomes, eg, the rates of the primary outcome of CV death and total (first and recurrent) worsening HF events were 22.8 (95% CI: 20.6-25.1), 16.3 (95% CI: 14.5-18.3), and 10.5 (95% CI: 9.2-11.9) per 100 patient-years in patients across KCCQ-TSS tertiles from T1 (score 0-<57), T2 (57-<81), to T3 (81-100), respectively (Supplemental Table 2, Supplemental Figure 2). Similar results were observed with other clinical outcomes, including total worsening HF events, total

FIGURE 1 Effect of Finerenone on Clinical Outcomes Across the Range of KCCQ-TSS at Baseline



(A) Cardiovascular (CV) death and total worsening heart failure events; (B) total worsening heart failure events; (C) CV death; (D) all-cause death. The models were stratified by geographic region and baseline left ventricular ejection fraction (<60%, ≥60%). Horizontal solid blue line = continuous rate ratio (or HR); shaded blue area = 95% CI; horizontal dashed green line = rate ratio/HR of 1.00, ie, unity. An RR or HR <1.00 = superiority of finerenone over placebo. KCCQ = Kansas City Cardiomyopathy Questionnaire; TSS = Total Symptom Score.

HF hospitalizations, total urgent HF visits, CV death or worsening HF, worsening HF, CV death, CV death or first HF hospitalization, first HF hospitalization, all-cause death, and renal composite (Supplemental Table 2). Covariate-adjusted models also showed broadly consistent results (Supplemental Table 2).

When examined as a continuous variable, there was a linear relationship between KCCQ-TSS and the risk of the primary outcome (Supplemental Figure 3, **Central Illustration**).

EFFICACY OF FINERENONE ACCORDING TO BASELINE TERTILES OF KCCQ-TSS. The effects of finerenone on the key clinical outcomes analyzed across KCCQ-TSS tertiles are summarized in **Table 2**. Compared with placebo, finerenone reduced the primary outcome consistently across baseline KCCQ-TSS categories: RR: 0.82 (95% CI: 0.68-1.00), 0.88 (95% CI: 0.70-1.11), 0.88 (95% CI: 0.69-1.14) for tertile 1 (lowest KCCQ-TSS: 0 to 57), tertiles 2 and 3, respectively (*P* for interaction 0.89). Similar results were observed for total worsening HF events, CV death or worsening HF, time-to-first worsening HF, CV death or first HF hospitalization, and time-to-first HF hospitalization. However, compared with placebo, treatment with finerenone did not reduce mortality (caused by CV or all-causes), and did not improve NYHA functional class across the tertiles of KCCQ.

Analyses of the effect of finerenone according to KCCQ-TSS examined as a continuous variable are shown in **Figure 1**. The overall findings were similar with a consistent reduction in the primary outcome with finerenone across the range of KCCQ-TSS.

TABLE 3 Safety Outcomes According to Baseline KCCQ-TSS Category Divided by Tertile

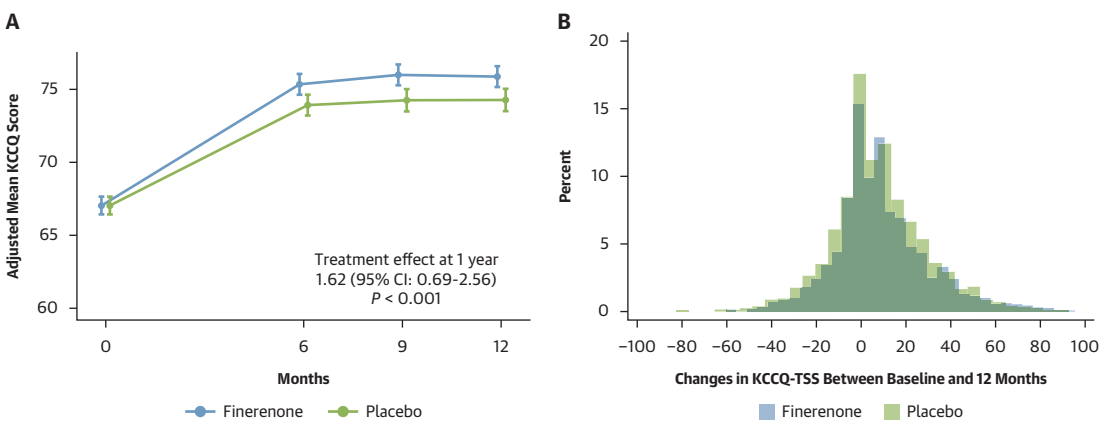
	Tertile 1: 0 to <57		Tertile 2: 57 to <81		Tertile 3: 81 to 100		
	Finerenone (n = 954)	Placebo (n = 995)	Finerenone (n = 962)	Placebo (n = 1,022)	Finerenone (n = 1,079)	Placebo (n = 974)	Interaction *P* Value
Systolic blood pressure <100 mm Hg	129 (14.1)	119 (12.4)	156 (16.7)	101 (10.2)	251 (23.8)	140 (14.8)	
OR (95% CI)[a]	1.17 (0.89-1.55)		1.94 (1.46-2.58)		2.00 (1.57-2.55)		0.01
Creatinine ≥3 mg/dL	24 (2.6)	18 (1.9)	16 (1.7)	11 (1.1)	17 (1.6)	5 (0.5)	
OR (95% CI)[a]	1.39 (0.75-2.60)		1.54 (0.71-3.35)		3.08 (1.13-8.40)		0.38
Creatinine ≥2.5 mg/dL	60 (6.6)	37 (3.9)	38 (4.1)	29 (3.0)	43 (4.1)	23 (2.4)	
OR (95% CI)[a]	1.76 (1.15-2.68)		1.45 (0.88-2.37)		1.72 (1.03-2.87)		0.81
Potassium >6 mmol/L	22 (2.4)	17 (1.8)	36 (3.9)	15 (1.5)	27 (2.6)	9 (1.0)	
OR (95% CI)[a]	1.38 (0.72-2.62)		2.54 (1.38-4.69)		2.69 (1.25-5.75)		0.30
Potassium >5.5 mmol/L	130 (14.3)	68 (7.1)	133 (14.3)	81 (8.3)	149 (14.2)	49 (5.2)	
OR (95% CI)[a]	2.21 (1.62-3.02)		1.86 (1.38-2.51)		3.00 (2.14-4.21)		0.10
Potassium <3.5 mmol/L	56 (6.1)	103 (10.8)	28 (3.0)	73 (7.4)	43 (4.1)	104 (11.0)	
OR (95% CI)[a]	0.54 (0.38-0.75)		0.39 (0.25-0.60)		0.35 (0.24-0.50)		0.21

Values are n (%) unless otherwise indicated. Safety analyses were carried out in patients who had undergone enrolment and received at least 1 dose of the randomized treatment (a total of 15 randomized patients were excluded from the safety analysis). Safety events were considered treatment-emergent if they occurred between the day of treatment initiation up to and including 3 days after treatment discontinuation. [a]Logistic regression model with randomized treatment as the dependent variable and stratification factors (region and baseline LVEF [<60%, ≥60%]) as independent variables.

Safety outcomes according to baseline KCCQ-TSS. Hyperkalemia and elevation of creatinine were more common, and hypokalemia was less common, in patients assigned to finerenone compared with placebo, but the between-treatment differences did not differ significantly across tertiles of KCCQ-TSS (**Table 3**, Supplemental Table 3). The risk of hypotension (defined as a systolic blood pressure <100 mm Hg) with finerenone compared with placebo, did appear to be modified by baseline KCCQ-TSS, with a greater risk in patients with a higher KCCQ-TSS.

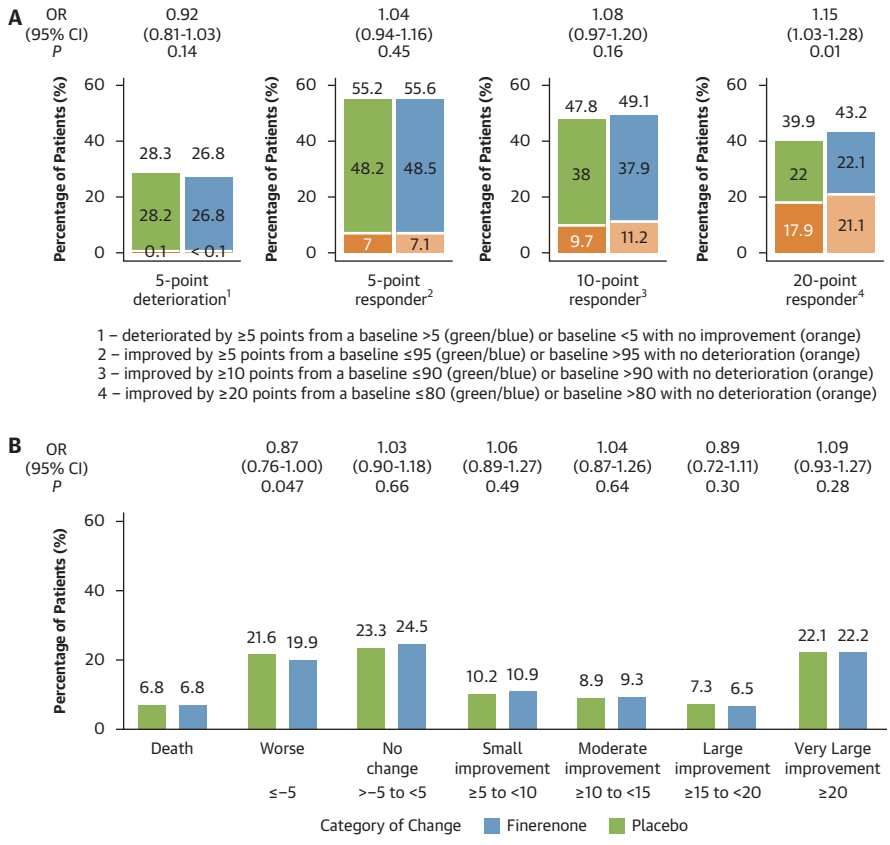
EFFECTS OF FINERENONE ON CHANGE IN KCCQ-TSS FROM BASELINE TO 12 MONTHS. Mean change in KCCQ-TSS from baseline to 12 months (pre-specified secondary endpoint). The mean change in KCCQ-TSS over time using the repeated measurement models is presented in **Figure 2A**, Supplemental Figures 4 and 5, and the **Central Illustration**. At month 12, patients treated with finerenone had a significant

FIGURE 2 Effect of Finerenone on KCCQ-TSS



(A) Mean change in KCCQ-TSS from baseline to 12 months by randomized treatment assignment. The estimated mean at baseline for the whole trial is shown at month 0 for both treatment groups. (B) Histogram of changes in KCCQ from baseline to 12 months in each treatment group. The model for repeated measurements was adjusted for baseline value, visit, treatment-group assignment, baseline value-by-visit interaction, treatment-by-visit interaction, geographic region, and baseline left ventricular ejection fraction. Abbreviations as in **Figure 1**.

FIGURE 3 **Responder Analysis of Change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score Between Baseline and 12 Months**



(A) Using prespecified analysis accounting for ceiling effects. Models were adjusted for baseline Kansas City Cardiomyopathy Questionnaire score, stratification factors region, and left ventricular ejection fraction (<60%, ≥60%). (B) Sensitivity analysis using mutually exclusive categories, as follows: worsening (≤−5-point decrease 1 year), no change (>−5 to <5-point change), small improvement (≥5 to <10-point increase), moderate improvement (≥10 to <15-point increase), large improvement (≥15 to <20-point increase) and very large improvement (≥20-point increase). Ceiling scores were not accounted for in these analyses.

improvement in mean KCCQ-TSS—the placebo-corrected increase was 1.62 points (95% CI: 0.69-2.56 points) ($P < 0.001$). Alternative analytical approaches using imputation gave very similar findings (Supplemental Table 4).

The between-treatment difference in improvement in KCCQ-TSS was statistically significant at all time points including when first evaluated at 6 months (Supplemental Figure 4).

The corresponding changes in other KCCQ scores and domain scores at 6 months, 9 months, and 1 year are shown in Supplemental Figure 4 (eg, increase of 1.07 [95% CI: 0.21-1.93] points in CSS and 0.92 [95% CI: 0.05-1.79] points in the OSS at 12 months).

Clinically meaningful responses in KCCQ scores ("responder analysis"). The distribution of changes in KCCQ-TSS from baseline to month 12, by treatment assignment, are shown in Figure 2B. The results of the prespecified responder analysis are illustrated in Figure 3A. There were numerically fewer patients with a clinically meaningful deterioration (≥5-point decline) in the finerenone group compared with the placebo group, but the difference between treatments was not significant. A slightly larger proportion of patients assigned to finerenone self-reported a small (≥5 points), moderate (≥10 points), or large (≥20 points) improvement in KCCQ-TSS compared with those assigned to placebo (only

the ≥20-point improvement was statistically significant). In the prespecified analysis accounting for ceiling effects, as described in the Methods section, an improvement of ≥20 points was self-reported in 43.2% of finerenone-treated patients and 39.9% of patients assigned to placebo (OR: 1.15; 95% CI: 1.03-1.28). However, a large proportion of these responders were participants with high baseline scores and no worsening in score, which was more common with finerenone than placebo (21.1% vs 17.9%). Therefore, in a sensitivity analysis using categories of change in KCCQ that were bound by ranges—ie, worsening (≤−5-point decrease), no change (>−5 to <5-point change), small improvement (≥5 to <10-point increase), moderate improvement (≥10 to <15-point increase), large improvement (≥15 to <20-point increase), and very large improvement (≥20-point increase)—there was no evidence of a benefit with finerenone (eg, 22.1% of placebo-treated patients vs 22.2% of finerenone-treated patients had a ≥20-point improvement, OR: 1.09; 95% CI: 0.93-1.27; $P = 0.28$) possibly because of the small size of the mutually exclusive groups (**Figure 3B**).

Effects of finerenone on KCCQ-TSS across selected subgroups. The effect of finerenone vs placebo on change in KCCQ-TSS from baseline to 1 year across relevant subgroups is shown in **Figure 4A**. The treatment effects of finerenone were generally consistent across most subgroups, including LVEF <50%, 50% to <60%, and ≥60% (P for interaction = 0.44). The one exception was the subgroup defined by the tertile of baseline KCCQ-TSS, where baseline KCCQ-TSS appeared to modify the improvement in KCCQ-TSS after treatment with finerenone (P for interaction = 0.002). Patients with the lowest baseline KCCQ-TSS seemed to have a greater improvement in KCCQ-TSS after treatment with finerenone compared with patients with a higher baseline KCCQ-TSS (**Figure 4B**).

DISCUSSION

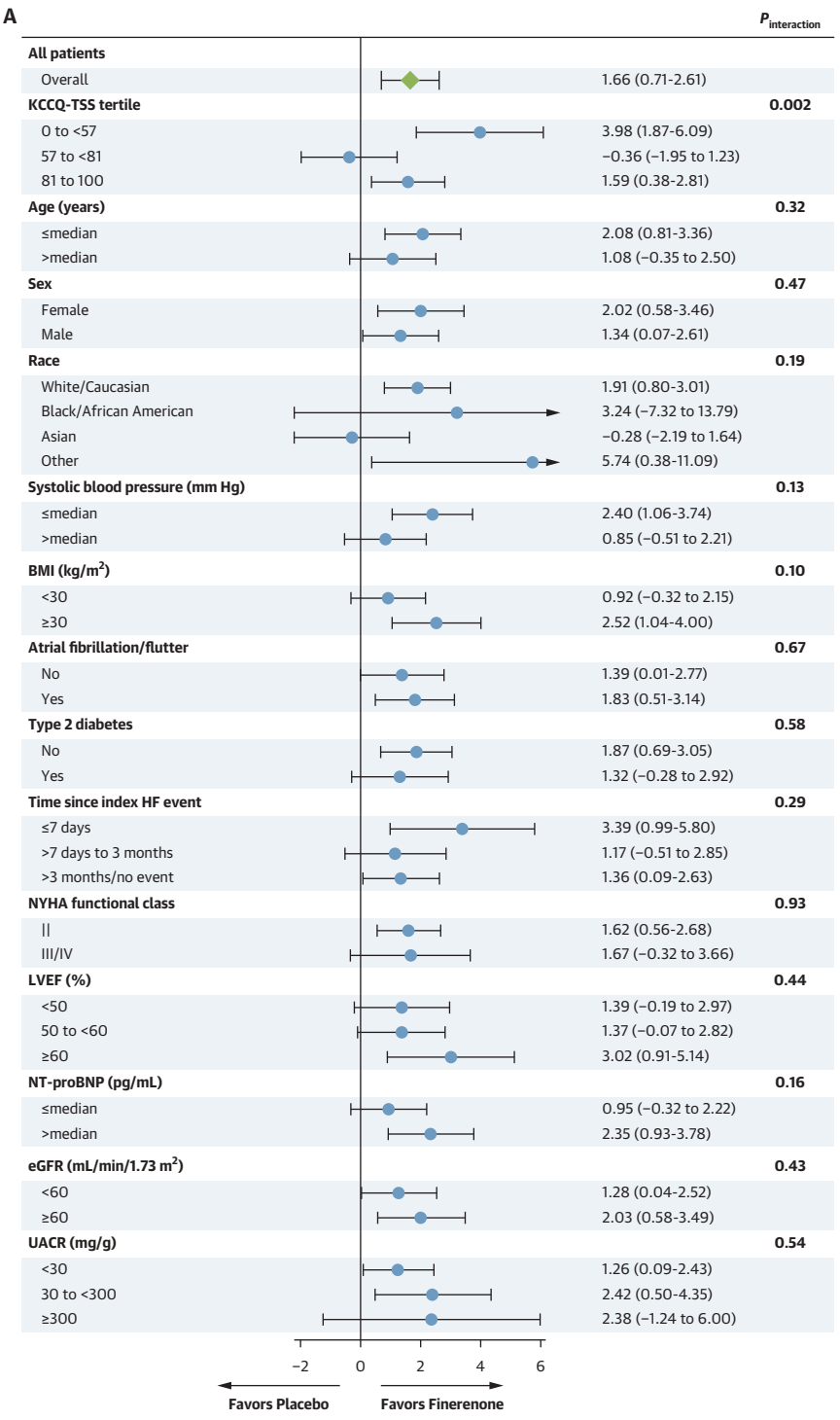
Before FINEARTS-HF, there were no data evaluating the effects of finerenone on health status in patients with HFmrEF/HFpEF. These prespecified analyses of FINEARTS-HF had 3 key findings: first, among patients with HFmrEF/HFpEF, low baseline KCCQ-TSS was associated with worse subsequent clinical outcomes; second, finerenone reduced the risk of the primary composite outcome (CV death and total worsening HF events) across the full range of KCCQ-TSS; and third, finerenone improved KCCQ-TSS by a small amount compared with placebo.

In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, the mean and median value of KCCQ-TSS in TOPCAT-Americas were 60.5 ± 25.0 and 62.5 (Q1-Q3: 41.7-81.3), respectively. In the FINEARTS-HF trial, the median KCCQ-TSS was 69.8 (Q1-Q3: 50.0-87.5) and the mean was 67.0 ± 23.9, compared with a median KCCQ-TSS of 72.9 (Q1-Q3: 55.2-87.5) in DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure) and a mean KCCQ-TSS of 76.7 ± 18.8 in PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HFpEF).[6,22] The somewhat lower scores in FINEARTS-HF probably reflect the enrollment of more patients either in hospital (in a few cases) or shortly after discharge in FINEARTS-HF compared with the other trials. Patients in the lowest KCCQ-TSS tertile in FINEARTS-HF had a particularly low mean KCCQ-TSS (38.5), supported by similarly low CSS (40.9) and OSS (39.7) and a mean EuroQol 5-dimension visual analog score of only 58.0. Not surprisingly, and in keeping with prior reports, patients with a lower (ie, worse) KCCQ-TSS had a higher subsequent risk of morbidity/mortality outcomes than participants with higher baseline scores, with approximately double the rate of all key outcomes among patients in the lowest KCCQ-TSS tertile compared with the highest.

The relative risk reduction in the primary composite outcome (and in total worsening HF events) with finerenone was consistent across baseline KCCQ-TSS tertiles despite the differences in clinical profile and risk in these categories. As a result, the absolute risk reduction was largest in patients with the lowest baseline KCCQ-TSS as shown in the **Central Illustration**.

Potentially as important for many patients, from a treatment perspective, was the improvement in KCCQ-TSS on finerenone. The difference between finerenone and placebo for the change in KCCQ-TSS from baseline over 12 months was a key secondary endpoint in FINEARTS-HF and there was a significant placebo-corrected increase (ie, improvement) of 1.62 points (95% CI: 0.69-2.56 points). Although this change was small and the clinical importance of a change of this magnitude might be debated, it is important to emphasize that this was the mean change in the overall population and it was similar or larger in size to the change observed in prior trials with several other therapies in HFmrEF/HFpEF.[6,22-28] For example, in PARAGON-HF, there was a 1.0-point improvement with sacubitril/valsartan compared with valsartan at 8 months.[6] In the 2 large SGLT2 inhibitor trials, DELIVER and EMPEROR-Preserved

FIGURE 4 Treatment Effect of Finerenone vs Placebo on Change in KCCQ-TSS From Baseline to 12 Months



(A) Across key patient subgroups, and (B) across the spectrum of Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS). In A, linear regression models adjusted for baseline value, geographic region, and baseline left ventricular ejection fraction (LVEF) (<60%, ≥60%) were performed to test for the treatment effect across relevant subgroups. The model used in B was adjusted for geographic region and baseline LVEF (<60%, ≥60%). BMI = body mass index; eGFR = estimated glomerular filtration rate; HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; UACR = urine albumin-to-creatinine ratio.

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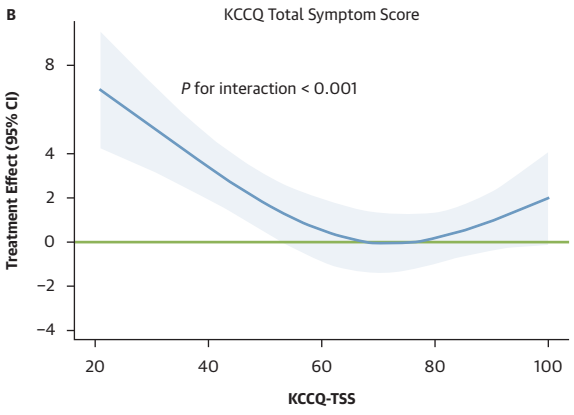
FIGURE 4 Continued



(Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction), dapagliflozin treatment led to a 2.4-point increase in the KCCQ-TSS by 8 months and empagliflozin a 1.50-point increase in the KCCQ-CSS by 52 weeks.[22,23] Several smaller SGLT2 inhibitor trials showed more variable effects on KCCQ scores.[24-26] In the TOPCAT trial, the placebo-corrected adjusted mean increase in KCCQ-OSS at 12 months was 1.35 points.[29] Other trials, such as VITALITY-HFpEF (Patient-Reported Outcomes in Vericiguat-Treated Patients With HFpEF) and NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction) showed no effect of treatment on KCCQ.[27,28] In FINEARTS-HF, the overall improvement in KCCQ-TSS was greatest in patients in the lowest KCCQ-TSS tertile, with a mean placebo-corrected increase of 3.99 points, a finding consistent with a similar analysis in DELIVER, and suggesting that those with the worst baseline health status have the greatest potential to improve this with effective therapies. This is also consistent with the recent STEP-HFpEF trials, where the baseline KCCQ-CSS was very low (approximately 59) and the mean placebo-corrected improvement was 7.5 points (95% CI: 5.3-9.8 points) with semaglutide, albeit in a very specific population with obesity.[30]

We also carried out a responder analysis, examining the proportion of patients self-reporting increases of ≥5, ≥10, and ≥20 points in KCCQ-TSS, representing small, moderate, and large improvements. There was a nominally significant difference in favor of finerenone for a ≥20-point improvement, which was self-reported in 39.9% of placebo-treated patients vs 43.2% of finerenone-treated patients (OR: 1.15; 95% CI: 1.03-1.28) in the prespecified analysis taking account of ceiling effects (but not in the responder analysis that did not account for ceiling effects [22.1% of placebo-treated patients vs 22.2% of finerenone-treated patients]; OR: 1.09; 95% CI: 0.93-1.27; $P = 0.28$). The corresponding proportions in DELIVER for a 15-point change in KCCQ-TSS at 8 months were 29% in the placebo group and 31% of the dapagliflozin-treated patients (OR: 1.12; 95% CI: 0.99-1.28) and for a ≥20-point improvement, 23.0% in the dapagliflozin group vs 21.2% with placebo (OR: 1.11; 95% CI: 0.97-1.28). In the STEP-HFpEF trials, the proportions with a 15-point change in KCCQ-CSS at 12 months were 31.0% for placebo vs 47.6% for semaglutide (OR: 2.0; 95% CI: 1.6-2.7) and a 20-point change were 19.6% vs 36.5%, respectively (OR: 2.4; 95% CI: 1.8-3.2).

This analysis of FINEARTS-HF supports the conclusion that finerenone is an effective therapy for improving health status in patients with HFmrEF/HFpEF. The improvement in KCCQ-TSS, along with the other benefits of finerenone, aligns with the primary goals of HF management to alleviate symptoms, improve quality of life, and reduce the risk of adverse clinical outcomes. That the improvement in KCCQ-TSS with finerenone was consistent across the other diverse subgroups examined, including those with higher baseline LVEF, suggests that finerenone may improve this patient-centered outcome in a broad population with HFmrEF/HFpEF. Our findings are also important considering the limited number of effective treatments available for patients with HFpEF, a group that historically has been challenging to treat.[8,31]

STUDY LIMITATIONS. As in other trials, the prespecified inclusion and exclusion criteria may have limited the enrollment of some very high-risk patients (eg, those with significant pulmonary disease, anemia, or obesity), which could affect the generalizability of our results. Additionally, a ceiling effect in KCCQ scores may have obscured the detection of further improvements in patients who already had high baseline scores, potentially underestimating the full impact of finerenone in this population. Some patients had missing KCCQ values during the follow-up period. KCCQ was collected at randomization and at 6, 9, and 12 months; the impact of treatment with finerenone on shorter (eg, 3 months) or longer-term (>1 year) health status was not assessed in the context of this study. Although FINEARTS-HF is one of the largest trials of individuals with HFpEF, some of the subgroups were modest in size, and subgroup analyses were not adjusted for multiple comparisons. Our thresholds for responder analyses may not necessarily correlate with a patient in the particular population studied in this specific trial feeling substantially better, and anchor-based analyses are needed to validate the change thresholds used; these will be done later using Patient Global Impression of Change and Severity data collected in FINEARTS-HF.

CONCLUSIONS

The FINEARTS-HF trial demonstrated that finerenone, when added to usual therapy, improved health status and reduced the risk of adverse clinical outcomes in patients with HFmrEF/HFpEF regardless of health status impairment at baseline. Collectively, these findings support the use of finerenone as an efficacious therapeutic option in this population.

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The FINEARTS-HF trial was funded by Bayer. Dr Yang has received Global CardioVascular Clinical Trialists (CVCT) Young Trialist Grant and travel grants from AstraZeneca and Bayer. Dr Atherton has received other support from Bayer, during the conduct of the study; and has received other support from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Novo Nordisk, Vifor Pharma, and Merck Sharp and Dome, outside of the submitted work. Dr Chiang has received personal fees from AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Menarini, Merck Sharp and Dohme, Novartis, Pfizer, and Sanofi. Dr Chopra has received modest speaker fees from Boehringer, AstraZeneca, Novartis, Pfizer, Novo Nordisk, Glenmark, Sun, Mankind, Lupin, Alembic, JB, Reddy's, Intas, Eris, and Cipla, outside of the submitted work. 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Dr Pitt is a consultant for Bayer, AstraZeneca, Boehringer Ingelheim, Lexicon, Bristol Myers Squibb, KBP Biosciences, Sarfez Pharmaceuticals, Pharmaceuticals, SQinnovations, G3 Pharmaceuticals, Sea Star medical, Vifor Prointel, and Brainstorm Medical; has stock/stock options in KBP Biosciences, Sarfez Pharmaceuticals, Pharmaceuticals, SQinnovations, G3 Pharmaceuticals, Sea Star medical, Vifor Prointel, and Brainstorm Medical; and has U.S. Patent 9931412-site specific delivery of eplerenone to the myocardium, U.S. Patent pending 63/045,783 Histone modulating agents for the prevention and treatment of organ failure. Dr Vaduganathan has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, BMS, Boehringer Ingelheim, Chiesi, Cytokinetics, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck,

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ADDRESS FOR CORRESPONDENCE: Prof John J.V. McMurray, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, United Kingdom. E-mail: john.mcmurray@glasgow.ac.uk.

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KEY WORDS ejection fraction, finerenone, heart failure, KCCQ, non-steroidal mineralocorticoid receptor antagonist

APPENDIX For supplemental tables and figures, please see the online version of this paper.